



Southern African HIV Clinicians Society 3rd Biennial Conference

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Sandton Convention Centre
Johannesburg

**Our Issues, Our Drugs,
Our Patients**

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MDR TB

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Southern African HIV Clinicians
Society



2016

Disclosures

- Research support from the TB Alliance and Janssen



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TB Burden in RSA

- TB patients initiated on treatment decreasing: 406,082 to 332,170 (2009 and 2013)
- Treatment success rate: 80,9 % for 2012 DS cohort

~4 YEAR LAG BETWEEN SCALE UP OF ART AND DECLINE IN MTB INCIDENCE

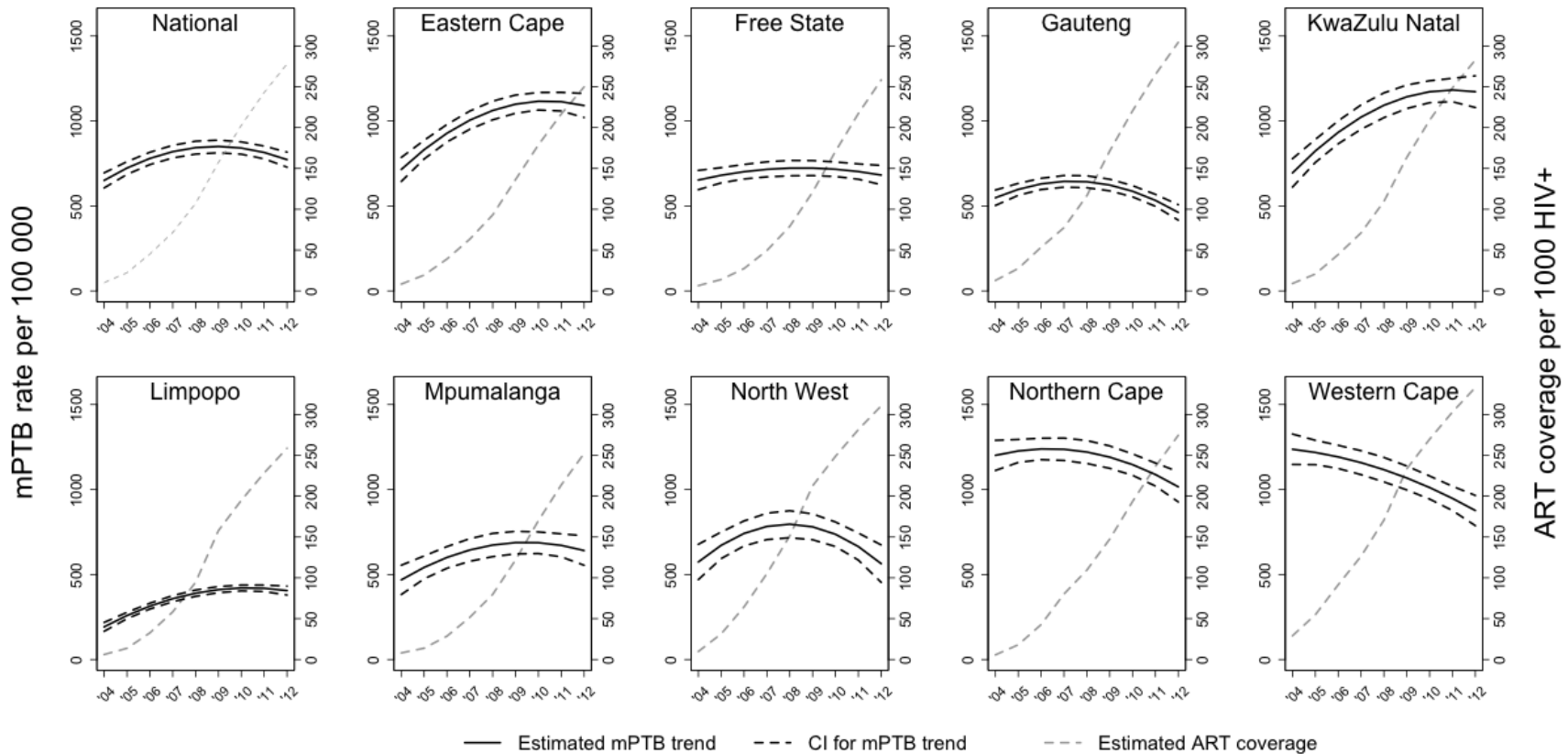


Figure 1: Incidence of microbiologically-confirmed pulmonary tuberculosis (per 100,000 population) and antiretroviral treatment coverage rates in HIV-infected individuals nationally in South Africa nationally and provincially from 2004 to 2012

The solid black line represents the estimated trend in PTB incidence per 100,000 population over the study period and the dotted black line the corresponding 95% confidence interval. The overlaid dotted grey line is the ART coverage per 1000 HIV positive individuals based on data from the ASSA 2008 model.

Nanoo A, Izu A, Ismail, NA, Ihekweazu C, Abubakar I, Mamejta D, Madhi SAM. 2015. Nationwide and regional decline in incidence of microbiologically-confirmed pulmonary tuberculosis in South Africa: a time series analysis from 2004 to 2012. *The Lancet Infectious Diseases*, In press

