TB and DM treatment: rational for strict glycemic control, overview on drug interactions (focus on mSTR drugs)

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Diabetes Mellitus and TB

TB patients with DM may face worse outcomes than those without DM for several reasons:

- as evidenced in vivo and in vitro studies, DM affects the innate and adaptive immune responses necessary to control TB infection ;
- reduced ability to clear infection could conceivably lead to TB-related deaths among people with DM specifically, it is also possible that these patients face a greater likelihood of death during TB therapy because of DM-associated complications, such as heart disease, stroke and renal failure. Unfortunately, the studies discussed above did not attribute the deaths to specific causes.
- DM may affect the pharmacokinetics of TB drugs so that the bactericidal activity is lessened.
- some patients with DM may have renal failure that requires fine-tuning of dose or interval of administration owing to potential toxicity by accumulation of drugs or potential dilution through hemodialysis
- the administration of rifampicin may interfere with pharmacokinetics of hypoglycemic agents, such as glyburide and rosiglitazone, which impedes glucose control. These pharmacodynamic interactions may all contribute to poorer outcome among TB patients with DM.
- patients with DM may face a higher chance of recurrent TB due to reduced immunity that increases the vulnerability to reactivation of the prior infection

Screening people with Tuberculosis for diabetes mellitus

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## _WHO and UNION recommend testing all adult TB patients for Diabetes Mellitus_

with limited resources, it is more cost effective to conduct targeted screening. Target groups can be considered patients with tuberculosis:

- aged 40 and above
- overweight or obese (with a body mass index of 25 and above);
- with family history DM
- with consume excessive amounts of alcohol
- with previous gestational DM or previous pre-DM

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- At the time of diagnosis and registration, TB patients should first be asked about whether they are already known to have DM or whether they are taking any DM medication. These patients should have their glycaemic control assessed using HbA1c or FBG (whichever test is available and convenient) and managed further based on the results.

- TB patients who state that they do not have DM should be offered a single RBG measurement at this time to identify those who are at risk and require further investigation with either FBG or HbA1c.

Algorithm for the diagnosis of DM among TB patients

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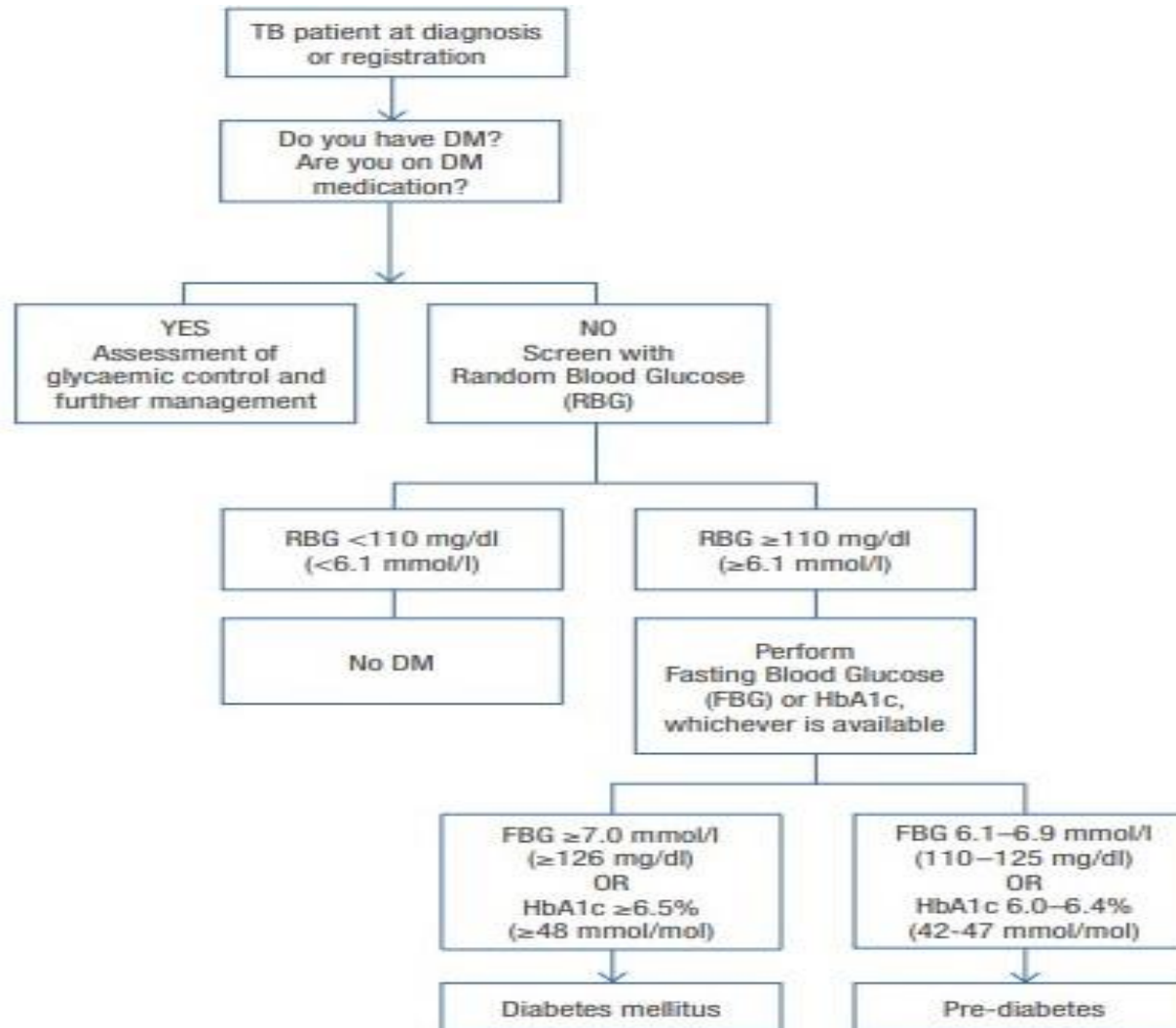
Main tests for diagnosing DM

