THE SOUTH AFRICAN EXPERIENCE IN ROLLING OUT AN INJECTION-FREE REGIMEN

Dr. Norbert NDJEKA
MD, DHSM (Wits), Dip HIV Man (SA), MMed (Fam Med) (MED)
DIRECTOR DRUG-RESISTANT TB, TB & HIV

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INTRODUCTION (1)

- The SA NTP recently modified MDR-TB treatment regimens
- Several individuals and organizations have been asking for the rationale to such a bold decision
- We came to a conclusion that RCTs alone are not going to bring about the revolution required in order to begin to reverse the negative effect of RR-TB on human kind hence we started working closely with researchers

The SA local context in relation to the global context for DR-TB

	GLOBAL		SOUTH AFRICA	
Incidence	601,000 RR and MDR-TB*		19,000 RR and MDR-TB*	
Treatment	129,689 RR and MDR-TB initiated annually*	54% 2014 RR and MDR-TB success rate	11,192 RR and MDR-TB initiated annually*	54% 2014 RR and MDR-TB success rate
	20% of MDR-TB cases are initiated on treatment		60% of DR-TB cases are initiated on treatment	
			27% Success rate of those started on second-line treatment in 2014	

**World Health Organisation (2016)*

http://www.who.int/tb/areas-of-work/drug-resistant-tb/MDR_TB_2017.pdf?ua=1

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ESSENTIAL ELEMENTS FOR DECENTRALIZATION

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ACHIEVEMENTS (1)

- Decentralisation of MDR-TB care: **86 % of sub-districts have at least one MDR-TB** treatment initiation sites
- Establishment of a large network of **portable audiometry with extended high frequency** (156 sites)
- Deployment of 130 **ECG machines** to treatment facilities
- **Training of DR-TB physicians on ECG** reading and understanding cardiac safety

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ACHIEVEMENTS (2)

- Establishment of a **National Advisory Committee** and Provincial Committees
- **Decentralisation of care was a key factor to the successful scale up of bedaquiline** as well as other new and repurposed drugs
- Introduction of bedaquiline for all pre and XDR-TB patients regardless of HIV status

CLINICAL PRACTICE

Clinical Access to Bedaquiline Programme for the treatment of drug-resistant tuberculosis

F Conradie, G Meintjes, J Hughes, G Maartens, H Ferreira, S Siwendu, I Master, N Ndjeka

Francesca Conradie is a researcher at the School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. Graeme Meintjes is Associate Professor at the Institute of Infectious Disease and Molecular Medicine and Department of Medicine, University of Cape Town, South Africa. Jennifer Hughes is a medical officer for Médecins Sans Frontières, Khayelitsha, Cape Town, South Africa. Gary Maartens is Head of the Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa. Hannetjie Ferreira is a medical officer at the MDR/XDR TB Unit, Klerksdorp/Tshepong Complex, North West Province, South Africa. Sweetness Siwendu is a medical officer at Metro TB Hospital Complex at Brooklyn Chest Hospital, Cape Town, South Africa. Dr Iqbal Master is a clinical manager at the MDR TB Unit, King Dinuzulu Hospital Complex, Durban, South Africa. Norbert Ndjeka is Director of the Drug-Resistant TB, TB & HIV, National TB Control & Management, National Department of Health, South Africa.

Corresponding author: *F Conradie (fconradie@witshealth.co.za)*

While clinical disease caused by drug-sensitive *Mycobacterium tuberculosis* (MTB) can usually be treated successfully, clinical disease caused by drug-insensitive MTB is associated with a poorer prognosis. In December 2012, a new drug, bedaquiline, was approved by the US Food and Drug Administration. This article documents the process whereby the National Department of Health, Right to Care and Médecins Sans Frontières obtained access to this medication for South Africans who might benefit from subsequent implementation of the Clinical Access to Bedaquiline Programme.

