TREATING DRUG-SENSITIVE TB IN INDIA: IMPLEMENTATION OF DAILY THERAPY WITH FIXED DOSE COMBINATIONS

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Tuberculosis (TB), a communicable disease that affects 9 million people worldwide, is one of the leading causes of mortality and morbidity in India. Every year in India nearly 20,00,000 people develop TB, and more than 3,00,000 people die of the disease.[1] Rates of drug-resistant TB (DR-TB) in India are particularly high, with 35,385 cases diagnosed with different forms of DR-TB, but only 20,753 people started on multidrug-resistant TB (MDR-TB) treatment in 2013.[2]

The Revised National TB Control Programme (RNTCP) has been providing treatment for TB since 1997, however, the treatment protocols being used in the national program are not consistent with current scientific evidence nor with World Health Organization (WHO) recommendations.

While RNTCP has taken some positive steps towards adopting daily FDC regimen for drug-sensitive TB (DS-TB) treatment, more concrete steps need to be taken towards implementing the recommended policy changes. This document provides an overview of the evidence base for implementing FDCs into a daily treatment regimen, as well as recommendations for steps to accelerate the implementation of India's new treatment protocols in line with WHO guidelines and best practices.

THE CASE FOR FIXED DOSE COMBINATIONS IN DAILY REGIMENS

Currently, India uses single-drug formulations for each of the drugs that are part of the recommended DS-TB treatment regimen. The drugs are administered three times a week as part of 'Directly Observed Treatment Short-course' (DOTS). Patients are required to take seven or eight anti-TB medicines on alternate days of the week. This is not only cumbersome for patients, but can also lead to adherence issues and further to development of drug resistance.[3, 4]

A Fixed Dose Combination (FDC) is a combination of two or more active drugs in a fixed dose. Evidence suggests that daily regimens of FDCs, especially in the intensive phase, are as effective as intermittent regimens with the added benefit of simplifying treatment for patients.

This evidence is also supported by World Health Organization (WHO) guidelines.[1, 5] The four-drug FDC (4-FDC), which includes the first line anti-TB drugs isoniazid, rifampicin, pyrazinamide and ethambutol, has been recommended by WHO for the intensive phase of DS-TB treatment since 1999 and is included on the WHO Model List of Essential Drugs.[6] WHO also recommends two-drug FDCs (2-FDC) for the continuation phase of DS-TB treatment.

A daily regimen of FDCs should, therefore, be preferred over an intermittent therapy with single drug formulations. Countries like Brazil and South Africa already use FDCs extensively in their treatment programmes.

The introduction of FDCs and daily therapy into India's DOTS programme has been long delayed by the RNTCP for reasons that are programme-based (e.g. logistics and cost) rather than patient-focused (e.g. simplification of treatment, reducing pill burden). Below, we challenge some of the stated reasons for this delay and provide evidence in support of the use of FDCs.

	Concerns about FDCs and daily regimens	**Relevant evidence in support of FDCs**
(i)	The cost of the daily regimen would be higher.	Relapse rates are much lower (5%) for the daily regimen when compared to the intermittent regimen (10%).[4] In India, where there is a high prevalence of resistance to isoniazid (40%), the relapse rate can be as high as 20%.[7] When taking into account the future costs of treating people who relapse and people who develop drug-resistant TB, the daily regimen is cost effective in the long run, particularly if the daily regimen is rolled out using 4-FDCs.
(ii)	FDC formulations for daily regimens may have reduced bioavailability.	The WHO pre-qualification programme has already assessed the bioavailability of the FDC formulations that are available from Indian generic producers. The generic 4-FDC formulations made by five generic manufacturers (Macleods, Lupin, Svizera, Sandoz and Strides) have been pre-qualified, with proven bioavailability.[8]
(iii)	FDCs may be more expensive than the individual drugs that the programme currently procures.	The cost of FDCs for patients requiring 3 pills per day (for people in the body weight 38-54 kg range)the range in which most of the TB patients fall) is nearly the same as the cost ofdrugs used in other DS-TB regimens (less than 10$).[5] With simpler drug procurement and distribution, FDCs can, in fact, be more cost-effective than single-drug formulations.[9]
(iv)	If a patient develops a side effect, it might be difficult to pinpoint the specific drug in the FDC that is causing the side effect.	Around 3-6% of the patients on single-drug treatment regimens experience adverse drug reactions that require treatment withdrawal. This proportion is not expected to vary significantly among FDC users.[5]
(v)	The daily regimen is burdensome to the patient and leads to poor adherence.	Treatment adherence rates are much higher with the daily regimen as it is simpler for the patient to understand, remember and adhere to. In fact, if a dose is missed, the chance of blood levels of the drug going down and contributing to resistance is lower in patients on the daily regimen than for patients on intermittent therapy.[4]

