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Setting up pharmacovigilance based on available endTB Project data for bedaquiline

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SUMMARY

SETTING: Active pharmacovigilance (PV) is recommended for TB programmes, notably for multidrug-resistant TB (MDR-TB) patients treated with new drugs. Launched with the support of UNITAID in April 2015, endTB (Expand New Drug markets for TB) facilitated treatment with bedaquiline (BDQ) and/or delamanid of >2600 patients in 17 countries, and contributed to the creation of a central PV unit (PVU).

OBJECTIVE: To explain the endTB PVU process by describing the serious adverse events (SAEs) experienced by patients who received BDQ-containing regimens.

DESIGN: The overall PV strategy was in line with the 'advanced' WHO active TB drug safety monitoring and management (aDSM) system. All adverse events (AEs) of clinical significance were followed up; the PVU focused on signal detection from SAEs.

RESULTS AND CONCLUSION: Between 1 April 2015 and 31 March 2019, the PVU received and assessed 626 SAEs experienced by 417 BDQ patients. A board of MDR-TB/PV experts reviewed unexpected and possibly drug-related SAEs to detect safety signals. The experts communicated on clusters of risks factors, notably polypharmacy and off-label drug use, encouraging a patient-centred approach of care. Organising advanced PV in routine care is possible but demanding. It is reasonable to expect local/national programmes to focus on clinical management, and to limit reporting to aDSM systems to key data, such as the SAEs.

KEY WORDS: multidrug-resistant tuberculosis; safety; active TB drug safety monitoring and management

IN 2015, THE WHO RECOMMENDED systematic safety reporting for patients receiving 1) multidrug-resistant TB (MDR-TB) treatment regimens with new agents, such as bedaquiline (BDQ) (Sirturo®; Janssen, Beerse, Belgium) and delamanid (DLM) (Deltyba®; Otsuka, Kyoto, Japan); 2) shortened novel regimens, such as the 'Bangladesh' regimen; and 3) extensively drug-resistant TB (XDR-TB) treatment regimens.[1] The new drugs improved short-term outcomes for MDR-TB patients[2–6] and were fast-tracked for licensure by regulatory authorities, conditioned on further research and use under close monitoring.[7–10] XDR-TB regimens also relied on repurposed drugs with limited use in TB. The shortened regimen was recommended following a series of cohort studies.[11–14]

Early detection of adverse events (AEs) through active, regular clinical and laboratory assessments is a crucial step to ensure their prompt and proper management, minimise harm to patients and maximise treatment adherence. Systematic AE recording and analysis allow close monitoring of the risk-benefit balance for medicines/regimens of interest, early detection and characterisation of new safety risks or changes in known risks, and timely communication and implementation of any action deemed necessary to minimise risks. This is particularly important when small numbers of patients have been

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exposed to new treatments, as was the case with BDQ and DLM in 2015.

The endTB (Expand New Drug markets for TB) Project, funded by UNITAID, was launched in April 2015 to support National TB Programmes (NTPs) and local partners in the routine use and safety monitoring of BDQ and DLM. The endTB Consortium, comprising Médecins Sans Frontières (MSF), Partners In Health (PIH) and Interactive Research and Development (IRD), collaborated in the treatment of >2600 patients according to WHO and national guidelines. Treatment was delivered and followed through local systems in Armenia, Bangladesh, Belarus, Ethiopia, Democratic People's Republic of Korea, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa and Viet Nam. An observational study captured baseline characteristics, treatment response and AEs among consenting participants (https://clinicaltrials.gov; NCT03259269).[15]

Irrespective of study participation, patients consented to receive treatment, including active pharmacovigilance follow-up. Here, we describe: 1) the pharmacovigilance unit (PVU) strategy and resources implemented by endTB for systematic tracking, collection and assessment of standardised safety data; and 2) serious AEs (SAEs), irrespective of their causes, detected among all endTB patients exposed to BDQ-containing regimens.

