Impact of the rapid detection of RIF-resistant MTB in patients with newly diagnosed, smear-positive pulmonary TB in Lviv/UA

The RAPIDOT Study

Thomas Bodmer for the ‚STOP TB LVIV' Study Group

Executive Summary

Impact of the rapid detection of RIF-resistant MTB in patients with newly diagnosed, smear-positive pulmonary TB in Lviv/UA

Background: The results of the Sykhiv pilot study revealed that almost 40% of newly diagnosed pulmonary tuberculosis (TB) patients were infected with drug-resistant *Mycobacterium tuberculosis* (MTB). Almost half of these cases were multidrug-resistant MTB (MDR-TB). Patients who are infected with such strains generally do not respond favourably to the standard drug regimen recommended by WHO. Inadequate drug therapy will result in treatment failures and continued transmission of drug-resistant strains. Therefore it is of the utmost importance to rapidly identify these patients and to treat them as soon as possible according to the results of drug susceptibility testing (DST). This can be done by standard DST within 3 to 4 weeks or by molecular techniques within one day.

Study goals: To prospectively evaluate the molecular detection of RIF-resistant MTB, and to prospectively study the effect of its rapid detection in combination with resistance-adapted, directly supervised drug therapy on the outcome of patients with newly diagnosed, sputum smear-positive pulmonary TB.

In addition, this study will help to prepare the implementation of molecular testing at Sykhiv.

Patients and methods: A total of 200 consecutive adult patients with newly diagnosed pulmonary TB (sputum smear-positive) from the city of Lviv/UA will be included in the study. In total, 4 sputum specimens per patient (2 specimens initially; after 2 and 5 months of treatment, one further specimen) will be submitted to the Core Laboratory at Sykhiv hospital and processed according to the new laboratory algorithm. Parts of the decontaminated sediment of each patient's first specimen will be sent to Berne for the molecular detection of rifampicin (RIF)-resistant MTB (Xpert® MTB/RIF, Cepheid) and for targeted DST (Bactec® MGIT 960, BD Diagnostics). Patients will be tentatively categorized according to the results of molecular testing (RIF-susceptible or RIF-resistant MTB) and treated accordingly, with pre-defined drug regimens. In addition, directly observed therapy (DOT) will be given to patients with RIF-susceptible TB by study nurses who report to the local study coordinator. The outcome data of the study group will be compared to the overall outcome data as the reference.

Relevance of the study: The study supports the consolidation of the new Core Laboratory at Sykhiv hospital and prepares the introduction of molecular testing for drug-resistant MTB. Data on the local drug resistance rates of MTB and risk factors that are associated with drug resistance will be generated. In addition, the effect of the rapid diagnosis of MDR-TB on patient management will be studied, and, importantly, some elements of WHO's DOT strategy will be implemented, and the results compared to the current situation.

Study goals

The STOP TB LVIV RAPIDOT study aims at:

- the prospective evaluation of the detection of rifampin (RIF) resistance by the Xpert® MTB/RIF assay in new patients with sputum smear-positive pulmonary tuberculosis (TB)
- studying the effect of the rapid detection of drug resistance on the outcome of patients with newly diagnosed, sputum smear-positive pulmonary TB in Lviv/UA
- assessing the overall rate and the patterns of drug resistance in Lviv/UA
- the characterisation of risk factors associated with drug-resistant TB in Lviv/UA
- establishing a collection of clinical MTB isolates from Lviv/UA

Local study coordinator

The realisation of the RAPIDOT study will be coordinated and supervised locally by the local study coordinator who's name is Dr. Sinowij Nakonechnyi, deputy chief of Sykhiv hospital. His duties and responsibilities as a RAPIDOT local study coordinator are described in a separate document (see RAPIDOT Study Coordinator).

The study coordinator will be supported by a personal assistant for data collection, translation and communication. Martha Nakonechna was appointed assistant to the study coordinator. Her duties and responsibilities as an assistant to the RAPIDOT local study coordinator are described in a separate document (see RAPIDOT Study Coordinator).

The coordinates of Martha Nakonechna are:

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Patients and methods

This section describes the phases of the RAPIDOT study.

Phase 0, Recruitment of study patients

Patients with a first episode of sputum smear-positive pulmonary tuberculosis (TB) who live in the City of Lviv are eligible. The recruitment procedure is summarized below. Overall, 10 to 15 cases per month of newly diagnosed patients with pulmonary TB from the city of Lviv are to be expected, i.e. recruitment of 200 patients may take between 14 and 20 months.

