THE SWIFT response project

Update on the use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis

The recent announcement from the Stop TB Partnership, the Global Drug Facility, and Otsuka Novel Products GmbH about the availability of delamanid through the Global Drug Facility means that for the first time, countries and programs will be able to offer both drugs—alone or in combination—to persons living with multidrug-resistant TB (MDR-TB). To date, there has been limited global clinical experience with delamanid but countries now have an additional therapeutic option when it comes to treating individuals with MDR-TB. The World Health Organization's PMDT Companion Handbook offers recommendations on the optimal use of delamanid. The SWIFT Response Project makes the following recommendations for the use of delamanid based on these WHO recommendations and the current clinical experience with the drug:

1) Delamanid should be used as the novel agent of choice in patients who have an indication for receiving a new TB drug based on second-line resistance or intolerance in the following populations:

- **Children between the ages of 6 and 18 years of age**, as there are data supporting the short-term safety and dosing of delamanid in this population. PK and safety data on children ages 5 years and under are currently being collected. Children ages 13 years and above should receive the standard 100mg twice daily dose of delamanid. Children between the ages of 6 and 13 years should receive 50 mg twice daily;

- **Individuals on antiretroviral therapy who cannot be changed from an efavirenz-based regimen**, since early data suggest that delamanid can be safely given with all antiretroviral medications;

- **Persons with a history of allergy, intolerance, or prior exposure to bedaquiline**

- **Persons with > 1 month history of clofazimine treatment**, as there are some early lab reports of cross resistance seen between bedaquiline and clofazimine, although the clinical implications of these findings are unclear;

- **Pregnant women**, as animal data show no evidence of teratogenicity with delamanid and the company allows for the use of delamanid in pregnant women in their compassionate use protocol following careful weighing of risk versus benefit by the treating physician

2) Delamanid should be added to a multidrug backbone regimen in individuals who are at high risk of treatment failure, including those with extensive disease, diabetics, persons with HIV, and other populations with poor outcomes according to local program data.

3) Although there are limited data on the use of bedaquiline and delamanid given in combination, there is growing experience using these two medications together, especially in patients with extensively drug-resistant TB. The combination of bedaquiline and delamanid along with other agents (i.e. linezolid) is recommended for individuals in whom a four drug regimen cannot be composed with other second-line drugs due to resistance or intolerance. Patients on the combination need close monitoring, with twice monthly ECGs for the first 12 weeks of therapy.

Of note, delamanid has a lower genetic barrier to develop resistance compared with bedaquiline and linezolid, and it is essential that it be used with a strong backbone regimen. Using delamanid only in individuals who have "no other options" will not likely yield positive results.

Programs that have developed implementation plans for bedaquiline can easily incorporate delamanid into such plans, and there is no additional monitoring or testing needed, aside from a baseline albumin. Delamanid is recommended for 6 months duration, although in the phase IIb trials, the drug was given for as long as 8 months. Delamanid comes as a 50mg tablet, and the dose is 100mg twice daily, although once daily dosing of 200mg could be considered and was used in the phase III trials of the drug after patients completed 2 months of delamanid at the twice daily dose. Delamanid has been well tolerated in clinical trials, with nausea, vomiting, insomnia, and mild QTc prolongation being reported. The drug has a 5 year shelf life and can be ordered through the Global Drug Facility for USD 1700 per 6 month course. Otsuka will continue to manage a compassionate use program on a case-by-case basis, and for information on how to access this program, please contact Jennifer Furin at jenniferfurin@gmail.com.