METHODS

endTB contributed to the creation of a central PVU. Procedures/guidelines, forms and a severity grading scale[16] were developed and used to train clinicians to ensure coherence and consistency across all countries. Data collection started at the time of initiating BDQ and/or DLM and lasted throughout full treatment, if possible. Information was collected in line with the 'advanced' WHO active TB drug safety monitoring and management (aDSM) system.[1] Clinical follow-up was performed according to routine monitoring schedules recommended for patients receiving BDQ/DLM.[16]

For all endTB patients, clinicians assessed, recorded and reported the following information to the PVU: SAEs, pregnancies and medication errors. SAEs were defined as untoward medical occurrences that were fatal or life-threatening, required/prolonged hospitalisation, caused disability/incapacity, led to congenital anomalies/birth defects, or were otherwise medically significant (Table 1).[1,17] These were reviewed by the PVU individually in real time and in aggregate to detect safety signals. Other predefined AEs of clinical significance[15] were reported, analysed in aggregate, and have been described elsewhere.[18]

Clinicians solicited and documented for all SAEs: 1) SAE description, management/monitoring strategy, outcome; 2) all TB drugs administered at time of event and relevant prior TB drugs, actions taken with each drug, and evaluation of their respective causal relationship with the event and other causal factors; 3) patient information: pre-conditions, risk factors (e.g., alcohol), concomitant treatments; and 4) reporter contact for follow-up. Causality assessment was binary, related/not related, and a conservative approach was recommended, meaning that all situations of unclear aetiology or where drugs were deemed possibly or potentially related were classified as 'related'. Only situations where clear other causal factors were identified were deemed 'not related' (Table 2).[19–21]

Training was provided from October 2015 at all sites, including on-site/regional workshops, web lectures and e-learning. The PVU trained all professionals involved in patient care, including MSF/IRD/PIH clinicians, national clinicians and local partners in close collaboration with NTPs, national PV/aDSM and the WHO. Materials are available online (http://endtb.org/resources) and were shared with implementing partners and NTPs; where necessary, the PVU supported adaptation of tools to local systems.

To exemplify the PVU functioning, all SAEs, regardless of cause, reported in endTB patients starting BDQ in an MDR-TB regimen between 1 April 2015 and 31 March 2019 were extracted from the central pharmacovigilance database (PVDB; BaseCon, Hedehusene, Denmark) and are summarised here. We do not present statistical analyses as our goal is to illustrate the type of data one can collect using pharmacovigilance methodology. In this paper, we also do not report SAEs among patients who received DLM-containing regimen, nor do we explicitly consider the role of other drugs. More endTB safety analyses are reported elsewhere.[18]

RESULTS

PVU processes

Reporting

Clinicians reported SAEs, pregnancies and medication errors within 24 hours of awareness using report forms and via email to the PVU mailbox. If complete report or full English translation was not immediately available, the clinicians notified the PVU and reported when possible. The clinicians also shared anonymised copies of other relevant documents (e.g., electrocardiogram). Upon receipt, the PVU transmitted back a unique case identification number generated by the PVDB. This allowed linkage of initial and follow-up reports. Clinical events were followed-up until resolution or stabilisation. Pregnancies were followed until their outcome was known and—if possible—a general health update was requested when the baby was 12 months. This required strong

Table 1 Definitions of the endTB safety parameters[1,17] reported to the endTB pharmacovigilance unit and other key terms

SAEs were defined as any untoward medical occurrences, that at any dose:
- Resulted in death (including death from TB progression)
  - When the cause of death was known, this information was to be captured as the SAE term (e.g., heart failure) and outcome captured as fatal. In most fatal cases, no autopsy was performed and therefore the fatal term(s) reflected the likely cause(s) of the death in the local death certificate and the result of a 'verbal autopsy': a discussion among the local clinicians (with or without the support of the central team or experts)
  - In cases where many events were occurring at the time of death and all rated as possibly contributing to the death, these were recorded as fatal
  - When the cause of death was completely unknown, for example, if the clinician learned about a death that occurred in the patient's home from the patient's family, then 'Death of unknown cause' without further specification was an acceptable SAE term
- Were life-threatening; life-threatening in this context referred to a situation in which the patient was at risk of death at the time of the event; it did not refer to a situation that hypothetically might have caused death had it been more severe
- Required hospitalisation or prolongation of hospitalisation, excluding hospital visits (e.g., Emergency Room) for <24 h that did not result in admission (unless the event was considered medically significant or life-threatening); hospitalisation scheduled before the start of the TB treatment for a pre-existing condition that did not deteriorate, for elective surgery, for case containment only, for procedures per clinical guideline recommendations or national treatment guidelines (e.g., electrocardiogram monitoring), for routine clinical care in TB treatment without deterioration of patient's condition, or for social reasons without deterioration of the patient's condition
- Resulted in persistent or significant disability/incapacity: defined as a substantial to permanent disruption of the patient's ability to conduct normal life functions
- Led to a congenital anomaly or a birth defect
- Were otherwise medically significant
  - Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via a drug is always considered an SAE
  - Example: we recommend that an adverse event that leads to the discontinuation of all the TB drugs be considered medically significant

