Médecins Sans Frontières Khayelitsha

DECENTRALIZED DIAGNOSIS AND TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN KHAYELITSHA, SOUTH AFRICA

OUTCOMES AND SUCCESSES OF THE DECENTRALIZED MODEL OF CARE
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MEDECINS SANS FRONTIERES

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ACKNOWLEDGEMENTS

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1. EXECUTIVE SUMMARY

Worldwide, drug-resistant tuberculosis (DR-TB) is a serious public health concern. In South Africa, tuberculosis (TB), including DR-TB, was determined to be the leading cause of death in 2012[1]. In Khayelitsha, a township on the outskirts of Cape Town with a high prevalence of HIV, there are epidemic levels of DR-TB, including multi and extensively drug resistant tuberculosis (MDR/XDR-TB). In late 2007, Médecins Sans Frontières (MSF), in collaboration with local department of health (DoH) authorities, began piloting a decentralized model of care in Khayelitsha to enable clinically stable patients with DR-TB to be diagnosed and managed by clinicians in facilities at a primary health care (PHC) level. This decentralized model of care has been described in previous MSF Khayelitsha reports in 2009[2] and 2011[3], which provide information on interim outcomes and developments of the model from late 2007 to early 2011. The aim of this report is to provide updated outcomes of the decentralized programme; to share new successes regarding DR-TB patient care and support; and to provide insight into further improvements in the model of decentralized DR-TB care.

Management and responsibility of the routine decentralized DR-TB programme was handed over to the local DoH at the end of 2013 following notable successes such as increased case detection, strengthened patient support, increased treatment initiation rates, decreased time from diagnosis to treatment initiation, improved infection control measures, and more efficacious treatment regimens. Treatment outcomes have not worsened since decentralization to primary care level, but despite the intensive patient support component of the Khayelitsha model, loss from treatment (LFT, defined as at least two months of treatment interruption without medical approval[4]) rates have remained high (~30%), suggesting that the current toxic, lengthy, and poorly efficacious standardized DR-TB regimen remains a major challenge of treatment. While proportional rates of successful treatment outcomes, defined as treatment cure or completion[4], have largely remained the same as those reported from other sub-districts and provinces, this should be considered in light of the increased proportion of prevalent DR-TB cases in the community accessing care due to decentralization of services. Over the past several years, the vast majority (>90%) of diagnosed cases in Khayelitsha have initiated DR-TB treatment, a significant achievement compared to other areas of South Africa. Thus even with treatment success rates remaining near 50%, a greater number of prevalent cases are being successfully treated than before 2007, with potential impact on the rate of ongoing DR-TB transmission in the community.

In addition to ongoing LFT, DR-TB treatment outcomes remain extremely poor for patients diagnosed with pre-XDR-TB or XDR-TB. Due to these challenges, MSF has continued its partnership with the DoH's DR-TB programme through various pilot initiatives aimed at reducing LFT and improving treatment success rates. These initiatives are integrated into the decentralized model of care, and focus on providing comprehensive counseling and patient support throughout treatment, identifying and supporting patients interrupting treatment prior to LFT, providing treatment outside of clinic based directly observed therapy (DOT), and strengthening the treatment regimens for both MDR and XDR-TB. The key successes of these initiatives are described are described herewithin.

Although decentralization of DR-TB services has been shown to increase access to rapid diagnosis and treatment for people infected with DR-TB, treatment outcomes are still adversely affected by the many challenges related to provision of adequate adherence support for patients with DR-TB, as well as access to shorter, more tolerable, and more effective DR-TB treatment regimens. The pilot initiatives and ongoing developments described in this report are aimed at addressing these challenges. A prioritization of resource commitment will be needed in South Africa and other high burden settings to ensure access to quality DR-TB care; only then will outcomes for patients suffering from DR-TB begin to change.

KEY SUCCESSES AND DEVELOPMENTS (2011-PRESENT):

- **Decentralization:** In 2014, of the 190 cases of DR-TB diagnosed, 183 (96.3%) initiated treatment. 79.0% of patients diagnosed with DR-TB in Khayelitsha were initiated on treatment by medical officers in one of eleven primary care clinics, with the remaining 6.0% starting treatment at the local district hospital, 2.0% in the local sub-acute facility (see below), and 13% at a hospital outside of Khayelitsha.
- **Cost savings of decentralization**: The MSF Khayelitsha project has contributed to costing studies which determined that a fully decentralized DR-TB model of care is 42% less costly than a centralized hospital model, making treatment more affordable.
- **Local network of DR-TB services:** DR-TB patients requiring short term inpatient care for treatment initiation or additional monitoring can access short term treatment support at a ten bed sub-acute care facility in Khayelitsha. If the patient is clinically stable but too weak to attend clinic, a community nursing service can provide daily care at the patient's home. Together with primary care clinics, this network of services provides continuity of care and allows the patient to remain with family in the community.
- **Improved patient support:** A DR-TB counseling model provides routine, standardized, patient-centered support for DR-TB patients throughout their course of treatment. Aside from counseling at the start of treatment, specific counseling sessions at pre-XDR or XDR-TB diagnosis, completion of intensive phase, treatment interruption (two weeks or less of missing treatment), or treatment failure aim to reduce LFT and increase support at specific time points during the difficult treatment journey.
- **Self-administered continuation phase treatment:** A pilot was started in 2011 to provide a weekly or monthly supply of DR-TB medication throughout the continuation phase to patients adherent to treatment during the intensive phase. Early outcomes of the pilot demonstrate that provision of a longer supply does not lead to increased LFT, and removing the requirement to attend daily DOT may improve quality of life.
- **Improved treatment regimens:** Since 2011, patients identified with extensive second-line drug resistance (pre-XDR or XDR-TB) - and later for those in whom standard MDR treatment regimens are inadequate or failing - have receive tailored treatment regimens with new or re-purposed drugs such as bedaquiline and linezolid in order to increase the chance of treatment success. In part due to use of these drugs in Khayelitsha, access to better drugs is increasing in the public sector in South Africa.
- **Advocacy:** MSF has played a pivotal role in local, national and international advocacy efforts to decrease the diagnosis and treatment gaps for patients with DR-TB; increase access to care through the decentralization of services; and improve treatment regimens with less harmful, more effective drugs.

2. INTRODUCTION

Khayelitsha is a peri-urban township of roughly 450,000 inhabitants on the outskirts of Cape Town, South Africa where nearly 200 cases of drug-resistant tuberculosis (DR-TB) are diagnosed each year. In addition, the rate of HIV co-infection is over 70%[5] - similar to that noted among drug-sensitive TB (DS-TB) cases. MSF has been working in collaboration with local stakeholders in Khayelitsha since 1999 to develop and implement models of care for tuberculosis (TB) and HIV. In late 2007, due to the rising incidence of DR-TB, MSF began piloting a decentralized model of care for DR-TB patients. This model of care enabled clinicians to diagnose and manage clinically stable patients at a primary care level throughout treatment, while the smaller proportion of clinically unstable patients were referred for admission and long term care in hospital. The decentralized model of care has been described in two previous MSF Khayelitsha reports in 2009[2] and 2011[3].

EARLY SUCCESSES OF THE DECENTRALIZED MODEL:

- Increased DR-TB case detection
- Improved patient support
- Improved rates of treatment initiation among those diagnosed
- Decreased time from diagnosis to treatment initiation
- Improved infection control measures in health care facilities
- More efficacious treatment regimens
- Improved survival of individuals diagnosed with DR-TB

Despite these successes, treatment outcomes remain relatively poor, reflecting those across the rest of South Africa and beyond[5]. DR-TB treatment regimens are expensive, toxic, and lengthy (with a recommended duration of at least 20 months), all of which impact patients' ability to maintain their usual daily activities[6]. The massive pill burden, common side effects, and relatively poor efficacy of current standard treatment regimens contribute to poor DR-TB programmatic outcomes, including high rates of loss from treatment (LFT) and stagnant treatment success rates.

Management and responsibility of the routine decentralized DR-TB programme in Khayelitsha was successfully handed over to local City Health and Western Cape Government Health in 2013. MSF has continued to work with local health authorities, through pilot initiatives aimed at improving current DR-TB treatment success rates and reducing rates of LFT, death, and treatment failure. This report provides updated outcomes from the DR-TB decentralized model of care, as well a description of further improvements to the model and advocacy efforts to disseminate results and lessons learned from the Khayelitsha experience.

3. THE BURDEN OF DR-TB IN KHAYELITSHA

The time to treatment initiation in Khayelitsha has been reduced by decentralization and further through national coverage of GeneXpert MTB/RIF (GXP), a rapid diagnostic test for rifampicin resistant TB, since December 2011. Although the use of GXP changed the specific definitions of DR-TB (**Table 1**), the generic term DR-TB will be used in this report unless specified otherwise. Patients diagnosed with isoniazid mono-resistant TB are not considered DR-TB patients for the purposes of this report as they are treated with first-line anti-TB drugs.

