Programmatic Implementation of New Medications for the Treatment of Drug-Resistant Tuberculosis: A Report on Global Progress and Challenges

Prepared by

A task force of the

Introduction

Drug-resistant tuberculosis (MDR-TB) is a serious global public health problem[1], and unless there are radical changes in the management of MDR-TB, it is estimated to be one of the three infections that will kill more people than cancer by the year 2050[2]. Current therapy for MDR-TB requires the use of multiple, toxic and expensive drugs given for a period of 18-24 months and results in success in only about half of the patients treated for the disease[3]. The introduction of two new medications for the treatment of MDR-TB—bedaquiline (BDQ) and delamanid (DLM)—has brought renewed hope to the field, both for improved individual outcomes and to stop the ongoing transmission of MDR-TB[4].

In June of 2013 BDQ was recommended for programmatic management of MDR-TB by the World Health Organization when other alternatives are not available[5]. DLM was recommended for use by the WHO in October, 2014 for the treatment of MDR-TB under specific conditions[6]. The WHO recommended both new drugs be used according to five criteria described in Table 1. Of note, while BDQ was generally recommended for patients with resistance or intolerance to the injectable agents, the fluoroquinolones, or both, DLM was additionally recommended for any MDR-TB patient at high risk of poor treatment outcome.

In spite of the conditional approval of these two new medications by stringent regulatory authorities and the WHO recommendations, global introduction of BDQ and DLM for the

programmatic treatment of MDR-TB has yet to reach a majority of those who have indications for receiving these drugs.[7] The high mortality rates seen with MDR-TB and the ongoing spread of the disease in communities[8]—especially those with high rates of HIV[9]—prompted more than 88 civil society groups to issue an open letter calling for more urgent action on making BDQ and DLM available on a global level[10]. This letter outlined a number of key aspirational and time bound targets to be achieved by the addressees of the letter, which are reviewed in Table 2. In response to this "Call to Action", a discussion was held in Geneva as part of a planned Global Laboratory Initiative/Global Drug Resistance Initiative (GLI/GDI) meeting, and a task force of the GDI known as "DR-TB STAT" (Scale-up Treatment Action Team) was formed[11]. The goal of DR-TB STAT is to monitor progress against set time- bound targets for the introduction of BDQ and DLM under programmatic conditions for the treatment of MDR-TB. This report will present the task force's findings on global progress and challenges encountered in new drug introduction.

Processes used by DR-TB STAT

Task Force

The DR-TB STAT task force is made up of stakeholders working on introducing new medications for the treatment of MDR-TB. A list of participating organizations is included in Table 3. DR-TB STAT officially became a task force of the GDI in July 2015; though task force status was pending, DR-TB STAT held its initial meeting in April of 2015 and since then has met once a month via conference call to discuss progress and challenges in new drug introduction both on a general level and as applies to specific countries and programs.

Information collected

Information was collected from multiple sources, including national TB programs, country reports, WHO reports, information from Janssen Therapeutics and Otsuka Pharmaceuticals, information from a variety of donors (including USAID, UNITAID, and The Global Fund), order data from the Global Drug Facility, and reports from non-governmental organizations (including Partners in Health, Médecins Sans Frontières, Treatment Action Group, and KNCV Tuberculosis Foundation). Data are collected and updated on a monthly basis using a standard collection form that included the following variables: 1) The number of patients treated with each drug as part of compassionate use/expanded access programs; 2) the number of patients treated with each drug under programmatic conditions; 3) the number of countries using each drug under programmatic conditions; 4) the number of orders placed for each drug; 5) the numbers of countries in which each drug has been registered or in which registration is pending; and 6) the projected number of patients and countries that will be receiving each drug in 2016. Summary data were tabulated to describe the overall assessment of global progress that is described here. For the purposes of this report, compassionate use was defined as use of the drug accessed from the company for a specific patient and expanded access defined as use of the drug accessed from the company for a group of patients who meet certain criteria[12].

In addition to focusing on global progress, DR-TB STAT also helps identify and address barriers to new drug introduction both on a general level and in program-specific settings.

Findings of the DR-TB STAT Task Force

Bedaquiline

As of November 1, 2015, there were “more than 700 persons” who had received BDQ via compassionate use and expanded access. In addition, there were 1,872 persons receiving BDQ

under programmatic conditions in nine different countries plus the European Union (EU); most of these patients were from South Africa or Russia, but Georgia, Belarus, and Swaziland also have significant patient populations on treatment. In addition to this, orders for BDQ had been placed through the GDF for 1,764 persons in 24 additional countries, and these programmatic treatments are expected to begin in the next 6 months. Table 4 lists the countries that are using or waiting to receive BDQ for use under programmatic conditions in the next 6 months. Figure 1 shows these data in a global map format.

