Federal Ministry of Health

Department of Public Health

National Tuberculosis, Leprosy and Buruli Ulcer Control Programme

Standard Operating Procedure for

BPaLM & BPaL Regimen Scale up

in Nigeria for Programme Staff and Healthcare providers

Version 1, October 2023

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1.0 Background

The burden of TB, TB/HIV and MDR-TB in Nigeria is huge. The BPaLM & BPaL regimen is new, shorter, and very effective all oral medications for the treatment of drug-resistant TB (DRTB).

2.0 Purpose

The purpose of this SOP is to provide programme staff and healthcare workers (HCWs) with a step-by-step approach to the scale-up of the BPaLM and BPaL regimen.

3.0 Target audience

State TB and Leprosy Control Programme Managers (STBLPM), State Quality Assurance Officers (SQA), Clinicians (DR-TB OPD doctors), Local Government TB, and Leprosy Supervisors, (LGTBLS), Nurses, Directly Observed Therapy (DOT), officers, General Healthcare Workers (GHCWs) and Community TB Workers.

4.0 Overview of the BPaLM and BPaL

4.1 Why introduce the BPaLM and BPaL regime

The NTBLCP based on the WHO recommendations and experiences from the BPaL pilot implementation is scaling the use of BPAL(M) regimen for use under programmatic conditions beginning in November 2023. The interim report from the BPaL pilot in Nigeria showed that the new BPaL(M) regime has a better treatment outcome than the current DR-TB treatment regime currently in use.

4.2 Regime composition and treatment duration.

- BPaLM regimen - Bedaquiline (Bdq), Pretomanid (Pa), Linezolid (Lzd), Moxifloxacin (Mfx)
- Duration – 6-9 months

4.3 Eligibility criteria

BPaLM/BPaL regimen is used in adults and adolescents aged 14 years and above who meet the following eligibility criteria:

4.3.1 Eligibility Criteria for BPaLM

- MDR/RR-TB
- Confirmed susceptibility to fluoroquinolones
- PTB and EPTB except TB involving CNS, osteoarticular and disseminated (miliary) TB
- HIV coinfection
- no known allergy to any of the BPaLM component drugs
- Not pregnant or Breastfeeding and on effective contraception or postmenopausal
- < 1-month previous exposure to Bdq, Lz, Pa or Dlm
- For exposure to any of the BPaLM component drugs longer than one month, use the regimen if resistance to specific medicines has been ruled out using DST
- Result of fluoroquinolone DST is never determined or not done

N.B: 1) If FQ resistance is identified after treatment initiation, discontinue moxifloxacin, continue as BPaL

Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated

4.3.2 Eligibility Criteria for BPaL

- MDR/RR TB with laboratory-confirmed resistance to fluoroquinolones (PreXDR TB)
- Floroquinolone (FQ) resistance is confirmed or highly likely
- The patient is a close contact of a FQ-resistant case
- Eligibility criteria listed under BPaLM except confirmed susceptibility to fluoroquinolones
- Treated for MDR/RR-TB and has documented non-response to treatment, and the Expert Committee has decided to shift the patient to the BPaL regimen

4.4 Those NOT ELIGIBLE for the BPaLM and BPaL regime

- Patients with additional Fluoroquinolone (FQ) resistance is not eligible for BPaLM
- Patients with a DST result showing resistance to any of the component drugs
- Known severe allergy to any of the BPaL(M) component drugs
- Previously exposed to any of the component drugs or Dlm for > 1 month
- Severe EPTB - TB meningitis, other CNS TB, or TB osteomyelitis, disseminated TB
- Pregnant or breastfeeding
- Children and Adolescents less than 14 years
- Unable to take oral medications

4.5 Dosing for Adult and children (aged ≥ 14years)

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Regimens for MDR/RR-TB in children and adolescents aged 0 - < 14 years

Fluoroquinolone susceptibility pattern	Regimen type
Fluoroquinolone susceptible (MDR/RRTB)	6 months of Bedaquilline, Levofloxacin, Clofazimine and Linezolid
Fluoroquinolone resistant (Pre-XDR)	6 months of Bedaquilline, Delamanid, Clofazimine and Linezolid

Refer to the 4th edition PMDT guideline for dosing on second line anti TB medicines in children.

