

# Introduction of New TB Drugs for DR-TB Treatment

Training Course for TB Physicians  
1 Day

March, 2015  
Tbilisi, Georgia

# *1 Day*

Module 1: Introduction of New Drugs for DR-TB under Program Conditions: The WHO Approach;

Module 2: Bedaquiline, Delamanid and Linezolid for the Treatment of DR-TB: Drug Information and Evidence for Use;

Module 3: Clinical Considerations in New Drug Introduction;

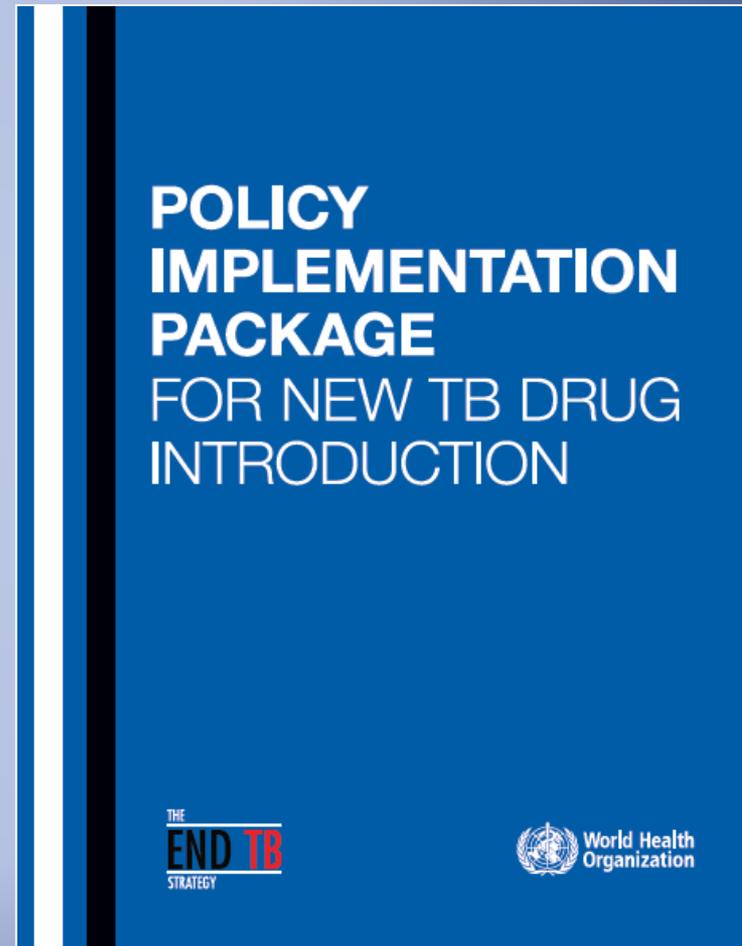
Module 1:  
Introduction of New Drugs for DR-TB  
under Program Conditions: The  
WHO Approach

# Objectives

- To describe the WHO approach to the introduction of bedaquiline and delamanid under program conditions;
- To summarize the WHO guidelines on the introduction of bedaquiline and delamanid under program conditions
- To discuss how the WHO approach can be adapted to other new drugs and regimens

# WHO Approach

- The **goal** is to support countries in preparing for introduction of new TB drugs and/or regimens, based on WHO policy guidance, in order to better serve patients and communities in need.



# WHO Policy Implementation Package for Rational Introduction of New TB Drugs or Drug Regimens in Countries

1. Minimum requirements for country preparedness and planning.
2. Implementation plan for introduction of new TB drugs or regimens.
3. Pharmacovigilance and drug resistance surveillance.
4. Private sector engagement.
5. Systems approach for ensuring uninterrupted supply of quality-assured medicines .
6. Operational research

- [http://www.who.int/tb/features\\_archive/pip\\_newtbdrugs/en/](http://www.who.int/tb/features_archive/pip_newtbdrugs/en/)



# WHO “Approval”?



- Country-directed process
- Country will certify they meet the WHO conditions
- WHO will work with implementing partners to provide TA and support needed by country to ensure drugs are used optimally

# WHO Policy Guidance on BDQ and DEL



## **The use of bedaquiline in the treatment of multidrug-resistant tuberculosis**

Interim policy guidance



## **The use of delamanid in the treatment of multidrug-resistant tuberculosis**

Interim policy guidance



# Conditions for Introducing BDQ

- 1) Treatment is administered under **closely monitored conditions** to enable optimal drug effectiveness and safety (sound treatment and management protocols must be in place, preferably submitted and approved by the relevant national ethic authority; oversight of treatment and management programmes by an independent group of experts in clinical management and public health – e.g. national MDR-TB advisory group - is recommended).
- 2) **Proper patient inclusion** (special caution in persons over 65 years old or adults living with HIV)
- 3) **Signed patient informed consent obtained**, after detailed explanation on the novel nature of the drug, reasons why it is added to the regimen, risk and benefits is provided to patient.

# Conditions for Introducing BDQ

4) Adherence to principles of designing a WHO-recommended MDR-TB regimen (typically composed of at least pyrazinamide and four second line drugs considered to be effective based on drug susceptibility test (DST) and/or previous use and/or drug resistance surveillance data): a fluoroquinolone, a second line injectable agent and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid. Bedaquiline may be indicated if such a regimen is not feasible because of: (i) in vitro resistance to a fluoroquinolone and/or the second line injectable drugs; (ii) known adverse reaction, poor tolerance or contraindication to any component of the combination regimen or (iii) unavailability or lack of a guaranteed supply of a drug(s)

5) Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug-drug interactions.

# Conditions for Introducing DEL

- 1) Treatment is administered under **closely monitored conditions** to enable optimal drug effectiveness and safety (sound treatment and management protocols must be in place, preferably submitted and approved by the relevant national ethic authority; oversight of treatment and management programmes by an independent group of experts in clinical management and public health – e.g. national MDR-TB advisory group - is recommended.
- 2) **Proper patient inclusion** (special caution in persons under 18 and over 65 years old or adults living with HIV)
- 3) **Due process for patient informed consent**, after detailed explanation on the novel nature of the drug, reasons why it is added to the regimen, risk and benefits is provided to patient.

# Conditions for Introducing DEL

4) Adherence to principles of designing a WHO-recommended MDR-TB regimen (typically composed of at least pyrazinamide and four second line drugs considered to be effective based on drug susceptibility test (DST) and/or previous use and/or drug resistance surveillance data): a fluoroquinolone, a second line injectable agent and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid. Delamanid may be indicated if such a regimen is not feasible because of: (i) in vitro resistance to a fluoroquinolone and/or the second line injectable drugs; (ii) known adverse reaction, poor tolerance or contraindication to any component of the combination regimen or (iii) unavailability or lack of a guaranteed supply of a drug(s).

5) Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug-drug interactions.

