LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

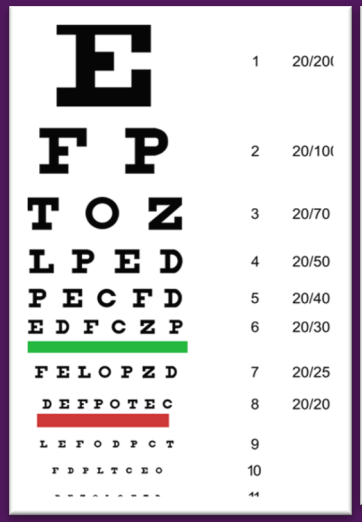
International Tuberculosis Research Center

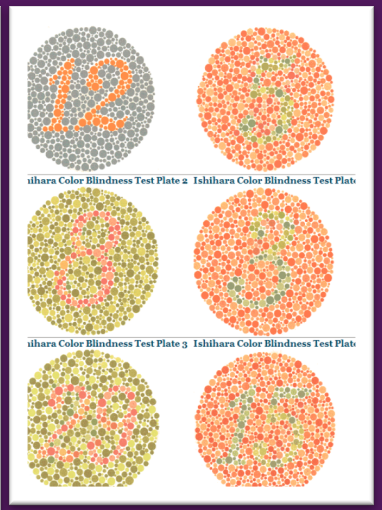
KNCV TUBERCULOSIS FOUNDATION

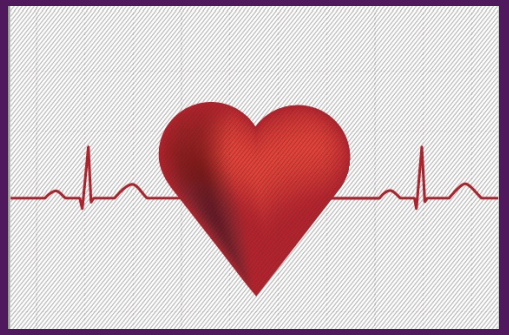
TB Alliance

Case studies on the BPaL regimen

Training of Trainers for the BPaL Operational Research
Philippines, 19-21 May 2021







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CASE 1

ASV, 30 year old male was started on the BPaL regimen.

On **month 2** of treatment, he presented to the OR site with poor appetite, nausea, vomiting 1-2X a day and abdominal pain since the last 3-4 weeks . He observed that the symptoms appear about 1-2 hours after intake of the regimen.

On physical examination, he had pale conjunctivae and anicteric sclerae. On palpation, the abdomen was soft, non-tender; liver was not enlarged.

ASV, 30 year old male

Laboratory results:

	Ref value	Baseline	Week 2	Month 1	Month 2
ALT/SGPT	5-55 U/L	53	48	75	385
AST/SGOT	5-34 U/L	30	32	50	128
Blirubin	0.2-1.2 mg/dL	0.3	0.4	0.3	0.6
Na	136-145 mmol/L	138	136	139	142
K	3.6-5.1 mmol/L	3.8	4.0	3.6	3.7
Ca	2-2.58 mmol/L	2.4	2.4	2.5	2.4

1. What are the significant clinical findings? (Project history and PE)

2. What other information would you like to know from the patient?

3. What are the significant laboratory findings?

	Ref. value	Baseline	Week 2	Month 1	Month 2
ALT/SGPT	5-55 U/L	53	48	75	385
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1. Clinical findings:

- Nausea, vomiting, abdominal pain for 3-4 weeks (month 1-2 of BPaL)

2. Other information needed:

- Other medical conditions (fever? Viral hep?)
- Other medications being taken
- Alcohol intake?

3. Laboratory:

-Elevated SGPT

-Elevated SGOT

From your interview, the patient denies any other medical condition. He has no fever, has no alcohol intake, and is not taking other meds.

4. Based on the clinical and laboratory findings, what is your clinical impression?

Clinical impression:

This patient has signs of hepatotoxicity.

5. How will you grade the AE? (Project the Severity Grading Scale)

Severity Grading Scale of hepatitis or elevated liver enzymes

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT) or	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	>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

	Ref. value	Baseline	Week 2	Month 1	Month 2
ALT/SGPT	5-55 U/L	53	48	75	385
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EndTB Severity Grading Scale for Adverse Events, version 5.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

Severity Grading Scale of hepatitis or elevated liver enzymes

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AST (SGOT)	>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

Severity Grade:

- Elevated SGPT 7X ULN (Grade 3)
- Elevated SGOT 3.7X ULN (grade 2)

EndTB Severity Grading Scale for Adverse Events, version 5.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

What is your management plan for this patient? (Project the Severity Grading Scale and management)

What is your management plan for this patient? (Project the Severity Grading Scale and management)

Management of hepatitis or elevated liver enzymes

Grade the event using this severity grading scale.

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT) or	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	>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, (LFTs returned to Grade 1)	**Stop full BPaL regimen**, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, LFTs returned to Grade 1)

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Grade 3 hepatitis

Management:

- Stop the full BPaL regimen
- Measure liver function tests (LFTs) weekly.

