Main Objectives:

- Background of BPAL-L

  Describe the background of shortened DR-TB regimens and why the BPAL-L regimen was adopted.
- Progress Assessment

  Evaluate the status of BPAL (Bedaquiline, Pretomanid, Linezolid) implementation efforts, including the adoption rates, accessibility, utilization of these drugs in the treatment of TB, supply chain issues, healthcare infrastructure limitations, and patient access barriers..
- Strategies for Scale-Up

  Explore effective strategies for scaling up BPAL implementation, including capacity building for healthcare workers, advocacy for policy changes, strengthening of healthcare systems, and collaboration with stakeholders at local, national, and international levels.

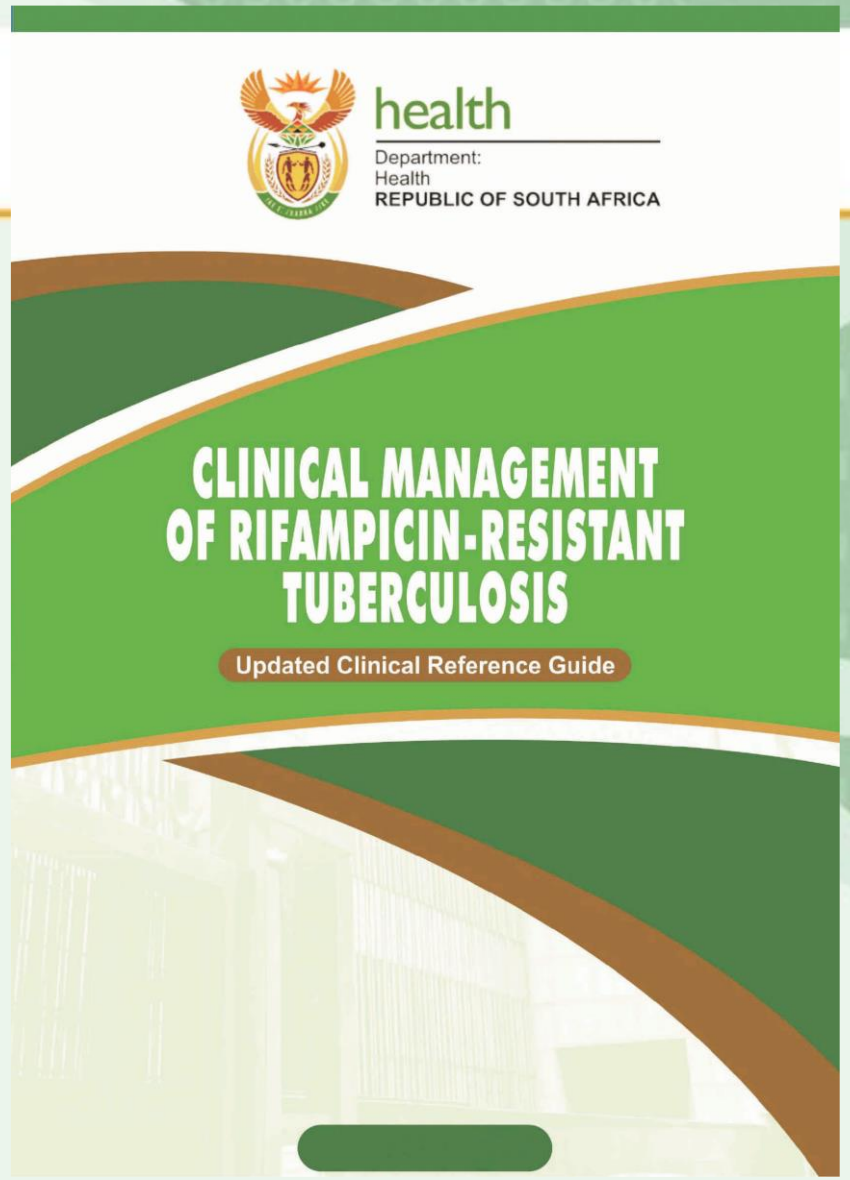
Key issues to be covered:

- Overview of DR-TB shorter regimens and BPAL-L
- Benefits of BPAL-L
- Update on implementation
- Capacity building and training
- Challenges: Pharmacy procurement processes
- Addressing Frequently Asked Questions regarding BPAL-L drugs and regimens

Treatment of RR-TB in South Africa

Dr Francesca Conradie

University of Witwatersrand



Two options for the treatment of RR-TB

BPaL L regimen (in preXDR TB: BPaL)

- Given for 6 months with option to extend to 9 months

Individualized longer regimen

What is the BPaL L regimen?

It is an all-oral treatment regimen

It consists of 4 medications

Bedaquiline
Pretomanid
Linezolid
Levofloxacin

It can be used in most people who have RR TB.

Who is eligible for BPaL L?

Non-pregnant patients (aged ≥15 years)

Not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).

Individuals who had more than 1 month exposure of second line drugs will be started on BPaL-L, but resistance to bedaquiline and linezolid must be excluded. Treatment initiation must not be delayed pending

This regimen may be used without levofloxacin (BPaL) in the case of documented resistance to fluoroquinolones.