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Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis

N. Ndjeka,* F. Conradie,†‡ K. Schnippel,†‡ J. Hughes,§ N. Bantubani,¶ H. Ferreira,# G. Maartens,**†† D. Mametja,* G. Meintjes,**†† X. Padanilam,‡‡ E. Variava,†# A. Pym,§§ Y. Pillay*

*National Department of Health, Pretoria, †Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, ‡Right to Care, Johannesburg, §Médecins sans Frontières, Khayelitsha, Cape Town, ¶TB/HIV Investigative Network of Kwazulu-Natal, Durban, #Klerksdorp Tshepong Hospital Complex, Klerksdorp, **Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, ††Department of Medicine, University of Cape Town, Cape Town, ‡‡Sizwe Tropical Disease Hospital, Johannesburg, §§Kwazulu-Natal Research Institute for TB and HIV, Durban, South Africa

SUMMARY

BACKGROUND: South Africa has a large burden of extensively drug-resistant tuberculosis (XDR-TB); only 15% of XDR-TB patients have successful outcomes.

OBJECTIVE: To describe the safety and effectiveness of bedaquiline (BDQ) in the South African BDQ Clinical Access Programme.

DESIGN: An interim cohort analysis.

RESULTS: Of the first 91 patients enrolled between March 2013 and July 2014 (with follow-up until August 2014), 54 (59%) were human immunodeficiency virus (HIV) infected. The median CD4 count was 239 cells/μl, and all patients were on antiretroviral therapy (ART) at initiation of BDQ; 33 had XDR-TB, 41 were pre-XDR-TB with fluoroquinolone resistance and 17 were pre-XDR-TB with resistance to an injectable. Of the 91 patients, 58 (64%) had completed 24 weeks of BDQ, 28 were still on BDQ, 3 were lost to follow-up, 1 had died and 1 had BDQ withdrawn following atrial fibrillation. Of the 63 patients with 6 months follow-up, 48 (76%) had either culture-converted or remained culture-negative after initiation of BDQ. QTcF was monitored monthly and exceeded 500 ms in three participants; this resolved in all three.

CONCLUSION: Interim safety and culture conversion outcomes for patients accessing BDQ in South Africa, including HIV-infected patients on ART and patients with pre-XDR- and XDR-TB, suggest that BDQ may be both efficacious and safe.

KEY WORDS: extensively drug-resistant tuberculosis; South Africa; compassionate access; adverse events

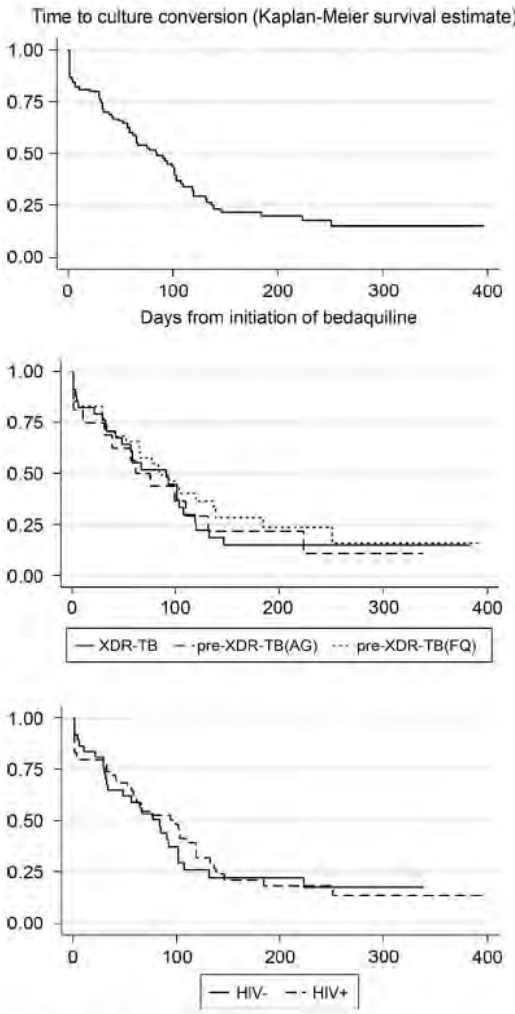

Figure 2 Time to culture conversion (Kaplan-Meier survival estimates). XDR-TB = extensively drug-resistant tuberculosis; AG = aminoglycoside; FQ = fluoroquinolone; HIV = human immunodeficiency virus.