TABLE 1. DR-TB DEFINITIONS[4]

DR-TB CLASSIFICATION	DEFINITION
Unconfirmed rifampicin resistant tuberculosis	Patients registered for and started on second-line anti-tuberculosis medication based on rapid molecular results (GeneXpert MTB/RIF, or GXP) but lacking laboratory confirmation of resistance
Rifampicin (RIF) mono-resistant tuberculosis	Resistance to RIF only, without resistance to isoniazid (INH), confirmed by first-line drug susceptibility testing
Presumptive multi-drug resistant tuberculosis*	Patients registered for and started on second-line anti-tuberculosis medication based on high risk but lacking bacteriological confirmation
Multi-drug resistant tuberculosis (MDR-TB)	Resistance to the two main first-line anti-tuberculosis drugs (RIF and INH), confirmed by first line resistance testing
Pre-extensively drug resistant tuberculosis (pre-XDR-TB)	Resistance to INH and RIF along with either one fluoroquinolone drug or any of the injectable second-line anti-tuberculosis drugs (amikacin, kanamycin, or capreomycin), confirmed by second-line resistance testing
Extensively drug resistant tuberculosis (XDR-TB)	Resistance to INH and RIF along with a fluoroquinolone and any of the injectable second-line anti-tuberculosis drugs (amikacin, kanamycin, or capreomycin), confirmed by second-line resistance testing

*Patients with presumed DR-TB have been excluded from outcomes as there are no bacteriological results to confirm resistance

Of the 227 cases registered with DR-TB in 2013, 45.8% were new TB diagnoses (no history of previous TB/DR-TB treatment), 43.6% were cases with a previous DS-TB treatment history, and 10.6% were DR-TB retreatment cases (**Table 2**). These figures suggest that a large proportion of DR-TB cases in Khayelitsha are due to direct transmission of already drug-resistant TB strains.

TABLE 2. BURDEN OF DR-TB IN KHAYELITSHA BY REGISTRATION STATUS, 2013

DRUG-RESISTANT TB CLASS	NO PREVIOUS TB OR DR-TB TREATMENT	PREVIOUSLY TREATED DS-TB CASES	PREVIOUSLY TREATED DR-TB CASES	TOTAL
Unconfirmed rifampicin resistant tuberculosis	15 (14.0%)	9 (9.0%)	3 (13.0%)	**27 (12.0%)**
Rifampicin mono-resistant tuberculosis	16 (15.0%)	28 (28.0%)	1 (4.0%)	**45 (20.0%)**
Multi-drug resistant tuberculosis	62 (60.0%)	47 (48.0%)	10 (42.0%)	**118 (51.0%)**
Pre-extensively drug resistant tuberculosis	8 (8.0%)	13 (13.0%)	7 (29.0%)	**28 (12.0%)**
Extensively drug resistant tuberculosis	3 (3.0%)	2 (2.0%)	3 (12.0%)	**8 (3.0%)**
TOTAL	**104**	**99**	**24**	**227**

Overall 203 (89.4%) of the 227 DR-TB cases identified had culture confirmed mycobacterium TB (MTB) at baseline, and 179 (88.2%) of these had second-line drug susceptibility testing (DST) results available. Only 27 cases (11.9%) did not have the initial diagnosis of rifampicin resistant TB (RR-TB) on GXP confirmed with DST. The majority (n=25; 92.6%) of these 27 unconfirmed cases were continued on DR-TB treatment despite lack of confirmation.

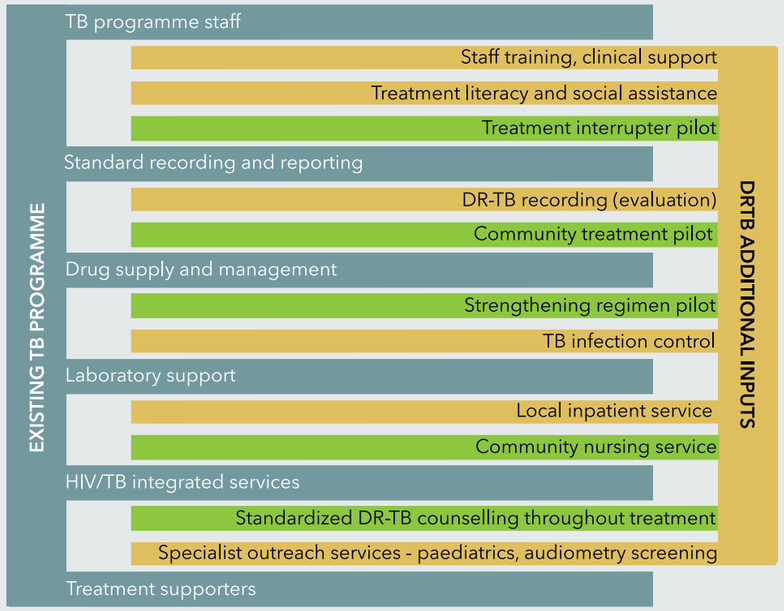
DUAL BURDEN OF HIV AND DR-TB

There is a very high rate of HIV co-infection among patients diagnosed with DR-TB in Khayelitsha[7]. Between 2008 and 2014 there were 1,400 diagnosed cases of DR-TB and 993 (70.9%) were known to be HIV infected, 366 (26.1%) were HIV uninfected, and 41 (2.9%) had an unknown HIV status.

4. DECENTRALIZED MANAGEMENT OF DR-TB IN KHAYELITSHA: OUTCOMES

The integrated, community based approach of decentralized DR-TB care implemented incrementally from 2007 included a range of additional supports to move DR-TB diagnosis and management to the primary care level (**Figure 1**). Many components of this model have since been adopted across other sub-districts within the Cape Metro in the Western Cape, and the decentralized programme in Khayelitsha influenced the development of a national policy for decentralization of DR-TB care by the National Department of Health (NDOH) in 2011[8]. There have been notable improvements in DR-TB programmatic and clinical outcomes over the years, as the model has adapted to the changing needs of patients; new or improved diagnostics, treatments, and local services became available; and additional innovations to the model of care have been piloted.

FIGURE 1. OVERVIEW OF THE PATIENT-CENTERED, DECENTRALIZED MODEL OF DR-TB CARE IN KHAYELITSHA; GREEN BARS REPRESENT PILOT PROGRAMMES IMPLEMENTED SINCE 2011



4.1 PROGRAMMATIC OUTCOMES

4.1.1 CASE DETECTION: The national roll out of GXP from 2011 meant that all individuals with presumptive TB could be screened for DR-TB, rather than just those patients considered at high risk. It was anticipated that this diagnostic tool would lead to an estimated increase in national case detection for TB and multi-drug resistant TB (MDR-TB) each year by 30%-37% and 69%-71% respectively, as well as reduce time to treatment initiation due to the shorter time between sputum collection and diagnosis[9]. In Khayelitsha, is estimated that the DR-TB case notification rate increased from 28/100,000 per year before decentralization (2005-2007) to 55/100,000 per year following decentralization (2007-2011)[5]; improved case detection was subsequently sustained by the local availability of GXP for all TB suspects by December 2011 (**Figure 2**)[10,11,12].

FIGURE 2. NUMBER OF DR-TB CASES DIAGNOSED IN KHAYELITSHA BY YEAR (2003-2014), EXCLUDING THOSE WITH A PREVIOUS HISTORY OF DR-TB

4.1.2. DR-TB TREATMENT INITIATION: The proportion of patients diagnosed with DR-TB in Khayelitsha who initiated treatment has been steadily improving since decentralization and the implementation of GXP. Early mortality has been the most common reason for not initiating treatment; encouragingly, the annual pre-treatment mortality rate has decreased over time. These improvements are likely due to improved access to diagnostic[11] and treatment services, improved health care worker knowledge and clinic capacity to provide DR-TB care, and increased awareness of the disease in the community due to intensive patient and family support and community mobilization activities.

KEY MESSAGE:

The proportion of diagnosed patients initiated on DR-TB treatment in Khayelitsha is relatively high (88.0% of all cases diagnosed from 2009 to July 2013 started DR-TB treatment[11]) compared to the reported national treatment initiation rate of 45.9% among laboratory confirmed cases of MDR-TB and XDR-TB[13].

4.1.3. TIME TO TREATMENT INITIATION: A notable success of the decentralized DR-TB programme in Khayelitsha is the dramatically reduced time from sputum collection to DR-TB treatment initiation, predominantly as a result of decentralization of services from 2008 (**Figure 3**)[11,12]. Reduction from 50 days in 2008 to 6 days in 2014 was also achieved through the introduction of rapid diagnostic tools (Hain Line Probe Assay [LPA] in 2009 and GXP in 2011)[10, 11, 12].

