Introduction of New Drugs for DR-TB Treatment

Training Course for TB Physicians

II Day

March, 2015

Tbilisi, Georgia

II Day

Module 4: Ethical Considerations and Informed Consent;
Module 5: Active Pharmacovigilance in the Field;
Module 6: Generating Evidence for Scale-Up;

Module 4: Ethical Considerations and Informed Consent

Objectives

- To review the ethical considerations in the use of new drugs for the treatment of DR-TB
- To discuss the development of information on new drugs for patients
- To review the process of informed consent for use of new drugs for the treatment of DR-TB
- To discuss other ethical considerations, including PV, operational research

Ethical Issues with New Drugs

- These drugs are being recommended for use under program conditions and not as a clinical trial
- Ethical issues/concerns arise based on the small numbers of patients included in the clinical trials
- Ethical issues/concerns arise from the lack of long-term safety data
- Specific ethical concern about the higher mortality rate seen with BDQ compared with placebo in the registration trial
- These ethical concerns must be placed in the context of current treatment of MDR-TB, including poor outcomes and high rates of adverse events

Informed Consent and DR-TB

- Most patients sign a consent form to receive DR-TB treatment
- In most cases, the form is short and non-specific
- Introduction of new drugs can be a catalyst for improving consent process overall
- Ensure the new drugs are not “exceptional-ized”
- Ensure that process facilitates patient understanding
- Ideally, informed consent is an ongoing process and dialogue between providers and patients

Informed Consent: A Symptom-Based Approach

- Provides information that is more relevant to the patient
- Provides equipoise in the process
- Allows for more patient interactions
- Can help contextualize risk

Developing Information for Patients

- Key part of informed consent process is making sure the patient understands and can contextualize the potential risks and benefits of therapy
- Information needs to be culturally appropriate, available in local languages, and developed with the input of patients and community

Living with Drug-Resistant TB

A Workbook for Making the Most of Your Treatment Experience

First Edition, February, 2015

Key Information Points: General

- Reason the drug is being offered: resistance or intolerance means a full regimen cannot be made without them
- Goal of the consent process: to ensure patient understands the role of the new drug and has the opportunity to ask questions and have them answered

Key Considerations for BDQ

- New TB drug that has been shown to increase cure rates in patients who received the drug compared with those that did not
- Side effects can include problems with the liver and problems with the rhythm of the heartbeat
- In one clinical study, patients who received BDQ had a higher death rate than those who did not, but this was felt not to be due to the drug
- To date more than 500 patients have received BDQ

Key Considerations for DEL

- New TB drug that has been shown to increase cure rates in patients who received the drug compared with those that did not
- Side effects can include problems with the liver and problems with the rhythm of the heartbeat
- To date more than 400 patients have received DEL

INFORMATION ON BEDAQUILINE FOR PATIENTS

What is Bedaquiline?

It is a new class anti-tuberculosis medication that has a new way of working against tuberculosis (TB) and has been developed to treat drug-resistant tuberculosis.

It should never be taken alone. It must always be taken in combination with other anti-TB medication, and always approved by your treating healthcare provider who needs to have a good understanding of your condition, multidrug-resistant tuberculosis (MDR TB), your medical history and the current medications you are taking.

What are the possible side effects?

Any drug can cause unwanted, unpleasant and sometimes harmful effects on the body.