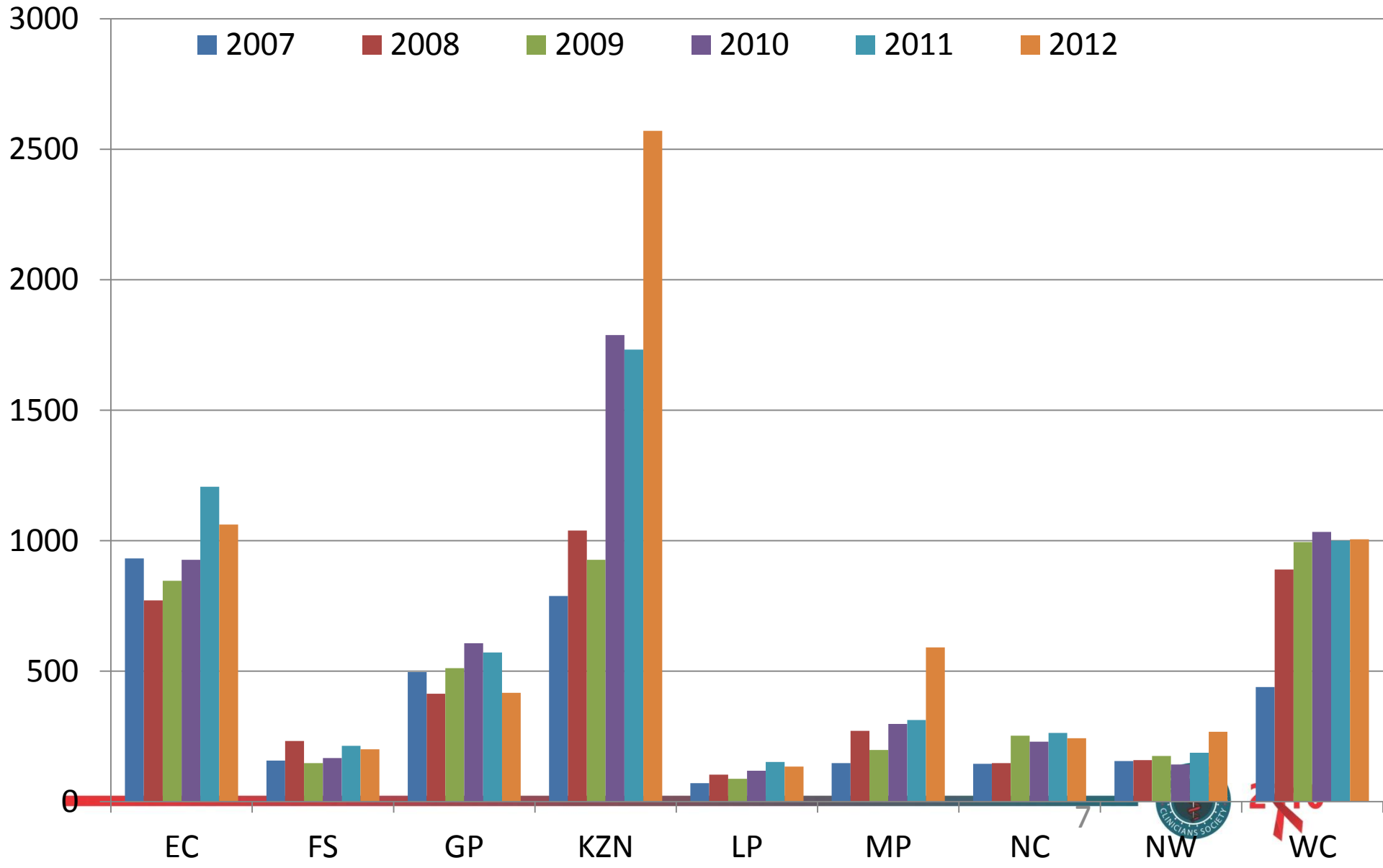


But the bad news

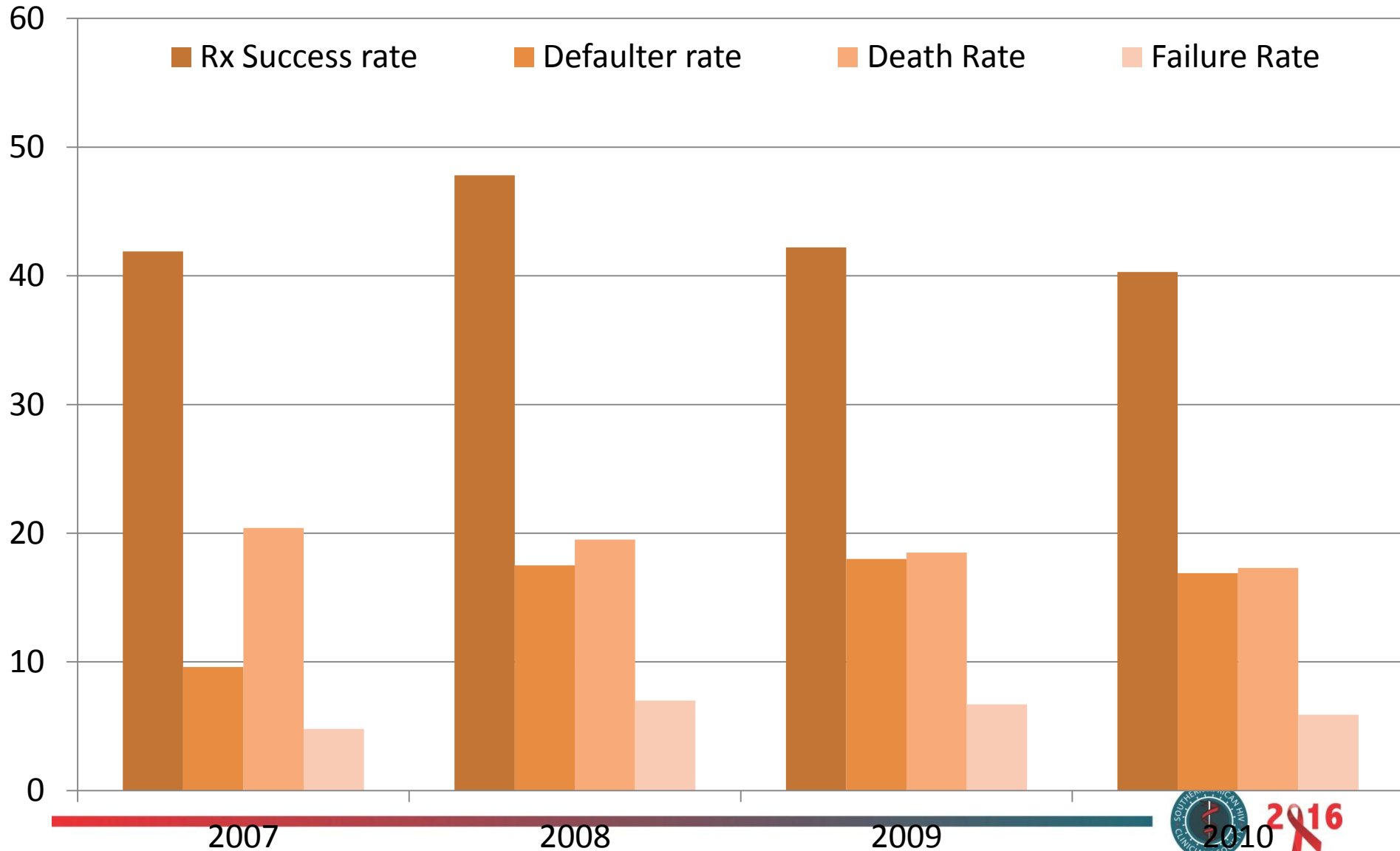
- MDR-TB numbers initiated on treatment doubled between 2010 and 2013 (5,313 to 10,719)
- MDR-TB treatment success rate of 49 % (2012 cohort > 8,000)
- XDR-TB treatment success rate is 20 %