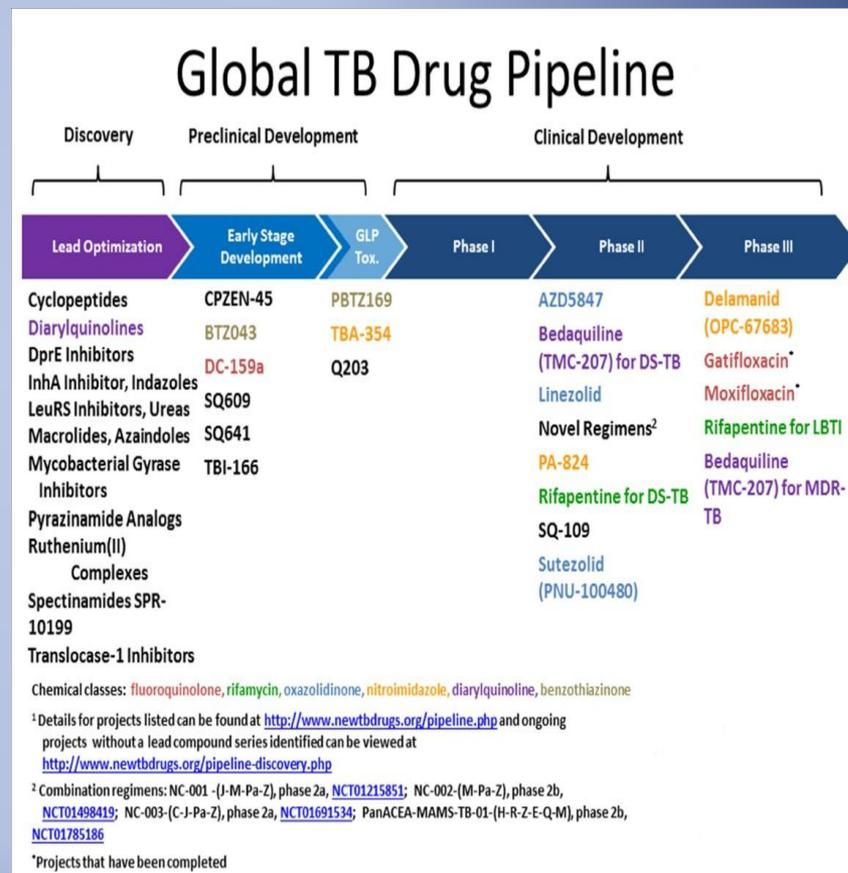
- Countries that do not follow these recommendations will be unable to procure drugs from the GDF using GF money.

# Correcting Common Misconceptions

- WHO recommendations for program conditions, not clinical trials
- WHO is NOT leading another clinical trial of either of these 2 new drugs
- Operational research on HOW to best introduce the new drugs is part of the program introduction
- No data (and thus no recommendations) on combining the two drugs

# WHO Process Will Apply to Other New Drugs and Regimens

- Principles will apply to all new drugs and new regimens
- Structures and processes set up for BDQ and DEL will allow for optimal introduction of other new technologies, including drugs, regimens, and diagnostics



# Summary

- Established WHO Policy Implementation Package for Introduction of New Drugs
- BDQ and DEL are the first
- Program conditions with operational research, NOT a clinical trial
- Country-initiated process with WHO support, but no “approval” needed
- WHO will support with TA along with other implementing partners
- Can be applied to other new technologies as they become available

Questions?

Module 2:  
Bedaquiline, Delamanid and  
Linezolid for the Treatment of DR-  
TB: Drug Information and Evidence  
for Use

# Objectives

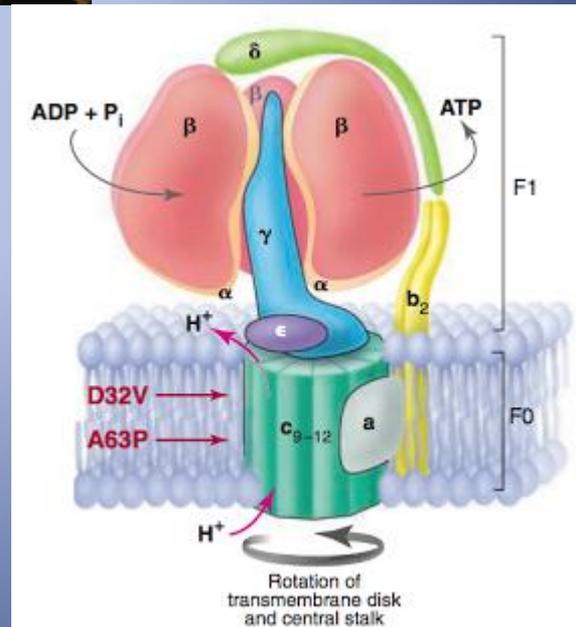
- To briefly review the evidence base for the drugs currently used in the treatment of DR-TB;
- To discuss information on the drugs bedaquiline, delamanid, and linezolid;
- To review the clinical trials data on bedaquiline, delamanid, and linezolid
- To review the data on BDQ and LZD from expanded access programs

# Evidence Base for Second-Line Drugs for the Current Treatment of DR-TB

- All data to support their use comes from observational cohorts and meta-analyses.
- NONE of the drugs used in the treatment of MDR-TB have ever been tested in a randomized clinical trial for the treatment of MDR-TB
- Entire regimen and treatment duration for current management of MDR-TB comes from observational data
- Ongoing STREAM trial is the first RCT to compare an experimental approach with current SOC

# Bedaquiline

- Antimycobacterial drug in the family of the diarylquinolines
- Novel mechanism of action that inhibits mycobacterial ATP synthase
- Approved by the US FDA in 2012 and the EMA in 2013



# Bedaquiline

- Tablets come in 100mg form
- Two-year shelf-life, no cold chain required
- Dose is 400mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 additional weeks
- Half life is 5.5 months
- Cross-resistance seen with CFZ



# BDQ Efficacy: Evidence

- Study C208: 2 arms comparing MBT+ BDQ versus MBT+ placebo
- Median time to culture conversion 83 days (BDQ) versus 125 days (placebo) ( $p < 0.0001$ )
- Rates of culture conversion at 6 months are 78.8% in BDQ group versus 57.6% in placebo group ( $p = 0.008$ )
- 120 week follow-up showed 62.1% patients with culture conversion in BDQ arm compared with 43.9% in placebo arm ( $p < 0.035$ );
- Proportion cured 57.6% in BDQ arm versus 31.8% placebo ( $p < 0.003$ )
- Other drugs used included ethio, PAS, CS, PZA, LFX, LZD, INH, CF

# BDQ Safety: Evidence

- Study C208 and C209 (open-label, one arm with pre-XDR and XDR-TB)
- Grade 3 and higher AEs similar in both groups
- Higher rates of hepatic AEs in BDQ group (8.8% versus 1.9%)
- QTc values > 450ms higher in BDQ group (26.6% versus 8.6%)
- Increase of >60msec higher in BDQ group (9.1% versus 2.5%)
- No cases of torsades or sudden death
- Of 12 deaths seen in the study, 10 occurred in BDQ group and 2 in the placebo group, although none were felt to be drug-related