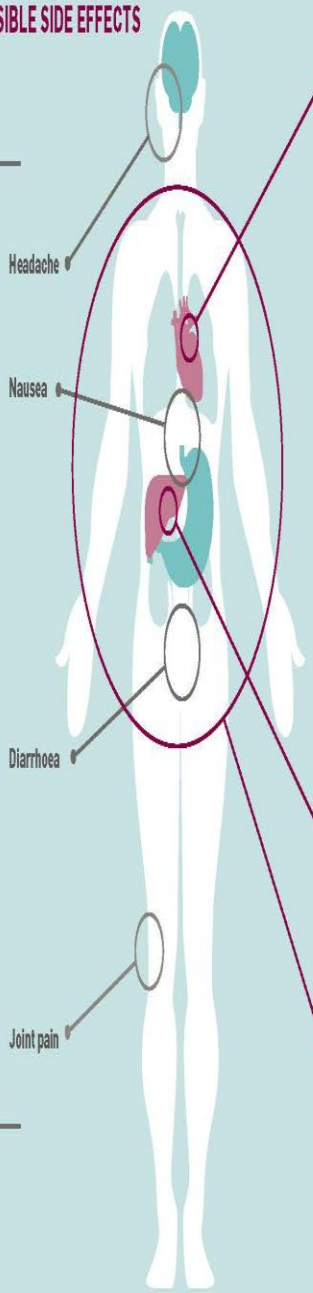
Not all potential side effects of bedaquiline in humans are known at this stage.

In one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive bedaquiline. It is unclear whether bedaquiline treatment itself caused any of these deaths.

The most common side effects reported in the studies to date were:

- Headache
- Nausea
- Diarrhoea
- Joint pain

POSSIBLE SIDE EFFECTS



POTENTIALLY SERIOUS SIDE EFFECTS

Increase in "QT" interval: QT interval is an electrical measurement of how the heart functions and can be seen on an ECG (electrocardiogram). An abnormally prolonged QT interval increases the risk of heart rhythm disturbances, which in rare cases may cause cardiac arrest and sudden death. No significant clinical side effects due to heart rhythm disturbances could be detected in the current studies, but it is important to remember that there have not been enough studies yet to say whether this drug is completely safe or not. Each patient should have regular ECGs to monitor the electrical activity of their heart and to measure the QT interval.

Long QT interval can be caused by inherited conditions (called "Congenital Long QT syndrome"), or medications. Some common medications can cause this (including TB medications, or medications given against clinical depression, allergy, fungal or microbial infections). It is important to tell your healthcare provider about all the medications that you are using.

If you have:

1. a family history of heart disease, or
2. if you have heart disease yourself or
3. if you are on medication that could have effects on your heart, you should first discuss this with your healthcare provider.

Symptoms like fainting, feeling an irregular, fast or slow heartbeat, or seizures should be reported to your healthcare provider immediately.

Bedaquiline can cause inflammation (irritation) to liver and pancreas tissue. Some symptoms to look out for are abdominal or back pain, persistent nausea and indigestion. A later symptom could be oily, smelly stools. Much of this inflammation can occur without symptoms, so blood tests should be done regularly to monitor for the possible development of injury to the liver or pancreas.

Bedaquiline takes a long time to be removed by the body (it takes up to 5 months for half of the amount of the drug to be removed). Detectable levels of the drug could remain in your body for up to 2 years. The significance of this slow removal process is currently not known.

What to do in case of any possible side effect

You should tell your healthcare provider immediately about any side effect that you experience while taking bedaquiline. By acting quickly, the chances that the side effects continue or become worse can be reduced. Sometimes other medications can be given to reduce the side effects and/or make you feel more comfortable.

You will be treated with other medicines for your TB infection as recommended by your doctor/health care facility/government's TB programme. These other medications could also have side effects not listed here. When different TB medicines are used together they can sometimes have unexpected side effects.

Tell your healthcare provider right away if you have any problems

You have the right to ask any questions concerning the potential and/or known dangers of bedaquiline at any time. If additional information becomes available about the risks of taking bedaquiline you should be informed by your healthcare provider.

Bedaquiline and HIV treatment

If you are HIV positive, your healthcare provider will discuss with you whether it is better to delay starting HIV treatment or to treat you with a drug regimen for HIV that available data suggests is appropriate for use with bedaquiline. Only a few HIV positive subjects with MDR TB were enrolled in the clinical studies, but so far bedaquiline appeared to be generally safe and well tolerated in people living with HIV.

What should you avoid while taking bedaquiline?

You should not drink alcohol while taking bedaquiline.