The patient was off BPaL until the next follow up.

On the next follow-up visit (month 3), symptoms had improved and SGPT and SGOT had returned to Grade 1.

How will you proceed with your management?

Management of hepatitis or elevated liver enzymes

Grade the event using this severity grading scale.

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT) or	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	>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, (LFTs returned to Grade 1)	**Stop full BPaL regimen**, including other non-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved, LFTs returned to Grade 1)

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Management:

- Consult with the TB MAC regarding your plan to reintroduce BPaL.
- Carefully monitor the symptoms and LFTs weekly.
- The patient has to make up the missed BPaL doses within 60 days after the end of treatment.

Plan:

- Should the LFTs increase again to grade 3, stop BPaL
- Refer to TB MAC re withdrawal of the patient from BPaL and shift to an individualized regimen.

Points to remember:

1. Be guided by the Severity Grading Scale in the management
2. It is possible to discontinue the full regimen if indicated (but not possible to discontinue only Bdq and/or Pa).
3. It is possible to reintroduce BPaL after consultation with the TB MAC.
4. Missed doses of BPaL need to be made up at the end of treatment within 60 days (Add 30 days).
5. Document all changes in the relevant BPaL Data collection form ,

CASE 2

Patient WTS, 45 years old is on her 4th month of the BPaL regimen

She has been very adherent and tolerated the treatment very well. She claims her coughing has improved.

- Weight has increased from 42 kg to 45 kg.
- Her sputum smear has been negative since month 1 and the last culture on month 2 was also negative.
- She complained that since the last 3 weeks, she has been experiencing:
  - Increasing numbness of both legs below the knee
  - occasional burning pain on both feet, felt more on the right for which she took **Ibuprofen** with relief.

Patient WTS, 45 years old is on her 4th month of the BPaL regimen

During this visit, BPNS was as follows:

Symptoms	Right	Left
a. Pain, aching, or burning in feet, legs	5	3
b. "Pins and needles" in feet, legs present for at least 2 weeks	0	0
c. Numbness (lack of feeling) in feet, legs present for at least 2 weeks	6	6

What is the sensory neuropathy score and the severity grade of the PN?

(May project Severity Grading Scale, if needed)

Grading scale of Peripheral neuropathy

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 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

Modified EndTB Severity Grading Scale for Adverse Events, version 4.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

Patient WTS, 45 years old is on her 4th month of the BPaL regimen

Severity grade 2 (Subjective sensory neuropathy score = 6)

- On non-narcotic analgesic (Ibuprofen)
- Subjective sensory neuropathy score of 6

Describe your management plan for this patient.

(Project Severity Grading Scale and management, if needed)

Management of Peripheral neuropathy

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 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, If symptoms improve, consider restarting Lzd at a lower dose 600 mg or 300 mg. Stop Lzd permanently if symptoms reappear .	Stop Lzd, do not restart. Provide symptomatic relieve.	Stop Lzd, do not restart. Provide symptomatic relieve.

Modified EndTB Severity Grading Scale for Adverse Events, version 4.0. Available at: http://endtb.org/resources/pharmacovigilance or https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf

Action:

Stop Lzd and continue Bdq and Pa.

Provide symptomatic relief:

- Provide NSAID, e.g., Celecoxib
- If with no relief, may give Gabapentin 100 mg OD.

During the patient's next month follow-up (month 5), she claimed to be greatly improved on Celecoxib (and Gabapentin 100 mg prn, if not relieved with the Celecoxib)

On BPNS, the sensory neuropathy score had gone done to 3 from 6 (Grade 1) .

How would you like to proceed?

Management:

- Refer to TB MAC re plan to resume Lzd.
- Restart Lzd at a reduced dose of 600mg once daily together with Bdq and Pa.
- Ask the patient to observe her symptoms carefully. For any worsening, Lzd may be discontinued.

Points to remember:

1. Be guided by the Severity Grading Scale in the management.
2. Temporary interruption of Lzd is allowed after:
   - A total of 4 weeks on 1200 mg daily dose
   - Smear negative (since month 1) and clinically improving (symptoms improved, weight gain)
3. Reintroduction of Lzd is possible at the same or at a reduced dose if the symptoms improve as long as tolerated, considering that full duration of Lzd leads to better outcomes.
4. No need to makeup missed doses of Lzd.
5. Document all changes in the relevant BPaL Data collection form.

CASE 3- Screening scenarios

As one of the OR sites in the OR, which of the following patients are your priority for BPaL OR screening? Why and why not?

A. 35 year old housewife, enrolled on the SSOR last May 1, 2021 made an *ad hoc* visit on yesterday, May 20 complaining of worsening nausea and vomiting over the past 5 days associated with anorexia and weakness. This was despite metoclopramide and split doses of Pto.