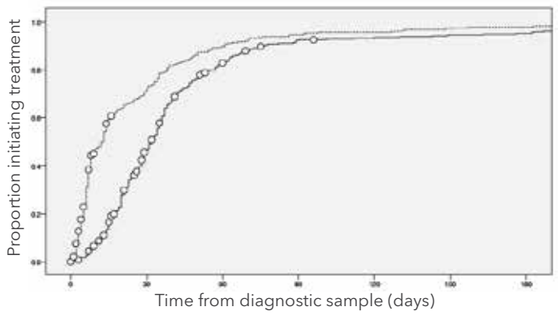
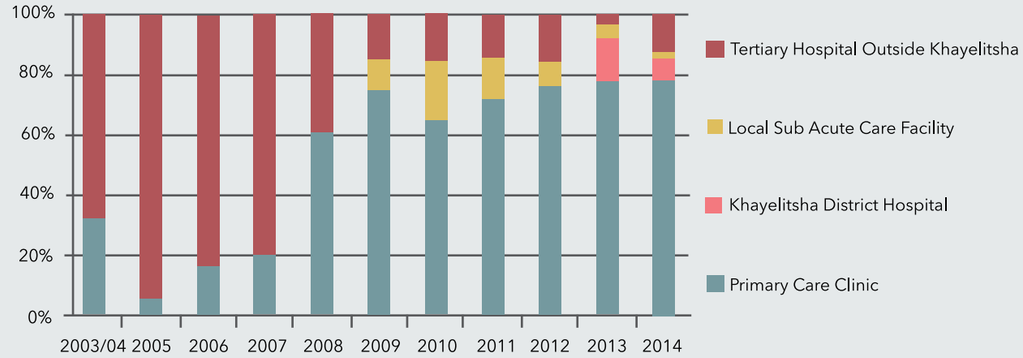


FIGURE 3. TIME TO TREATMENT INITIATION COMPARING PATIENTS DIAGNOSED IN 2010-11 WITH THOSE DIAGNOSED IN 2012-1311

4.1.4. SITE OF TREATMENT INITIATION: One of the aims of decentralization was to train and mentor primary care clinicians to initiate standardized DR-TB treatment for clinically stable patients at the primary care level, including a local sub-acute care facility (Lizo Nobanda TB Care Center). Lizo Nobanda was set up to enable clinicians to refer patients for short term inpatient treatment initiation and support while still retaining clinical responsibility for their care. **Figure 4** demonstrates the increase in the number of patients initiating treatment at primary care level from 2003 to 2014, which has relieved the demand on specialist hospital beds and reduced DR-TB programmatic costs.

FIGURE 4. SITE OF DR-TB TREATMENT INITIATION BY YEAR OF TREATMENT START



4.1.5 COST OF THE DECENTRALIZED MODEL OF CARE:

MSF Khayelitsha contributed to vital costing studies for a fully decentralized model of care. These studies determined:

A fully hospitalized model was 42% more costly than the fully decentralized model (US$13,432 vs. US$7,753 per patient). A much shorter hospital stay in the decentralized model (44–57 days), compared to 128 days of hospitalization in the hospitalized model, was the key contributor to the reduced cost of treatment[14].

When costing was undertaken based on individual patients and their outcomes in the 2009-2011 Khayelitsha cohort, the mean cost per patient treated was $7,916. Importantly, the mean cost for successful treatment was $8,359 compared with $23,006 for patients who failed treatment. This highlights that improved treatment regimens with better drugs are likely not only to improve outcomes but also enhance cost effectiveness (still be published).

4.2 CLINICAL OUTCOMES

4.2.1 TREATMENT OUTCOMES: DR-TB treatment outcomes are poor, particularly among those with XDR-TB. According to the WHO 2014 report, the global MDR-TB treatment success rate was 48% with a 25% LFT rate, while the global XDR-TB treatment success rate was 22%, with rates of 35%, 10% and 33% for death, treatment failure and LFT, respectively. In South Africa alone, the rate of treatment success among XDR-TB patients who started treatment in 2009 was only 15%, while 40% of patients died and 36% were LFT or not evaluated[15]. DR-TB treatment outcomes in Khayelitsha are defined according to WHO recommendations[4] with the exception of treatment failure, which is defined separately by the National DoH as lack of culture conversion after 6-8 months of treatment (due to the high rate of HIV co-infection in South Africa)[8]. Final treatment outcomes are assigned upon completion of the recommended duration of treatment or following premature termination of treatment due to death, treatment failure or LFT. **Table 3** shows final outcomes for new DR-TB patients (without a previous DR-TB treatment history) who initiated treatment from 2008 through 2012.

TABLE 3. FINAL TREATMENT OUTCOMES FOR NEW DR-TB PATIENTS INITIATED ON TREATMENT BY YEAR IN KHAYELITSHA, 2008-2012

	2008	2009	2010	2011	2012
OUTCOMES	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Treatment success*	53 (36.6%)	75 (43.6%)	79 (53.4%)	68 (50.4%)	86 (52.4%)
Death	25 (17.2%)	36 (20.9%)	20 (13.5%)	19 (14.1%)	24 (14.6%)
Lost from treatment	49 (33.8%)	46 (26.7%)	42 (28.4%)	46 (34.1%)	48 (29.3%)
Treatment failure	18 (12.4%)	15 (8.7%)	7 (4.7%)	2 (1.5%)	6 (3.7%)
TOTAL**	**145**	**172**	**148**	**135**	**164**

*Treatment success = 'cure' or 'treatment completion'
** 96 patients transferred out were excluded from analysis (12 in 2008, 16 in 2009, 21 in 2010, 28 in 2011, 19 in 2012)

Treatment success rates for patients initiating DR-TB treatment in Khayelitsha remain stable at around 50% each year, similar to rates reported across the rest of South Africa. Given the availability of resources and patient support activities, the stagnant outcomes may largely be due to the long duration of standardized treatment regimens that are poorly tolerated and lack efficacy. Encouragingly, treatment success rates did not deteriorate after decentralization to primary care level in 2008. In fact, increased DR-TB case detection, coupled with rapid treatment initiation in the vast majority of identified cases, has led to a larger proportion of prevalent DR-TB cases entering into care and a greater absolute number of patients achieving cure or treatment completion than before. This may contribute to reduced DR-TB transmission within the wider community, and could explain the relatively unchanged DR-TB incidence rate reported in Khayelitsha even after introduction of GXP for routine TB screening in 2011 - which was anticipated to dramatically increase DR-TB case detection.

Between 2008 and 2012 there were a total of 65 patients who had previously received treatment for DR-TB and who were reregistered for another treatment episode in Khayelitsha. While a small proportion of these patients had completed DR-TB treatment successfully in the past, the majority (47, 72.3%) had been previously discharged as LFT before returning to care to restart treatment again. Unfortunately, most of these patients again had unsuccessful treatment outcomes in subsequent treatment episodes, as seen in **Figure 5.**

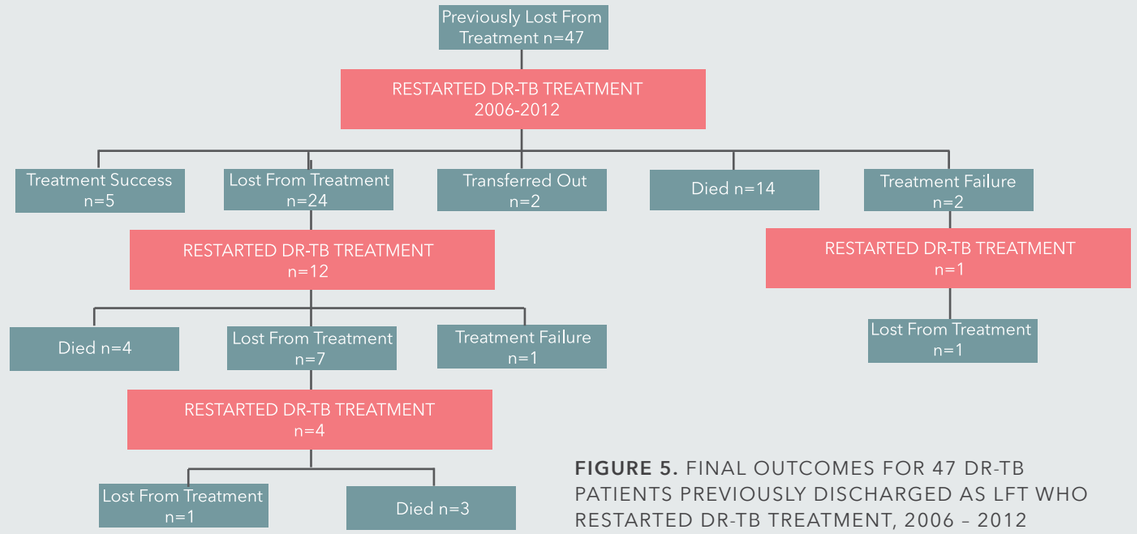
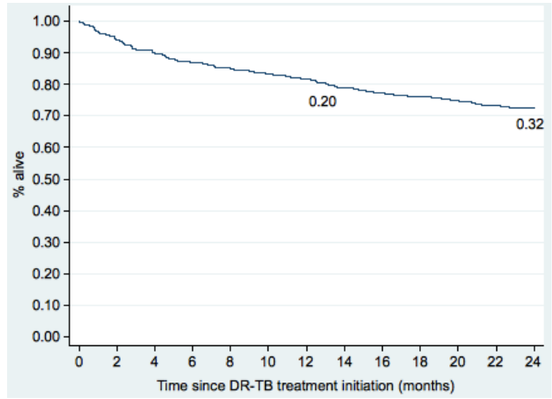