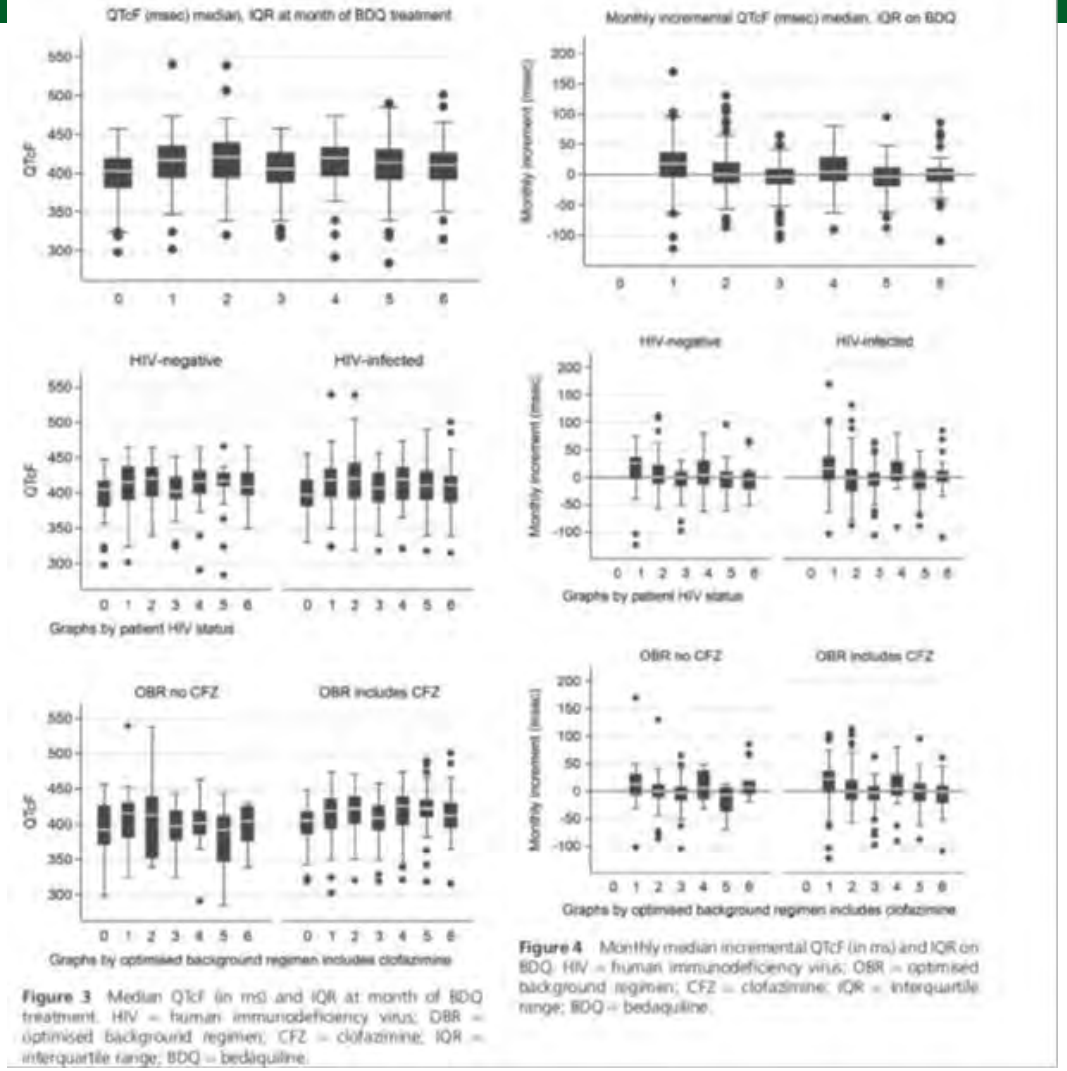

Figure 3 Median QTcF (in ms) and IQR at month of BDQ treatment. HIV = human immunodeficiency virus; OBR = optimised background regimen; CFZ = clofazimine; IQR = interquartile range; BDQ = bedaquiline.