MDR-TB Cases Started on Treatment

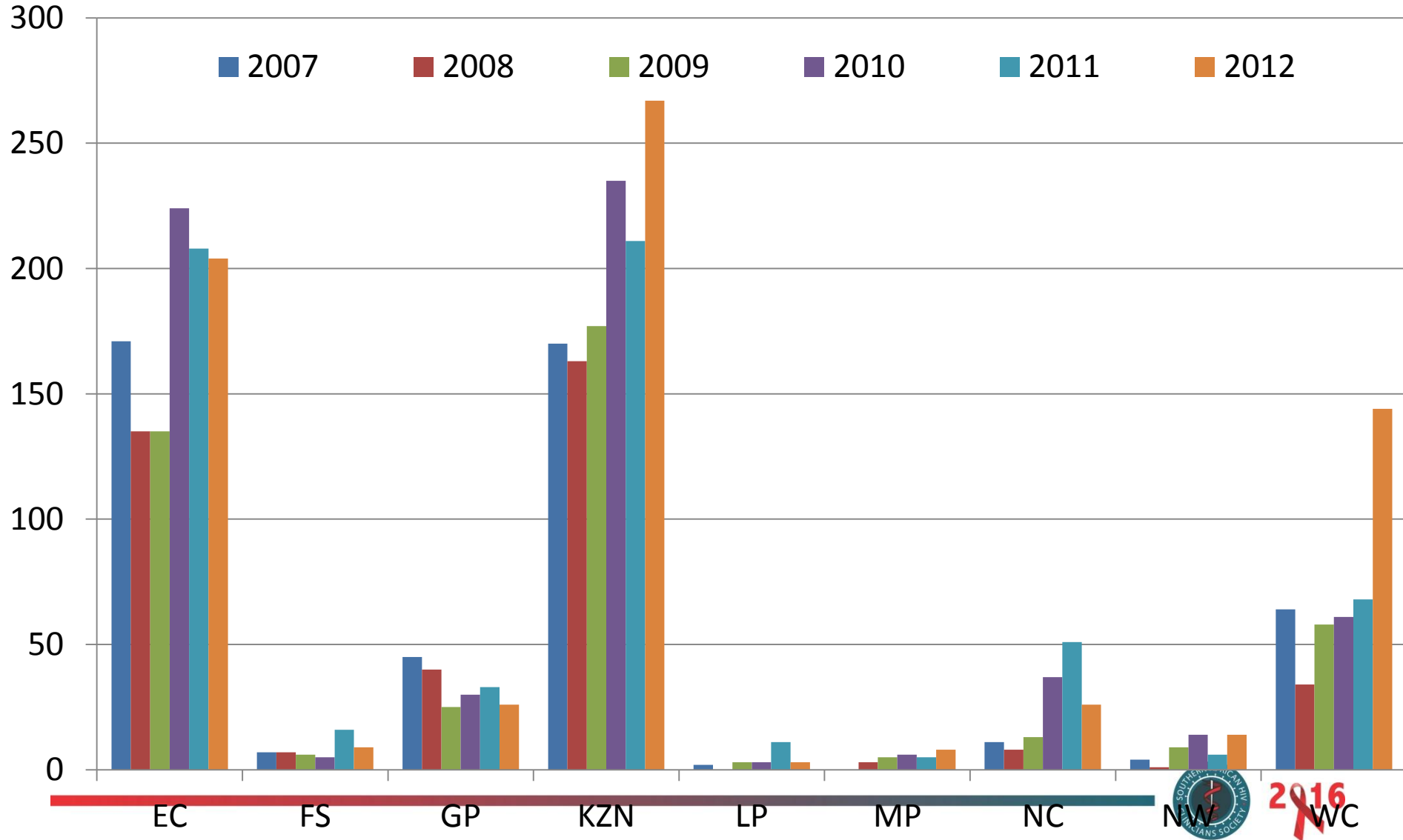
Extent of the problem in South Africa



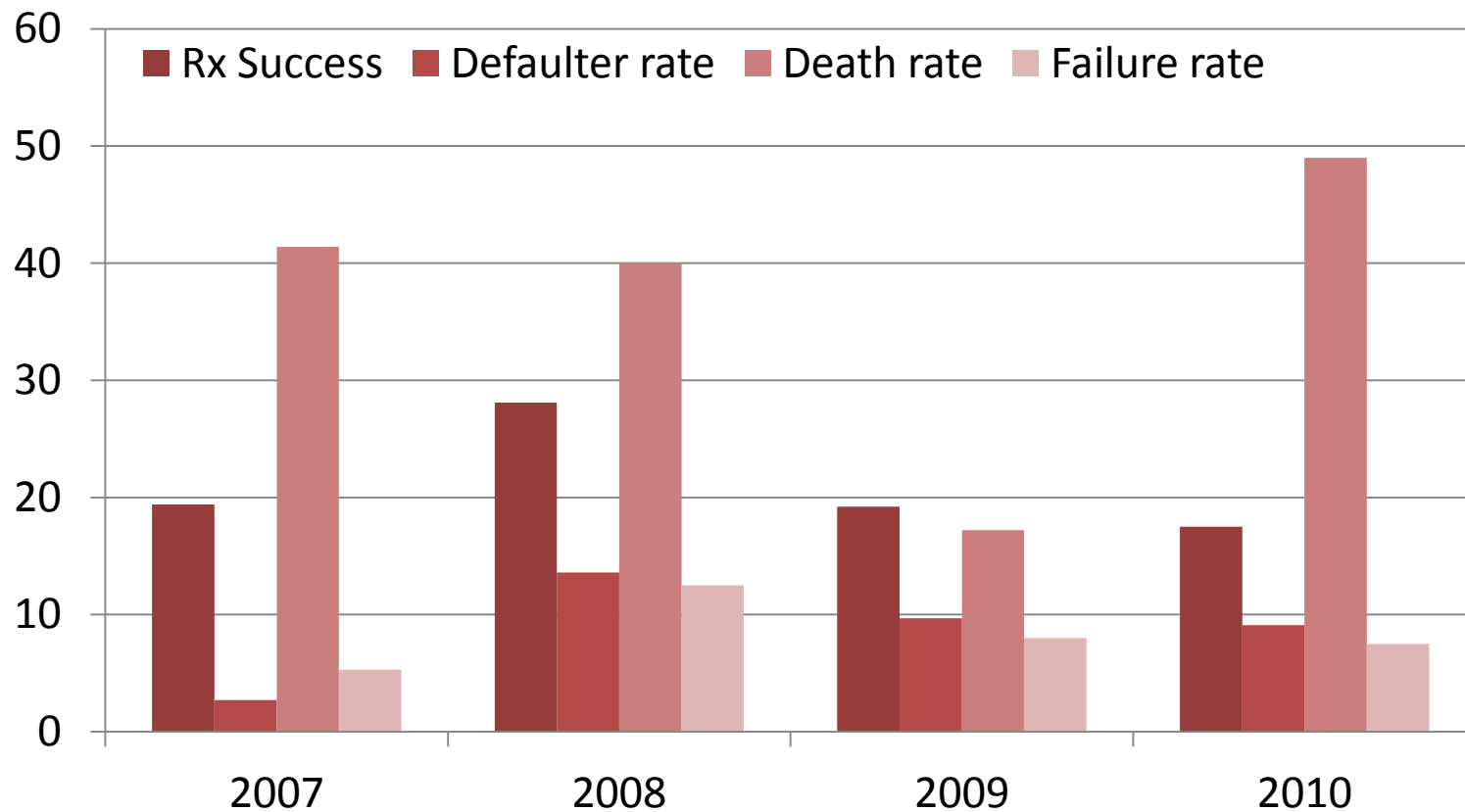
MDR-TB Treatment Outcomes (24 months)



