

Safety and tolerability of an all oral shorter MDRTB regimens: Monitoring, management and reporting of adverse events

Global Consultation on Best Practices in MDR-TB Care

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Objectives

- Monitoring of safety:
 - Why is safety important? How and what to monitor? How does it differ from monitoring for longer or older regimens? When to adapt monitoring.
- Management of adverse events?
 - What tools can help me manage adverse events on all oral shorter treatment regimen?
- Reporting of adverse events
 - What do we already know? What do we need to know?
 - What level of PV reporting is adapted to your setting
 - Examples of SAE and SUSAR reporting forms.
 - Where to report to and when

Monitoring: Why is safety important

- Patients are able to complete well tolerated regimens
- Less morbidity and mortality amongst patients
- Better overall treatment results, less interruptions, less lost to followup
- Well tolerated MDRTB regimens are better for patients and programs

Monitoring: How and what to monitor for patient on all oral short regimens

- What to monitor?
- How does it differ from monitoring for longer or older regimens?
- When to adapt monitoring?

Monitoring: what to monitor?

- Monitor for important and documented adverse events particularly those which:
 - can results in serious consequences eg anemia, QT prolongation
 - those who are irreversible eg peripheral neuropathy, optic neuritis
 - that patients might not notice eg QT prolongation, low platelets, white blood cells
- Different monitoring between long and short?
 - Depends on the drugs but in general the same.. ***Just shorter!***
 - ***No more*** injectables so no more audiometry or systematic electrolytes and renal function
 - ***No more*** PAS or Prothionamide/ethionamide: so no more systematic thyroid function

Monitoring

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Until end of treatment	End of treatment	3 months post-end-of-treatment	6 months post-end-of-treatment	9 months post-end-of-treatment	12 months post-end-of-treatment
Clinical evaluation														
Vital signs	X		X	X	X	X	X	X	Monthly	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	Monthly	X	X	X	X	X
Post-end-of- treatment consultation										X	X	X	X	X
Assessment and follow-up of adverse events	X	X	X	X	X	X	X	X	At each scheduled /unscheduled visit	X	X	X	X	X

[illegible]

Monitoring when to adapt from standard

Pre-existing conditions or risk factors

- cardiac risk factors
- High baseline QT
- >3 QT prolonging drugs
- Pre-existing peripheral neuropathy

Adverse events during treatment

- High QT interval
- Electrolyte disturbances
- Increased liver enzymes

Management of adverse events

- All oral clinical guide
- ? WHO companion handbook
- Have a plan

Why is reporting of safety data important

- To improve clinician and programmatic knowledge of what AE are expected and how to manage them
- To compare different regimens
- To identify subpopulations with specific risks (HIV, hepatitis C, children, pregnant women)
- To detect rare events

Reporting: what we already know

- Adverse events profile of drugs used extensively in the past such as fluoroquinolones, cycloserine, clofazamine
- Drugs used at large scale more recently: bedaquiline, linezolid
- Drug combinations from recent trials
 - Nix: high dose linezolid, high linezolid associated adverse events: 70% Lzd related adverse events, 1200 mg Lzd
 - STREAM: injectable adverse events still present in shorter regimen
 - Delamanid phase III: no safety issues of delamanid, low QT prolonging potential



Frequency and Incidence of clinically relevant AEs

AE term and grade	Patients N (%)	Time to first AE Median [IQR]	Incidence /100 person-months (95% CI)
Hypokalemia/ hypomagnesia	327 (26.3)	3.0 [1.0-8.0]	2.15 (1.93-2.40)
Hearing loss	211 (17.0)	3.7 [2.0-6.9]	1.29 (1.13-1.47)
Peripheral neuropathy	107 (8.6)	4.1 [2.0-7.5]	0.60 (0.50-0.73)
Hepatotoxicity	71 (5.7)	2.1 [1.0-7.0]	0.38 (0.30-0.49)
Hypothyroidism	59 (4.7)	4.0 [2.9-7.3]	0.32 (0.25-0.42)
Acute renal failure	52 (4.2)	1.9 [0.9-5.2]	0.28 (0.22-0.37)
Myelosuppression	49 (3.9)	1.9 [0.6-4.9]	0.27 (0.20-0.35)
QT prolongation	34 (2.7)	2.0 [0.7-6.4]	0.18 (0.13-0.26)
Optic neuritis	30 (2.4)	7.2 [3.6-13-1]	0.16 (0.11-0.23)

