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# Examples of bedaquiline introduction for the management of multidrug-resistant tuberculosis in five countries

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## SUMMARY

**BACKGROUND—**For the first time in almost 50 years, there are new drugs available for the treatment of tuberculosis (TB), including bedaquiline (BDQ) and delamanid (DLM). The rate of introduction, however, has not kept pace with patient needs. It is estimated that as many as 23% of multidrug-resistant TB (MDR-TB) patients have an indication for receiving BDQ. As this is the first time the MDR-TB community is introducing new medications, it is important to understand how implementation can be developed in a variety of settings.

**METHODS—**A qualitative assessment of country TB programs in which more than 5% of MDR-TB patients were started on BDQ under program conditions.

**RESULTS—**National TB programs in Belarus, France, Georgia, South Africa, and Swaziland all started sizeable cohorts of patients on BDQ in 2015. Common factors observed in these programs included experience with compassionate use/expanded access, support from implementing partners, and adequate national or donor-supported budgets. Barriers to introduction included restriction of BDQ to the in-patient setting, lack of access to companion drugs, and the development of systems for pharmacovigilance.

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**CONCLUSION—**The five countries in this paper are examples of the introduction of new therapeutic options for the treatment of TB.

**Keywords**

tuberculosis; MDR-TB; BDQ; national TB programs; introduction

For the first time in over 50 years, there are two new drugs for the treatment of tuberculosis (TB), bedaquiline (BDQ) and delamanid (DLM).[1] BDQ was recommended by the World Health Organization (WHO) for the treatment of selected patients with multidrug-resistant TB (MDR-TB) in 2013[2] and DLM in 2014.[3] This is the first time in the modern history of TB control that new drugs have been developed and approved for the treatment of MDR-TB, and the first time that national and international TB stakeholders have tried to introduce new drugs in a programmatic way.[4] Uptake of these drugs as part of MDR-TB treatment, however, has not kept pace with the need for these drugs, even in settings where resistance or intolerance to second-line drugs is common or where treatment outcomes are poor.[5]

Multiple early barriers to programmatic introduction of new drugs have been identified, including lack of technical expertise and guidance, confusion about pharmacovigilance requirements, challenges with registration and import, and difficulties in obtaining the other medications needed for successful treatment outcomes.[6] Despite these barriers, however, some countries have made progress, especially in the introduction of BDQ.

This paper reports on examples of BDQ introduction under program conditions in five countries. These experiences could be useful to other country programs and also for the introduction of DLM and novel regimens, including the shortened regimens recently recommended by the WHO.[7,8]

## METHODS

A review of public databases containing country-level data on the number of MDR-TB cases in 2014 and 2015,[9] as well as the number of persons started on BDQ-containing regimens in 2015,[10] was conducted. When reliable data could not be obtained through public databases, national TB program (NTP) directors were contacted and asked to provide the number of persons started on MDR-TB treatment and on BDQ in 2015. Countries were considered for inclusion in the analysis if ≥5% of their treated MDR-TB cases had been started on BDQ. The 5% cut-off was chosen as an indicator that the program had moved beyond compassionate and pilot use of BDQ. We then conducted a descriptive analysis for each of the countries meeting the 5% benchmark using a series of qualitative methods that have been successfully deployed in a variety of health settings.[11] These methods included a review of program documents, interviews with NTP directors, interviews with other key stakeholders working on BDQ introduction, and direct observation of meetings on and activities involving BDQ introduction that took place between December 2015 and June 2016. Variables of interest are given in Tables 1 and 2.

The need for ethics approval was waived for this study, but verbal consent was obtained from all persons interviewed.