4.6 When to extend BPaLM/BPaLM regimen duration from 6 to 9 months

- The standard duration of BPaLM/BPaLM treatment is 6 months
- If the sputum culture taken at 4 months of treatment (or later) is still positive, patients can receive an additional 3 months of treatment (total 9 months) as long as the patient is clinically well and /or improving

4.6.1 When to discontinue BPaLM/BPaLM regimen

i. Treatment of a patient is interrupted for 2 months or more after being treated for more than 1 month
ii. Intolerance, or toxicity to medicine in the regimen especially Linezolid
iii. If pregnancy occurs during treatment
iv. Withdrawal of consent.
v. Loss to Follow-Up
vi. Treatment failure

Note

- If either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued.
- If linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued.
- If linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be completed with the remaining component drugs

4.7 Management of Interruption/Missed Appointment for patients on BPaLM and BPaL regimen

Any TB patient who has not come to receive his/her treatment for two consecutive days either in the intensive or continuation phase should be regarded as having interrupted treatment and therefore must be traced.

As appropriate the LGTBLS, GHCW, and CBOs are to develop and implement a defaulter tracking plan. They are to document all actions taken to track and recommence DR-TB patients who interrupted treatment.

a. Trace patient
b. Find out the cause(s) of interruption
c. Counsel/Solve the cause(s) of interruption
d. Continue treatment and prolong it to compensate for the missed doses if ≤ 1 month. For those >1 month re-evaluate and manage appropriately in consultation with the DR-TB consilium of experts

4.8 Steps for monitoring DR-TB patients on BPaLM and BPaL regimen

Response to treatment is monitored based on monthly sputum smear microscopy, as well as culture, ideally at the same frequency. This is similar to the schedule used in patients on the longer all-oral regimen

Monitoring checklist for patients on the BPaLM and BPaL regimen

Parameter	Baseline	2 weeks	Monthly	End of treatment
Weight / BMI	X	X	X	X
Monitoring for adverse drug reactions	X	X	X	X
Visual acuity and colour (Snellen's chart and Ishihara)	X	X	X	X
Random Blood Sugar	X	X	X	X
Sputum smear	X		X	X
Sputum culture	X		X	X
LPA (first and second line)	X			
***DST	X			
Chest X-Ray	X			X
ECG	X	X	X	X
Full blood count (FBC)	X	X	X	X
Liver function tests (AST, ALT, bilirubin)	X	X	X	X
Serum electrolytes	X		X	X
Urea, creatinine (Renal function)	X		X	X
TSH	X	Every 6 months		
Pregnancy test	X			
HIV/HBV/HCV tests	X			
Serum Albumin	X	Every 2 months		
Serum Amylase	X			
HIV Positive Patients				
CD4 Count	X			
Viral Load	X	Every 6 months		

Note
Where no capacity to conduct/review a FBC test before starting a patient on BPaL(M) regime, it is mandatory to have patients packed cell volume (PCV) and Platelets count) tests done, and review at baseline before starting treatment, and monitor its parameter 2 weeks and monthly to end of treatment.

5.0 Prompt diagnosis and treatment approach for managing DR-TB cases

The entry point for diagnosis of drug-resistant TB (DR-TB) is through the rapid TB molecular diagnostic platforms i.e., GeneXpert, and Truenat. All Multidrugresistant and rifampicin-resistant TB patients (MDR/RR-TB) are to be promptly diagnosed and started on treatment within 24 – 48 hours of diagnosis. This is the overall goal of the diagnose and treat approach.

5.1 What to do after identifying a Rifampicin-resistant TB (RR-TB) case(s)

For every diagnosed Rifampicin-resistant TB (RR-TB) case, we expect HCW to:

1. Health workers/TBLS will provide comprehensive supportive and adherence counselling (see below)
2. Health workers in collaboration with TBLS arrange with the identified Lab and OPD clinics to have the baseline tests and assessment done immediately.
3. Eligible patients can be started on treatment the same day if hemoglobin level is greater than 8 g/dL (PCV > 24%) or a platelet count is greater than 75 000/mm3 while waiting for the result of another baseline test
4. Health workers will provide appropriate information to patient before initiation of treatment (see SoP)
5. Linezolid is associated with anaemia and thrombocytopenia; care should be taken in patients with anaemia.
6. Patients with neuropathy of Grades 3–4 should be treated with caution when commencing the BPaLM/BPaL regimen (A preliminary report from BPaL pilot in Nigeria revealed that 52.9% of the patients had peripheral neuropathy)

5.2 Steps for an Effective Adherence Counselling

- Provide health education and counselling in the patient's own language.
- Counselling should be done at every interaction with the patient, with relevant emphasis at each phase e.g., at pre-and post-diagnosis, treatment and follow-up
- Educate treatment supporters to help patients' adherence to treatment.
- Prepare the patient well by educating him/her on basic drug information, reason for treatment, importance/benefits of adherence, consequences of poor adherence and drug side effects.
- Identify potential barriers and support system e.g., financial constraints, transport cost, family, and social supports as well as healthcare provider's attitude.
- Regular monitoring and assessment of patients during treatment.

