Tuberculosis: What's new in diagnostics and management?

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Objectives of this talk:

• Discuss what is new in the diagnostics of tuberculosis in South Africa.

• Discuss what is new in the management of drug sensitive and resistant tuberculosis.

• Discuss the management of TB in the setting of HIV co-infection – drug interactions and side effects.
Epidemiology of tuberculosis

- The WHO estimated 10.4 million new TB cases in 2015, and 580,000 people were estimated to have had MDR-TB or RR-TB worldwide. An estimated 9.7% of people with MDR-TB had XDR-TB.

- People living with HIV accounted for 1.2 million of all new cases.

- TB is still one of the top 10 causes of death – the number of TB deaths fell by 22% between 2000 and 2015 – but there still were 1.4 million deaths.

- South Africa is one of the countries with the highest burden of TB. It has an incidence of 454,000 cases of active TB with MDR-TB accounting for about 3.3% of these new TB cases.

WHO 2015; https://www.tbfacts.org/
Tuberculosis in the critically ill patient

• Some of the reasons for ICU admission include organ failure - acute respiratory failure, liver failure and renal failure.

• Mortality for patients admitted with active TB and respiratory failure requiring mechanical ventilation is poor, with in-hospital mortalities of 33 to 67%.

• It is a treatable disease and a proactive approach is required. Delays to starting therapy can be associated with worse survival.

• TB patients in ICU present special challenges - confirmation of the diagnosis, providing effective anti-tuberculosis treatment in the setting of poor absorption and organ dysfunction, is a challenge.

Hagan G et al. Critical Care 2013; 17:240
Diagnosis of TB

- In clinical practice, the diagnosis can be difficult.
- Culture is the gold standard – it has the highest sensitivity for confirming active TB but take 4-6 weeks.
- Although microscopy is rapid and inexpensive, it has a low sensitivity.
- Nucleic acid amplification tests are highly sensitive for the rapid detection of MTB in a variety of specimens.

<table>
<thead>
<tr>
<th>Test</th>
<th>Type available</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>LED/ Fluorescent microscopy</td>
<td>High specificity, Short TAT</td>
<td>Low sensitivity in people with low bacillary load i.e. children and PLWHA</td>
</tr>
<tr>
<td>Culture</td>
<td>Liquid (MGIT) Solid</td>
<td>High sensitivity</td>
<td>Long TAT, High contamination rates (liquid culture)</td>
</tr>
<tr>
<td>PCR based assays</td>
<td>Line Probe Assay</td>
<td>Short TAT, Detects Rif and INH resistance, High sensitivity for MDR-TB</td>
<td>Reduced sensitivity in smear negative</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>Xpert MTB/RIF</td>
<td>Short TAT, Detects Rif resistance, High sensitivity for Rif resistance</td>
<td>Does not detect INH resistance, Reduced sensitivity in smear negative</td>
</tr>
</tbody>
</table>
Xpert® MTB/RIF

- Automated molecular platform to detect MTB complex and rifampicin resistance - targeting specific mutations in the rpoB gene in sputum.

- Results available within 2 hours. It can also be used on CSF, aspirates and tissue.

- More sensitive test than smear microscopy, therefore it is possible to detect TB in smear negative patients – in fact, case detection rates in HIV positive patients have increased by 45%.

Genotype® MTBDRplus assay for first line drugs

- This a PCR based hybridisation assay. Can only be performed on smear or culture positive sputum. Compared to phenotypic DST, results available within 48 hours.

- Simultaneously detects MTB complex, mutations in the rpoB gene (rifampicin resistance) and mutations on the katG gene (higher levels of isoniazid resistance) and inhA gene (lower levels of isoniazid resistance which is associated with ethionamide resistance).