How should I store bedaquiline?

Store bedaquiline at 77°F (25°C).

Keep bedaquiline in the original container, and keep bedaquiline out of light.

General information about the safe and effective use of bedaquiline

This Medication Guide summarizes the most important information about bedaquiline. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about bedaquiline that is written for health professionals.

Reproductive risks

If you are pregnant or breastfeeding, there may be risks to you or your baby that are not known at this time. It is not advised to use bedaquiline when pregnant or breastfeeding at this stage.

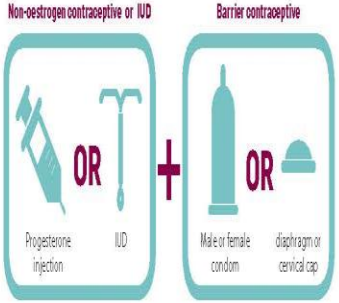
Females

All women must avoid falling pregnant while taking bedaquiline. If you are a woman able to become pregnant (i.e. not sterilised or less than 2 years since menopause), you should **use 2 methods of birth control.** These methods should be openly discussed with your healthcare provider and partner, so that they are acceptable to you, effective and safe. You should continue with these methods throughout the entire time of treatment with TB medications.

The 2 methods of birth control could be, for example,

a) non-oestrogen hormonal based contraceptives (such as the depot progesterone injection) in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap, or female condom), or

b) an intrauterine device (IUD) used in combination with a barrier contraceptive.



A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.

Oestrogen based methods of birth control (such as the contraceptive pill) may not be reliable when taking bedaquiline and/or other TB drugs

You should tell your healthcare provider at once if you fall pregnant or think that you might be pregnant.

Males

All men should avoid fathering a child while on treatment with Bedaquiline. This is advised as the effects of the medication on your sperm are unknown; the effect of the medication also persists in the body for a period of many months.

If you are a man, it is important that you use a condom or other appropriate contraceptive measures to prevent pregnancy when having intercourse. These precautions apply throughout the entire period of treatment.

You should inform your healthcare provider if your partner becomes pregnant while you are taking bedaquiline or if she falls pregnant within one month after stopping your medication.

How should you take bedaquiline?

Bedaquiline should always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with bedaquiline.

- Take bedaquiline with food. Swallow the tablets whole with water.
- Take bedaquiline exactly as your healthcare provider tells you to take it. Take bedaquiline for a total of 24 weeks.

Week 1 and Week 2:

- Take 400 mg (4 tablets) 1 time each day.

If you miss your bedaquiline dose during Week 1 or Week 2: Do not take a double dose to make up for the missed dose. Take the next dose as usual.

Week 3 to Week 24:

- Take 200 mg (2 tablets) a day 3 times a week.

For example, you may take bedaquiline on Monday, Wednesday and Friday every week.

Do not take more than 600 mg (6 tablets) bedaquiline during a 7 day period.

- You may need to take your other TB medicines for longer than 24 weeks. Check with your health care provider.
- **Do not skip bedaquiline doses.** If you skip doses, or do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.
- If you take more bedaquiline than you should, talk to a healthcare provider right away.

If you miss your bedaquiline dose during Week 3 to Week 24: Take the missed dose as soon as possible and resume the three times a week schedule.

Do not take more than 600 mg (6 tablets) in total during a 7 day period. You should take 2 tablets per day, three times a week.

If you miss a dose and you are not sure what to do, talk to your healthcare provider.

Do not stop taking bedaquiline without first talking to your healthcare provider.

Patient Information: Other Approaches

- Counselors
- Peer educators
- Videos, role plays
- Waiting room educational sessions
- Community health workers
- Other?