- Oral glucose tolerance test (OGTT);
- Fasting blood glucose (FBG)
- Glycosylated haemoglobin (HbA1c).

(recommended by WHO and the American Diabetes Association)

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RBG<6.1mmol/l (<110mg/dl)	The TB patient is at low risk of DM and no further investigation is required
RBG≥6.1mmol/l (>110mg/dl)	The TB patient requires further investigation. This can be done on the same day using a HbA1c or on another day in a fasting state for a FBG test
HbA1c≥6,5% (≥48mmol/mol)	The patient is diagnosed as having DM
FBG ≥7.0 mmol/l (≥126 mg/dl):	The patient is diagnosed as having DM

Treatment of diabetes mellitus in tuberculosis patients

Important aspects of a successful treatment of TB in DM patient is to achieve good glycemic control as early as possible and maintain it throughout the entire course of anti-TB treatment, without causing drug interactions or side effects. Strict glycemic control makes antiTB drugs more effective. It is also required for better clinical, radiological, and bacteriological resolution of the disease. The glycemic target for a patient with co-morbidity of TB-DM is like that of DM itself. However, individualized glycemic targets might be needed considering

- the age of the patient
- duration of DM
- risk of adverse events (hypoglycemia, nephropathy, neuropathy hepatic dysfunction).

Targets for glycemic control during TB treatment

Measurement	Targets
Fasting blood (capillary) glucose (FBG)	<10mmol/l (<180 mg/dl)
Post-prandial blood glucose (PPG)	<11.1mmol/l (<200 mg/dl)
HbA1c	<8%

Treatment of diabetes mellitus in tuberculosis patients

Several factors except drug–drug interaction determine the choice of anti–diabetes drugs to be used in patients with tuberculosis, such as availability, cost, ease of administration, and safety. Safety concerns include:

- hypoglycaemia with sulphonylureas and insulin,
- lactic acidosis (especially under hypoxic conditions) with biguanides,
- gastrointestinal complaints wih biguanides, meglitinides, and alpha–glucosidase inhibitors, and
- hypersensitivity to sulphonylureas (which might overlap with side–effects of antituberculous drugs).

Treatment of diabetes mellitus in tuberculosis patients

What glucose-lowering drugs should be used in TB patients?

- Metformin
- SUs
- insulin

Newer drugs for treating DM, such as incretin-based therapies (glucagon-like peptide 1 receptor agonists /GLP1-RI and dipeptidyl peptidase 4 inhibitors/DPP4-i) and sodium glucose transporter 2 inhibitors/SGLT2-i, are generally not available for resource-limited persons, besides, there is less information on their use in TB patients

Treatment of diabetes mellitus in tuberculosis patients

Insulin

- ❑ is the preferred agent for control of diabetes in patients with TB.
- ❑ It has anabolic action (improves appetite and promotes weight gain in malnourished TB patients, apart from lowering the pill burden).
- ❑ is the best agent for fastest reduction of HbA1c.
- ❑ is the best anti-DM medication for patients with coexistent nephropathy/hepatotoxicity with contraindication for oral anti-diabetic drugs (OADs);
- ❑ should preferably be given throughout the entire course of anti-TB treatment.

