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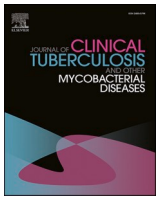

Effectiveness and safety of the BPaL regimen in the Philippines

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ABSTRACT

Background: Treatment success among multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) patients in the Philippines increased with the introduction of a 9-month all-oral treatment regimen; however, this remained sub-optimal, and patients continued to endure the burdensome and toxic effects of component medicines. In 2022, the World Health Organization recommended a 6-month MDR-TB regimen (bedaquiline, pretomanid, and linezolid or BPaL given for 26 weeks).

Method: Operational research was conducted in 12 TB treatment centers in 10 regions in the Philippines using the BPaL regimen. From June 2021 to December 2022, patients with pre-extensively drug-resistant TB or MDR/RR-TB that was treatment intolerant or nonresponsive to a previous MDR-TB regimen were enrolled. Linezolid was started daily at either 1200 mg or 600 mg.

Results: A total of 103 patients received the BPaL regimen; 96 patients were included in the cohort analysis. Despite fluoroquinolone resistance in 42 %, cavitary TB 31 %, diabetes mellitus 42 %, and HIV coinfection 8 %, treatment success was 98 %, with 1 (1 %) death and 1 (1 %) patient not evaluated. Sputum culture conversion was 78 % at month 1 of treatment, and 96 % by month 4. Sustained success at 6 and 12 months post-treatment were 92 % and 90 %, respectively, with the remainder attributable to patients not returning for post-treatment follow-up.

Adverse events were mostly grade 1–2, which fully resolved in almost all patients. Linezolid dose modifications, and BPaL regimen interruption occurred in 66 % and 18 %, respectively.

Conclusion: The BPaL regimen had a remarkably high treatment success, rapid culture conversion, and a manageable safety profile among MDR/RR-TB patients in this study despite fluoroquinolone resistance and comorbidities.

1. Background

Globally, an estimated 400,000 people developed multidrug-resistant/rifampin-resistant tuberculosis (MDR/RR-TB) in 2023. In the Philippines, the estimated MDR/RR-TB incidence was 25/100,000, with 29,000 prevalent cases. Only 7,900 were initiated on treatment, with 30 pre-extensively drug-resistant TB (pre-XDR-TB) cases [1].

In 2016, the shorter 9-month injectable-based regimen was introduced as the preferred MDR/RR-TB treatment rather than the longer 18–20 month regimens [2]. In 2019, this was replaced by a shorter 9-

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month bedaquiline-containing all-oral regimen [3]. In the Philippines, adoption of such shorter regimens was associated with a steady rise in treatment success rate (TSR) from 42 % in 2010 to 79 % in 2021, and a considerable decrease in loss to follow-up (LTFU) from 36 % to 8 %, respectively [4]. In May 2022, the World Health Organization (WHO) recommended an even shorter regimen of 6 months, BPaL consisting of bedaquiline, pretomanid, and linezolid under operational research (OR) for pre-XDR-TB patients without exposure to bedaquiline and linezolid [5]. This was based on the Nix-TB trial (2015–2017), an open-label study that achieved 90 % favorable outcome among 109 highly drug-resistant TB patients [6]. In December 2022, WHO recommended BPaL with or without moxifloxacin (BPaLM/BPaL) as the regimen of choice for eligible MDR/RR-TB patients under program conditions rather than the 9-month or longer regimens [7,8], based on the ZeNix [9] and TB PRACTECAL [10] clinical trials. Between 2020 and 2022, the LIFT-TB (Leveraging Innovation for Faster Treatment of Tuberculosis) project was launched by TB Alliance (TBA) [11] in 7 countries including the Philippines [12–14], to conduct BPaL OR with technical support from KNCV and the International Tuberculosis Research Center, Korea [14]. KNCV's Generic OR Protocol [15] was used that aimed to assess the efficacy and safety of BPaL among eligible MDR/RR-TB patients.

2. Methods

2.1. Study design

The BPaL OR was implemented in 12 OR sites in 10 regions of the Philippines [16]. Eligible pre-XDR-TB or MDR/RR-TB patients were initiated on the BPaL regimen and prospectively followed until 12 months post-treatment.