All the pregnancies in patients or their female partners (while the male patient is on bedaquiline or delamanid and for 3 months after stopping these drugs) with or without associated medical events were reportable. The medical consequences of pregnancy (e.g., miscarriage) were to be additionally reported

Medication errors were defined as any unintended mistake in the prescribing, dispensing and administration of a TB drug that could cause harm to a patient (e.g., wrong drug prescribed, overdose). Medication errors with or without associated medical events were to be reported using the most appropriate term, e.g., 'overdose of linezolid', 'administration of clofazimine twice daily instead of daily'. The medical consequences of medication error (e.g., liver injury following overdose) were also collected

Unexpected adverse events are events that are not consistent, in nature or severity, with the applicable product information (e.g., the package insert, summary of product characteristics)

A safety signal is any information arising from one or multiple sources, which suggest a new potentially causal association, or a new aspect of a known association between an exposure and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification action

SAE = serious adverse event; TB = tuberculosis.

Table 2 Causality assessment approach

Related (likely to possibly related)	Reasonable possibility that the AE is related to the drug(s). Elements in favour of a causal relationship include: • A favourable temporal relationship, • A positive dechallenge and/or rechallenge, • A plausible pharmacological/biological mechanism of action (proven or potential), • Previous knowledge of similar reactions with the drug(s), or • No other evident cause (e.g., pre-existing conditions, ancillary drug) Insufficient information to evaluate the causal relationship between the AE and the exposure: conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e., upon receipt of follow-up information)
Not related	No reasonable possibility that the AE is related to the drug(s): this implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE

AE = adverse event.

site commitment to share regular updates to the PVU, sometimes several months after patients completed treatment. In parallel, clinicians documented SAEs in patient charts and in the endTB electronic medical record (EMR; https://www.bahmni.org). The PVDB and EMR records were reconciled quarterly by the PVU to identify and resolve discrepancies.

Triage

Upon receipt, the PVU conducted triage of reports by screening information and establishing case priority for further processing based on AE seriousness, novelty (unexpectedness) and causal relationship with TB treatment (e.g., urgent, life-threatening, unexpected, related case).

Processing

All the parameters in the form were captured in the PVDB by the PVU: description; TB drugs; patient demographics; relevant pre-conditions, TB history, concomitant/relevant prior drugs; and tests/investigations. A narrative was written for each case merging the information from the various available documents.

Medical review

Each SAE narrative and relevant chest X-rays or electrocardiograms were reviewed by another medically qualified person(s) from MSF/IRD/PIH. The organisation of reviews varied across partners: in MSF, the central medical referent responsible for the site provided this review; in PIH, the central physicians met weekly to discuss the cases and provide reviews; and in IRD, anonymised cases from one site were discussed by the medical team at another site. These reviewers were asked to provide a second opinion on the causal relationship between the SAE and the TB drug, taking into account the clinician's assessment. This was an opportunity for active constructive feedback, when, for example, the reviewer(s) identified different related drugs. The reviewer(s) could also provide feedback to sites regarding case or comorbidity management, providing support in the decision-making process. Expert evaluation, notably involving cardiologists, was organised as needed.

Difficult cases, particularly unexpected SAEs that are possibly drug-related or those potentially indicative of a safety signal (Table 1) after medical review, were shared by the PVU for prompt assessment by a committee, the Medical Review Board (MRB). The core MRB was composed of international TB experts and the PVU. Specialists were appointed as necessary (e.g., electrophysiologist). The MRB was responsible for validating potential safety signals, i.e., to ensure that the available, in-house and published documentation on the signal contained sufficient evidence demonstrating the existence of a new potential causal association or a new aspect of a known association that might justify further analysis, or in case of significant safety issues, immediate actions. The MRB issued recommendations on risk minimisation measures for valid signals.