BENEFITS OF DAILY FDC THERAPY OVER INTERMITTENT THERAPY WITH SINGLE DRUGS

Better treatment

i. A reduced pill burden during the intensive phase, with only three or four 4-FDC pills required per day instead of the current 7-8 pills required for the single-drug regimen.[5]
ii. The large number of pills in the current regimen increases the chance that patients will miss taking a specific dose, which can lead to incomplete treatment, or worse, monotherapy with a single drug, increasing the risk of developing drug resistance. This risk can be mitigated with introduction of FDCs, since the essential drugs of the regimen are combined in a single pill.[8, 10]
iii. Better adherence leads to better treatment outcomes and helps avoid treatment failure and relapses. This is especially true for people with HIV-TB co-infection who are on daily antiretroviral therapy (ART). Poor adherence to either DOTS or ART can lead to drug resistance and in turn lead to poor treatment outcomes for both TB and HIV. In addition, people living with HIV who are on ART are also most in need of daily FDCs (already being implemented for ART), to reduce their over pill burden, simplify treatment literacy and improve levels of adherence.[8, 10]
iv. Adherence is also expected to improve for pediatric TB patients, as FDCs ensure that children are receiving the right doses with a minimal pill burden.[10]
v. A daily FDC regimen simplifies treatment protocols, which can enable higher treatment literacy.[10]
vi. A daily FDC regimen can be easily adapted to self-administered treatment (SAT) protocols, which are used, for example, for people located in difficult-to-reach areas of India.[10]
vii. The newest TB guidelines for paediatric treatment (WHO, 2014) recommend an increase in the dosage of DS-TB medications to make the treatment more effective.[11] New FDCs that match the doses recommended in the new paediatric guidelines will be available in 2016[12] from a few producers including Svizera[13] and Macleods.[14]

Better case management

i. FDCs simplify the drug supply chain by reducing the number of formulations that must be ordered and distributed, particularly to peripheral parts of the country.[5]
ii. FDCs can be cheaper than other regimens because program costs for procurement and distribution are lower. High-volume procurement by the government of India could further reduce costs.[5]
iii. Adoption of FDCs will make national treatment protocols much more acceptable to the private sector, which provides care to almost 50% of India's TB patients. This could lay the ground for future reforms:
    a. TB drugs could be exclusively purchased and distributed by the Ministry of Health (MoH) across both the public and private sectors, making it easier to introduce regulations that would phase out the large number of different TB drug formulations, dosages and strengths currently available from private pharmacies.
    b. The MoH could standardize the management of DS-TB across the public and private sectors, according to WHO treatment guidelines. This is the practice followed in Brazil where there is no private market for TB drugs. As a consequence, the rate of multidrug-resistant (MDR) TB in the country has remained low.