The following definitions were used in the analysis: compassionate use, free BDQ obtained from companies on an individual named patient basis; expanded access, free BDQ obtained from companies for a group of patients using criteria defined by the company; programmatic use, BDQ obtained by the NTP with their funds and used according to criteria specified by the program. Of note, the US Agency for International Development (USAID) donation program launched in 2015 provides BDQ to qualifying countries at no cost via the Global Drug Facility, and is considered programmatic use.[12]

## RESULTS

Five countries were identified that treated ≥5% of their MDR-TB patients with BDQ between 1 January 2015 and 31 December 2015: Belarus, France, Georgia, South Africa, and Swaziland. Table 1 lists the number of patients started on MDR-TB treatment in 2015, the number of patients started on BDQ in 2015, and the percentage of BDQ coverage in the country in 2015. Each program's experiences with BDQ are described in Table 2. A narrative description of unique aspects and challenges encountered in each country is provided below.

### Belarus

Given the overwhelming burden of MDR-TB and extensively drug-resistant TB (XDR-TB) in Belarus,[9] BDQ was introduced in the country in 2015, with the objective of providing the drug to all patients who need it by 2018. Early challenges to BDQ introduction included developing clinical protocols, concerns about QTc prolongation, procuring the necessary electrocardiography (ECG) machines, and the initial importation of the drug. Challenges to BDQ scale-up in Belarus have included the heavy burden of work associated with the initial cohort event monitoring pharmacovigilance program (which requires reporting of all adverse events experienced by patients, regardless of severity), and the need for hospitalization in Minsk, Belarus, which ultimately excluded a significant number of potentially eligible patients. Possible challenges to further scale-up include drug supply, decentralized treatment, management of children and adolescents, and other special populations and management of patients in whom BDQ-containing treatment has failed. Belarus is an example of BDQ introduction in a high-burden country with few implementing partners, led by a strong NTP and clinical management team at the referral hospital.

### France

Although France is a low TB incidence country, the incidence of XDR-TB cases increased in 2011 due to a migratory flux from the former Soviet Union countries.[15] In 2011, France was one of the first countries in the world to introduce BDQ via a compassionate use program. Early challenges to introduction included concerns about QTc prolongation and the need to provide a consistent national framework for the implementation of the new TB drugs. Challenges in scale-up have included increasing the coverage of the national review committee, especially outside the Paris region, and optimizing the follow-up of out-patients. Possible future challenges for scale-up include supporting quality patient care in multiple decentralized settings, defining optimal treatment duration with new drugs in patients who have limited options, and management of patients belonging to specific populations

(children and adolescents, pregnant women). France is an example of BDQ introduction among the vulnerable population of migrants that is characteristic of the MDR-TB problem in many resource-rich countries.

### Georgia

Georgia began using BDQ in 2011 to help address the high burden of MDR-TB and poor treatment outcomes seen in the country. Early challenges to introduction included drug importation, concerns about drug safety, lack of a formal pharmacovigilance system, development of clinical protocols, and concomitant use of imipenem in many BDQ-based regimens. In 2015, the compassionate use of BDQ was phased out and replaced by the programmatic introduction of BDQ-containing regimens. A major challenge to further roll-out has been that most BDQ patients are treated in Tbilisi, Georgia, which has led to delays in treatment initiation and has limited the number of patients on treatment. Possible challenges to further scale-up include planning and training for decentralized treatment, management of patients in whom BDQ-containing treatment has failed, and inclusion of children and adolescents. Georgia is an example of a high-burden country that was able to introduce BDQ with the assistance of implementing partners.