Information sharing

Reports (using national forms where possible) were shared with NTPs, national pharmacovigilance/aDSM, the WHO and drug manufacturers in accordance with applicable regulations or agreements. Some required immediate reporting (first step, Figure), while others required periodic pharmacovigilance reports that summarised SAEs, signals and MRB recommendations. These were shared with countries and partners. Information on SAEs was also transferred to the WHO aDSM database.[22]

SAE description

During the project, the PVU was informed of 626 SAEs in 417 of 2257 MDR-TB patients who received a BDQ-containing regimen (129 experienced >1 SAE). SAEs, irrespective of causality, were reported any time during treatment, not only during BDQ exposure. Latency between BDQ initiation and SAE onset was between 0 (i.e., the SAE occurred the day BDQ was started) and 26.5 months (mean 5.6; standard deviation 5.5; interquartile range 7.1; data on 16 SAEs were missing).

Common SAEs among patients who experienced ≥1 SAE (417/2257 patients, 18.5%) were respiratory disorders (96/417, 23%), hepatic abnormalities (66/417, 15.8%), anaemia/bone marrow suppression (50/417, 12%), cardiovascular abnormalities (mostly based on electrocardiograms) (41/417, 9.8%), infections (28/417, 6.7%), heart failures (27/417, 6.5%) and peripheral neuropathy (21/417, 5%) (Table 3).

The discontinuation of ≥1 TB drugs following SAEs was common (272/626 SAEs, 43.4%). Although it was not the most commonly withdrawn drug (linezolid), using BDQ as an example of one drug in the regimen: in 284/626 SAEs (45.4%), BDQ could be maintained (with/without interruptions); for 216/626 SAEs (34.5%), no action could be taken as BDQ had already been discontinued (e.g., due to treatment completion); for 113/626 SAEs (18%), BDQ was withdrawn; reasons varied from death, intolerance (e.g., hepatotoxicity), development of risk factors (e.g., hypokalaemia) or TB treatment change after an SAE concerning the regimen; in 13/626 SAEs (2.1%), final BDQ action taken was not shared with the PVU.

A favourable outcome was reported for 48.1% (301/626) of SAEs. The event was ongoing at time of last contact in 13.3% (83/626 SAEs), and outcome was not known despite follow-ups in 3.3% (21/626 SAEs).

About a third (35.3%; 221/626) of the SAEs were fatal (192 patients). Most deaths (110/192 deaths, 57.3%) were TB-related, and due to respiratory failure, disease progression/deterioration and pulmonary embolisms. Other causes included myocardial infarctions (10 deaths), cardiac failure ($n=9$), hepatic failure ($n=8$), renal failure ($n=8$), neoplasms ($n=7$), sepsis ($n=5$), alcohol/drug abuse ($n=3$), stroke ($n=2$), seizures ($n=2$), pneumonia ($n=2$) and in 1 patient each of HIV, malaria, pyelonephritis, coronary artery insufficiency, suicide, cardiomyopathy, gastroenteritis. Eleven patients died at home and the exact cause of death was unknown.

Eight patients died suddenly—in three cases, prolonged QT was documented at some time; one patient had undiagnosed and untreated pre-existing cardiac condition and one pre-existing ischaemic heart disease with uncontrolled diabetes. All suffered from important comorbidities and/or presented with important risk factors, such as diabetes, HIV (treatment failure), hepatitis B virus, dyselectrolytemia, immobility, cachexia or herbal consumption. No autopsies were performed for these eight patients, except in one case that concluded a probable TB-related sudden death. A hypothetical effect of the QT-prolonging medications in their regimen—clofazimine, BDQ, levofloxacin/

