Introducing BPaL-L

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USAID
FROM THE AMERICAN PEOPLE

health
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Health
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WITS HEALTH CONSORTIUM

Topics to be covered

- What is the BPaL L regimen?
- Patients' selection and follow up
- Adverse events monitoring

BPaL L regimen

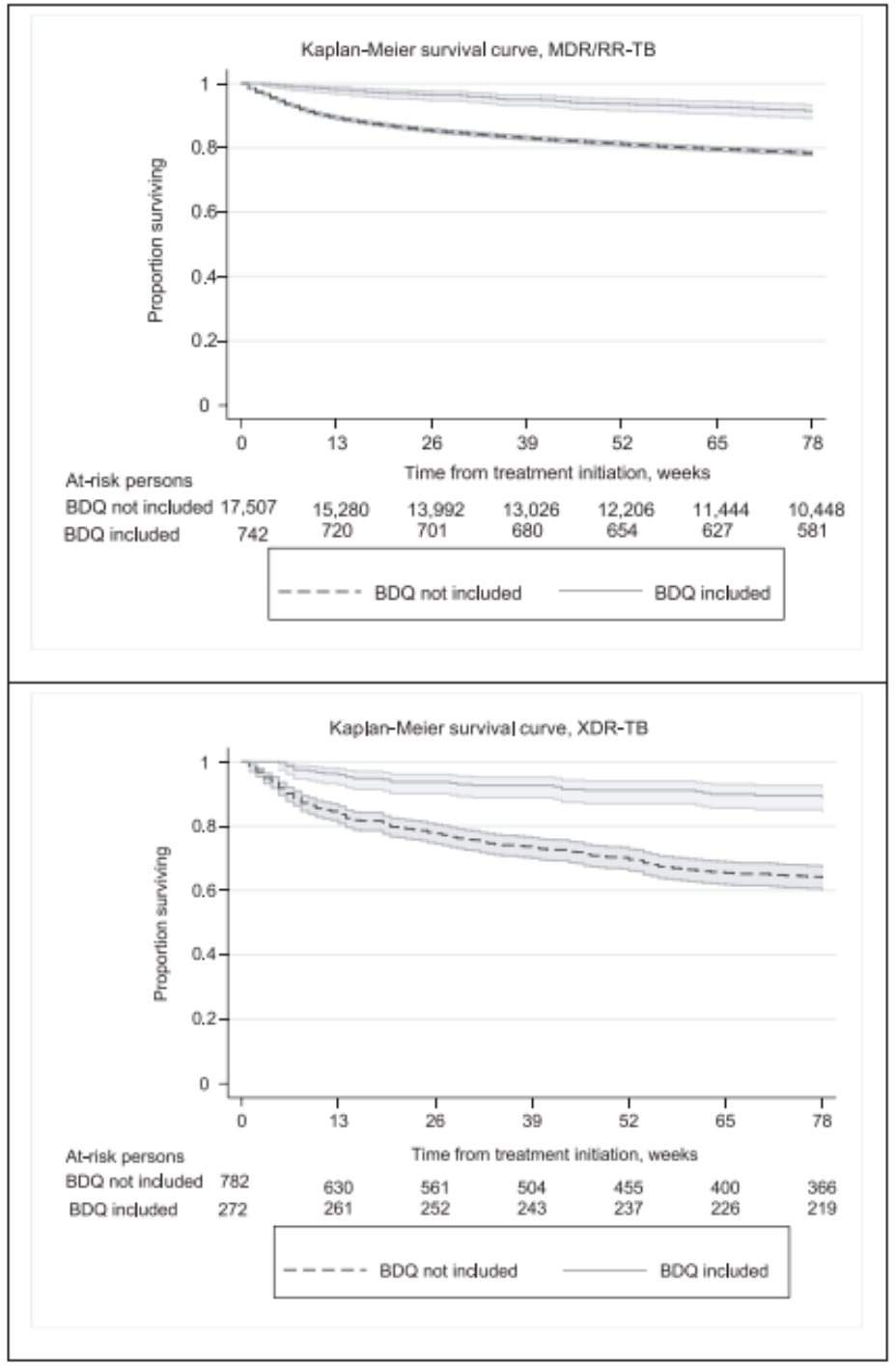
- Is a short all oral regimen for the treatment of Rifampicin Resistant TB (RR-TB) and for PreXDR TB (FQ resistant RR-TB)
- Given for 6 months but can be extended to 9 months at the clinician's discretion

Quick overview of drugs

- Bedaquiline
  - Diarylquinoline, bactericidal and works inhibiting mycobacterial ATP synthase
  - Conditional approval by the US FDA and SAPHRA on Phase 2 data December 2012
  - Category A by WHO
  - Widely adopted by National TB programs (around 300 000 courses have been prescribed especially South Africa
  - Dosage 400mg daily for two weeks followed by 200mg three times a week.