BPaL L Adverse events

In clinical trials

Adverse events rates are driven by linezolid

- Zenix 13%-38%
- Practecal 23%

Can be immediately life threatening thus require rapid detection and follow up

Myelosuppression
or suppression of the bone marrow

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

Detection and management of anemia (1)

- 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

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

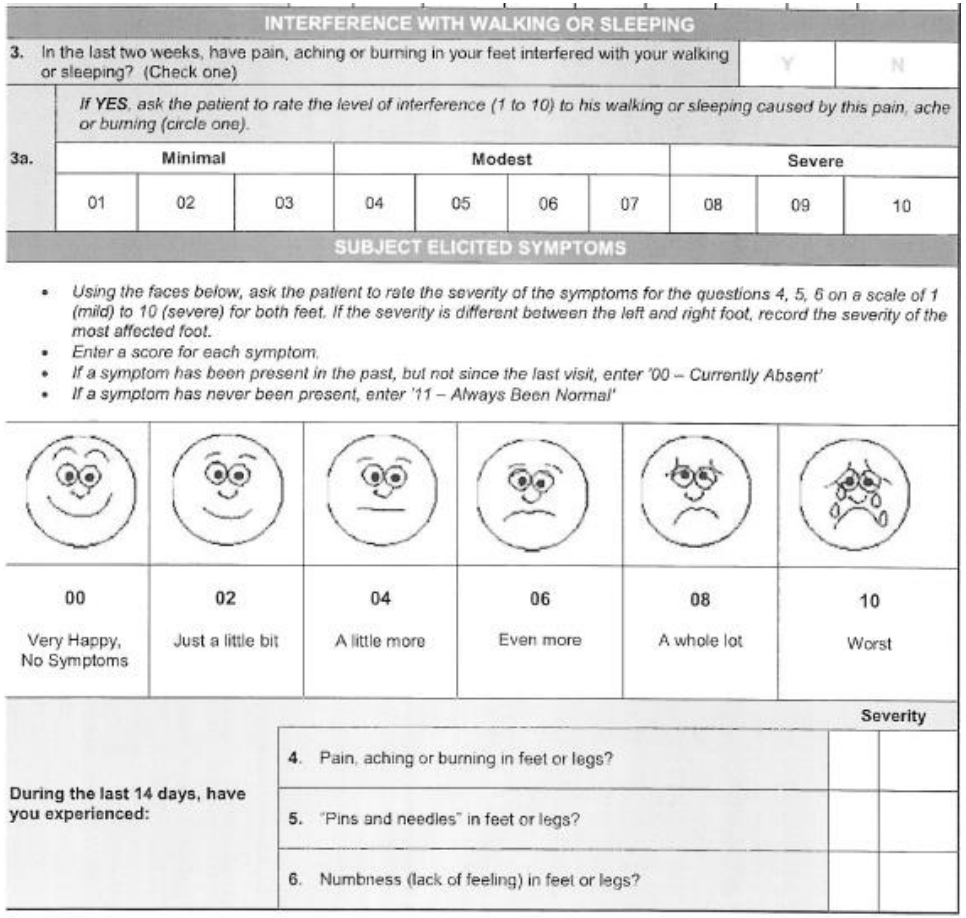
Detection and management of peripheral neuropathy

- 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	

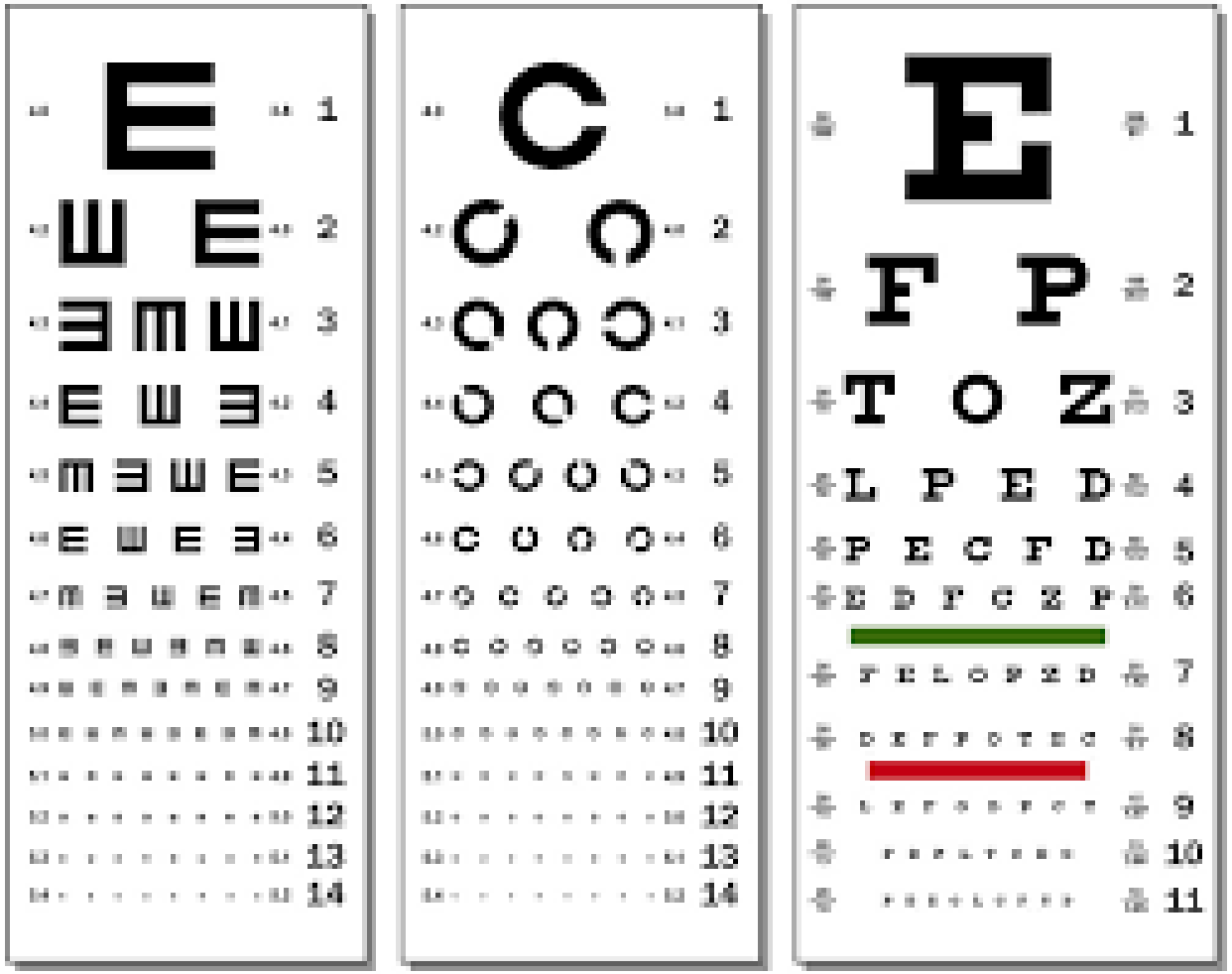
If occurs later in treatment after to clinical and microbiological response