# BDQ and ART

- Short-term studies done show that BDQ has the potential to have DDI with ART
- Efavirenz cannot be used, as it decreases the concentration of EFV
- NVP considered best option
- Lopinavir/ritonavir can be considered but fewer data exist

# Ongoing or planned trials

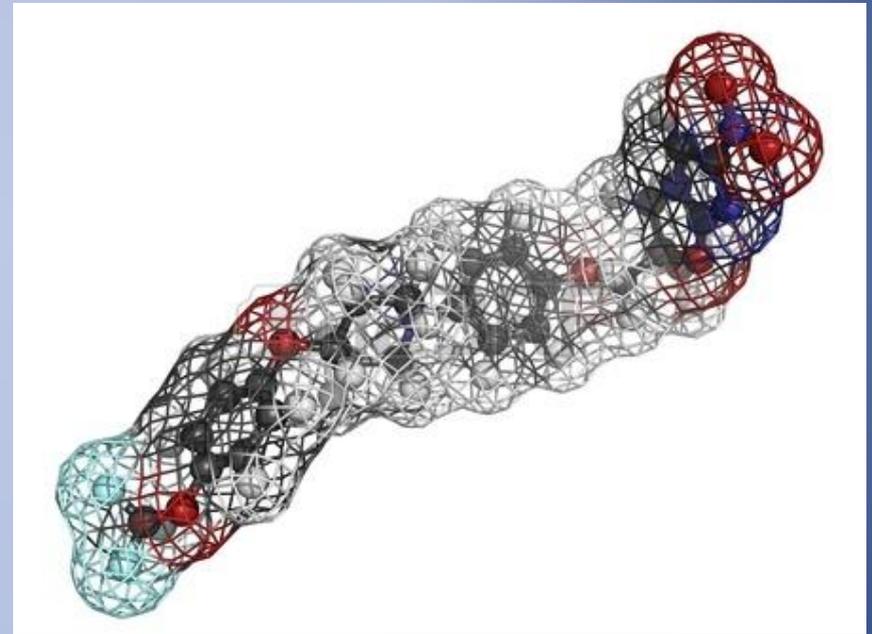
- STREAM 2 will serve as the phase III trial
- Drug-drug interaction (DDI) study
- Key component of most planned combination clinical trials

# BDQ and Expanded Access

- 565 patients globally have received BDQ through expanded access/compassionate use protocols
- Countries accounting for the largest populations: South Africa, Armenia, France, Georgia, Latvia
- Overall excellent outcomes seen
- Main adverse events reported were those due to other drugs (i.e. psychosis from CS)
- Some QTc prolongation noted, but no clinical consequences
- Demonstrates results hold outside of clinical trials

# Delamanid

- Antimycobacterial drug in the nitroimidazole family
- Works by inhibiting synthesis of mycobacterial cell wall
- Conditional approval provided by EMA in 2013 and the Japanese Regulatory Authority in 2014



# Delamanid

- Tablets come in 50mg form
- Dose is 100mg twice daily for 24 weeks
- Shelf-life: 4 years
- Half-life: 30-38 hours
- Cross-resistance with other nitroimidazoles (i.e. PA-824)
- Relatively low threshold to develop resistance



# DEL Efficacy : Evidence

- Data come from 3 trials: trial 204 (RCT of 2 doses of DEL added to MBT versus MBT plus placebo for 2 months); trial 208 (open-label 6 month extension of 204 for willing participants ); and study 116 an observational study of long-term treatment outcomes from 204 and 208
- Of note, only the 2 month data from trial 204 is considered to be an RCT
- Delamanid as effective at dose of 100mg twice daily compared with 200mg twice daily
- Two month culture conversion higher in the DEL 100mg twice daily arm versus placebo (45.4% versus 29.6%,  $p=0.008$ );
- Long-term efficacy not from RCT showed that 90.9% of patients who got DEL for 6 or more months had culture conversion versus 70.9% in those who got DEL for 2 months or less;
- Favorable treatment outcome at 24 months was 74.5% among those who got DEL for  $\geq 6$  months versus 55.0% in those who got DEL for  $\leq 2$  months ( $p<0.00001$ )

# DEL Safety: Evidence

- Pooled data from all DEL trials;
- Drug relatively well tolerated with minimal Aes
- Only difference between placebo and DEL groups was seen in QTc prolongation (4.3% in DEL group versus 1.9% in placebo)
- No torsades or sudden death reported
- Risk of QTc prolongation may be higher in persons with low albumin, as the drug is reported to be metabolized by albumin

# DEL and ART

- No long-term studies done
- Safe with EFV, TDF and lopinavir/ritonavir
- Generally considered safe to administer with ART

# Ongoing or Planned Trials

- Phase III trial has finished recruiting, results expected in 2017-2018
- PK and long-term safety in adolescents and children ongoing
- DDI study
- May be considered in combination trials once ACTG DDI study is complete

# DEL and Expanded Access

- Very limited number of patients have been able to access this drug via expanded access (fewer than 10, most in Europe)
- Drug is available in Georgia
- Very little experience in the field with this drug
- For access, contact [medical@otsuka.de](mailto:medical@otsuka.de)

# Linezolid

- Antimycobacterial drug in the oxazolidinone family
- Works by inhibiting mycobacterial protein synthesis
- “Off-label” use in the treatment of DR-TB

# Linezolid

- Comes in 600mg tablets
- Available from Pfizer (very expensive but going off patent), or generic from Hetero (still expensive)
- Dose not yet well-established; usually 600mg daily
- Shelf-life is 3 years
- Half life is 5 hours
- No special storage needed
- Available as a suspension



# LZD Evidence: Efficacy

- Multiple observation studies showing culture conversion in XDR-TB patients
- Two meta-analyses show efficacy at doses as low as 300mg once a day
- Randomized “delayed start” XDR-TB trial in South Korea by Lee et al (NEJM, 2012)
- Trial randomized 41 patients to 600mg LZD immediately or after 2 months of MBT
- Faster culture conversion seen in the early starters
- Most patients converted culture after 6 months

# LZD Evidence: Safety

- High rates of AEs seen at a dose above 600mg daily
- Most common AEs: peripheral neuropathy and bone marrow toxicity
- Optic neuropathy rare
- Neuropathy in up to 30% of patients, marrow toxicity in up to 10%
- May be related to trough concentrations
- Most programs start at 600mg then drop dose to 300mg if toxicity seen

# LZD: Ongoing or Planned Trials

- No ongoing trials
- Planned dose ranging study in the ACTG (very early in development)
- Part of backbone for most planned all oral MDR-TB regimens
- Other oxazolidinones not far in development
- Sutezolid in treatment of DS-TB
- EBA of AZD5847 results available soon

# LZD and special populations

- No interactions with ART
- Can be given during pregnancy and breastfeeding
- Can be given to children

# Unresolved Issues

- Clinical trials assessed these drugs effectiveness when ADDED to a MBT regimen
- **WHO recommendations differ from this, in part for logistic reasons**
- No data on the use of these two drugs together
- Larger patient cohorts needed to establish full safety profile of the drugs
- Need to consider inclusion of high-risk groups (i.e. children, pregnant women, HIV infection) even in the absence of clinical trial data

# Summary

- Evidence from phase IIb trials show that both BDQ and DEL are effective against MDR-TB when added to MBT;
- Evidence from delayed start trial shows LZD results in more rapid culture conversion
- Primary safety concerns are with LFT abnormalities and QTc prolongation (although no clinical cardiac events have been observed; for LZD, marrow toxicity and PN
- Higher mortality rate seen with BDQ concerning but drug has been used in more than 565 patients worldwide
- Ongoing trials are planned with earliest results in 2017-2018 (phase III DEL trials; likely 2019 for STREAM 2; ACTG LZD study)
- Stronger evidence to support the use of these drugs for the treatment of MDR-TB than other agents used in current SOC
- Full safety profile of the drugs needed

Questions?