6.0 Monitoring Adverse Events and Drug-Drug Interactions

6.1 Monitoring Adverse Events

- Monitoring Adverse Events (AEs) and Drug-Drug interactions for patients on the BPaLM and BPaL regime should be active, systematic, and timely.
- **Weekly screen for AEs** including adverse drug reactions during the first month of treatment and then monthly for the remaining months of treatment.
- Know, monitor, manage promptly and document AEs (see 4th edition of the PMDT treatment guideline for common AEs).
- Institute prompt referrals where applicable and as appropriate • Grade AEs appropriately and initiate referrals for patients with severe (grade 3) and Life-threatening (grade 4) AEs.
- Involve patients in the decision on managing their AEs and provide psychological support to patients on treatment experiencing AEs

6.2 Monitoring and guidance on Drug-Drug interactions

i. For PLHIV on BPaLM and BPaL regime, Dolutegravir-based first-line ARV is preferred. Efavirenz reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid forms part of the BPaLM/BPaL regimen

ii. Use with caution or avoid in following situations (refer to the 4th edition of the PMDT guideline):
   - Drugs known to significantly prolong the QTc interval (use with caution especially antiarrhythmic agents, particularly amiodarone, quinidine,)
   - Strong CYP3A4 inducers (e.g. Efavirenz, phenytoin, carbamazepine),
   - Strong CYP3A4 inhibitors (e.g. Ritonavir, azole antifungals: ketoconazole, and macrolide antibiotics other than azithromycin) for more than 2 weeks;
   - Monoamine oxidase inhibitors (phenelzine, isocarboxazid and tranylcypromine); and
   - Drugs known to induce myelosuppression (e.g., zidovudine, azathioprine and cytotoxic agents).

7.0 Updated DR-TB treatment regimen for Adult in Nigeria

REGIMEN	COMPOSITION	DURATION	
SHORTER REGIMEN			
BPaLM/BPaL	6Bdq + Pretomanid (Pa) + Linezolid + Moxifloxacin	6-9months	Preferred treatment regimen for MDR/RR-TB
Shorter all-oral bedaquiline containing regimen (STR)	4-6 Bdq-Mfx-Cfz-Pto-Z-E-Hh / 5 Mfx-Cfz-E-Z	9-11 months	
LONGER REGIMEN			
Long oral MDR/RR-TB	6Bdq-Mfx**-Cfz-Lzd/ 12Mfx-Cfz-Lzd	18 months	
INDIVIDUALIZED REGIMEN			
XDR-TB (with resistant to Bdq)	6Dlm-Lzd-Cfz-Cs/12Cfz-Cs-Lzd	18 months	
XDR-TB (with resistant to Lzd)	6Bdq-Dlm-Cfz-Cs/12Cfz-Dlm-Cs	18 months	
Beyond XDR-TB	Dlm, Am, Meropenem + Am/Clv, Pto, E, Z, PAS	18 months	

8.0 Recording and reporting on patients on BPaLM and BPaL regime

Tool	Use	Personnel	Location
TB register presumptive	Capture data of both presumptive DSTB and DRTB patients	DOTS officer	DOTS centre
DR-TB Register facility	To capture data of diagnosed DR-TB patients to be enrolled	DOTS officer	DOTS centre
DR-TB register central	To capture data of enrolled DR-TB patients from each DOTS centre in the LGA	LGTBLS	LGA
DR-TB case finding and cohort reporting forms	To report DR-TB cases diagnosed and also the outcome of those treated	LGTBLS	LGA
Line List	To line list cases and be able to account for cases rolled over if there be and the ones that needs to be traced for enrolment in the LGA	LGTBLS	LGA

9.0 Supply chain management for BPaLM and BPaL regimen

The overall logistics and supply chain management for BPaLM and BPaL regimen is streamlined into the routine NTBLCP LMIS. The state logistics officer is expected to regularly liaise with the national PSM unit to ensure continued supplies of the regimens in the state. The unavailability of the regimens in the state is a sign of a poorly performing state logistic officer.

In any doubt, discuss the patient with Expert TB committee

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