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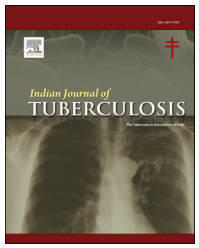

Editorial

Can Pan-TB shorter regimens be a promising hope for ending TB in India by 2025 in ongoing COVID-19 era?

Keywords:
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Shorter
Universal regimen

Tuberculosis (TB) remains a considerable public health burden with substantial morbidity and mortality worldwide. 10 million incident TB cases were reported globally with 2.9 million remain undiagnosed in 2019.[1] 1.2 million TB deaths occurred among HIV-negative people with additional 0.21 million among HIV positive ones. TB affects around 30,000 people every day with daily mortality of 4000 worldwide despite this disease is preventable and curable. Standardized 6 months regimen containing four anti-tubercular drugs- Rifampin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z) in combination, remains the cornerstone of treatment for drug sensitive tuberculosis (DS-TB) with favourable treatment outcome of 85%.[1] However, drug-resistant TB (DR-TB) has evolved by development of acquired as well as transmitted resistance among strains of TB bacilli, creating important forms like rifampicin resistant-TB (RR-TB), multi-drug resistant tuberculosis (MDR-TB), and extensively drug resistant TB (XDR-TB). Multi-drug and Rifampicin-resistant tuberculosis (MDR/RR-TB) is now creating a potential hazard to control of TB. 3–4% of new and 18–21% of re-treatment TB cases worldwide had MDR/RR-TB since last one decade.[1] The World Health Organization (WHO) End TB Strategy has placed targets for eliminating TB with 80% and 90% reduction in incident rate as well as 90% and 95% reduction in mortality rate by 2030 and 2035 respectively.[1,2] The government of India aims to end TB by 2025 which is an admirable initiative.[3] The first step is to prevent emergence of new drug resistant cases. WHO has recommended universal drug susceptibility testing (DST) for rapid reduction of drug resistance by genotypic tests such as cartridge based nucleic acid amplification test (CBNAAT) and line probe assays (LiPA).[4,5] Another issue is that global treatment outcome of MDR/RR-TB cases remains sub-optimal. 186,772 MDR-TB cases were diagnosed among 500,000 notified cases of MDR-TB in 2019 with treatment success rate of 57%.[1] The favourable treatment outcome was achieved only in 48% even in India. Drug resistant cases are usually treated with conventional regimens containing a combination of second line drugs (SLDs') including injectables for duration of atleast 18–24 months.[4] The reasons for sub-optimal outcome are possibly due to prolonged treatment duration, expensive and toxic SLDs' particularly injectables leading to poor compliance. Fortification of regimens with newer drugs like Bedaquiline (Bdq) and Delamanid (Dlm) as well as repurposed drugs like Linezolid (Lzd) and Clofazimine (Cfz) in combination, has revolutionized management of DR-TB over last decade. WHO is working aggressively on enhancement of treatment success rate. All oral longer regimens containing newer drugs have been introduced for DR-TB patients with treatment duration of 18–20 months.[5] WHO has also introduced a shorter treatment regimen of 9–12 months duration with potential ability to curtail various aspects such as drug burden, culture conversion time, risk of infection transmission, incidence of adverse drug events, cost and treatment duration leading to improvement of adherence.[4,5] The regimen was introduced on the basis of STREAM (Standard Treatment Regimen of Anti-TB Drugs for Patients with MDR TB) Stage 1, a phase 3 randomized control trial (RCT) that reported non-inferiority of shorter regimen compared to longer regimen regarding primary efficacy outcome (78.8% versus 79.8%) and safety in patients with MDR/RR-TB having susceptibility to both FQs' and second line injectable drugs (SLID).[6,7] Shorter regimens