- Cannot be used for monitoring patients on treatment.
MDR with inhA and katG mutations

Specimen received: Sputum
Tests requested: TB mic, TB cult, TBPCR, TB sens 2nd line

**Auramine O Stain:**
Result (concentrated) Positive + (10-99 AFB/100 immersion fields)

**TB Culture:**

**PCR/Line Probe Assay (MTBDRplus):**
Test performed on Clinical sample
PCR/Line Probe Assay Result Mycobacterium tuberculosis complex

**Isoniazid (INH)**
Resistant

**Rifampicin**
Resistant

This patient has multi-drug resistant tuberculosis. Please ensure that this patient has been referred to an appropriate treatment facility. 2nd line susceptibility testing will follow.

This isolate has a mutation in the inhA gene, which has been shown to correlate with ethionamide resistance. There is also a mutation in the katG gene which may represent high level INH resistance.

**Culture result**
Culture positive. AFBs observed.

**Incubation time**
14 days
What’s new in TB diagnostics? MTBDRsl

- The availability of rapid second line drug testing in MDR TB smear positive and negative patients to exclude XDR TB.

- Allows for the rapid detection of fluoroquinolone and second line injectable resistance.

- It is now available with the introduction of the short MDR-TB treatment regimen.

- Cannot be used for monitoring patients on treatment.

Proposed South African draft 2017 guidelines – courtesy of Dr Nazir Ismail, NICD
Evaluation of the genotype MTBDRs/ version 2.0 assay for second-line drug resistance detection of *Mycobacterium tuberculosis* isolates in South Africa

<table>
<thead>
<tr>
<th>Drug (n = 268)</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
<th>% PPV (95% CI)</th>
<th>% NPV (95% CI)</th>
<th>Diagnostic efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FQ (OFX) (n = 267)</td>
<td>100.0 (95.8–100)</td>
<td>98.9 (96.1–99.9)</td>
<td>97.7 (91.9–99.7)</td>
<td>100.0 (98.0–100.0)</td>
<td>99.3</td>
</tr>
<tr>
<td>SLID (AG/CAP)</td>
<td>89.2 (79.1–95.6)</td>
<td>98.5 (95.7–99.7)</td>
<td>95.1 (86.3–99.0)</td>
<td>96.6 (93.2–98.6)</td>
<td>96.3</td>
</tr>
<tr>
<td>AMK* (n = 226)</td>
<td>93.8 (79.2–99.2)</td>
<td>98.5 (95.5–99.7)</td>
<td>90.9 (75.7–98.1)</td>
<td>99.0 (96.3–99.9)</td>
<td>97.8</td>
</tr>
<tr>
<td>KAN (n = 268)</td>
<td>89.2 (79.1–95.6)</td>
<td>98.5 (95.7–99.7)</td>
<td>95.1 (86.3–99.0)</td>
<td>96.6 (93.2–98.6)</td>
<td>96.3</td>
</tr>
<tr>
<td>CAP* (n = 226)</td>
<td>86.2 (68.3–96.1)</td>
<td>95.9 (92.2–98.2)</td>
<td>75.8 (57.7–88.9)</td>
<td>97.9 (94.8–99.4)</td>
<td>94.7</td>
</tr>
</tbody>
</table>

*Excludes isolates from NHL5 Braamfontein TB Referral Laboratory.


<table>
<thead>
<tr>
<th></th>
<th>FLQ</th>
<th></th>
<th></th>
<th>SLID</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published studies</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td>Tagliani <em>et al</em> (n=228)</td>
<td>83.6</td>
<td>100</td>
<td>86.4</td>
<td>90.1</td>
<td></td>
</tr>
<tr>
<td>Gardee <em>et al</em> (n=268)</td>
<td>100</td>
<td>98.9</td>
<td>89.2</td>
<td>98.5</td>
<td></td>
</tr>
</tbody>
</table>
Culture result: Culture positive. AFBs observed. Incubation time: 10 days

Antimycobacterial Drug Sensitivity Testing:

**Second Line Drugs - MGIT Culture Based:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

The culture was contaminated with bacteria and is thus unsuitable for further culture based drug susceptibility testing.