B. 53 year old male had QT prolongation on (with 2X repeated ECG) on the 3rd month of SLOR – FQS.

C. 23 year old female just enrolled in SSOR on May 13, 2021 with pending SL-LPA from NTRL..

D. 44 year old male with pDST results of FQ resistance enrolled on SLOR FQR in Dec 2020. Pending SL-LPA result.

E. Three patients recently confirmed RR-TB by Xpert MTB-RIF awaiting treatment.

Screening question

A. 35 year old housewife, enrolled on the SSOR last May 1, 2021 made an *ad hoc* visit on yesterday, May 20 complaining of worsening nausea and vomiting over the past 5 days associated with anorexia and weakness. This was despite metoclopramide and split doses of Pto. Patient appeared weak and dehydrated.

Answer

A. 35 year old housewife, enrolled on the SSOR last May 1, 2021 made an *ad hoc* visit on yesterday, May 20 complaining of worsening nausea and vomiting over the past 5 days associated with anorexia and weakness. This was despite metoclopramide and split doses of Pto. Patient appeared weak and dehydrated.

Priority because of intolerance

Inability is defined as to continue the second-line MDR-/RR-TB regimen due to a documented adverse event to any of the component drugs.

Eligible for screening because Bdq <4 weeks. Patient is not on Lzd nor Dlm.

May be enrolled if there are no contraindications.

Send for SL-LPA, if not done withing the last three months.

Screening question

B. 53 year old male had QT prolongation on (with 2X repeated ECG) on the 3rd month of SLOR–FQS.

Answer

B. 53 year old male had QT prolongation on (with 2X repeated ECG) on the 3rd month of SLOR – FQS.

Not a priority because patient has been on Bdq for 3 months (Cutoff is 4 weeks)

Screening question

C. 23 year old female just enrolled in SSOR on May 13, 2021 with pending SL-LPA result from NTRL.

Answer

C. 23 year old female just enrolled in SSOR on May 13, 2021 with pending SL-LPA from NTRL.

Priority

Coordinate with NTRL re specimen for SL-LPA to be sent asap to TDF

If Fq-resistant by SL-LPA, screen for BPaL.

Screening question

D. 44 year old male with pDST results of FQ resistance doing well on SLOR FQR since Dec 2020. Pending SL-LPA result.

Answer

D. 44 year old male with pDST results of FQ resistance doing well on SLOR FQR since Dec 2020. Pending SL-LPA result.

Not a priority. Has been on Bdq and Lzd for 4-5 months (cutoff is 4 weeks).

Doing well on current treatment.

Screening question

E. Three patients previously treated on first-line regimen recently confirmed RR-TB by Xpert MTB-RIF awaiting treatment.

Answer

E. Three patients recently confirmed RR-TB by Xpert MTB-RIF awaiting treatment.

Priority

Send SL-LPA asap to TDF

If Fq-resistant by SL-LPA, screen for BPaL.

Review

Inclusion criteria

1. MTB patient with laboratory-confirmed (rapid and/or p ST) resistance to at least **R and FQ** within the last three months* of the screening date

2. Patient with strong **clinical and radiological** evidence of active TB AND has been a close household contact of an index patient with:
    a. active laboratory-confirmed resistant TB to at least R and FQswithin the last 3 months of screening date AND
    b. no documented resistance to any of the BPaL component drugs (Bdq, Pa, Lzd) within the last three months * of the screening date; or

3 & 4. Has been treated for MDR-/RR-TB and has documented **non-response** OR **intolerance** to treatment, has bacteriologically active TB ** within the last three months* of the screening date, and a decision has been made by the TB Medical Advisory Committee (TB MAC) to shift the patient to the BPaL regimen;

Review

Inclusion criteria

Any of the above AND

a) Patient is willing and able to give informed assent or consent (signed or witnessed consent, if illiterate) to be enrolled in the OR and adhere to the OR procedures including the follow-up schedule; AND

b) Patient is at least 18 years old at the time of enrolment.

Review

Relative indications

Relative indications needing TB MAC recommendation for inclusion in the BPaL OR as long as any of the above inclusion criteria is fulfilled:

1. Is 15-17 years old at the time of enrolment
2. Has a mild form of extrapulmonary TB with or without pulmonary TB

Review

Exclusion criteria

1. Known severe **allergy** to any of the BPaL component drugs (Bdq, Pa, Lzd); or
2. DST showing **resistance** to any of the component drugs; or
3. Previous **exposure** to any of the component drugs or Dlm >4 weeks; or
4. Known **severe adverse event** associated to any of the BPaL component drugs,; or
5. **EPTB** that would require treatment **longer** than would be usual for pulmonary TB (e.g., TB meningitis, other central nervous system TB, or TB osteomyelitis); or
6. **Inability** to take **oral medications**; or
7. Body weight of **<35 kg**; or
8. **Pregnant**; or plan to conceive within the next year; or
9. Childbearing ability and is reluctant to use effective **contraception** while on the BPaL treatment;
10. **Breastfeeding**; or
11. The **TB MAC** decides that it is not in the best interest of the patient to be enrolled on the BPaL OR due to the need of an individualized treatment regimen.

BPaL REFERENCES

TDF LIFT-TB PHL BPaL

Funding for LIFT-TB

Leveraging Innovation for Faster Treatment of Tuberculosis