### South Africa

South Africa first started using BDQ in clinical trials research in 2007 and began providing clinical access to the drug to address its high burden of disease and poor treatment outcomes. Based on the early clinical trial results, several key stakeholders from the National Department of Health (Pretoria, South Africa), Médecins Sans Frontières (MSF; Paris, France), Right to Care (Johannesburg, South Africa) and a number of research institutions developed an expanded access program at four pilot sites in 2013 that was later scaled up to 12 sites in 2014 after early successful results were obtained. BDQ is now registered in the country and available nationally, decentralized down to the subdistrict level. There are plans to enroll 3000 patients on BDQ in 2016. Early challenges to introduction included the selection of the initial BDQ sites, concerns about safety, access to high-cost companion drugs such as linezolid, and concomitant use with antiretroviral therapy. Major challenges in the roll-out of BDQ have included the large number of patients in need of BDQ, and the difficulty in ensuring consistent management strategies and equality throughout the country. Other possible challenges include determining optimum usage with shortened MDR-TB regimens, and the management of patients in whom BDQ-containing treatment has failed. South Africa is an example of a country treating a large number of persons with BDQ—most of whom have human immunodeficiency virus (HIV) co-infection—via district treatment programs. South Africa is also one of the first countries to use BDQ as a therapeutic option for managing toxicity, most notably the hearing loss that occurs with injectables.

### Swaziland

Swaziland first started using BDQ under compassionate use in 2014 at one facility supported by MSF, and quickly scaled up its program. Early challenges to introduction included development of clinical protocols, concerns about safety, concomitant use with antiretroviral therapy, obtaining ECG equipment for safety monitoring, and lack of a formal

pharmacovigilance system. The reason for initial use was the poor outcomes seen in XDR-TB patients as well as a number of chronically ill MDR-TB patients who were not improving on treatment. Challenges to drug introduction have included the need for additional companion medications, initiation of treatment in the hospital, and the need for enhanced adherence support. Other potential challenges include the management of patients in whom BDQ-containing treatment or shortened MDR-TB regimens (which is being piloted in the country) have failed, as well as maintaining quality care during the ambulatory phase of treatment. Swaziland is an example of a country with a high-burden of both MDR-TB and HIV in which regional guidance—provided largely by South Africa as well as MSF—supported BDQ use.

## DISCUSSION

Each of the five countries described has introduced BDQ for the treatment of MDR-TB under program conditions, with ≥5% of their MDR-TB patients receiving the drug as part of treatment. Each of these countries faces a different set of specific challenges when it comes to programmatic management of MDR-TB, and offers insight into how BDQ (and other novel therapeutic approaches) could be introduced in similar settings. France, for example, is a low TB burden country, with high rates of MDR-TB in migrant populations. Both South Africa and Swaziland have extremely high rates of both MDR-TB and HIV, and South Africa has one of the highest caseloads of MDR-TB in the world. While rates of HIV infection in Georgia and Belarus are low, these former Soviet Union republics have in the past reported incredibly high rates of MDR-TB among both new (10.5% in Georgia and 35.5% in Belarus) and previously treated TB patients (53.1% Georgia and in 76.5% in Belarus).[16,17]

These programs also share common features in their introduction of BDQ in their settings. Four of the five countries began using BDQ as part of compassionate use/expanded access programs, and a positive experience with the drug under these conditions led to the decision to scale up access to the drug more widely. Three of the five countries worked closely with non-governmental implementing partners—most notably MSF—to kick-start the use of BDQ during the early implementation period. This may have helped overcome funding challenges as well as provide local data to secure support from Ministries of Health and other agencies. Working with non-governmental organizations in the early phases of BDQ introduction may also have allowed pathways to be developed for importation, registration, and pilot testing systems for broader use, including clinical indications and pharmacovigilance. Such support was notably absent in France, a resource-rich country where such support may not have been necessary, and in Belarus, where a strong centralized TB program may have allowed BDQ use to move forward even in the absence of implementing partners. In additional to implementing partners, the countries reported here also had other technical support from the WHO, Management Sciences for Health/Systems for Improved Access to Pharmaceuticals and Services (Medford, MA, USA), and other in-country partners.

Most of the funding support for BDQ came from the Global Fund (Belarus, Georgia, and Swaziland) or from national sources (France and South Africa). Belarus, Georgia, and

Swaziland are also all receiving BDQ through the USAID/Janssen (Beerse, Belgium) donation program described in the Methods section, Georgia and Swaziland after initial support from MSF. This suggests that countries with limited national TB resources need support to overcome the financial difficulties that may be associated with early introduction of new TB drugs.