Figure 4 Monthly median incremental QTcF (in ms) and IQR on BDQ. HIV = human immunodeficiency virus; OBR = optimised background regimen; CFZ = clofazimine; IQR = interquartile range; BDQ = bedaquiline.

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Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study

Kathryn Schnippel, Norbert Ndjeka*, Gary Maartens, Graeme Meintjes, Iqbal Master, Nazir Ismail, Jennifer Hughes, Hannetjie Ferreira, Xavier Padanilam, Rodolfo Romero, Julian te Riele, Francesca Conradie*

Summary

Background Addition of bedaquiline to treatment for multidrug-resistant tuberculosis was associated with an increased risk of death in a phase 2b clinical trial, resulting in caution from WHO. Following a compassionate access programme and local regulatory approval, the South African National Tuberculosis Programme began widespread use of bedaquiline in March, 2015, especially among patients with extensively drug resistant tuberculosis for whom no other effective treatment options were available. We aimed to compare mortality in patients on standard regimens with that of patients on regimens including bedaquiline.

Methods In this retrospective cohort study, we analysed patient data from the South African rifampicin-resistant tuberculosis case register (EDRweb), and identified additional mortality using the national vital statistics register. We excluded patients who started treatment before July 1, 2014, or after March 31, 2016; patients younger than 15 years or older than 75 years; patients without documented rifampicin resistance, and patients with pre-extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with further resistance to a second-line injectable or fluoroquinolone). We compared all-cause mortality between patients who received bedaquiline in treatment regimens and those who did not. Patients who did not receive bedaquiline had kanamycin or capreomycin and moxifloxacin as core medicines in their regimen. We estimated hazard ratios for mortality separately for multidrug-resistant or rifampicin-resistant tuberculosis and extensively drug-resistant tuberculosis and adjusted using propensity score quintile strata for the potential confounders of sex, age, HIV and antiretroviral therapy status, history of prior tuberculosis, valid identification number, and year and province of treatment.

Findings 24 014 tuberculosis cases were registered in the EDRweb between July 1, 2014, and March 31, 2016. Of these, 19 617 patients initiated treatment and met our analysis eligibility criteria. A bedaquiline-containing regimen was given to 743 (4·0%) of 18 542 patients with multidrug-resistant or rifampicin-resistant tuberculosis and 273 (25·4%) of 1075 patients with extensively drug-resistant tuberculosis. Among 1016 patients who received bedaquiline, 128 deaths (12·6%) were reported, and there were 4612 deaths (24·8%) among 18 601 patients on the standard regimens. Bedaquiline was associated with a reduction in the risk of all-cause mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis (hazard ratio [HR] 0·35, 95% CI 0·28–0·46) and extensively drug-resistant tuberculosis (0·26, 0·18–0·38) compared with standard regimens.

Interpretation Our retrospective cohort analysis of routinely reported data in the context of high HIV and extensively drug-resistant tuberculosis prevalence showed that bedaquiline-based treatment regimens were associated with a large reduction in mortality in patients with drug-resistant tuberculosis, compared with the standard regimen.

Research in context

Evidence before this study

In 2014, only 54% of patients initiating treatment for multidrug-resistant or rifampicin-resistant tuberculosis had successful outcomes. In South Africa, about 20% of such patients die during the standard long-course 18–24 months of second-line treatment. Patients with multidrug-resistant or rifampicin-resistant tuberculosis who are co-infected with HIV and those with resistance to second-line injectable drugs and fluoroquinolones, including those with extensively drug-resistant tuberculosis, are 2–3 times more likely to die compared with people who are HIV-negative and those without second-line injectible or fluoroquinolone resistance. Results from phase 2b clinical trials of bedaquiline (TMC207-C208) showed significant benefit in terms of the proportion of patients who culture converted, time to culture conversion, and proportion of patients achieving cure when bedaquiline was added to the standard multidrug-resistant tuberculosis treatment. However, more deaths occurred in the bedaquiline plus background regimen arm compared with the standard multidrug-resistant tuberculosis treatment arm (10 of 79 patients *vs* 2 of 81 patients). The deaths in the bedaquiline arm were not attributed to bedaquiline by the investigators, but the significant increased risk of mortality led to a black box warning attached to the 2012 US Food and Drug Administration bedaquiline approval. WHO bedaquiline guidelines (2013 and 2017 revision) were also cautious, recommending bedaquiline only when an effective treatment regimen could not be constructed with other WHO-recommended drugs.