FIGURE 5. FINAL OUTCOMES FOR 47 DR-TB PATIENTS PREVIOUSLY DISCHARGED AS LFT WHO RESTARTED DR-TB TREATMENT, 2006 – 2012

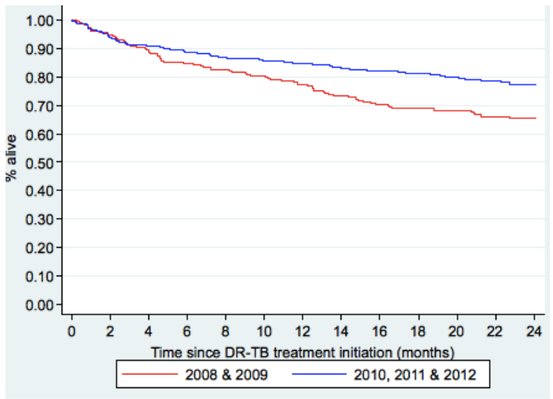
4.2.2 SURVIVAL: Among 860 patients initiated on DR-TB treatment from 2008 through 2012, 764 were assigned final outcomes (96 patients transferred out). The overall mortality rate at 24 months was 28% and was calculated as death during treatment or after a final treatment outcome (success, LFT, or treatment failure) had been assigned. **Figure 6** demonstrates 24 month survival rates.

FIGURE 6. KAPLAN-MEIER CURVES DEMONSTRATING 24 MONTH SURVIVAL OF ALL PATIENTS INITIATED ON DR-TB TREATMENT IN KHAYELITSHA FROM 2008 THROUGH 2012 (A) OVERALL, (B) YEAR OF TREATMENT INITIATION, (C) KNOWN HIV STATUS, AND (D) CONFIRMED DR-TB CLASSIFICATION

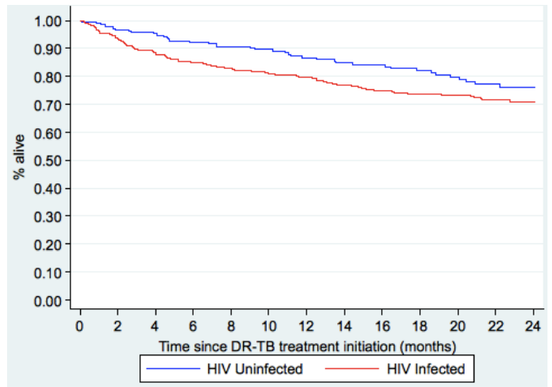
A. OVERALL SURVIVAL (24 MONTH CUMULATIVE HAZARD RATE = 0.32)



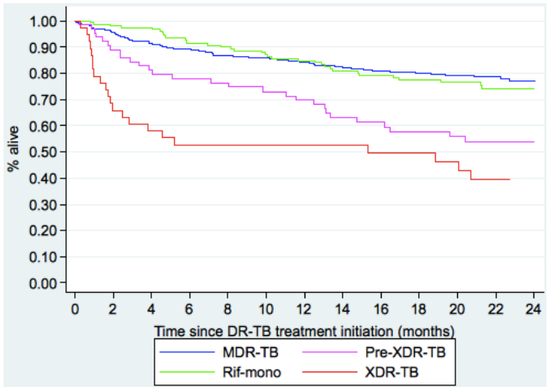
B. SURVIVAL BY YEAR OF TREATMENT INITIATION (P=0.0016)



C. SURVIVAL BY KNOWN HIV STATUS (P=0.12); 7 PATIENTS WITH UNKNOWN STATUS EXCLUDED

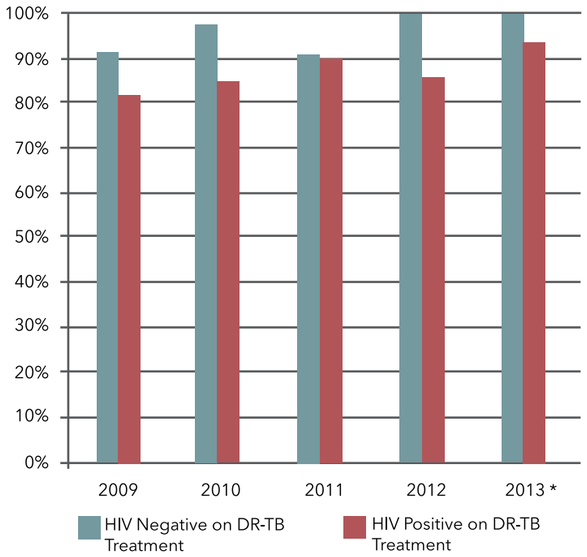


D. SURVIVAL BY DR-TB CLASSIFICATION (P<0.0001); 10 PATIENTS WITH UNCONFIRMED RR-TB EXCLUDED



4.2.3 DR-TB/HIV CO-INFECTION: Between 2009 and July 2013 a gradually increasing proportion of diagnosed DR-TB patients who were HIV co-infected initiated DR-TB treatment, as seen in **Figure 7**. This improvement was likely due to integration of HIV and DR-TB services at all primary care clinics in Khayelitsha, improved access to DR-TB care through decentralization of services, and more rapid case detection with rollout of GXP for TB screening[11].

FIGURE 7. PROPORTION OF DIAGNOSED DR-TB PATIENTS INITIATING DR-TB TREATMENT ANNUALLY BY HIV STATUS, 2009 – JULY 2013



*Only includes patients diagnosed through the end of June 2013

The association between HIV infection and DR-TB treatment outcomes in patients with known HIV status initiated on DR-TB treatment from 2008 to 2012 is shown in **Table 4**. While treatment success is comparable between the two groups, HIV infected individuals have a significantly higher risk of death during treatment compared to HIV uninfected DR-TB patients, potentially due to HIV-related comorbidities, while the LFT rate was significantly higher among HIV uninfected patients.

TABLE 4. ASSOCIATION BETWEEN HIV STATUS AND DR-TB TREATMENT OUTCOMES, 2008-2012

TREATMENT OUTCOME	HIV INFECTED (%)	HIV UNINFECTED (%)	P-VALUE
Treatment success*	259 (48.1%)	100 (45.9%)	0.59
Lost from treatment	149 (27.6%)	78 (35.8%)	0.027
Treatment failure	30 (5.6%)	18 (8.3%)	0.17
Death	101 (18.7%)	22 (10.1%)	<0.003
TOTAL	**539 (100%)**	**218 (100%)**	

* Treatment success = "cure" or "treatment completion

5. PILOT INITIATIVES TO IMPROVE DR-TB TREATMENT OUTCOMES IN KHAYELITSHA

The programmatic and treatment outcomes reported above suggest that the Khayelitsha DR-TB model of care is associated with improved case detection, increased DR-TB treatment initiation, and shortened time to treatment initiation. However, the process of determining what works in the clinical management and adherence support for patients with DR-TB is ongoing, and retention in care remains key to improving programmatic treatment outcomes. MSF has maintained its strong partnership with local and provincial Department of Health (DoH) managers and non-governmental partners to pilot innovative strategies aimed at solving remaining challenges in the successful management of DR-TB patients.

