**LIFT-TB** Philippines

Leveraging Innovation for Faster Treatment of Tuberculosis

# CLINICAL GUIDE

*for the*

## INTRODUCTION OF THE BPAL REGIMEN IN THE PHILIPPINES UNDER OPERATIONAL RESEARCH

# CLINICAL GUIDE FOR THE INTRODUCTION OF THE BPAL REGIMEN IN THE PHILIPPINES UNDER OPERATIONAL RESEARCH

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Clinical guideline for BPaL introduction and scale-up under operational research conditions – Philippines

This clinical guide is designed to give guidance to the BPaL Operational Research sites. It is intended to support physicians on the management of adverse events for patients on the BPaL treatment. However, it is the responsibility of the physician to use his/her medical knowledge to provide appropriate care to the patient.

In cases where additional guidance is required, patients can be referred initially to the respective Regional TB Medical Advisory Committee (TB MAC) then to the National TB MAC.

If further guidance is necessary, the National TB MAC can refer the patient to the KNCV / TB Alliance International MAC (email: veriko.mirtskhulava@kncvtbc.org).

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# Abbreviations

| | |
|---|---|
| **ABC** | Abacavir |
| **aDSM** | Active drug-safety monitoring and management |
| **AE** | Adverse event |
| **AESI** | Adverse event of special interest |
| **ALT** | Alanine aminotransferase |
| **ARV** | Antiretroviral |
| **AST** | Aspartate aminotransferase |
| **AZT** | Zidovudine |
| **Bdq** | Bedaquiline |
| **BMI** | Body mass index |
| **BPaL** | Bedaquiline, pretomanid and linezolid |
| **BPNS** | Brief Peripheral Neuropathy Screen |
| **BSL** | Blood sugar level |
| **CHMP** | Committee for Medicinal Products for Human Use |
| **CNS** | Central nervous system |
| **CSF** | Cerebrospinal fluid |
| **Dlm** | Delamanid |
| **DMID** | Division of Microbiology and Infectious Diseases |
| **DOT** | Directly observed therapy |
| **DR-TB** | Drug-resistant tuberculosis |
| **DST** | Drug susceptibility testing |
| **DTG** | Dolutegravir |
| **ECG** | Electrocardiogram |
| **EFV** | Efavirenz |
| **EMA** | European Medicines Agency |
| **FDA** | United States Food and Drug Administration |
| **FQ** | Fluoroquinolones |
| **HBV** | Hepatitis B virus |
| **HCV** | Hepatitis C virus |
| **HIV** | Human immunodeficiency virus |
| **ITR** | Individualized treatment regimen |
| **Lzd** | Linezolid |
| **M. tb** | *Mycobacterium tuberculosis* |
| **MDR-TB** | Multidrug-resistant tuberculosis |
| **FDA** | Food and Drug Administration |
| **NTP** | National Tuberculosis Control Programme |
| **Pa** | Pretomanid |
| **PI** | Protease Inhibitor |
| **Pre-XDR-TB** | Pre-extensively drug-resistant TB |
| **RAL** | Raltegravir |
| **RR-TB** | Rifampicin-resistant TB |
| **SAE** | Serious adverse event |
| **STR** | Shorter treatment regimen |
| **TB** | Tuberculosis |
| **TDF** | Tenofovir |
| **TDR** | Special Programme for Research and Training in Tropical Diseases |
| **ULN** | Upper limit of normal |
| **WHO** | World Health Organization |
| **XDR-TB** | Extensively drug-resistant TB |

# 1 Introduction

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide and one of the infectious diseases severely affected by the emergence of antimicrobial drug resistance. According to the World Health Organization (WHO) 2020 report, the global burden of multidrug or rifampicin-resistant TB (MDR/RR-TB) TB cases remain stable. It is estimated that 465,000 of the 10 million TB cases were resistant to rifampicin, an estimated 3.3% of new TB cases and 18% of previously treated cases had MDR/RR-TB and the global treatment success rate reported to WHO was 57% for MDR/RR-TB.

Drug-resistant tuberculosis (DR-TB) poses serious problems in the fight against TB and at the same time, hinders progress of global TB control paving the way for an urgent need for safe, effective, and tolerable anti-tuberculosis regimens.

**Tuberculosis Classification:**
**Tuberculosis case:** asymptomatic or symptomatic person, diagnosed by a physician (or a nurse based on country regulations) of having tuberculosis and a decision to start treatment, whether the diagnosis has been confirmed with laboratory testing (confirmed case) or not.

**Bacteriologically confirmed tuberculosis case** is laboratory identification of *Mycobacterium tuberculosis* (*M.tb*) on a patient's specimen either by microscopy, culture or molecular tests.

**Site of Infection/disease**
**Pulmonary TB (PTB):** an active TB case affecting the lung parenchyma as confirmed by sputum examination (microscopy, culture, or molecular testing) or x-ray changes. Tuberculous pleural effusion, without any sputum or parenchymal X-ray changes, constitutes a case of extra-pulmonary TB.

**Extrapulmonary TB (EPTB)** an active case of TB affecting organs other than the lungs, e.g pleura, lymph nodes, abdomen, genitourinary tract, skin, brain, joints, and bones. The diagnosis of EPTB should be based on at least one clinical specimen with laboratory confirmation of *M.tb* or strong clinical or histological evidence of active EPTB and a decision by a clinician to treat. PTB and EPTB can exist simultaneously.

**Result of bacteriological investigation for tuberculosis**
**Drug-sensitive TB (DS-TB)**: caused by *M.tb* strains sensitive to first-line drugs (isoniazid [H], rifampicin [R], ethambutol [E] and pyrazinamide [Z]) and second-line anti-TB drugs.

**Drug-resistant TB (DR-TB)**: caused by *M.tb* strains resistant to anti-TB drugs (most importantly rifampicin [R], isoniazid [H] amongst the first-line drugs and any of the second-line anti-TB drugs).

**Types of DR-TB:**

- **Rifampicin-resistant TB (RR-TB) –** *M.tb* strains resistant to at least rifampicin (may be resistant to other drugs as well, but not H)

- **Multidrug-resistant (MDR-TB) –** *M.tb* strains resistant to at least rifampicin and isoniazid (may be resistant to other drugs as well, but not fluoroquinolones [FQ])

- **Fluoroquinolone-resistant MDR/RR-TB (FQ res MDR-TB) –** *M.tb* strains resistant to either both rifampicin and isoniazid or just rifampicin, plus resistant to at least one fluoroquinolone (levofloxacin [Lfx], moxifloxacin [Mfx]). This is also called "Pre-Extensively Drug Resistant TB [Pre-XDR-TB]). [a]

- **Extensively Drug-Resistant TB (XDR-TB) –** TB caused by *M.tb* strains that fulfil the definition of MDR/RR-TB that is also resistant to any fluoroquinolone [a] and at least one additional Group A drug. [b]

[a] From late 2020, WHO has defined "**Pre-XDR-TB"** as TB caused by *M.tb* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any FQ. The fluoroquinolones include Lfx and Mfx , because these are the FQs currently recommended by WHO for inclusion in the all-oral shorter and longer treatment regimens for DR-TB.
[b] The Group A drugs are currently Lfx or Mfx, Bdq and Lzd. Therefore, as from late 2020, **XDR-TB** is defined by WHO as MDR/RR-TB that is also resistant to a FQ and either Bdq or Lzd (or both). The Group A drugs may change in the future therefore, the terminology "Group A" is appropriate here and will apply to any Group A drugs in the future.

DR-TB is more difficult to treat and is often more fatal than DS-TB. Treatment requires a longer duration with more toxic drug combinations and with lower favourable outcomes. A recent development of new drugs such as bedaquiline (Bdq), delamanid (Dlm) and pretomanid (Pa), and the approval of the BPaL (Bdq plus Pa and Lzd) regimen by the US Food and Drug Administration (FDA), have shown promising new developments in the treatment of DR-TB.

In August 2019, the US FDA, and in March 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) have recommended approval of the new drug pretomanid for the treatment of pulmonary extensively drug-resistant forms of TB (XDR-TB[1]) or treatment-intolerant or non-responsive MDR-TB, in a combination with Bdq and Lzd. This regimen was trialled in the Nix-TB study, sponsored by the TB Alliance, for use in patients with XDR-TB, or intolerance or failure of an MDR-TB treatment regimen. The BPaL regimen was given for 6 months with the possibility to extend the duration to 9 months. The results showed a favorable outcome (culture-negative) in 98 of 109 (90%) enrolled patients after 6 months post-treatment follow-up and were recently published.[2] A later analysis showed that this high efficacy was sustained through a two-year follow-up.

The most recent WHO Guidelines on the treatment of DR-TB, released in June 2020, includes a new section with recommendations on the use of the novel BPaL regimen under operational research (OR) conditions. Due to the high rate of adverse events, the regimen may not yet be considered for programmatic use until more evidence on efficacy and safety has been generated. In addition, WHO recommends countries to replace the injectable in the shorter treatment regimen (STR) with Bdq and use the shorter all-oral Bdq-containing as the preferred option for eligible MDR/RR-TB patients. The guidelines stress the increased requirements for drug susceptibility testing (DST) and active TB drug safety monitoring and management (aDSM).

[1] As per WHO definition of XDR-TB used at the time of MDR/RR-TB plus additional resistance to a FQ and any second-line injectable agent.
[2] N Engl J Med 382;10 nejm.org March 5, 2020

The recently completed Zenix trial observed that lower doses and/or shorter durations of linezolid than 1200mg for 6 months appear to have high efficacy and improved safety.[3]

The main objective of the BPaL OR is to estimate the effectiveness and safety of the regimen in MDR/RR-TB patients with additional FQ resistance (i.e Pre-XDR-TB) and MDR/RR-TB patients with documented treatment intolerance or failure. The study results will be used to develop a national scale-up plan and contribute to global evidence.
This Clinical Guide provides the following instructions to aid the clinician on:

- Initiating patients on the BPaL regimen;
- Monitoring patients' treatment and providing adequate management of potential adverse events;
- Grading and managing adverse events of special interest (AESI) related to the BPaL regimen;
- Recording and reporting of (serious) adverse events (SAEs) and their management; and
- Managing comorbidities
- Determining outcomes and managing post-treatment follow-up

# 2 Treatment initiation for patients on BPaL

For details of the patients' eligibility criteria for BPaL, please refer to KNCV's "Generic BPaL OR protocol. Version 4, updated December 2021", pages 14-16. This is the Philippine protocol version 14, awaiting approval from the Single Joint Research Ethics Board (SJREB).

Before treatment initiation, ensure that all baseline tests, including clinical evaluation, bacteriological and clinical laboratory investigation, are done according to the baseline monitoring schedule (see table 5 in KNCV's "Generic BPaL OR protocol. Version 4, Updated December 2021", pages 25-26).

The clinical evaluation should include physical examination (with brief peripheral neuropathy screening), weight/BMI, visual acuity and colour discrimination screen, and performance status assessed by Karnofsky Performance Status Scale. ECG recording should be available for all patients.

Check that all baseline results are within normal limits or allowed by the OR protocol prior to treatment initiation with BPaL regimen. If necessary, consider further investigations or specialist consultations in case of comorbidity or relative contraindications. Baseline investigation results may guide additional tests during the monitoring during treatment.

Patients with prior used of bedaquiline and linezolid for more than 4 weeks (which is an exclusion criterion) can be considered for the BPaL treatment regimen, if DST result reveals susceptibility to both drugs and the TB MAC decide the benefits of treating the patient with the BPaL regimen outweigh the risk. Patients with prior use of Dlm (a drug related to Pa) for more than 4 weeks can also be considered for BPaL treatment if they are shown to be susceptible to Pa.

## 2.1 Contraindications and warnings

[3] Conradie F, Everitt D, Olugbosi M, et al, for the ZeNix Study Team High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid. Abstract at 11th IAS Conference on HIV Science, 18-21 July 2021.

There are no absolute contraindications for the use of any drug in the treatment of MDR/RR-TB, Pre-XDR-TB and XDR-TB, a disease that poses serious risk of death or debilitation to the patient if treated inadequately. However, there are relative contraindications for the BPaL regimen and warnings on possible drug-drug interactions or overlapping toxicities as listed in Tables 1, 2 and 3. If the clinician judges that the potential benefits outweigh the potential risk (also considering alternative treatment options), treatment may proceed with caution. In these situations, advice needs to be sought from the assigned expert TB committee.

**Table 1. Selected relative contraindications to the use of the BPaL regimen**

| **Relative contraindication** | **Notes** |
|---|---|
| High risk of cardiac arrhythmia | Baseline QTcF > 500ms<br>History of syncopal episodes, ventricular arrhythmias, heart failure or severe coronary artery disease<br>Family history of long-QT syndrome |
| Severe anaemia,<br>Moderate thrombocytopaenia<br>Moderate neutropaenia | Haemoglobin level < 8.0 g/dL<br>Platelet count <75,000/mm3<br>Absolute neutrophil count < 1000/mm3 |
| Severe peripheral neuropathy | Grade 3 or Grade 4, according to the Division of Microbiology and Infectious Diseases (DMID) [4] |
| Evidence of hepatic impairment | AST/ALT > 3.0 x ULN<br>Total bilirubin > 2.0 x ULN<br>Albumin < 32 g/L |
| Significant renal insufficiency | Serum creatinine > 3.0 x ULN<br>No dose adjustment, other than an interruption for an adverse event, should be made for Bdq or Pa. Lzd dose reductions, interruptions or discontinuations are allowed (see section 5.2). Primary metabolites of Lzd accumulate in renal impairment and the clinical significance of this is unknown. Due to limited experience, caution should be exercised in patients with significant renal impairment. |

[4] Paresthesia grade 3: severe discomfort; narcotic analgesia required with symptomatic improvement; and /or BPNS subjective sensory neuropathy scare 7-10 on any side. Grade 4: incapacitating; or not responsive to narcotic analgesia.

**Table 2. Possible drug-drug interactions or overlapping toxicities with the BPaL regimen**

| Mechanism | Drugs to be avoided |
|---|---|
| Moderate/strong inducers of CYP450 enzymes may decrease blood levels of Bdq or Pa | ● Efavirenz (EFV)<br>● Rifamycins (rifampicin, rifapentine, rifabutin)<br>● Antiepileptics (phenytoin, carbamazepine, phenobarbital) |
| Moderate/strong inhibitors of CYP450 enzymes may increase blood levels of bdq | ● Ritonavir-boosted Protease Inhibitors (PI)<br>● Fluconazole/itraconazole (can be used up to two weeks e.g oral/oesophageal candidiasis)<br>● Clarithromycin/erythromycin |
| Mechanism not clear | First line TB drugs (HRZE) in fixed-dose combination |
| Drugs that cause QT prolongation[5] or affect the heart rhythm | ● Oral azole antifungals (see also above): ketoconazole, itraconazole, fluconazole<br>● Macrolide antibiotics: azithromycin, clarithromycin, erythromycin<br>● Antipsychotics (all have some risk): e.g haloperidol, risperidone)<br>● Many anti-nausea drugs: e.g ondansetron, granisetron, domperidone, chlorpromazine<br>● Methadone<br>● Cardiac drugs that may affect the heart rhythm: e.g amiodarone, beta-blockers, digoxin, quinidine |
| Medicines that increase serotonin levels [6] | ● Serotonin re-uptake inhibitors: fluoxetine, paroxetine<br>● Tricyclic antidepressants: amitriptyline, nortriptyline<br>● Serotonin 5-HT1 receptor agonists<br>● MAO inhibitors: phenelzine, isocarboxazid<br>● Other serotoninergic agents: meperidine, bupropion, or buspirone, quetiapine |

**Table 3. Possible drug-drug interactions/overlapping toxicities between antiretrovirals and the BPaL regimen**

| ARVs to be avoided | Instructions |
|---|---|
| Efavirenz (EFV) | ● Check viral load:<br>- if suppressed, substitute preferably with an integrase inhibitor such as dolutegravir (DTG) or nevirapine (NVP). Allow a 5 to 7 day wash |

[5] This is not a comprehensive list. Clinicians should inform themselves about potentially QT-prolonging drugs that their DR-TB patients may be taking (see https://www.crediblemeds.org/).