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

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

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

Individualized long regimen
Must be referred to a DR TB centre

Documented resistance to pretomanid and/or BDQ and/or LZD.

Extended DST will be done on request

Individualized long regimen the composition of the regimen will depend on the drug resistance pattern, prior drug exposure and toxicity.

Complicated extrapulmonary disease

Special populations: Pregnant women

01

Family planning as part of care

02

Safety of pretomanid has not been established in pregnancy

03

Consider bedaquiline, delamanid, linezolid and levofloxacin. (BDLL)

Special populations: Children under the age of 14 years

01

Diagnosis may be difficult to make esp in younger children.

02

Safety of pretomanid has not been established in children

03

Consider bedaquiline, delamanid, linezolid and levofloxacin. (BDLL)

Management of HIV co-infection

01

Follow the South African Guidelines

02

Most individuals can be treated with a DTG based regimen.

03

Cannot use AZT or EFV

Conclusion

- BPaL L is recommended for most individuals with RR-TB
- Low pill burden
- Predictable adverse events
- Excellent success rate around 90%

BPaL-L Implementation Progress report

BPAL-L ROLL-OUT

UPDATES, LESSONS ANS CHALLENGES

Ms Y Kock

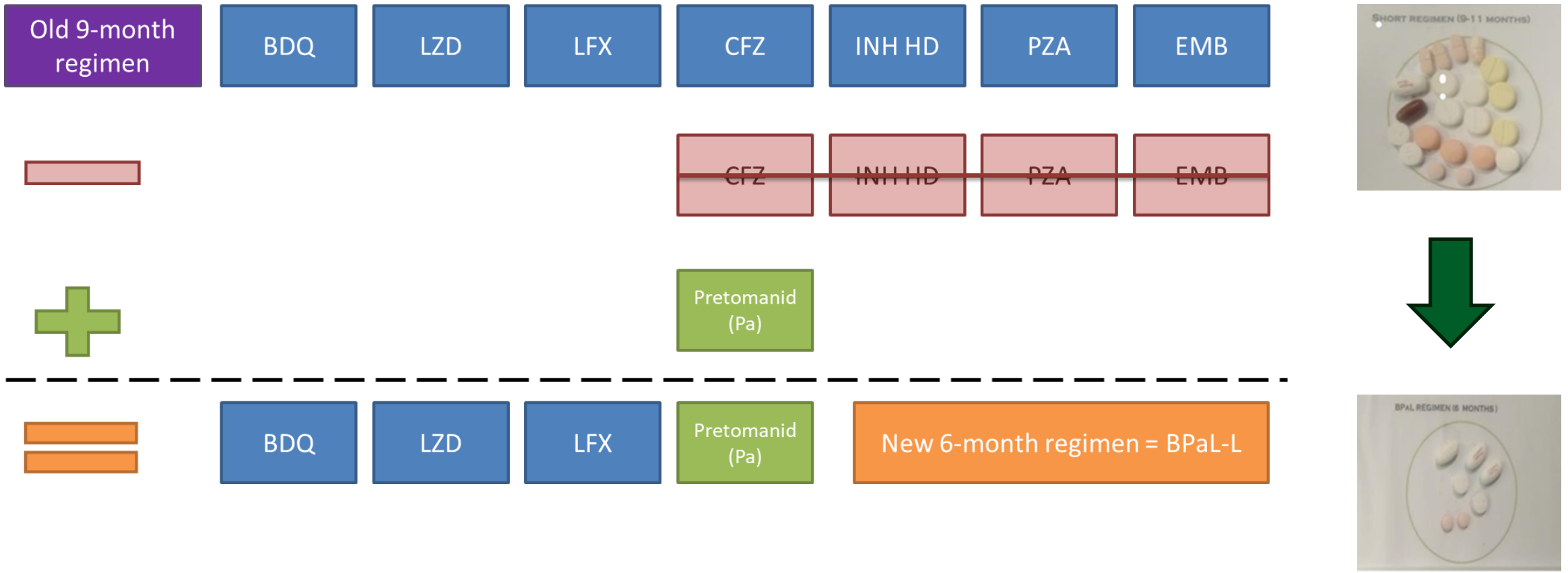
Special thanks to Thato Mathabathe & Deanne Goldberg for the updates on the drugs