Treatment of diabetes mellitus in tuberculosis patients

Metformin as a hypoglycaemic agent when combined with TB treatment

- ❑ This is the first choice glucose-lowering agent recommended in type 2 DM, including patients with TB. Its advantages include extensive experience in its use, extremely low risk of hypoglycaemia, effectiveness, low cost, beneficial effects on cardiovascular disease, lack of clinically relevant interaction with rifampicin and finally a potential benefit on TB itself. Its two main disadvantages are gastrointestinal side effects and rarely, the development of lactic acidosis which may be fatal if unrecognized and untreated.

- ❑ In resource-limited settings it is difficult to diagnose lactic acidosis, so this condition needs to be suspected in any patient with DM and TB receiving metformin who deteriorates during the course of TB treatment. The starting dose of 500 mg od/bid can be titrated to 1,000 mg bid or 500 mg bid for those with a renal clearance (eGFR) <50 ml/min.

Treatment of diabetes mellitus in tuberculosis patients

Sulphonylureaderivates as a hypoglycaemic agent when combined with TB treatment

- ❑ These are second choice glucose-lowering agents which can be used as "add-ons" to metformin if metformin alone is ineffective or if there is intolerance or a contraindication to metformin. The most widely used SUs are gliclazide, glibenclamide, glimepiride and glipizide. The two main disadvantages are a) the risk of hypoglycaemia and b) strong interactions with rifampicin that show wide individual variation but result in their efficacy being reduced by 30–80%.

- ❑ Rifampicin increases the hepatic metabolism of all sulphonylurea derivatives, the most widely used class of oral diabetes drugs worldwide. This effect on sulphonylurea derivatives has great inter-individual variation, which makes dose adjustments difficult and increases a patient's risk of hyperglycaemia or hypoglycaemia. Inter-individual variation in the induction of the metabolism of diabetes drugs makes dose adjustment difficult when rifampicin treatment is interrupted or stopped; the same is true for most other oral antidiabetes drugs.

Management of DM in TB: insulin therapy

- Management of DM in TB should be aggressive. An optimal glycemic control results in a better patient outcome; therefore vigorous efforts should be made to achieve such control. However, this approach should be balanced against the possible harm and additional efforts needed for implementation. Personalized pragmatic glycaemic targets might be needed that account for an array of factors, such as severity and prognosis of a given patient's tuberculosis disease, risk of adverse events such as hypoglycaemia, duration of diabetes, comorbidities, age, patient capabilities and treatment preferences, and available resources. Frequent monitoring is needed to ensure good glycaemic control. Self-measurement of blood glucose should be recommended.

- Insulin therapy should be started from the beginning. The American Association of Clinical Endocrinologists recommends the use of modern insulins or insulin analogs because they are more predictable in action and cause less hypoglycemia, and do not involve specific drug interactions. The use of traditional human insulins is not recommended.
- If a diabetic patient receiving insulin develops tuberculosis, the insulin dose should be adjusted as required.
- If a diabetic patient receiving OAD develops tuberculosis, he should be switched to insulin with OAD.
- If diabetes is first detected in a patient with tuberculosis, the patient should be started on insulin treatment to control the diabetes.

Management of diabetes in TB patients

- Insulin is indicated in cases of severe hyperglycemia (eg, HbA1c> 10% or FBG> 15 mmol / L (> 270 mg / dL), or if glucose control goals cannot be met with metformin and other oral medications. The use of insulin is usually accompanied by the need for self-monitoring of blood glucose levels using glucometers.

- If the patient is taking metformin, continue. If the patient is taking other oral glucose-lowering drugs, consider switching to metformin, which does not interact with rifampicin.

- Provide appropriate nutritional instructions.

- If not already prescribed, aspirin should be started in patients who have cardiovascular disease or a history of heart attack or stroke.