Added value of this study

Since March 2015, bedaquiline has been used within the South African National Tuberculosis Programme for all patients for whom an effective regimen could not be constructed (ie, those with second-line drug resistance or toxicity to the standard regimen). In our study, we analysed the South African drug-resistant tuberculosis case register from July 1, 2014, and March 31, 2016, and 18 601 patients who initiated drug-resistant tuberculosis regimens without bedaquiline were compared to 1016 patients who initiated bedaquiline-containing regimens. We used propensity score strata to adjust for potential confounders. In this cohort, bedaquiline was associated with a 3 times reduction in the adjusted hazard ratio for mortality. Results from our large cohort treated under the state tuberculosis programme and in a population with high prevalence of HIV and second-line drug resistance provided evidence that bedaquiline is associated with reduced rather than increased mortality in drug-resistant tuberculosis.

Implications of all the available evidence

Initial recommendations for bedaquiline weighed the benefits of the increased rate of culture conversion and cure against the unexplained higher risk of mortality observed in randomised controlled trials. However, given the evidence from our study that patients receiving bedaquiline are not at increased mortality risk, this risk evaluation could change. As bedaquiline was associated with increased culture conversion and cure in clinical trials and with decreased mortality in our large observational cohort, clinicians and policy makers should re-evaluate the practice and guidance of only using bedaquiline in drug-resistant tuberculosis treatment when there are no other options.

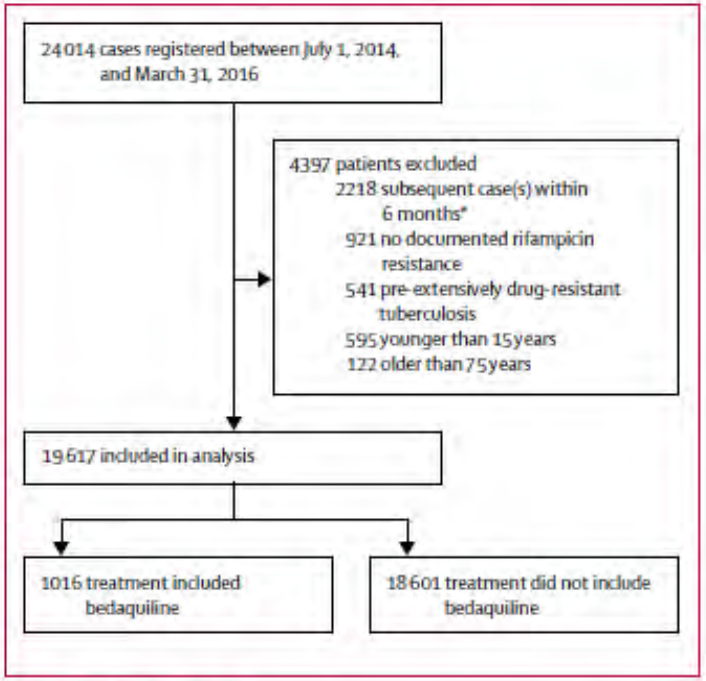

Figure 1: Study flow chart

*For time-to-event analyses in which two or more cases had identical South African ID numbers, surname, date of birth, and sex, starting from the 6 months before the analysis period, the initial case record was maintained and subsequent case records excluded.