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reported to have statistically-significant higher likelihood of treatment success than those received longer conventional regimens. (80%–83% versus 56%–75.3%)[4–9] However, there are various shortcomings associated with these regimens. The shorter regimen still requires a minimum 4 months of treatment in an intensive phase using drugs such as an SLID, Lzd and Cfz that have poor toxicity profile and also logistical challenges of multiple intramuscular drug administration leading to poor adherence. Another concern is that evidence remains sparse regarding potency of shorter MDR/RR-TB regimens in all settings with respect to DST pattern, HIV status, extrapulmonary involvement (except lymph node and pleura), disseminated or central nervous system involvement and pregnancy. Although higher success rate with shorter regimen was due to less default rate but was also associated with unfavourable outcome (failure or relapse) in the presence of documented resistance to medications included in the regimen especially FQs' and Z either at baseline or subsequently during ongoing treatment. Shorter regimens can be applied to 1/3 to 1/4 (5–25%) of MDR/RR-TB based on clinical criteria and prevalent drug resistance pattern in most countries.[10,11] All these inferences demand for enhanced approach to reliable DST. A search for innovative shorter regimens is essential that can overcome these limitations. A second stage of STREAM 2 trial is already evaluating two additional shorter regimens containing Bdq.[6] Many trials are ongoing and hunting for innovative shorter regimens for DS-TB (APT, CLO-FAST, PredictTB, TBHDT, TRUNCATE-TB) and DR-TB (BEAT TB, DELIBERATE, endTB, endTB-Q, MDR-END, NeXT, TB-PRACTICAL). Research Excellence to Stop Tuberculosis resistance (RESIST-TB), an initiative adopted by WHO is conducting all these trials for rapid control of DR-TB.[12] Pretomanid (Pa) is one of the promising newer drug that has shown to increase treatment success in M/XDR-TB.[13] The Nix-TB trial is evaluating Bdq-Pa-Lzd regimen of 6–7 months duration with minimum potential resistance in treatment of XDR-TB and also MDR-TB patients either non-responsive to treatment or not tolerating SLDs' requiring treatment discontinuation.[14] A cure rate of 90% was achieved after a 6 month course of treatment (MDR-TB- 92%; XDR-TB-89%). WHO has recommended that eligible XDR-TB patients can be treated with Bdq-Pa-Lzd regimen under programmatic research settings in whom design of effective regimen not possible and also no prior exposure to Bdq and Lzd over two weeks.[5] Acceptance and practical viability of this regimen is impressively high among TB stakeholders in Indonesia, Kyrgyzstan, and Nigeria as compared to that of individualized treatment regimen of 18–20 months duration (93% Vs 45%).[15] 88% of stakeholders are willing to implement Bdq-Pa-Lzd upfront among eligible patients despite various barriers related to long term efficacy, monitoring of adverse events and implementation at programmatic level.

Further, few trials are ongoing to design elusive shorter regimens that can serve the purpose to treat DS-TB in addition to DR-TB cases simultaneously favouring universal treatment approach as shown in Table 1.[12,16–19] These universal shorter regimens are also termed as Pan-TB regimens. Pa can be considered as backbone of pan-TB regimens. It has a distinct mechanism of action and is unaffected by bacterial mutations that confer resistance to other TB drugs, so it is equally effective against DR-TB as it is against fully DS-TB.[13] A multi-centric phase 2b trial included a non-randomized group for RR-TB patients treated with regimen containing Bdq-Pa-Mfx-Z.[19] The Pa containing regimen showed significantly higher bactericidal activity against DS-TB for the groups with the daily dose or loading dose of Bdq as compared to HRZE group. However, limitations exist with this trial such as shorter duration for assessment of bactericidal activity, non-placebo-controlled or blinded aspect and possibility of bias created by sponsor in methodology and data compilation. A modelling analysis from South Africa predicted that implementing the Bdq-Pa-Mfx-Z regimen universally could simultaneously improve cure rate for DR-TB patients from 60% to 90%, nearly 90% cure rate for DS-TB patients, curb treatment duration by atleast 2 months, and curtail transmission rate of infection by 3% for DS-TB to 50% for DR-TB.[20] The cure rate may remain exceptionally high after adopting this regimen even in settings having high prevalence of drug resistance or sparse DST coverage. Other advantages would include shorter treatment duration as well as culture conversion time, adequate infection control among all forms of TB patients including HIV co-infection and establishment of well-organized or co-ordinated health care delivery system between providers and patients.[21,22] Another mathematical modelling study has projected that if high burden countries like India implements pan-TB regimen by 2022, the annual incidence of TB will decline by 23.9% while treating all TB cases, and by 2.30% while treating only RR-TB cases in 2030.[23] However, economic feasibility must be kept in mind while implementing these regimens under programmatic conditions. It will be economically more productive if all forms of diagnosed TB cases should be treated with pan-TB regimen rather than treating only drug resistant ones considering cost around US dollar 360 on an average. Implementation of these regimens at national level could be epidemiologically purposeful and also cost-effective to TB control programmes on long run despite being more expensive than existing TB treatment.[23,24] Various theoretical advantages have been proposed like increased treatment initiation rates in public sector to 95%, treatment completion rate of DS-TB to 95%, improved adherence with less probability of missed dosing leading to 50% reduction in recurrence rates and also equal efficacy for both DS as well as DR-TB patients. Private sector should also be engaged in addition to public sector while implementing these regimens. Many disadvantages while using universal drug regimens have also been postulated such as rapid resistance amplification with loss of effective newer drugs due to strain variation, selection of drug resistant strains and pharmacokinetic variability, impairment of precise diagnostic tests and newer drug development due to lesser requirement for DST, encounter of more challenging management of drug resistance and toxicity with anti-TB drugs, lack of alternative regimens or rescue drugs, vigorous effort to maintain drug stocks by ensuring adequate supplies and scaling up productivity considering expenses, deviation from the patient centric or individualized approach recommended by WHO and probability of sub-optimal dosing in pediatric cases.[25] However, use of novel universal drug regimens should not be deferred in view of these uncertainties. The advantage of reduction of DR-TB transmission will be counterbalanced by development of resistance in DS-TB cases. It has been projected that the universal approach will remain only for limited duration due to