1244 patients in 15 countries,

Results: Clinically Relevant AEs while on Drug of Interest

Safety

AEs	Patients with ≥ 1 N, % (95% CI)	Person time exposure (months)	Incidence per 100 person- months (95% CI)
QT prolongation \geq grade 3 (bedaquiline and/or delamanid)	34/1244 2.7 (1.5-4.8)	BDQ only: 12,968 DLM only: 4916 Combined: 620	0.18 (0.13-0.26)
Hearing loss all grade (injectable)	128/643 19.9 (12.5-30.1)	3803	3.36 (2.83-4.00)
Hearing loss all grade; Acute renal failure \geq grade 2; or Hypokalemia, hypomagnesemia (injectable)	229/643 35.6 (28.0-44.0)	4236	6.16 (5.46-6.93)
Peripheral neuropathy \geq grade 2; Myelosuppression; or Optic neuritis all grades (linezolid)	112/1020 11.0 (7.9-15.0)	12,685	0.94 (0.78-1.13)

Reporting: where data is lacking

- Use of bedaquiline or delamanid more than 6 months (endTB observational study)
- Use of bedaquiline and delamanid together (endTB observational study, endTB-Q clinical trial)
- Effect of different Lzd doses and durations (ZeNix)

endTB Bdq and Dlm use summary

- From the cohort of **2241** patients enrolled on MDRTB treatment in the endTB study and starting Dlm or Bdq before May 2018
 - **923** (41%) patients had **more 24 weeks of Bdq**
 - Median duration of Bdq was **317 days**
 - **619** (28%) patients **had more than 24 weeks of Dlm**
 - Median duration of Dlm was **300 days**
 - **334** patients **had Dlm and Bdq concomittantly**
 - **219** started Dlm and Bdq together
 - **115** had one added to the other (Dlm added to a Bdq containing regimen, or Bdq added to Dlm containing regimen)
 - **238** had more than 24 weeks of Dlm and Bdq together in a MDRTB regimen

Use of bedaquiline more than 24 weeks

Results: 146 patients with at least 12 months of Bdq from the cohort of MDRTB patients started Dlm or Bdq before 1/1/2017

	First 6 months of bedaquiline	Second 6 months of bedaquiline
Number of QtcF prolongation events of clinical relevance (grade 3 and 4)	6	0
Number of patients with QtcF prolongation events of clinical relevance (grade 3 and 4)	6 (4.1%)	0

Use of delamanid more than 24 weeks

- Results: 70 patients with at least 12 months of Dlm from the cohort of MDRTB patients started Dlm before 1/1/2017

	First 6 months of delamanid	Second 6 months of delamanid
Number of QtcF prolongation events of clinical relevance (grade 3 and 4)	4	1
Number of patients with QtcF prolongation events of clinical relevance (grade 3 and 4)	4 (5.7%)	1 (1.4%)

Combination of delamanid and bedaquiline

- How many had clinically relevant QT prolongation: only amongst those who **started** Dlm and Bdq together before 1/7/2017 and in the first 6 months of combination

N= 42	0-6 months of delamanid and bedaquiline together
Number of QtcF prolongation events of clinical relevance (grade 3 and 4)	1
Number of patients with QtcF prolongation events of clinical relevance (grade 3 and 4)	1(2.4%)

Reporting: some definitions

- Adverse event (AE): any untoward event, whether caused by drug or not

AE or not AE?

- I had headache from time to time before but now it is every day.
- My skin feels dry.
- I cut myself badly yesterday.
- My voice is different.
- I have no more fever and less cough.



Reporting

Adverse event (AE): any untoward event, whether caused by drug or not

- Adverse drug reaction (ADR): noxious and toxic effect which is reasonably possibly *caused by a drug*
 - Unexpected adverse drug reaction: drug reaction that is not yet documented
 - Expected

« Side effect: a secondary, typically undesirable effect of a drug or medical treatment »

Severity and seriousness

- Severity = intensity
 - General scale
 - Specific severity scale
- Seriousness
 - Fatal
 - Immediately life threatening
 - Leading to hospitalisation or prolongation of hospitalisation
 - Leading to a significant disability / incapacity
 - Birth defect or congenital anomaly
 - Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes
- Severity \neq seriousness



Serious or not serious?