28th February 2024

DR-TB Regimens Over Time – Key Facts

Period	RR/MDR-TB Shorter Regimen	RR/MDR-TB Longer Regimen	XDR-TB Longer Regimen
2011 – 2016	• Not applicable	• 24 months (at least) • 5 drugs • **180 injections + 7 200 pills**	• 24 months (at least) • 7 drugs • **180 injections + 7 200 pills**
2017 – 2018 (Aug)	• 9 – 11 months • 7 drugs • **Up to 180 injections + at least 2 880 pills**	• 18 – 20 months • 5 drugs • **Up to 180 injections + at least 5 400 pills**	• 18 – 20 months • 5 drugs • All-oral: **at least 3 968 pills**
2018 (Aug) – 2023	• 9 – 11 months • 7 drugs • All-oral: **at least 3 038 pills**	• 18 – 20 months • 5 drugs • All-oral: **at least 5 048 pills**	• 18 – 20 months • 5 drugs • All-oralL: **at least 3 968 pills**

New Regimen – BPaL-L



NEW REGIMEN for MDR-TB

BPaL – L is better for you!

ONLY 6 months of treatment	3 to 4 medicines	90% cure rate	Simplified regimen

BPaL-L = Bedaquiline + Pretomanid + Linezolid + Levofloxacin

The new regimen for **MDR-TB patients** has many advantages, including:

- Fewer pills required – only 23 pills per week
- Shorter treatment – only 6 months
- Fewer facility visits, which means a lower costs for you to get treated

Speak to your healthcare worker today to find out if you are eligible!

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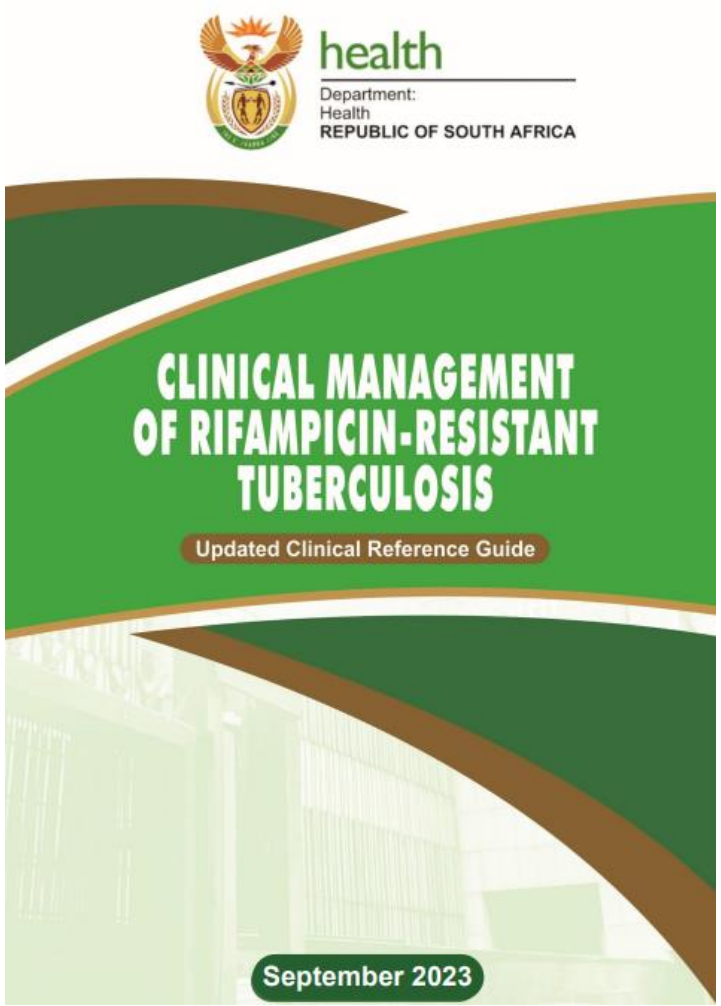
UPDATES



- Donation acquired and stock distributed
- Guidelines updated and training materials/ manual developed
- Phase-in approach
  - Training conducted across the 9 provinces
  - District training
- Dashboard developed

RSA Department of Health

BPaL Programme Dashboard

Aim

Monitor the implementation of the new 6-month TB treatment regimen
Monitor accurate, clean, timeous data capturing

Inclusion criteria

All patients initiated on RR-TB treatment
Patients above 15 years of age
All patients registered with Pretomanid in their current treatment

Exclusion criteria:

Patients diagnosed with XDR-TB treatment
Patients less than 15 years of age
Pregnant women

To date:

- 49 out of 52 districts enrolling patients on BPaL-L
- 397 facilities initiating patients on BPaL-L
- Total number of patients enrolled since 1st September 2023

