Injectable-Free Regimens for DRUG RESISTANT TUBERCULOSIS

What is Drug Resistant Tuberculosis?

Drug Resistant (DR) TB is a form of TB where the TB germ is resistant to one or more medicines. Resistance to medicines by the TB germ enhances it survival to the detriment of the infected persons. There are several forms (resistance patterns) of DR TB. The commonest forms are **Multidrug resistant (MDR) TB** and **Rifampicin resistant (RR)**. MDR TB refers to a form of TB where the germ is resistant to isoniazid and rifampicin. Rifampicin resistant (RR) TB refers to resistance to rifampicin only. Rifampicin and isoniazid are the most important TB drugs. There exist other forms of DR TB depending on the medicines that the TB germ is resistant to.

This form of TB mainly occurs in the following 2 ways;

1. Poor treatment of TB, hence emergence of resistant TB germs. This occurs when there is poor adherence to the treatment as advised, under dosing, wrong treatment of TB sub optimal follow up of those on TB treatment etc. This form of TB is largely man made.
2. Transmission of DR TB from a person with the resistant form of TB to others within the household, and congregate settings such as crowded schools, prisons and work places.

Drug resistant TB is transmitted the same way as drug susceptible TB (this form is not resistant to any of the TB medicines). Transmission occurs when a person with DR TB affecting their lungs coughs, sneezes, talks or sings. Drug resistant TB is more challenging to diagnose and treat, with a majority of patients requiring treatment for longer than 6 moths (as is the case for

689

Number of DR TB cases notified in Kenya in 2018.

2,300

Number of MDR/RR TB cases in 2018 that Kenya should have notified, according to WHO estimates.

485

Number of MDR/RR TB cases (70% of all DR TB cases) in 2018 that Kenya diagnosed, according to WHO estimates.

REPUBLIC OF KENYA
MINISTRY OF HEALTH

Ministry of Health
National Tuberculosis, Leprosy and Lung Disease Program

NATIONAL TUBERCULOSIS, LEPROSY AND LUNG DISEASE PROGRAM

forms of TB without resistance). Diagnosis of DR TB requires specialized tests that can detect TB and resistance of the TB germ to anti TB medicines. Testing for drug resistance is referred to as drug susceptibility testing (DST). All persons with TB should ideally have a DST.

Treatment of DR TB requires use of other TB medicines that have a high side effect profile and require longer treatment periods. This is in comparison to first line TB medicines (used for treatment of drug susceptible TB) which are taken for 6 months and are relatively safe with good tolerance in a majority of patients. These drugs are known as second line drugs. Some of the side effects due to these drugs are permanent. Due to this nature, treatment is given by health care workers on a daily basis with monthly monitoring for response to treatment and side effects. Injectable medicines that have been in use include kanamycin and Capreomycin.

DR TB burden

GLOBAL

484,000
Number of MDR/RR TB cases notified in 2018

3.4%
Percentage of new cases that had MDR/RR TB

18%
Percentage of previously treated TB cases that had MDR/RR TB

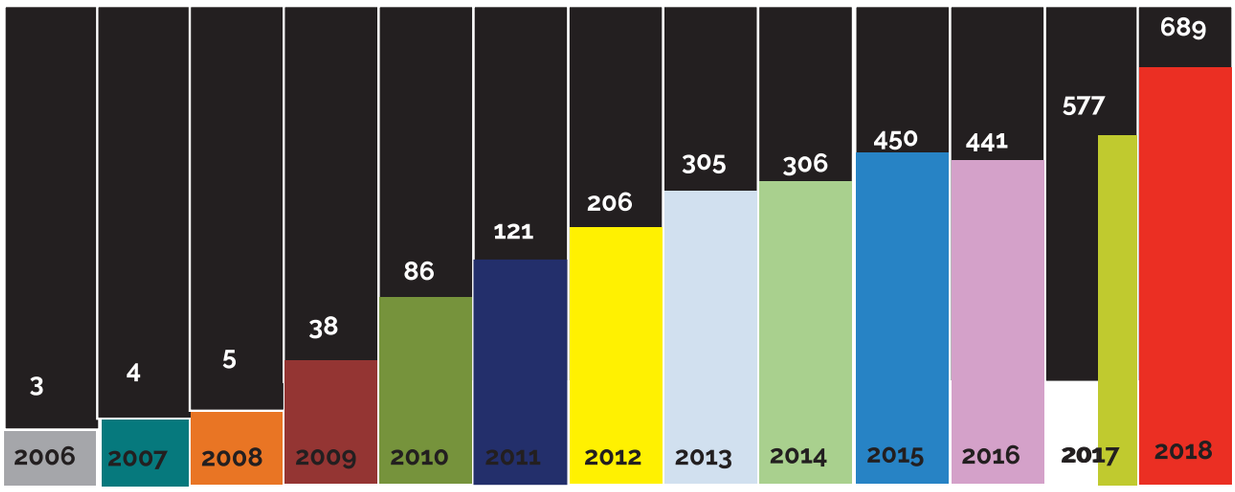
56%
Treatment Success Rate (TSR) for 2017 cohort

214,000
Deaths reported

KENYA

Kenya is a high burden country for MDR TB. A total of 689 DR TB cases were notified in 2018.