Drug susceptibility testing for second-line agents was performed by PCR (MTBDRsl Version 2.01). This is a qualitative in vitro test for the identification of the Mycobacterium tuberculosis complex and its resistance to fluoroquinolones (e.g. ofloxacin and moxifloxacin) and/or aminoglycosides/cyclic peptides (injectable antibiotics as kanamycin, amikacin/capreomycin).
Anything new in the treatment of drug-susceptible tuberculosis?

• Current treatment includes a four drug regimen. This allows for a more than 95% cure rate.

• Use of rifampin with isoniazid allowed treatment to be shortened from 18 to 9 months, and the addition of pyrazinamide for the initial 2 months, allowed further shortening to 6 months.

• Trials conducted between 1948 and 1986 showed completion of 6 months therapy lead to a cure of drug sensitive tuberculosis.

• This is still exceptionally long compared to duration of treatment of other bacterial infections. It is associated with toxicity, affecting adherence which results in the interruption or discontinuation of treatment.

• By adding a fluoroquinolone, trials were undertaken to shorten treatment further to 4 months.

Drug-susceptible TB disease: fluoroquinolone-containing regimens vs. the standard TB drug regimen.

• Unfortunately, higher relapse rates were noted at 18 months of follow-up, even though at 2 months a slightly higher (not statistically significant) rate of culture conversion was noted.

• No evidence of reduction of adverse events and no difference in all-cause and TB-related mortality was noted.

• As a result, there is a concern that this may lead to a rise in resistance and loss of fluoroquinolones for the treatment of drug-resistant TB. Therefore, fluoroquinolones not recommended for now.

Change in ART guidelines - ART interactions with rifampicin?

<table>
<thead>
<tr>
<th>Class</th>
<th>ART drug</th>
<th>Interaction</th>
<th>Dose of ART drug with rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>All in class</td>
<td>No significant pharmacokinetic interactions</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>Mild reduction in EFV concentrations. In some patients on TB treatment, EFV concentrations may increase</td>
<td>No dose adjustment required (600 mg <em>nocte</em>).</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Moderate reduction in NVP concentrations with increased risk of virological failure compared with EFV</td>
<td>Use standard dosing, but omit the lead-in dose phase and start 200 mg NVP 12-hourly.</td>
</tr>
<tr>
<td></td>
<td>ETR and RPV</td>
<td>Marked reduction in concentrations</td>
<td>Do not prescribe concomitantly with rifampicin.</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/r</td>
<td>LPV plasma concentrations significantly decreased</td>
<td>The preferable strategy is to double the dose of LPV/r to 800/200 mg 12-hourly. Alternatively, add 300 mg RTV 12-hourly to standard dose of two tablets of LPV/r 12-hourly. There is an increased risk of hepatotoxicity with these strategies. These dose adjustments can be made gradually over 1–2 weeks†.</td>
</tr>
<tr>
<td></td>
<td>All other PIs</td>
<td>Marked reduction in PI concentrations</td>
<td>Do not prescribe concomitantly.</td>
</tr>
<tr>
<td>InSTI</td>
<td>RAL</td>
<td>Reduction in concentrations, but a clinical trial showed that standard dosing results in adequate virological suppression†</td>
<td>No dose adjustment required (i.e. RAL 400 mg 12-hourly).</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>Significant reduction in concentrations</td>
<td>Dosing frequency increased to 50 mg 12-hourly.</td>
</tr>
</tbody>
</table>

What’s new in the treatment of drug resistant TB disease?

• Two new drugs are available for the treatment of drug resistant TB – this includes bedaquiline and delamanid.

• The leprosy drug, clofazimine, repurposed for the treatment of MDR TB.

• In addition, with the availability of rapid second line resistance testing – one can opt for the short “Bangladesh” MDR TB regimen.