In terms of registration, BDQ has been registered in the EU (28 countries) and an additional 13 countries. Registration is pending in another 13 countries. Based on countries' reported plans and the plans of other implementing groups, BDQ could potentially be given to a cumulative total of more than 7,000 individuals under programmatic conditions by the end of 2016. Turnaround time from placement of order to drug delivery ranged from 3-6 months

Delamanid

Despite repeated requests, Otsuka Pharmaceuticals did not provide specific information on delamanid access, citing this information as being "proprietary". Therefore, data on the use of delamanid were compiled from other sources. According to the company, as of November 1, 2015, there were "more than 100 patients" who had received DLM via compassionate use. DLM orders cannot be placed through the GDF, and Otsuka Pharmaceuticals did not provide any information on pending drug orders. Figure 2 show these data in a global map format.

In terms of registration, DLM has been registered in the EU, Japan, and South Korea. There was no information that could be found on registration pending in any additional countries. Based on countries' reported plans and the plans of other implementing groups, DLM could potentially be

given to more than 550 individuals under program conditions by the end of 2016. No information on turnaround time for drug orders could be obtained.

Challenges in Using New Drugs Under Programmatic Conditions

Data collected on barriers to new drug use that were discussed during DT-TB STAT calls revealed a variety of reported challenges to using new drugs under programmatic conditions. In general, the problems reported fell into ten different areas, including: 1) lack of awareness of drug availability and procurement process; 2) limited availability of adequate technical expertise; 3) confusion around WHO "requirements," most notably pharmacovigilance; 4) limited availability of quality clinical trials data supporting the use of new drugs under programmatic conditions; 5) challenges in sharing rapidly changing information on new drugs with key stakeholders and incorporating such information into national guidelines; 6) concerns that the process of new drug introduction is "too complicated" under programmatic conditions; 7) prolonged turn-around time for drug procurement; 8) difficulties in import and customs clearance; 9) limited access to companion MDR-TB medications, especially linezolid and clofazimine; and 10) lack of high level national government support.

Table 5 summarizes the progress made in achieving the targets set out in the Global Call to Action. It shows that while many of the goals have been met for BDQ, it is unlikely the goals set out for DLM will be met. Table 6 summarizes the progress on new drug introduction in the 27 "high-burden" MDR-TB countries, none of which are accessing DLM under program conditions, and only half of which are using or have placed orders to use BDQ.

Table 1: WHO Recommendations for the Programmatic use of Bedaquiline and Delamanid

WHO recommends bedaquiline and delamanid be used according to the following recommendations:

1. The drug be used under carefully monitored conditions;
2. Patients to receive the drug are carefully selected;
3. The drug is used as part of a WHO recommended treatment regimen;
4. Patients to receive the drug sign an informed consent; for delamanid, the recommendation is only for "due process" for informed consent.
5. There be active management of adverse events, including active pharmacovigilance.

Table 2: Summary Points from the "Global Call to Action"

1. **"Quickstart"**: Ensure 500 patients are started on routine regimens which include BDQ by July 2015, and 500 patients started on routine regimens which include DLM by January 2016.
2. **Optimal MDR-TB treatment**: Technical assistance provided for 25 countries by 2016 and 52 countries by 2017 for drafting implementation plans; implementation plans are adopted by 25 countries by 2016 and 52 countries by 2018; and BDQ and DLM are routinely used by 20 countries by end of 2016 and 52 countries by end of 2019. Key repurposed drugs (especially linezolid and clofazimine) should be on the national Essential Medicines List (EML), and countries and national TB programmes (NTPs) should be using these drugs.
3. **Regulatory status**: BDQ and DLM dossiers are submitted for registration in 25 countries by beginning of 2016 and 52 countries by 2017; and drugs are registered, or import waivers are in place, by 2016.
4. **Pharmacovigilance (PV)**: The consortium supports a flexible approach for countries implementing BDQ (such as sentinel PV), proposes a set of standardised data for monitoring and reporting on adverse events, and works towards a supranational body to collect and analyse data.

5. **Procurement**: Forecasting of drugs is completed; procurement strategies are developed for 52 countries by 2018; and, the turnaround time between ordering and drug delivery is reduced.

Table 3: Core Organizations Participating in DR-TB STAT (listed alphabetically)

National TB Program Directors	Implementing Partners	Technical Assistance Providers	Donors	Advocacy Groups
Belarus	Global Drug Facility	Clinton Foundation	Global Fund for AIDS, TB, and Malaria	Global Coalition of TB Activists
China	KNCV Tuberculosis Foundation	MSH/SIAPS	UNITAID	Global TB Community Advisory Board
India	Médecins Sans Frontières	Stop TB Partnership	United States Agency for International Development	Moldovan Society Against Tuberculosis (SMIT)
Russian Federation	Partners in Health	SWIFT Response Project		RESULTS UK
South Africa		World Health Organization		Treatment Action Campaign
Vietnam				Treatment Action Group

Table 4: High-Burden, Low- and Middle-Income Countries Currently Using or Waiting for Drug Arrival to Begin Using BDQ under Program Conditions