Patients on BPaL-L by Province						
Province	**Sep-2023**	**Oct-2023**	**Nov-2023**	**Dec-2023**	**Jan-2024**	**Total**
EC	69	70	72	57	76	344
FS			6	6	8	20
GP	18	45	62	39	43	207
KZN	11	38	65	71	94	279
LP	1	16	15	9	9	50
MP	1	9	13	15	16	54
NC	21	17	21	16	18	93
NW	5	10	11	6	9	41
WC		1	4	22	61	88
Total	**126**	**206**	**269**	**241**	**334**	**1 176**

MONTHLY/ WEEKLY ENROLMENT

On BPaL-L, as % of BPaL eligible patients	EC	FS	GP	KZN	LP	MP	NC	NW	WC	Total
1 Jan, 24	85%	50%	100%	53%	50%		100%		36%	66%
8 Jan, 24	65%	50%	85%	70%	67%	100%	100%	100%	59%	72%
15 Jan, 24	73%		33%	66%		100%	75%		67%	67%
22 Jan, 24	82%	100%	100%	67%			100%		67%	79%

DRUG SECURITY & AVAILABILITY

BPaL-L/M Stock on Hand: Pretomanid

Pretomanid 200mg Tablet as of 26.02.2024				
Province	30's Stock on Hand	30's Quantity on Order	26's Stock on Hand	26's Quantity on Order
Eastern Cape	1 125	50	-	-
Free State	315	645	200	125
Gauteng	2 238	297	142	-
KwaZulu-Natal	10	350	20	57
Limpopo	16	84	-	-
Mpumalanga	19	-	-	-
Northern Cape	-	-	-	-
North West	485	372	-	-
Western Cape	-	-	330	-
National	4 208	1 798	692	182

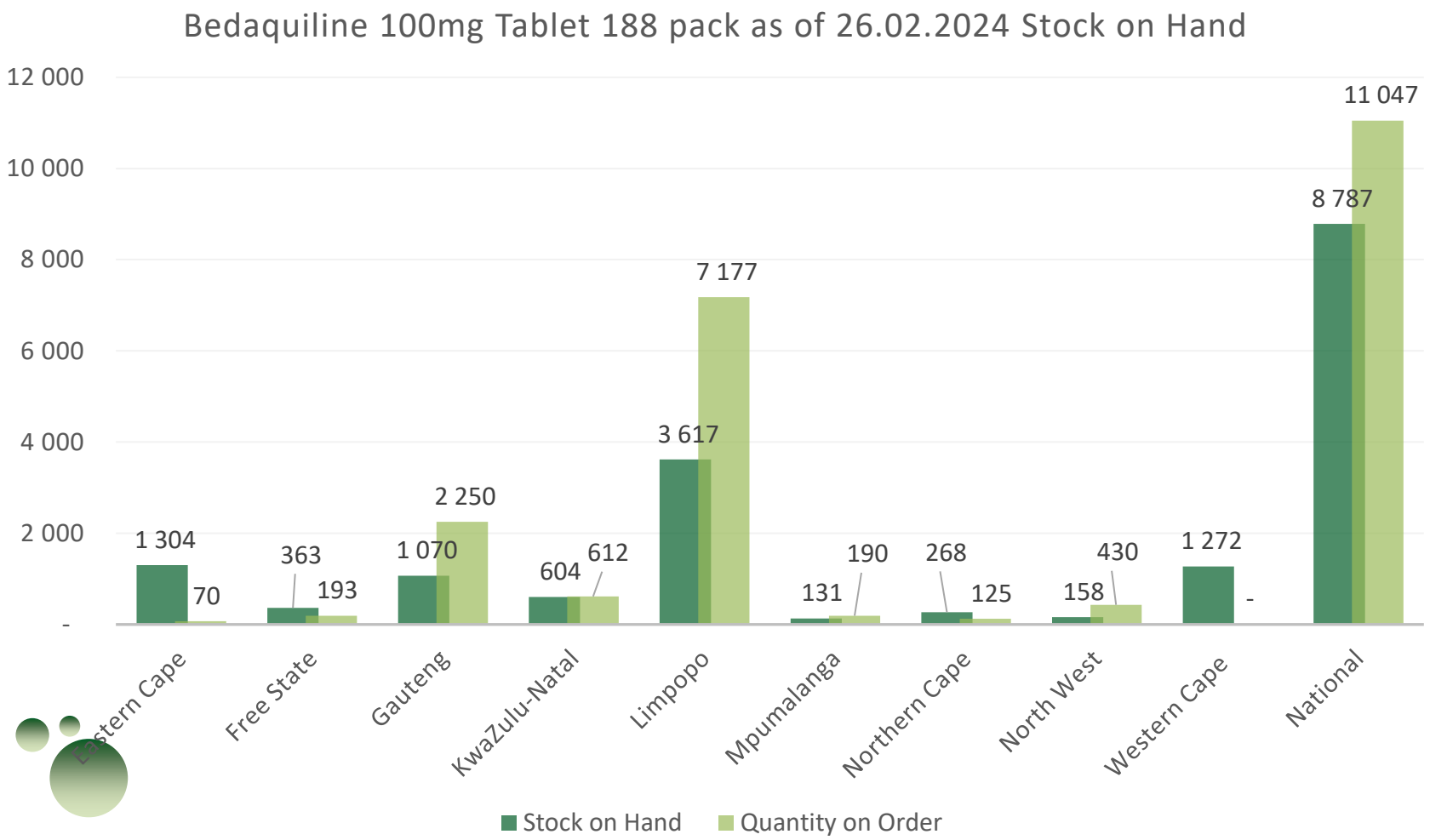
Supply Pipeline:

- 4,800 packs in QA expected delivery week of the 26 February 2024
- 12 000 packs expected early March 2023
- 12 000 pack commitment by supplier per quarter thereafter

Additional notes

- Pack size on tender is the 30's pack
- The current SOH is sufficient for ~801 patients The anticipated entry of QA and inbound stock should stabilize Pa supply security
- Active management of available stock is essential to protecting the BPaL-L regimen's success and impact

BPaL-L/M Stock on Hand: Bedaquiline



Additional notes

- Strong SOH position
  - 1 pack p/patient with an expected patient cohort of 10,00 means a significant portion of annual demand is covered (based on available reports)
  - Stringent management of orders required to avoid overstock

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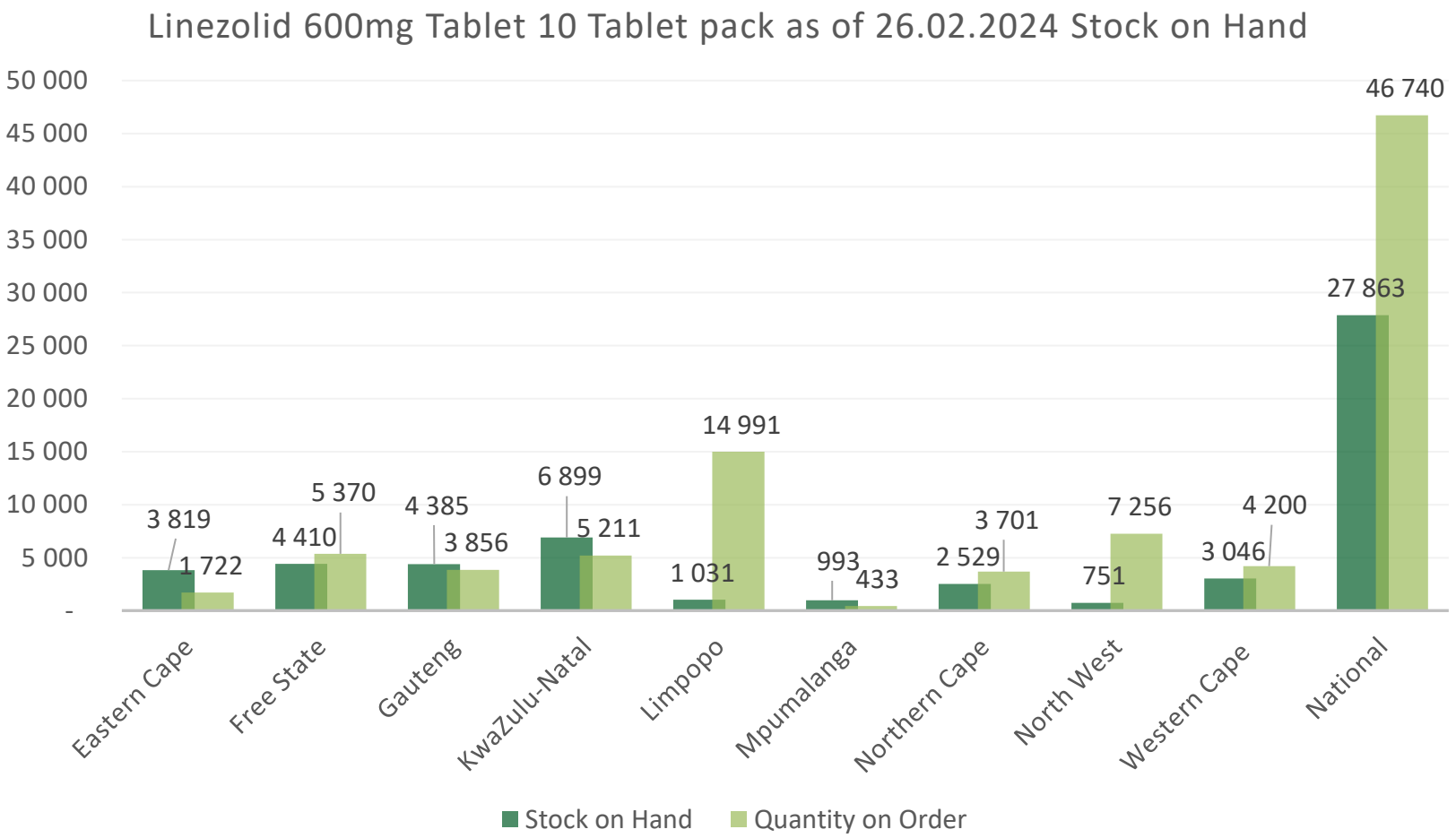
NATIONAL DEVELOPMENT PLAN 2030

Phila

BPaL-L/M Stock on Hand: Linezolid



Supply Pipeline:

Stock in QA (RSA Pharma)-54 530 packs

Additional notes

- Ongoing monitoring required

BPaL-L/M Stock on Hand: Levofloxacin

Levofloxacin Tablets as of 26.02.2024				
Province	250mg Tablet 28's Stock on Hand	250mg Tablet 28's Quantity on Order	500mg Tablet 28's Stock on Hand	500mg Tablet 28's Quantity on Order
Eastern Cape	2198	566	4 150	5 522
Free State	781	5 478	616	384
Gauteng	1 401	2 810	2 510	8 203
KwaZulu-Natal	6 104	2 987	10 803	7 437
Limpopo	3	7 244	925	18 337
Mpumalanga	1 139	4 781	177	240
Northern Cape	1 324	7 296	-	-
North West	180	514	991	9 655
Western Cape	2 291	8 915	-	3 564
National	15 421	40 591	20 172	53 342

Supply Pipeline:

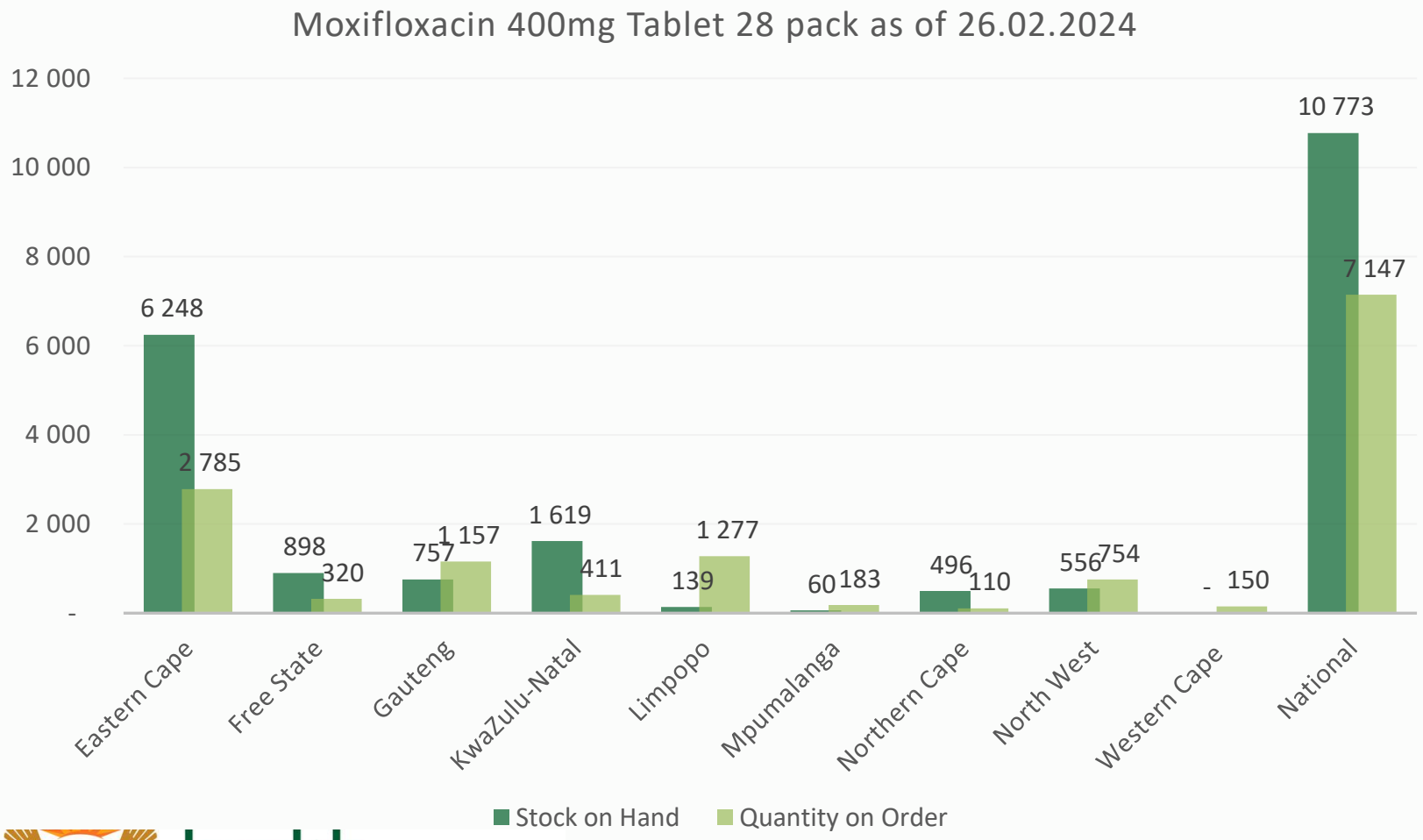
250mg: 23 097 packs received on 2 February 2024 & 36 429 packs expected later in February 2024

500mg: 5000 packs received on 2 February 2024 & 24 000packs expected later in February 2024

Additional notes

- The process of recalculating the forecast for national demand is currently in progress.
- Active communication is essential and monitoring available moxifloxacin stock should supplement LFX management

BPaL-L/M Stock on Hand: Moxifloxacin



Supply Pipeline:
Supplier stock holding (RSA Pharma)-28 702 packs

Additional notes

- MFX can be considered as an option where the supply of LFX is too low to implement a BPaL-L regimen

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Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL DEVELOPMENT PLAN 2030