[6] List with drugs that can increase serotonin level
https://www.msdmanuals.com/professional/multimedia/table/v1114640

| | |
|---|---|
| | out of EFV if possible (substitute on day 1 and then start BPaL regimen 5-7 days later). If a patient is critically ill, no wash out period is necessary.<br>- If viral load if not suppressed, switch to 2nd line ART and try to avoid PIs<br>● Switching back to EFV can be done immediately after BPaL is stopped at the end of treatment. |
| Ritonavir-containing protease inhibitors (PIs) | ● Check viral load:<br>- if suppressed, use an ARV regimen without PI. One possible solution is to substitute the PI with an integrase inhibitor, e.g DTG or raltegravir (RAL)<br>- If viral load not suppressed, adjust regimen according to national guidelines<br>● If a ritonavir-containing PI is used, check ECG every two weeks |
| Zidovudine (AZT) | ● High risk for myelosuppression in combination with Lzd. If possible, stop AZT and use tenofovir (TDF) or abacavir (ABC) |

## 2.2 Dosing of the regimen components

The BPaL regimen consists of bedaquiline, pretomanid and linezolid which was studied in an open-label, phase 3 clinical trial (Nix-TB trial) on patients with XDR-TB [1] and treatment-intolerant or non-responsive MDR/RR-TB for six months, with the possibility of extension to nine months when needed.

Treatment was initiated based on the dosage of each of the drugs in the regimen as shown in the table. All medicines should be given daily for the whole duration of the treatment (except Bdq) with food.

**Table 4. Dosing of the component drugs for adults (aged 18 and over) and [adolescents] ≥ 35 kg [7]**

| Drug | Dose | Total number of tablets |
|---|---|---|
| Bedaquiline (100 mg tablets) * | 400 mg once daily for 2 weeks, then 200 mg 3 times per week for 24 weeks afterwards | 200 |
| Pretomanid (200 mg tablets) | 200 mg once daily | 182 |

[7] Bdq is recommended for use in patients aged 6 and over by the WHO, and Lzd for all ages. There is no recommendation for Pa. Adolescents from 14 years of age could be included in treatment with the BPaL regimen on the decision of the respective Expert TB Committee. In August 2021, WHO released a "Rapid Communication on updated guidance on the management of tuberculosis in children and adolescents" informing NTPs and other stakeholders that Bdq may be used in children of all ages as part of the shorter all-oral Bdq-containing regimen or as part of longer treatment regimens. Updated Guidelines and Operational Handbooks are expected to be released by the end of 2021.

| | | |
|---|---|---|
| Linezolid (600 mg tablets) | 1200 mg once daily (adjustable) BPaL | 264 to maximum of 364 (based on Nix trial) |

***Notes***

*[@] If a patient who is eligible for the BPaL regimen but has recently taken the WHO-recommended Bdq-containing all-oral STR, a concern would be whether the patient may have developed resistance to Bdq. If Bdq has been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs (Bdq, plus Lzd if used in previous regimen) is required for the patient to be eligible for BPaL regardless of the timing of the previous exposure. The respective Expert TB Committee needs to review the individual patient and decide whether the patient can be enrolled on BPaL.*

*However, as Bdq DST may not always be available, there will need to be an individual patient judgement on their risk of exposure having led to resistance developing based on drug history and response:*

***Dosing recommendations after interruption of Bdq***

| **Timing of interruption of Bdq** | **Duration of interruption of Bdq** | **Required loading dose** |
|---|---|---|
| Within 2 weeks of loading | ≤ 2 weeks | Finish remaining loading days, then continue with Bdq 200 mg/day thrice weekly until end of treatment |
| Within 2 weeks of loading | > 2 weeks | 1 week of 400 mg/day |
| After completion of 2 weeks loading | ≤ 2 weeks | No need for reloading, proceed with Bdq 200 mg/day thrice weekly until end of treatment |
| After completion of 2 weeks loading | > 2 weeks – < 6 months | 1 week of 400 mg/day, then continue with Bdq 200 mg/day thrice weekly until end of treatment |
| After completion of 2 weeks loading | > 6 months | 2 weeks of 400 mg/day, then continue with Bdq 200 mg/day thrice weekly until end of treatment |

*If the patient has been treated for MDR/RR-TB with a Bdq-containing regimen for more than 4 weeks, susceptibility to Bdq (plus Lzd if used in previous regimen for more than 4 weeks) is required for the patient to be eligible for BPaL. If DST shows susceptibility to Bdq (and Lzd) and there is no documented intolerance to Bdq (or Lzd), the patient is eligible for BPaL. Bdq should be given throughout the full course of the BPaL regimen i.e* ***6 to 9 months****. Previous Bdq exposure should not alter the duration of Bdq use in the BPaL regimen. Previous Bdq exposure should only be considered in relation to the adjustment of loading dose of Bdq as described above. Remember: Use of Pa is only recommended as part of the BPaL regimen.*

*Linezolid high dose in the BPaL regimen can be reduced in patients with linezolid-induced peripheral neuropathy or myelosuppression, see paragraph 8.1. for more details on Lzd dose reduction. Dose modifications for Bdq and Pa are not allowed. For more information on managing AEs, a clinical guide is available for the study sites to refer to.*

## 2.3 Duration of treatment

The BPaL regimen is given for a duration of 6-9 months (26 – 39 weeks):

- The standard treatment duration is 6 months (26 weeks)
- If the sputum culture taken after the patient has taken 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment (total 9 months) if the patient is clinically well and /or improving. During the Nix-TB trial treatment was extended to 9 months in only 2 out of 109 enrolled patients. Positive cultures after extension of treatment should be dealt with on a 'case by case" basis, considering the clinical response of the patient as well. These cases can be presented to the TB MAC for decision on further management.

## 2.4 Inpatient and ambulatory treatment

- Treatment initiation may be on ambulatory or in-hospital settings based on national policy.
- If there are concerns on the safety monitoring, patients may be hospitalized for the initial 2 weeks of treatment to ensure the patient is well informed, baseline tests are done to monitor patient's tolerability of the regimen.
- All patients should have a clinical staff (facility nurse or physician) and a trained treatment supporter based on the national policy.
- DOT should be administered seven days a week throughout the full length of treatment. Adherence support (e.g health facility or community-based DOT / VOT) should be initiated based on country specifications
- Enablers to cover travel expenditures (and food supplements if relevant) should be provided during the whole treatment course.
- Responsibilities of the trained treatment supporter to:
    - Administer strictly DOT and update the patient treatment card daily
    - Ensure that the patient attends all scheduled follow-up visits and examinations; and
    - Monitor AEs closely and address AEs in a timely manner by informing clinical staff; and
    - Initiate contacting the patient if the patient fails to return for treatment as per schedule.

## 2.5 Procedure following missed doses

- Interruption of the full BPaL regimen may occur at any time during the treatment period.
- The full BPaL regimen can be temporarily interrupted for a maximum of 14 days (either consecutive or non-consecutive) during the first 4 weeks of treatment and for a maximum of 35 consecutive days after the first 4 weeks.
- If the regimen is interrupted for more than 14 days in the first 4 weeks or for more than 35 consecutive days after the first 4 weeks, the patient should be referred to

the expert TB clinical committee to decide on further management (an individualized regimen needs to be designed)

- Any missed doses of the full BPaL regimen (including both consecutive and non-consecutive) should be made up at the end of the treatment to complete 26 weeks or 39 weeks of therapy within a maximum period of 60 days after the intended end of treatment duration.
- Missed doses of linezolid alone due to adverse reactions are not to be made up at the end of treatment
- Reasons for missing treatment must be identified and addressed early and noted in the patient's file for analysis for factors associated with (lack of) treatment success.
- Timely and adequate management of adverse events improves patient's adherence.
- Interruption of treatment for two consecutive months will be classified as "lost to follow-up" and in this case the patient will no longer be eligible for further BPaL treatment.

## 2.6 Discontinuation of the regimen

There might be a need to discontinue the BPaL regimen in some patients, the most common reasons for permanent discontinuation of the BPaL regimen are:

- **Intolerable Toxicity**[8]. In case Bdq and/or Pa need to be suspended permanently owing to intolerable toxicity, the patient will need to be shifted to another regimen as advised by the MAC. In case of intolerable toxicity to Lzd, the drug may be permanently or temporarily discontinued only after:
    - i. A total of at least 4 weeks of Lzd 1200 mg/day has been completed; or
    - ii. A total of at 9 weeks of Lzd at least 600 mg/day has been completed, if the Lzd has had to be reduced to 600 mg/day during the initial 4 weeks of treatment; and
    - if there is clinical and radiological evidence of improvement after at least 4 weeks of BPaL treatment.

  A permanent discontinuation of Lzd with a total exposure of less than 4 weeks (1200mg/ day) or less than 9 weeks (600mg/day), should be avoided if possible, and any proposal to permanently discontinue the Lzd needs to be discussed with the MAC.
  For further details on modification and discontinuation of the BPaL regimen and/or drugs, please refer to KNCV's "Generic BPaL OR protocol. Version 4, Updated December 2021", pages 29-30.
- **Treatment failure**. If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated if culture is still positive at month 4, whether the regimen is changed or not, to inform future management decisions.
- **Resistance to drugs in the BPaL regimen**. For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to any of the BPaL component drugs is discovered after treatment is initiated, the BPaL regimen must be discontinued, and the patient switched to another regimen.
- **Pregnancy during treatment**. For patients who become pregnant during treatment, it may be advisable to modify or discontinue the BPaL regimen. The patient needs referral

[8] WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. ISBN 978-92-4-000699-7

to the MAC for review and discussion on future treatment. The patient needs to be involved in any discussions and decision making in relation to future treatment.

In all above cases, patients should be evaluated by the MAC and switched to an individualized regimen, based on the WHO guidelines for regimen design.

## 2.7 Patient monitoring schedule

All patients receiving treatment with the BPaL regimen should undergo appropriate evaluation at baseline, during and after treatment, including clinical evaluation, bacteriological and laboratory testing, according to the monitoring schedule (see table 5 in KNCV's "Generic BPaL OR protocol. Version 4, Updated December 2021", pages 25-26).

Additional remarks:

- Results for baseline clinical evaluation, laboratory blood tests and ECG are valid if dated < 2 weeks before enrolment
- Blood tests/ECG dated > 2 weeks before enrolment should be repeated, and results should be checked before enrolment
- A sputum sample for culture and DST should be collected just before start of treatment. Isolates from all positive cultures collected during every visit, including baseline and after treatment completion, will be stored to allow additional investigations if necessary. If a patient who is eligible for the BPaL treatment following treatment on the any RR/MDR-TB regimen and has a negative baseline culture, the last positive culture isolate collected within the last 3 months from when the patient was on the previous regimen, should be stored for future testing.
- Monitoring should be continued at monthly intervals (where indicated) for the duration of treatment (i.e 6 months or 9 months in case of treatment prolongation).
- More frequent monitoring may be advisable in specific situations, including elderly people, patients infected with HIV, affected by HBV- or HCV-related hepatitis, diabetes mellitus, or with moderate to severe hepatic or renal impairment.
- In case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed, (see management of adverse events Chapter 3).

The performance status of all patients should be assessed at baseline using the Karnofsky Performance Scale Index (Table 6). This allows patients to be classified as to their functional impairment and can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses. The score should be indicated on the patient enrollment form to identify possible factors related to poor outcomes of the BPaL regimen.

**Table 6. Karnofsky Performance Scale**

| Definitions Rating (%) Criteria | | |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | **100** | Normal no complaints; no evidence of disease |
| | **90** | Able to carry on normal activity; minor signs or symptoms of disease |
| | **80** | Normal activity with effort; some signs or symptoms of disease |

| | | |
|---|---|---|
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | **70** | Cares for self; unable to carry on normal activity or to do active work |
| | **60** | Requires occasional assistance, but can care for most of his personal needs |
| | **50** | Requires considerable assistance and frequent medical care |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | **40** | Disabled; requires special care and assistance |
| | **30** | Severely disabled; hospital admission is indicated although death not imminent |
| | **20** | Very sick; hospital admission necessary; active supportive treatment necessary |
| | **10** | Moribund; fatal processes progressing rapidly |
| | **0** | Dead |

# 3 Monitoring and management of adverse events

Effective adverse events management is a central component of DR-TB treatment. Poorly managed AEs can lead to inadequate or irregular treatment or to abandonment of treatment altogether. Effective management entails both rapid identification and timely management.

Patients with a current diagnosis or history of concomitant disease should be assessed and managed as appropriate in collaboration with a specialist based on national policy recommendations.

Most patients taking the BPaL regimen will experience an adverse event of some kind (in the Nix-TB study, all patients experienced at least one AE). Active follow-up of monitoring test results is required (e.g FBC, liver function, electrolytes within the investigational schedule and more frequently when necessary) to identify and manage AEs early and ensure patient safety.

An AE is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment. AEs may be mild, moderate, severe or life threatening, and may be caused by something other than the drug or therapy being given.

- Management of AEs should take patient safety and treatment requirements into consideration.
- Mild or moderate AEs can usually be managed by using adjunct medications, reducing the dose of responsible drug (e.g Lzd), or temporarily stopping the full regimen.
- For refractory and more severe AEs, Lzd or the full BPaL regimen may need to be discontinued.
- Each AE should be graded according to the severity grading scale for AEs (Table 7).

**Table 7. General severity scale to grade adverse events**

| Grade 1 mild | Grade 2 moderate | Grade 3 severe | Grade 4 life-threatening |
|---|---|---|---|
| Transient or mild discomfort (<48 hours); no medical intervention/therapy required. | Mild to moderate limitation in activity* - some assistance may be needed; no or minimal medical intervention/ therapy required. | Marked limitation in activity*, some assistance usually required; medical intervention/therapy required, hospitalizations possible. | Extreme limitation in activity*, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable. |

*The term 'activity' covers basic self-care functions such as bathing, dressing, toileting, transfer/ movement, continence and feeding; but also, usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

## 3.1 Recording and reporting adverse events

All AEs leading to temporary or permanent discontinuation of Lzd or the full BPaL regimen should be carefully recorded in the patient file and documented on data collection Form 3**.** Evaluation. When an AE occurs, the clinician responsible for the care of the patient must first assess whether the event is serious or is of special interest.
A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is life-threatening.
- Cause a congenital anomaly or a birth defect.
- Is otherwise medically important

All AESI/SAEs should be reported (using the aDSM reporting form) in-line with national policy. However, Form 6. Adverse Event should be completed within 72 hours as mentioned below to the national pharmacovigilance committee/national regulatory authority in-charge of existing aDSM framework.