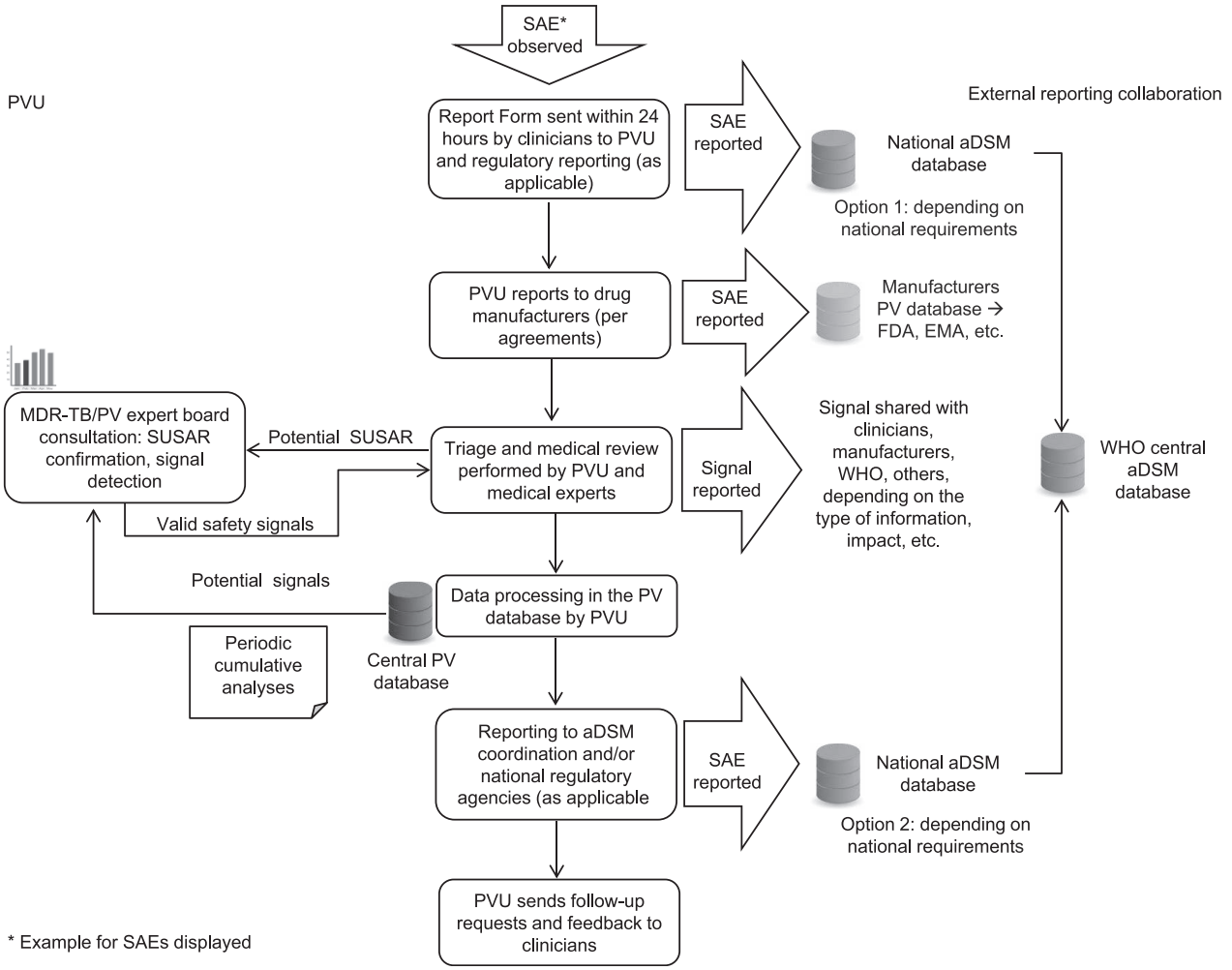

Figure Flow of safety data processing, medical review and reporting in the endTB pharmacovigilance unit. SAE = serious adverse event; PVU = PV unit; aDSM = active TB drug safety monitoring and management; PV = pharmacovigilance; FDA = Food and Drug Administration; EMA = European Medicines Agency; SUSAR = suspected unexpected serious adverse reaction; WHO = World Health Organization.

moxifloxacin or DLM—was considered possible (ranging from likely to possibly related) in all of the cases, except one in whom septic shock appeared likely. Polypharmacy was identified as an important risk factor, with some patients having been prescribed multiple QT-prolonging medications for their comorbidities. Notably, beta-blockers prescribed to treat sinus tachycardia without a clear cardiac indication (off-label) was identified as a possible contributing factor in two instances. More details on deaths will be reported elsewhere.