	Bedaquiline (n=1016)	No bedaquiline (n=18 601)	Total (n=19 617)	p value*
Age, years	38 (30-45)	36 (29-44)	36 (29-44)	<0·0001
Sex	–	–	–	0·015
Male	605 (59·5%)	10 354 (55·7%)	10 959 (55·9%)	–
Female	411 (40·5%)	8247 (44·3%)	8658 (44·1%)	–
Resistance category	–	–	–	<0·0001
Multidrug-resistant or rifampicin-resistant	743 (73·1%)	17 799 (95·7%)	18 542 (94·5%)	–
Extensively drug-resistant	273 (26·9%)	802 (4·3%)	1075 (5·5%)	–
Previous tuberculosis treatment	–	–	–	<0·0001
No reported previous tuberculosis	447 (44·0%)	7168 (38·5%)	7615 (38·8%)	–
History of first-line treatment	392 (38·6%)	10 419 (56·0%)	10 811 (55·1%)	–
History of second-line treatment	177 (17·4%)	1014 (5·5%)	1191 (6·1%)	–
HIV and ART	–	–	–	<0·0001
HIV-negative	295 (29·0%)	4811 (25·9%)	5106 (26·0%)	–
HIV-positive, on ART	701 (69·0%)	11 729 (63·1%)	12 430 (63·4%)	–
HIV-positive, no or unknown ART	8 (0·8%)	1455 (7·8%)	1463 (7·5%)	–
HIV status unknown	12 (1·2%)	606 (3·3%)	618 (3·2%)	–
Vital statistics	–	–	–	<0·0001
South African ID number for matching	773 (76·1%)	12 562 (67·5%)	13 335 (68·0%)	–
No ID number	243 (23·9%)	6039 (32·5%)	6282 (32·0%)	–
Treatment year	–	–	–	<0·0001
Initiated in 2014	59 (4·9%)	5778 (31·1%)	5828 (29·7%)	–
2015	730 (71·9%)	10 462 (56·2%)	11 192 (57·1%)	–
2016	236 (23·2%)	2361 (12·7%)	2597 (13·2%)	–
Province	–	–	–	<0·0001
Eastern Cape	173 (17·0%)	3320 (17·8%)	3493 (17·8%)	–
Free State	11 (1·1%)	830 (4·5%)	841 (4·3%)	–
Gauteng	163 (16·0%)	2221 (11·9%)	2384 (12·2%)	–
KwaZulu-Natal	335 (33·0%)	5571 (30·0%)	5906 (30·1%)	–
Limpopo	7 (0·7%)	692 (3·7%)	699 (3·6%)	–
Mpumalanga	69 (6·8%)	1614 (8·7%)	1683 (8·6%)	–
North West	24 (2·4%)	1109 (6·0%)	1133 (5·8%)	–
Northern Cape	72 (7·1%)	684 (3·7%)	756 (3·9%)	–
Western Cape	162 (15·9%)	2560 (13·8%)	2722 (13·9%)	–

Data are median (IQR) or n (%). ART=antiretroviral therapy. ID=identity. *Calculated using Pearson's χ^2 difference of proportions for counts and Wilcoxon rank-sum (Mann-Whitney) for continuous variables.