Informed Consent and New Drugs

- Signed consent required for BDQ
- “Due process” recommended for DEL
- Goal is to begin a dialogue
- SHOULD NOT mirror consent forms used in clinical trials
- Avoid laundry lists of possible effects
- Ensure patient is truly informed but do not place all responsibility for decision-making on the patient

Informed Consent and New Drugs

- Frequent feedback and re-assessment of understanding patient and his or her support system
- Remember that it can be difficult for patients being given serious health news to remember all the facts and information they are given, so repetition is important
- Encourage patients and social support to write down their questions or concerns

Beware of informed consent process making the new drugs seem exceptionally dangerous or otherwise problematic; focus on the limited experience with them compared with other drugs used for MDR-TB

Ethical Considerations for Other Aspects of New Drug Introduction

- PV and other “registries” that collect data outside of routine patient conditions
- Operational research conditions
- Research projects used to inform scale-up
- Operational and other research will require review by ethical committees

Ethical Considerations: Case Review

- RR is a 24 year-old woman with KM-resistant MDR-TB for whom DEL has been recommended for treatment.
- The plan is to start her on her treatment regimen tomorrow, and she is meeting with you to "give consent for her treatment."
- What would you tell her? Can she start treatment tomorrow? Who else should be involved in the discussion

Ethical Considerations and Informed Consent: Summary

- Ethical concerns with the new drugs mostly related to limited patient experience
- Informed consent is a process between providers, patients, and their social support systems
- Appropriate patient information materials need to be developed and communicated on an ongoing basis
- Additional consent and ethical review may be needed for other aspects of new drug introduction, including case registries and operational research

Questions?

Module 5: Active Pharmacovigilance in the Field

Objectives

- To review the principles and need for active pharmacovigilance (PV) when using new drugs to treat DR-TB
- To discuss the responsibilities of field providers in active pharmacovigilance
- To discuss other important issues in the management of AEs

Active Pharmacovigilance: Definitions

- Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug.
- In active PV, routine monitoring of a cohort on the drug is carried out to look for unexpected AEs
- Cohort Event Monitoring is a very specific type of active PV often used with new drugs

Why the need for Active PV?

- Monitoring known AEs associated with the new drug(s): i.e. QTc prolongation, LFT abnormalities, anemia, thrombocytopenia, neuropathy
- Cohort event monitoring recommended for BDQ and DEL because these drugs have only been used in smaller patient populations, and the full AE profiles have not yet been established
- Need cohort of approximately 10,000 individuals to establish the full safety profile of a drug, including rare events

Partners in Active PV

- Field staff to collect and report data
- Central staff—including the NTP and a Pharmacovigilance body—to receive and analyze data and report back to the field
- Supranational coordinating staff to monitor combined cohorts

CEM does not need to be permanent but active PV does

- Once full AE profile established and there are no new AEs reported for a certain period of time, active PV for that drug can be transitioned out
- Reporting of severe AEs should continue

Active PV: What Happens?

- Patient is seen by medical staff on a routine basis (monthly for 6 months then quarterly) or when a problem occurs
- Symptom screening and routine labs are done and noted in the medical record
- If symptoms are present or lab abnormalities seen, clinical staff then decide SEVERITY of the event, attribute likely CAUSALITY, and make an ACTION PLAN, all of which are recorded in the medical record

Active PV: What Happens?

- Data entry staff transcribe or enter the data in an electronic database on an ongoing basis
- This data is sent to the central level for analysis
- Trends are reported back to the field

PV and Severe Events

- Events requiring hospitalization or that are deemed severe, should be reported to the central level within 24-48 hours.
- This includes the occurrence of a pregnancy while on the new drug
- Each country will need to establish a mechanism for this

PV Responsibilities in the Field

- Minimal burden on physicians and nurses, as good patient care includes the monitoring and documenting of adverse events
- May require additional details in the chart/medical record about severity, causality and plan of action
- If this information is well documented in the chart, then PV will be straightforward
- Some sites may use special forms for collecting this data

Assessing Severity

- Several standardized scales can be used to assess severity
- Many use “mild”, “moderate”, “severe”, “life-threatening” or corresponding numeric grades (1,2,3,4).
- If the patient requires hosptialization to manage the adverse event, then it is usually considered “life-threatening” or grade 4