The following initiatives are described in this section:

- Standardization of DR-TB counseling
- Early identification of patients interrupting DR-TB treatment
- Community supported, self-administered treatment (SAT) in the continuation phase
- Improved treatment regimens for patients with DR-TB with additional second-line resistance
- Community nursing service

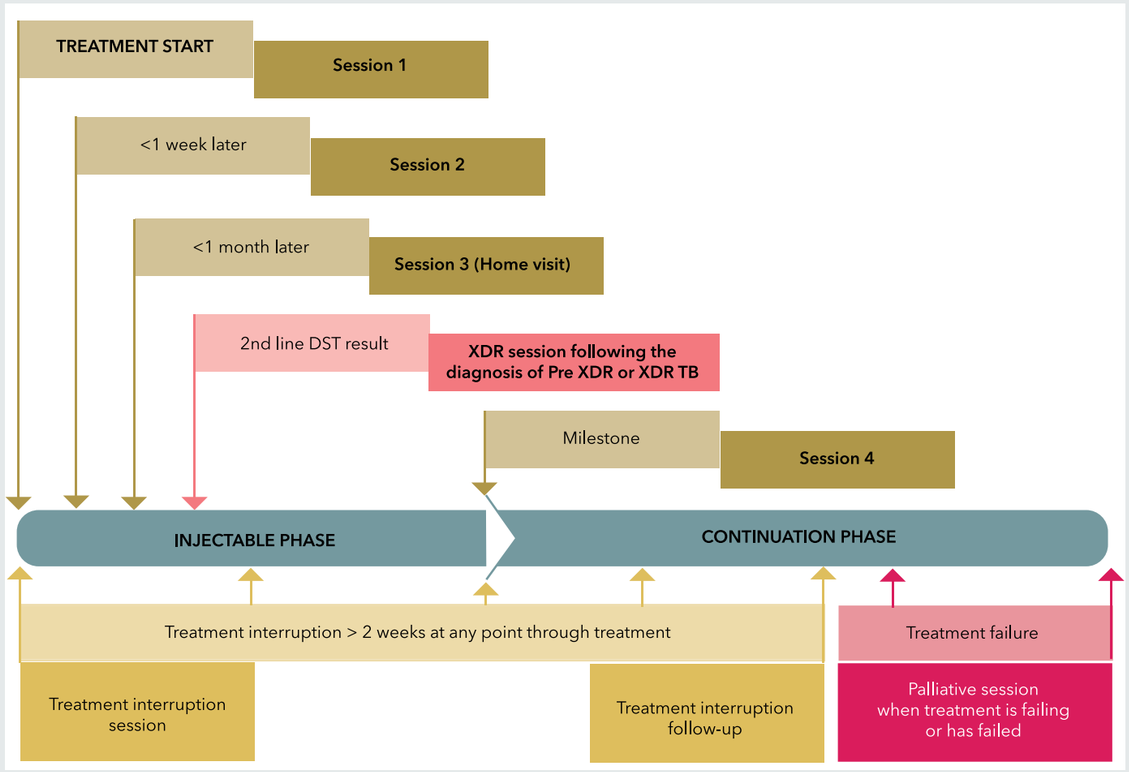
5.1 STANDARDIZATION OF DR-TB COUNSELING

KEY MESSAGE:

- DR-TB counseling is essential to support patients through their difficult treatment journey.
- Counselors benefit from standardized scripted content which covers vital treatment literacy and structured steps to determine and overcome adherence barriers.

Although the policy for the decentralized management of DR-TB was welcomed in South Africa, it lacks specific information on how to provide structured patient support and counseling despite its recommendation to provide such services. In Khayelitsha, DR-TB counseling has been standardized to provide routine psychosocial support for patients from the onset of treatment. The counseling sessions provide guidance on how to improve patients' understanding of DR-TB disease and treatment, promote adherence to difficult treatment regimens, and maintain retention in care throughout the two year course of treatment[16]. **Figure 8** provides an overview of the various counseling sessions that span across the entire DR-TB treatment journey.

FIGURE 8. OVERVIEW OF THE DR-TB COUNSELING SESSIONS



The goals of the initial sessions are treatment literacy, adherence planning, family involvement, contact tracing, and infection control advice. The additional sessions provide detailed scripts for counselors or health care workers who must address very sensitive topics with patients and their families should their treatment be challenging or unsuccessful.

Implementation of the counseling sessions includes several essential components: DR-TB counseling session guides for counselors and their supervisors; adherence plans for patients; a DR-TB flipchart that is used as an educational tool during counseling sessions; and a structured training programme for counselors. The training programme provides counselors with the tools necessary to ensure standardized quality of counseling and provides counselor supervisors with techniques to oversee and evaluate counseling sessions for quality assurance purposes[16, 17].

The DR-TB counseling model is detailed in the "Patient support interventions to improve adherence to drug resistant tuberculosis treatment counseling toolkit"[16]. The toolkit contains the specific counseling session plans with structured scripts for counselors that include simple, essential key points for patients: steps to follow to determine and overcome adherence barriers, information on treatment literacy, and problem solving approaches to encourage patients to take ownership of their treatment.

As summarized in the toolkit, "it is essential that all DR-TB clinicians, nurses and counsellors work together to ensure productive and successful support for patients with drug resistant tuberculosis; this support is as essential as the pills they take every day, and must continue throughout the long treatment journey."

5.2 EARLY IDENTIFICATION OF PATIENTS INTERRUPTING DR-TB TREATMENT

KEY MESSAGE:

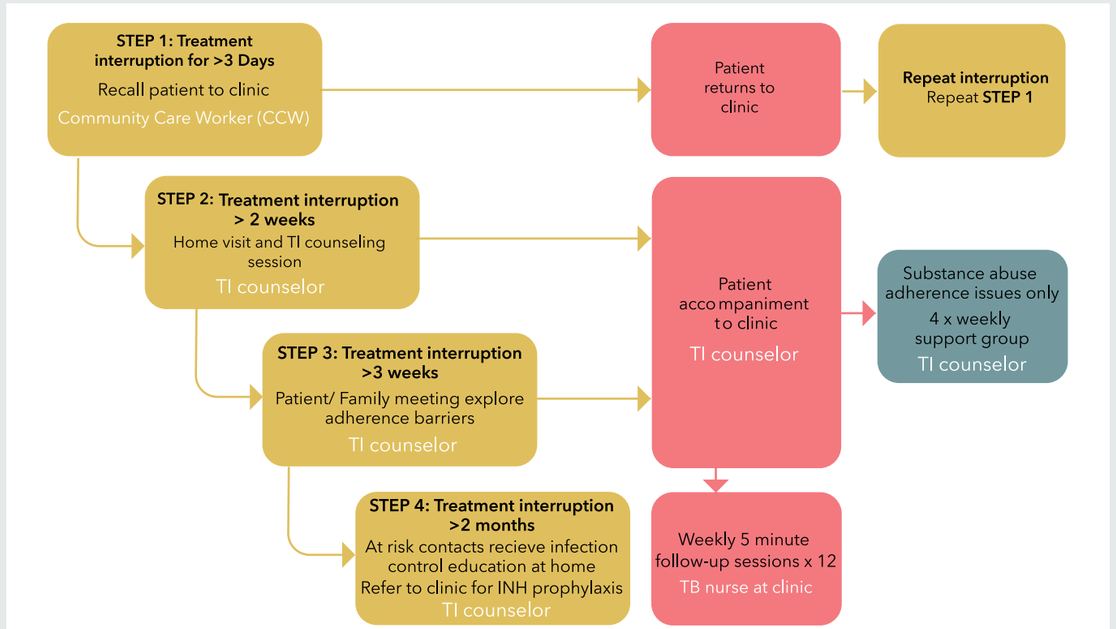
- Routine tracing of patients with treatment interruption greater than 2 weeks is not sufficient.
- A structured counselor and nurse intervention is required to ensure these vulnerable patients are guided back onto treatment.

The routine management of patients interrupting treatment includes identification of missed clinic visits for directly observed therapy (DOT) and attempts to trace the patient; at two consecutive months of treatment interruption, the patient is allocated an outcome of LFT. Risk factors associated with treatment interruption and LFT have been previously investigated in Khayelitsha[18]. Methods to promptly identify treatment interruption when it first occurs during treatment, as well as structured adherence support to identify and overcome barriers to continuing treatment, are essential in order to identify patients who are at increased risk for LFT. Since September 2013, the treatment interrupter pilot was implemented at six clinics in Khayelitsha. The objective was to intensify support for patients not returning after 3 days of missing daily DOTS. Our experience in Khayelitsha showed that the longer a patient interrupts treatment, the less likely the patient is to return to care despite attempts to trace and recall the patient.

Episodes of treatment interruption are identified after 2-3 days of missed treatment; a counselor or community care worker (CCW) contacts the patient either by telephone or home visit and the patient is encouraged to return to the clinic for care. If the patient returns to the clinic, s/he will continue with DOT and be monitored for further missed clinic visits. If the patient continues to interrupt care, two weeks after the interruption started, they are enrolled onto the treatment interrupter intervention and a counselor visits the patient at home. **Figure 9** shows the adherence support for patients enrolled in the treatment interrupter intervention. The counselor interviews the patient to uncover the determinants driving the individual patient's treatment interruption, including a screen for substance abuse or mental illness. Once these obstacles have been identified, the counselor devises a plan with the patient, including modification of the time the patient arrives at the clinic, increased family support, or transportation support. In addition, they discuss motivational factors for completing DR-TB treatment with patients.