2.2. Study patients

The inclusion criteria covered patients diagnosed with pulmonary *Mycobacterium tuberculosis* documented by molecular testing within 3 months from screening, who had a) pre-XDR TB by phenotypic or genotypic drug susceptibility testing (DST), or b) MDR/RR-TB non-responsive or intolerant to a prior MDR treatment, and were decided by the TB Medical Advisory Committee (TB MAC) to be shifted to BPaL. Also included were close contacts of laboratory-confirmed pre-XDR TB patients with a strong clinical and radiological evidence of active TB, and MDR/RR-TB patients not eligible for the 9-month all-oral regimen. Patients aged ≥14 years were enrolled, regardless of human immunodeficiency virus (HIV) status and CD4 cell count.

The exclusion criteria included body weight <35 kg; known allergy, drug resistance, or severe uncontrolled adverse event (AE) to any of the BPaL component drugs, or delamanid, or previous exposure to these drugs for >4 weeks unless confirmed susceptible; severe extrapulmonary TB, pregnancy, and/or lactation. Relative contraindications included severe peripheral neuropathy, myelosuppression, alanine aminotransferase (ALT) >3× the upper limit of normal, and QTcF (corrected QT interval by Fridericia) >500 ms.

3. Intervention

Per protocol [15], patients received 26 weeks of daily BPaL oral treatment extendable to 39 weeks if bacteriologically positive on month 4. Bedaquiline dose was 400 mg once daily for 2 weeks, followed by 200 mg thrice weekly for 24 weeks; pretomanid 200 mg dose was once daily and linezolid 1200 mg was once daily throughout treatment. The starting dose of linezolid was reduced to 600 mg daily after 14 months of the OR following WHO advice [5] from the Zenix trial [9] suggesting 600 mg as the optimal daily linezolid dose with possible dose reduction, interruption, or discontinuation in the event of toxicity or poor tolerability. Interruption of the BPaL regimen was also allowed at certain periods during treatment in case of AE. These modifications were supervised by the research team and the TB MAC. Data were entered into Data Collection Forms and encoded into the standardized electronic collection system, REDCap, with core variables.

Baseline screening was done within 14 days prior to treatment start, to detect any comorbidities or reasons for exclusion. Patients were examined by a physician before the first BPaL dose with a follow up period of every two weeks for the first month, then monthly thereafter until completion, and at 6- and 12-months post-treatment. Chest radiographs were taken at baseline, on month 6 and post-treatment [15]. Following the National Tuberculosis Program (NTP) Manual of Procedures (MOP) [17], each patient was assigned a treatment supporter, typically a family member, responsible for supervising daily medication intake. Enrolled patients received the same support extended to non-research counterparts, including transportation assistance, ancillary medications for comorbidities or adverse drug reactions (ADRs), routine bacteriological and laboratory assessments, and psychosocial counseling. Treatment interruptions were closely tracked by health facility staff through phone calls and home visits, as necessary.

4. Microbiological assessments

Two sputum samples were obtained for smear microscopy and solid culture using Ogawa media at baseline then monthly during treatment, and at 6- and 12-months post-treatment in designated subnational laboratories. *M. tuberculosis* was identified by a rapid molecular method (GeneXPert Ultra®) or culture. Isolates were transported to the National TB Reference Laboratory or a private laboratory for phenotypic DST to first- and second-line agents, and for *Mycobacteria* Growth Indicator Tube (MGIT) DST. Rifampicin resistance was determined by GeneXpert Ultra® and fluoroquinolone resistance by GenoType® MTBDR*sl* or by a low complexity nucleic acid amplification test (GeneXpert MTB/XDR®) [15].

5. Safety assessments

Active TB drug safety monitoring and management (aDSM) was carefully observed in this study with prompt detection, management and reporting of adverse events of special interest (AESI) that were monitored per protocol [18] based on AEs associated with BPaL in the clinical trials [6,9,10]. Safety assessments included haematology and liver function test among others, visual acuity test (Snellen Chart), color vision test (Ishihara plates), brief peripheral neuropathy screen, and electrocardiography for QT prolongation [15]. These tests were done during the follow-up period, and *ad hoc*. Serial test results were documented in patients' records, and AEs were managed according to severity grading scales per protocol. Differences in the proportion of individuals experiencing each AE by dose group of linezolid (1200 mg and 600 mg daily) were assessed using the two-sample test for equality of proportions with continuity correction (prop.test() function in R). AE reporting used electronic or paper format according to national policy [17].