Assessing Causality

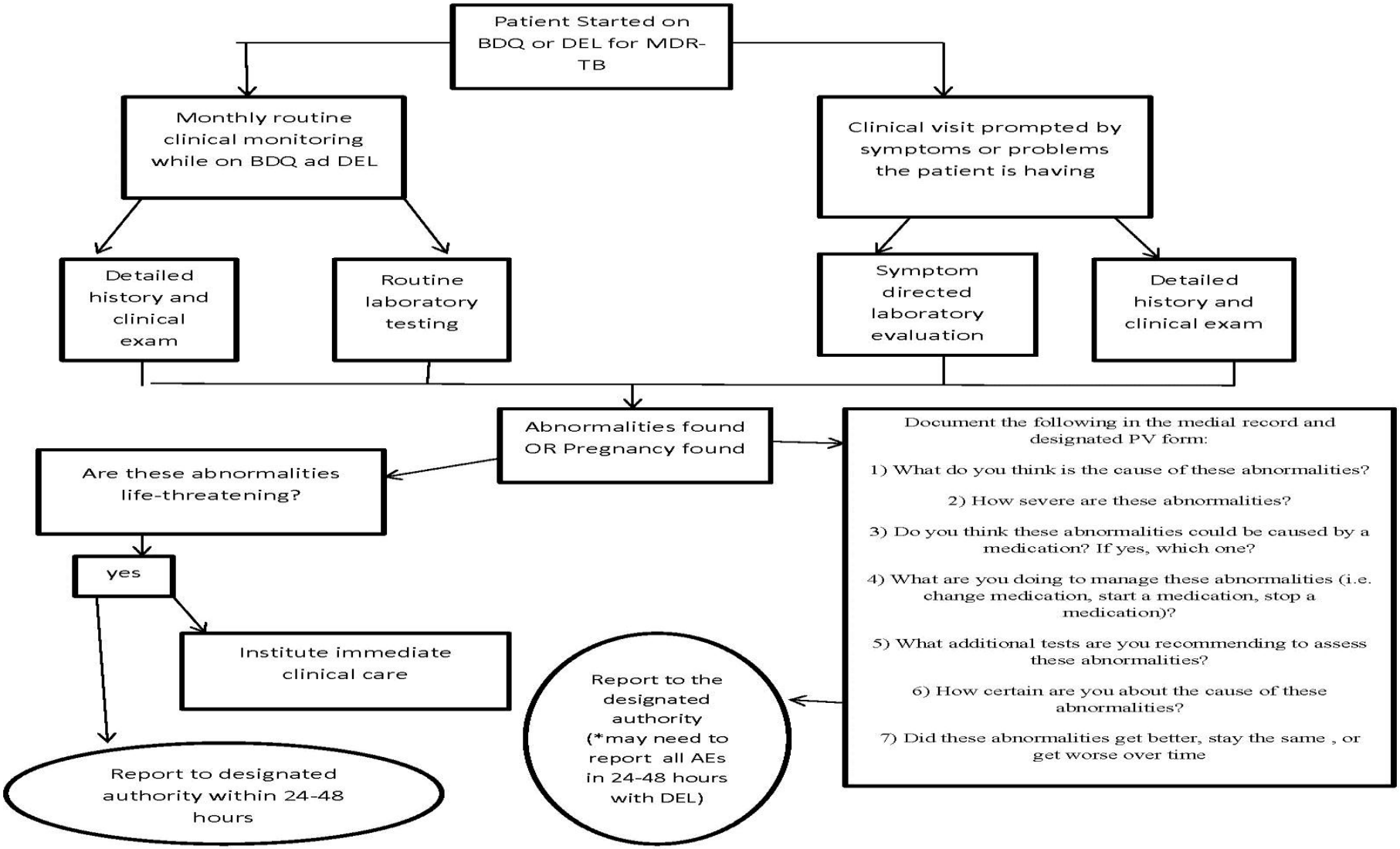
- This is done routinely in clinical care (i.e. patient with hypothyroidism, likely due to ethionamide)
- Can be difficult to determine causality in a multi-drug regimen
- Could be done by central level staff