Adverse events of special interest (AESI) for the BPaL regimen are:

- QT-prolongation;
- Peripheral neuropathy;
- Myelosuppression;
- Optic neuritis; and
- Hepatotoxicity.

Any of the above adverse events of special interest and any AE leading to treatment discontinuation or change in drug dosage should also be reported to the national pharmacovigilance committee/national regulatory authority in-charge of existing aDSM. In addition, aDSM related data should be entered directly from the aDSM form into the **REDcap** or **Epi info** database within 72 hours. The adverse event data, as a minimum, must contain the information required in data collection Form 6. Adverse Event.

Pregnancy during treatment with the BPaL regimen should also be reported as an adverse event. Although the patient will be switched to another regimen in most cases, follow-up visits should be scheduled to document the outcome of the pregnancy and information concerning the infant if the patient is willing to collaborate and share the necessary information (Form 6. Adverse event, sections 7 and 8).

It is important that all adverse events be evaluated to determine their causal relationship with the drugs in the treatment regimen, especially novel drugs, or any other drug used for comorbidity management. This evaluation should consider all other possible causal factors (e.g medical history, risk factors, past drug use, concomitant procedures, TB progression). This will determine the relationship of the AE by ruling out other possible factors which can support the management plan. Causality Assessment (CA) should be done by a higher level of the health system e.g by the National Pharmacovigilance Unit, and not by the attending physician. Inaccurate statements could have major impact on a new drug such as Pa, so CA should only be done by those with the expertise on how to do CA.

## 3.2 Regimen modification

Safe management of AEs may warrant dose reduction or discontinuation of the component drugs. However, the BPaL regimen has been studied as a standardized course of treatment. Modification of the regimen through early discontinuation or replacement of any of the component drugs may result in poor treatment outcomes.

**Acceptable modifications for the BPaL regimen in the management of AEs**

**Linezolid**

The starting dose of Lzd should be 1200mg daily.

- Linezolid can be temporarily or permanently interrupted, or the dosage can be reduced.
  - Temporary (or permanent) interruption of Lzd (while Bdq and Pa are continued) due to for example Lzd-related toxicity issues, is only allowed after participants have received at least 4 weeks of treatment with a daily Lzd dose of 1200 mg or at least 9 weeks of Lzd 600mg daily if the dose was reduced, and with evidence of clinical and radiological improvement after at least the initial 4 weeks of BPaL treatment. Any interruptions or dose reductions should be followed by a careful clinical assessment to observe the effect and manage accordingly. The Lzd dose may be reduced to 600mg daily during the initial 4 weeks of treatment, but then must be given for at least 9 weeks.
  - For Lzd alone, any interruption in the first 4 weeks of 1200mg daily or within the first 9 weeks if the Lzd dose has been reduced to 600mg daily is not allowed. Such a patient would need to be switched to another regimen.
  - If an AE occurs during the first four weeks of treatment that does not require a dose modification, interruption, or discontinuation of Lzd, then an interruption of the **FULL BPaL REGIMEN** is allowed for a maximum of 14 days (all three component medicines must be withheld together consecutively or non-consecutively), after which the **FULL BPaL REGIMEN** should be recommenced, including Lzd 1200mg daily or 600 mg mg daily if the dose had had to be reduced. If the interruption exceeds 14 days, the patient must be withdrawn from the BPaL treatment cohort and switched to an alternative regimen. Also, in cases where the full BPaL regimen is interrupted for more than 35 consecutive days after the first four weeks of treatment, the

patient should be referred to the expert TB committee to decide on further management, including the need for change to a new individual regimen, based on clinical assessment and reason for interruption.

- If there are any concerns about the clinical progress and response to treatment, then interruptions to Lzd ought to be minimized, or the regimen should be strengthened with the patient being switched from the BPaL regimen and withdrawn from the study.
- Response to treatment must always be closely monitored. Interruptions/reductions to Lzd without clinical improvement should be regarded with additional caution.

Any modification of the Lzd dosage needs to be discussed with the MAC. In case of toxicities requiring Lzd interruption/dose reduction, the TB MAC should balance the risk of inadequate treatment and relapse with the burden of additional/prolonged treatment. The regimen may need to be strengthened, with the patient being switched from the BPaL regimen and withdrawn from the study.

**Bedaquiline and/or Pretomanid**

- No dose modifications are allowed for both Bdq and Pa at any time during treatment with the BPaL regimen (only dose modification of Lzd is allowed, according to the restrictions above). The doses of Bdq and Pa are fixed (except for the routine reduction of Bdq 400mg daily to 200mg 3 times a week after the first 14 days of treatment).
- Loading dose of Bdq should follow the recommendations given in Table 5.
- No interruption of Bdq or Pa alone is allowed. If Bdq or Pa need to be interrupted, then the full BPaL regimen must be interrupted at once.
- Permanent discontinuation of Bdq or Pa is not allowed. If Bdq or Pa need to be discontinued, then the full BPaL regimen must be discontinued, and the patient transferred to an alternative regimen.
- **Pa should not be used ever outside the BPaL treatment regimen.**

**The full BPaL regimen**

- If an AE occurs during the first four weeks of treatment that does not require a dose modification, interruption, or discontinuation of Lzd, an interruption of the **FULL BPaL REGIMEN** (all three component medicines must be withheld together during this time) **is allowed for a maximum of 14 days,** after which the **FULL BPaL REGIMEN** should be recommenced, including Lzd 1200mg daily. The Lzd daily dose of 1200mg should be counted for at least 4 weeks, or at least **9 weeks** if the Lzd dose had had to be reduced to 600 mg/day during the first 4 weeks. After the first four weeks, an interruption of the full BPaL regimen may be allowed for a maximum of 35 days. If the interruption exceeds 14 days during the first 4 weeks or 35 days after the first 4 weeks, the patient must be withdrawn from the BPaL treatment cohort and provided with an alternative regimen.

Any treatment interruptions should be discussed in advance or preferably within 1-2 days with the TB MAC, and optimally prior to interruption of treatment.

If a patient is failing treatment, he/she should be referred to the TB MAC for review and design of a new individualized regimen based on WHO recommendations on regimen design.

**Medication errors** are defined as unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient (e.g prescription of wrong drug, wrong dosage, overdose). This must be managed on a case-by-case basis, especially

when regimen modification is required. Reporting for medication error should follow national policy guide. However, if it requires hospitalization then it should be reported as SAE and should also be reported when it required treatment interruption.

In cases where the medication error leads to either a treatment interruption or permanent discontinuation of the regimen should be discussed with the TB MAC to assess the patient's condition and plan management.

## 3.3 Clinical management of adverse events of special interest

### 3.3.1 Peripheral neuropathy

Occurs in conditions in which nerves that carry messages to and from the brain or spinal cord to the rest of the body are damaged or diseased. Peripheral nerves make up an intricate network that connects the brain and spinal cord to the muscles, skin, and internal organs.

Peripheral neuropathy is extremely common in patients taking Lzd and was experienced by 80% of the patients in the Nix-TB study. However, in most patients the symptoms of peripheral neuropathy disappeared after reduction, interruption, or discontinuation of Lzd. The recently completed Zenix trial observed that lower doses and/or shorter durations of linezolid than 1200mg for 6 months appear to have high efficacy and improved safety, including in relation to peripheral neuropathy.

All patients should be assessed monthly for symptoms suggestive of neuropathic pain using the Brief Peripheral Neuropathy Screen (BPNS), see Annex 1, which allows subjective grading of the symptoms.

Although difficult to define and variable for everyone, neuropathic pain is often described as "burning", "electric", "tingling", and "shooting" in nature. It can vary from a constant pain to intermittent sharp shooting pains. As described, the pain is most often present without associated stimulation, but can be exacerbated by stimuli.

Other common causes of peripheral neuropathy include alcohol use, other medications, HIV infection or diabetes mellitus, and these causes should also be assessed in any patient found to have peripheral neuropathy.

**Peripheral neuropathy at baseline**
Patients with signs and symptoms of peripheral neuropathy (not associated with linezolid) at baseline should have a differential diagnosis, check electrolytes, and screen for other conditions impacting on peripheral neuropathy such as alcohol use disorder or diabetes. Consider solving/stopping all the contributing factors and invite the patient for rescreening. If the symptoms resolve, enroll the patient on the BPaL OR. In patients with grade 1 and 2 symptoms, weigh the risks and benefits of treatment with the BPaL regimen and consider enrolment with a monitoring plan prior to treatment initiation. Grade 3 and 4 peripheral neuropathy at baseline is a relative contraindication for the BPaL regimen, these patients should be discussed with TB MAC and management should include a specialist support wherever possible.

In addition, all patients with symptoms of peripheral neuropathy should be examined including deep tendon ankle reflexes, light touch perception with a cotton swab / monofilament or vibration testing with a 128-Hz tuning fork (Annex 1).

**Table 8. Clinical management of peripheral neuropathy according to severity grading**

| Grade<br>Severity | Grade 1<br>Mild | Grade 2<br>Moderate | Grade 3<br>Severe | Grade 4<br>Life-threatening |
|---|---|---|---|---|
| Neurosensory alteration | Mild discomfort: no treatment required; and/or BPNS subjective sensory neuropathy score 1-3 on any side | Moderate discomfort: non-narcotic analgesia required; and / or BPNS subjective sensory neuropathy score 4-6 on any side | Severe discomfort: or narcotic analgesia required with symptomatic improvement; and / or BPNS subjective sensory neuropathy score 7-10 on any side | Incapacitating; or not responsive to narcotic analgesia |
| Action | Stop or reduce dose of Lzd. If symptoms improve, consider restarting Lzd at a lower dose 600 mg or 300 mg. | Stop Lzd, provide symptomatic care. If symptoms improve, consider restarting Lzd at 600 mg or 300 mg. Stop Lzd permanently if symptoms reappear | Stop Lzd, do not restart. Provide symptomatic relief | Stop Lzd, do not restart. Provide symptomatic relief |

Symptomatic relief:

- In grade 1, consider increasing the dose of pyridoxine to 200 mg/day
- In grade 2, counsel the patient and monitor closely. If painful, consider starting non-steroidal anti-inflammatory drugs, acetaminophen. If there is no improvement, consider changing to gabapentin or pregabalin to alleviate symptoms. May increase pyridoxine up to 200 mg/day.

**Table 9. Drugs used in the treatment of peripheral neuropathy**

| | | | |
|---|---|---|---|
| **Gabapentin** | Peripheral neuropathy | *Neuropathic pain*, initially 100–300 mg daily; increase dose gradually every 3–7 days according to response; usual range 1.8–3.6 g daily in 3 divided doses | Adverse events: drowsiness<br>Caution: Dose adjustment in renal failure<br>Avoid stopping abruptly (may cause anxiety, insomnia, nausea, pain, and sweating); gradually reduce dose over at least a week |
| **Pregabalin** | Peripheral neuropathy | Initial: 150-300 mg daily divided q8-12hr<br>Maintenance: May increase to 300 mg daily divided q8-12hr after 1 week, as needed | Adverse events: dizziness, somnolence<br>Avoid stopping abruptly (may cause anxiety, insomnia, nausea, pain, and sweating); gradually reduce dose over at least a week |

**Use of pyridoxine**

Previously pyridoxine has been advised to be used in TB patients, both drug-susceptible and drug-resistant, who are at high risk of drug-induced peripheral neuropathy, e.g patients treated with high dose isoniazid or linezolid, or those being given cycloserine/terizidone. An example of the recommended preventive dosage is 50 mg daily for every 250mg of

cycloserine. For those who develop signs and symptoms related to peripheral neuropathy, the dosage can be increased to a maximum of 200 mg daily. However, there is no evidence for pyridoxine reducing the risk of developing Lzd-induced peripheral neuropathy.

### 3.3.2 Myelosuppression

Is referred to as bone marrow suppression in which there is a decrease in bone marrow activity resulting in reduced production of blood cells. This leads to:

- Anaemia
- Neutropaenia
- Thrombocytopaenia

Myelosuppression is very common in patients taking Lzd and was experienced by 47% of the patients in the Nix-TB study with anaemia being the most prevalent. Myelosuppression occurred generally within the first 3 months of treatment and could be managed with Lzd dose reduction or interruption.

Close monitoring of changes in haemoglobin is necessary especially over the first 4 weeks of treatment, with a routine check of full blood count (FBC) at week 2 and week 4 and then monthly.

Other causes of anemia (TB, iron-deficiency, occult GI bleeding, etc.) are possible and should be checked and excluded, although these are less likely to occur in the middle of treatment, especially if the patient is clinically improving. There is limited evidence that adding pyridoxine to the BPaL regimen will prevent myelosuppression.

**Table 10. Clinical management of myelosuppression according to severity grading**

| **Severity Grade** | **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3 Severe** | **Grade 4 Life-threatening** |
|---|---|---|---|---|
| Anaemia | 10.5 - 9.5 g/dL | 9.4 – 8.0 g/dL | 7.9 – 6.5 g/dL | < 6.5 g/dL |
| Platelets decreased | 99,999-75,000/mm³ | 74,999-50,000/mm³ | 49,999-20,000/mm³ | < 20,000/mm³ |
| While blood cells decreased | <LLN - 3,000/mm³ | <3,000 - 2,000/mm³ | <2,000 - 1,000/mm³ | < 1,000 /mm³ |
| Absolute neutrophil count low | 1500 - 1000/mm³ | 999 - 750/mm³ | 749 - 500/mm³ | <500/mm³ |
| Action | Monitor carefully, do weekly FBC and consider reduction of Lzd dose to 600 mg or 300 mg daily | Monitor carefully, do weekly FBC and consider reduction of Lzd dose to 600 mg or 300 mg daily. In case of Grade 2 neutropenia, stop Lzd. Restart at lower dose once toxicity has reduced to Grade 1 | Stop Lzd immediately. In case of Grade 3 anemia, consider EPO if available. Restart at reduced dose once toxicity has decreased to Grade 1 or consider stopping Lzd permanently | Stop Lzd immediately. Hospitalize patient and consider blood transfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1 or consider stopping Lzd permanently |

**Additional work up and management in case of anaemia**

- Review of FBC, differentials and other investigations to determine possible etiology of anaemia;
- Review of other medications that could possibly be associated with anaemia;
- Test for pregnancy in women; and
- Assess for other infections, including parasites and viral pathogens (i.e parvovirus).

It is important to note that, since TB disease is a common cause of anaemia, treatment with an effective regimen including Lzd may sometimes cause the haemoglobin to improve. For this reason, all efforts should be made to reintroduce Lzd with close clinical monitoring and to identify and treat other causes of a low haemoglobin. FBC should be checked weekly for the subsequent 4 weeks during reintroduction.

