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NOTES FROM THE FIELD

Operational aspects of bedaquiline implementation in Swaziland: report from the field

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Bedaquiline (BDQ) has been recommended by the World Health Organization for the treatment of multidrug-resistant tuberculosis (MDR-TB) since 2013, but experience using the drug in high-burden, lower-income countries is limited and case studies are needed. Swaziland started using BDQ under national TB programme conditions in 2015 in four pilot sites. As of 1 December 2016, 93 patients had been initiated on BDQ, i.e., 19% of MDR-TB patients treated in the country. Swaziland has developed a systematic and efficient model for BDQ introduction in collaboration with several partners. This model is also being used to introduce other innovations and can serve as an example for other countries facing similar challenges.

Bedaquiline (BDQ) is a novel anti-tuberculosis drug that has been approved by stringent regulatory authorities and recommended by the World Health Organization (WHO) for the treatment of selected patients with multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid [INH] and rifampicin [RMP]).[1] BDQ has been shown to improve treatment outcomes and minimise the toxicity associated with the current second-line regimens in a number of observational cohorts.[2] There is growing global experience with programmatic use of the drug,[3,4] and, as of June 2017, approximately 8500 individuals were receiving BDQ through national TB programmes (NTPs).[5] Swaziland has one of the highest burdens of MDR-TB in the world, high rates of human immunodeficiency virus (HIV) co-infection (79%), and a success rate as low as 60% using the standardised regimen consisting of kanamycin, ethionamide, levofloxacin, terizidone, pyrazinamide and sometimes para-aminosalicylic acid. The low rates of success are due to both death/treatment failure and loss to follow-up from treatment due either to adverse effects or to the long duration of the regimen.[6] Given the poor treatment outcomes and the growing burden of MDR-TB cases resistant to second-line drugs, Swaziland made the decision to introduce BDQ for the treatment of MDR-TB in 2015. This case report describes the status of BDQ use 1 year after the introduction of the drug as well as the processes followed to systematically introduce BDQ under programme conditions.

SWAZILAND CASE STUDY

Initial cohort

As of 31 December 2016, 93 patients were on or had been treated with BDQ-containing regimens. This represents approximately 19% of the patients started on MDR-TB treatment in Swaziland during that same period. Persons are eligible to receive BDQ if they have MDR-TB with resistance or intolerance to the fluoroquinolone (FQ), the injectable agent, or both, or if they have both the *inh*A and *kat*G mutations that confer resistance to INH, as these patients were shown to have worse treatment outcomes in South Africa, a setting similar to that in Swaziland. HIV-infected patients are offered BDQ, as are adolescents aged >14 years. Patients with adverse events were given BDQ as a single drug substitution. Those with resistance to the injectable, the FQ or both, or with both *inh*A and *kat*G mutations were given BDQ in combination with other agents. When given for resistance, the backbone of treatment in these cases consisted of BDQ, linezolid and clofazimine; other agents were added based on the likelihood of effectiveness and the adverse event profile.

Timeline of events

The first patients were started on BDQ in 2015 in partnership with Médecins Sans Frontières (MSF). Swaziland began to develop a national implementation plan at this time, and in 2016 BDQ use was scaled up to four sites in the country after readiness assessment that included availability of monitoring tools and training of clinicians. The plan was to scale up to other regional sites by mid-2016 and to complete by 2017. In the first year, four of a total of 11 decentralised drug-resistant TB (DR-TB) sites in Swaziland began initiating patients on BDQ. The challenge of immediate scale-up was the unavailability of electrocardiogram (ECG) in these facilities.

Referral pathways

Swaziland set up a system that enabled all patients to have access to the new drugs, as shown in the Figure. All persons with RMP-resistant TB diagnosed on Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) have their sputum specimens sent for first- and second-line line-probe assay testing, with the results sent back to the MDR-TB clinic in their region, where routine monitoring also occurs. All patients with MDR-TB who