Module 3:  
Clinical Considerations in New Drug  
Introduction

# Objectives

- To review the clinical issues involved in new drug introduction, including selection of patients, baseline tests, regimen composition, clinical monitoring, cardiac issues, case management, adherence, and special populations
- To discuss the role of clinical review committees in the treatment and monitoring of patients on new drugs

# Clinical Considerations: Important Point 1

- Both BDQ and DEL were tested and licensed as additions to backbone therapy for patients with MDR-TB, and this is how they will be indicated for use in countries where the drugs are registered
- The studies only included individuals with pulmonary disease between the ages of 18-65 years, and thus this is the population for whom the drugs are licensed

Evidence for LZD has never been reviewed by the WHO

Off-label use suggests this drug has an important role in the management of DR-TB

# Clinical Considerations: Important Point 2

- For multiple reasons (including costs and logistics) the WHO guidelines recommend using these drugs in patients with resistance or intolerance to SLDs, especially the quinolones and the injectables.
- Because of the lack of data in other populations (i.e. children, pregnant women), the WHO recommends that these drugs be used with caution in these populations

# Clinical Considerations: Important Point 3

- BDQ and DEL have never been tested in combination together, and thus there are no data on the efficacy and safety of this combination.
- Data on the cardiac safety of this combination will likely be available in early-mid 2017
- LZD considered safe with all the new and repurposed drugs

# Clinical Considerations: Important Point 4

- New drugs should be introduced in the context of overall PMDT
- New drugs should be considered additional tools in the fight against DR-TB and parallel systems should not be created just for these drugs

# Clinical Considerations: Patient Selection

- There are a small number of absolute contraindications to the use of BDQ and DEL;
- These ABSOLUTE CONTRAINDICATIONS are: patient refuses to consent, patient has an allergy to either medication, or patient has a history of certain cardiac complications, including a QTcF>500ms, a history of Torsades de Points, a history of ventricular arrhythmias, or a history of known severe cardiac disease
- LZD is contraindicated in patients taking SSRIs or tricyclic antidepressants given risk of serotonin syndrome

# Clinical Considerations: Patient Selection

- The new drugs should be USED WITH CAUTION in persons under the age of 18 and over the age of 65, patients who are pregnant or nursing, patients with renal and hepatic impairment, and with certain antiretroviral medications

# Clinical Considerations: Patient Selection

- Prior to initiating either new drug, ensure the electrolytes are normal and the LFTs are < 3 times the upper limits of normal.
- Prior to initiating DEL, ensure that the albumin is 2.8 g/dL or higher.
- Prior to initiating LZD, ensure the HgB is above 8g/dL and the platelet count is above 75,000.
- Minimize the use of other QTc prolonging agents as much as possible when using either BDQ or DEL

# Clinical Considerations: SLD Resistance

- Documented resistance to FQ or injectables or both
- Obtaining results from SLDST can take weeks to months to obtain
- All patients with documented RR-resistant TB should have resistance tested done to at least aminoglycosides and the FQ
- Rapid testing is acceptable as a rule-in test
- Patients likely to have resistance to an injectable or FQ or both can be started on BDQ or DEL even in the absence of confirmed DST, including persons who have received these drugs in the past, persons with contacts who are resistant to these drugs, and persons failing MDR-TB treatment

# Clinical Considerations: What Constitutes “Intolerance?”

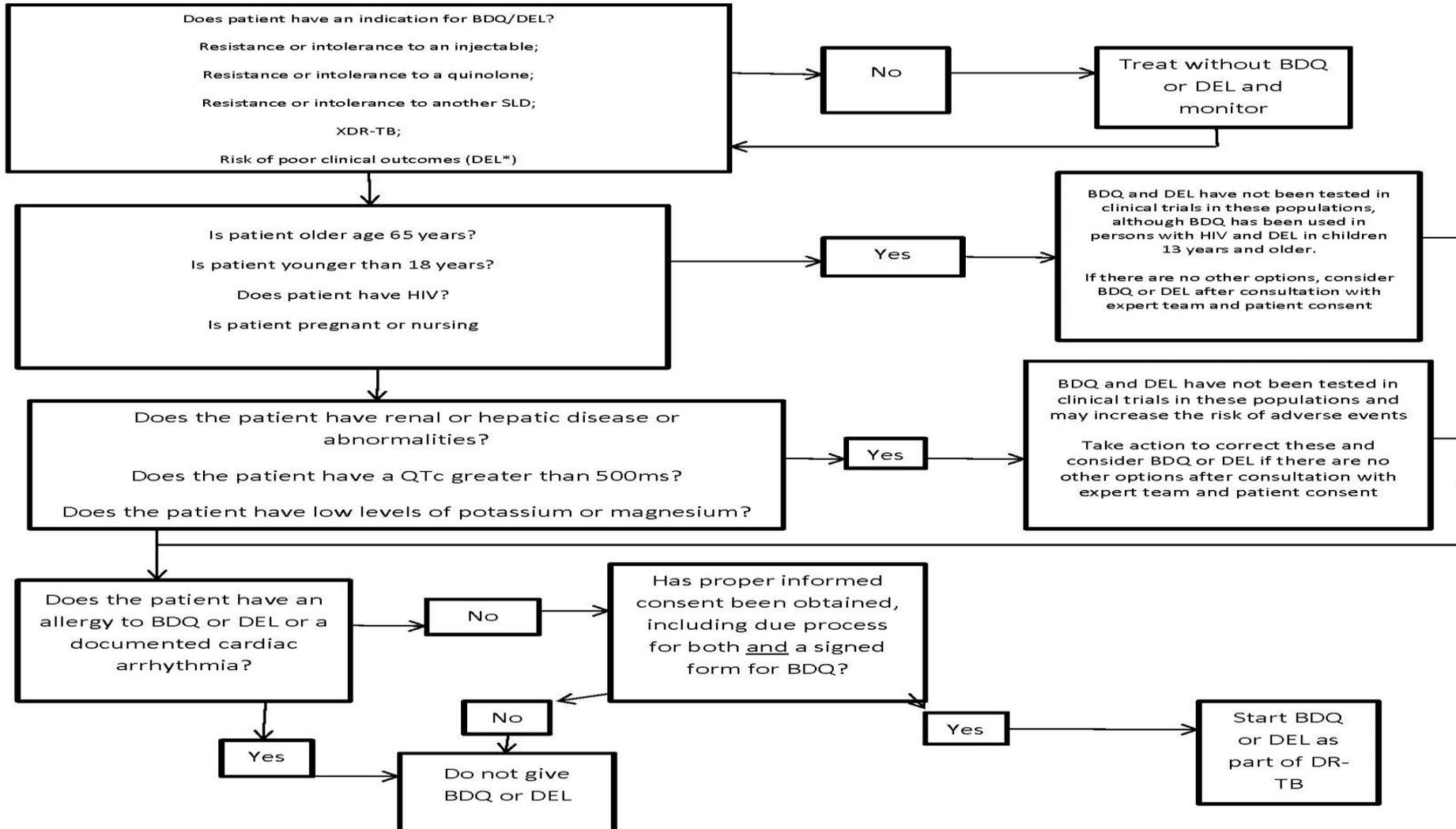
- At the discretion of the clinical teams
- Includes AEs such as hearing loss, renal problems, abscess, etc.
- Should not wait until these effects are severe and irreversible
- In some settings, the delivery of a daily injection could be seen as “intolerable” depending on the circumstance