Treatment of diabetes mellitus in tuberculosis patients

Common glucose-lowering drugs used for managing DM in TB patients

Characteristic	Metformin**	Sulphonylureaderivates	Insulin
Drug of choice	First choice	Add-on Used in case there is a contraindication or intolerance to metformin	Use if targets for HbA1c or FBG cannot be reached or if there is symptomatic hyperglycaemia
Risk of hypoglycaemia	No	Yes	Yes
Contraindication if eGFR<30 ml/min * dose (od = once a day; bid = twice a day)	500 mg od or bid, titrated to a maximum dose of 2,000 mg daily	Gliclazide 40–80 mg OD Glibenclamide 2.5–5 mg OD Glimepiride 1–2 mg OD Glipizide 5 mg OD	10 units basal insulin per day as the starting point
Interaction with rifampicin	Not clinically relevant	Yes, 30–80% lower efficacy with rifampicin	None
Main side effects	Gastrointestinal Lactic acidosis	Hypoglycaemia	Hypoglycaemia
Use in reduced kidney function(GFR = glomerular filtration rate)	Dose adjustment if eGFR Contraindication if eGFR<30 ml/min *	Increased risk of hypoglycaemia Preference gliclazide	Can be safely used
Cardiovascular events	Recognised benefit	Neutral	Neutral

Management of HbA1c or blood glucose at the start of TB treatment

HbA1c or FBG at the start of TB treatment	TB patient diagnosed with new DM	TB patient already receiving treatment for DM
If HbA1c <8% or FBG <10.0 mmol/l (180 mg/dl)	No further immediate action is taken; re-assess blood glucose levels at 2 months and again at the end of TB treatment	No further action is taken; the patient continues on current medication for DM
If HbA1c ≥8% but less than 10% or FBG ≥10 mmol/l (180 mg/dl) but less than 15 mmol/l (270 mg/dl)	Start metformin 500 mg once a day, reassess in two weeks and increase the dose to 500 mg twice a day or refer if blood glucose levels have not improved	Intensify current glucose-lowering treatment and reassess one-two weeks later

Most common side effects of the four main anti-TB drugs, their association with diabetes, and proposed treatments

Drug	Adverse Effect	Considerations from DM	Management
Isoniazid	Peripheral neuropathy Hepatitis	May be worsened by DM	Give pyridoxine Stop all medication
Rifampicin	Gastrointestinal complaints Hepatitis Red urine	May be worsened by metformin	Symptomatic treatment Stop all medication Reassure
Pyrazinamide	Arthralgia Hepatitis	Arthralgia and hepatic toxicity may be more common in DM	Aspirin or NSAID Stop all medication
Ethambutol	Retro-bulbar neuritis	May be worsened by DM retinopathy	Stop all medication

Programmatic management of TB and Diabetes

Program issue	Intervention	Considerations
Length of anti-tuberculosis	treatment	
	Currently 6 months for new drug-susceptible TB: RMP, INH pyrazinamide and EMB for the first 2 months, followed by RMP and INH for 4 months	Increased rates of treatment failure and recurrent TB suggest need to consider extended treatment; this should be evaluated in formal clinical trials Reasons for increased failure and recurrent TB are not known and include more extensive TB disease, altered DM immune response, reduced concentrations of anti-tuberculosis drugs

Programmatic management of TB and Diabet

Programme issue	Intervention	Considerations
Drug–drug interactions	leading to reduced drug	concentrations
	RMP increases hepatic metabolism of oral sulphonylurea derivatives, thus reducing their plasma concentrations and making dose adjustments difficult. Little is known about the interaction of RMP with newer anti-diabetes drugs Diabetes (due to the disease or sulphonylurea derivatives) may reduce plasma RMP concentrations	Insulin and metformin are largely unaffected by RMP and should be strongly considered if drug treatment of DM is needed Weight–adjusted doses of anti–tuberculosis drugs might be needed, although this is difficult to implement in routine programmatic practice Associated antiretroviral therapy for HIV–infected TB patients may incur additional interactions

Programmatic management of TB and Diabet

Programme issue	Intervention	Considerations
Drug-drug toxicity	leading to reduced drug	concentrations

	INH and DM
	
	EMB and DM
	
	Metformin and anti-tuberculosis drugs
	
	All drugs
		Peripheral neuropathy induced by both INH and DM. Use adjunctive pyridoxine
		   EMB-induced ocular effects and DM-induced retinopathy
		   Gastrointestinal toxicity from metformin and anti-tuberculosis drugs. Potentially fatal lactic acidosis from interaction with INH
		   There may need to be more intensive laboratory monitoring of patients with DM and TB