Impact on mortality

Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn? N. Ndjeka, et al INT J TUBERC LUNG DIS 24(10):1073–1080 Q 2020



Quick overview of drugs

- Pretomanid
  - Nitroimidazole inhibiting mycolic acid biosynthesis, thereby blocking cell wall production
  - Approved by the FDA in August 2018 as part of BPaL for the treatment of highly resistant TB
  - Suitable for most people with RR TB including PLHIV
  - Safety in pregnancy and children not yet established
  - Not yet categorized by the WHO
  - Dosage 200mg daily

Quick overview of drugs

- Levofloxacin
  - Quinolone
  - Extensive use in RR TB
  - Category A Drug
  - Dose 750 to 1000mg.
  - Can be used in children and pregnant women.

Quick overview of drugs

- Linezolid
  - Oxazolidinone first approved for the treatment of drug-resistant, gram-positive bacterial infections in 2000
  - Repurposed for treatment of Mycobacterium Tuberculosis
  - WHO Category A
  - Dosage is 600mg daily
  - Substantial adverse event profile

Who should get BPaL L in South Africa?

- Most individuals with RR TB
- Replaces the 9–11-month regimen
- Can also be used in a modified form for pre-XDR TB (BPaL)
- Can be used in PLHIV
- Cannot be used in pregnancy and in children under the age of 15 years

Patients follow up: mycobacterial

- Smear and culture to be done prior to starting treatment
- At 2 weeks
- At month 1 and every month thereafter until treatment is completed
- Follow up at 6 months and 12 months
- Culture conversion usually occurs by the end of month 2
- If month 3 culture is still positive, this should prompt action.
- Seek advice of the NCAC if needed

What to do when you get DSTs back

Genotypic/ Phenotypic results	Action
INH resistant (InhA or KatG)	Continue BPaL L
INH susceptible	Continue BPaL L
Fluroquinolone susceptible	Continue BPaL L
Fluroquinolone resistant	Continue BPaL
Second-line injectable susceptible/resistant	Continue BPaL L
Ethionamide susceptible/resistant	Continue BPaL L

Monitoring for adverse events

Myelosuppression

- May affect all the cells lines but tends to cause anaemia
- Tends to occur in the first 8 weeks.
- Anaemia is common co-morbidity with TB
  - Undernutrition
  - Anemia of chronic disorder
  - HIV co-infection
  - Blood loss due to hemoptysis

(BPaL CAP data Median Hb when starting treatment was 10.4g/dl)

Detection and management of anemia (1)

- Management of anemia when starting treatment
  - Baseline full blood count
  - If HB is above 8g/dl start BPaL M and repeat in 2 weeks
  - If Hb is below 8g/dl
    - Consider admission
    - Consider transfusion
    - If starting treatment, repeat in 1 week
    - Warn patient about symptoms of anemia and how to get help

There is no place for starting the regimen without linezolid

Detection and management of anemia (2)

- Repeat full blood count at 2 weeks and then every month while on linezolid
  - If HB is above 8g/l continue at full dose (600mg)
  - If Hb is below 8g/l
    - Consider admission
    - Consider transfusion
    - Assess for symptoms of anemia
    - Interruption of linezolid and repeat FBC in a week or less
    - Reintroduced linezolid at 600mg or 300mg
    - Warn patient about symptoms of anemia and how to get help
    - Keep dose interruptions to the minimum

Detection and management of neutropenia and thrombocytopenia

- Full blood count at initiation, 2 weeks and then every month while on linezolid
- If absolute neutrophil counts is less that 0.75 10^6 /l or platelet counts is less that 100 10^9/L, repeat in a week or less
  - If persistent, consider interruption of linezolid Interruption of linezolid and repeat FBC in a week or less
  - Reintroduced linezolid at full dose
  - Keep dose interruptions to the minimum