# Clinical Considerations: Other SLD Resistance

- WHO recommendations if resistance or intolerance to “two or more”
- Unclear evidence for this recommendation
- Programs could consider adding new drugs in the setting of resistance to other SLDs (i.e. high rates of resistance to Ethio) or intolerance (i.e. psychosis, hypothyroidism)

## Implementation Tool: Careful Patient Selection

Patients being considered for the use of bedaquiline or delamanid should be carefully selected. The clinical trials of BDQ and DEL only included patients between the ages of 18 and 65 years, did not include patients with HIV nor those who were pregnant or nursing. BDQ and DEL can be considered for use in these populations provided other treatment options are limited. Of note, patients with HIV have been treated with BDQ in expanded access programs successfully. Careful patient selection is needed to ensure good outcomes but should not be used to exclude vulnerable populations, such as prisoners, children, and migrants.



# Clinical Considerations: Important Point 5

- Saving the new drugs BDQ and DEL for only “the most resistant” patients or the “most desperate cases” will result in poor outcomes and is likely NOT the best way to maximize the benefits of these drugs
- DEL is recommended in cases where “there is an increased likelihood for poor outcomes.”

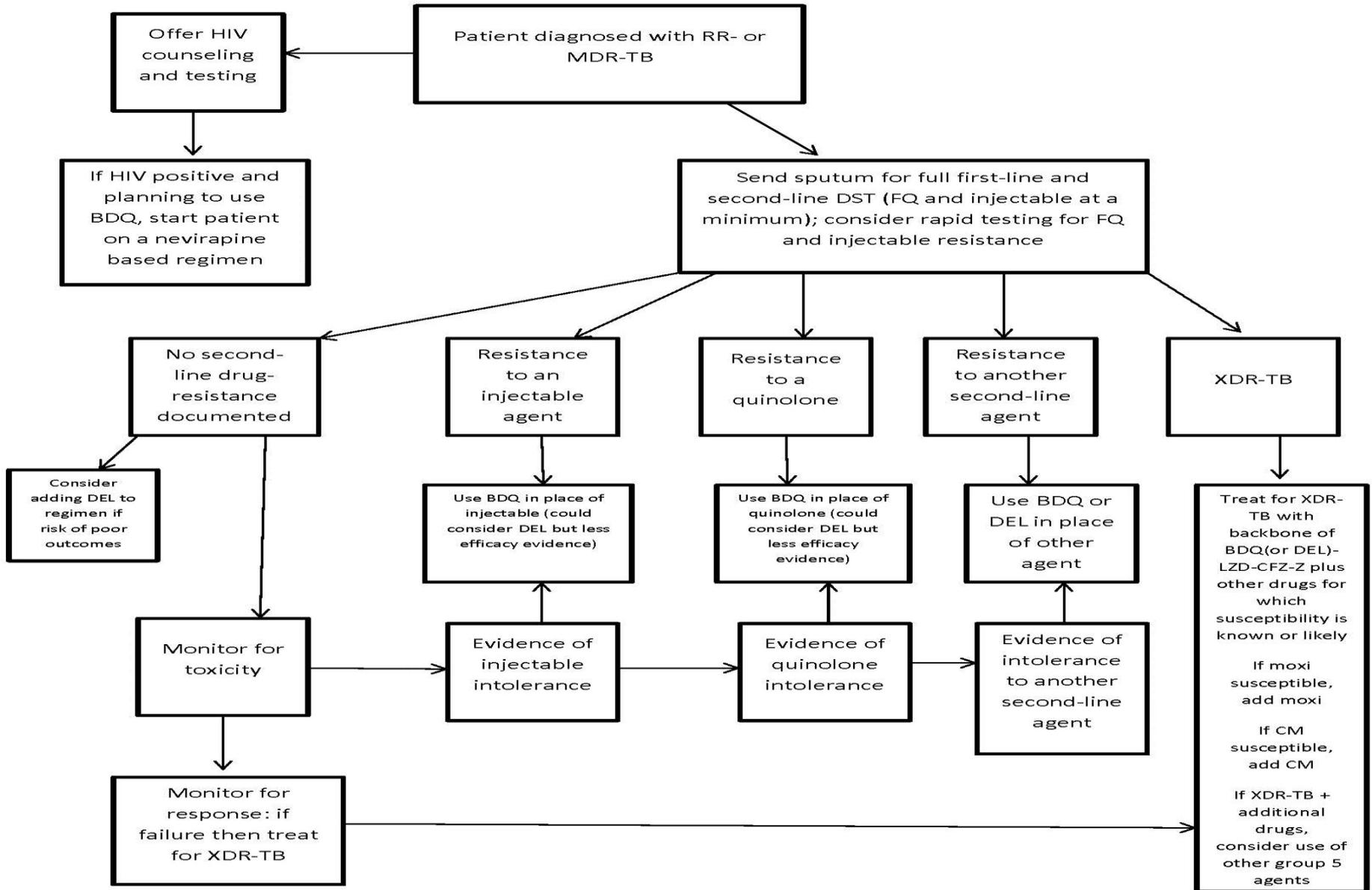
# Clinical Considerations: Baseline Testing

- Similar to testing for PMDT, with the following additions:
- 1) ECG to assess for arrhythmias, calculate QTc interval;
- 2) Lipase for patients to be started on BDQ;
- 3) Albumin for patients to be started on DEL
- 4) Complete blood count for patients to be started on LZD

# Clinical Considerations: Regimen Construction

- Never add either BDQ or DEL as a single drug to a failing regimen
- If patient is culture negative, and the new drugs are being SUBSTITUTED for toxicity reasons, can make a single drug substitution
- If the patient is failing a current MDR-TB regimen, need to add at least 3 new drugs, including BDQ or DEL
- Use with caution with other drugs that can prolong the QTc interval (i.e. moxifloxacin, clofazimine)