- Consider iron replacement if relevant.
- Give iron supplementation at least 2 hours before or after TB drugs. Iron supplementation may exacerbate GI adverse events and will not correct anaemia of chronic disease.
- There are several oral iron products - the example of use of ferrous fumarate is given below (Table 11). However, countries may use ferrous gluconate or ferrous sulphate. Please refer to https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults#H5 for further information.

**Table 11. Ferrous fumarate for treatment of anaemia**

| | | | |
|---|---|---|---|
| **Ferrous Fumarate**<br>**185 mg of iron (60 mg elemental Fe) + folic acid 0.4 mg tablet** | Treatment of iron deficiency anaemia | 1-2 tablets per day for 3 months, then repeat haemoglobin<br>Preferably taken in evening with dinner to reduce stomach upset | Adverse events: abdominal pain, constipation, changes in stool to dark colour |

NOTE: Blood transfusion should be undertaken according to local guidelines. Many younger patients with reasonable cardio-respiratory reserve will tolerate haemoglobin levels less than 7.0g/dL. Lzd-induced anaemia is reversible, and patients will recover over days to weeks

**Other forms of myelosuppression** aside from anemia are thrombocytopenia (or low platelet count) and neutropenia or low absolute neutrophil count (ANC).

ANC is calculated as follows:

White blood cell count (WBC in $10^3$/uL or $mm^3$) X neutrophils (% expressed in decimals)
Example: WBC = 3.7 X $10^9$/L Neutrophils = 40% (express as 0.4)
Mulitply by 1000 = 3,700 X $10^{3/}$uL
Multiply by the neutrophil count = 3,700 X 0.4
**ANC = 1,480**

### 3.3.3 Optic neuritis

Optic neuritis is an inflammation of the optic nerve eventually resulting in permanent vision loss. Linezolid is the most common cause of optic neuritis amongst all the TB drugs, mostly developing after three months of treatment. Patients may develop painless, progressive, bilateral, symmetrical visual disturbances.

In the Nix-TB study, optic nerve disorders were reported in 11% of the patients, most AEs were Grade 1 or Grade 2. Two cases were reported as SAE with confirmed optic neuritis/ neuropathy, both resolved after discontinuation of Lzd, with visual acuity returning to baseline levels.

The first sign of optic neuritis is usually the loss of red-green colour distinction. This is best tested using the Ishihara test or a visual acuity test (e.g Snellen chart) should be used to detect any sign of visual impairment. See Annex 2 for detailed instructions on these tests. Always compare test result to baseline/previous test to establish a *change* in (colour) vision or visual acuity. Patients with limited visual acuity (less than 20/40 or 6/12) or an abnormal colour vision test at baseline should be referred to the ophthalmologist for an assessment.

**Additional steps**

- After discontinuation of Lzd, all patients with suspected optic neuritis should be referred to an ophthalmologist for immediate evaluation and management.
- Optic neuritis generally improves following cessation of the offending drug, if it can be stopped early enough.
- If optic nerve pathology is confirmed, do not restart Lzd.
- If there is an alternative diagnosis unrelated to Lzd, consider restart at lower or same dose once the symptoms have resolved and follow up with close monitoring.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention.

**Table 12. Clinical management of optic nerve disorder according to severity grading**

| Grade<br>Severity | Grade 1<br>Mild | Grade 2<br>Moderate | Grade 3<br>Severe | Grade 4<br>Life-threatening |
|---|---|---|---|---|
| Optic nerve disorder | Asymptomatic or mild symptoms; clinical or diagnostic observations only or unable to read 4 or more plates in color vision test | Symptomatic; moderate decrease in visual acuity (20/40 [6/12] or better) or drop of 2 lines on VA (Snellen) chart or unable to read 4 or more plates in color vision test | Limiting vision in the affected eye; visual acuity worse than 20/40 [6/12] but better than 20/200 [6/60]) or drop of more than 2 lines (Snellen chart) or unable to read 4 or more plate (color vision test) | Blindness (20/200 [6/60] or worse) in the affected eye |

| | | | | |
|---|---|---|---|---|
| Action | Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist | Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist.<br>Do not restart unless there is an alternative diagnosis | Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist. Do not restart if diagnosis is confirmed | Stop Lzd immediately if there are any suspicions of optic neuritis and refer to an ophthalmologist. Do not restart if diagnosis is confirmed |

### 3.3.4 QT-interval prolongation

The possible anti-TB drug causing QT-prolongation in the BPaL regimen can be related to Bdq. In addition, many other drugs can cause QT-prolongation (please refer to https://crediblemeds.org/new-drug-list/) as well as genetic causes such as long QT syndrome, electrolyte abnormalities or hypothyroidism. Other anti-TB drugs that can be associated with QT prolongation can be fluoroquinolones, delamanid, or clofazimine.

In the Nix-TB study, 6 patients (6%) developed QT-prolongation Grade 1 or Grade 2. None of these AE lead to discontinuation of the BPaL regimen.

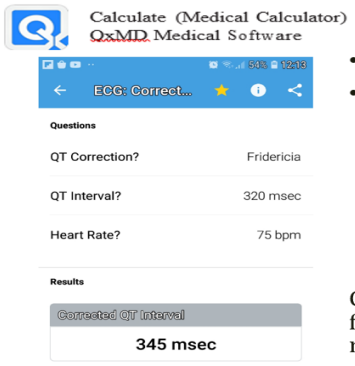
To monitor patient safety whilst on treatment or follow up period, ECG should be done during scheduled visits according to the monitoring schedule in all patients. Additional monitoring in the form of unscheduled visits can be done for those patients experiencing any clinical symptoms suggestive of cardiotoxicity such as tachycardia, syncope, palpitations, weakness or dizziness or patients with QT prolongation as described in Table 10.

In the monitoring process:

- Perform ECG
- Evaluate the ECG and rule out arrhythmia.
- Calculate QT-interval using the Fridericia's formula which corrects for the heart rate and has been shown to be more accurate at slower or faster heart rates than other correction formulae.

Methods for QT calculation: There are mobile apps or web-based formulas that can be used to simplify the calculation. However, RR and QT intervals should be measured manually when in doubt.

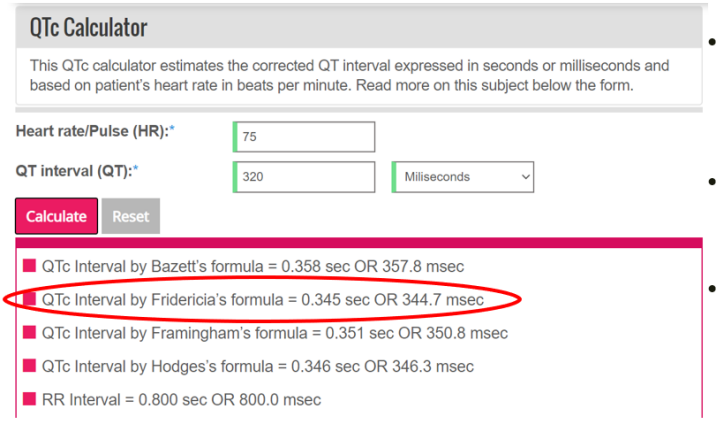
**Smart phone application**




- Open the QxMD app
- Go to cardiology, select ECG
  - *ECG: Corrected QT*
  - *QT correction?*
  - *Select Fridericia*
  - *QT interval ?*
  - *Enter uncorrected QT interval*
  - *Heart rate?*
  - *Enter HR*

QT interval and HR can be taken from ECG reading or counted manually when in doubt

**Website:** http://www.thecalculator.co/health/QTc-Calculator-385.html




- Enter uncorrected QT interval and heart rate from ECG reading (or manually counted if in doubt)
- Click on "calculate"; four QTc values will automatically appear.
- Choose **Fridericia**, this is QTcF

For "QTcF Normogram" table, see Annex 3.

Steps to take in a patient with of **grade 1 QT prolongation (451-480 ms) or grade 2 (481 – 500 ms)**:

- Repeat ECG after at least 30 minutes to confirm abnormal value.
- Check with the patient any history of symptoms – syncope, palpitations etc.
- Monitor the patients and repeat ECG based on the clinical management (see table 5 in KNCV's "Generic BPaL OR protocol. Version 4, updated December 2021", pages 25-26).
- Review the patient's medication history for any possible contributing non-TB drugs associated with QT prolonging apart from the BPaL regimen and discontinue or replace, if possible, see list of QT-prolonging drugs: https://crediblemeds.org/new-drug-list/.
- ART is usually not stopped unless the patient is severely unstable.
- If potassium is low, always check magnesium and ionized calcium and compensate as needed. (If unable to check, consider oral empiric replacement doses of magnesium and calcium).

**Table 13. Clinical management of prolonged QT interval according to severity grading**

| Severity Grade | Grade 1 Mild | Grade 2 Moderate | Grade 3 Severe | Grade 4 Life-threatening |
|---|---|---|---|---|
| Normal values:<br>Male (M): <450 ms<br>Female (F): <470 ms | QTcF 450 – 480 ms | QTcF 481 – 500 ms | QTcF> 500 ms on at least two separate ECGs ≥30 min apart, without signs and symptoms of serious arrhythmia | QTcF >= 501 or >60 ms change from baseline and one of the following: (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) |

| | | | | |
|---|---|---|---|---|
| Action | ● Monitor ECG more closely (at least weekly) until QTcF has returned to less than grade 1<br>● Check electrolytes and replete as necessary<br>● Check for other potential causes and manage accordingly | ● Monitor ECG more closely; at least weekly until QTcF has returned to less than grade 1<br>● Check electrolytes and replete as necessary<br>● Check for other potential causes and manage accordingly | ● Hospitalize, check, and replace electrolytes as necessary<br>● Stop the BPaL regimen and other suspected causative drugs, including non-TB drugs<br>● Check for other potential causes and manage accordingly<br>● Repeat ECG after ≥24 hours but < 48 hours, until QTcF < 500 ms | ● Hospitalize, check, and replace electrolytes as necessary<br>● Stop the BPaL regimen and all other suspected causative drugs, including non-TB drugs<br>● Check for other potential causes and manage accordingly<br>● Repeat ECG after ≥24 hours but < 48 hours, until QTcF < 500 ms |

Patients with a **grade 3 QT prolongation (>500ms) or grade 4 (>501 or >60 ms change from baseline and signs and symptoms of serious arrhythmia or Torsade de pointes -TdP):**

- Are at 2-3 times an increased risk of TdP. This risk increases with increasing QT prolongation and therefore, patients with extremely long QT and/or marked deformation of the T and U waves should be treated cautiously. Whenever possible, hospitalize the patient if there is high risk of TdP and ensure access to a cardiac monitor. Stop full BPaL regimen immediately and any other QT prolonging drug and monitor closely with ECG until QTcF has returned to grade 1 or less.
- Restart full BPaL regimen with close ECG monitoring initially at least weekly.
- If unable to restart the full BPaL regimen within 35 days, refer to expert TB committee to construct a new treatment regimen.

### 3.3.5 Hepatotoxicity

Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, fatigue, and diminished appetite in the setting of elevated liver function tests. Mild elevation of liver enzymes, especially at baseline, may be related to TB disease rather than an adverse effect of treatment. Hepatitis can also be asymptomatic and only show in increased liver enzymes (transaminases, bilirubin).

Hepatotoxicity in patient treated with the BPaL regimen can be related to Bdq and Pa.
In the Nix-TB study, most hepatic disorder AEs were grade 1 or grade 2. The BPaL regimen was interrupted in 8 patients due to increased transaminases/hepatic enzyme and drug-induced liver injury. In all 8 patients, the events resolved and BPaL was restarted, resulting in full completion of the intended length of therapy.

**Table 14. Clinical management of elevated liver enzymes according to severity grading**

| Grade<br>Severity | Grade 1<br>Mild | Grade 2<br>Moderate | Grade 3<br>Severe | Grade 4<br>Life-threatening |
|---|---|---|---|---|
| ALT /AST | >ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| Bilirubin | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN |

| | | | | |
|---|---|---|---|---|
| Action | Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation | Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation | Stop full BPaL regimen, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, (liver enzymes returned to Grade 1) | Stop full BPaL regimen, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, (liver enzymes returned to Grade 1) |

Additional steps from those in Table 14 in case of hepatotoxicity:

- Consider other potential causes such as HIV, viral hepatitis (A, B, C), alcohol, other drugs.
- In HIV co-infection, NVP and/or cotrimoxazole can be a cause of hepatotoxicity, if patient has already been on ART regimen for more than 6 months it is unlikely that this is the underlying cause and ART should be continued, but cotrimoxazole should be stopped.
- In case of **JAUNDICE: Stop all anti-TB drugs** until resolution.
- Check ALT/AST/bilirubin once a week.
- Reintroduce full BPaL regimen once liver enzymes return to baseline or at least Grade 1 and monitor AST/ALT/bilirubin weekly for the first month and then monthly.
- If unable to restart the full BPaL regimen within 35 days, refer to expert TB committee to construct a new treatment regimen.

Increased liver enzymes at baseline:
Patients with mild pre-existing transaminitis (<3x ULN) can be consider a candidate to participate in the BPaL OR. Such patients should be carefully screened for alcohol and other substance use. Consider performing an abdominal ultrasound in case of risk factors for hepatotoxicity, (evidence of cirrhosis, hepatocellular carcinoma, ascites). Rule out all contributing factors and allow a washout period if the patient is taking medication or substance impacting on the liver enzymes.

### 3.3.6 Other adverse events **(Annex 4)**

All other adverse events should be graded according to the general severity grading scale (see Table 6). Management of these AEs should be according to National guidelines, including recording and reporting. All patients with a (serious) adverse event, resulting in discontinuation of the full BPaL regimen, should be discussed with the expert TB committee.

There are certain adverse events which require attention as they may be related to one of the AESI or lead to treatment interruption and should be managed carefully.

**Nausea and vomiting**

Nausea is a disorder characterized by a queasy sensation and/or the urge to vomit and vomiting is a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. These AEs are frequent in patients taking DR-TB treatment due to the anti-TB drugs or they can be signs and symptoms of hepatotoxicity.

In patients with nausea and vomiting, rule out more serious causes of nausea and vomiting (e.g hepatitis, food poisoning, gastritis, surgical emergency etc.).

**Table 15. Management of nausea and vomiting**

| | | | |
|---|---|---|---|
| Metoclopramide<br>10 mg tablet | Nausea and vomiting | 10 mg, 30 minutes before taking TB drugs, can be increased to 20 mg if patient continue vomiting | Adverse events: drowsiness, very rarely headache, abdominal upset, muscle spasm of face and neck muscles, QT prolongation |
| Ondansetron Hydrochloride<br>8mg tablet | Nausea and vomiting | 8 mg, 30 minutes before taking TB drugs | Adverse events: very rare, QT prolongation |

Side effect medications, such as metoclopramide, ondansetron which are commonly used in the management of nausea and vomiting, have QT interval prolonging effects, and should be used carefully in patients with QT interval prolongation.

Dose replacement after vomiting: the likelihood of drug absorption within the first 30 minutes of drug intake is very unlikely, therefore patients who vomit immediately after (within 30 minutes of the dose intake) should have the whole dose re-administered.