Programmatic management of TB and Diabet

Programme issue	Intervention	Considerations
Adherence to medication	Adherence could be compromised by symptoms of both diseases, high pill counts, side effects of drugs	Adherence could be compromised by symptoms of both diseases, high pill counts, side effects of drugs Appropriate patient education, use of fixed-dose combinations of anti-tuberculosis drugs
TB infection control	Ensure DM clinics are designed for good ventilation—open windows, skylights	More information needed about the role of DM clinics in facilitating transmission of Mycobacterium tuberculosis

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Programme issue	Intervention	Considerations
Lifestyle modifications	Getting patients to quit smoking and reduce alcohol consumption Dietary advice Exercise	Smoking and alcohol are both risk factors for TB and compromise healthy outcomes in non-communicable diseases such as DM The classic dietary advice for controlling DM and TB may be conflicting: calorie restriction to lose weight (DM) vs. high protein, high calorie intake to gain weight (TB). Health care workers will require specific guidance to deal with this. It can also be confusing for patients, who will require proper counseling DM patients should have daily physical activity; when they also have TB, this may be practically difficult due to the physical condition of the patient. As the condition of the patient improves, gradual increase in exercise could be introduced TB ¼ tuberculosis; DM ¼ diabetes mellitus; RMP ¼ rifampicin; INH ¼ isoniazid; EMB ¼ ethambutol; HIV ¼ human immunodeficiency virus.

DM and R/MDR/ TB

- Antituberculosis (anti-TB) treatment is affected by DM and hypoglycemic agents;
- glucose control in DM is affected by both TB and some anti-TB drugs
- DM may affect the pharmacokinetics of different drugs, including those used to treat TB. DM may affect absorption (owing to changes in subcutaneous adipose blood flow, muscle blood flow, and gastric emptying), distribution (owing to nonenzymatic albumin glycation), biotransformation (owing to enzyme/transporter regulation involved in this process), and drug excretion (owing to nephropathy)

Pharmacokinetics: use of bedaquiline and delamanid in diabetes patients

Oral hypoglycemic agent	Sirturo® (bedaquiline)	Deltyba® (delamanid)
Meglitinides		
Starlix® (nateglinide)	3A4	3A4
Prandin® (repaglinide)	3A4/2C8	3A4
Thiazolidinediones		
Actos® (pioglitazone)	3A4/2C8	3A4
Avandia® (rosiglitazone)	2C8	NC
Sulfonylureas		
Glyburide® (glibenclamide)	3A4	3A4
Diamicron® (gliclazide)	2C8	NC
Glurenorm® (gliquidone)	3A4	3A4
DPP–IV inhibitors		
Januvia® (sitagliptin)	3A4/2C8	3A4
Onglyza® (saxagliptin	3A4	3A4
Other		
Cycloset® (bromocriptine mesylate)	3A4	3A4

Abbreviations: NC, no crossing; DPP–IV, dipeptidyl peptidase IV.

Pharmacokinetics: use of bedaquiline and delamanid in diabetes patients

Advantages and disadvantages of the use of insulinanalogs and metformin in multidrug-resistant tuberculosis patients treated with bedaquiline/delamanid

Clinical impact	Metformin	Insulin analogs
Advantages	No interaction at the ABCB1, CYP3A4, or protein-binding site levels	No interaction at the transporter or CYP3A4 levels Possible interaction at the protein-binding site (detemir, degludec)
	Anti-inflammatory properties	Anti-inflammatory, vasodilatory, and antioxidant properties
	No risk of QT prolongation	No risk of QT prolongation More predictable hypoglycemic effect in severe infection compared to metformin Allowed in renal and hepatic impairment
Disadvantages	Enhanced gastrointestinal toxicity	
	Unpredictable hypoglycemic effect in severe infections Not allowed with renal or hepatic impairment	Possibly increased risk of hypertensive episodes and muscle damage (glargine)

Pharmacokinetics: use of bedaquiline and delamanid in diabetes patients

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Possible pharmacokinetic interactions between bedaquiline/delamanid and hypoglycemic agents and their expected clinical effects

