

# Multi-Drug Resistant tuberculosis in Women

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## Introduction

The World Health Organisation (WHO) estimates a staggering 8.6 million new tuberculosis cases every year (Global TB report, 2013).<sup>1</sup> Seventy five percent of the 8.6 million cases are from the Africa region. More than 500 000 of these cases are new multi-drug resistant tuberculosis (MDR TB) that has doubled from 2009 as well as 2011 and this number is currently doubling annually. Many of these cases are primary MDR TB infection or re-infection rather than previously treated tuberculosis progressing to MRD TB.<sup>2</sup> Evidence is growing for increased transmission in congregate settings and hospitals. Currently drug susceptible tuberculosis treatment rapidly induces negative transmission compared to multi- and extreme drug resistant tuberculosis treatment that is not effective and the patient can be positive for months and still transmitting disease.<sup>2</sup>

South Africa has the highest incidence and prevalence of active tuberculosis disease in the world.<sup>3</sup> Between the years 1994 and 2012 the South African notification figures for tuberculosis soared from around 200 per 100 000 of the population to 1003 cases per 100 000 of the population. Drivers of this misfortune includes the very high HIV figures (especially among females), the lack of infection control at home and at health care facilities, poverty and lack of early correct diagnosis and sufficient treatment to prevent transmission.

## Definitions of Multi-Drug Resistant (MDR) and Extreme Drug Resistant (XDR) tuberculosis.

Drug resistant tuberculosis can consist of

- *Mono resistant tuberculosis*: TB strains resistant to a single first line anti-tuberculosis drug (Rifampicin, Isoniazid, Pyrazinamide or Ethambutol)
- *Poly-resistant tuberculosis*: Tuberculosis strains that are resistant to two or more first line tuberculosis drug ((Rifampicin or Isoniazid or Pyrazinamide or Ethambutol) but never Rifampicin and Isoniazid together.
- *Multidrug resistant tuberculosis* is defined as tuberculosis bacilli strains resistant to Isoniazid and Rifampicin ± other first line drugs.

- *Extreme drug resistant tuberculosis* is tuberculosis strains resistant to Isoniazid, Rifampicin as well as to one or more second line injectable drugs such as Kanamycin, Amikacin, and Capreomycin and to any fluoroquinolone.
- *Rifampicin resistance* is tuberculosis strains that are resistant to Rifampicin detection using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. RR TB includes Mono-, poly-, MDR- and XDR tuberculosis.<sup>4,5</sup>

## Epidemiology of female drug resistant tuberculosis

Gender variances in multi and extreme drug resistant tuberculosis also seem to be driven by the high HIV and AIDS rates in South Africa. Females between 25-29 years of age have a peak HIV prevalence of 32.7% compared to men aged between 30-34 years old with a maximum prevalence of 25.8%. Several observational studies in South Africa indicated that women more prone to XDR TB (50-56%) compared to MDR TB (43-53%).<sup>3,6</sup> In low HIV prevalence countries the opposite seems to be true as MDR TB infected females were 36% and XDR TB 38% respectively from a USA based study. In similar studies from Peru, Russia and Latvia the same trend seems to be true and MDR TB (17- 40%) and XDR TB patient (29-35%).<sup>12,13,14</sup> Max O'Donnell et al., (2011) from KwaZulu-Natal, South Africa showed that females have unexplainable higher XDR tuberculosis infection even after adjustment for HIV.<sup>9</sup>

Case studies in MDR TB and pregnancy are not commonly reported on in the literature and only one study was found from high HIV burdened countries. Khan, et al., 2007 reported on 5 cases showing prematurity and intra-uterine growth restrictions.<sup>8</sup>

According to a retrospective study by Max O'Donnell et al. (2010) female health care workers are at the forefront of the MDR TB and XDR TB epidemic. In this study nosocomial tuberculosis transmissions in health care workers from KwaZulu-Natal from January 1, 2003 to December 2008 were studied.<sup>10</sup>

During this period 231 health care workers (5% of total admissions) were admitted to King George Hospital of which 208 were MDR TB and 23 were XDR TB according to the definitions. Seventy eight percent of the 231 cases were female (78%) with a median age of 31 years. HIV infection was extremely high at 67% among those patients tested.<sup>10</sup>