## Implementation Algorithm: Using Bedaquiline or Delamanid in WHO-Recommended Regimen



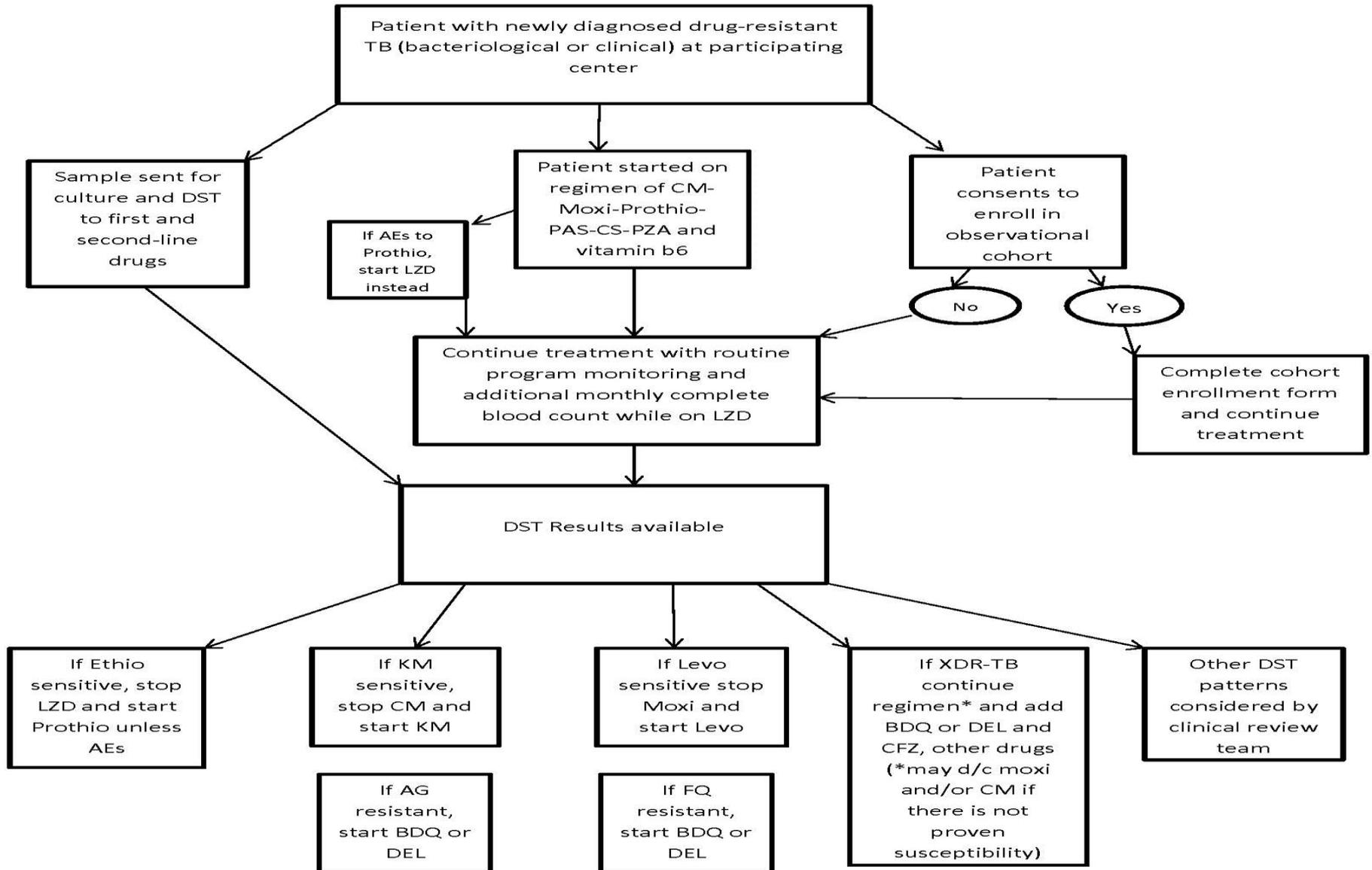
# Clinical Considerations: New Drugs and the “Nine Month Regimen”

- Nine month (“Bangladesh”) regimen being introduced under operational research conditions in many settings
- This strategy can be complementary to the use of new drugs, as the 9 month regimen is likely to be of limited utility in patients with resistance to the FQ or injectable
- In some settings, all patients with RR-TB undergo rapid screening for FQ and KM resistance (HAIN Lineprobe Assay); those with no resistance receive the 9 month regimen and those with resistance to either or both receive either BDQ or DEL

# Clinical considerations: new initial regimen in Georgia

- CM-Moxi-Prothio-CS-PAS-PZA
- If patient unable to tolerate prothio (severe vomiting, other Aes), then LZD will be given instead
- Could consider using BDQ or DEL instead of LZD in this setting
- If FQ or AG resistance confirmed, consider adding BDQ or DEL
- If DEL available, could consider ADDING it to all DR-TB patients' regimens

Annex: Algorithm for New Regimen Introduction



# Regimen Construction: XDR-TB and Failures to MDR-TB Treatment

- Backbone regimen of new drug (BDQ or DEL), linezolid, CFZ, and PZA
- Other possible agents could include imipenem+ amoxi/clv (requires placement of medi-port), clarithromycin (evidence of inducible resistance and also prolongs the QTc), any other SLD to which susceptibility is likely
- Use of moxifloxacin controversial as it prolongs the QTc interval; should be considered if there is evidence of susceptibility/no evidence of resistance

# Clinical Considerations: Length of Therapy with New Drugs

- Both DEL and BDQ were tested in 6 month trials and are recommended for the first 6 months of therapy only
- DEL has been given in research conditions for up to 8 months
- 6 months chosen for ease of endpoint analysis
- In patients with high-level resistance or intolerance, drugs can be used for longer periods of time on a case-by-case basis

# Clinical Considerations: BDQ or DEL?

- There have been NO studies comparing the two drugs head-to-head
- Use BDQ if patient has a history of DEL use, PA-824 use, or allergy to DEL
- Use DEL if patient has a history of BDQ or CFZ use (cross-resistance) or an allergy to BDQ
- DEL has fewer interactions with ART than BDQ
- DEL has been assessed in pediatric populations

# Inpatient or Outpatient?

- Experience thus far has been to hospitalize patients receiving new drugs for some period of time
- If there is sufficient adherence support, there is no need to hospitalize patients
- If hospitalizing for cardiac monitoring, consider that DEL takes 8 weeks to reach its peak and BDQ up to 16 weeks
- If hospitalizing for cardiac safety, ensure access to a defibrillator