All of the countries had clinical review committees to help provide guidance on clinical management issues and eligibility criteria, as well as patient monitoring and follow-up. All the countries described here followed the WHO guidelines for the use of BDQ, but they also adapted these to their local settings. For example, both South Africa and Swaziland included HIV-infected patients, although there were limited data on these populations; furthermore, South Africa and Swaziland also gave BDQ to patients with both *inh*A and *kat*G mutations, as available national epidemiological data suggested that constructing an effective regimen to treat MDR-TB strains harboring both mutations was a serious challenge.[18] South Africa, Swaziland, and France also allowed for the use of BDQ in combination with DLM in circumstances where clear criteria were met,[19] and for treatment courses beyond 24 weeks. These findings show that countries can be successful in adapting WHO recommendations to fit their specific needs, a process that is supported by the WHO as their guidelines are intended to be adapted at the field level to best meet local needs.

The major obstacles encountered by these pioneering countries also have some points in common. First, although the countries were relatively advanced (i.e., beyond the compassionate use/expanded access phase) in their introduction of BDQ, all of them faced similar problems in their early attempts to use BDQ. These included development of specific clinical protocols, concerns about QTc safety of the drug, the initial importation process, and optimal use of and access to companion medications. The need to decentralize the inclusion, monitoring, and clinical management of new patients from the main TB hospitals is a concern in Belarus, Georgia, and Swaziland. In France, decentralized treatment is available; however, ensuring uniform standards of care throughout the whole country is a challenge. Moreover, all countries except South Africa require hospitalization for new MDR-TB patients, in particular when starting new drugs, and this can slow the scale-up of patients. Although the limited registration of BDQ may have slowed the more widespread use of the drug, all of the countries followed a clear process for pre-approval access, importation and use of TB diagnostics and other second-line medications such as clofazimine and capreomycin. These same processes were used to access BDQ while registration was pending. Furthermore, many countries were able to define the specific processes for importation during their early experience with the drug’s compassionate use or expanded access. Finally, setting up an effective pharmacovigilance framework where no prior system was present is a major issue in many countries, as reported in Belarus.

There are several important limitations to this paper. First, the use of 5% of patients on BDQ as the criteria for including countries in the analysis may have been problematic. Some estimates found that as many as 23% of MDR-TB patients worldwide have clinical indications for receiving BDQ, and compared with this 5% is low.[20] The figure of 5% was chosen because it indicated the country had moved beyond compassionate use and pilot projects, and this figure also allowed for a number of different settings to be explored in the

analysis. Moreover, the proportion of patients requiring BDQ may vary greatly in each country, as eligibility is linked to the local prevalence of drug resistance. Furthermore, data on BDQ use in individual countries may not have been complete, and some countries that were not included in this paper are using BDQ in nearly 5% or more of their patients. Two notable examples are Armenia and Russia. Variables described in this paper may not have included all the factors associated with successful BDQ introduction, and these are not predictive of, but are rather associated with, BDQ introduction. More research is clearly needed as additional countries begin using BDQ on a larger scale; additional research should also focus on other novel therapeutic strategies such as DLM and the shortened regimens. Finally, this paper describes what country programs report they are doing; however, independent verification to check whether these activities were indeed taking place was beyond the scope of this work.

Despite these limitations, the experiences of these five countries not only show that BDQ can be introduced into TB programs in a variety of sites, they also offer possible examples for how this could be done in other settings. At a minimum, countries need to have access to an uninterrupted supply of BDQ and companion drugs as well as the funding to secure this supply and cover other program costs. A clinical review committee should be present, providers should feel comfortable using BDQ, and there must be access to ECG testing. A basic pharmacovigilance system should be introduced along with BDQ if one does not exist already. In analyzing the experiences of these five countries, some additional common themes emerge, although these variables cannot be considered predictive of BDQ use. For example, there was early experience with BDQ via compassionate use and expanded access programs in four of the five countries described here. Close collaboration with skilled implementing partners can also facilitate introduction of new drugs, as can targeted technical support provided by outside groups, especially for pharmacovigilance. Adequate funding from national resources or international donors is also essential, especially given the wide range of BDQ pricing in each of the countries. Funding, however, was needed not just for buying the medication but also for supporting all aspects of the optimal use of BDQ. New drugs have the much-needed potential to improve outcomes and to limit toxicity of MDR-TB treatment, and these five countries show how such promises can be fulfilled through programmatic implementation.