6. Treatment outcome definitions

The treatment outcome definitions were as follows: cured referring to BPaL completion without evidence of failure AND with ≥2 consecutive negative cultures at least 30 days apart within the last three months of treatment; treatment completed for BPaL treatment completion without evidence of failure but with no record of ≥2 negative cultures taken at least 30 days within the last three months; treatment success for the sum of cured and treatment completed; **treatment failed** for patients switched to an individualized regimen due to a) resistance to any of the BPaL component drugs; b) lack of culture conversion at month 6, or culture reversion at month 5 or later; or c) a decision for early treatment termination because of poor clinical or radiological response or ADRs, as decided by the TB MAC; or permanent discontinuation of

bedaquiline and/or pretomanid at any time, or permanent discontinuation of linezolid earlier than 4 weeks of 1200 mg daily or 9 weeks of 600 mg daily due to AE; LTFU for treatment interruption ≥2 consecutive months; and not evaluated for the absence of assigned treatment outcome, including but not limited to participants who were withdrawn after enrolment due to a protocol violation [15].

7. Results

7.1. Cohort profile

Of the 121 RR-TB patients detected in the OR sites, 18 (15 %) were excluded during screening because of: a) patient refusal to participate in research or to pursue further TB treatment (8, 44 %), b) clinical TB MAC decision (3, 17 %), c) death pre-enrolment (2, 11 %), d) stringent institutional research requirements (2, 11 %), and e) others: distance from research site, missing baseline tests, and unavailable medicines at the site (3, 17 %). A total of 103 patients were initiated on the BPaL regimen between June 2021 to December 2022, but 7 (7 %) patients were excluded from the cohort analysis due to suspected baseline resistance to a BPaL component drug, for which validation testing is ongoing. Of the 96 patients in the cohort, 42 % (40) had pre-XDR-TB, 52 % (50) had intolerance, 2 % (2) had non-response to a previous MDR-TB regimen; 3 % (3) was not eligible for the 9-month all-oral regimen, and 1 % (1) was a pre-XDR patient contact. The daily linezolid dose was 1200 mg in the first 79 (82 %) patients, and 600 mg in the remaining 17 (18 %) patients. The patient demographic and clinical characteristics are summarized below Table 1.

There were more males in the cohort; average body mass index (BMI) was normal; almost all were previously treated for TB, with fluoroquinolone resistance in less than half, and cavitary TB in a quarter. Comorbidites included diabetes mellitus, and HIV, all on antiretroviral therapy.

7.2. Clinical and microbiological assessment

All 96 patients had bacteriologically confirmed RR-TB by rapid molecular testing and had clinical signs and symptoms of tuberculosis with radiographic findings suggestive of TB, except for three patients living with HIV, whose chest radiographs appeared normal. There were 51 (53 %) culture-positive patients at baseline; negative cultures in nearly half of the patients, being attributed to poor sputum quality and long specimen transport time. MGIT DST was performed on 40 isolates (11 non-viable), with ongoing validation of minimum inhibitory concentration results based on WHO critical concentrations for new drugs [19].

7.3. Effectiveness analysis

Treatment success was 98 % (94) [cured 48 % (45) and treatment completed 52 % (49)] based on bacteriologic and clinical signs and symptoms, chest radiograph, and TB MAC decision. One patient died from community-acquired pneumonia, and one discontinued treatment and was not evaluated. There was no treatment failure nor LTFU. One patient had treatment extended to 39 weeks, following a positive smear in month 4 but was culture-negative until completion, and was eventually a treatment success.

Of the 51 culture-positive patients at baseline, 40 (78 %) culture converted as early as month 1 of treatment, and 49 (96 %) by month 4 (Fig. 1). The remaining 2 patients had specimen contamination.

At 6 months post-treatment (n = 94 patients), 86 (92 %) showed sustained treatment success (84 bacteriological, 2 clinical), 1 died at home with no medical documentation, and 7 (7 %) failed to return for follow-up. At 12 months post-treatment (n = 93 patients), 84 (90 %) showed sustained treatment success (81 bacteriological, 3 clinical), 1 died from a cerebrovascular accident, and 8 failed to return for follow-up. Missed post-treatment follow-ups were from refusals as patients were feeling well, or had distance or work constraints.