Reporter assessment was determined for 94.6% (592/626) of all SAEs. Half (356/626, 56.9%) of SAEs were considered as possibly related to any TB drugs, including a third (207/626, 33.1%) of all SAEs assessed by reporters and/or medical reviewers as having a possible causal relationship with BDQ. Alternative causes, risk factors and confounders were present in most cases, including MDR-TB, neoplasms, HIV or concomitant medications with potential additive effects (e.g., QT-prolonging amiodarone).

DISCUSSION

endTB created sentinel sites in 17 countries to perform advanced aDSM, follow all AEs of clinical significance and report to a centralised PVU detailed information about SAEs, among >2600 patients on BDQ and/or DLM. Not surprisingly, in a population on MDR/XDR-TB treatment and under close monitoring, SAEs were common (18.5%). Site clinicians assessed causality for most SAEs (94.6%), and half (56.9%) of SAEs were evaluated as possibly related to any TB drugs (including BDQ). Only a third of the SAEs were thought possibly related to BDQ. Overall, 35% of all SAEs resulted in death, and pharmacovigilance assessments revealed that deaths from TB represented a large proportion; the remainder of the deaths were multifactorial (i.e., comorbidities, polypharmacy). The primary concern emerging from the BDQ Phase II study[4]—sudden death due to cardiotoxicity—was very rare, and the reported sudden deaths occurred in complex cases with multiple causal factors.

Table 3 Description of the most frequent SAEs reported between 1 April 2015 and 31 March 2019 in endTB patients exposed to BDQ-containing regimens

MedDRA high-level group term	Patients *n*	SAEs *n*	SAE by severity grade, *n*				Mean time-to-onset* month	Fatal SAEs *n*	SAEs leading to withdrawal of BDQ *n*	SAEs possibly related to BDQ *n*	SAEs possibly related to other TB drugs *n*	SAEs related to		
			1	2	3	4						Non-TB drugs *n*	Comorbidities *n*	Other *n*
Respiratory disorders (not classified elsewhere)	96	99	0	9	6	84	7	77	12	6	10	4	99	8
Respiratory failure	55	56			1	55		52	8	3	5	4	56	5
Dyspnoea	24	25		6	3	16		12		3	4		25	2
Haemoptysis	8	8		3	1	4		4			1		8	
Respiratory distress	6	6			1	5		5	2				6	
Pulmonary haemorrhage	2	2				2		2					2	1
Chronic respiratory failure	1	1				1		1	1				1	
Acute respiratory failure	1	1				1		1	1				1	
Hepatic and hepatobiliary disorders and hepatobiliary investigations†	66	71	1	4	40	26	5	10	16	61	66	13	33	7
Hepatic enzyme increased	19	19		2	15	2			2	14	18	3	8	1
Hepatitis	15	17			9	8		1	4	16	17	1	5	2
Transaminases increased	12	13		2	10	1			3	13	12	2	8	1
Hepatotoxicity	4	4			2	2			1	4	4	1	2	
Hyperbilirubinaemia	3	3			1	2		1	1	3	3	2	1	
Drug-induced liver injury	3	3			2	1			2	3	3	2	1	
Acute hepatic failure	3	3				3		3	1	2	3	1	2	1
Hepatic failure	3	3				3		3	1	3	3	1	1	1
Alanine aminotransferase increased	1	1				1								
Blood bilirubin increased	1	1	1								1		1	
Gamma-glutamyltransferase increased	1	1			1								1	
Hepatorenal syndrome	1	1				1		1	1	1	1		1	
Hepatic cirrhosis	1	1				1				1	1		1	
Chronic hepatic failure	1	1				1		1		1			1	1
Anaemia, non-haemolytic and marrow depression	50	52	1	5	17	29	4	6	8	6	44	19	24	4
Anaemia	43	45	1	5	13	26		5	7	5	38	17	19	3
Pancytopenia	4	4			1	3		1	1	1	3	1	3	1
Normochromic normocytic anaemia	1	1			1						1	1	1	
Anaemia of chronic disease	1	1			1						1		1	
Bone marrow failure	1	1			1						1			
Cardiac and vascular investigations (excluding enzyme tests)	41	43	1	6	21	15	3	2	12	41	42	6	10	3
Electrocardiogram QT prolonged	40	42	1	6	21	14		1	11	41	42	6	9	2
Ejection fraction decreased	1	1				1		1	1				1	1
Infections: pathogen unspecified	28	29		2	13	14	9	9		2	5	2	5	2
Gastro-enteritis	6	6		2	2	2		2		2	5	2		
Pneumonia	5	6			3	3		1						
Sepsis	4	4			1	3		3						
Device related infection	2	2			2									1
Appendicitis	2	2				2								
Respiratory tract infection	1	1			1									
Tubo-ovarian abscess	1	1			1									
Cholecystitis infective	1	1			1								1	
Empyema	1	1			1								1	
Burn infection	1	1				1		1					1	
Septic shock	1	1			1									
Post procedural pneumonia	1	1				1		1						1
Pyelonephritis acute	1	1				1		1					1	
Infectious pleural effusion	1	1				1							1	
Heart failures	27	29		1	3	25	7	23	9	7	9	6	23	7
Cardiopulmonary failure	12	13				13		12	3	3	5	1	11	3
Cardiac failure	4	4				4		3	2	2	2	2	1	1
Cor pulmonale chronic	3	3		1	2				1				3	
Cor pulmonale	3	3			1	2		2	1	1	1	1	3	
Right ventricular failure	2	2				2		2					1	1
Cardiac failure congestive	2	2				2		2	2	1	1	1	2	1
Cardiac failure acute	1	1				1		1					1	
Cor pulmonale acute	1	1				1		1				1	1	1
Peripheral neuropathies	21	21		6	13	2	5		1		21	2	6	1
Neuropathy peripheral	21	21		6	13	2			1		21	2	6	1