Table 1: Cohort characteristics

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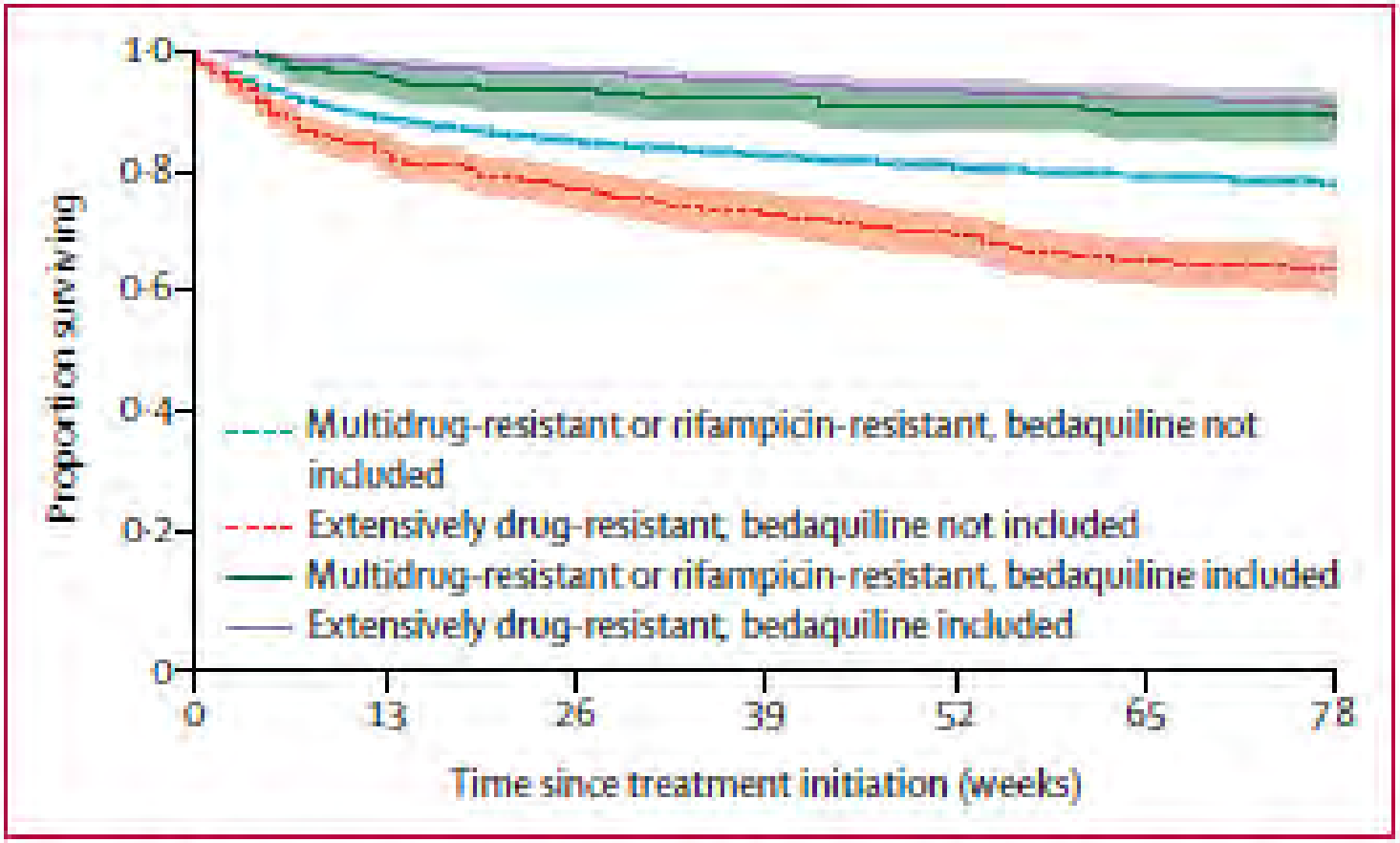
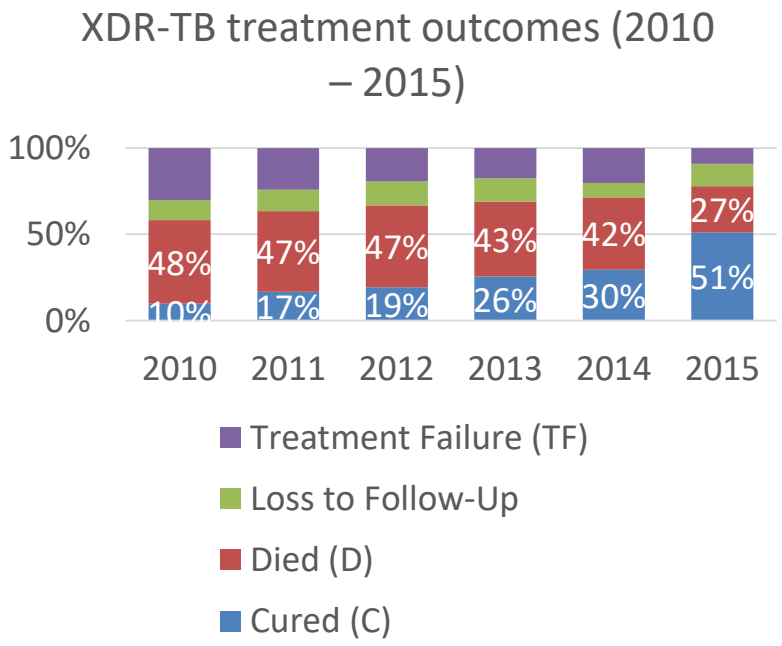


Figure 4: Kaplan-Meier survival curves, by regimen inclusive of bedaquiline and drug resistance

The shaded area indicates 95% CI.