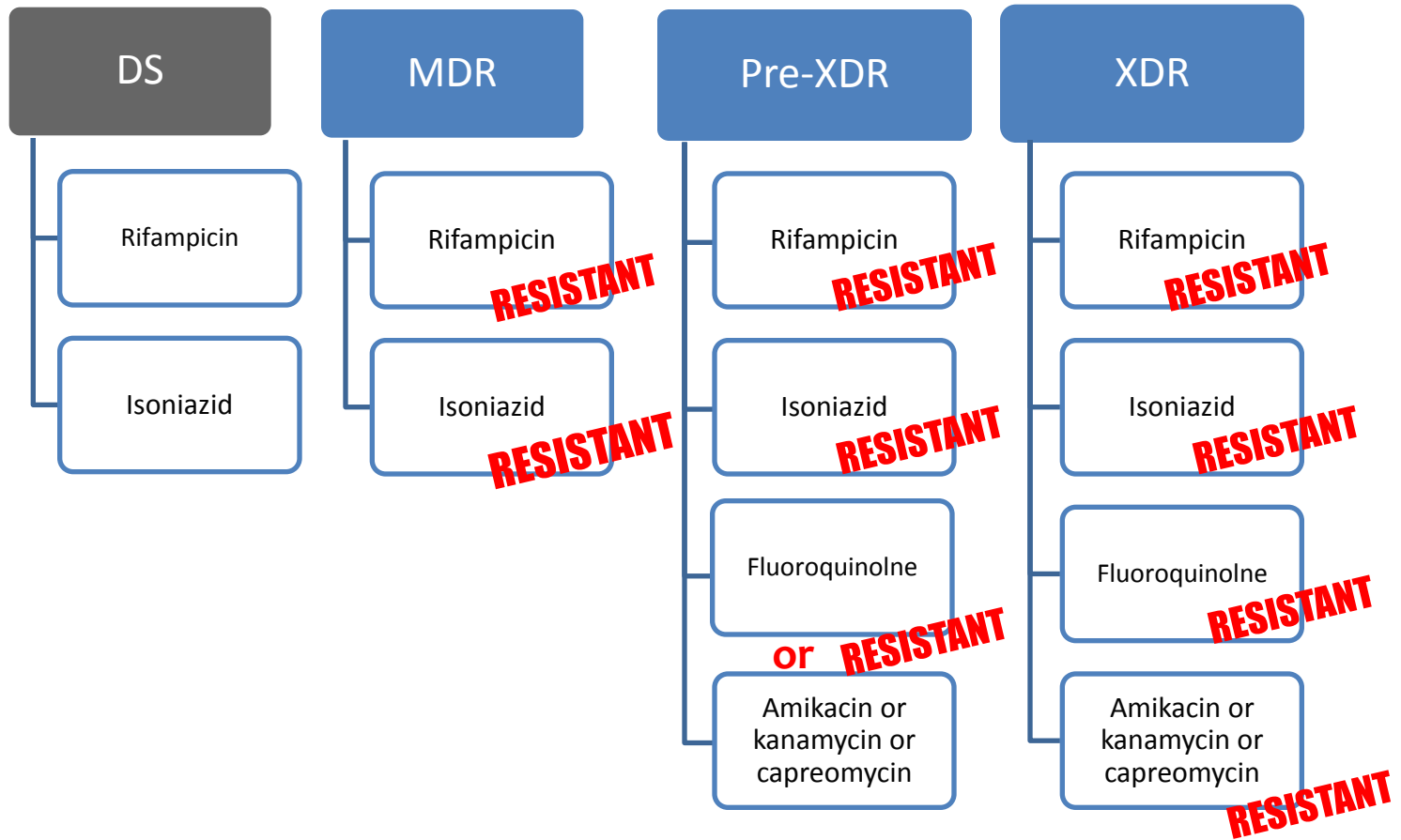
XDR- TB Started on treatment



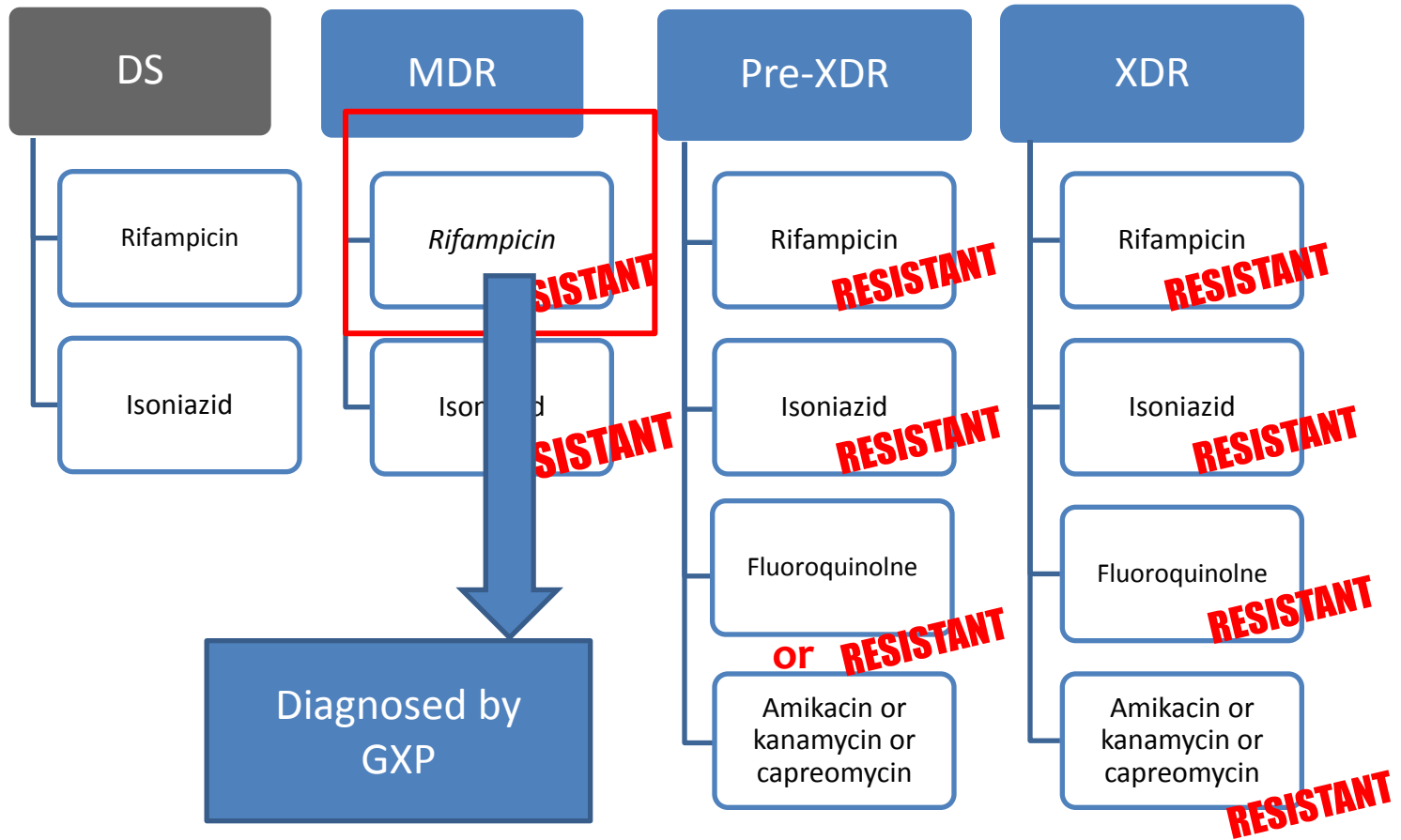
XDR-TB Treatment Outcomes (24 months)