* Average time in months between the date of the first dose of BDQ and the SAE onset date; a same patient can experience >1 SAE pertaining to the same or different categories; the severity grading corresponds to the severity grading scale grades applicable in endTB (1 = mild; 2 = moderate; 3 = severe; 4 = very severe/life-threatening).

† Pooled High-Level Group Terms.

SAE = serious adverse event; endTB = Expand New Drug markets for TB; BDQ = bedaquiline; MedDRA = Medical Dictionary for Regulatory Activities; TB = tuberculosis.

Overall, no unexpected safety signals were detected. Clusters of risk factors, notably polypharmacy and off-label drug use (e.g., beta-blockers), constituted signals that were evaluated. With regard to this issue, we recommended a concerted effort by TB and other specialists (e.g., cardiologists) involved in patient care to review TB and ancillary drug prescriptions; limit the numbers of prescriptions; switch to alternatives with fewer overlapping toxicities, if possible; and ensure comorbidity monitoring and management in accordance with the patient's individual risk profile.

This report is limited to SAEs occurring at any time during MDR-TB treatment among patients who ever received BDQ and does not include all SAEs reported to the PVU, notably SAEs in patients on DLM. SAEs rates were not compared to those in other programmes, which is complex as such comparisons need to take into account reporting completeness and case severity.

This analysis highlights the fact that on the basis of SAE reports alone, which constitutes core aDSM/pharmacovigilance, it is possible to detect, review and validate safety signals without exhaustively reporting all AEs. It also highlights the benefit of mutualising resources centrally. Although demanding in terms of coordination, a centralised PVU allows systematic follow-up in multiple countries and facilitates signal detection. At field-level, having a dedicated team at the site/hospital, or a focal person in the city/area/region/country, is key to ensuring proper data transmission to the PVU and national systems. Information exchanges on difficult cases as they occur, discussion on the best use of drugs, investigations, actions to take, and retrospective assessment of deaths enabled ongoing learning at sites and at project level, and improved quality of care. This also encouraged reporting as physicians perceived added value in sharing and receiving feedback.

As noted by others as well,[23–25] in the absence of a strong national system in place or special funding for this activity, it is unreasonable to expect local projects/NTP to attempt advanced aDSM. It is essential instead to focus on core aDSM, i.e., active detection and management of all drug-related issues in all patients, while limiting collection and reporting only to SAEs, SAEs deemed possibly related to TB drugs or judged otherwise important (e.g., unexpected SAEs). Implementation of a national reporting system focusing only on core requirements, possibly with centralisation of reports, would increase the overall global signal detection capacity and ensure the sustainability of these reporting systems.