Phila

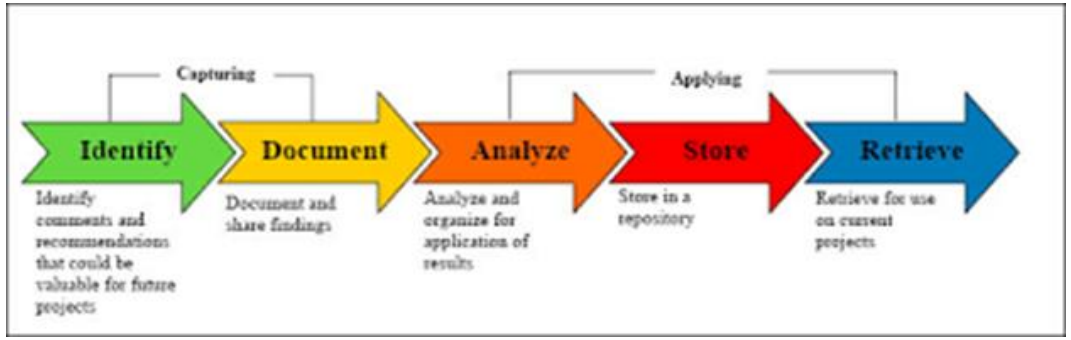
Key facts

Medicine	What do patients need	Unit(s)	Regimen length
Bedaquiline; 100mg; Tablet; 188 Tablets	1	pack	6-month course
Delamanid; 50mg; Tablet; 48 Tablets	15	packs	12-month course
Pretomanid; 200mg; Tablet; 30 Tablets	6	packs	6-month course
Levofloxacin; 500mg; Tablet; 28 Tablets	12*	packs	6-month course at 1000mg per day
	6*	packs	6-month course in a 750mg combination
Levofloxacin; 250mg; Tablet; 28 Tablets	6*	packs	6-month course in a 750mg combination
Linezolid; 600mg; Tablet; 10 Tablets	18	packs	6-month course

* These figures are dispensed in 28 tablet packs, indicating 1 month = 4 weeks; increase to 7 or 13 packs to accommodate extra

LESSONS LEARNT

- Buy-in is of upmost importance (on all levels)
- Multi-disciplinary approach
    - » Clinicians, pharmacist, partners
- Communication and feedback mechanism is key
    - » Support groups, WhatsApps and dashboard
- Live data capturing enables proactive management of rollout
- Drug availability and security of utmost importance



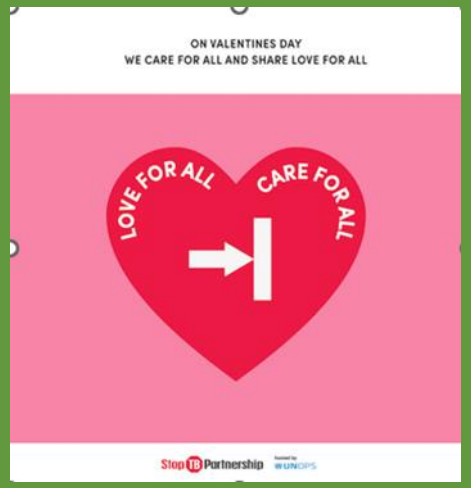
CHALLENGES

- ***"Fear of the unknown"*** – new regimen represents a significant departure from older, extended regimens
    - *New regimen*: move from 7 drugs to 3/4
    - *Novel drugs*: Pretomanid
    - *Adverse events*: LNZ is key to regimen so requires active monitoring and early response

- Centralised training not conducive

- Drug security and ordering
    - Supply security is key to stabilising scale-up.
      This requires careful demand planning and advanced ordering

Thank you


ON VALENTINES DAY
WE CARE FOR ALL AND SHARE LOVE FOR ALL
LOVE FOR ALL
CARE FOR ALL
Stop TB Partnership


ON VALENTINES DAY
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Stop TB Partnership

BPaL-L Implementation Dashboard

Mr Sajid Sherif
TB Technical Support Unit

28 February 2024

Outline

1. **Rationale & Background Information**
2. **Dashboard Demonstration**

1. Rationale & Background Information

Why Another Dashboard?

- The BPaL-L dashboard:
  i. serves a specific purpose,
  ii. is easy to use, &
  iii. is disseminated weekly to all provinces.

- It enables precise monitoring of the regimen's uptake and evaluates the timeliness and consistency of patient data recording on EDRWeb.

Data & Methodology

- The dashboard's data source is EDRWeb.

- Three data elements (numbers):
  - **All initiated on RR TB treatment:** All patients registered and started on treatment for Rifampicin Resistant (RR) TB. **[A]**
  - **BPaL-L eligible:** As above, but only clients 15 years and older, excluding all XDR-TB, pregnant women and severe extrapulmonary TB cases per guidelines. **[B]**
  - **On BPaL-L:** All registered patients with Pretomanid in their current treatment regimen. **[C]**

- Two indicators (percentages):
  - **BPaL eligible, as % of All initiated on RR TB treatment [B / A *100%]**
  - **On BPaL-L, as % of BPaL eligible [C / B *100%]**

How the Dashboard is Being Used?

- NDoH shares the dashboard with provinces weekly.
- NDoH uses it to engage with provinces to understand the factors contributing to the regimen's uptake.

- Provinces & Districts – please share how you use the dashboard in the chat box.

2. Dashboard Demonstration

Thank you