**Dyspepsia (heartburn)**
A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea, and vomiting.

**Table 16. Management of dyspepsia and gastritis**

| | | | |
|---|---|---|---|
| **Omeprazole**<br>**20 mg capsule** | Heartburn<br>Gastritis | 20 mg once daily<br>If severe gastritis, 20mg twice daily can be given for a short time | Adverse events: very rare. May occasionally cause refractory hypomagnesaemia which can lead to QT prolongation |
| **Ranitidine**<br>**150mg tablet** | Heartburn<br>Gastritis | 150mg twice daily | Adverse events: may cause rebound gastritis if used on a prolonged basis. Less effective than omeprazole |

NOTE: Avoid the use of antacids due to interactions with anti-TB drugs. It should only be prescribed in exceptional cases and given at least 2 hours before or 2 hours after the anti-TB drugs.

**Hypokalemia**: common in patients receiving DR-TB treatment. The most common causes can be vomiting and diarrhea. Another cause is related to injectable anti-TB agents which the patient may be on – however this should not be the cause for patients in the BPaL regimen. However, careful monitoring should be applied to patients on proton pump inhibitors (e.g., Omeprazole) as it causes refractory hypomagnesemia which may lead to hypokalemia contributing to QT interval prolongation.

**Table 17. Management of hypokalemia**

| **$K^+$ level (in mmol/L)** | **C Drug dosages** (600 tablet) | **When to monitor $K^+$ levels:**<br>Repeat test earlier if patient has continuous symptoms or if risk patient (see above) |
|---|---|---|
| 3.0 – 3.4 (grade 1) | C 2 tablets 3 times per day | Repeat tests after 2 weeks, if normal $K^+$ level, reduce the dose of KCl to 1-2 tablets 2 times daily. Monitor creatinine and potassium on monthly basis |
| 2.5-2.9 (grade 2) | KCl 2 tablets 4 to 6 times a day<br><br>Also, prescribe magnesium tablets (1 tablet of $Mg^{2+}$ a day in the evening) | Repeat tests after 3 days. If the $K^+$ level does not increase, give magnesium supplement together with KCl. Consider hospitalization for IV infusion of KCl (becomes grade 3) |
| 2.0 – 2.4 (grade 3) | Hospitalization. Infusion of potassium and magnesium. Once $K^+$ level is more than 2.5, then change to oral therapy | Repeat tests daily until $K^+$ level is more than 2.5 and the symptoms of hypokalaemia disappear |
| <2.0 (grade 4) | As per grade 3. | Twice daily $K^+$ until $K^+$ level is more than 2.5 and the symptoms of hypokalaemia disappear. |

# 4 Management of concomitant disease

- **SARS-CoV-2 (COVID-19) disease**

  SARS-CoV-2 disease (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus which is primarily spread from person to person through respiratory droplets released when an infected person coughs or sneezes. Because droplets usually fall within a few metres, the likelihood of transmission is decreased if people remain at least 1.5 – 2 m apart or avoid encountering infected surfaces.

  The median incubation period, from exposure to symptom onset, is approximately 4 to 5 days, and 97.5% of patients who are symptomatic will have symptoms within 11.5 days after infection. SARS-CoV-2 symptoms are like TB symptoms and may include fever, cough, sore throat, malaise, anosmia, and myalgia. Some patients reported gastrointestinal symptoms, including anorexia, nausea, and diarrhea. Most people with COVID-19 develop mild or uncomplicated illness. However severe cases require hospitalization and oxygen support.

  Risk factors for complications of COVID-19 include older age (e.g., >65 years), cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity. There are concerns amongst TB experts, that TB may also be a risk factor for poor outcomes, although published evidence of this is currently lacking.

Treatment of COVID-19 is generally supportive. This may be in-or outpatient care as per local protocols. Interruption of TB treatment should be minimized and all efforts should be made to continue care where it is safe to do so.

Pharmacological treatments (e.g. dexamethasone) may be considered according to local guidelines. Whichever drugs are proposed as therapies, drug to drug interactions need to be checked for. The risk benefit of suspending TB treatment should be determined in conjunction with the treatment team and TB MAC.

Collaboration should be established with the COVID-19 and TB expert management teams for the safe and effective treatment of the patient.

- **Diabetes mellitus (DM)**

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Amongst sufferers, it confers significant immunosuppression leading to a higher risk of TB disease due to reactivation or relapse and poorer treatment outcomes. There should be an approach for management of diabetic patients to support diabetic therapy whilst on BPaL regimen due to overlapping toxicities. Diabetic patients are at higher risk for cataract, retinopathy, nephropathy, peripheral neuropathy, and chronic heart disease. Patients should be carefully evaluated for pre-morbid disease.

Glucose levels may increase during TB disease and the treatment period. Patients may require escalation in their treatment of the DM, and this should be reviewed carefully. In some countries, local endocrinologists are the principal diabetic care provider, in others this may be the primary health care doctors. Whoever it is, a close collaboration should be formed in the early phase of DR-TB treatment and the local guidelines followed.

Glucose lowering therapy should be comprehensive and individualized according to local guidelines. Below is an example of a stepwise approach to type II diabetic therapy.

**Table 18. Management of type II diabetes mellitus**

| Step 1 | Step 2 | Step 3 | Step 4 |
|---|---|---|---|
| Lifestyle changes<br>+<br>METFORMIN | Add Glibenclamide<br><br>Continue Metformin<br>Lifestyle change | Add INSULIN<br><br>Continue Metformin/ Lifestyle change<br>Halve the dose of Glibenclamide | Adjust INSULIN<br><br>Refer if poorly controlled on insulin<br>Balance risks with benefits and avoid hypoglycemia |

- **Co-infection with Human Immunodeficiency Virus (HIV)**

Bedaquiline interactions with ART: When bedaquiline and efavirenz (EFV) are used in combination, EFV has been shown to decrease the concentration of Bdq by 20-50%. Drug-drug interaction studies with single dose studies and non-linear mixed effects modelling have suggested no significant interactions with Bdq and nevirapine (NVP). A similar study with Bdq and lopinavir/ritonavir suggests there is a significant interaction with an increase in the levels of Bdq and its metabolite M2.

Pretomanid interactions with ART: In a phase 1 open label cross-over study in healthy volunteers 1 week of combined EFV and Pa resulted in a reduction in Pa levels with plasma Pa values for maximum concentration (Cmax), area under the concentration-time curve from 0 to 24 hours, and trough concentration (Cmin) were reduced 28%, 35%, and 46%, while EFV levels were not significantly changed. The clinical significance of this reduction in Pa levels is not clear. Interactions between lopinavir/ritonavir and Pa were not significant, and similarly interactions with NVP or NRTIs are thought not to be significant.

All other anti-TB drugs used for the treatment of DR-TB, including Dlm, do not have documented significant drug-drug interactions with the commonly used ARV drug classes.

Given the evidence above, there are concerns regarding the use of some specific ARTs in patients taking Bdq and /or Pa. Therefore, guidance is given to support the management of TB/HIV co-infected with HIV taking the BPaL treatment regimen (refer to Table 3). The local HIV treatment guidelines should be followed as much as possible but if there are difficulties in designing a regimen, the TB MAC can be consulted for further support.

# 5 Adherence and patient support

TB infection/disease can be an emotionally devastating experience for patients and their families, while stigma attached to the disease, the long duration of TB treatment and drug side effects may interfere with treatment adherence. These may lead to depression, anxiety and further jeopardize treatment adherence. Health education should be seen as an ongoing process throughout the treatment period. Thus, counselling should be performed on a regular basis, whether adherence problems exist or not. The following factors should be considered when addressing the challenges:

Side effects (adverse event) management;

Health education and importance of adherence to treatment;

Transportation support;

Financial difficulties;

Psychosocial support

Poorly managed side effects (adverse events) generally lead to patient abandoning treatment. It's good to collaborate with patients prior to initiation and during the whole treatment period to manage expectations. Management of side effects (adverse events) may require different approaches to get adequate symptom control. Give clear information to patients and DOT nurses/supporters on timely detecting and reporting, duration and how best to administer the ancillary drugs to avoid overloading patient with many drugs at once. Give the patients as much as possible to participate in the side effect management.

Social issues such as difficulty with transportation and/or inadequate income should be anticipated. If possible, assess how the patient is managing financially. Where possible provide transportation reimbursements, social or food packages.

Substance use, particularly alcohol abuse is common in certain areas. Patients may not have disclosed it prior to treatment initiation and may also mimic mood disorders. Patients may sometimes be under pressure to continue their usual activities such as work or school due to

stigma. These patients and their families need extra psychosocial support and may benefit from counsellor support.

# 6 Post-treatment follow-up

Post-treatment follow up is important to assess the effectiveness of the regimen and detect any relapse early. After completion of treatment, patients should be informed of the risk of recurrent TB and advised to return for clinical assessment in case of any TB symptoms, including follow-up of AEs. Patients should also be advised to return for post-treatment follow up 6 and 12 months after completion of treatment, which includes a clinical evaluation, vision tests, brief peripheral neuropathy screening, chest X-ray and collection of a single sputum specimen for smear and culture. If indicated, also repeat ECG, FBC, liver function, or electrolytes.

In a patient who has a positive culture documented during the post-treatment follow-up period, a post-treatment DST should be performed, including pDST for Bdq, Pa and Lzd. Next generation sequencing should be done and compared to the sputum sample frozen at baseline to differentiate between relapse and reinfection. If the culture is positive without clinical signs and symptoms or radiographic deterioration, a second sputum specimen will be collected 30 days apart for smear and culture as an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB. These visits at months 6 and 12 should also be incorporated into the routine monitoring for DR-TB patients.

# Annexes

## Annex 1. Brief Peripheral Neuropathy Screen (BPNS) [9]

### i. Grading of subjective symptoms

Ask the patient to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for right and left feet/legs. Enter the score for each symptom in the columns marked Right and Left.

| Normal | Mild ----------Severe | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 00 | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 07 | 09 | 10 |

| Symptoms | Right | Left |
|---|---|---|
| a. Pain, aching, or burning in feet, legs | | |
| b. "Pins and needles" in feet, legs present for at least 2 weeks | | |
| c. Numbness (lack of feeling) in feet, legs present for at least 2 weeks | | |

Use the single highest severity score above to obtain a subjective sensory neuropathy score

| Subjective Sensory Neuropathy Score | Severity grade |
|---|---|
| 00 | 0 |
| 01 - 03 | 1 |
| 04 - 06 | 2 |
| 07 - 10 | 3 |

ii. Evaluate Perception of Vibration

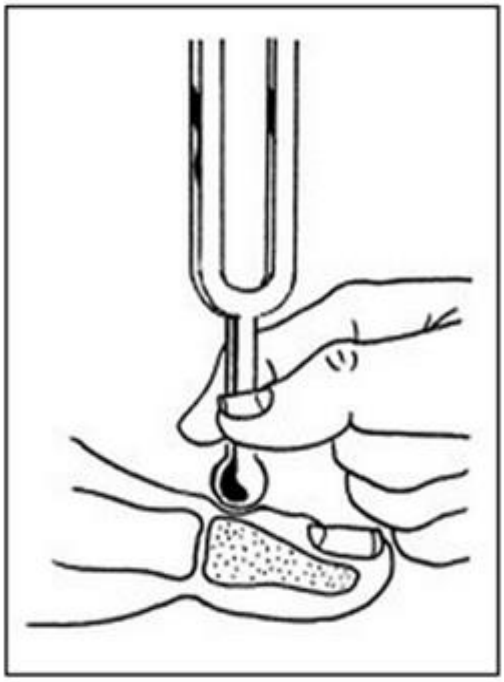
Explain the procedure to the patient before conducting the test.

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch each other. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand for the patient to recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of

[9] Developed and validated by the National Institutes of Health–funded AIDS Clinical Trials Group

one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

The diagram below illustrates where to place the tuning fork (adapted from International Working Group on the Diabetic Foot, Practical guidelines on the management and prevention of the diabetic, 2007)



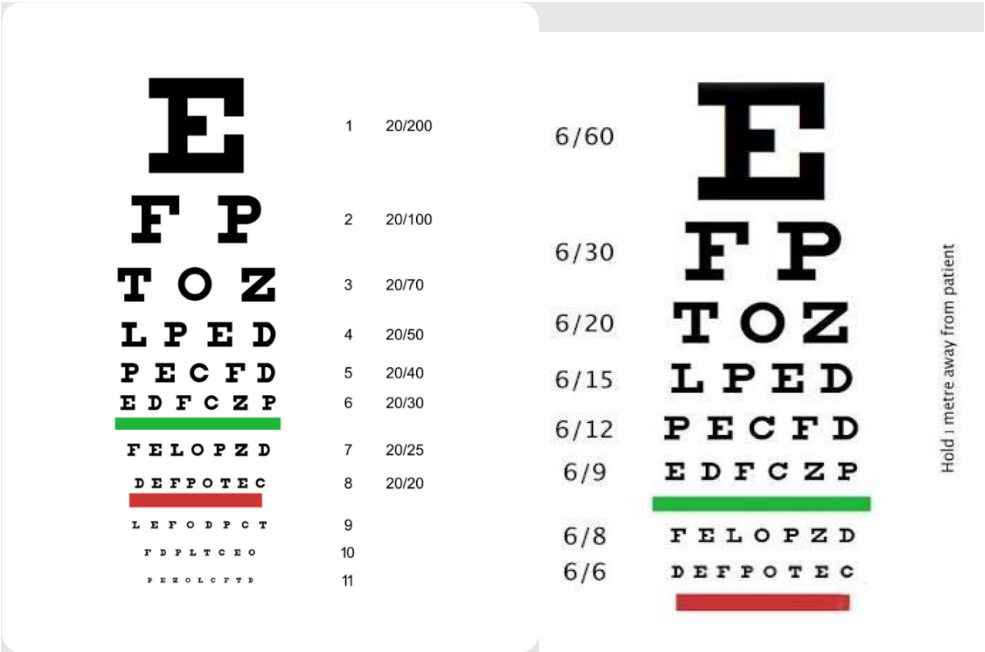
| Vibration perception | Result | Score |
|---|---|---|
| Felt > 10 seconds | Normal | 0 |
| Felt 6-10 seconds | Mild loss | 1 |
| Felt <5 seconds | Moderate loss | 2 |
| Not felt | Severe loss | 3 |

iii. Evaluate Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsi-flexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clenching his/her fist before classifying the reflex as absent.

## Annex 2. Vision Tests

### 1. The Snellen Eye Chart [10]




- The Snellen Eye Chart is a tool to test for visual acuity or sharpness of central vision. The chart can have an imperial or metric scale, as shown in the pictures above
- The chart is standardized for size and contrast and so do not photocopy or make your own; rather, get a chart that is officially available.
- It usually shows 11 rows of capital letters. These are numbered. The first line has one very large letter. Each row after that has increasing numbers of letters that are smaller in size.

**Performing visual acuity testing using the Snellen Eye Chart**

1. Ensure good natural light or illumination on the chart.
2. Explain the procedure to the patient.
3. Position the patient, sitting or standing, at 20 feet away (or 6 metres) from the chart
4. If the patient is currently using distance spectacles, he/she may wear

[10] Steven Sue. Test distance vision using a Snellen Chart. Community Eye . 2007 S Health ep; 20(63): 52. PMCID: PMC2040251 PMID: 17971914 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2040251/ (Accessed 3 Jun 2020)

them, but keep in mind to put on record that the test was done with spectacles on. All future vision tests will be done with spectacles on.

