endTB Medical Committee

Terms of reference

The endTB Medical Committee (referred to as the "Committee" in this document) formulates recommendations for off-label and compassionate use of the new anti-TB drugs for M(X)DR-TB and provides advice to any MSF[1], PIH[2] and IRD[3] projects for individual patient's management on a case-by-case basis in answer to requests initiated by clinicians from the projects.

The role of the Committee is to provide advice to the clinicians and projects in three main circumstances:

1. Management of difficult cases
   These may include difficulty in choosing a drug regimen in a patient with high level of resistance, co-morbidities, concomitant treatment, or adverse events linked to treatment, during pregnancy or lactation.
2. Request for off-label use of bedaquiline or delamanid
   Off-label use is defined as the use of a drug for an indication, age group, dose regimen, eligible population or any other parameter that is not mentioned in the approved labeling. The off-label use of bedaquiline or delamanid that may be presented to the Committee includes use of drug:
   - In children aged 6-17 years old;
   - Any other unapproved indication.
3. Request for Compassionate Use (CU) of new anti-TB drugs includes
   - Patients treated in countries where delamanid and bedaquiline cannot be imported or used in routine care but can be available through CU programs.
   - Requests for the use of a new anti-TB compound in the event that it would be available through CU programs (e.g. pretonamid, sutezolid, etc.).

The Committee takes into consideration the patient's medical condition and history, the resistance profile, the therapeutic options and the other available information, as well as international recommendations and experience regarding the drugs. While the committee proposes the best possible alternative it also takes into consideration the national regulations regarding the use of the drugs.

Off-label use and CU can only be done after prior approval from national authorities. The approval of the Committee does not constitute a statement on the safety and efficacy of the off-label use and CU of the new drug.

The Committee reviews each individual patient's situation on a case-by-case basis. When found appropriate by the members, the Committee may define sets of criteria of indications

[1] Médecins Sans Frontières
[2] Partners In Health
[3] Interactive Research and Development

for the off-label use of the drugs. For patients who meet such pre-defined set of criteria the Committee may decide to set-up an expedited mechanism for reviewing requests in order to allow a quick answer to the requesting physicians and projects.

While the committee formulates recommendations, it is the responsibility of the project teams to ensure compliance with the national regulations regarding off-label use or CU of drugs. Recommendations should be considered in light of the local context and patient's particular circumstances as known to his or her treating physician. The final decision with respect to patient's treatment regimen remains with his or her treating physician.

Patients under off-label use or CU should be closely monitored in terms of safety and efficacy. Off label use and CU should be adequately documented and data made publicly available.

Functioning

A Secretariat is in charge of being the focal point for requests, forwarding the requests to the Committee members, gathering answers, organizing teleconferences whenever necessary. The Secretariat is hosted by PIH.

Requests from the field should be initially sent to the "coordinating medical staff" of each endTB consortium member. The coordinating medical staff for PIH consists of the central Clinical Coordinators; for MSF the central TB advisors and for IRD clinical coordinators; the coordinating medical staff should check the requests for completeness and send them to the Secretariat.

The secretariat is in charge of:

- Allocating each request to 3 members on a rotating basis (one member from the requesting institution, one member from another participating institution and one external member) and making all requests available for comments to all members;
- Preparing a predefined call schedule in consultation with the members and the Chair in order to ensure that at any time at least one member from each participating institution and one external member are available on a rotating basis to review the requests;
- Ensuring that the designated members answer in due time;
- Compiling the answers and forwarding the committee's recommendations after review and endorsement by the Chairperson of the Committee to the concerned the "coordinating medical staff" of each endTB consortium member.

Role of MSF Ethical Review Board

The MSF Ethical Review Board (ERB) will be asked to review any sets of criteria of indications for the off-label use of the drugs and expedited mechanisms that the Committee may produce.

The Committee reports to MSF ERB every 6 months through a report compiled by the chairperson of the Committee. Reporting includes: number of requests received and

reviewed, projects where the requests were initiated, recommendations from the Committee (in case of refusal justification is provided), information on patient's follow-up (culture conversion, outcome, adverse events).

The patients are asked to sign an Informed Consent Form for CU and for "off-label" use of a new drug. The consent forms are approved by MSF ERB. Amendments made to the initially approved documents and in particular the Informed Consent Form must be submitted to the MSF ERB for approval

Decision making process

Decision on an agreement of a list of pre-defined criteria and on an expedited decision making mechanism requires a consensus of the Committee with a quorum of 10 members.

Decisions are made on consensus. The committee provides the clinicians and projects with recommendations on best possible treatment regimen and patient management. Recommendations are finalized within 5 working days.

- For difficult cases the advices of the members are compiled and forwarded to the requesters within a week, no quorum is required.
- For off-label use and CU of bedaquiline and delamanid: the members designated by the Secretariat are in charge of reviewing and answering the requests as appointed within 8 working days. Though 3 members are specifically in charge of each request, all members of the committee have the possibility to comment and advice on all cases and their input is reflected in the final recommendation. In case no agreement is reached among the 3 designated members or there is contradictory opinion from any member, the request is brought to the entire committee. In case of refusal of the request by the 3 designated members the decision and its justification will be specifically sent for information to all Committee members in order to allow them to object if they think appropriate.
- For CU of new anti-TB compound the quorum is defined as the presence of 5 voters. In case of refusal of the request the decision and its justification will be specifically sent for information to all Committee members in order to allow them to object if they think appropriate.