Table 1
Baseline characteristics of the patients, N = 96.

Characteristic	Value
Median age (range, IQR) – years	42 (18–74, 22.2)
Male sex – No. (%)	63 (65 %)
Median body mass index (range, IQR)	20.05 (14–31, 5.5)
Previous treatment	93 (97 %)
Fluoroquinolone resistance	40 (42 %)
Cavitary TB	30 (31 %)
Unilateral	14 (14.5 %)
Bilateral	16 (16.5 %)
Diabetes – No. (%)	40 (42 %)
HIV positive – No. (%)	8 (8 %)
*Karnofsky score 80–100 – No. (%)	90 (94 %)

* Karnofsky score: a clinical tool to assess a patient's ability to perform everyday activities and overall functional status.

7.4. Safety analysis

7.4.1. Adverse events of special interest (AESI)

Out of the 96 patients, 88 (92 %) experienced at least one AESI of any grade during treatment.

Among the five AESIs in BPaL, peripheral neuropathy and hepatotoxicity (defined as any transaminase increase) regardless of severity grade, were the most frequent, followed by myelosuppression. Peripheral neuropathy and myelosuppression were significantly more frequent in the 1200 mg linezolid group compared to the 600 mg group, suggesting a dose-dependent effect.

7.4.2. Severity and outcome of AESIs

Table 3 presents the patients with grade ≥3 AESIs according to linezolid dose. Due to low expected counts, Fisher's exact test was used to compare the proportion of Grade 1–2 versus Grade 3–4 events. No significant differences in severity were observed across dose groups for any of the 5 AESIs Table 2.

A total of 163 AESIs occurred throughout the treatment course, of which only 32 (20 %) were grade ≥3, two-thirds (22) of which fully resolved by treatment completion, or by post-treatment follow-up, while a third (10) resolved with sequelae. It is notable that only peripheral neuropathy had sequelae, 9 belonging to the 1200 mg group. All other AESIs had complete resolution.

7.4.3. Serious adverse events (SAEs)

SAEs occurred in 21 (22 %) of the 96 patients at a certain point during treatment: a) persistent disability, 8 (8 %); b) hospitalizations, 10 (10 %) for appendicitis, hypersensitivity reaction, transient ischemic attack, etc.; c) life-threatening condition (severe anemia) in 2 and death in 1 from acute respiratory failure from pneumonia.

7.4.4. Drug and regimen modifications

Among the 96 patients, 63 (66 %) had linezolid modifications according to protocol due to AEs (Fig. 2), the earliest occurring on the 5th week of treatment in 10 % of patients. Some patients had multiple linezolid modifications during the entire treatment course: a) dose reduction in 50 (52 %) patients; b) interruption in 31 (32 %) patients; c) discontinuation in 23 (24 %) patients. It is noteworthy that 33 (34 %) patients had no linezolid modification during the entire treatment course.

Fig. 3 shows that 17 (18 %) patients had at least one BPaL regimen interruption due to AE, with 6 (6 %) occurring within the first four weeks of treatment due to grade ≥3 hepatotoxicity, QT prolongation, or hypersensitivity reaction, etc.