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## References

1. Zumla A, Schito M, Maeurer M. Advancing the portfolio of tuberculosis diagnostics, drugs, biomarkers and vaccines. Lancet Infect Dis. 2014; 14:267–269. [PubMed: 24670623]
2. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim guidance. Geneva, Switzerland: WHO; 2013. WHO/HTM/TB/2013.6
3. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva, Switzerland: WHO; 2014. WHO/HTM/TB/2014.23

4. Field S, Fisher D, Jarand J, et al. New treatment options for multidrug-resistant tuberculosis. Ther Adv Respir Dis. 2012; 6:255–268. [PubMed: 22763676]
5. Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: Patient, provider and community perspectives. Int J Infect Dis. 2014; 32:56–60.
6. Furin J, Brigden G, Lessem E, et al. Global progress and challenges in the implementation of new medications for the treatment of multidrug-resistant tuberculosis. Emerg Infect Dis. 2016; 22(3)
7. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis. 2015; 19:979–985. [PubMed: 26162365]
8. Guglielmetti L, Le Dû D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis. 2015; 60:188–194. [PubMed: 25320286]
9. World Health Organization. Tuberculosis country profiles. Geneva, Switzerland: WHO; 2016. http://www.who.int/tb/country/data/profiles/en/ [Accessed October 2016]
10. Stop TB Partnership. December Task Force Update. Geneva, Switzerland: Stop TB Partnership; 2016. DR-TB STAT. http://drtb-stat.org/archive/ [Accessed December 2016]
11. Jones RG, Trivedi AN, Ayanian JZ. Factors influencing the effectiveness of interventions to reduce racial and ethnic disparities in health care. Soc Sci Med. 2010; 70:337–341. [PubMed: 19914755]
12. Stop TB Partnership. The bedaquiline donation program begins today. Geneva, Switzerland: Stop TB Partnership; 2015. http://www.stoptb.org/news/stories/2015/ns15_015.asp [Accessed October 2016]
13. Uffredi ML, Truffot-Pernot C, Dautzenberg B, et al. An intervention program for the management of multidrug-resistant tuberculosis in France. Int J Antimicrob Agents. 2007; 294:434–439.
14. Guglielmetti, L., Bernard, C., Brossier, F., et al. French tuberculosis multidisciplinary team for the management of multidrug-resistant tuberculosis: nine years of activity. Paper Poster session VI: Tuberculosis—clinical issues. Poster presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases; Copenhagen, Denmark. 25–28 April 2015; [Poster P1177]
15. Bernard C, Brossier F, Sougakoff W, et al. A surge of MDR and XDR tuberculosis in France among patients born in the Former Soviet Union. Euro Surveill. 2013; 18:33.
16. Mdivani N, Zangaladze E, Colkova N, et al. High prevalence of multidrug resistance in Georgia. Int J Infect Dis. 2008; 12:635–644. [PubMed: 18514008]
17. Skrahina A, Hurevich H, Zalutskaya A, et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. Eur Respir J. 2012; 39:1235–1241.
18. Ndjeka, N. Incorporation of bedaquiline in the South African National TB Program. Poster presentation at the 23rd Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA. 22–25 February 2016; [Abstract no 754]. http://www.croiconference.org/sessions/incorporation-bedaquiline-south-african-national-tb-programme
19. Mattelli A, D'Ambrosio L, Centis R, et al. Compassionate and optimum use of new tuberculosis drugs. Lancet Infect Dis. 2015; 15:1131–1132.
20. Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. Int J Tuberc Lung Dis. 2016; 20:177–186. [PubMed: 26792469]
21. Poster presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases; Copenhagen, Denmark. 25–28 April 2015; [P1177]