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Sixty five percent of the health care workers with XDR TB were previously treated for tuberculosis. The incidence of MDR TB cases among health care workers was 64.8 per 100 000 compared to 11.9 per 100 000 of the general population.<sup>11</sup>

From the 8.6 million notified tuberculosis cases globally 1.3 million patients died overall and 170 000 deaths was due to MDR TB. In South Africa (global TB report 2013).<sup>1</sup> Treatment success has increased in drug susceptible tuberculosis from 64% in 2004 to 81% in 2012. Notified drug sensitive tuberculosis in South Africa also declined from 400 000 cases in 2010 to 332 000 cases in 2013. Treatment success rate in MDR TB in South Africa is 44% and 18 % for XDR TB respectively.<sup>3</sup>

**Diagnosis of MDR and XDR TB**

More than 70% of tuberculosis infected patients are co-infected with HIV in South Africa. This not only increases mortality and morbidity of patients but also complicates diagnosis and treatment. Sensitivity of sputum smear diagnosis is poor at best as 10 000 bacilli per millilitre of sputum are needed for detection of tuberculosis by microscopy.<sup>4,15,16</sup> In 2011 the National Government introduced the GeneXpert MTB/RIF test (Cepheid GeneXpert, Sunnyval, Ca USA) to replace the sputum microscopy test in South Africa; therefore, increasing sensitivity and decreasing turn-around time for diagnosis

and treatment of early tuberculosis especially MDR TB disease. The GeneXpert MTB/RIF test can detect 15 bacilli per millilitre of sputum and complete the test within 2 hours.

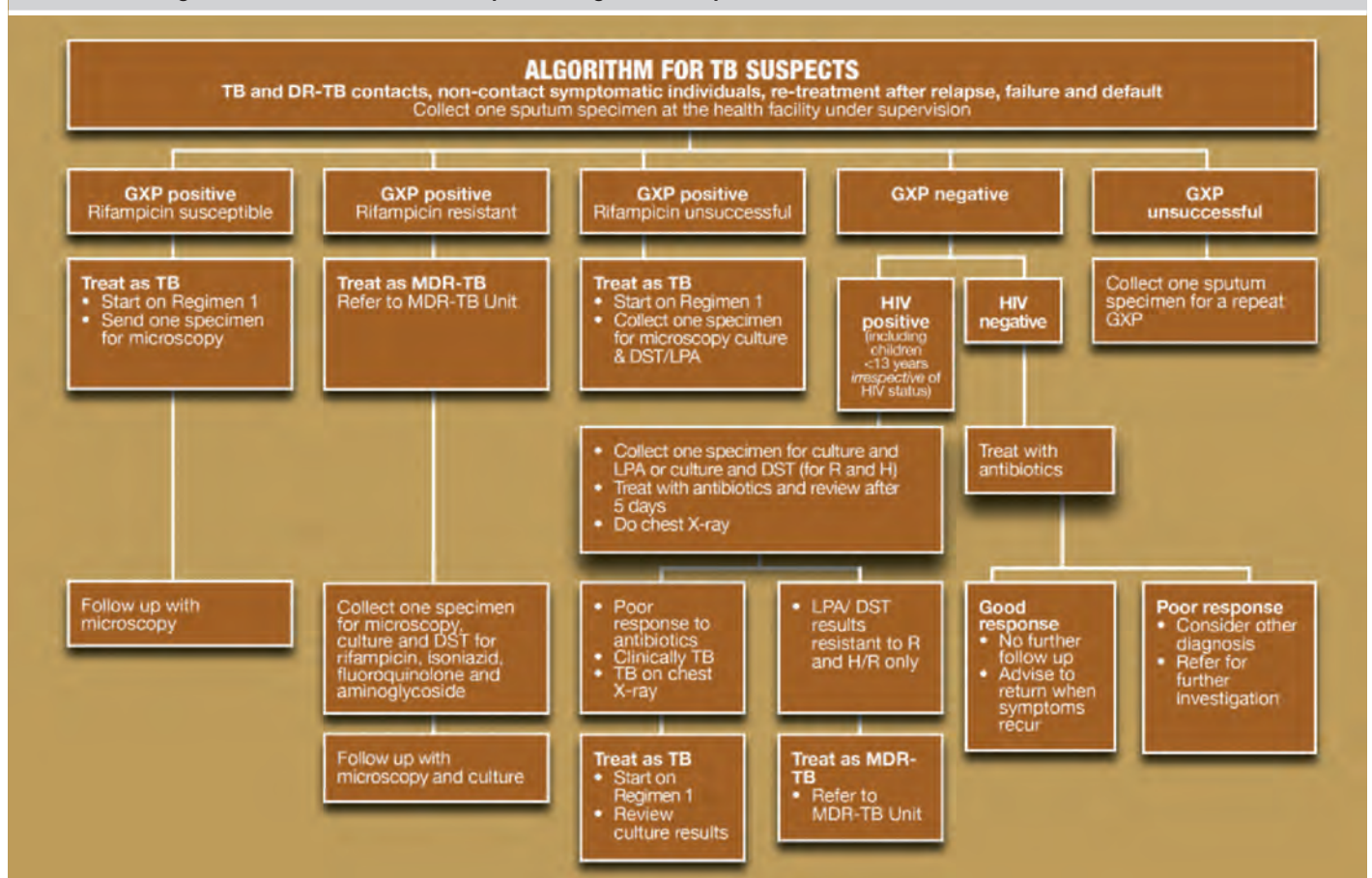
This nucleic acid test also has the ability to detect Rifampicin (Rif) sensitivity; thus, sensitise health care workers to test for MDR tuberculosis. More than 90% of the Rifampicin resistant cases are associated with Isoniazid (INH) resistance.<sup>17,18,19</sup>