Interaction level	Possible pharmacokinetics	Expected clinical effects
Transporter level (ABCB1)	Inhibition of SU and SGLT-2 inhibitors	Lack of hypoglycemic efficacy
Protein-binding level	Competition for protein-binding sites (bedaquiline/delamanid vs SU, glinides, SGLT-2 inhibitors)	Unclear
Hepatic metabolism level	Decreased exposure to bedaquiline/delamanid with strong CYP3A4 inducers (bromocriptine)	Lack of antituberculosis efficacy
	Increased exposure to oral hypoglycemic agents mainly metabolized by CYP3A4 (nateglinide, sitagliptin, saxagliptin) due to inhibitory effect of M	Hypoglycemic episodes
	Increased exposure to bedaquiline in severe infection (downregulation of P450 expression)	
	Increased exposure to oral hypoglycemic agents in severe infections (downregulation of P450 expression)	Toxicity of bedaquiline
		Hypoglycemic episodes

Note: ABCB1 is a P-glycoprotein, and M2 is the bedaquiline metabolite.
Abbreviation: SU, sulfonylureas.

Clinical considerations related to the use of bedaquiline and delamanid in diabetes patients

Renal impairment

- Mild renal impairment (50–80 mL/min creatinine clearance [CrCLN]) does not appear to affect bedaquiline/delamanid exposure, as their renal excretion is not substantial ($<0.001\%$ for bedaquiline and $<5\%$ for delamanid);

- in patients with severe renal impairment or in patients who required hemodialysis or peritoneal dialysis, drug concentrations could be elevated owing to renal dysfunction-mediated alteration of drug pharmacokinetic

- bedaquiline should be used with caution in patients with severe renal impairment (<30 mL/min), but to use delamanid in this patient group discourages (Summary of Product Characteristics –SmPC)

- delamanid is contraindicated in patients with albumin <2.8 g/dL

Clinical considerations related to the use of bedaquiline and delamanid in diabetes patients

Hepatic impairment

- bedaquiline and delamanid discourage their use in in patients with severe hepatic impairment (SmPC)

Hypokalemia

- Diabetes patients often present electrolyte disturbances, including hypokalemia resulting from insulin administration, and gastrointestinal or renal loss of K^+. Special precautions should be taken when del or Bdq is administered to patients with hypokalemia.

Phospholipidosis

- Bedaquiline and delamanid have been shown to induce phospholipidosis at most doses and exposures in drug-treated animals. However, this finding may be of special interest for diabetes patients, as there are reports suggesting the role of drug-induced phospholipidosis in progressive renal insufficiency in humans

Adverse drug reactions

cardiovascular system

- delamanid and bedaquiline are metabolized by CYP3A4, CYP3A4 inhibitors may further prolong the QTc interval, especially the potent CYP3A4 inhibitor SU and glinide agents (they are inhibit ATP-dependent K+ channels, delaying repolarization times and prolonging the QTc);

- hypotension was commonly seen in clinical studies with delamanid. The pathophysiology of delamanid-induced hypotension is not clear yet, but its concurrent use with other potentially hypotensive agents should be closely monitored.

- Cardiovascular toxicity is not common among insulin analogs. However, there are numerous case reports describing hypertensive episodes with glargine (Lantus) [SmPC does not include hypertension as a possible side effect]. Delamanid has also produced hypertension in patients with MDR/TB. Although the causal relationship between hypertension and glargine exposure has not been established yet, monitoring this side effect when combining glargine and delamanid is recommended.

Hepatic-related adverse drug reactions and gastrointestinal disorders

❑ special attention should be given to the concurrent use of bedaquiline and thiazolidinediones and acarbose, also known for their hepatotoxic potential

❑ vomiting, diarrhea, nausea, and upper abdominal pain may be potentiated when bedaquiline/delamanid are combined with biguanides, alpha-glucosidase inhibitors, bromocriptine, glinides, and SGLT-2 inhibitors, which also produce gastrointestinal disturbances, similarly to insulin analogs, GLP-1 receptor agonists, and pramlintide.

❑ precaution should be taken when bedaquiline is combined with DPP-IV inhibitors, exenatide, and GLP-1 receptor agonists that could produce pancreatitis or alter pancreatic enzymes.