**Table 1**

MDR-TB patients who started MDR-TB treatment and patients who initiated BDQ treatment, per country, 2015

| Country | Estimated number of laboratory-confirmed MDR-TB patients in country in 2015* | Laboratory-confirmed MDR-TB patients in country in 2015* *n* | MDR-TB patients initiated on treatment in 2015 *n* | MDR-TB patients started on BDQ in 2015 *n* | Estimated proportion of treated patients started on BDQ % |
|---|---|---|---|---|---|
| Belarus | 1710 | 1282 | 1949 | 138 | 7.1 |
| France | 56 | 111 | 98 | 45 | 45.9 |
| Georgia | 640 | 441 | 466 | 128 | 27.5 |
| South Africa | 6200 | 18 734 | 12 516 | 1085 | 8.6 |
| Swaziland | 460 | 358 | 483 | 30 | 6.2 |

*Estimates are based on WHO modeling and include very wide confidence intervals; there may thus be more individuals diagnosed with MDR-TB than the estimates. Of note, there may in some countries be more persons started on MDR-TB treatment than those with confirmed MDR-TB from that year because persons with extra-pulmonary disease, children, close contacts, and others may be started on treatment empirically even in the absence of culture confirmation.

MDR-TB = multidrug-resistant tuberculosis; BDQ = bedaquiline; WHO = World Health Organization.

**Table 2**

Summary findings for key variables, per country

| | Belarus | France | Georgia | South Africa | Swaziland |
|---|---|---|---|---|---|
| Year and conditions of first BDQ use | 2015, program use | 2011, CU/EA | 2011, CU/EA | 2012, CU/EA | 2014, CU/EA |
| Impetus for wider use | High rates of MDR-TB and second-line drug resistance<br>Poor treatment outcomes<br>Safety and efficacy of BDQ reported in other settings | Migrant population with high rates of MDR-TB and second-line drug resistance<br>Safety and efficacy of BDQ seen in CU/EA program | Poor treatment outcomes<br>Concerns over amplification of drug resistance<br>Green Light Committee recommendations<br>Safety and efficacy of BDQ seen in the CU/EA program | High rates of second-line drug resistance<br>Poor treatment outcomes<br>Safety and efficacy of BDQ seen in CU/EA program | Hopes to implement an oral MDR-TB treatment regimen using new DR-TB drugs |
| Planned annual patient population to receive BDQ and location of care | 250 patients annually at a centralized in-patient center | 50 patients annually at in-patient and out-patient centers throughout the country | 200 patients annually at in-patient and out-patient sites throughout the country | 3000 patients annually at in-patient and out-patient sites throughout the country down to district level | 200 patients annually at 6 in-patient and out-patient public MDR-TB treatment initiation sites |
| Clinical indications | Patients with resistance to an FQ, an injectable or both<br>Patients in whom a WHO-recommended regimen with 4 effective drugs cannot be constructed due to resistance or intolerance to medications, including drug substitution for hearing loss | Patients in whom a WHO-recommended regimen with 4 effective drugs cannot be constructed due to resistance or intolerance to medications, including drug substitution for hearing loss | Patients with resistance to an FQ, an injectable or both<br>Previous treatment failures<br>Intolerance to two or more second-line drugs, including drug substitution for hearing loss | Patients with resistance to an FQ, an injectable or both<br>Patients with intolerance to two or more second-line drugs, including drug substitution for hearing loss | Patients with resistance to an FQ, an injectable or both<br>Patients with intolerance to two or more second-line drugs, including drug substitution for hearing loss |
| Special populations | Children as young as 14 years included | Extra-pulmonary cases, children and pregnant women included<br>BDQ treatment courses beyond 24 weeks, BDQ in combination with DLM | | Patients with both *inh*A and *kat*G mutations<br>HIV-infected patients included and efavirenz changed to nevirapine or lopinavir/ritonavir for the duration of BDQ treatment<br>Children as young as 14 years of age included | HIV-infected patients included and efavirenz changed to nevirapine or lopinavir/ritonavir for the duration of BDQ treatment<br>Children as young as 12 years of age included |
| Number of initial implementing sites | 1 | 1 | 1 | 4 | 2 |
| Number of implementing sites in 2015 | 1 | 3 | 2 | 12 | 6 |
| Hospitalization required for BDQ initiation? | Yes | Yes | Yes | No | Yes |
| Number of clinical review committees and their scope | One national review committee, reviews all BDQ patients | One national review committee,[13,14] reviews all BDQ patients, but national coverage is not complete | One national review committee, reviews all BDQ patients | One national review committee and 10 provincial review committees<br>National committee reviews all complicated cases | One national review committee and two district review committees<br>National committee reviews all complicated cases |