Following the initial counseling session, patients will have follow up sessions at their clinic by the clinic TB nurse. These sessions are 5-10 minutes in duration for a twelve week period during which the TB nurse will reinforce short term, easily achievable treatment adherence goals and assess the patient's progress. Patients who are identified as abusing substances are encouraged to attend weekly support groups to assist patients with harm reduction activities and enrollment in rehabilitation support.

FIGURE 9. ADHERENCE SUPPORT FOR PATIENTS ENROLLED IN THE TREATMENT INTERRUPTER PILOT



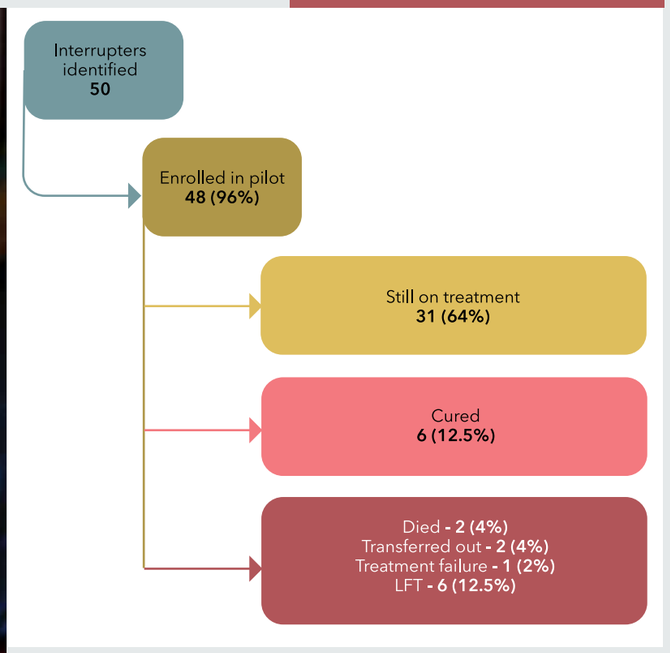
To date there have been 48 (96%) out of 50 eligible patients (1 refused, 1 was not enrolled) enrolled in the pilot. Reasons for enrollment included the patients missing more than two weeks of treatment (n=45, 94%) and chronic treatment interruption (n=6%).

Interim treatment outcomes of patients enrolled in the pilot to date are shown in **Figure 10**. The results are encouraging for retaining a challenging group of patients in care with a low resource intervention.

The determinants which led to treatment interruption included:

- Substance abuse including alcohol abuse and resultant chronic LFT
- Poor treatment insight
- Location of residence and transportation to clinic
- Financial difficulties
- Fear of loss of employment due to frequency of clinic visits
- Travel to Eastern Cape province
- Family emergency

FIGURE10. INTERIM TREATMENT OUTCOMES FOR PATIENTS ENROLLED IN THE TREATMENT INTERRUPTER PILOT, SEPTEMBER 2013 TO DECEMBER 2014



5.3 COMMUNITY SUPPORTED, SELF-ADMINISTERED TREATMENT (SAT) IN THE CONTINUATION PHASE

The aim of the community supported, self-administered treatment (SAT) pilot is to assess the feasibility of providing an alternative option to daily clinic based DOT for patients on continuation phase of DR-TB treatment in primary care clinics, in an attempt to improve retention in care. A regular (weekly or monthly) supply of DR-TB medication is offered to adherent patients for daily self-administration outside of the clinic setting, with individual counseling to identify and tackle specific barriers to adherence, as well as weekly home visits and ongoing support from a Community Care Worker (CCW). This pilot is described in **Figure 11**.

KEY MESSAGE:

- SAT allows compliant patients to take responsibility for their own DR-TB treatment while continuing their usual responsibilities and activities of daily living.

FIGURE 11. FLOW CHART TO DESCRIBE THE ACTIVITIES INVOLVED IN THE SAT PILOT PROGRAMME

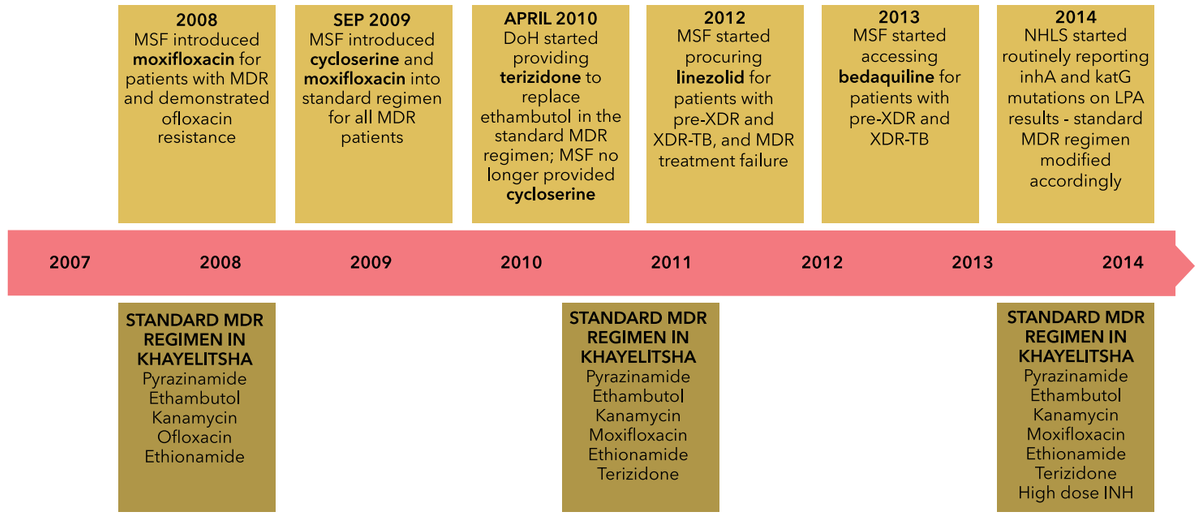
The SAT pilot was initially implemented in one primary care clinic in mid-2012 and was integrated into local TB and HIV services using existing resources. Since then, the pilot has been progressively rolled out to an additional five clinics across Khayelitsha. Between July 2012 and December 2014, a total of 161 potentially eligible DR-TB patients were identified and presented to multi-disciplinary (MDT) meetings across 6 different clinics in Khayelitsha, and 133 (83%) were approved to receive a supply of medication for SAT. The reasons that 28 patients were NOT approved for SAT were: previous adherence concerns, patient choice to remain on DOT, HIV-related issues, poor clinical condition, or possible treatment failure. Ten (8%) of the 133 patients approved for SAT were not supported by a CCW due to lack of staff; these patients were supported adequately by specific treatment partners at work or home.

Early findings from this pilot were presented at the 4th South African TB conference held in Durban in June 2014[19]. Further analysis of treatment outcomes among DR-TB patients enrolled on the pilot to receive community supported, self-administered treatment will be presented for publication in 2016.

5.4 STRENGTHENED DR-TB TREATMENT REGIMENS

Previous MSF Khayelitsha reports[2, 3] have described gradual improvements to the standard MDR-TB treatment regimen offered to patients over the years since decentralization in 2008; these modifications are summarized in **Figure 12**.

FIGURE 12. TIMELINE DEMONSTRATING INTRODUCTION OF SPECIFIC DRUGS AND MODIFICATION OF THE STANDARD MDR REGIMEN OVER TIME IN KHAYELITSHA



Since 2014, all patients diagnosed with any RR-TB in Khayelitsha initially receive a standard treatment regimen consisting of pyrazinamide, ethambutol, kanamycin, moxifloxacin, terizidone and either ethionamide or high dose isoniazid (15mg/kg), depending on the presence of inhA or KatG mutations detected on line probe assay. While this treatment may be suitable for MDR-TB, it remains inadequate for the treatment of MDR-TB with additional second-line drug resistance (pre-XDR or XDR-TB) or in cases where both INH mutations are present. In these cases, treatment regimens should be individually tailored with any potentially effective drugs as soon as second-line DST results become available, in order to provide these patients with any chance of cure. The diagnosis of second-line drug resistance (to amikacin and ofloxacin specifically) is currently still dependent on conventional culture-based DST methods. Second-line DST is carried out routinely on all diagnostic MTB specimens shown to be resistant to RIF (+/- INH), however there is considerable delay (4 – 6 weeks) before results are received in the clinic, during which time the patient continues potentially inadequate standard MDR-TB therapy.