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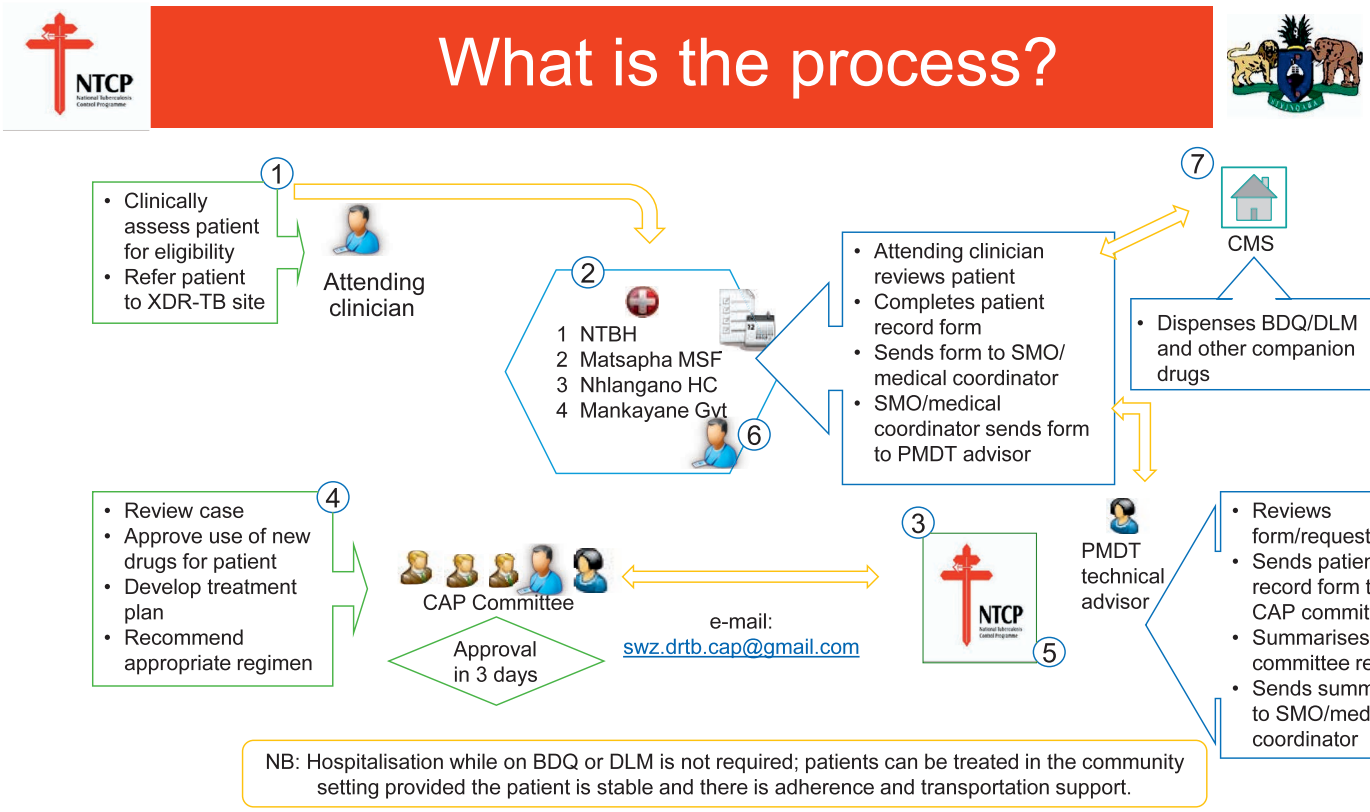

FIGURE Referral processes for BDQ in Swaziland. NTCP = National Tuberculosis Control Programme; XDR-TB = extensively drug-resistant tuberculosis; NTBH = National Tuberculosis Hospital; MSF = Médecins Sans Frontières; HC = Health Centre; Gvt = government; SMO = Senior Medical Officer; PMDT = Programmatic Management of Drug-resistant TB; CMS = Central Medical Stores; BDQ = bedaquiline; DLM = delamanid; CAP = Clinical Access Programme.

have an indication for BDQ are then referred to one of the four regional sites, and their clinical details are sent to the National Clinical Review Committee. The committee, which is part of the Clinical Access Programme, is made up of national and international experts who receive the clinical summary by e-mail and provide input via the MDR-TB focal point within the NTP. There is a 3-day turnaround time for all cases to be reviewed, after which a final decision is made. Once the decision has been made to start BDQ, treatment is initiated at one of the four sites and routine follow-up is provided at the referring centre.

Treatment initiation and patient monitoring

All patients undergo baseline assessment of liver function, renal function, potassium and an ECG to assess the QTc interval according to national protocols. They also undergo intense counselling about BDQ and the reason they are being offered this drug. Patients sign an informed consent form, and are usually started on treatment as out-patients. Patients who are critically ill or have comorbidities that need close monitoring are admitted for initiation, after which, once they are stable on therapy, they are transferred to an out-patient setting, provided they are able to have adherence support. If adherence support is not available, the patient remains hospitalised while the NTP identifies and provides training to a community supporter who is then able to provide the necessary adherence monitoring and management. Once this support is in place, the patient is discharged. Patients receive daily directly observed treatment; they also receive home visits from outreach teams on a routine basis. Monthly ECGs are performed in additional to standard MDR-TB follow-up assessments. Sputum samples are also sent each month for culture and patients are assessed monthly for clinical signs, symptoms and findings. Pill counts, adherence counselling and support groups are also held at the monthly follow up.