| | Belarus | France | Georgia | South Africa | Swaziland |
|---|---|---|---|---|---|
| Planned monitoring as per country guidelines | Monthly culture and DST, ECG and renal/liver function tests per national guidelines for patients on BDQ<br>Currently available for all patients on BDQ per NTP reports | Monthly culture and DST, ECG and renal/liver function tests per national guidelines for patients on BDQ<br>Currently available for all patients on BDQ per NTP reports | Monthly culture and DST, ECG and renal/liver function tests per national guidelines for patients on BDQ<br>Currently available for all patients on BDQ per NTP reports | Monthly culture and DST, ECG and renal/liver function tests per national guidelines for patients on BDQ<br>Currently available for all patients on BDQ per NTP reports | Monthly culture and DST, ECG and renal/liver function tests per national guidelines for patients on BDQ<br>Currently available for all patients on BDQ per NTP reports |
| Registration, supply and import | Waiver program, as BDQ is not yet registered<br>BDQ supplied by Pharmastandard and the GDF via a donation program (at no cost) | Waiver program, as BDQ is not yet registered (registration due in 2016)<br>BDQ supplied by Janssen directly to country (cost is approximately 27 137 USD [25 000€] per 6-month course) | Waiver program, as BDQ is not yet registered<br>BDQ supplied by the GDF via the USAID donation program at no cost after initial supply from MSF | BDQ registered in 2014 by the MCC: 'Section 21 waiver' prior to registration;<br>BDQ supplied by Janssen directly to country (cost is approximately 700 USD per 6-month course) | Waiver program, as BDQ is not yet registered, although its registration in South Africa allows it to be imported into Swaziland: regulatory activities performed by the Office of the Chief Pharmacist; Oversight by Central Medical Stores<br>BDQ supplied by the GDF via the USAID donation program at no cost after initial supply from MSF |
| Active pharmacovigilance | Initially cohort event monitoring; currently aDSM in accordance with WHO recommendations<br>When BDQ use started, Belarus was using a cohort event monitoring protocol it had developed for patients on linezolid. This required the pharmacovigilance center to be notified of all adverse events, regardless of severity. This protocol was time-consuming and required substantial resources, and was phased out to focus only on serious, severe, and targeted events, such as QTc prolongation | aDSM in accordance with WHO recommendations through the national regulatory agency (ANSM) | aDSM core and advanced packages in accordance with WHO recommendations<br>In this model, all serious and severe adverse events are reported to the national pharmacovigilance center, as are targeted events of any severity, including QTc prolongation, peripheral neuropathy, and hypokalemia | Targeted spontaneous reporting of all serious adverse events at a provincial level as required by the MCC<br>In this model, all serious and severe adverse events are reported to provincial pharmacovigilance centers. These are then collated and sent to the national pharmacovigilance center | aDSM in line with WHO recommendations per National Pharmacovigilance Center policies<br>When BDQ use started, there was limited pharmacovigilance available in Swaziland. BDQ use thus helped develop the national system for TB pharmacovigilance. In this system, providers report all serious and severe adverse events to the national pharmacovigilance center |
| BDQ resistance testing available? | Via supranational reference laboratory for research purposes only | Via national laboratory for routine patient management since 2014. BDQ resistance testing is performed for all patients started on BDQ at baseline and in case of treatment failure | Via supranational reference laboratory for research purposes only | Via national laboratory for research purposes only<br>All patients started on BDQ have a sample taken at baseline, week 8, and week 24, with specimens saved for BDQ resistance surveillance | Via supranational reference laboratory for research purposes only |
| Key implementing partners | National TB Program, Global Fund, National Pharmacovigilance Center, WHO | ANSM, National Reference Center for Mycobacteria | National Center for TB and Lung Disease; MSF France; National Center for Disease Control; Ministry of Labor, | National Department of Health, MSF, Right to Care | National TB and Leprosy Program, MSF Holland, MSF Swiss, MSH/SIAPS, URC, ICAP, EGPAF and CHAI, WHO |