Developing an Action Plan

- This is done routinely in clinical care (i.e. will start levothyroxine and check TSH in one month)
- Should note carefully any new drugs introduced, any changes in drug dosing, and when follow-up will be done

Implementation Tool: Pharmacovigilance for DR-TB Clinical Providers

Active pharmacovigilance is recommended for BDQ and DEL because these drug are new, have been used in a limited number of patients, and the full side effect profile is not yet known. The role of clinical providers in active pharmacovigilance is to collect as much detailed clinical information as possible and report this information to the designated management team. This algorithm is intended to guide clinical providers in their role in active pharmacovigilance.



PV Responsibilities at a Central Level

- Joint activities with the NTP and an appointed PV group
- Develop protocol and forms for PV in the field
- Collect and analyze data reported from the field
- Review quality of data
- Participate in causality assessment
- Provide support for field teams
- Provide ongoing feedback to the field teams

Do we need a PV Center?

- Many countries have small or limited PV programs who have limited experience with TB/DR-TB
- Building PV expertise is important but can take time
- NTP can manage a number of the functions of a PV center, provided the number of patients is small and that this role is not permanent

Do we need a full active CEM program to start using new drugs?

- No, as long as there is a system in the field to collect the necessary data and report it to some central body for analysis
- PV capacity can be built as new drugs are being used

Sources of Funding for PV

- Not just the responsibility of the NTP
- Health systems strengthening activity with support from MOH
- Multiple donors are interested in supporting PV
- New partners can be engaged, including MSH, SIAPS, etc.
- Role of drug companies

Supranational Level

- No single country will have a large enough cohort on new drugs to quickly reach the cohort of 10,000
- Need for supranational collection and analysis of data
- Multiple possible groups could play this role
- No plan for this yet, and countries should not wait for this to start BDQ

Contextualizing PV Requirements

- Active PV is a requirement for new drug introduction
- Good patient care will cover most aspects of PV in the field
- This requirement should not distract from other important activities around AEs, such as procuring medications, obtaining diagnostics, etc.

Active PV: Case Example

- RM is a 36 year-old woman with MDR-TB who developed worsening hearing after 2 months on standard MDR-TB treatment (Z-KM-Ethio-Levo-CS) and had her injectable stopped and BDQ started.
- She is tolerating therapy well, but in her 5 month of treatment (3rd month on BDQ), she begins to hear voices that are commanding her to go to the river and drown herself. She is also agitated and confused and is brought to the clinic by her family after she barricades herself in her room to "hide from the devil".
- What should be done as part of the clinical management of this patient?

Active PV: Case Example

- What should be done as part of active PV for this patient?

Active PV: Summary

- Important for establishing the full safety profile of a drug
- Much of the information needed is collected as part of good patient care, although there may need to be additional information on severity, causality, and plan of action documented
- Data should be sent to a recognized central body coordinated by the NTP and a PV body for analysis
- Supranational database important to reach cohort completion more quickly
- Method for collection and reporting of data needed in order to start new drugs, but fully established CEM system can be built over time
- Important to make sure patients have access to diagnostics and treatment for AEs

Questions?

Module 6: Generating Evidence for Scale-Up

Objectives

- To discuss the types of research and data needed to help inform national scale-up
- To review strategies for collecting and analyzing this data
- To discuss optimal timelines for reviewing such data
- To consider optimal platforms for sharing these data

Operational Research

- Data that helps answer questions of programmatic significance under program conditions
- Countries need to understand how best to introduce new drugs in their local conditions but do NOT need to repeat randomized clinical trials to assess
- Ideally, will answer both outcome and process questions
- Often collected as part of routine patient care