SHIFT IN POLICY, BUT DELAYS IN IMPLEMENTATION

In line with increasing evidence of the benefits of introducing FDCs as a daily regimen, India has taken the first steps towards adopting daily FDC regimen for drug-sensitive TB treatment, or DOTS. The RNTCP's recently released policy, "Standards for TB Care in India"[1], recommends implementation of a daily DOTS regimen using FDCs. In addition, the government is planning to conduct a pilot project of the daily regimen in 100 districts and is contemplating bringing in 4-FDC formulations.

While these are positive signs, more concrete steps need to be taken towards implementing the recommended policy changes. For example, while the last round of tenders for TB drugs (dated 2nd September, 2014) did not include FDC formulations[15], the government should ensure that TB drug

tenders in 2015 include FDCs. Furthermore, there has been no public announcement of the selected districts in which the pilot is being planned, or of any training or preparation being offered by RNTCP to facilitate the process. With India bearing such a huge burden of tuberculosis and drug-resistance, immediate actions need to be taken by the government to roll out daily FDCs in the DOTs program.

PRIORITY RECOMMENDATIONS

MSF recommends the following actions be implemented as quickly as possible:

- India should swiftly implement the policy changes it has made with regards to revised TB treatment regimens. The time has come to phase out intermittent therapy for drug-sensitive TB and to switch to daily FDC drug regimens for treatment of DS-TB, including the use of FDCs for children with DS-TB. The adoption of FDCs and a daily regimen should be a priority particularly for vulnerable groups, including people living with HIV and People Who Inject Drugs (PWID).

- The next procurement cycle should include the required FDCs. Quality-assured 4-FDCs should be procured to ensure bioavailability of the constituent drugs. If the tender does not specify WHO prequalification for FDCs, the bioavailability of FDCs needs to be established by an independent qualified laboratory, particularly for rifampicin. WHO has developed a model protocol for the evaluation of the bioequivalence of rifampicin in FDCs, which should be used.

- The necessary training and orientation to prepare RNTCP staff, health personnel and program managers to switch to daily DOTS with FDCs should begin immediately.

- Programs to impart treatment literacy to people living with HIV should begin immediately to ensure a smooth transition to the use of FDCs in daily regimen.

- Proper streamlining of the existing stock of single drug formulations to non-pilot districts must be implemented.

- A plan must be developed for the eventual rollout of daily DOTS using FDCs in the whole country.

Table 1
Recommended FDC pills for daily use in India

Drug	Tablet Strength[a] (in mg)
4-FDCs for Intensive Phase (IP)	
HRZE[b]	H(75) + R(150) + Z(400) + E(275)
HRZ[c] (Pediatric use)	H(30) + R(60) + Z(150)
2-FDCs for Continuation Phase (CP)	
HR[b]	H(75) + R(150) H(150) + R(300)
(Pediatric use)	H(30) + R(60)

Source: World Health Organization, Global Partnership to STOP TB.

[a] Number of pills depends on the body weight
[b] H- Isoniazid, R- Rifampicin, Z- Pyrazinamide, E- Ethambutol
[c] Based on WHO recommendations, countries with high levels of Isoniazid resistance (including India) should opt for a four drug regimen in the IP for pediatric TB too.

Table 2
Manufacturers of WHO pre-qualified FDCs

Drug	WHO- pre qualified Manufacturers
4-FDCs for Intensive Phase (IP)	
HRZE[a]	Macleods, India Lupin, India Sandoz, India Svizera, India Strides Acrolab, India
HRZE (Pediatric use)[b, c]	None
HRZ (Pediatric use)[b, d]	Macleods, India Lupin, India
2-FDCs for Continuation Phase (CP)	
HR	Macleods, India Lupin, India Sandoz, India Svizera, India Strides Acrolab, India S.C Antibiotice S.A, Romania
HR (Pediatric use)[b, d]	Macleods, India Lupin, India

Source: World Health Organization, Global Partnership to STOP TB.

[a] H- Isoniazid, R- Rifampicin, Z- Pyrazinamide, E- Ethambutol
[b] Dispersible pills
[c] The recommended regimen for India
[d] Not in the recommended dosage.

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