Due to poor training of clinicians on the GeneXpert test flow chart plus high MDR TB mortality rate (24%) together with a 17% defaulter rate of patients, only 70% of patients diagnosed with tuberculosis was put on correct MDR treatment within one month.<sup>20</sup> The Rifampicin resistance detected by the GeneXpert compared with the gold standard (culture and drug sensitivity testing) is discordant in about 8.8%. This is disturbing as these patients are treated as MDR TB patients without having resistant tuberculosis disease.

**Management of MDR tuberculosis**

MDR-TB management are usually conducted in specialised MDR units. These units are concentrating on correct combination drug treatments to minimise side effects as well as correct environmental infection control divisions to prevent nosocomial spread to health care workers.<sup>4,5</sup>

Flow chart 1: Algorithm for evaluation of TB suspects using the GeneXpert<sup>4</sup>



## REVIEW

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MDR and XDR TB anti-tuberculosis drugs are categorised under:

- **Aminoglycosides:** Kanamycin (Km), Amikacin (Am)
- **Polypeptides:** Capreomycin (Cm)
- **Fluoroquinolone:** Moxifloxacin (Mfx), Levofloxacin (Lfx)
- **Thioamides:** Ethionamide (Eto)
- **Serine analogues:** Terizidone (T), Cycloserine (Cs)
- **Other drugs:** Class 5 drugs [Clofazimine (Cfs), Linezolid (Lzd), Amoxicillin-Clavulanate (Amx-Clv)], Pyrazinamide (Z)

A standardized MDR TB treatment (Z – Km - Mfx – Eto – Trd(Cs) plus minus Etb is recommended for newly diagnosed MDR tuberculosis in South Africa. It starts with a six month intensive phase followed by an 18 month (or less) active phase (without Km). All regimens including Cs, T or high dose INH must be supplemented with pyridoxine/Vit B6 (50 mg per 250 mg cycloserine).

Birth control is strongly recommended for all females that receive resistant anti-tuberculosis drug treatment due to adverse drug reactions and harmful outcomes for mother and the foetus with MDR-TB. Female patients must be warned that the effectiveness of these contraceptive drugs may be impaired and that barrier contraceptive (condom, diaphragm) or medroxy – progesterone should be considered for the rest of the treatment period.<sup>4,5</sup>

All female patients of child bearing age should have a pregnancy test at the first consultation. Pregnant patients should be evaluated for gestational age and severity of disease. Risks and benefit should be discussed with the patient as second line drugs can be teratogenic. If the patient agrees to start treatment, three to four oral drugs with demonstrated efficacy can be used. An injectable can be added after the second trimester or post-partum as aminoglycosides are toxic to the developing foetal ear. Capreomycin is also ototoxic but is the drug of choice if an injectable cannot be avoided. Ethionamide is teratogenic and also increases nausea and vomiting.<sup>4,5</sup>

Breastfeeding mothers should be on full MDR-TB treatment to prevent transmission to the neonate. Most of the anti-tuberculosis drugs are excreted in small amounts in breast milk; therefore, the use of infant formula milk is a sensible way of preventing adverse drug events in the neonates.