Types of Data

- Quantitative research: includes numbers, percentages, usually collected and analyzed for larger groups
- Qualitative research: includes themes and quotes, usually collected and analyzed for smaller groups with more in-depth collection techniques
- Careful use of both types of research will yield the most complete picture

New Drug Introduction: Outcomes

- Efficacy (short and long term)
- Safety (short and long term)
- Tolerability (short and long term)
- Important to define comparator group

Potential Long-Term Efficacy Indicators

- 1) percentage of patients on new drugs with successful treatment outcomes (cure and completed treatment);
- 2) percentage of patients on new drugs with unsuccessful treatment outcomes (treatment failure, losses to follow-up and death);
- 3) average time to sputum culture conversion; and
- 4) percentage of patients treated with new drugs who developed resistance to the medication

Timing of Efficacy Assessments

- For assessments of long-term efficacy outcomes, it can take 3-5 years before all data on final outcomes can collected and analyzed
- This time frame does not promote scale-up or support real-time decision making
- Important to define interim efficacy outcomes, including 2, 3 and 6 month rates of culture conversion; time to culture conversion, etc.
- Recommend quarterly assessments but caution not to over-interpret data from small numbers of patients

Potential Safety Indicators

1) Percentage of patients on new drugs who experience cardiac adverse events;

2) Percentage of patients on new drugs who experience liver adverse events;

3) Percentage of patients on new drugs who experience other targeted adverse events; and

3) Percentage of patients on new drugs who need to have their regimens changed to exclude the new drugs due to the development of adverse events.

Potential Tolerability Indicators

- 1) percentage of patients defaulting from treatment;
- 2) number of missed doses of new drug in the 6 month treatment period; and
- 3) qualitative assessment of the patients' experience with new drugs

New Drug Introduction: Process Indicators

- 1) number of patients screened for new drug eligibility;
- 2) percentage of patients screened who are declared eligible for new drugs and reasons for prescribing new drugs;
- 3) percentage of eligible patients enrolled on treatment with new drugs;
- 4) percentage of patients eligible for treatment with new drugs who were NOT enrolled on treatment, and reasons why; and
- 5) stock outs of new drugs;

New Drug Introduction: Process Indicators

- In addition, operational challenges (such as human resources constraints, laboratory issues, challenges in supportive supervisory visits, etc.) should be described
- Interviews with patients/providers or collecting data outside of routine program consditions may require additional ethical review and informed consent

Cost-Benefit Analysis?

- Programs should monitor the costs of the implementation of the drug to have a realistic sense of budget planning and resource allocation
- Must also consider impact of new drug on patient outcomes and decreased transmission
- Need to have a way to calculate the costs of not using the new drugs for true comparison

Generating Evidence For Scale Up: Case Example

- Country Y decides to introduce BDQ for the treatment of patients with resistance or intolerance to the aminoglycosides and/or fluoroquinolines.
- They plan to introduce the drug in 3 pilot sites (one in the north, one in the central, and one in the south) for a total of 100 patients in 2015
- They ordered the drug for these 100 patients in July of 2014 and the drug is expected to arrive in January 2015
- In order to plan for additional patients in 2016, a drug order will need to be placed in June of 2015
- What kind of data should the program collect and assess to determine how much (if any) new drug to buy for 2016?

Generating Evidence for Scale-Up: Vulnerable Populations

- Often excluded from clinical trials for a number of reasons
- Often include persons in desperate need of new drugs, such as children and persons with HIV
- Can provide information on mobile or isolated individuals, including migrants and prisoners

Possible platforms for data sharing

- Published literature
- National and international conferences
- Case reports and examples
- Inclusion in supranational databases
- Popular media
- Community and patient groups
- Webinars

Generating Evidence for Scale-Up

- Important in identifying facilitators and barriers in local settings
- Most can be collected as part of routine program implementation
- Focus on outcomes and process with an eye to program needs
- Include vulnerable populations who may be left out of more formal research
- Consider timelines and logistical issues when defining optimal data set

Questions?

Thank You
for
Attention