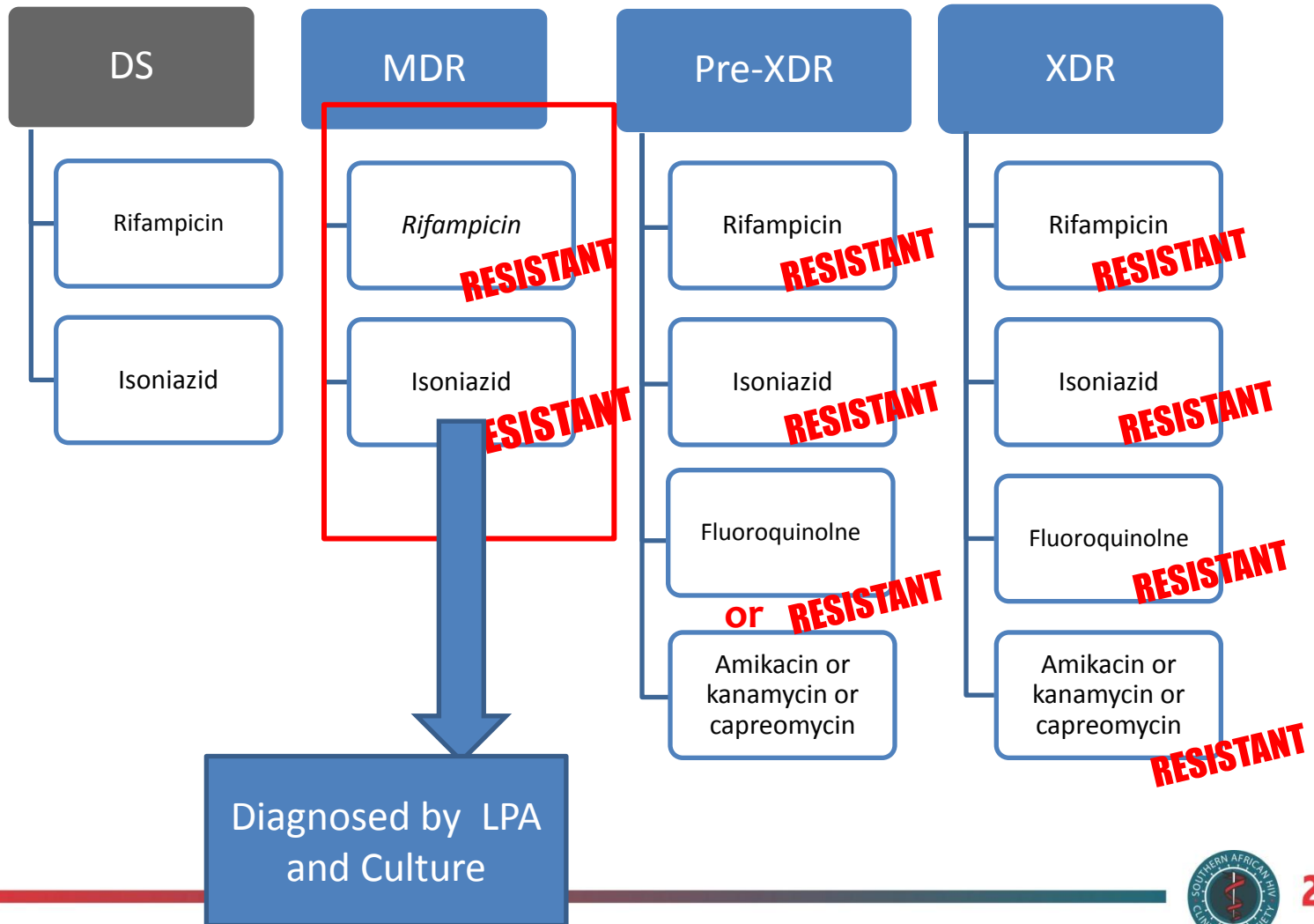
TB resistance



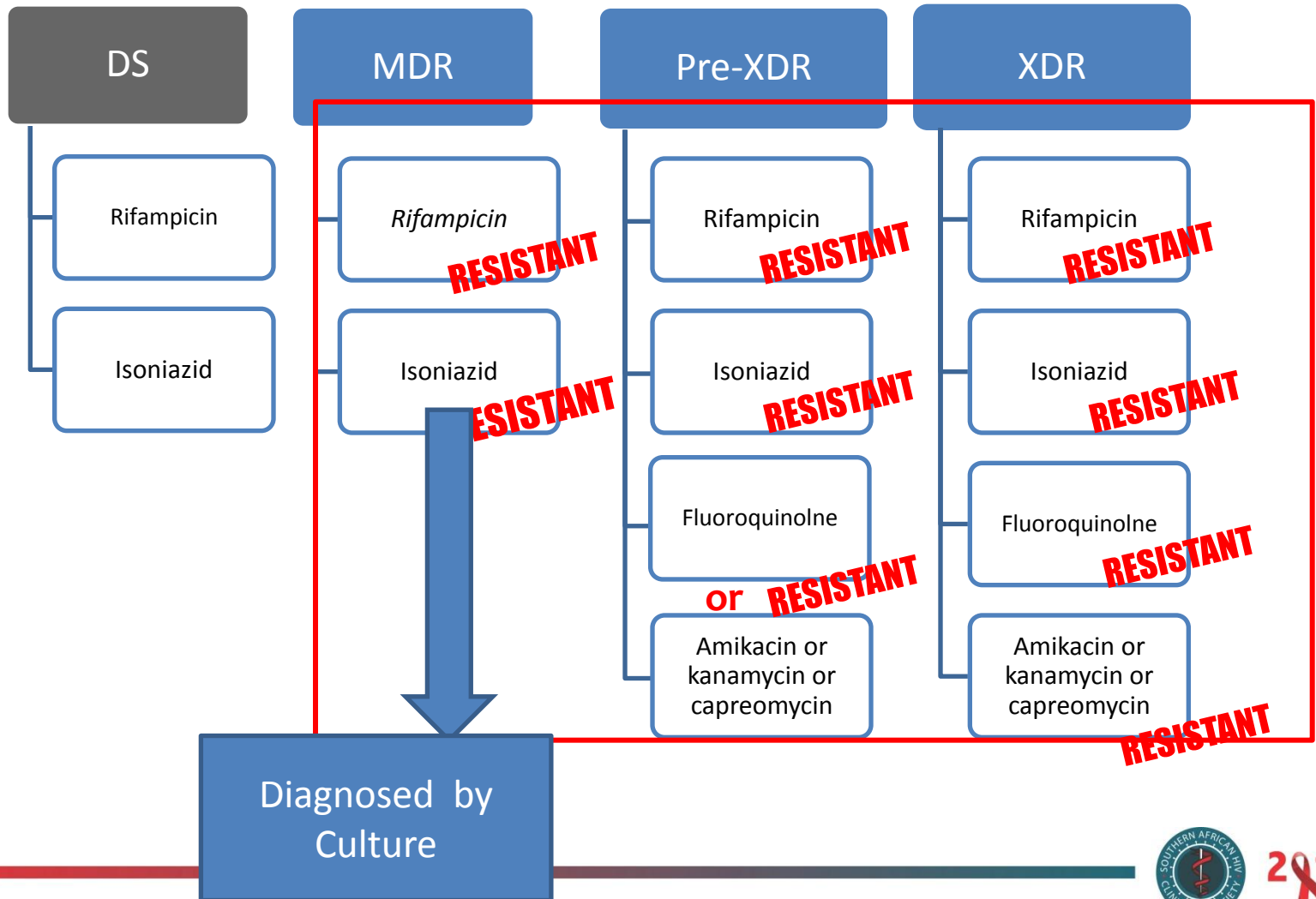
TB resistance



TB resistance



TB resistance



Treatment of Drug sensitive TB

- 6 months of treatment consisting of
 - Intensive phase- INH, Rif, PZA and Ethambutol for 2 months
 - Continuation phase- INH and Rif
 - Medications are co-formulated
 - Do not interact with standard first line antiretrovirals
 - Can be used in pregnancy
 - Basis of DOTS

Challenges in DR TB treatment

- Toxic medications
- Poor efficacy
- Very long duration
- Overlapping toxicities with ART
- Poor evidence on treatment options

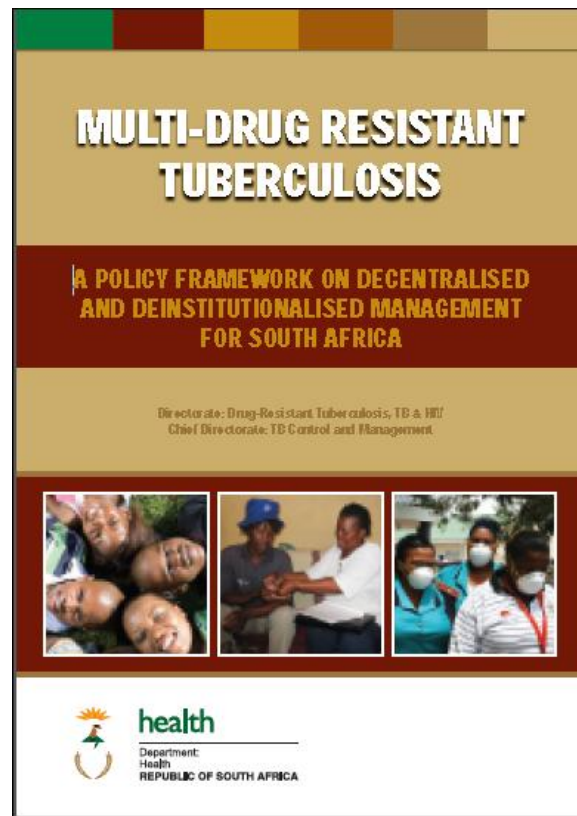
South Africa guidelines for the management of Drug Resistant TB