5. Test each eye separately, the "bad" eye first.
6. Cover one eye with an occluder (e.g., a piece of paper) and let him/her read out from top down to the smallest line of letters he/she can see. The patient may use the palm of his hand but make sure his/her hand is clean. If with spectacles, the paper or palm is on top of the glass.
7. To score, refer to the number next to the line of letters, e.g., 20/200 or 6/60 up to 20/20 or 6/6. The smallest line he can read (the VA) will be expressed as a fraction, e.g., 20/50 or 6/15. The upper number refers to the distance the chart is from the patient (20 feet or 6 metres) and the lower number is the distance in feet or metres at which a person with no impairment should be able to see the chart
8. Repeat the procedure on the other eye.
9. To document, record the visual acuity (VA) for each eye, stating whether it is with or without correction (spectacles), for example:

| | |
|---|---|
| Right VA = 20/20 or 6/6 with correction | Left VA = 20/50 or 6/15 with correction |

   - The right eye was able to read up to the 8th line and the vision is 20/20 or 6/6 with glasses on. He/she is considered to have normal visual acuity. This means that he can see what an average person can see on an eye chart when standing 20 feet or 6 metres away.
   - The left eye was able to read up to the 4th line only and the vision is 20/50 or 6/15 with glasses on. This means that he/she can see what an average person can see on an eye chart when standing 50 feet or 15 metres away.

10. In case the patient cannot read the largest (top) letter at 20 feet or 6 metres, move him closer to the chart, 1-3 feet or one metre closer to the chart at a time, until the top letter can be seen – the VA will then be recorded as 17/200 if patient was 17 feet away or 5/60 if the patient was 5 metres away etc.
11. If the top letter cannot be read at 3 feet (3/200) or one metre (1/60), hold up your fingers at varying distances of less than 3 feet or 1 metre and check whether the patient can count them. This is recorded as counting fingers (CF). Record as: VA = CF

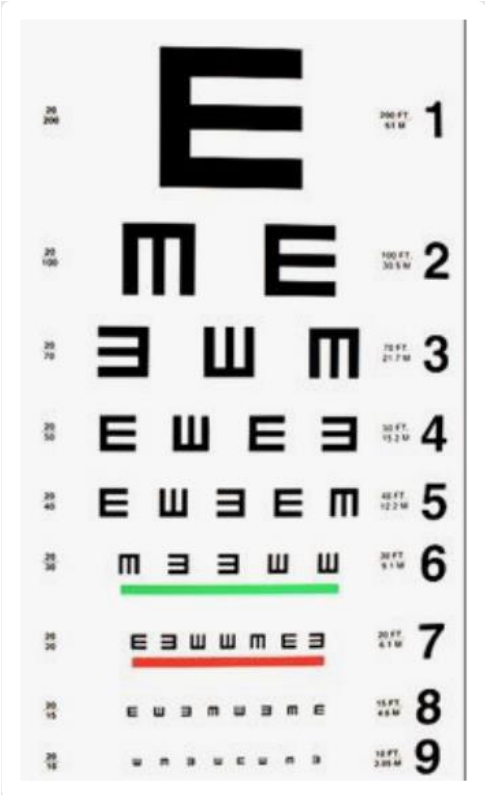
12. If the patient cannot count fingers, wave your hand, and check if he can see this. This is recorded as hand movements (HM). Record as: VA = HM

13. If the patient cannot see hand movements, shine a flashlight toward his eye from four directions of a quadrant. Record this in the documentation, in the relevant quadrant, as perception of light (PL or √), or no perception of light (NPL or X). Record as:

| | | | | | |
|---|---|---|---|---|---|
| Right VA= | NPL or X | NPL or X | Left VA = | PL or √ | NPL or X |
| | NPL or X | NPL or X | | PL or √ | NPL or X |

- *The right eye had no light perception in all 4 quadrants.*
- *The left eye was able to perceive light on the left upper and lower quadrants but not on the right upper and lower quadrants.*

**2. The "E" Eye Chart**



Also called the "Tumbling E" Eye Chart, it can be used by people who cannot read(illiterate), or by young children who don't know the alphabet. Instead of using different letters, the "Tumbling E" eye chart uses a capital letter E that faces in

different directions. The eye doctor asks the person being tested to use their fingers to show the direction in which the "fingers" of the E are pointing.[11]

Instruction to the patient as you point to each letter on each line:

- Ask the patient to point in the direction toward which the open end of the letter is facing
- Follow the same procedure and recording methods as in the Snellen Eye Chart.

**3. Peek Acuity test [12]**

Peek Acuity is a smartphone-based vision check app developed by eye experts to allow anyone to check visual acuity using only an Android smartphone. Peek Acuity helps screen and identify people who need further examination. It is not intended to replace detailed examinations from a qualified eye health professional. Peek Acuity is a standalone app, which only provides a measure of visual acuity and a visual representation of the result.


Features and benefits

- Proven to be as accurate as conventional vision tests in peer-reviewed research
- Fast and easy to use with step-by-step tutorial
- Accurate and repeatable results
- Creates a visual representation of results for easy explanation to patients
- Includes simulated representation that helps explain results to patients
- Includes equivalents of "count fingers", "hand movement" and "light perception"
- Does NOT collect any personally identifiable data

[11] Celia Vimont. All About the Eye chart. American Academy of Ophthalmology. 30 November 2016. https://www.aao.org/eye-health/tips-prevention/eye-chart-facts-history (Accessed on 5 June 2020)

[12] https://www.peekvision.org/en_GB/peek-solutions/peek-acuity/

- Scores are provided in standard units of Snellen - including metric (6/6) and imperial (20/20) - and LogMAR (0.0)

There are two versions of Peek Acuity available to download FREE from the Google Play store:

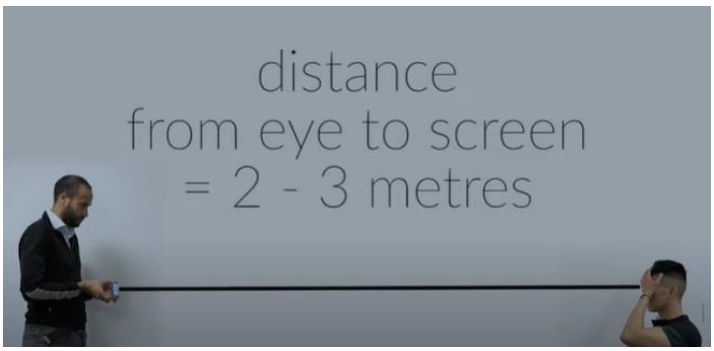
- **Peek Acuity Pro** is a CE registered class 1 medical device available in countries where it is registered for use.
- **Peek Acuity** is not registered for medical use and is available globally.

It is important to always keep the application up to date so that you receive the latest technical updates. Older versions of the app may not function correctly on the latest operating systems. Please ensure you perform the manual calibration check, as described here, before using the application to measure visual acuity.

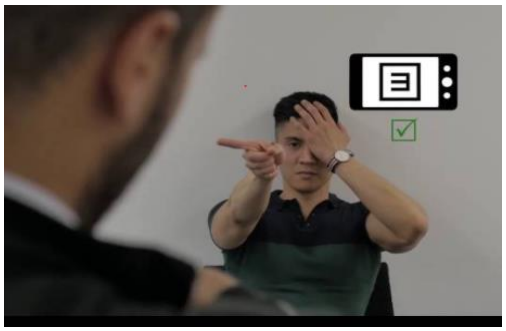
With the Peek Acuity test, it is not possible to see the difference in number of lines that a patient can read like on a Snellen chart, so please check result against a picture of a Snellen chart, (see under 1) to identify the drop in number of lines, e.g., first test at baseline Peek vision was 6/6, second test after 2 weeks Peek vision result is 6/9, this is a drop of 2 lines.

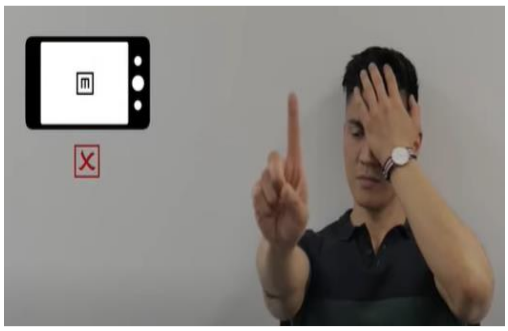
How to perform the Peek Acuity:
https://www.youtube.com/watch?v=Xw3qMLjdpfM

- Explain the procedure to the patient
- Stand 2 – 3 meters away from the patient and make sure to hold the smartphone at eye level




- Swipe the phone screen in the same direction as the patient point even if the answer is not correct

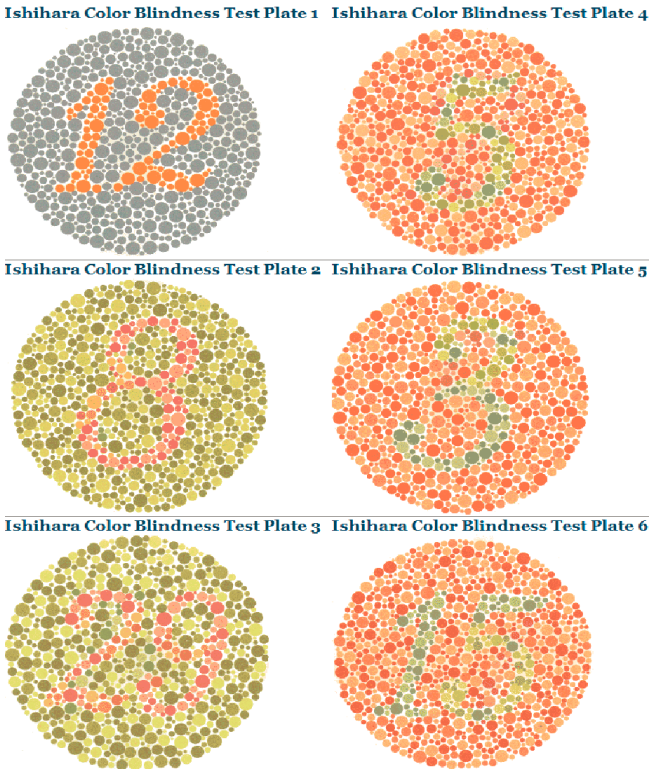




- If the patient indicates that he/she cannot see the letter, then shake the smartphone and it moves to the next line

- The examiner should always watch on the patient responses and there is no need of watching the screen of the smartphone
- At the end of the test the phone will vibrate indicating the test score on the smartphone screen
- Show the score to the patient and explain what does it mean. Do not forget to record the test score as the VA test result.
- If this is not a baseline test, then compare the result with previous tests to see if there are drops in the number of lines

### 4. Ishihara color vision test [13]




To test for color vision deficiency, the Ishihara test is the most common tool, but there are other tests including the H-R-R. test, the D-15, or D-100 tests.

The chart is standardized for size and contrast and so do not photocopy, use online tests, or make your own because accurate color scales are important.

The Ishihara Color Vision Test Chart consists of a booklet, each page containing a circular pattern (or "plate") comprising many dots of various colors, brightness, and sizes. The complete Ishihara Color Vision Test contains 38 plates, there are “shorter”

[13] Ishihara Charts. https://www.challengetb.org/publications/tools/country/Ishihara_Tests.pdf (Accessed 31 Mar 2020)

versions of 24 or 14 plates, but the first 11 plates are useful to test the color vision of MDR-/RR-TB patients at baseline and during follow-up.

**Performing colour vision testing using the Ishihara Color Vision Chart**

1. Ensure good natural light in the room. Direct sunlight may alter the shade and is therefore not advisable.
2. Explain the procedure to the patient.
3. Position the patient, such that he sits comfortably on a chair.
4. If the patient is currently using distance spectacles, he may wear them but keep in mind to put on record that the test was done with spectacles on. All future vision tests will be done with spectacles on.
5. Test each eye separately.
6. Cover one eye with an occluder like a paper. The patient may use the palm of his hand but make sure his hand is clean. If with spectacles, the paper or palm is on top of the eyeglass.
7. The Ishihara plates are shown 75 cm away from the patient with the circles at eye level.
8. The patient must read each plate within 5 seconds.
    a. A patient with normal color vision will be able to see a number or symbol that is distinguishable from the surrounding dots if.
    b. A patient with impaired color vision will not be able to see the number or symbols or may have difficulty distinguishing patterns among the dots.
9. Repeat the same procedure with the other eye.
10. To document, write down the number of plates correctly read by each eye and number of plates missed. The first plate with number 12 is just to check whether someone can read numbers and is not counted.

| **Plates that were correctly read** | **Vision** |
|---|---|
| 10 plates | Normal |
| 8 -9 plates | Further testing is needed to determine if the patient is truly exhibiting red and green deficient tendencies. |
| ≤7 plates | Abnormal |