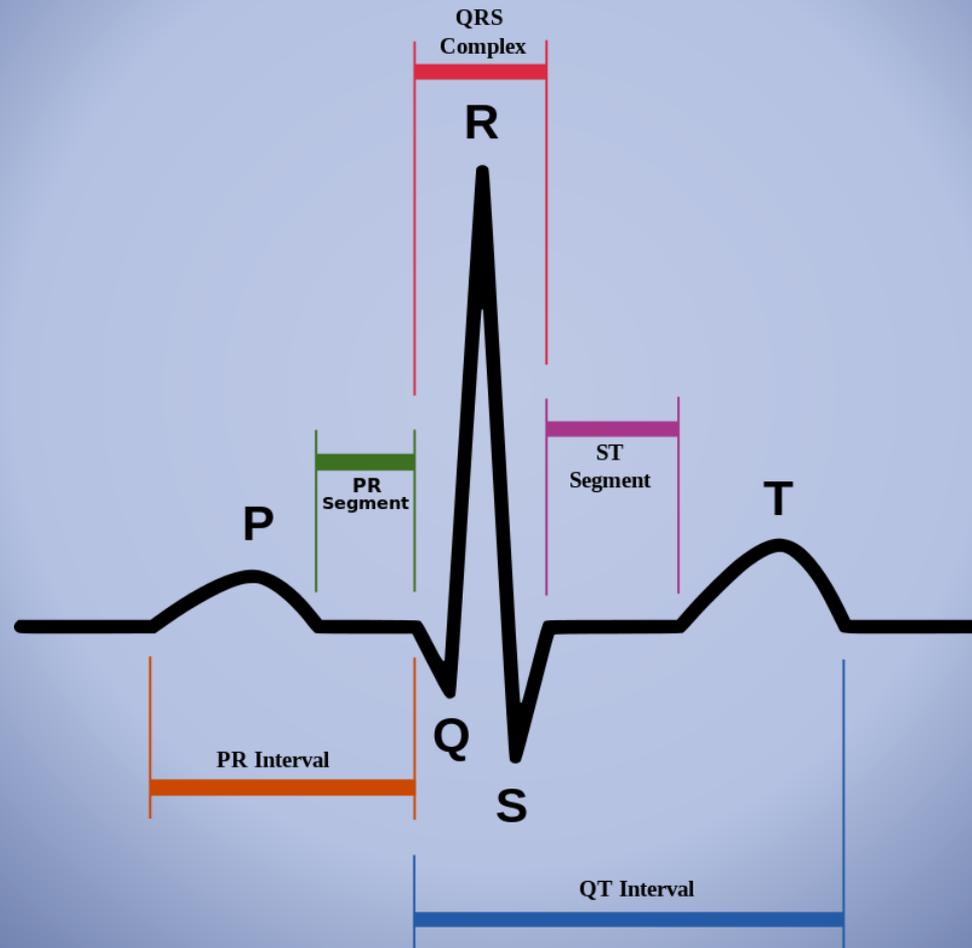
# Clinical Considerations: Routine Monitoring

- Monthly visits during first 6 months of therapy
- ECG for QTc monitoring at weeks 2, 12, and 24
- Monthly LFTs for both BDQ and DEL
- Monthly albumin if on DEL
- Monthly CBC if on linezolid
- At each visit, ask the patient if they have had any syncope or palpitations

# Clinical Consideration: Cardiac Issues

- Focus on QTc prolongation as a RISK FACTOR for developing Torsades de Points (TdP), not as an AE in and of itself
- Both BDQ and DEL have been shown to prolong the QTc but neither have been associated with clinical cardiac events
- QTc assessment important part of drug registration in some countries (i.e. US, EU)
- Multiple drugs can cause QTc prolongation and do not cause TdP
- Other risk factors for TdP include gender, advanced age, low heart rate, electrolyte abnormalities, congestive heart failure, and genetic predisposition
- Programs must weigh the risk of QTc prolongation and possible cardiac events with the risks of under-treated MDR-TB and the risks of the other SLDs

# Clinical Considerations: Calculation of QTc Interval



# Clinical Considerations: Calculation of QTc Interval

- Interval measured in milliseconds
- Interval must be corrected for the heart rate
- Several formulas available—most recommend the use of the Fridericia formula
- Formula is measured QT interval/ $\sqrt[3]{\text{calculated RR interval}}$
- Multiple online calculators for this

# Handheld ECG Machines

- Tend to overcall the QTc interval
- If QTc prolongation seen, then patient will need a 12 lead ECG
- Successfully used in the field for patients on the nine month regimen