Figure 1: Number of Drug resistant TB cases notified in Kenya, 2006 to 2018



WHO estimates that Kenya should have notified 2,300 MDR/RR TB cases in 2018. However, Kenya diagnosed only 485 (70% of all DR TB cases) MDR/RR TB cases.

Figure 2: Resistance patterns for DR TB in 2018

Resistance Patterns		
MDR/RR	485	70.39%
INH Mono	157	22.79%
PDR	16	2.32%
Pre-XDR	12	1.74%
E mono	4	0.58%
Z mono	3	0.44%
XDR	1	0.15%
Missing	11	1.60%

An estimated 79% cases remain undiagnosed. High risk of severe disease with permanent complications, death and transmission within household's workplaces, communities

Proportion of DR TB patients who have never been treated for TB has increased significantly due to transmission from persons with DR TB.

For those initiated on treatment in 2017, those successfully treated were 65%.

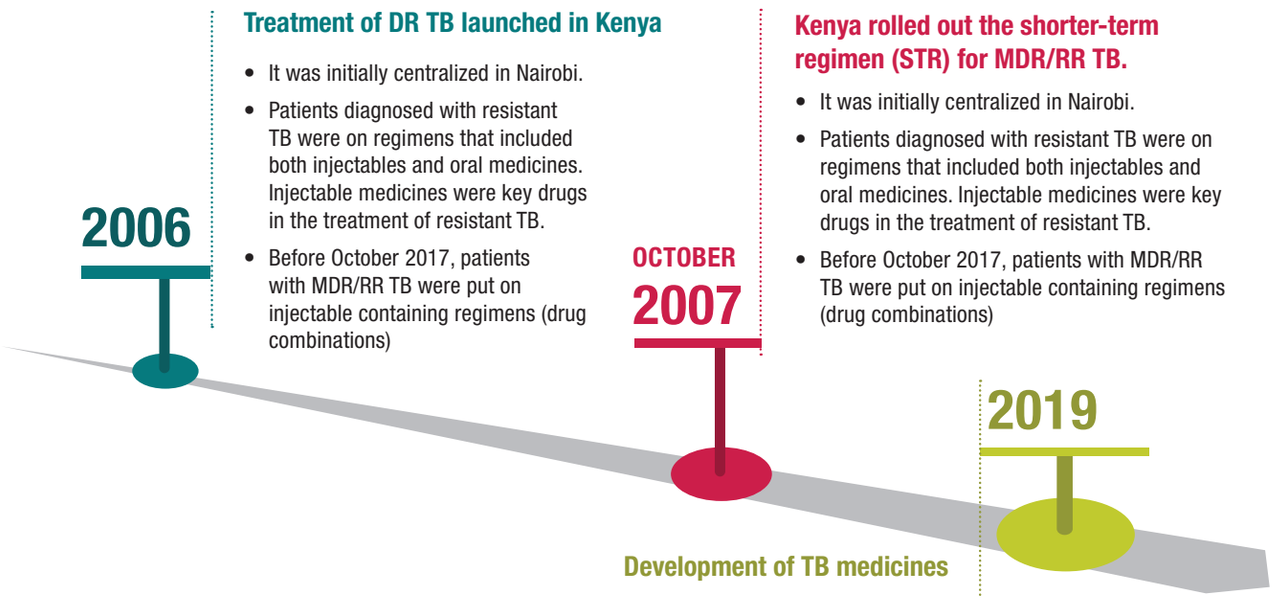
History of DR TB treatment

Treatment of DR TB in Kenya began in 2006. It was initially centralized in Nairobi before decentralization. Patients diagnosed with resistant TB were on regimens that included the use of injectables (given via injection) and other medicines taken by mouth. Injectable medicines were key drugs in the treatment of resistant TB. Before October 2017, patients with MDR/RR TB were put on injectable containing regimens (drug combinations) given for 20 months. The injectables were given for 8 months on a daily basis.

In October 2017, Kenya rolled out the shorter term regimen (STR) for MDR/RR TB. The STR was given for a period of 9 months. The injectable medicines were given for 4months.

The use these regimens were associated with a high side effect profile. Of major concern was the use of injectables. The injectables are associated with permanent hearing loss, kidney damage, and painful injections given over months. Hearing loss has devastating effects to the affected persons including depression, loss of independence, and difficulty in socialization. In children, hearing loss leads to difficulty in learning, speech and language development, low self-esteem and reduced ability to succeed.

The TB world has seen a slow development of new TB medicines to tackle the emerging problem of resistant TB. Only 3 new drugs have been developed for TB in over 50 years. Bedaquiline, Delamanid and pretomanid were licensed for use in 2012, 2013 and 2019 respectively. Kenya has been using regimens containing Bedaquiline and Delamanid since 2014. These regimens were customized and did not contain injectable medicines. They were used for patients with higher levels of resistance and those who could not use the injectable containing regimens.