Pharmacovigilance and programme monitoring

All patients on BDQ are evaluated on a monthly basis for adverse events in addition to undergoing the laboratory tests described above. When serious adverse events occur, they are reported to the NTP and the pharmacovigilance centre, according to national recommendations. Quarterly clinical expert meetings for all the DR-TB sites are undertaken and reports from those implementing sites are shared as a way of monitoring progress and updating other sites.

Technical and implementing partners

The Swaziland NTP has worked with multiple advisory and implementing partners for BDQ implementation in the country, including MSF (Geneva, Switzerland), the International Center for AIDS Care and Treatment Programs (ICAP, Colombia University, New York, NY USA), University Research Corporation (Chevy Chase, MD, USA), Management Sciences for Health (Medford, MA, USA), Elizabeth Glazer Pediatric AIDS Foundation (Washington, DC, USA), Baylor College of Medicine Children's Foundation (Houston, TX, USA), the Clinton Foundation (New York, NY, USA), the WHO (Geneva, Switzerland) and expert consultants from the National Department of Health in South Africa (Pretoria). BDQ has been supplied to the country through the USAID (United States Agency for International Development) Bedaquiline Donation Program via the Global Drug Facility.

Enrolment results

All eligible patients were offered treatment with BDQ. The total number of patients who had been initiated on BDQ by 1 December 2016 was 93, of whom 53% were male, 77% were HIV-positive, and 66% had resistance to an injectable, an FQ, or both. Most patients initiated treatment at the national TB hospital. The majority of the persons with HIV were placed on nevirapine-containing regimens. In June 2016, the criteria were expanded to include persons with intolerance to the drugs used for treating MDR-TB.

There have been some operational challenges in the introduction of BDQ in Swaziland. Initially patients were reluctant to take the medication because they heard BDQ was still being tested and they did not want to be 'guinea pigs'. This fear was reinforced when they were asked to sign a separate, complicated consent form to receive BDQ. These issues were addressed through counselling, using standard terms when talking about the drug and ensuring that patients had a chance to discuss their fears with health professionals. The other main operational challenge has been equipping the sites with ECG machines, but this has been addressed by increasing the budget for supplies and equipment within the programme.

Future directions

The Swaziland NTP is continuing to expand the use of BDQ and is considering several operational cohort studies to further optimise the use of the drug in the country. Such projects include BDQ resistance surveillance and an assessment of a BDQ-containing, injectable-free regimen. The country has also started implementing delamanid under programme conditions, and has been able to use the same structures and processes that were put in place for BDQ introduction to streamline the delamanid introduction process.

CONCLUSION

The Swaziland NTP has been one of the first in the world to implement widespread BDQ use under programme conditions. This was done in a systematic, efficient fashion with the support of multiple partners. While the implementation of new drugs for MDR-TB may seem out of reach for similar countries, the successful roll-out in Swaziland is a reason for optimism regarding global scale-up. Furthermore, the processes and structures put in place for BDQ could be used to introduce other innovations, as has been the case for delamanid in Swaziland. Swaziland's experience with the programmatic introduction of BDQ for the treatment of MDR-TB is a model of success that can and should be replicated in other settings.

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La bédaquiline (BDQ) a été recommandée par l'Organisation Mondiale de la Santé pour le traitement de la tuberculose multirésistante (TB-MDR) depuis 2013, mais l'expérience de son utilisation dans des pays à faible revenu et durement touchés est limitée et des études de cas sont requises. Le Swaziland a commencé à utiliser la BDQ dans des conditions de programme national TB en 2015 dans quatre sites pilotes. Au 1er décembre 2016, 93 patients avaient été mis sous BDQ, c'est-à-dire 19% des patients TB-MDR traités dans le pays. Le Swaziland a élaboré un modèle systématique et efficace d'introduction de la BDQ en collaboration avec plusieurs partenaires. Ce modèle est également utilisé pour introduire d'autres innovations et peut servir d'exemple à d'autres pays confrontés à des défis similaires.

La Organización Mundial de la Salud recomienda desde el 2013 la bedaquilina (BDQ) en el tratamiento de la tuberculosis multirresistente (TB-MDR), pero la experiencia con su utilización en los países con alta carga de morbilidad es limitada y se precisan estudios de casos. En Swazilandia, se comenzó a utilizar la BDQ en el contexto del programa nacional contra la TB en cuatro centros piloto en el 2015. Al 1° de diciembre del 2016, 93 pacientes habían iniciado el tratamiento con BDQ, es decir, el 19% de los casos de TB-MDR tratados en el país. En Swazilandia se ha elaborado un modelo sistemático y eficiente de introducción de este medicamento en colaboración con diversos asociados. El modelo se utiliza también con el propósito de aplicar otras medidas innovadoras y puede servir como ejemplo a los países que afrontan dificultades semejantes.

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