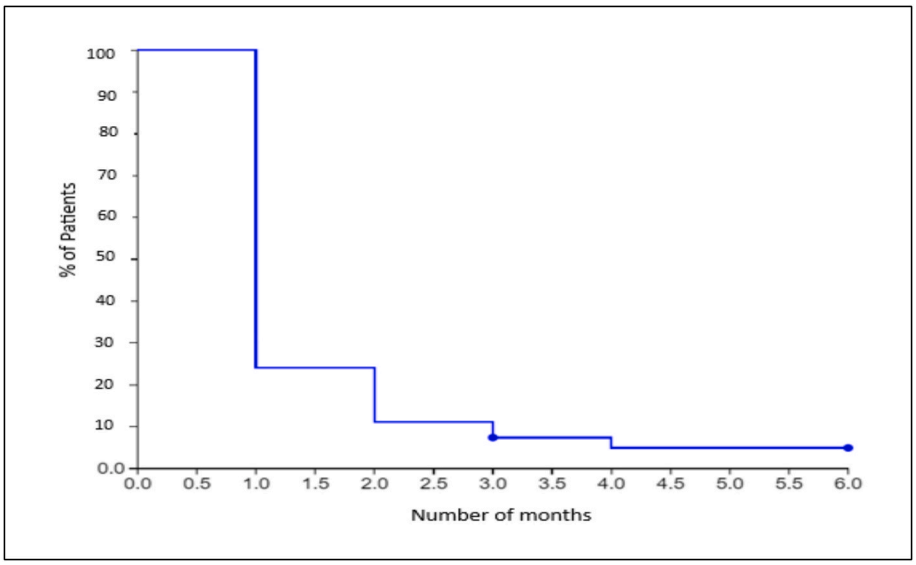

Fig. 1. Time to culture-negative among baseline culture-positive patients, n = 51.

Table 3
Patients with grade ≥ 3 AESIs and outcomes by linezolid daily dose.

AESI	Daily linezolid dose	Grade ≥ 3 AESI episodes/total recorded (%)	AE outcome among grade ≥ 3 AESIs (%)
1. Peripheral neuropathy (n = 58)	600 mg	2/6 (33 %)	(1) 50 % resolved (1) 50 % resolved with sequelae
	1200 mg	16/52 (31 %)	(7) 44 % resolved (9) 56 % resolved with sequelae
2. Myelosuppression (n = 37)	600 mg	0/1 (0)	Not applicable (N/A)
	1200 mg	8/36 (22 %)	(8) 100 % resolved
3. Optic neuritis (n = 3)	600 mg	0	N/A
	1200 mg	2/2 (100 %)	(2) 100 % resolved
4. Hepatotoxicity (n = 58)	600 mg	1/10 (10 %)	(1) 100 % resolved
	1200 mg	2/48 (4 %)	(2) 100 % resolved
5. QT prolongation (n = 8)	600 mg	0	N/A
	1200 mg	1/8 (12 %)	(1) 100 % resolved

Table 2
AESI by linezolid daily dose.

AESI	linezolid daily dose 1200 mg (n = 79)	linezolid daily dose 600 mg (n = 17)	*p-value*
1. **Peripheral neuropathy (n = 58)**	**52 (66 %)**	**6 (35 %)**	***0.039***[†]
2. **Myelosuppression (n = 37)**	**36 (46 %)**	**1 (6 %)**	***0.006***[†]
3. Optic neuritis (n = 3)	3 (4 %)	0 (0 %)	*1.000*[‡]
4. Hepatotoxicity (n = 58)	48 (61 %)	10 (59 %)	*1.000*[†]
5. QT-prolongation (n = 8)	8 (10 %)	0 (0 %)	*0.343*[‡]

[†] Proportions were compared using a Chi-square test with continuity correction.
[‡] Fisher's exact test was used for comparisons with low expected counts.

8. Discussion

In this study, the BPaL regimen was found to have a remarkably high treatment success, rapid culture conversion, and a manageable safety profile among MDR/RR-TB patients despite the added impediments of fluoroquinolone resistance and comorbidities. The predominant MDR/RR-TB regimen in the Philippines whilst the BPaL OR was ongoing, was the 9-month all-oral regimen, with a minority receiving longer/18-month regimens. While treatment shortening from 18 to 9 months was associated with an increase in DR-TB TSR, the regimen was burdensome with as many as 15 pills per day, and AEs that were difficult to manage. BPaL in this Philippine cohort had an outstanding TSR of 98 %, similar to that in Indonesia [13], which was unprecedented and never deemed achievable during the early years of Programmatic Management of Drug-resistant TB where TSR was as low as 22 % amongst pre-XDR patients [20]. This remarkable outcome is largely attributable to the combination of powerful novel and repurposed agents given for a short period with only 4–6 pills a day, with regimen flexibility, and a manageable safety profile, and administered under OR where close follow-up was made, avoiding treatment LTFU and death. It is worth noting that a considerable proportion of the cohort had highly resistant TB, harbored comorbidities, and cavitary disease. Linezolid modifications and BPaL regimen interruption also did not appear to detract from having a favorable outcome. In addition, patients on BPaL had rapid sputum culture conversion of almost 80 % by month 1 of treatment. It should be noted though, that most patients in this study were on 1200 mg linezolid daily.