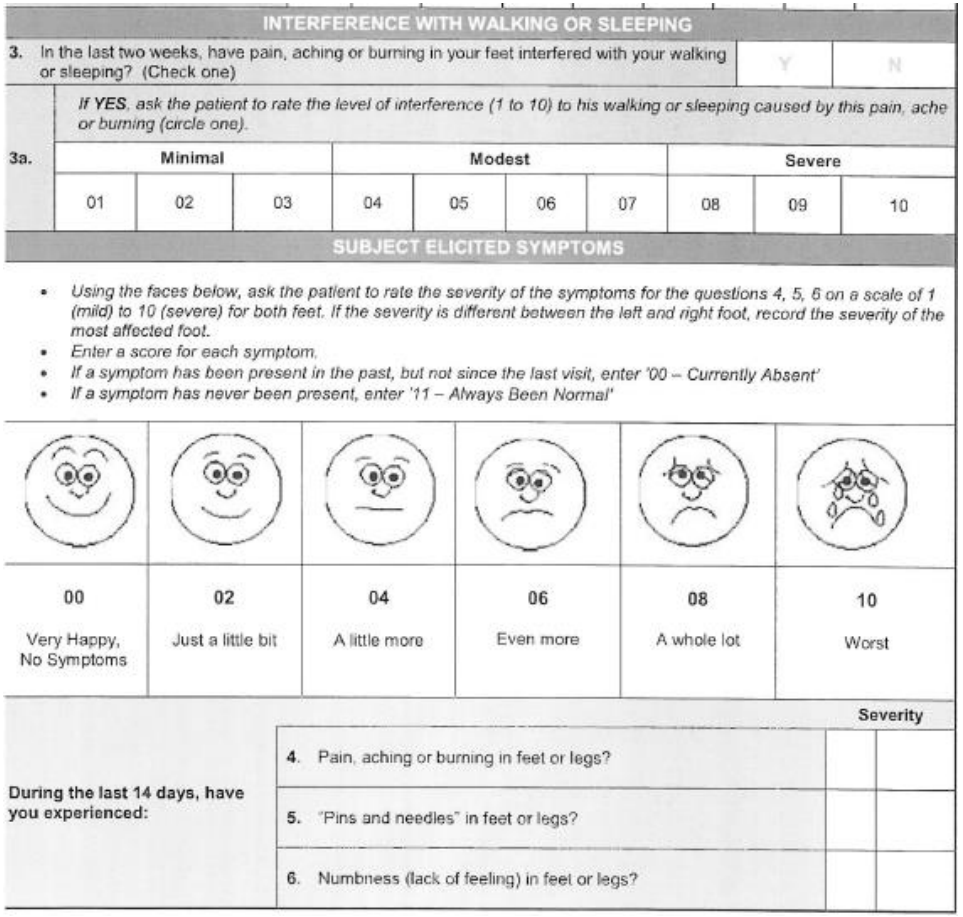
Detection and management of peripheral neuropathy

- Requires clinician and patient awareness
- Other common causes of peripheral neuropathy
  - Diabetes
  - HIV infection
  - Alcohol
  - Other medications e.g., INH
- Tends to occur later in treatment (from 16 weeks)
- Check at every visit of there is pain, pins and needles, loss of sensation or paresthesia

Detection and management of peripheral neuropathy

Difficult to grade severity

Ask patient about interruptions of daily life esp. sleep



INTERFERENCE WITH WALKING OR SLEEPING

3. In the last two weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one) — Y / N

3a. *If YES, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one).*

Minimal			Modest				Severe		
01	02	03	04	05	06	07	08	09	10

SUBJECT ELICITED SYMPTOMS

- *Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.*
- *Enter a score for each symptom.*
- *If a symptom has been present in the past, but not since the last visit, enter '00 – Currently Absent'*
- *If a symptom has never been present, enter '11 – Always Been Normal'*

00	02	04	06	08	10
Very Happy, No Symptoms	Just a little bit	A little more	Even more	A whole lot	Worst

During the last 14 days, have you experienced:		Severity
	4. Pain, aching or burning in feet or legs?	
	5. "Pins and needles" in feet or legs?	
	6. Numbness (lack of feeling) in feet or legs?	

Detection and management of peripheral neuropathy

If occurs early in treatment prior to clinical and microbiological response

Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Re-introduce	• When symptoms are manageable at a lower dose
Permanently discontinue if recurs	