CONCLUSION

By concentrating on high-quality, but limited reporting, pharmacovigilance in the context of MDR-TB routine care can provide information to detect critical clusters likely to pose a risk for treatment management (e.g., beta-blockers for sinus tachycardia without arrhythmia) or safety signals and provide reassurance about the level of risk engendered by new treatment modalities, such as BDQ, in the treatment of MDR-TB.

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RÉSUMÉ

CONTEXTE : Une pharmacovigilance (PV) active est recommandée aux programmes de tuberculose (TB), notamment pour les patients atteints de TB multirésistante (MDR-TB), traités par de nouveaux médicaments. *endTB*, lancé avec le soutien d'UNITAID en avril 2015, a facilité le traitement par la bédaquiline (BDQ) et/ou le délamanide de >2600 patients dans 17 pays et a contribué à la création d'une unité centrale de PV (PVU).

OBJECTIF : Détailler le processus de PVU d' *endTB* et illustrer son fonctionnement en décrivant les effets indésirables graves (SAE) subis par des patients qui ont reçu des traitements incluant BDQ.

SCHÉMA : La stratégie d'ensemble de PV a correspondu à la version avancée du suivi et gestion actifs de l'innocuité des médicaments contre la TB (aDSM) de l'OMS. Tous les effets indésirables cliniquement significatifs ont été suivis et la PVU s'est concentrée sur la détection de signaux provenant des SAE.

RÉSULTATS et CONCLUSION : Entre le 1 avril 2015 et le 31 mars 2019, la PVU a reçu et évalué 626 SAE chez 417 patients sous BDQ. Un panel d'experts en MDR-TB/PV a revu les SAE inattendus et possiblement reliés au médicament pour détecter des signaux de sécurité. Les experts ont rapporté des regroupements de facteurs de risque, notamment une poly médication et l'utilisation de médicaments dans une indication non approuvée, encourageant une approche centrée sur le patient. Organiser une PV avancée en soins de routine est possible mais exigeant. Il est raisonnable de s'attendre à ce que les programmes locaux/nationaux se concentrent sur la prise en charge clinique et limitent les rapports aux systèmes aDSM aux données clés, comme les SAE.

RESUMEN

MARCO DE REFERENCIA: La farmacovigilancia (PV) activa se recomienda en los programas de TB, en especial para los pacientes con TB multidrogoresistente (MDR-TB) tratados con nuevos fármacos. El consorcio *endTB*, iniciado con el apoyo de UNITAID en abril del 2015, facilitó el tratamiento de más de 2600 pacientes con bedaquilina, delamanid o ambos en 17 países y contribuyó a la creación de una unidad central de PV (PVU).

OBJETIVO: Especificar el proceso operativo de la PVU de *endTB* y presentar su funcionamiento mediante la descripción de los eventos adversos graves (SAE) que ocurrieron en los pacientes que recibían pautas con bedaquilina.

MÉTODO: En general, la estrategia de PV correspondió al método avanzado de farmacovigilancia activa de la OMS (aDSM). Se dio seguimiento a todos los eventos adversos de importancia clínica y la PVU se centró en la detección de señales de los SAE.

RESULTADOS Y CONCLUSIÓN: Del 1 de abril del 2015 al 31 de marzo del 2019, la PVU recibió información y evaluoró 626 SAE de 417 pacientes que recibían bedaquilina. Una junta de expertos en la PV de la MDR-TB examinó los SAE inesperados y posiblemente relacionados con los medicamentos, con el objeto de detectar señales de toxicidad. Los expertos comunicaron grupos de factores de riesgo, en especial la multimedicación y el uso medicamentos en indicaciones no autorizadas e fomentando un enfoque de atención centrada en el paciente. Es posible organizar una PV avanzada en la atención de rutina, pero es exigente. Es razonable esperar que los programas locales o nacionales se centren en el manejo clínico y que circunscriban la información que envían a los sistemas de aDSM a los datos clave como los SAE.