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| | Belarus | France | Georgia | South Africa | Swaziland |
|---|---|---|---|---|---|
| | | | Health, and Social Assistance; USAID/SIAPS | | |
| Financing | National budget, GF grant | National budget | National budget, GF grant, USAID/SIAPS, MSF (BDQ and companion drugs) | National budget | National budget, GF grant, USAID/SIAPS, MSF (companion drugs) |
| Early implementation challenges | Clinical protocol development<br>Concerns about safety<br>Procuring equipment to monitor ECGs<br>Initial process for importation | Concerns about safety<br>Development of national implementation framework | Initial process for importation<br>Concerns about safety<br>Lack of a developed pharmacovigilance system<br>Clinical protocol development<br>Concomitant use of imipenem | Selection of initial implementing sites<br>Concerns about safety<br>Use of high-cost companion drugs, especially linezolid<br>Concomitant use with ART | Clinical protocol development<br>Concerns about safety<br>Concomitant use with ART<br>Procuring equipment to monitor ECGs<br>Lack of a developed pharmacovigilance system |
| Possible challenges to scale-up | Drug supply<br>Decentralized treatment<br>Inclusion of children and adolescents<br>Management of patients in whom BDQ-containing treatment has failed | Decentralized treatment<br>Definition of BDQ treatment duration<br>Inclusion of children, adolescents, and pregnant women | Decentralized treatment<br>Management of patients in whom BDQ-containing treatment has failed<br>Inclusion of children and adolescents | Management of patients in whom BDQ-containing treatment has failed<br>Quality monitoring and consistency in care in large-scale program<br>Optimizing use in shorter regimens | Management of patients in whom BDQ-containing treatment has failed<br>Management of patients in whom shortened regimen (which are being piloted in the country) has failed<br>Maintaining quality during ambulatory treatment |

BDQ = bedaquiline; CU = compassionate use; EA = expanded access; MDR-TB = multidrug-resistant tuberculosis; FQ = fluoroquinolone; WHO = World Health Organization; DLM = delamanid; HIV = human immunodeficiency virus; DST =drug susceptibility testing; ECG =electrocardiography; NTP = National TB Control Program; GDF =Global Drug Facility; USAID = United States Agency for International Development; MSF = Médecins Sans Frontières; MCC = Medicines Control Council; aDSM = active drug safety monitoring and management; ANSM = Agence Nationale de Sécurité du Médicament et des produits de Santé; MSH = Management Sciences for Health; ISIAPS = Systems for Improved Access to Pharmaceuticals and Services; URC = University Research Corporation; CAP = International Center for AIDS Care and Treatment Program; EGPAF = Elizabeth Glaser Pediatric AIDS Foundation; CHAI = Clinton Health Access Initiative; GF = Global Fund to Fight AIDS, Tuberculosis, and Malaria; ART = antiretroviral therapy.