## Annex 3. QTcF nomogram

| Heart rate (beats per minute) | | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 | 95 | 100 | 105 | 110 | 115 | 120 | 125 | 130 | 135 | 140 | 145 | 150 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R-R interval (sec) | | 1.33 | 1.20 | 1.09 | 1.00 | 0.92 | 0.86 | 0.80 | 0.75 | 0.71 | 0.67 | 0.63 | 0.60 | 0.57 | 0.55 | 0.52 | 0.50 | 0.48 | 0.46 | 0.44 | 0.43 | 0.41 | 0.40 |
| QT interval (msec) | **300** | 273 | 282 | 291 | 300 | 308 | 316 | 323 | 330 | 337 | 343 | 350 | 356 | 362 | 367 | 373 | 378 | 383 | 388 | 393 | 398 | 403 | 407 |
| | **310** | 282 | 292 | 301 | 310 | 318 | 326 | 334 | 341 | 348 | 355 | 361 | 368 | 374 | 379 | 385 | 391 | 396 | 401 | 406 | 411 | 416 | 421 |
| | **320** | 291 | 301 | 311 | 320 | 329 | 337 | 345 | 352 | 359 | 366 | 373 | 379 | 386 | 392 | 397 | 403 | 409 | 414 | 419 | 424 | 429 | 434 |
| | **330** | 300 | 311 | 321 | 330 | 339 | 347 | 355 | 363 | 371 | 378 | 385 | 391 | 398 | 404 | 410 | 416 | 421 | 427 | 432 | 438 | 443 | 448 |
| | **340** | 309 | 320 | 330 | 340 | 349 | 358 | 366 | 374 | 382 | 389 | 396 | 403 | 410 | 416 | 422 | 428 | 434 | 440 | 446 | 451 | 456 | 461 |
| | **350** | 318 | 329 | 340 | 350 | 359 | 368 | 377 | 385 | 393 | 401 | 408 | 415 | 422 | 428 | 435 | 441 | 447 | 453 | 459 | 464 | 470 | 475 |
| | **360** | 327 | 339 | 350 | 360 | 370 | 379 | 388 | 396 | 404 | 412 | 420 | 427 | 434 | 441 | 447 | 454 | 460 | 466 | 472 | 477 | 483 | 489 |
| | **370** | 336 | 348 | 359 | 370 | 380 | 390 | 399 | 407 | 416 | 424 | 431 | 439 | 446 | 453 | 460 | 466 | 473 | 479 | 485 | 491 | 497 | 502 |
| | **380** | 345 | 358 | 369 | 380 | 390 | 400 | 409 | 418 | 427 | 435 | 443 | 451 | 458 | 465 | 472 | 479 | 485 | 492 | 498 | 504 | 510 | 516 |
| | **390** | 354 | 367 | 379 | 390 | 401 | 411 | 420 | 429 | 438 | 446 | 455 | 462 | 470 | 477 | 484 | 491 | 498 | 505 | 511 | 517 | 523 | 529 |
| | **400** | 363 | 376 | 389 | 400 | 411 | 421 | 431 | 440 | 449 | 458 | 466 | 474 | 482 | 490 | 497 | 504 | 511 | 518 | 524 | 531 | 537 | 543 |
| | **410** | 373 | 386 | 398 | 410 | 421 | 432 | 442 | 451 | 460 | 469 | 478 | 486 | 494 | 502 | 509 | 517 | 524 | 531 | 537 | 544 | 550 | 556 |
| | **420** | 382 | 395 | 408 | 420 | 431 | 442 | 452 | 462 | 472 | 481 | 490 | 498 | 506 | 514 | 522 | 529 | 536 | 543 | 550 | 557 | 564 | 570 |
| | **430** | 391 | 405 | 418 | 430 | 442 | 453 | 463 | 473 | 483 | 492 | 501 | 510 | 518 | 526 | 534 | 542 | 549 | 556 | 563 | 570 | 577 | 584 |
| | **440** | 400 | 414 | 427 | 440 | 452 | 463 | 474 | 484 | 494 | 504 | 513 | 522 | 530 | 539 | 547 | 554 | 562 | 569 | 577 | 584 | 590 | 597 |
| | **450** | 409 | 423 | 437 | 450 | 462 | 474 | 485 | 495 | 505 | 515 | 524 | 534 | 542 | 551 | 559 | 567 | 575 | 582 | 590 | 597 | 604 | 611 |
| | **460** | 418 | 433 | 447 | 460 | 472 | 484 | 496 | 506 | 517 | 527 | 536 | 545 | 554 | 563 | 571 | 580 | 588 | 595 | 603 | 610 | 617 | 624 |
| | **470** | 427 | 442 | 457 | 470 | 483 | 495 | 506 | 517 | 528 | 538 | 548 | 557 | 566 | 575 | 584 | 592 | 600 | 608 | 616 | 623 | 631 | 638 |
| | **480** | 436 | 452 | 466 | 480 | 493 | 505 | 517 | 528 | 539 | 549 | 559 | 569 | 578 | 587 | 596 | 605 | 613 | 621 | 629 | 637 | 644 | 651 |
| | **490** | 445 | 461 | 476 | 490 | 503 | 516 | 528 | 539 | 550 | 561 | 571 | 581 | 590 | 600 | 609 | 617 | 626 | 634 | 642 | 650 | 658 | 665 |
| | **500** | 454 | 471 | 486 | 500 | 514 | 526 | 539 | 550 | 562 | 572 | 583 | 593 | 603 | 612 | 621 | 630 | 639 | 647 | 655 | 663 | 671 | 679 |
| | **510** | 463 | 480 | 495 | 510 | 524 | 537 | 549 | 561 | 573 | 584 | 594 | 605 | 615 | 624 | 634 | 643 | 651 | 660 | 668 | 676 | 684 | 692 |
| | **520** | 472 | 489 | 505 | 520 | 534 | 547 | 560 | 572 | 584 | 595 | 606 | 617 | 627 | 636 | 646 | 655 | 664 | 673 | 681 | 690 | 698 | 706 |
| | **530** | 482 | 499 | 515 | 530 | 544 | 558 | 571 | 583 | 595 | 607 | 618 | 628 | 639 | 649 | 658 | 668 | 677 | 686 | 694 | 703 | 711 | 719 |
| | **540** | 491 | 508 | 525 | 540 | 555 | 568 | 582 | 594 | 606 | 618 | 629 | 640 | 651 | 661 | 671 | 680 | 690 | 699 | 708 | 716 | 725 | 733 |
| | **550** | 500 | 518 | 534 | 550 | 565 | 579 | 592 | 605 | 618 | 630 | 641 | 652 | 663 | 673 | 683 | 693 | 702 | 712 | 721 | 729 | 738 | 746 |
| | **560** | 509 | 527 | 544 | 560 | 575 | 590 | 603 | 616 | 629 | 641 | 653 | 664 | 675 | 685 | 696 | 706 | 715 | 725 | 734 | 743 | 751 | 760 |
| | **570** | 518 | 536 | 554 | 570 | 585 | 600 | 614 | 627 | 640 | 652 | 664 | 676 | 687 | 698 | 708 | 718 | 728 | 738 | 747 | 756 | 765 | 774 |
| | **580** | 527 | 546 | 563 | 580 | 596 | 611 | 625 | 638 | 651 | 664 | 676 | 688 | 699 | 710 | 720 | 731 | 741 | 751 | 760 | 769 | 778 | 787 |
| | **590** | 536 | 555 | 573 | 590 | 606 | 621 | 636 | 649 | 663 | 675 | 688 | 700 | 711 | 722 | 733 | 743 | 754 | 763 | 773 | 783 | 792 | 801 |
| | **600** | 545 | 565 | 583 | 600 | 616 | 632 | 646 | 660 | 674 | 687 | 699 | 711 | 723 | 734 | 745 | 756 | 766 | 776 | 786 | 796 | 805 | 814 |

Source: The endTB Consortium. endTB Clinical and Programmatic Guide for Patient Management with new TB drugs. Version 4.0; January 2018.

## Annex 4. Selected adverse events (all grades) reported in ≥5% of subjects receiving the combination regimen of pretomanid, bedaquiline and linezolid in the Nix Study

| | Treated with the BPaL regimen<br>(Total number of patients = 109) |
|---|---|
| Adverse events | All grades<br>n (%) |
| Peripheral neuropathy* | 88 (81) |
| Acne* | 42 (39) |
| Anaemia | 40 (37) |
| Nausea | 40 (37) |
| Vomiting | 37 (34) |
| Musculoskeletal pain* | 32 (29) |
| Headache | 30 (28) |
| Transaminases increased* | 30 (28) |
| Dyspepsia | 26 (24) |
| Decreased appetite | 24 (22) |
| Rash* | 23 (21) |
| Pruritus* | 22 (20) |
| Abdominal pain* | 21 (19) |
| Pleuritic pain | 21 (19) |
| Gamma-glutamyltransferase increased | 19 (17) |
| Lower respiratory tract infection* | 16 (15) |
| Hyperamylasaemia* | 15 (14) |
| Haemoptysis | 14 (13) |
| Cough* | 13 (12) |
| Visual impairment* | 13 (12) |

| | |
|---|---|
| Hypoglycaemia | 12 (11) |
| Abnormal loss of weight | 11 (10) |
| Diarrhoea | 11 (10) |
| Constipation | 9 (8) |
| Gastritis | 9 (8) |
| Neutropaenia | 9 (8) |
| Dry skin | 8 (7) |
| Hypertension* | 8 (7) |
| Electrocardiogram QT prolonged | 6 (6) |
| Hyperlipasaemia* | 6 (6) |
| Insomnia | 6 (6) |
| Thrombocytopaenia | 6 (6) |

*Select terms are collapsed, as follows: peripheral neuropathy (burning sensation, hypoesthesia, hyporeflexia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy); acne (acne, dermatitis acneiform); musculoskeletal pain (arthralgia, back pain, costochondritis, myalgia, pain in extremity); transaminases increased (alanine aminotransferase [ALT]) increased, aspartate aminotransferase [AST] increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, liver function test increased, transaminases increased); rash (rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular); pruritus (pruritus, pruritus generalized, rash pruritic); abdominal pain (abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness); lower respiratory tract infection (bronchitis, influenza, lower respiratory tract infection, pneumonia); hyperamylasaemia (amylase increased);cough (cough, productive cough); visual impairment (vision blurred, visual acuity reduced, visual impairment);; hypertension (blood pressure increased, hypertension); hyperlipasaemia (lipase increased).

For more information, see: https://www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf

## Annex 5. Frequently Asked Questions, Version 2, Updated 20 December 2021

**Eligibility criteria**

**Q1.** As bedaquiline and linezolid are being used more in standard DR-TB treatment regimens, should we amend definitions for non-response and intolerance to MDR-/RR-TB treatment?

**Answer: Yes**

Amended definitions in the Generic BPaL OR protocol v4 updated Dec 2021 on page 15:

[15] Non-response is defined as: a) two consecutive positive cultures of sputum samples collected after the end of the 2nd month (separated by 30 days) of treatment with lack of clinical improvement or deterioration; or b) treatment outcome of "failure" according to the WHO definition. A DST should be performed immediately and an individualized treatment regimen or BPaL is to be used. If Bdq or Lzd or Dlm have been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs is required for the patient to be eligible for BPaL regardless of the previous exposure, with the respective Expert TB Committee subsequently to decide whether the patient is to be enrolled on BPaL.

[16] Intolerance is defined as: Inability to continue the second line MDR/RR-TB regimen due to a documented adverse event to any of the component drugs. If Bdq or Lzd or Dlm have been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs is required for the patient to be eligible for BPaL regardless of the previous exposure, with the respective Expert TB Committee subsequently to decide whether the patient is to be enrolled on BPaL. However, if either bedaquiline or linezolid is the suspected drug causing the intolerance, the patient is immediately deemed to be ineligible for the BPaL regimen.

**Q2.** Is there a timeline attached to having had exposure of more than four weeks to any of the BPaL component drugs?

**Answer:** In cases where there has been previous exposure for more than 4 weeks to any of the BPaL component drugs (i.e Bdq and Lzd) or Dlm, DST should be performed immediately, regardless of how long ago the exposure was, and an individualized treatment regimen or BPaL can be used. If susceptibility to Bdq, Lzd and Dlm is observed the patient is eligible for BPaL regimen. The respective Expert TB Committee, with the DST result available to them, can decide whether the patient is to be enrolled on BPaL or an individualized treatment regimen.

However, if resistance is demonstrated to any of the BPaL component drugs, the patient is ineligible for the BPaL regimen.

Q3.a. In view of the expanded eligibility criteria for BPaL to include patients with previous use of component or related drugs Bdq, Dlm and Lzd of more than 4 weeks if susceptibility is proven, will DST be done only to drugs which the patient has previously used or to all three agents?

Q3.b. If a patient has been on the shorter all-oral Bdq-containing regimen for > 4 weeks (with no Lzd), is there a need to also do DST to Lzd to confirm susceptibility to these drugs prior to BPaL enrolment?

**Answer:** If possible, it would be best to perform DST for all three BPaL component drugs and Dlm. In previously exposed patients, documented susceptibility is required to the BPaL component drugs and Dlm to prior to being started on BPaL. As a policy, all positive culture isolates need to be frozen for further testing as needed.

Q4. Age: The WHO guidelines consider children at least 14 years of age at the time of enrolment as eligible for BPaL. In the generic protocol "adolescents from 15 years of age could be included." Can we include patients who are at least 14 years old in our eligibility criteria?

**Answer: Yes**, if the country wishes to enroll such patients onto BPaL at the discretion of the respective Expert TB Committee. The statement in the generic protocol was guided by earlier data. However, adolescents from 14 years of age and above could be included on treatment with the BPaL regimen in the OR patient cohort, in line with the WHO 2020 guidelines.[14]

Q5. Is a result of FQ "low resistance" in Xpert MTB/XDR considered one of the eligibility criteria BPaL?

**Answer: Yes**, a patient with a result of FQ "low resistance" in Xpert MTB/XDR is considered eligible for BPaL if the other criteria are met.

**Q6.** If the Hb is <8 g/dL during the screening, can it first be corrected, and the patient enrolled on BPaL once corrected?

**Answer: Yes**, this would be an acceptable course of action.

**Q7.** Can patients with SGPT/SGOT above 3x the ULN be enrolled on BPaL?

**Answer:** Although this is a relative contraindication, if repeated and found to be normal or less than 3x ULN, the patient can be enrolled on BPaL.

**Q8.** In the Nix trial, PLHIV patients with CD4 counts of <50 cells/$mm^3$ were excluded (see NEJM article). In the generic BPaL OR protocol, CD4 count is not mentioned as a factor for exclusion. Would a 30-years old PLHIV patient with a CD4 count of 16 cells/$mm^3$ be eligible for treatment with BPaL?

**Answer:** Although a CD4 count and viral load (VL) should be done at baseline for all HIV positive patients, there is no definite cutoff for either regarding eligibility for BPaL. Hence for example a low CD4 cell count is not an exclusion criterion. If the condition of the patient influenced by the level of the VL and/or CD4 count can be adequately managed by the health providers e.g a patient with a high viral load on a failing ART regimen, then patients regardless of the levels may be enrolled in the BPaL regimen if there are no other contra-indications.

A patient with a low CD4 cell is more likely however to have a disseminated form of TB, with involvement of the liver and/or bone marrow. Hepatotoxicity and myelosuppression risk in such patients is high, and you will need to monitor these patients very closely. The patient should also be thoroughly examined to exclude extrapulmonary TB such as TB meningitis and osteomyelitis. Patients with low CD4 counts who are not yet on ART or on a failing regimen, have a higher risk of TB IRIS once started on effective ART, which could also involve the liver (usually cholestatic).

[14] Current recommendations by the WHO is that Bdq can be used in patients aged 6 years and over, and Lzd for all ages. There is no recommendation for Pa. The cut-off of 18 years was suggested in the initial versions of the generic BPaL OR protocol due to the yet limited data in younger age groups.

In August 2021, WHO released a "Rapid Communication on updated guidance on the management of TB in children and adolescents" informing NTPs and other stakeholders that Bdq may be used in children of all ages as part of the shorter all-oral Bdq-containing regimen or as part of longer treatment regimens. Updated Guidelines and Operational Handbooks are expected to be released by the end of 2021.

**Diagnostics**

**Q9.** What should be done if a patient who is eligible for the BPaL treatment following treatment on the shorter all-oral regimen but has a negative baseline culture? Hence there is also no isolate for storing as they have had treatment with the previous regimen.

**Answer:** Documented proof of active TB (LPA or culture) is required within the last 3 months before deciding that a patient is eligible for the BPaL regimen, regardless of history or timing of previous TB treatment. If the patient has not been on treatment during the previous 3 months, a repeat LPA, culture, and pDST are needed. If available, the last positive culture isolate collected from when the patient was on the previous regimen, should be stored for future testing (for Bdq, Lzd and Pa DST, as well as possibly for genome sequencing) if there is no positive baseline culture available.

**Q10**. How should the 10-colour Xpert machines and XDR-TB cartridge be used? Does the proposed OR diagnostic algorithm need revising?

**Answer:** Their use is already in the diagnostic algorithm included in the generic BPaL OR protocol version 4 ("FL & SL LPA ***OR*** Xpert MTB/XDR", p17-18). This needs to be included in the respective national BPaL OR protocols. The respective countries may choose to initially perform parallel testing with SL LPA and Xpert MTB/XDR to validate the use of Xpert MTB/XDR on its own. This addition/change needs to be reflected in the respective CRF.

