Use of New and Repurposed Medications in Special Populations

As noted previously, although clinical trials of bedaquiline (BDQ) and delamanid (DLM) tended to exclude special populations, the experiences of compassionate use/expanded access programs have allowed for the treatment of some of the special populations, albeit in low numbers. In general, it is recommended that a country have a clinical expert committee that can quickly review the use of new medicines in these populations on a case-by-case basis. Some general considerations for use of new and repurposed medications are discussed below.

Children

In general, children have not been included in clinical trials of DLM and BDQ for the purposes of registration of these medications and, thus, there is limited information about their long-term safety and pharmacokinetics (PK) in children. Linezolid (LZD) and clofazimine (CFZ) have been used in children, but there are currently no formal studies on their PK and safety (although LZD PK studies are currently being carried out at the Desmond Tutu TB Centre in Cape Town).

However, children are often desperately in need of these medicines, especially in settings where rates of primary transmission of resistant strains are high. Programs must therefore weigh the risk of using these medications in children or letting them die of untreated or poorly treated drug-resistant tuberculosis (DR-TB) or lose their hearing to the injectable agents, which can be a disaster for child development.

DLM is being tested for PK and safety in children and has been given for compassionate use in children as young as 13 years. For this reason, it is preferable to BDQ. There is also a pediatric formulation of DLM available, which comes as a 50 mg scored, dispersible tablet.

Recommendations for pediatric dosing are given below, however, they have not been confirmed with intensive PK studies.

Pediatric Doses of New and Repurposed Medications

Medicine	Recommended Dose	Comment
DLM	Age bands: 13 years and above: same as adult dose 6-12 years: 100 mg/daily 2-6 years: 50 mg daily 0-2 years: Not yet established	Currently being assessed Medicine of choice in children under the age of 14 years
BDQ	6 mg/kg loading dose daily for two weeks followed by 3 mg/kg thrice weekly	This is based on current dosing with an adult weight of 65 kg estimated
LZD	10 mg/kg/daily	Available as a suspension Could be divided into three separate doses
CFZ	1 mg/kg daily	Comes as capsule or gel cap of 50 or 100mg; consider compounding. Gel caps cannot be split,

Medicine	Recommended Dose	Comment
		but could be given every other day if need be with the dose averaged

It should be noted that parents and guardians will need to provide consent for children below the age of formal consent (16 years in South Africa), and assent will also be needed from the child.

Adolescents

Adolescents (those aged 13 years and above for the purpose of this document) have not been included in clinical trials, usually because obtaining consent can be problematic and many groups do not wish to invest the extra time needed to get approval to include adolescents in their trials. DLM can be used in children aged 13 years and older, and it is likely that BDQ can be used safely in this population as well. It should be noted that adolescents may need additional adherence support and are at high risk of "falling through the cracks" at each step of the DR-TB cascade.

Elderly

Persons over the age of 65 years were left out of the clinical trials and many compassionate use programs, but DLM and BDQ can be used in this population, provided that there is no active congestive heart failure or severe coronary artery disease. LZD has been used in this population, although rates of adverse events are likely to be higher, especially bone marrow toxicity.

Pregnancy and Breastfeeding

There are no data on the safety of the new medicines on the developing fetus or on breastfed children. Animal studies with BDQ showed no signs of reproductive toxicity; it is considered class B during pregnancy according to the US Food and Drug Administration (safety based on animal studies; note that most other second-line drugs [SLD] are considered class C, and the injectables are considered class D, definitely unsafe based on human data). DLM studies in animals have shown signs of reproductive toxicity. LZD can be used safely in pregnancy and breastfeeding. Because CFZ accumulates in the lipids, it will be passed on during breastfeeding. When a woman who is pregnant or breastfeeding is in need of new medicines, programs must weigh the risks and benefits of using the medications versus the risks of untreated or undertreated DR-TB in a woman. Clinical expert committees can help make decisions in this population.

As with all programmatic management of drug-resistant TB (PMDT), contraceptive methods should be offered to women free of charge as part of routine management. There are very limited data on the interactions between different forms of contraceptives and the new medicines. If a woman is on a BDQ-containing regimen and becomes pregnant, the long half-life of this

medication should be considered when trying to decide whether or not to continue therapy. In many cases, the woman may already be past her first trimester of pregnancy and even if the medicine is stopped, it will persist in the serum for up to six months.

Extrapulmonary TB

Patients with primary extrapulmonary (EP) DR-TB were not included in the registration trials largely because it is difficult to define outcomes in this population if routine culture specimens cannot be obtained. There is no reason to believe that the new and repurposed medications cannot be used in this population.

Hepatitis B and C

In some regions of the world, there are significant rates of hepatitis B and C in patients who have DR-TB. There are no data on the safety or efficacy of BDQ or DLM in this population. LZD and CFZ have been used, but there can be overlapping toxicity with some of the medicines used to treat hepatitis. The new protease inhibitors for treating hepatitis C have never been used with BDQ and DLM, thus, there is no information on drug-drug interactions. If patients with hepatitis B or C meet the criteria for using one of the new medications, care should be taken to ensure that there is no acute liver problem, that the transaminases are < 3 times the upper limit of normal, and that the bilirubin is < 1.5 times the upper limit of normal when starting the medicine. More frequent monitoring of liver function tests may also be needed. Clinicians will need to weigh the risks of untreated or poorly treated DR-TB versus the risk of hepatotoxicity when making a decision about using BDQ or DLM.

Substance users

Many patients with DR-TB suffer from alcohol and substance use. Such individuals were not included in the clinical trials for these new and repurposed agents, and thus, there is limited information on their safety. While all attempts should be made to offer persons with alcohol or substance abuse effective treatment, the new and repurposed medicines can be introduced in people using alcohol and other substances. These medicines should be used with caution in patients with active liver damage, and all substance users should undergo testing for hepatitis B and C in regions of the world where these diseases are common. There may also be a higher risk for QTc prolongation among persons actively consuming alcohol, and more frequent electrolyte and QTc monitoring should be considered. Substance abusers also need harm reduction treatment and additional adherence support.