Table 5 demonstrates the second-line resistance patterns among a total of 1037 laboratory confirmed MDR-TB cases detected in Khayelitsha from 2008 through October 2014, excluding patients with a previous history of DR-TB. On average, second-line DST results are available for more than 85% of MDR-TB cases detected, and over this period one-fifth (21.4%, n=192) of the 899 confirmed MDR-TB cases with available second-line DST results appear to have additional second-line drug resistance, with 7.6% (n=68) diagnosed as full XDR.

TABLE 5. NUMBER OF CONFIRMED MDR-TB CASES DETECTED, WITH SECOND-LINE DST RESULTS AVAILABLE AND SECOND-LINE DRUG RESISTANCE DETECTED IN KHAYELITSHA, 2008 – 2014

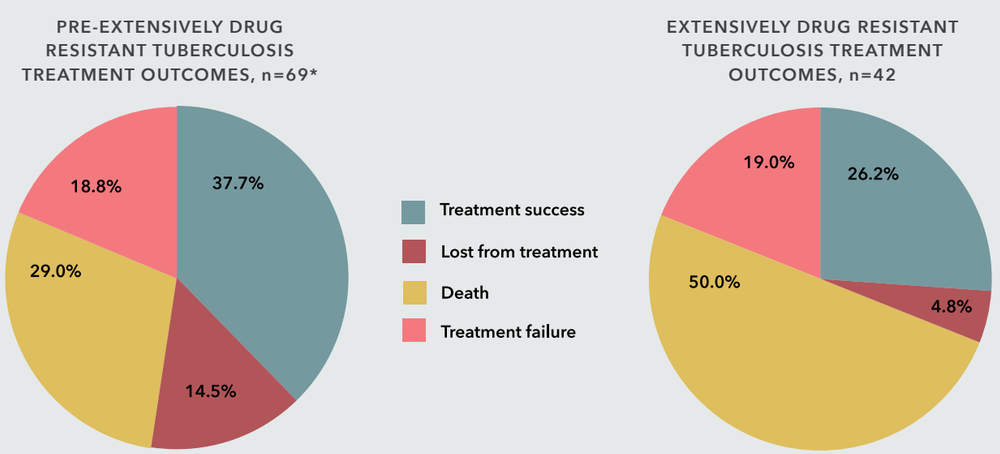
YEAR	MULTI-DRUG RESISTANT *	SECOND-LINE DST RESULTS AVAILABLE, N (% OF MDR-TB)	PRE-XDR, OFLOXACIN RESISTANCE ONLY, N (% OF SECOND-LINE AVAILABLE)	PRE-XDR, INJ** RESISTANCE ONLY, N (% OF SECOND-LINE AVAILABLE)	XDR-TB (BOTH OFLOXACIN AND INJ** RESISTANCE), N (% OF SECOND-LINE AVAILABLE)
2008	158	122 (77.2%)	9 (7.4%)	6 (4.9%)	11 (9.0%)
2009	165	149 (90.3%)	8 (5.4%)	6 (4.0%)	14 (9.4%)
2010	164	139 (84.8%)	8 (5.8%)	18 (12.9%)	10 (7.2%)
2011	150	138 (92.0%)	11 (8.0%)	10 (7.2%)	8 (5.8%)
2012	149	129 (86.6%)	8 (6.2%)	9 (7.0%)	10 (7.8%)
2013	135	118 (87.4%)	13 (11.0%)	8 (6.8%)	5 (4.2%)
2014	116	104 (89.7%)	5 (4.8%)	5 (4.8%)	10 (9.6%)
TOTAL	**1037**	**899 (86.7%)**	**62 (6.9%)**	**62 (6.9%)**	**68(7.6%)**

*Laboratory confirmed MDR-TB cases
**inj = injectable drugs, e.g. aminoglycosides or capreomycin

The high level of second line TB drug resistance is a concern given the limited treatment options available for these cases and the poor outcomes associated with current treatment. **Figure 15** indicates treatment outcomes among pre-XDR and XDR patients starting DR-TB treatment in Khayelitsha from 2007 through 2012.

In an attempt to improve treatment success rates, particularly among patients with pre-XDR and XDR-TB, MSF started the 'Strengthened Regimen' (SR) pilot in mid-2011. The initial aim of the pilot was to offer selected patients, in whom standard second-line DR-TB therapy was failing, or those with limited treatment options - individualised treatment regimens using existing drugs thought to still be effective along with any available new or repurposed drugs. Initially, MSF was only able to access repurposed drugs such as linezolid (LZD) and clofazimine to support individualised regimens for patients with second-line drug resistance. The addition of LZD was based on two systematic reviews which found that rates of treatment success with regimens containing LZD for complicated cases of MDR-TB are equal to or better than those reported for uncomplicated MDR-TB[20, 21] and better than reports of patients treated for XDR-TB[22, 23].

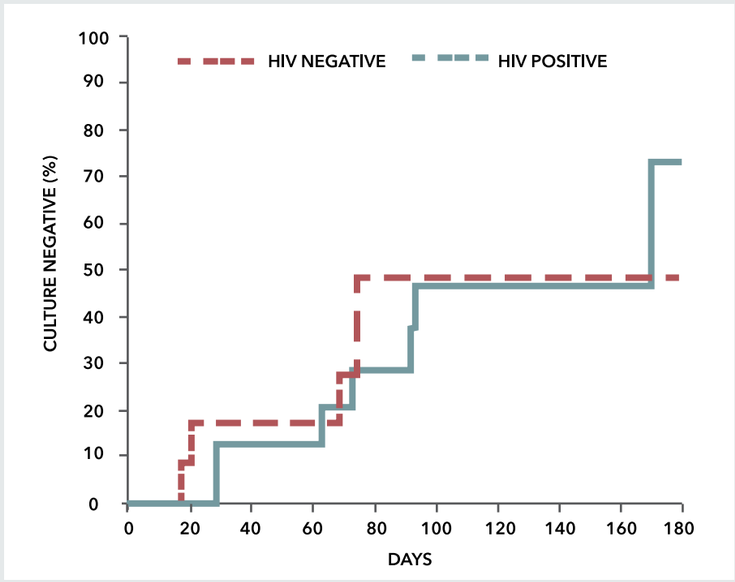
FIGURE 13. TREATMENT OUTCOMES FOR PRE-XDR-TB AND XDR-TB PATIENTS INITIATING TREATMENT IN KHAYELITSHA, 2007-2012

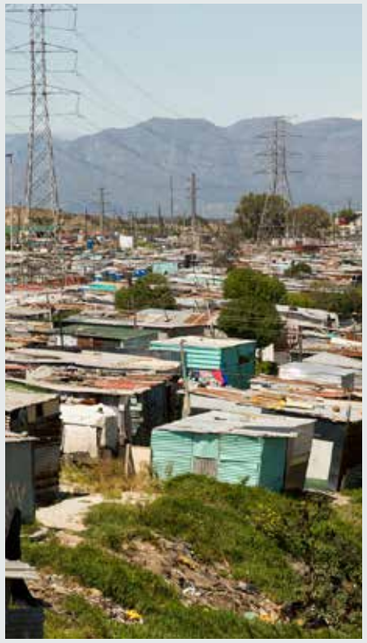


*Excludes 14 pre-XDR-TB patients who were transferred out

Initial experiences and early outcomes among HIV-infected and uninfected patients receiving LZD in a combined cohort from MSF projects in Khayelitsha and Mumbai, India, have been reported in a letter to the European Respiratory Journal (recently accepted for publication). Of the 28 patients who had positive cultures at the start of treatment with LZD, 50% had culture converted within 3 months of treatment initiation (**Figure 14**). There was no difference in culture conversion over time related to HIV infection, resistance pattern, or weight[24]. Those patients who started LZD as early as possible on initial detection of second-line drug resistance had more rapid culture conversion compared to those offered LZD after failure of DR-TB treatment, suggesting that individualized regimens containing LZD should be offered early to improve the chance of treatment success.

FIGURE 14. TIME TO CULTURE CONVERSION AMONG 28 PATIENTS CULTURE POSITIVE AT LINEZOLID START BY HIV STATUS[24]





Prior to August 2014, MSF had to procure LZD from the pharmaceutical company, Pfizer, through a local South African distributor at a cost of 767 rand (€59.6) per tablet. Following a number of appeals and attempts to access LZD more cheaply throughout 2013 and 2014, MSF finally got approval from the Medecines Control Council in August 2014 to import a much more affordable generic version of linezolid, produced by Hetero in India, for use in DR-TB patients enrolled onto the SR pilot in Khayelitsha. It then became possible to expand the eligibility criteria for patients enrolled in the SR pilot to increase access to LZD for MDR-TB patients with pre-existing contra-indications or new adverse events resulting in necessary omission of one or more drugs from the current standard MDR regimen, resulting in sub-optimal treatment regimens for MDR-TB.