**Linezolid dosage interruption and discontinuation**

**Q11.** Regarding the statement "Permanent discontinuation of Lzd while Bdq and Pa are continued, is only allowed for patients with toxicity issues that prohibit further treatment of Lzd after every effort has been made for them to receive a total of 4 weeks of treatment of Lzd preferably with 1200 mg daily (or 600mg if dosage had to be reduced) and 9 weeks in total," does this mean at least 4 weeks of 1200 mg daily together with at least 9 weeks of 600-1200mg daily are needed before permanent discontinuation of Lzd can be allowed? Or if the patient has had at least 4 weeks of 1200mg daily, then can Lzd be discontinued?

**Answer:** The starting dose of Lzd should be 1200mg daily. Lzd can be permanently or temporarily discontinued in patients with toxicity issues that prohibit further Lzd treatment, only after:

i. A total of at least 4 weeks of Lzd 1200 mg/day has been completed; or

ii. A total of at 9 weeks of Lzd at least 600 mg/day has been completed, if the Lzd has had to be reduced to 600 mg/day during the initial 4 weeks of treatment; and

iii. if there is clinical and radiological evidence of improvement after at least 4 weeks of BPal treatment.

Any modification of the Lzd dosage needs to be discussed with the TB MAC

**Q12.** Regarding the modification and discontinuation of Lzd: "Permanent discontinuation of Lzd while Bdq and Pa are continued, is only allowed for patients with toxicity issues that prohibit further treatment with Lzd, after every effort has been made for to them to receive a total of four weeks of treatment of Lzd preferably with 1200 mg daily (or 600mg if dosage had to be reduced) and 9 weeks in total, and evidence of bacteriological and clinical improvement," can patients with only clinical improvement and still smear-positive be also eligible for Lzd modification?

**Answer:** Lzd dose modification or discontinuation is allowed as per guidance given above and clinical and radiological improvement, irrespective of smear status after at least 4 weeks of BPaL treatment. Where any modification occurs, patients must be closely monitored for signs of unfavorable outcome.

**Q13.** Regarding the statement "If an AE which requires an interruption for more than 14 days within the first 4 weeks or dose modification of Lzd occurs and the patient cannot continue with the reduced dose of 600mg within the first 9 weeks of treatment, the patient needs to be withdrawn from the BPaL regimen and transferred to an alternative regimen," is this 14 consecutive days?

**Answer:** For Lzd alone, any interruption in the first 4 weeks is not allowed. Such a patient would need to be switched to another regimen.

If an interruption is required during the first 4 weeks, this would need to be of the whole BPaL regimen. The interruption must not exceed 14 days (consecutive or non-consecutive). If the interruption is more than for 14 days, the patient would need to be switched to another regimen.

**Bedaquiline dosage**

**Q14.** How should a patient who is eligible for the BPaL regimen, but has recently taken the WHO-recommended Bdq-containing all-oral shorter regimen and has just finished the loading two-week dose of Bdq (400 mg a day), be treated?

**Answer:** (Generic BPaL OR protocol v4, Updated December 2021, page 22)**:** A major concern would be whether the patient may have developed resistance to Bdq. If Bdq has been used in the previous MDR/RR-TB treatment regimen for more than 4 weeks, susceptibility to these drugs (Bdq, plus Lzd if used in previous regimen) is required for the patient to be eligible for BPaL regardless of the timing of the previous exposure. The respective Expert TB Committee needs to review the individual patient and decide whether the patient can be enrolled on BPaL.

However, as Bdq DST may not always be available, there will need to be an individual patient judgement on his risk of exposure having led to resistance developing based on drug history and response:

**Dosing recommendations after interruption of Bdq**

| **Timing of interruption of Bdq** | **Duration of interruption of Bdq** | **Required loading dose** |
|---|---|---|
| Within 2 weeks of loading | ≤ 2 weeks | Finish remaining loading days, then continue with Bdq 200 mg/day thrice weekly until end of treatment |
| Within 2 weeks of loading | > 2 weeks | 1 week of 400 mg/day |
| After completion of 2 weeks loading | ≤ 2 weeks | No need for reloading, proceed with Bdq 200 mg/day thrice weekly until end of treatment |
| After completion of 2 weeks loading | > 2 weeks – < 6 months | 1 week of 400 mg/day, then continue with Bdq 200 mg/day thrice weekly until end of treatment |
| After completion of | > 6 months | 2 weeks of 400 mg/day, then continue with |

| | | |
|---|---|---|
| 2 weeks loading | | Bdq 200 mg/day thrice weekly until end of treatment |

If the patient has been treated for MDR/RR-TB with a Bdq-containing regimen for more than 4 weeks, susceptibility to Bdq (plus Lzd if used in previous regimen for more than 4 weeks) is required for the patient to be eligible for BPaL. If DST shows susceptibility to Bdq (and Lzd) and there is no documented intolerance to Bdq (or Lzd), the patient is eligible for BPaL. Bdq should be given throughout the full course of the BPaL regimen i.e **6 to 9 months**. Previous Bdq exposure should not alter the duration of Bdq use in the BPaL regimen. Previous Bdq exposure should only be considered in relation to the adjustment of loading dose of Bdq as described above. Remember: Use of Pa is only recommended as part of the BPaL regimen.

**Q15.a.** For patients who were shifted from a previous Bdq-containing regimen to BPaL, when does the counting for a total duration of 26 weeks start?
**Q15.b.** And in relation to the intervals from the last Bdq intake and the current one, are we referring to the last dose of the Bdq(200mg thrice weekly) or the last dose of the Bdq loading (400mg/day)?
**Answer:** The counting for a total duration of 26 weeks will start on Day 1 of BPaL rather than on Day 1 of the previous Bdq-containing regimen. And this is counted from the last dose of Bdq irrespective of whether it is during the loading or continuing phase.

**Adverse events of pretomanid**

**Q16.** The protocol mentions testicular atrophy and impaired fertility as adverse effects of pretomanid (Pa) in male rats with no adequate evaluation made on human males. What is the update on studies undertaken on this concern?
**Answer:** Testicular toxicity was only observed in repeat-dose toxicity studies in rats and mice, but not in monkeys. Given this observation, testicular toxicity has been a signal that has been closely monitored across the entire clinical programme. Clinically, no testicular toxicity associated with adverse events has been reported from TB Alliance-sponsored or supported clinical trials. The potential for testicular toxicity was further examined by looking into reproductive hormone data in later phase Pa studies; specifically, NC-002, NC-005, NC-006 and NC-008. These data showed no evidence of adverse effects of Pa on male reproductive function and was presented at the Union Meeting in 2021.

In addition, TB Alliance is conducting a paternity survey where male patients who were treated with Pa-have been born to men who participated in these studies. TB Alliance is also conducting a study to specifically analyze the effect of Pa treatment on semen. Started recruiting patients and will share the results once available.

**Peripheral neuropathy**

**Q17.** Peripheral neuropathy is listed as the most common AE in Nix-TB. What was the experience for those not relieved by NSAIDs and other non-narcotic drugs who needed stronger agents to avoid interruption or discontinuation of Lzd? From experience and in literature, Amitriptyline, gabapentin or pregabalin may have drug-drug interaction with Lzd since they increase serotonin levels endangering a serotonergic syndrome. Amitriptyline is also QT-prolonging and thus may interact with Bdq.
**Answer:** The risks and benefits of tricyclic antidepressants/SSRI/NSRI taken simultaneously with linezolid should be considered in consultation with the TB MAC. There is a risk of serotonin syndrome and QT prolongation.

Caution should be applied as pregabalin with its serotonergic action has a liability to cause serotonin syndrome and gabapentin increases serotonin concentrations in the human body.

Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS). Mental status changes can include anxiety, agitated delirium, restlessness, and disorientation. Autonomic manifestations can include diaphoresis, tachycardia, fever, hypertension, vomiting, and diarrhoea. Neuro-muscular hyperactivity can manifest as tremor, muscle rigidity, myoclonus and hyperreflexia.

Drugs that could potentially cause serotonin syndrome include:

- Selective serotonin reuptake inhibitors (SSRIs), antidepressants such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
- Serotonin and norepinephrine reuptake inhibitors (SNRIs), antidepressants such as duloxetine and venlafaxine
- Bupropion, an antidepressant, and tobacco-addiction medication
- Tricyclic antidepressants, such as amitriptyline and nortriptyline (Pamelor)
- Monoamine oxidase inhibitors (MAOIs), antidepressants such as isocarboxazid and phenelzine
- Anti-migraine medications, such as carbamazepine, valproic acid and triptans, which include almotriptan, naratriptan and sumatriptan
- Pain medications, such as opioid pain medications including codeine, fentanyl, hydrocodone, meperidine, oxycodone, and tramadol

For more information, see:
https://www.msdmanuals.com/professional/SearchResults?query=serotonin+syndrome
file:///C:/Users/user/Downloads/Serotonin_Syndrome_after_Initiation_of_Pregabalin_.pdf

**Treatment outcome definitions**

**Q18.** Treatment failed: An additional definition states “Permanent discontinuation of Lzd if having less than nine weeks of dosage (of at least 600mg if dosage had to be reduced) due to adverse event.” Will there be cases that did not reach the 9 weeks of at least 600 mg/day that are considered cured?

**Answer:** According to the outcome definition (minimum of Lzd 1200mg/day for at least 4 weeks or 600mg/day for at least 9 weeks), this patient would be declared as “treatment failed”. The BPaL regimen would be stopped, and the patient placed on an individualized LTR. The patient could eventually be cured, but they would not have been cured by BPaL but by the individualized LTR.

**Q19.** It is expected that some patients will culture convert after 4 months of treatment as it is stated that "If the sputum culture taken after the patient has had 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment" (Generic BPaL OR protocol v4, pages 22-23). Question is "whether the extended regimen applies only when Lzd has not been fully taken for the preceding 4 months or even when a full dose of Lzd has been taken for 4 months?"

**Answer:** Culture conversion is acceptable after 5 or 6 months of the BPaL treatment if a patient has clinical and radiological improvement. The patient preferably should receive at least 9 weeks of Lzd with at least 600mg daily. If the culture result is positive after four months of the BPaL treatment, the extended regimen applies to all patients regardless of the total Lzd dose that they have taken up to that point in treatment. As per the protocol, it is essential however to perform DST from the positive culture after 4 months of treatment, and have the DST result available as soon as possible. The TB MAC should assess the clinical

and radiological status of the patient before a decision on the regimen extension is made. The TB MAC needs to re-assess the patient once the DST results are available.

In case a clinician feels that a patient is failing due to poor clinical/radiological improvement with positive culture at month 3, they should consider repeating a DST and refer to the TB MAC for consideration of switching the regimen. Furthermore, if the patient has Lzd discontinued early in the BPaL treatment, it is essential to repeat the DST for the BPaL component drugs as soon as possible.

**Q20.** One of the definitions of "treatment failed" is lack of culture conversion at the 6th month of treatment. Patients who lack culture conversion by the 4th month (known around the 6th month) are likely candidates for failure, why is treatment extended to 9 months in a non-converting patient (which is known only by the 8th month)?

**Answer:** This is indeed a valid question. If the 4th month culture shows no conversion yet, close monitoring should continue looking for other signs of failure. DST should be repeated if the culture is still positive at month 4 to inform future management decisions.

However, the BPaL protocol still allows for continued treatment, and clinical and bacterio-logical observation. If the sputum culture taken after the patient has taken 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment (i.e receive a total of 9 months of BPaL treatment) if the patient is clinically well and / or improving. Positive cultures after the treatment duration has been extended, should be dealt with on a 'case by case" basis, taking into account the clinical response of the patient.

However, if the patient is not improving, consider that patient as clinically failing and needs to be referred to the TB MAC for consideration of switching onto an alternative treatment regimen.

**Q21.a**. Treatment failed: Culture reversion** at 5th month or later in a patient with previous culture conversion to negative. Does this mean that the BPaL can be stopped after month 6 if a patient had converted at month 4, but cannot be declare "cured" yet because we must wait for the month 5 culture result?

Answer: Yes, if the cultures at months 3 and 4 are negative, then the BPaL can be stopped after 6 months of treatment. However, to declare the patient "cured" as a treatment outcome, you need to wait for the culture result from the month 6 in order to have 2 or more negative cultures over the last 3 months (months 4,5,6). Hence with negative cultures at months 3 and 4, you cannot declare the patient "cured". The result of at least the culture of month 5 is needed (this will be available in the 7th month).

However, if the month 5 culture is positive, the patient cannot be declared "cured". You then need to wait for the result of the month 6 culture. If the month 6 result is also positive, then reversion is confirmed, the patient is declared a "treatment failure" and started on an individualized LTR.

**Q21.b.** If the month 5 culture is positive and the patient has stopped treatment, should we recall him/her and refer for individualized LTR?

**Answer:** The patient should be under close monitoring and regular follow-up. If the patient is clinically well, wait for the month 6 culture result. If not then, consider the patient is clinically failing and place on an alternative treatment regimen.

**Q22.** The WHO's 2020 definition for bacteriological conversion is a situation with bacteriologically confirmed TB where at least two consecutive cultures taken on different occasions at least 7 days apart, are negative. Likewise, "bacteriological reversion" describes a patient with at least two consecutive cultures taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB. Can this also apply to the BPaL protocol?

**Answer:** The WHO guidelines says ".. at least .." 7 days. Hence the BPaL OR protocol definitions of conversion and reversion remain valid. Also, operationally it will probably be very difficult for many countries to perform cultures so frequently to meet this new definition of 7 days apart.

**Miscellaneous**

**Q23**. Can Pa supplied for the BPaL OR be used for patients as a "last resort" treatment outside of the OR activities? Are there eligibility criteria for such use (e.g previous exposure, need of DST results, etc)?

**Answer:** The unambiguous answer to the first question is **No** (refer to statement issued by the WPR rGLC, November 2021). Use in such patients should follow the eligibility as used for the "standard" BPaL patients i.e MDR/RR-TB plus FQ resistance, with less than 4 weeks of exposure to either Bdq and/or Lzd and/or Dlm. If there has been ≥ 4 weeks of exposure to any of these 3 drugs, DST needs to be performed immediately to demonstrate susceptibility or not. If susceptible, such a patient could be considered by the Expert TB Committee for inclusion in the BPaL OR patient cohort, with careful documentation of the patient's past TB drug taking history and DST results.

**Q24.** What is to be done for patients in whom the National TB MAC is unable to resolve clinical dilemmas, etc?

**Answer:** Such issues may be elevated to the International Expert Committee (refer to the respective SOP).

## References


1. EndTB Clinical and Programmatic Guide for patient management with new TB drugs v.4.0
2. TB Practecal Clinical guideline, Part A version 5.0.
3. WHO Operational Handbook on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2020 https://www.who.int/publications/i/item/9789240006997
4. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. https://www.nejm.org/doi/full/10.1056/NEJMoa1901814
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# LIFT-TB Philippines

**L**everaging **I**nnovation for **F**aster **T**reatment of **Tu**berculosis

Introducing the BPaL Regimen under Operational Research