• Criteria for the short MDR TB regimen include confirmed rifampicin resistance or MDR TB with no resistance to second line injectables or fluoroquinolones.
Bedaquiline as a new drug for DR-TB

• It offers a new mechanism by specifically inhibiting mycobacterial adenosine triphosphate synthase enzyme.

• When given with other existing MDR-TB drugs - increases the proportion of sputum culture conversion to negative after 2 and 6 months of treatment, essentially reducing the time to culture conversion and offering a shorter treatment duration.

• Approved by SA MCC for the national TB program to treat XDR- TB or pre-XDR TB patients in December 2012 via the Bedaquiline Clinical Access Programme (BCAP).

• Now registered in South Africa since October 2014 for use in HIV-negative or HIV-positive, ART naïve patients, 18 years or older and have laboratory confirmed MDR-TB. It is offered via the TB Directorate within the NDOH.
Delamanid as a new drug for DR-TB

• A nitroimidazole with activity against replicating bacilli through inhibition of mycolic acid synthesis and active against nonreplicating bacilli through generation of reactive nitrogen intermediates.

• When given with other existing MDR-TB drugs - shown to improve sputum-culture conversion at 2 months.

• One must have the standard background therapy for MDR TB disease when using delamanid.

• Delamanid will be introduced in South Africa in a phased approach similar to bedaquiline via the Delamanid Clinical Access Programme. It is currently not registered in SA.

Clofazimine

• It is thought that it acts by inhibiting the formation of matrixes within the MTB DNA and thus delaying the growth of the bacterium.

• It was discovered in 1954 for TB treatment. At the time, the drug proved to be ineffective at treating TB but showed efficacy in treating leprosy.

• A meta-analysis of studies show that it could have a major role in the treatment of MDR-TB.

• The most effective treatment regimen required to achieve a relapse-free cure of 87.9% includes a minimum of 9 months with clofazimine, gatifloxacin, ethambutol and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin and high-dose isoniazid during an intensive phase of a minimum of 4 months.

The short MDR TB treatment regimen

- Up to now, the total treatment duration recommended for MDR-TB patients 18–20 months. However, the optimal duration of treatment has been a matter of debate for years.

- Shorter regimens have recently been evaluated in Bangladesh and in other countries in Africa.

- The WHO guidelines have been updated in May 2016 in accordance with these findings, and have included a recommendation for the use of shorter treatment options if criteria are met.
Treatment success rates: shorter MDR-TB regimen vs longer MDR-TB regimens

<table>
<thead>
<tr>
<th>RESISTANCE PATTERN</th>
<th>SHORTER MDR-TB REGIMEN</th>
<th>LONGER MDR-TB REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% (95% CL)</td>
</tr>
<tr>
<td>All cases regardless of pyrazinamide and fluoroquinolone susceptibility</td>
<td>1008/1116</td>
<td>90.3% (87.8%–92.4%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone resistant</td>
<td>19/28</td>
<td>67.9% (47.6%–84.1%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone susceptible</td>
<td>90/100</td>
<td>88.8% (47.3%–98.6%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone resistant</td>
<td>12/15</td>
<td>80.0% (50.0%–94.1%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone susceptible</td>
<td>121/125</td>
<td>96.8% (77.3%–99.6%)</td>
</tr>
</tbody>
</table>

* Treatment success (cured or treatment completed (10,15)) versus treatment failure/relapse/death in patients not previously treated with second-line TB medications; percentages shown have been adjusted where possible (see also online Annex 4; Section 1 for more details).
Short MDR TB regimen  
“Bangladesh Regimen”

- This includes a duration 9 to 12 months in adult, and paediatric populations.

- Intensive phase: 4-6 months of Kanamycin, Moxifloxacin, Ethionamide, Clofazimine, Ethambutol, Pyrazinamide, INH (high dose).

- Continuation phase: 5-6 months of Moxifloxacin, Clofazimine, Ethambutol, Pyrazinamide.

- Pregnant women offered the possibility of this short regimen with linezolid or bedaquiline or delamanid. Patients need to be treated at a referral centre after approval has been received from the National Advisory Committee.