The standardised regimen consists of at least six months intensive phase treatment with five drugs:

- Kanamycin/amikacin,
- moxifloxacin,
- ethionamide,
- terizidone and
- pyrazinamide

These are taken at least six times per week during the injectable phase followed by a continuation phase treatment with four drugs (moxifloxacin, ethionamide, terizidone and pyrazinamide) taken at least six times per week.

Levofloxacin is used in patients who may not tolerate moxifloxacin



Current treatment for MDR TB

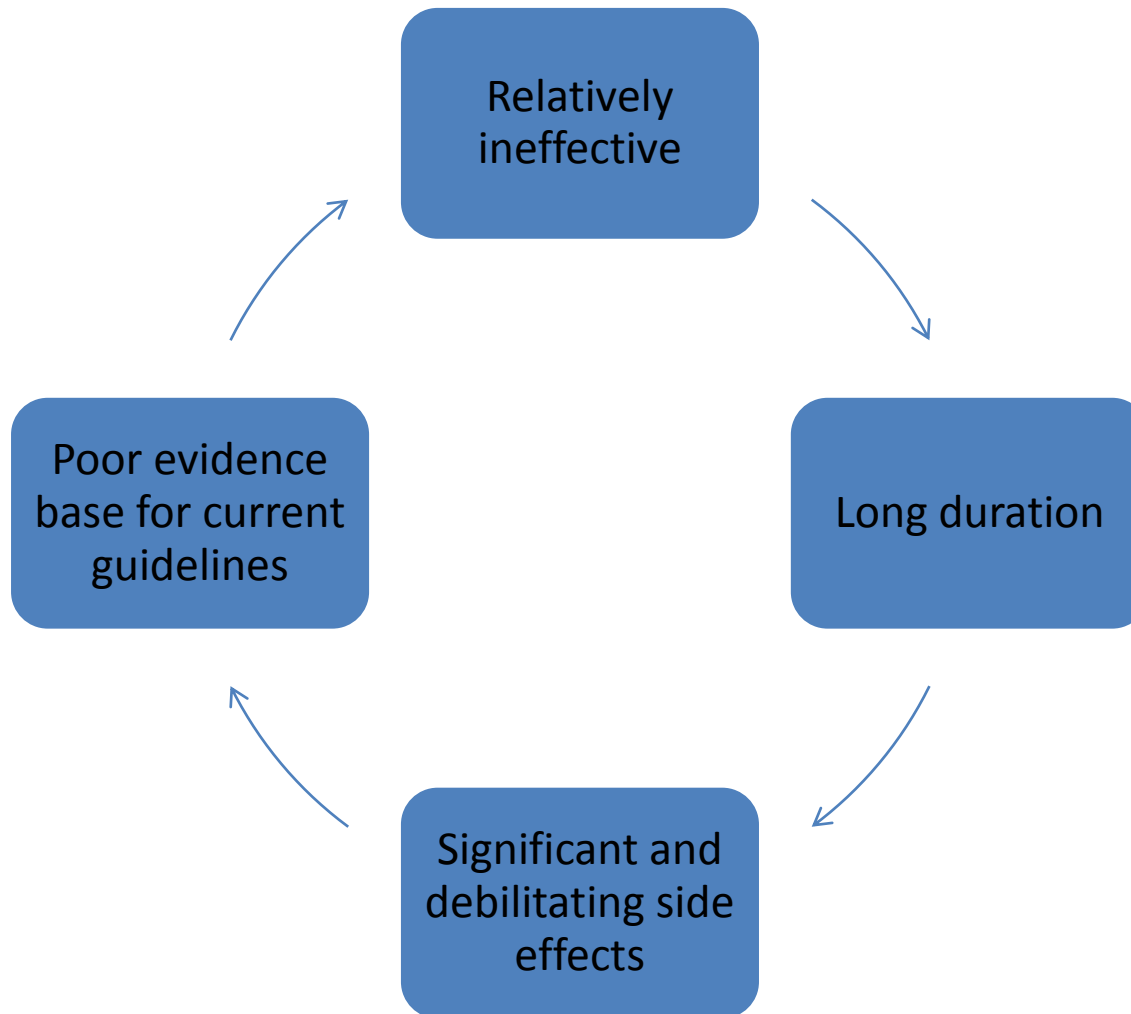
- +/- ethambutol
- Continuation phase- for at least 18 months following culture conversion
- Guidelines are based on expert opinion
- Strong advice with weak/ no evidence