XDR-TB treatment outcomes (2010 – 2015)



Year	Cured (C)	Died (D)	Loss to Follow-Up	Treatment Failure (TF)	Grand Total
2010	48	238	57	148	491
2011	100	278	74	144	596
2012	115	282	82	115	594
2013	149	252	79	102	582
2014	188	267	53	129	637
2015	424	221	108	76	829
Total	1024	1538	453	714	3729

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2015 XDR-TB Patients Outcome

Number started on treatment case registration	**832**

Treatment outcomes	BDQ/ BDQ & Injectables containing regimen	%	Km containing regimen	%	Cm containing regimen	%	Am containing regimen	%	No injectables/BDQ containing regimen	%	No regimen captured	%
Started on treatment	497	**60%**	109	**13%**	58	**7%**	57	**7%**	94	**11%**	17	**2%**
Treatment Success	**321**	**65%**	**27**	**25%**	**14**	**24%**	**15**	**26%**	**28**	**30%**	**5**	**29%**
Died	**83**	**17%**	**35**	**32%**	**21**	**36%**	**25**	**44%**	**47**	**50%**	**11**	**65%**
Loss to follow up	56	**11%**	16	**15%**	13	**22%**	10	**18%**	8	**9%**	1	**6%**
Treatment failure	24	**5%**	25	**23%**	7	**12%**	6	**11%**	11	**12%**	0	**0%**
Not evaluated	13	**3%**	6	**6%**	3	**5%**	1	**2%**	0	**0%**	0	**0%**

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LABORATORY TESTING

- GeneXpert/Xpert Ultra done for all presumptive TB individuals
- All Rifampicin-Resistant TB (RR-TB) patients are started on treatment
- A sample taken for LPA 1st and 2nd line from all RR-TB
- Phenotypic DST done for patients who do not respond to their treatment

CONVENTIONAL SHORT MDR-TB REGIMEN

	4 MONTHS	9 MONTHS
High dose Isoniazid		Continue for **another 2 months** if smears still positive at 4/12
Ethionamide		
Kanamycin		
Moxifloxacin		
Clofazimine		
Pyrazinamide		
Ethambutol		

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SA MODIFIED SHORT MDR-TB REGIMEN

	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
Linezolid		Can be stopped earlier if LPA 2nd line results received		
High dose Isoniazid			Continue for another 2 months if smears still positive at 4/12	
Ethionamide			Drop if inhA mutation present	
Bedaquiline				Continue in some
Levofloxacin/ Moxifloxacin				
Clofazimine				
Pyrazinamide				
Ethambutol				

CONCLUSION (1)

- Management of DR-TB is complex and requires careful assessment and monitoring of patients
- Effective assessment of patients during 1st visit (pre-treatment), 2 weeks, 4 weeks after treatment initiation and subsequent monthly visits are very important

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CONCLUSION (2)

- Laboratory results are critical, they need to be checked at each and every visit
- The clinician needs to adjust treatment regimen and clearly indicate whether the patients stays on short regimen or moves to a long regimen
- Record and reporting is essential

CONCLUSION (3)

- There is a great need for operational research within NTPs around the world
- Collaboration with the World Health Organization, local researchers, NGOs and civil society is key to improvement of patient's experience

ACKNOWLEDGEMENTS

- The World Health Organization for guiding us through our decentralization process that has culminated into massive success
- Provincial TB managers and facilities staff
- National and provincial advisory committees

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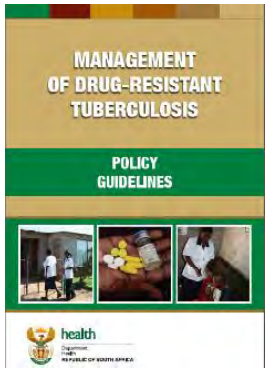
THANK YOU FOR YOUR ATTENTION



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