At the start of the SR pilot, two new drugs, bedaquiline (BDQ) and delamanid (DEL), were in the development pipeline and showed promising results in clinical trials for the treatment of TB and DR-TB. These drugs have slowly become available through national treatment programmes in some countries and the WHO has produced recommendations for their use in treatment of DR-TB[25, 26, 27, 28]. At the end of 2012, Khayelitsha was included as one of the four initial sites in the South African Bedaquiline Clinical Access Programme (BCAP), which was set up by the National DoH to enable early access to BDQ for selected patients[29]. Janssen Pharmaceutical provided access to BDQ free of charge through their global compassionate use programme for use in the BCAP. Eligibility criteria for the BCAP were quite strict (e.g. MDR and XDR-TB treatment failure cases were excluded), and only a handful of patients were approved to receive BDQ, thus the BCAP was added as a component of the broader Strengthened Regimen pilot in Khayelitsha. Results from the national BCAP have been described in more detail elsewhere[29].

Over the years, eligibility criteria have gradually expanded for patients enrolled on the SR pilot to receive individualised regimens with new or repurposed drugs, and outcomes are now reported for patients in three categories:

- **Cases with any second-line drug resistance (pre-XDR and XDR)** – this is sub-divided into those eligible to receive a SR either with or without BDQ
- **MDR and XDR-TB treatment failure cases** – none of these

cases are eligible for BDQ
- Failure to convert positive cultures to negative after 6 months of second-line therapy
- Re-conversion of negative cultures to positive at any point in treatment

- **MDR-TB cases with inadequate treatment regimens** – these cases were not eligible for BDQ until recently, when the national BDQ clinical committee advised that these patients be offered BDQ if possible following registration of the drug by the South African Medicines Control Council (MCC) in November 2014

As of February 2015, 58 patients with pre-XDR, XDR, or any treatment failure in Khayelitsha have been offered a strengthened regimen, and 28 have received BDQ. Since expansion of eligibility criteria in 2014, 26 MDR-TB patients with inadequate regimens have been offered a modified regimen including LZD. A number of potentially eligible cases in each of the categories above have not been considered due to adherence concerns or limited availability and restricted access to new or repurposed drugs. Complete analysis of treatment outcomes among DR-TB patients enrolled on the strengthened regimen pilot will be presented for publication in 2016.

5.5 COMMUNITY NURSING SERVICE

In October 2012, the Western Cape Provincial Department of Health partnered with MSF to pilot a DR-TB Community Nursing (CN) service in Khayelitsha to cater for DR-TB patients who required closer monitoring and management while being supported in their own homes. Khayelitsha District Hospital staff, along with staff from the local sub-acute care facility, work closely with the CN service to ensure a continuum of care for DR-TB patients at sub-district level. Patients are visited at home daily by a trained nurse and counselor for a maximum of 3-4 weeks; the CN staff can monitor side effects, complete laboratory investigations, dispense medications, ensure appropriate infection control measures, and provide nursing support; the counselor ensures appropriate patient and family support. Over a 10 month period in 2013-2014, 55 patients were enrolled into the CN service: 27% for treatment initiation, 38% for comorbid illnesses, 17% for monitoring on XDR-TB regimens, 9% for adverse events, 7% for social reasons and 2% for palliative care. Forty five (82%) patients were referred from a clinic (25) or sub-acute facility (20) that would otherwise have required hospital admission. The average length of stay for all 55 patients was 14 days and only 9 (16%) patients were referred on to hospital. The CN service provides intermediate options between clinic and hospital services which reduces bed pressure, length of stay, and risk of nosocomial transmission in local inpatient facilities.

6. DR-TB ADVOCACY

MSF Khayelitsha is involved in a great deal of advocacy work related to access and best practice management of DR-TB at a provincial, national, and global level. The advocacy agenda is regularly updated as new drugs become available, changes are made to DR-TB management, and DoH policies are revised.

The current foci of advocacy efforts include:

- Decentralized and patient-centred models of care
  - Rapid implementation of comprehensive decentralized care across South Africa including diagnosis, initiation and management by primary health clinicians at primary healthcare clinics.
  - Rapid implementation of nurse-Initiated-MDR (NIMDR) treatment to support a higher proportion of patients diagnosed with MDR-TB starting treatment quickly.
  - Training and mentoring of both doctors and nurses at primary healthcare level to improve treatment initiation rates and strengthen the quality of care provided to DR-TB patients post treatment initiation.
- Prioritization of patient support strategies to improve retention in care
  - Implementation of standardized DR-TB counseling approach across South Africa for newly diagnosed DR-TB patients.
  - Nationwide early identification, tracing and tailored support of treatment interrupters.
  - Funded counsellors to carry out DR-TB counseling including facility based initiation counseling, home visit, treatment interruption and palliative care counseling sessions.
  - Training and mentoring of counselors to provide the full DR-TB counseling package.
- Improved evaluation capacity of the national DR-TB reporting database (EDR.web)
  - Patients being registered on EDR.web at diagnosis not only when commencing treatment to allow for accurate evaluation of patients being lost before treatment initiation.
  - Prioritization of improved data collection within EDR.web to ensure accurate and timely monitoring and evaluation of the DR-TB programme throughout South Africa.
- Diagnosis and treatment of paediatric DR-TB
  - Prioritization of research funding for better diagnostic tools and drug formulations for paediatric patients to improve management.

- Reliable access to new and repurposed drugs for DR-TB
  - **Clofazimine (Cfz):**
    - › Registration by Novartis with MCC to allow broader national access.
    - › Improved country forecasting and communication with Novartis to ensure uninterrupted supply.
    - › Registration and availability of generics within South Africa, once available.
  - **Linezolid (LZD):**
    - › Accessible throughout the public sector.
    - › MCC to expedite registration of other generic manufacturers to create a more competitive market and a better price.
  - **Bedaqualine (BDQ):**
    - › Accessible throughout the public sector.
    - › Should be offered in standard regimens to all patients with MDR-TB through a staged implementation approach.
  - **Delamanid (DEL):**
    - › Otsuka to pursue registration in South Africa.
    - › Otsuka to interact with NDOH to make DEL available through clinical access programme similar to BDQ.
  - **Improved DR-TB drug regimens:**
    - › Government to actively enable compassionate use access to new and repurposed drugs for DR-TB patients with limited treatment options.
    - › Government and research institutions in South Africa to provide financial and political backing for alternative innovation models that will deliver affordable complete DR-TB regimens out of the development pipeline as an end stage product.

7. CONCLUSIONS

7.1 CHALLENGES

Although there have been many successes noted in the management of DR-TB care in Khayelitsha over the years, especially with the implementation of the decentralized model of care, there are still many challenges concerning DR-TB care and treatment.

The ever increasing burden of DR-TB in South Africa is one of the biggest challenges to overcome in light of the TB epidemic. This will require greatly improved case detection and diagnosis followed by rapid treatment initiation, which can impact transmission rates within the community. Treatment efforts need to largely focus on patient centered support and retention in care in order to reduce rates of LFT. Strengthened regimens are urgently needed in order to provide patients with improved second-line treatment options and reduce rates of treatment failure; more effective regimens will also improve treatment success rates and reduce mortality rates. Regimens with less serious side effects would decrease adverse events associated with treatment and could impact LFT.

Paediatric DR-TB treatment remains a neglected part of DR-TB treatment programmes, despite the increased risk for children who are under the age of five and/or who are HIV infected of acquiring DR-TB30. There are even fewer treatment options for children with DR-TB than for adults; additionally, the diagnostic tools are limited and often not available at primary care level. In Khayelitsha, paediatric DR-TB contacts are monitored and placed on prophylaxis; however, decentralization of DR-TB paediatric services for stable children remains a distant possibility.

DR-TB CARE AND TREATMENT CHALLENGES

- Decreasing the burden of DR-TB
- Retention in care to reduce rates of LFT
- Improved regimens for DR-TB
- The management and treatment of paediatric DR-TB

7.2 THE WAY FORWARD

Since implementation of the decentralized program for DR-TB in Khayelitsha in 2008, MSF and its partners have achieved many successes in DR-TB care and management. In the coming years, MSF will continue to implement and report on new DR-TB models of care. The overarching goal of MSF's work in Khayelitsha, similar to many others working in the field of DR-TB, is to reduce the suffering for patients with drug resistant tuberculosis. It is hoped that in the near future, DR-TB patients, their families, and their health care providers will see more patients celebrating their cure from this disease; each such celebration is worth the fight.

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