- I had headache from time to time before but now it is every day. I cannot work anymore
- My skin feels dry. It is cracking at joint levels
- I cut myself badly yesterday. I did it on purpose
- My voice is different. There is a mass in the larynx, sample sent for biopsy
- Liver failure; patient sent to Intensive Care.



The assessment of the seriousness of an event is NOT linked to whether it is caused by a drug or not.

Causality and relatedness

- Causality:
 - Drugs
 - Comorbidities
- Relatedness
 - Possible?

Reporting forms: use national forms

СООБЩЕНИЕ

о побочных реакциях или отсутствии эффективности лекарственных средств (желтая карта) (заполняется медицинским или фармацевтическим работником)

ПР - побочная реакция

ОЭ - отсутствие эффективности

ЛС - лекарственное средство

1. Информация о пациенте

1. ФИО пациента

6. Клинический диагноз (указанием шифра по МКБ-10)

Основной: _____

Сопутствующий: _____

7. Последствие ПР

☐ выздоровление без последствий



SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Sponsor: Médecins Sans Frontières Protocol/Program n°: _____ Site n° (for studies) or country: _____

Initial report: ☐ Follow-up report: ☐ Date of report: ____ / ____ / ____ (dd/Mmm/yyyy)

Patient information

Patient n°: _____ Initials: _____ Date of birth: ____ / ____ / ____ (dd/Mmm/yyyy) Gender: F ☐ M ☐ Height: _____ cm Weight: _____ kg

Serious adverse event(s) information		SAE 1	SAE 2	SAE 3
Adverse event term		_____	_____	_____
Event onset date (dd/Mmm/yyyy)		____ / ____ / ____	____ / ____ / ____	____ / ____ / ____
Date event became serious (dd/Mmm/yyyy)		____ / ____ / ____	____ / ____ / ____	____ / ____ / ____
Event end date (dd/Mmm/yyyy)		____ / ____ / ____	____ / ____ / ____	____ / ____ / ____
Duration if <1 day (hrs/min)		____ / ____	____ / ____	____ / ____
Seriousness criteria	Death	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	In case of death:		Death date: ____ / ____ / ____	Autopsy: Yes <input type="checkbox"/> No <input type="checkbox"/>
	Life-threatening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Hospitalization required / prolonged	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Hospitalization dates:		Admission: ____ / ____ / ____	Discharge: ____ / ____ / ____
Persistent or significant disability / incapacity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

ინფორმაცია სერიოზული გვერდითი გამოვლინების შესახებ

	SAE 1
გვერდითი მოქმედების დასახელება	Heart attack / გულის შეტევა
გვერდითი მოქმედების გამოვლენის თარიღი (რიცხვი/თვე/წელი)	____ / ____ / ____
თარიღი, როდესაც გვერდითი მოქმედება გახდა სერიოზული (რიცხვი/თვე/წელი)	____ / ____ / ____
გვერდითი მოქმედების გამოვლენის დასრულების თარიღი (რიცხვი/თვე/წელი)	____ / ____ / ____

Case number: _____

სიკვდილის შემთხვევაში: ☒ გარდაცვალება

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ჰოსპიტალიზაციის ვადები:

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ხარისხი 1 ☐ 2 ☐ 3 ☐ 4 ☒

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9. Торговое наименование:

10. МНН (генерическое):

11. Фирма-производитель ЛС:

12. Указать номер серии:

20. Показания к назначению

Reporting: what shall I REPORT on?

- Possible choices:
 - Serious adverse events?
 - Only adverse drug reactions?
 - Serious ADRs?: serious and reasonably probably caused by the drug
 - Adverse event of interest? (list of pre-specified AEs)
 - Suspected unexpected serious adverse drug reaction(SUSAR)
- BUT decide what you will collect and collect it well and completely
- DO not collect data that is not needed
- YES monitor, YES manage adverse events... but don't try to report too much as it won't answer all questions

Reporting: Where shall I report to?

- NOT NEEDED: a full functioning aDSM system
- NEEDED: basics in place to collect your identified level of safety data
 - A method to collect data on the adverse events: SAE forms
 - Staff properly trained to collect the data
- Collect your own data
- Where to send..
 - Any existing National authorities – NTP, drug authorities
 - Can also be sent to other PV databases
 - Central WHO database
 - Upsulla
 - For endTB countries: PV unit

summary

- Monitor your patients to keep them safe: dont monitor for the sake of monitoring but do pay attention where needed
- Manage the adverse events to keep your patients safe and on treatment
- Report only a limited amount of info, and dont make it a barrier