Apart from being a highly effective regimen, a cost analysis study in the Philippines [21] showed that BPaLM/BPaL is far cheaper if used instead of the 9-month and longer regimens, resulting to 23 % annual cost savings per patient.

Whereas the effectiveness of the BPaL regimen has been demonstrated in clinical trials [6,9,10] and supported in this study, a functioning aDSM system needs to be in place, to be able to predict, detect, and manage AEs in a timely manner. aDSM was given priority in this study which allowed generation of drug safety data revealing that most AESIs were reversible. This study also showed that the proportion of patients with sequelae after BPaL were mostly patients that received 1200 mg daily of linezolid, consistent with the Zenix [9] finding. Of 163 AESIs, only about 20 % were grade ≥3, with the majority needing minimal or no intervention. However, despite fewer AEs encountered with linezolid 600 mg daily, the WHO aDSM framework [18] should remain a critical component in the programmatic use of novel regimens. Health care providers engaged in the treatment of DR-TB patients should be trained to identify, manage, and report AEs, with a referral mechanism in place for difficult cases. Having a clinical advisory group can support facilities in decision-making on clinical dilemmas, and ensures

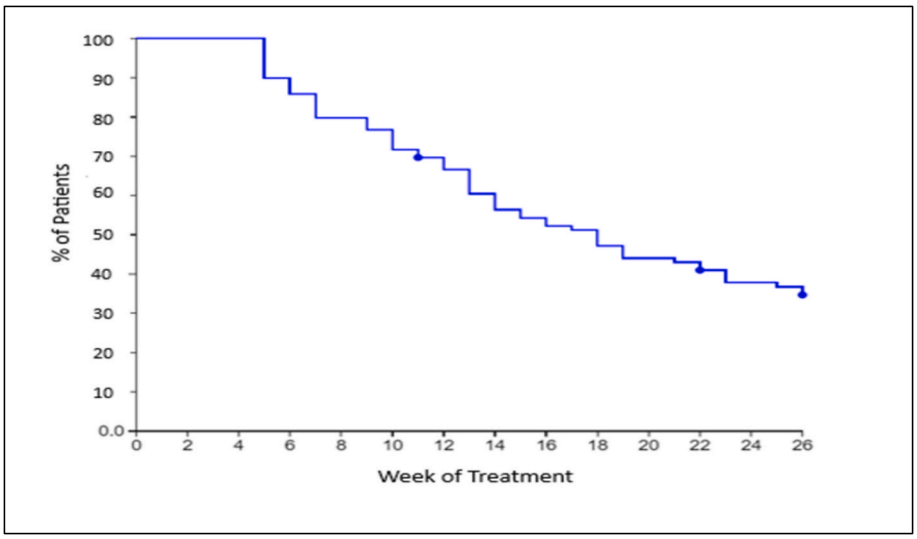

Fig. 2. Time to modification of linezolid, N = 96.

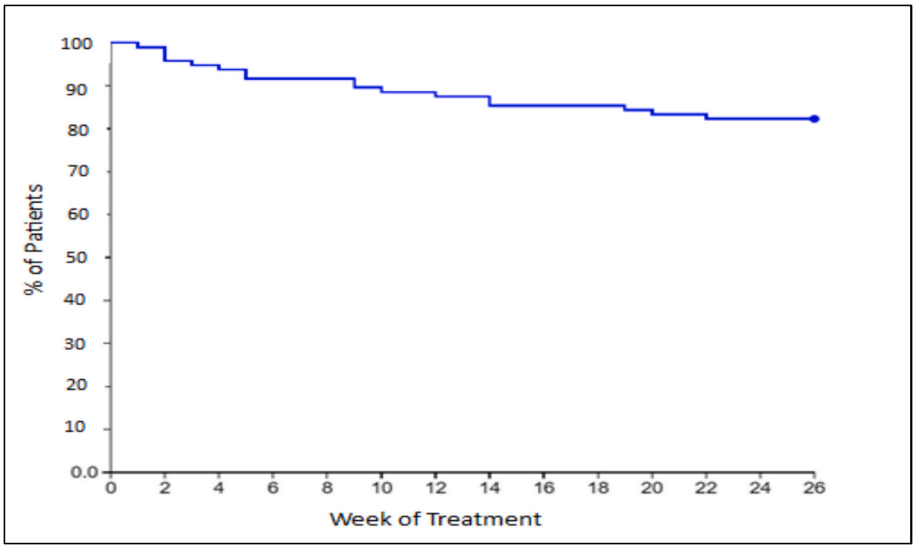

Fig. 3. Time to modification of BPaL, N = 96.