It is not desirable to force the mother and baby separate but if the mother is smear positive it is advisable to let the mother wear a surgical mask or let someone else take care of the child until she is sputum negative.<sup>4,5</sup>

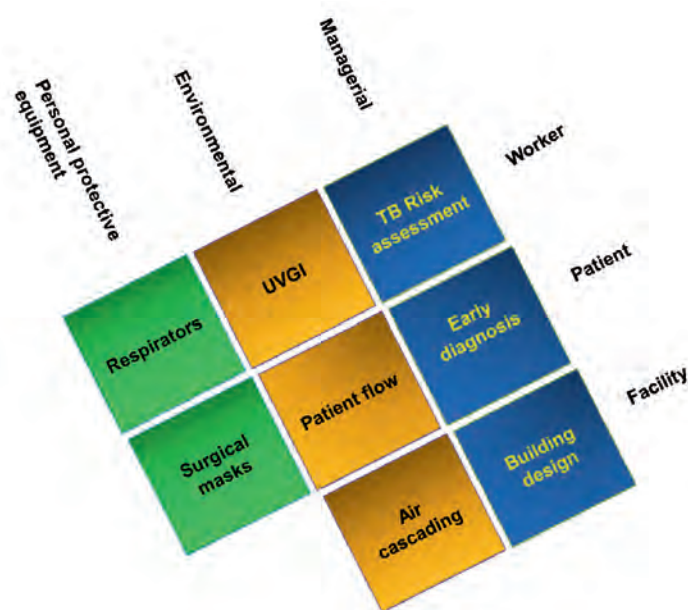
All patients that are co-infected with multi-drug resistant tuberculosis and HIV should start ART irrespective of their CD4 count. Co-infected patients must be fast tracked and treatment should be started within 2 weeks since it increases survival. Cotrimoxazole preventive therapy can be started to prevent numerous other infections such as PJP, Toxoplasmosis, Pneumococcus, Salmonella and Malaria.<sup>4,5</sup>

### Tuberculosis Infection Prevention and control

Tuberculosis is the only obligate airborne transmission infectious disease. Particles containing tuberculosis bacilli is 1 to 5 micrometres in size and is expectorated during talking, coughing and sneezing plus have the ability to stay afloat for up to 8 hours or longer.

Infection prevention is a precise science that works on the level of the health care worker the patient and the facility. On each level controls must be implemented by Infection Prevention and Control Specialists.

Figure 1: Levels of infection and prevention control in tuberculosis



From Figure 1:

- **Managerial and Administrative controls measures**
  - Workers: A full tuberculosis risk assessment must be performed
  - Patients: Early diagnosis will decrease transmission possibilities
  - Facility : Health care facilities need to be designed that transmission of airborne particles are kept to a minimum
- **Environmental controls**
  - Workers: Ultraviolet germicidal irradiation can be used to minimise transmission
  - Patients: The flow of patients is important to minimise the transmission of tuberculosis between infected to non-infected patients
  - Facility: Air flows and cascading in healthcare facilities help to decrease infected air into sensitive areas.
- **Personal protective equipment controls**
  - Workers: Should wear respirators that was fit tested
  - Patients: All coughing patients should wear surgical masks to decrease infected particles to all other patient around them.



Understanding transmission of tuberculosis is the most important element of infection control. By supplying normal surgical masks to coughing patients visiting health care facilities 50% of nosocomial infection can be prevented.<sup>21</sup> By doing ultraviolet germicidal irradiation correct 83% of infections may be prevented. (Unpublished data, AIR facility)

**Conclusion**

Our future in South Africa encompasses MDR - and XDR tuberculosis infection. Due to treatment limitations we will not be able to prevent future infections. As a result of the high HIV rates and certain unknown factors, females in South Africa will keep on bearing the burden of resistant tuberculosis. Pregnancy plus HIV co-infection in MDR patients challenge our treatment ability and outcomes. Infection control will have to play a major role in the future for tuberculosis infection and prevention.

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