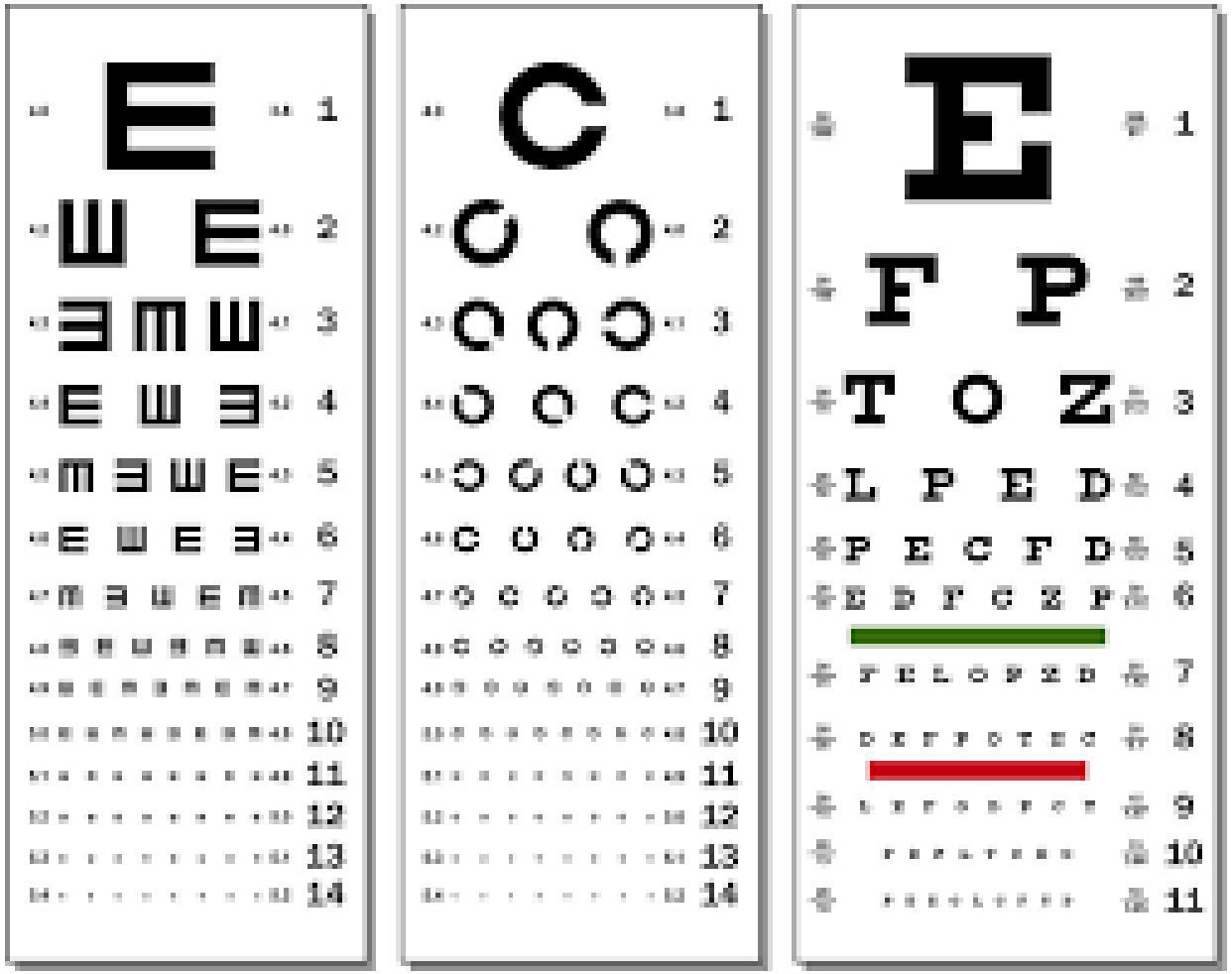
If occurs later in treatment after to clinical and microbiological response

Interrupt	• Interrupt linezolid only
Monitor	• Monitor for resolution of symptoms
Consider	• Consider permanent discontinuation of 16 weeks of treatment have been completed

Detection and management of optic neuritis

Routine visual screening

- Done at initiation and at every visit while of linezolid
- If there is a two-line drop, consider optic neuritis.
- If possible, fundoscopy or ophthalmology referral
- Interrupt linezolid until diagnosis is excluded.



Adverse events to bedaquiline

Prolongation of the QT interval

- Consider QTc F above 500 ms
- In STREAM 2 , small proportion of participants (3–6%) did the QTcF interval reach 500 ms or higher, the threshold at which the risk of serious arrhythmia starts to increase
- If QTcF above 500
  - Check for reversible courses e.g. electrolytes, hypothyroidism
  - Exclude other QT prolonging drugs
  - If persistent, stop BDQ and moxifloxacin

Adverse event to Bedaquiline (1)

Hepatotoxicity

- AST, ALT and bilirubin done while on treatment
- Symptoms of Hepatotoxicity:
  - Nausea
  - Vomiting
  - Right upper quadrant pain
  - Jaundice

Adverse event to Bedaquiline (2)

- ALT/AST increase to 5 times upper limit of normal (with/out symptoms) or to 3 times upper limit of normal with symptoms
  - Stop whole regimen
  - Look for other causes e.g.
    - Viral Hepatitis
    - Alcohol
    - Other hepatoxic drugs
  - Re-start regimen when ALT/AST less than 5 times upper limit of normal

Adverse events to pretomanid

- Newest drug
- Low AE profile
- For hepatoxicity see previous slides

Who cannot get BPaL L and what to do?

- Pregnant women: Give BDL L
- Children: see guidelines
- Severe extra pulmonary disease e.g. TBM, osteoarticular TB (see guidelines)

What to do if there is prior exposure to BDQ or linezolid?

- Higher risk of resistance
- Longer individualized regimen uses the same backbone
- Start BPaL L but ensure that DST is done

In conclusion

BPaL L is a breakthrough in the treatment of RR-TB

The clinical trial results are being replicated in programmatic setting

The Adverse events are predictable and can be managed mostly at a primary care level.