LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

International Tuberculosis Research Center

KNCV TUBERCULOSIS FOUNDATION

TB Alliance

Dose modification, interruption and discontinuation in BPaL

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Definitions in the BPaL OR context

- **Dose modification:**
  - any change in the dosage of Lzd from the recommended daily dose of 1200 mg
- **Interruption**:
  - any period (temporary or permanent) where a medicine (Lzd) or regimen (BPaL) is stopped because of toxicity (AE or drug-drug interaction)
- **Discontinuation:**
  - Stopping a drug (Lzd) or regimen (BPaL) without resuming its administration in the course of MDR treatment

General guidelines

- **Any dose modification/interruption/discontinuation** of the BPaL regimen should be done carefully and monitored clinically to observe the effect and managed accordingly and documented on the **study evaluation form**
- Interruptions/reductions **without clinical improvement** should be regarded with **added caution**
- **In any doubt,** discuss patient with TB MAC (regimen may need to be strengthened and patient withdrawn from study)
- **NOTE: Any modification of dose, interruption and discontination** should be documented on **the study evaluation forms**

Linezolid dosing flexibility in the BPaL OR

The following modifications in the management of AEsmay be considered based on experience in the Nix-TB study:

- After **four weeks** of treatment at full dose of 1200 mg daily, Lzd can be:
  - Dosage can be reduced to 600 mg or 300 mg
  - Temporarily interrupted and restarted at same or lower dose (not < 300 mg once daily)
  - Permanently discontinued, as long as smear-negative and clinically improving

  Note: missed doses of Lzd due to AEs are **not to be made up** at the end of treatment

- If total exposure is **less than 4 weeks** and a change needs to be made with Lzd, discuss with the TB MAC for shifting to an individualized regimen.

Adjustments in Nix-TB Trial (N=109)

Adjustments in the regimen (BPaL)

- All patients **completed** treatment except those who died during treatment or withdrew
- Entire regimen was interrupted in 20 patients for AEs
  - All patients who interrupted (excluding deaths) able to **complete** full 6 months of therapy or were ongoing

Adjustments in Lzd

Among those who **completed** the full course of treatment: 90% success rate, regardless of changes in **Lzd** dosing

- 34 patients had no **Lzd** dose interruptions (31%)
- 50 patients interrupted and resumed **Lzd** at same or lower dose (46%)
- 33 patients permanently discontinued **Lzd** (30%)

Treatment modifications allowed for Bdq and Pa

- **For Bdq and/or Pa**
  - No dose modifications or temporary interruptions are allowed at any time with 1 or 2 of these drugs
  - However, the full BPaL regimen can be interrupted for a maximum of:
    - **14 consecutive days DURING** the **first four weeks of treatment** and
    - **35 consecutive days AFTER the first four weeks of treatment**

    Note: upon, resuming, the patient should be referred to the TB MAC for assessment prior to restating BPaL

  Note: missed doses of the full BPaL regimen have to be made up at the end of treatment within **60 days.**

(Permanent) discontinuation of the BPaL regimen and the patient is withdrawn from the OR

When:

- Lzd needs to be changed before completion of 1200 mg daily dose for at least four weeks weeks of treatment
- Lzd needs to be changed after receiving 1200 mg daily for at least the first 4 four weeks of treatment without evidence of negative smear and clinical improvement
- Permanent discontinuation of either Bdq or Pa

In all the above cases, the patient should be referred to the TB MAC to advise the constructiong of a new regimen

The most common situations in which the drug or the regimen may be discontinued permanently and shifted to a new regimen

Regardless of reason, the TB MAC has to be consulted.

1. Intolerable toxicity

- Bdq and/or Pa need to be suspended permanently
- Lzd needs to be suspended permanently or temporarily or the dosage changed BEFORE completing a total of four weeks of 1200 mg/day
- Lzd needs to be suspended permanently or temporarily or the dosage changed even with four weeks of1200 mg/day but smear positive and not clinically improving.

2. Treatment failure

- Poor clinical and bacteriological responses to treatment

  Note: DST should be repeated if culture is still positive at month 4

The most common situations in which the drug or the regimen may be discontinued permanently and shifted to a new regimen

Regardless, the patient has to be discussed with the TB MAC

3. Resistance to Drugs in the BPaL Regimen

- Resistance to any of the BPaL component drug is discovered after initiating treatment, the patient should be switched to another regimen.

4. Pregnancy

- Happening during treatment

  Note: TB MAC decision needed in rare cases when the patient is nearing completion

SOP on the referral of cases to the International Expert Committee

International TB Expert Committee: created to assist countries implementing the BPaL OR manage patients

Procedure:

1. The PI and Research Team with TB MAC will present the ff patients to the International TB Expert Committee:
   - Patients with SAE
   - Patients withdrawn from the BPaL regimen (permanent discontinuation of the full BPaL regimen)
   - Patients who died during the BPaL treatment or during post-treatment follow-up period
   - Other patients where the National TB Committee wants guidance from the International TB expert committee
2. The PI/Research Team to email a cover page/summary of **de-identified medical information** relevant to the patient's status, accompanied by scanned OR data collections forms (Screening, Enrollment, Evaluation, AE).

- International TB Expert Committee can ask for additional information. PI to respond. At least two members of the Committee will provide their response within 48-72 hours in writing. If there is different advice provided on future patient management, the final decision rests with the PI.

International TB Expert Committee

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Thank you

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