Poor evidence base for current regimen

Recommendations

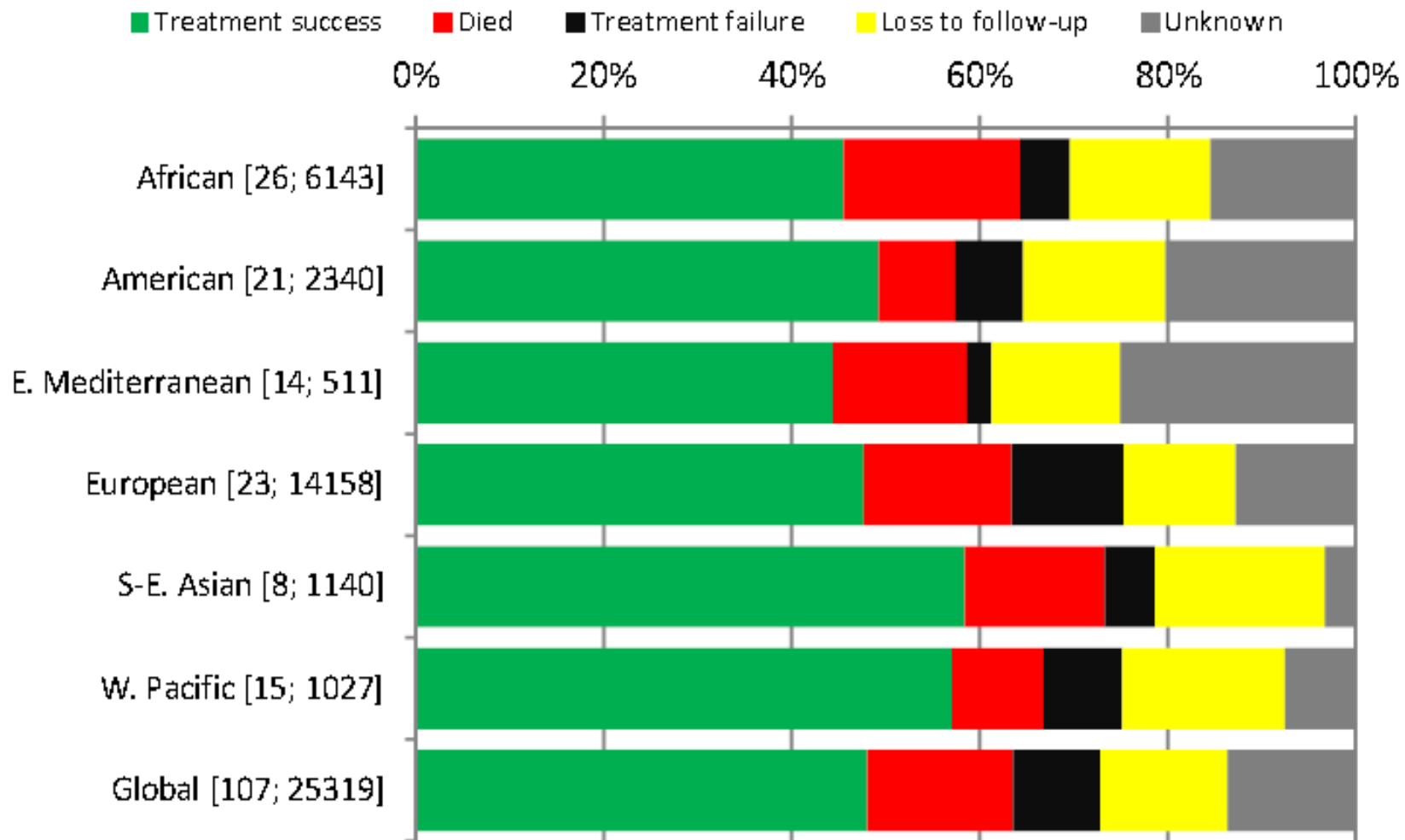
- 3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕○○○/very low quality evidence).
- 3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕○○○/very low quality evidence).
- 3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕○○○/very low quality evidence).
- 3.4 In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase³ (conditional recommendation, ⊕○○○/very low quality evidence).
- 3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ⊕○○○/very low quality evidence).

In summary



Relatively ineffective

Treatment outcomes for MDR-TB patients started on treatment in 2009, by WHO Region and Global



Significant and debilitating side effects

Short term and usually reversible

- Painful injections
- Nausea and vomiting
- Hepatitis

• Medium term

- Kidney failure
- Psychiatric side effects (depression, paranoia)
- Peripheral neuropathy (tingling, numbness, pain)

• Long term and usually irreversible

- Hearing loss due to the injectable drugs (~30% of patients in some settings)

Promising new drugs

- New Drugs
 - bedaquiline
 - sutezolid
 - PA-824
 - Delaminid
- Re-purposed:
 - Linezolid
 - Clofazamine

Bedaquiline

BDQ is diarylquinoline compound with a new mechanism of antituberculosis action by specifically inhibiting mycobacterial ATP synthase

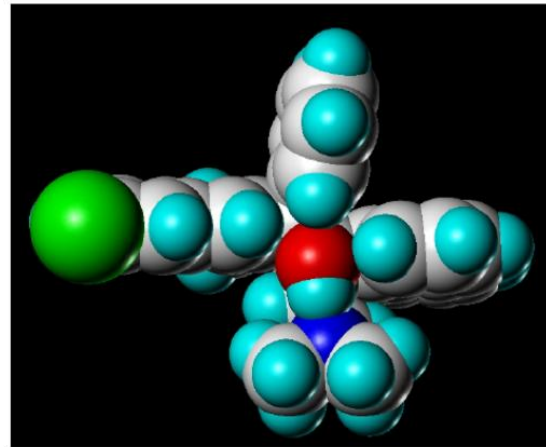
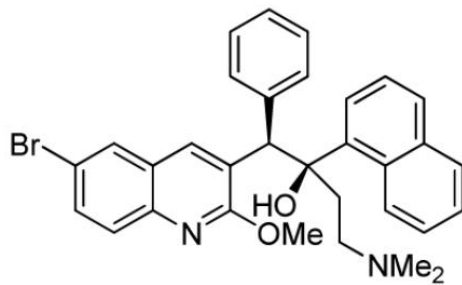


Figure 8 Chemical Structure of Bedaquiline (TMC207)

Registration of Bedaquiline

- EU – March 2014
- India – Jan 2015
- Russia – October 2013
- US – Dec 2012
- RSA – October 2014



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Bedaquiline Clinical Access program,

- Granting access to drugs prior to approval for patients who have exhausted all alternative treatment options and do not match clinical trial entry criteria.
- Previous examples- Kaletra EAP, Tipranavir EAP, intravenous oseltamivir, chemotherapeutic agents.