Membership

The committee is composed of 16 members.
The members are selected according to their expertise in the field of clinical management of MDR TB. The members are proposed by each partner of the endTB consortium and endorsed by the endTB leadership team.

The members commit themselves to provide answers in due time (5 working days after they are appointed to review a request by the Secretariat), to participate in necessary teleconferences and to organize between themselves in order to always have the quorum of 5 voters.

A Chairperson is designated among the members of the Committee by the endTB leadership team and will serve for at least one year. The Chairperson is selected on the basis of his/her expertise and availability, and can be affiliated or not to the participating organizations.

The Chairperson oversees the functioning of the Committee, reviews and endorses the recommendations sent to requesters on behalf of the Committee, convenes and chairs ad hoc meetings or teleconferences, sends regular updates to the respective ERBs. (MSF Ethical Review Board, …)

Membership is for 2 years, renewable.

Proposition:

Secretariat:
Sarah McAnaw, PIH

Internal Experts:
MSF: Cathy Hewison, Alex Telnov, Krzysztof Herboczek, Anita Mesic, Gabriella Ferlazzo

PIH: Askar Yedilbayev, Hind Satti, Michael Rich, KJ Seung
IRD: Uzma Khan, Naseem Salahuddin

External experts:
Jose A. Caminero (MD, Chest Physician. Consultant for The Union)
Domingo Palmero (Hospital Muniz. Buenos Aires, Argentina)
Charles Daley (MD, Division chief, National Jewish Hospital, Denver, USA)
Mathilde Jachym (MD, Sanatorium de Bligny, France)
Saiful Qayum (MD, IOM)

Preamble to the annexes

As stated in the Terms of reference of the endTB Medical Committee, “the Committee may define sets of criteria of indications for the off-label use of the drugs”. The Annex 1 represent such a set of criteria, which are meant to guide the decision-making of the Committee without modifying the regular review process.
In the Terms of reference of the Committee, it is also noted that “for patients who meet… pre-defined set of criteria the Committee may decide to set-up an expedited mechanism for reviewing requests”. The Annex 2 defines the mechanism of this expedited review and establishes the specific roles inside the Committee during this process.

Annex 1

Criteria for approval of the co-administration of bedaquiline and delamanid by the endTB Medical Committee

The following set of criteria aims to provide a help to the decision by the committee to recommend or not the co-administration of Bdq and Dlm.
Each case should be reviewed individually by the endTB committee following the regular review process.

Criteria:

1. Ensure that the patient and treating center fulfill all the following pre-requisites (Table 1)
2. Assess if the patient responds to the main inclusion criterion (Table 2)

Table 1. Pre-requisites for co-administration of bedaquiline (Bdq) and delamanid (Dlm)

Pre-requisites for Bdq/Dlm co-administration	Definition
Good adherence, if MDR-TB treatment already started	Good treatment adherence (at least for all the effective drugs), if treatment already started. OR Previous challenges to adherence addressed and a significant improvement expected
Good tolerability, if MDR-TB treatment already started	No serious adverse events (SAE) linked to Bdq or Dlm, if treatment already started, or SAE is resolved.
No contraindications to the use of Dlm or Bdq	Baseline ECG demonstrating a QTcF > 500 ms (finding confirmed by at least two different ECGs performed at least 5 minutes apart); or History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease Severe hepatic failure Serum albumin < 2.8 g/dL Known hypersensitivity
Informed consent	Patient should be correctly informed about the potential risks and benefits, as well as on the available evidence on Bdq/Dlm association. Additional informed consent should be requested and obtained specifically for the association of Bdq and Dlm.
Closely monitored treatment	Treatment should be monitored closely according to available guidance for timely detection and management of adverse events. Treatment adherence should be carefully monitored. Hospitalisation (or living in close proximity to a medical facility and having full time support at home), weekly ECG and serum electrolytes (K+ and Mg++) for 10 weeks

Table 2. Criterion for the co-administration of bedaquiline (Bdq) and delamanid (Dlm)

Criterion for Bdq / Dlm co-administration	Definition
Insufficient number of effective drugs* in the treatment regimen	Less than 4 effective drugs in the regimen if Bdq and Dlm are not included together (ethambutol, high dose isoniazid and pyrazinamide are not counted as effective drugs in MDR-TB conventional regimen). This can be applicable to initial regimen design or later if one or more drugs have to be permanently discontinued. The paucity of effective drugs in the treatment regimen may be due to drug resistance pattern, inability of the project to adequately administer imipenem/cilastatin (40-60 minutes infusions twice daily), adverse events or any other contraindications

* Effective drug = never used before in a failing regimen, susceptible according to a reliable DST result

Annex 2

Decision making mechanism for expedited review by the endTB medical Committee for off-label use of new anti-TB drug(s):

The expedited review is initiated by the specific request of the physician from the field. The request is done using a standard template, which will be available in the field, reflecting the predefined set of criteria agreed upon by the endTB medical Committee for expedited review. The Secretariat sends the request to one member of the Committee not affiliated to the requesting institution for expedited review according to a pre-established schedule. If the member agrees, the Secretariat forwards the request to the chairperson of the Committee. If the chairperson of the Committee endorses the request, it is approved. If the member disagrees or has any doubts, or if the chairperson of the Committee does not endorse the request, the request is sent back to the Secretariat for review following the regular review process by the Committee.