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Table 1 – Ongoing trials working on PAN TB shorter regimens to treat DS-TB and DR-TB cases simultaneously favouring universal treatment approach.

Trial	Phase	Regimens compared	Study population	Primary objectives	Result	Outcome
NCT01215851[16]	Phase 2A, partially double-blinded, randomized trial	-Bdq (n = 15) -Bdq-Z (n = 15) -Bdq-Pa (n = 15) -Pa-Z (n = 15) -Pa-Mfx-Z (n = 15) -RHEZ (n = 10)	Treatment naïve uncomplicated DS-TB (n = 85)	Assessment of 14 day EBA as estimated from the daily fall in CFU of M. tb/ml of daily collected sputum	Mean 14 day EBA of Pa-Mfx-Z (0.23) significantly higher than Bdq (0.061), Bdq-Z (0.131), Bdq-Pa (0.114) but not Pa-Z (0.15) and comparable with RHEZ (0.14)	Pa-Mfx-Z is potentially suitable for treating both DS-TB and MDR-TB
NCT 01691534[17]	Phase 2A, two-center, open-label, randomized clinical trial	-Bdq-Pa-Z-Cfz (n = 15) -Bdq-Pa-Z (n = 15) -Bdq-Pa-Cfz (n = 15) -Bdq-Z-Cfz (n = 15) -Z (n = 15) -Cfz (n = 15) -RHEZ (n = 15)	Treatment naïve uncomplicated DS-TB (n = 105)	Assessment of EBA expressed as the rate of change in CFU counts over the 14 days of treatment	Mean 14 day EBA: - Bdq-Pa-Z (0.167), standard treatment (0.151), Bdq-Z-Cfz (0.124), Bdq-Pa-Z-Cfz (0.115), Bdq-Pa-Cfz (0.076) Z alone had modest activity Cfz had no activity alone (20.017) or in combinations	Bdq-Pa-Z is a potential new TB treatment regimen Regimen suitable for patients with MDR-TB with relatively high reported rates of phenotypical Z resistance in many areas
NCT01498419[18]	Phase 2b, multicentre, open-label, partly randomised clinical trial	-Mfx-Pa100-Z (n = 60), -Mfx-Pa200-Z (n = 62) -HRZE (n = 59) -DRMfx-Pa200-Z (n = 26)	Treatment naïve DS-TB (n = 181) MDR-TB patients (n = 26)	Assessment of 8 weeks EBA measured by mean daily rate of reduction in CFUs of M. tb/mL overnight sputum collected once a week	DS-TB:- mean BA of MPa200Z (0.16) and MPa100Z (0.13) were significantly greater than for HRZE (0.11) DRMPa200Z:- mean BA of 0·12	Mfx-Pa-Z showed superior bactericidal activity in DS-TB during 8 weeks of treatment Results consistent between DS-TB and MDR-TB Ready to enter Phase 3 trials
NCT02193776[19] NC-005	Multi-centre, open-label, partially randomized, phase 2b trial	Bdq_{load}-Pa-Z (59), Bdq200PaZ (60), HRZE (61) DRBdq-Pa-Mfx-Z (60)	DS-TB (n = 180) MDR/RR-TB (n = 60)	Daily percentage change in time to sputum culture positivity in liquid medium over 0–56 days in DS-TB population	Bdq200-Pa-Z highest daily percentage change in TTP (5·17%) followed by Bdq_{load}-Pa-Z (4·87%) and HRZE group (4·04%) In DRBdq-Pa-Mfx-Z group, the Z-susceptible RR-TB group showed the highest cumulative percentage of culture negativity in liquid culture medium compared to Z-resistant RR-TB group	Bdq200PaZ is a promising regimen to treat patients with DS-TB Bactericidal activity of these regimens have the potential to shorten treatment Simplified dosing schedule of Bdq200PaZ could improve treatment adherence in the field