CLINICAL PRACTICE

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

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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.

S Afr Med J 2014;104(3):164-166. DOI:10.7196/SAMJ.7263



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

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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/ μ l, 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

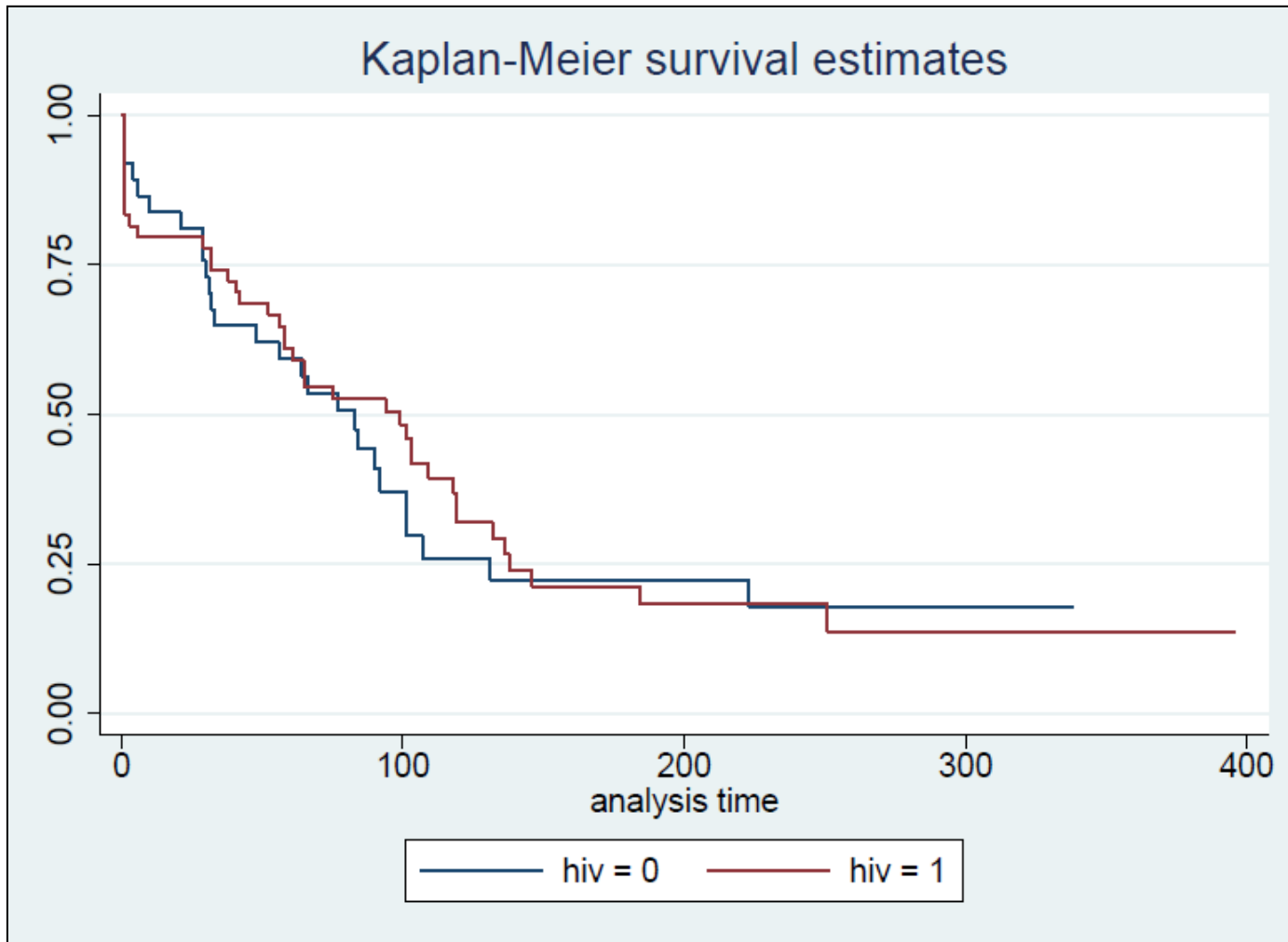
patients, 58 (64%) had completed 24 weeks of BDQ, 28 were still on BDQ, 3 were lost to follow-up, 1 had died and 1 had BDQ withdrawn following atrial fibrillation.

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

Results - culture conversion



Conclusion

- The programme has allowed access to better treatment and interim outcomes for (pre-)XDR patients with otherwise limited options and poor prognosis
- Bedaquiline is now registered in South Africa

**INTRODUCTION OF NEW DRUGS
AND DRUG REGIMENS FOR THE
MANAGEMENT OF DRUG-
RESISTANT TUBERCULOSIS IN
SOUTH AFRICA:
POLICY FRAMEWORK
Version 1.1: June 2015**

Who is eligible for BDQ in the SA NTP?

- Patients ≥ 18 years of age
and
- Laboratory-confirmed RR-TB (at least resistance to RIF) by culture-based phenotypic drug sensitivity testing or genotypic line probe assay or PCR testing (Xpert MTB/RIF) from both pulmonary and/or extrapulmonary sites
and
- No history or family history of QT prolongation or baseline QTcF > 450 msec; *and*

Who is eligible for BDQ in the SA NTP?

- Drug resistance in addition to RR TB:
 - XDR TB; or pre-XDR TB (resistant to either fluoroquinolone or second line injectable drug); or
 - inhA and katG mutations;
- Documented / recorded intolerance to 2nd line anti-TB treatment at baseline or during RR TB treatment
- History of, or surgical candidate for pneumonectomy or lobectomy
- Patients who meet the above criteria are *not required* for review by the National or Provincial DR TB committees

Patients who meet the above criteria are not required for review by the National or Provincial DR TB committees

Which cases should be reviewed by the prior to prescribing BDQ?

- Patients does not have at least one other drug to which their TB is susceptible or predicted susceptible (because not previously exposed)
OR
- Age < 18 years
OR
- Pregnant
OR
- Patients with MDR treatment failure (smear or culture positive at 8 months on MDR treatment) without proven 2nd line resistance.

How far have we got?

At last count over 2000 patients have got BDQ



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Conclusion

- For the first time in over we have new drugs for the treatment of DR TB
- Clinical trial data is very encouraging
- Pending the results of the new trials, we have to develop pragmatic protocols to use the drugs safety in high risk patients.

Thanks

- Dr Norbert Njceka
- DCAP committee
- NCAC committee



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