that the regimen flexibility is used with care and according to recommended guidelines. Mentorship and monitoring are priorities that the NTP must centrally establish through all health care levels for quality care, to facilitate proper patient management setting the stage for good program outcomes. These strategies are particularly important in a decentralized setup like the Philippines where 2700 peripheral health centers are mandated to manage DR-TB patients nationwide, in line with the Universal Health Care Act [22].

Favorable clinical and programmatic TB experience in the Philippines has paved the way for the NTP's easy transition from research to programmatic uptake of the BPaL-based regimens. Even prior to the publication of WHO guidelines in December 2022 [7,8], the NTP had created a BPaL Transition Core Group to update the TB MOP [17] anticipating WHO's forthcoming recommendation for programmatic use of the regimen. After a series of technical consultations, by December 2023, the Department of Health approved the Key Updates to the Current DR-TB Treatment Guidelines [23] that was immediately used for nationwide capacity building, leading to the rapid programmatic roll-out of BPaLM/BPaL in all regions of the country (data not shown). As of December 2024, almost 6,000 patients, representing around 70 % of the yearly MDR-/RR-TB patient enrolment, had been started on BPaLM/BPaL, aiming to reach an even wider coverage this year. As the country expands its use of this regimen, the potential to achieve a TSR comparable or even exceeding that of drug-susceptible TB is within reach.

9. Limitations

Several limitations need to be noted in interpreting the data presented here. First, specimen collection issues, such as long specimen transport time from facility to laboratory, and poor quality of sputum samples received, led to a low percentage of culture-positive patients at baseline, despite bacteriologic confirmation of RR-TB, and clinical manifestations of active disease. Second, despite the efforts of healthcare providers in locating patients, assisted by patient support groups and community leaders, some patients refused or went missing for post-treatment follow-up. Third, the TSR was achieved at a linezolid dose of 1200 mg daily and under research which may not be replicable at 600 mg daily under program conditions. Lastly, the protocol focused on certain AESIs, and did not intend to obtain a comprehensvie assessment

of all AEs.

10. Conclusion

BPaLM/BPaL given for 6 months is a revolutionary breakthrough in MDR/RR-TB care that not only leads to remarkable treatment success but is also less burdensome to patients, has a manageable safety profile, and is cheaper compared to other regimens. The experience in the Philippines of a systematic and smooth transition from research to programmatic use has proven that this regimen can be implemented even in peripheral health facilities, making it a regimen worth adopting tailored to country settings, in line with the WHO recommendation to use BPaLM/BPaL as the priority MDR/RR-TB regimen globally. To achieve good outcomes in a sustainable manner, it is critical to strengthen mentoring, monitoring, and aDSM frameworks at the point of care, and to integrate patient management strategies into the broader health care system.

CRediT authorship contribution statement

Irene Flores: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing. **Maria Imelda Quelapio:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Charlotte Cabalitan:** Validation, Supervision, Software, Investigation, Formal analysis, Data curation. **Jeam Carpin:** Validation, Supervision, Software, Investigation, Formal analysis, Data curation. **Maria Rhoda Torres-Cervas:** Validation, Supervision, Software, Investigation, Formal analysis, Data curation. **Maricel Trono:** Data curation, Formal analysis, Project administration, Validation, Writing – review & editing. **Charisse Malbacias:** Writing – review & editing. **Ramon Basilio:** Validation, Data curation. **Alma Palparan:** Validation, Data curation. **Fraser Wares:** Project administration, Writing – review & editing. **Veriko Mirtskhulava:** Data curation, Formal analysis, Software, Validation, Writing – review & editing. **Jin-Kyung Jung:** Funding acquisition, Resources, Project administration, Writing – review & editing. **Sang Nae Cho:** Resources, Project administration, Funding acquisition. **Salah Foraida:** Writing – review & editing. **Maria Diachenko:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Sandeep Juneja:** Resources, Funding acquisition. **Agnes Gebhard:** Funding acquisition, Resources, Writing – review & editing.

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Declaration of competing interest

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