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Table 1 – (*continued*)

Trial	Phase	Regimens compared	Study population	Primary objectives	Result	Outcome
SimpliciTB[12] NCT03338621 NC008	Phase 2c/3, multi-center, open-label partially randomized clinical trial	DS-TB (n = 150): Bdq-Pa200-Mfx-Z (4 months) DS-TB (n = 150) RHEZ (2 months)/RHE (4 months) DR-TB (n = 150)- DR Bdq-Pa200-Mfx-Z (6 months)	DS-TB patients (n = 300) DR-TB patients (n = 150)	Time to culture conversion to negative status over 8 weeks Proportion of participants experiencing bacteriologic failure or relapse or clinical failure (unfavourable outcome) at 52 weeks Incidence of bacteriologic failure or relapse or clinical failure at 104 weeks from the start of therapy Proportion of participants with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 6, 12 and 17 weeks to be explored as a potential biomarker of outcome at 52 weeks from start of therapy	To be published	To be published
STAND[12] NCT02342886 NC-006	Phase 3 Open-Label parallel assignment Partially Randomized Trial	Mfx-Pa200-Z (6 months) (n = 67) Mfx-Pa200-Z (4 months) (n = 71) Mfx-Pa100-Z (4 months) (n = 65) RHEZ (6 months) (n = 68) DR-TB DRMfx-Pa200-Z (6 months) (n = 13)	DS-TB patients (n = 271) DR-TB patients (n = 13)	Incidence of combined bacteriologic failure or relapse or clinical failure at 12 months from start of therapy (modified ITT) Incidence of combined bacteriologic failure or relapse or clinical failure at 12 months from start of therapy (PPP) Incidence of bacteriologic failure or relapse or clinical failure at 24 months from the start of therapy Rate of change in TTP over time in liquid culture (MGIT) in sputum (at Screening, Day 1, 7; Week 2–7; Month 2–6, 9, 12, 15, 18, 24) Proportion of subjects with sputum culture conversion to negative status in liquid culture (MGIT) at 4, 8, 12 and 17 weeks	Favourable outcome (ITT/PPP) Mfx-Pa200-Z (6 months):- 43/56 (76.8%)/43/47 (91.5%) Mfx-Pa200-Z (4 months):- 46/61 (75.4%)/46/57 (80.7%) Mfx-Pa100-Z (4 months):- 38/57 (66.7%)/38/52 (73.1%) RHEZ (6 months):- 52/60 (86.7%)/52/53 (98.1%) DRMfx-Pa200-Z (6 months):- 10/11 (90.9%)/10/10 (100%)	Mfx-Pa200-Z is a promising regimen to treat patients with DS-TB Bactericidal activity of these regimens have the potential to shorten treatment

Abbreviations used:-Bdq- Bedaquiline; Cfz-Clofazimine; CFU-Colony forming unit; DS-TB-Drug sensitive tuberculosis; DR-Drug resistant; E-Ethambutol; EBA-Early bactericidal activity; H-Isoniazid; ITT-Intention to treat; Mfx-moxifloxacin; MDR-TB- Multi-drug resistant tuberculosis; MGIT-Mycobacterium growth indicator tube; M. tb-*Mycobacterium tuberculosis*; Pa-Pretomanid; PPP- Per protocol population; R-Rifampin; RR-TB-Rifampin resistant tuberculosis; STAND-Shortening treatment by advancing novel drugs; TTP-Time to culture positivity; Z-Pyrazinamide.

probability of gradual development (5–10 years) of acquired resistance to newer drugs like Bdq, Dlm or Pa by 5–10%.[26,27] These drugs can still be continued even if there is documented resistance. The regimens can be implemented but need to have backup with strong drug resistance surveillance and rapid DST for newer drugs as well. An important concern remains whether TB patients can be treated effectively with these upcoming shorter regimens in all settings particularly outside trial conditions or not requires robust evidence. Most of these investigational novel universal drug regimens in pipeline are currently undergoing through phase 2 trials and have to clear phase 3 trials for further approval. Phase 3 trials require larger sample size with thousands of patients and take atleast three to five years to commence. The Project to Accelerate New Treatments for TB (PAN-TB) collaboration among philanthropic, non-profit and private sectors has been launched with aim to fast-track development of these regimens through phase 2 clinical trials with further preparation for phase 3 trials.[28] This project is working on regimens that can be prescribed upfront with reduced requirement for drug resistance testing and also for baseline resistance to any component drug.