Adverse drug reactions

Rhabdomyolysis potential

- Degenerative changes in skeletal muscles were seen in mice, rats, and dogs treated with bedaquiline. Fibrohistiocytic infiltration and degeneration of muscle fibers in the tongue and quadriceps were detected in rats treated for 13 weeks with bedaquiline at high doses (24 mg/kg). This myopathy was reversible 12 weeks after the treatment period.In clinical trials with bedaquiline, there were no reported cases of rhabdomyolysis.However, myalgia was reported as a common side effect for both bedaquiline and delamanid.Since bedaquiline-induced muscle damage is reversible, the risk of possible muscle effects may not outweigh the benefit that this drug has for MDR-TB treatment. However, combining bedaquiline with other drugs that may cause muscle damage, such as pioglitazone or insulin glargine, may be dangerous. Pioglitazone was reported to cause severe acute rhabdomyolysis, with dose-independent myalgia as a common side effect.Further studies are needed to elucidate bedaquiline's potential for inducing rhabdomyolysis in humans and the effects of its concomitant use with other agents that could potentially induce muscle damage.

Peripheral neuropathy

- Transitory, acute painful peripheral neuropathy has been observed in patients with a rapid improvement in glycemic control with detemir. Peripheral neuropathy has been reported as a common side effect of delamanid, but it remains unclear whether the concurrent use of these drugs would aggravate this side effect
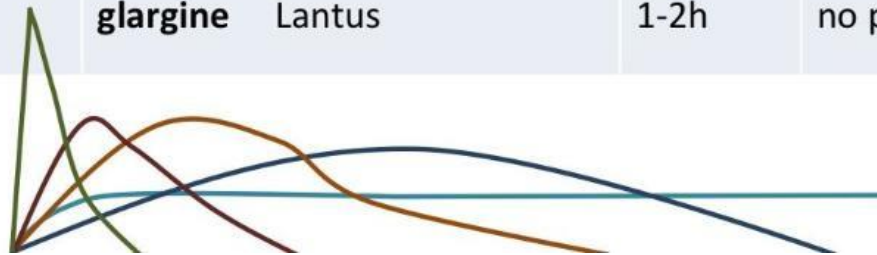
DIABETES
Insulin Types

		Type	Trade Name	Onset	Peak	Duration
Bolus	Rapid Acting	**aspart** **glulisine** **lipsro**	NovoRapid Apidra Humalog	10-15m	1-1.5h	3-5h
	Short Acting	**Regular**	Humulin-R Novolin grToronto	30-45m	2-3h	6.5h
Basal	Intermediate	**NPH**	Humulin-N Novolin ge NPH	1-3h	5-8h	14-18h
	Long Acting	**detemir** **glargine**	Levemir Lantus	1-2h 1-2h	8-10h no peak	12-24h 22-24h

- **linezolid + insulin glulisine**

  linezolid increases effects of insulin glulisine by unknown mechanism. Use Caution/Monitor.

- **levofloxacin + insulin glulisine**

  levofloxacin increases effects of insulin glulisine by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely.

- **levofloxacin + bedaquiline**

  levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

- **levofloxacin + insulin lispro**
  levofloxacin increases effects of insulin lispro by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely.
- **linezolid + insulin lispro**
  linezolid increases effects of insulin lispro by unknown mechanism. Use Caution/Monitor.
- **levofloxacin + bedaquiline**
  levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

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- **levofloxacin + insulin regular human**
  levofloxacin increases effects of insulin regular human by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely.
- **linezolid + insulin regular human**
  linezolid increases effects of insulin regular human by unknown mechanism. Use Caution/Monitor.
- **levofloxacin + bedaquiline**
  levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

- **linezolid + insulin NPH**
  linezolid increases effects of insulin NPH by unknown mechanism. Use Caution/Monitor.
- **levofloxacin + insulin NPH**
  levofloxacin increases effects of insulin NPH by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely.
- **levofloxacin + bedaquiline**
  levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

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- **linezolid + insulin glargine**
  linezolid increases effects of insulin glargine by unknown mechanism. Use Caution/Monitor.
- **levofloxacin + insulin glargine**
  levofloxacin increases effects of insulin glargine by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely.
- levofloxacin + bedaquiline
  levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

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chemoptherapy regimen	metformin
Lfx +Bdq+Lzd+Clz+Cs	**levofloxacin + metformin** levofloxacin increases effects of metformin by pharmacodynamic synergism. Use Caution/Monitor. Quinolone antibiotic administration may result in hyper- or hypoglycemia. Gatifloxacin is most likely to produce dysglycemia; moxifloxacin is least likely. **linezolid + metformin** linezolid will increase the level or effect of metformin by unspecified interaction mechanism. Use Caution/Monitor. **levofloxacin + bedaquiline** levofloxacin and bedaquiline both increase QTc interval. Modify Therapy/Monitor Closely. ECG should be monitored closely

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