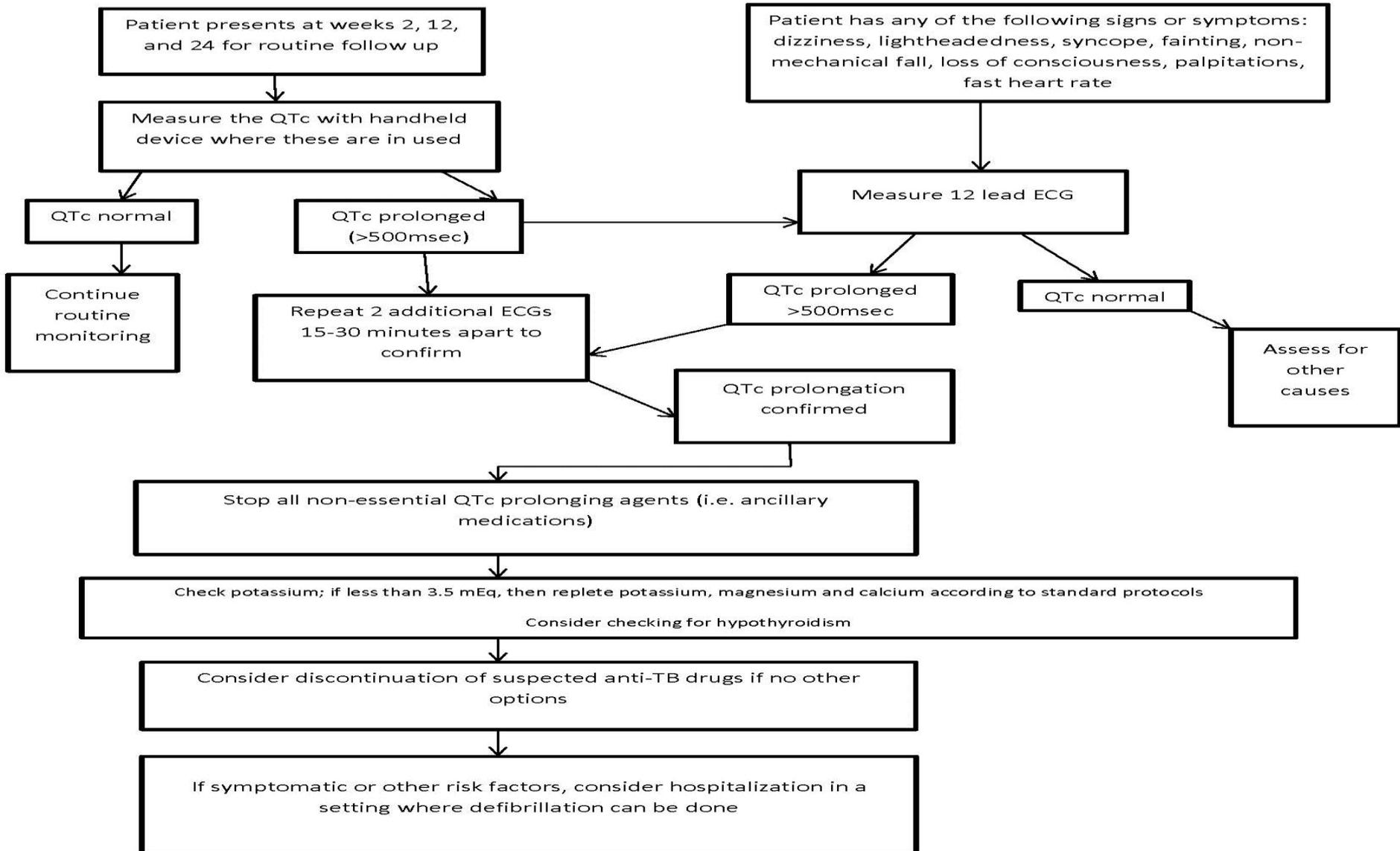


# Clinical Considerations: Management of Prolonged QTc

- Repeat the ECG two additional times within 15-30 minutes of one another to confirm
- Assess for symptoms, including dizziness/syncope, palpitations, chest pain
- Discontinue all un-necessary QTc prolonging drugs
- Check and replete electrolytes (i.e. potassium, magnesium, calcium)
- Assess for hypothyroidism
- If no other options discontinue BDQ or DEL
- If symptomatic, consider admission to a facility where defibrillation is available

## Management Approach to Patients on QTc Prolonging Antituberculous Drugs

Drugs known to prolong the QTc interval include BDQ, DEL, CFZ, Moxifloxacin, Levofloxacin, and Clarithro



# Clinical Considerations: Adherence Support

- New drugs cannot succeed if patients are not given proper adherence support
- This includes transportation, nutrition, and economic support
- Community-based care essential
- Protein-based nutritional support important with DEL; BDQ better absorbed when given with a meal

# Clinical Considerations: Children

- Have not been included in clinical trials
- DEL is being tested for PK and safety in older children and for this reason is preferable to BDQ
- Pediatric formulation of DEL is available (50mg scored, dispersible)

# Clinical Considerations: Adolescents

- Have not been included in clinical trials
- Should be able to use both BDQ and DEL safely in older adolescents
- May need additional adherence support
- High risk of “falling through the cracks”

# Clinical Considerations: The Elderly

- Should be able to use BDQ and DEL in this population, provided there is no active congestive heart failure or severe coronary artery disease

# Clinical Considerations: HIV

- Patients with HIV can be given BDQ or DEL, although they were not included in significant numbers in the registration trials
- Concern over choice of ART
- DEL can be used with most ART regimens
- EFV can decrease levels of BDQ; BDQ is not recommended to be used with PI-containing regimens; therefore, patients on BDQ will need to be on NVP while on BDQ or on an integrase inhibitor
- Given the high rates of HIV co-infection in some settings, and the higher mortality rates seen in HIV co-infected populations, new drugs should be prioritized in this population

# Clinical Considerations: Pregnancy and Breastfeeding

- No data on the safety of these drugs on developing fetus or on breastfed children
- Must weigh the risks and benefits of using either of these drugs in pregnancy
- Birth control should be used as with routine PMDT
- Long half-life of BDQ should be considered if a patient becomes pregnant on therapy

# Clinical Considerations: Extra-pulmonary TB

- Patients with primary EP DR-TB were not included in the registration trials
- No reason to believe these medications cannot be used in this population

# Clinical Considerations: Substance Users

- Use these drugs with caution in patients with active liver damage
- May need additional adherence support
- Therapy for substance abuse

# Clinical Considerations: Prisoners

- Given high rates of DR-TB in prison populations, new drugs should be made available to incarcerated populations
- These drugs are recommended for use by the WHO and thus can be used in prison populations

# Clinical Considerations: Clinical Review Committees

- Most countries and programs have clinical review committees/consilia as part of PMDT
- These groups can be used to review patient cases where new drugs are being considered, provided they are able to meet and make decisions in a timely fashion
- Should use standardized referral forms
- Can be helpful in difficult situations (i.e. children, pregnancy)
- Can link with international community for support (i.e. ERC committee)

# Clinical Considerations: Case Example

- MP is a 35 year-old female on treatment for MDR-TB. She was diagnosed via Xpert MTB/RIF and was found to have resistance to HRES on solid media.
- She is started on a regimen of Z-KM-Levo-Ethio-CS but fails to improve, and her cultures fail to convert. Here culture from month 5 comes back positive after 14 days.
- What should be done for MP? How might new drugs be used in her situation?

# Clinical Considerations: Case Example

- ZL is a 22 yo female diagnosed with XDR-TB. Upon household screening, three of her siblings are also diagnosed with XDR-TB, including her two sisters, ages 19 and 21, and her brother who just turned 17.
- What treatment regimens should be constructed for each of her family members?

# Clinical Considerations: Case Example

- RP is a 31 yo male with HIV and a CD4 count of 125. He is started on therapy with 3TC-TDF-EFV. 5 weeks into his ART, he develops fever, hemoptysis and lethargy. He is diagnosed with RR-TB and also found on HAIN Lineprobe to have resistance to INH and KM.
- How should his MDR-TB be treated?

# Clinical Considerations: Case Example

- PT is a 44 yo male with XDR-TB who is currently in his third month of treatment for MDR-TB with resistance also to the FQs with a regimen consisting of Z-KM-BDQ-Ethio-CS-PAS.
- He has HIV co-infection and is stable on a regimen of NVP-3TC-TDF.
- His 12 week ECG shows QTcF prolongation at 510msec.
- What should be done for him?

# Clinical Consideration: Case Example

- MG is a 32 yo woman with newly diagnosed pulmonary MDR-TB in Georgia
- What should her initial treatment regimen be?
- What tests (microbiologic and otherwise) should be sent prior to starting this regimen?

# Clinical Considerations: Case Example

- MG is started on a regimen of CM-Moxi-Prothio-PZA-CS-PAS.
- She begins to vomit after taking her pills and her vomiting does not improve even with antiemetics. This goes on for 2 weeks and she decides she wants to stop taking therapy because she is so miserable. What should be done next?

# Clinical Considerations: Summary

- BDQ, DEL, LZD can be used with minimal modifications to the current PMDT clinical programs
- Patients with resistance or intolerance to SLDs should be prioritized
- Most data on patients 18-65 with pulmonary disease, but can likely be used safely in other populations
- Important to use as part of effective combination therapy

# Clinical Considerations: Summary

- Additional baseline tests include ECG, lipase (BDQ) and albumin (DEL)
- Inpatient or outpatient, monthly assessments for first 6 months
- QTc prolongation must be placed in context
- DEL likely better in children and with ART
- Plans should be made for vulnerable populations
- Clinical review committees can be helpful in difficult cases but must be nimble and responsive

Questions?

Thank You  
for  
Attention