### Proposed algorithm

<table>
<thead>
<tr>
<th>Xpert MDR/RIF Positive and resistant to Rif</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Send second specimen for DR TB Reflex testing)</td>
</tr>
</tbody>
</table>

If no contraindications (baseline renal condition or hearing impairment) or exclusion criteria (see above), start shorter MDR-TB regimen (may be used in HIV infected patients and children)

#### INH Sensitive
- Continue shorter MDR-TB regimen

#### INH Resistant
- KatG Mutations only
- InhA Mutation only
- Both InhA & KatG mutations

#### Check LPA 1st Line Drugs
- Continue Shorter MDR-TB regimen BUT stop High dose INH

#### Check LPA 2nd Line Drugs
- Continue shorter MDR-TB regimen BUT stop Ethionamide

#### Resistant to Fluoroquinolones and/or Aminoglycosides or Capreomycin
- Urgently refer to next level of DR-TB care for regimen that contains bedaquiline (requires approval from Drug Resistance TB Committee)

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Proposed South African draft 2017 guidelines – courtesy of Dr Nazir Ismail, NICD
### Anti-TB drugs recommended for the treatment of rifampicin resistant and MDR TB

<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A. Fluoroquinolones</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Levofloxacin, Moxifloxacin, Gatifloxacin</td>
</tr>
<tr>
<td><strong>Group B. Second-line injectable agents</strong></td>
<td>Amikacin, Capreomycin, Kanamycin, (Streptomycin)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Group C. Other core second-line agents</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ethionamide / prothionamide, Cycloserine / terizidone, Linezolid, Clofazimine</td>
</tr>
<tr>
<td><strong>Group D. Add-on agents</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td><strong>D1</strong> Pyrazinamide, Ethambutol, High-dose isoniazid</td>
</tr>
<tr>
<td>(not part of the core MDR-TB regimen)</td>
<td><strong>D2</strong> Bedaquiline, Delamanid</td>
</tr>
<tr>
<td></td>
<td><strong>D3</strong> &lt;sup&gt;d&lt;/sup&gt; p-aminosalicylic acid, Imipenem–cilastatin&lt;sup&gt;d&lt;/sup&gt;, Meropenem&lt;sup&gt;d&lt;/sup&gt;, Amoxicillin-clavulanate&lt;sup&gt;d&lt;/sup&gt;, (Thioacetazone)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

WHO Guidelines for treatment of drug-resistant tuberculosis and patient care (2016 update)
## Shared side effects of TB drugs and ART

<table>
<thead>
<tr>
<th>Side effects</th>
<th>ART</th>
<th>TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>AZT, ddI, PIs</td>
<td>Pyrazinamide, ethionamide</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NVP, EFV, PIs (NRTIs can cause steatohepatitis)</td>
<td>RIF, rifabutin, INH, pyrazinamide, bedaquiline and many second-line drugs, including quinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>d4T, ddI</td>
<td>INH, ethionamide, terizidone/cycloserine, linezolid</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>TDF</td>
<td>Aminoglycosides, RIF (rare)</td>
</tr>
<tr>
<td>Rash</td>
<td>NVP, EFV, RAL</td>
<td>RIF, rifabutin, INH, pyrazinamide, ethambutol, streptomycin and many second-line drugs, including quinolones</td>
</tr>
<tr>
<td>Neuropsychiatric complications</td>
<td>EFV, DTG</td>
<td>Terizidone/cycloserine, quinolones, INH</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>AZT</td>
<td>Rifabutin and linezolid</td>
</tr>
</tbody>
</table>

Conclusion

- South Africa is currently using all WHO endorsed DR-TB technologies and treatment therapies.

- All patients should be tested for drug resistance as per diagnostic algorithm.

- Early detection of SLT resistance is available since Jan 2017 but one must send off pDST.

- Need to monitor closely for drug side effects.