Currently Using BDQ	**Awaiting BDQ Arrival**
Armenia	Bangladesh

Belarus	Bolivia
Georgia	Brazil
Indonesia	Cameroon
Lesotho	Cote d'Ivoire
Papua New Guinea	Democratic People's Republic of Korea
Russia	Democratic Republic of Congo
South Africa	Ethiopia
Swaziland	India
	Kazakhstan
	Kenya
	Kyrgyzstan
	Mozambique
	Myanmar
	Namibia
	Nigeria
	Peru
	Philippines
	Republic of Korea
	Thailand
	Turkmenistan
	United Republic of Tanzania
	Uzbekistan
	Vietnam

Table 5: Progress in Achieving Targets Set in "Global Call to Action"

Target	**Status**
500 patients on BDQ by July 2015	1872 by November1, 2015
500 patients on DLM Jan 2016	"More than 100" by November 1, 2015
TA given to 25 countries by 2016	Ongoing, already provided in 21 countries
BDQ and DLM are routinely used by 20 countries by end of 2016	BDQ: 9 countries plus the EU by October 1, 2015; additional 24 by the mid-2016 DLM: 2 countries plus the EU by October 1, 2015; plans for other countries expected to be discussed in December, 2015
BDQ and DLM dossiers are submitted for registration in 25 countries by beginning of 2016	BDQ: 26 by October 1, 2015 DLM: 3 by October 1 2015

Table 6: Summary Progress on New Drug Introduction in 27 High-Burden MDR-TB Countries*

Country	Using BDQ programmatically or in routine use	Orders for BDQ placed, and awaiting arrival to begin programmatic use
Armenia	X	
Azerbaijan		
Bangladesh		X
Belarus	X	
Bulgaria		
China		
DR Congo		X
Estonia	X	
Ethiopia		X
Georgia	X	
India		X
Indonesia	X	
Kazakhstan		X
Kyrgyzstan		X
Latvia	X	
Lithuania		
Myanmar		X
Nigeria		X
Pakistan		
Philippines		X
Republic of Moldova		
Russian Federation	X	
South Africa	X	
Tajikistan		
Ukraine		
Uzbekistan		X
Vietnam		X

* Of note, according to the information collected by DR-TB STAT no high burden countries are using DLM under programmatic or routine conditions and none of them have orders pending for the drug.

Figure 1: Global Progress on BDQ

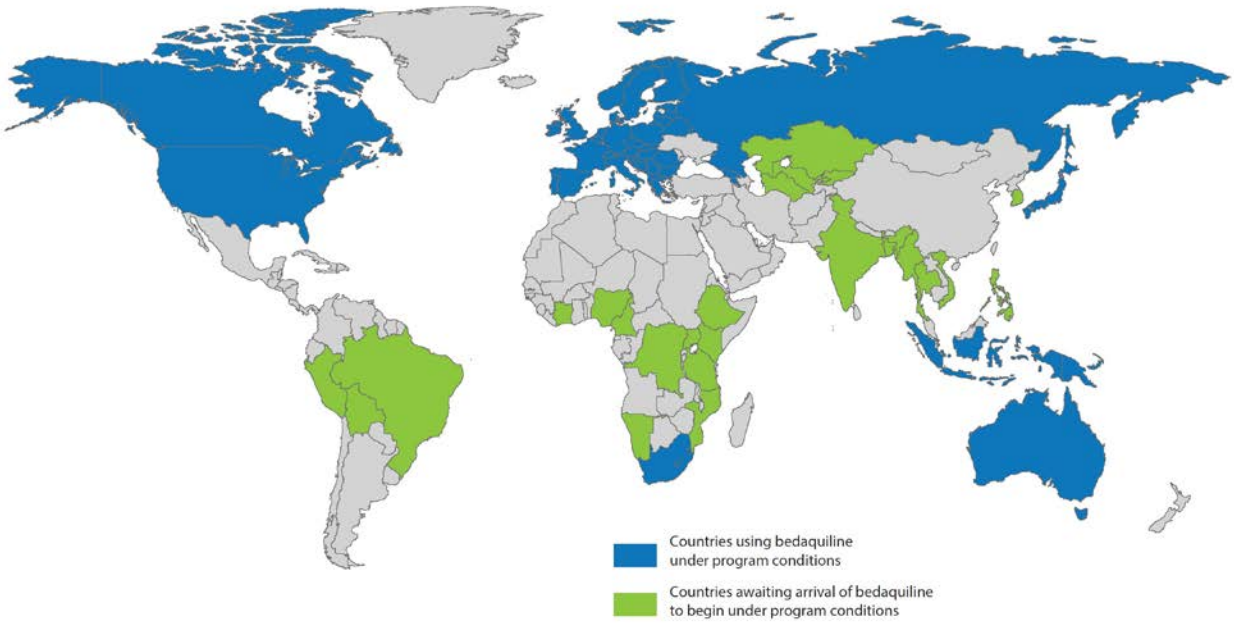

Figure 2: Global Progress on DLM

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