The National Tuberculosis Elimination Programme (NTEP) has introduced fixed dose combination (FDC) for treatment of DS-TB patients with potential advantages such as prevention of emergence of drug resistance, less probability of medication errors, better compliance, less adverse events, reduction of cost and proper maintenance of supply chain. The impact of FDC on treatment outcome still need to be defined. NTEP is also customizing treatment of DR-TB patients especially XDR and pre-XDR-TB ones with individualized regimens although it remains quite challenging to implement in settings with limited resources. These regimens require strong support of highly standardized laboratory facilities and expertise in analysis of DST results. Recently, the unprecedented COVID-19 pandemic has created a potential threat to healthcare system in managing patients with TB leading to undermining of global target of elimination of TB. The 2021 WHO global TB Report states that there is significant drop of 18% in notification of newly diagnosed TB cases worldwide as it remains only 5.8 million in 2020 as compared to 7.1 million in 2019.[29] India (41%), Indonesia (14%), the Philippines (12%) and China (8%) are the countries mainly responsible for this global fall in notification. A total of 157,903 DR-TB cases were notified with a drop of 22% in 2020 as compared to 201,997 in 2019. Global mortality due to TB among HIV-negative people is 1.3 million in 2020, up from 1.2 million in 2019 with an additional mortality of 0.22 million among HIV-positive ones as compared to 0.21 million in 2019. The global TB related mortality was double as caused by HIV. Mortality due to HIV continued to decline in comparison to that of TB from 2019 to 2020. TB was responsible for highest mortality among infectious diseases in 2019 but it was superseded by COVID-19 in 2020. The pandemic has derailed the momentum of global progress achieved by TB control programme from 2000 to 2019 and has created a setback as existing parameters in 2020 reversing to the level of 2012–2017.[29] The milestones of End TB Strategy for reduction in burden of TB by 2020 has been off tracked as these have not been achieved globally in most countries. A modelling analysis by STOP TB partnership predicted that numbers of TB including DR-TB cases will upsurge due to interruption of TB healthcare delivery services by COVID-19 between 2021 and 2025 resulting in unfavourable outcome. India has witnessed 25% drop in notification for both DS-TB and DR-TB cases within a span of one year (2019–2020).[30] The substantial reduction in TB case notification between 2019 and 2020 probably confined to imbalance between demand and supply for health services. More than 200 countries especially high TB-burden countries had to reallocate manpower, budget and other resources from TB control programmes creating acute shortage to combat COVID-19 pandemic. Factors responsible for such interruptions include reduced access to routine health care services due to imposed restrictions on movement during lockdowns, inability to provide direct services including medications to both DS as well as DR-TB patients, reluctance to avail health care facilities in view of fear of getting infected during a pandemic, under-reporting of data, re-prioritization of TB laboratories to enhance COVID-19 testing, lack of streamline infection control policies to protect vulnerable TB patients from COVID-19, shortage of ventilator beds for critically ill TB patients, lack of community participation due to social stigma associated with similarities in symptoms as well as myths created by media hype and apprehension due to COVID-19 infection even among frontline TB health care providers. In the current scenario, NTEP has to work on multi-dimensional domains in order to achieve the desired goal that still seems to be a herculean task. Therefore, it has become an utmost priority for proper allocation of budgets, attainment of target for TB control at double pace, hastening of newer TB diagnostics aiming for rapid detection and funding more on trials working on novel shorter regimens particularly pan-TB ones containing newer drugs in pipeline. Given the considerable global burden of TB accompanied with unfavourable outcome created by COVID pandemic, it is vital to evaluate these novel pan TB shorter regimens in various settings and implement under programmatic conditions as early as possible with aim to fulfil the goal of end TB strategy by 2025 in India.

Conflict of interest

The authors have none to declare.

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