Injectable-Free Regimens

The World Health Organization in 2018 recommended the use injectable-free regimens (IFR) following new evidence that indicated that the newer drugs were safer and more effective compared to the injectable medicines. The newer drugs are taken orally thus eliminating the need for injectables.

Kenya convened several meetings to discuss a way forward for the country. These meetings involved multiple stakeholders including TB experts, current and former DR TB patients, patient advocates, civil society organizations and the TB program. It was unanimously agreed to transition to the injectable free regimens on 1st January 2020. A transition plan was developed and funds sourced for this landmark change in the treatment of DR TB. The country successfully transitioned as scheduled and no new patients have been put on injectable containing regimens.

Patients initiated on older regimens before the transition date shall continue with what they were initiated on.

Rationale for change to the IFR

WHO in 2018 issued a rapid communication on key changes in the treatment of DR TB. In the new recommendations drugs used for treatment were reclassified, with the new drugs prioritized for use based on benefit versus risk, preference for oral regimens and drug tolerability. The use of newer oral drugs had been shown to have the following advantages:

1. Reduced deaths, treatment failures and recurrence of TB after treatment
2. No hearing loss
3. Drugs can be taken orally
4. Better quality of life for patients.

Injectable agents were no longer recommended due to the safety concerns, offered no benefit in reducing number of deaths and seemed to increase the risk of treatment failure and recurrence of TB after treatment.

Current treatment

Treatment of DR TB can be given at a health facility, in the community or as an inpatient (in an isolation unit). The new regimens have prioritized the use of new and repurposed drugs for maximum effectiveness and safety.

Duration of treatment

The new regimens shall be given by mouth for 6 to 20 months depending on which drugs the TB germ has resistance (resistance pattern) to.

Resistance pattern	Duration
MDR/RR TB	18 months
Pre-XDR TB	20 months
XDR TB	20 months or more
Isoniazid monoresistant TB	6 months
Poly drug resistant TB	9 months

Side effects

While the new medicines are relatively safer, they are still associated with side effects of concern. The majority of side effects of concern are known and therefore monitoring of the same has been institutionalized as a standard of care.

Main side effect associated with the new regimens are:

1. Anemia, reduced white cell and platelet count
2. Burning, tingly or painful sensation in the feet
3. Darkening of the skin
4. Nausea, vomiting, diarrhea
5. Dizziness, increased and/or irregular heart rate

Medicines for DR TB are given by health care workers who also monitor the progress of treatment and to aid in early detection of side effects.

What to do when one experience side effects

Side effects are common during the initial treatment period and tend to subside with time. All side effects experienced, including those that are not thought to be significant, should be reported to the health care worker at the health facility where they receive treatment. Reporting Significant side effects may require treatment or change of some TB medicines.

FREQUENTLY ASKED QUESTIONS
ON DRUG-RESISTANT TB

1. ***What is drug-resistant TB disease?***

Drug-resistant TB is a disease caused by mycobacterium tubercle bacilli that are resistant to anti-tuberculous medicines.

2. ***What causes drug-resistance TB?***

Resistance Occurs when micro-organisms are NOT **killed** or **inhibited** by a specific antibiotic due to the selection of naturally occurring resistant mutants through inadequate therapy.

Clinically manifests as:

- disease progression (despite treatment)
- failure to achieve negative sputum or cultures, and/or
- treatment failure.

3. ***What action should I take if I am exposed to someone with DR TB?***

One should visit the nearest health facility to report and be tested for the disease.

4. ***How long does treatment for DR TB usually last?***

Treatment duration for DR TB is longer than the conventional treatment, with a minimum duration lasting up to 1 year. Treatment may sometimes be extended up to 2 years in some cases especially if the disease is extensive.

5. ***Are there side effects related to drug-resistant TB medicines, and what should I do if I experience any?***

Patients on treatment for DR TB may experience side effects related to ant TB medicines, which range from mild to moderately severe, and should be reported or brought to the attention of the Health care provider.

6. *Are there measures in place to prevent the spread of drug-resistant TB?*

Preventive measures include:

1. Screening and early detection of the disease in all the high risk suspects. This includes adults and children/infants who are contacts of DR TB patients.
2. Avoid staying in overcrowded areas.
3. Living in well ventilated houses / households.
4. Seeking medical attention in case you have a respiratory infection
5. Avoid spitting on the ground
6. Observing proper coughing etiquette (covering your mouth with a clean handkerchief when sneezing or coughing)
7. Getting tested for HIV as it is risk factor for TB disease.
8. Good adherence and compliance to treatment to prevent selection of mutant strains.

7. *Is drug-resistant TB curable?*

Yes, with adequate treatment Drug-resistant TB is a CURABLE disease.

National Tuberculosis, Leprosy and Lung Disease Program,

Afya House Annex 1st Floor | Kenyatta National Hospital Grounds
P.O. Box 20781-00202 Nairobi, Kenya | **Cell:** 0773 977 440
Website: www.nltp.co.ke | **Facebook:** NTLDKenya | **Twitter:** @NTLDKenya