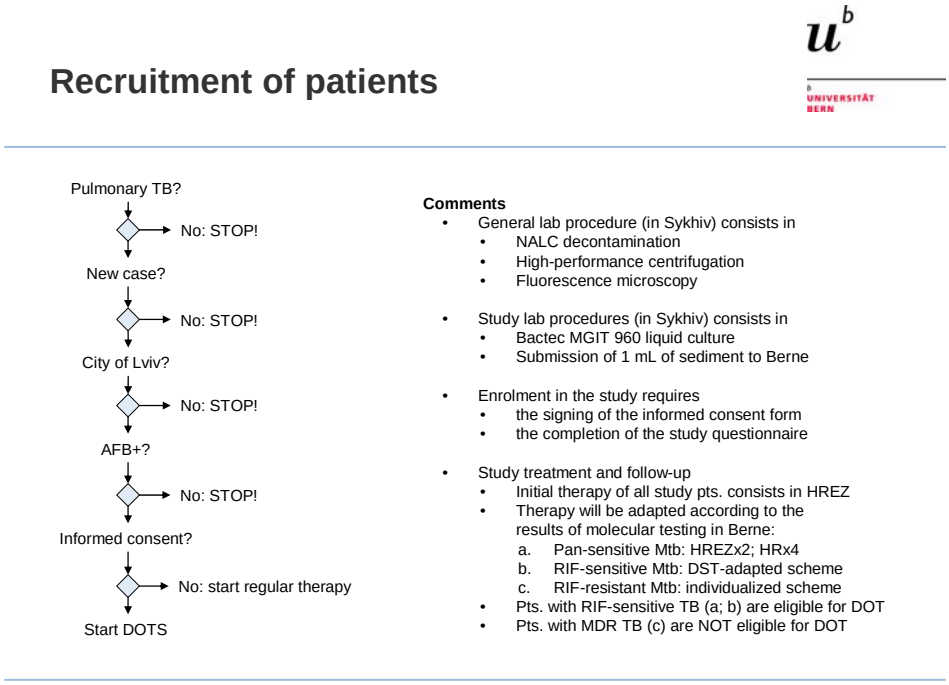


Figure 1: Recruitment of study patients

Sputum will be obtained from each patient and submitted to the central TB laboratory in Sykhiv. There, sputum specimens are processed upon receipt (NALC decontamination; high-performance centrifugation; fluorescence microscopy; both Bactec® MGIT 960 liquid and solid culture), and the microscopy results are reported to the attending physician and the local study coordinator.

Patients with a first episode of sputum smear-positive pulmonary TB who live in the City of Lviv are eligible, but definitive enrolment requires that patients give informed consent to be part of the study and complete the study questionnaire. Definitive enrolment is authorized by the local study coordinator who is responsible for the correct patient selection and enrolment procedure and the completeness of the study data.

Phase 1, Hospitalization and initiation of intensive phase drug therapy

All study patients will be hospitalized and intensive phase drug therapy (intensive phase; 0 to 8 weeks) will be initiated with HREZ according to the WHO recommendations (see figure 2).

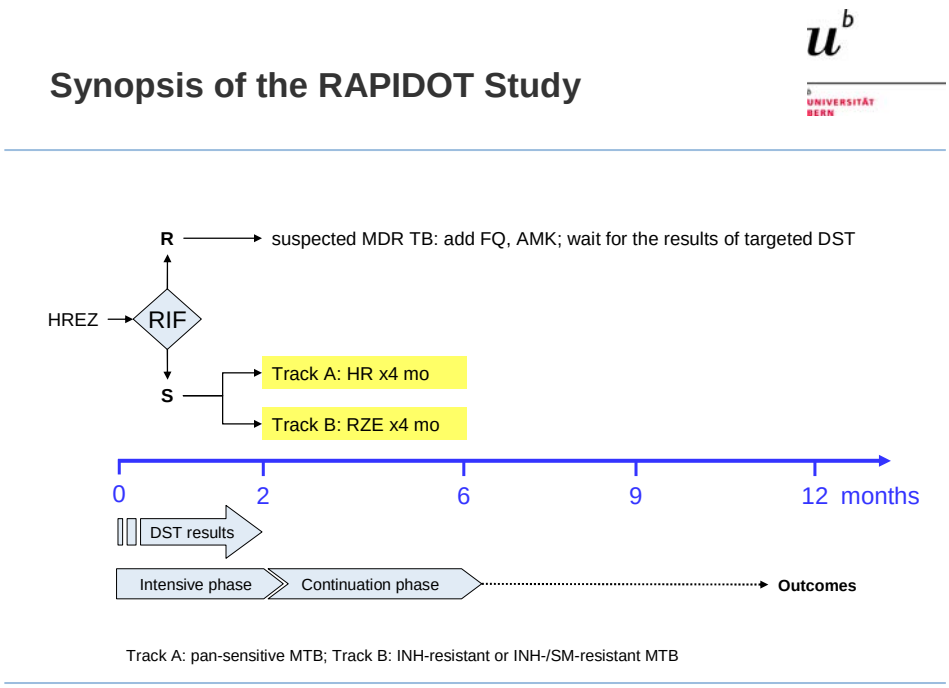


Figure 2: Synopsis of the RAPIDOT Study

Molecular detection of RIF-resistant MTB

The first sputum sediment of each study patient will be cultured locally using the Bactec® MGIT 960 system; in addition, study questionnaire and approx. 1 mL of the sediment will be sent to Berne by courier for the molecular detection of RIF-resistant MTB and targeted DST (target: at least 10 specimens per shipment, but within 21 days after specimen processing; see figure 3).

Patients will be categorized into RIF-susceptible and RIF-resistant TB on the basis of the Xpert® MTB/RIF test results. Testing will be done in Berne (see figure 3), and laboratory reports will be transmitted from Berne to Sykhiv by e-mail (nakonechna_m@yahoo.com) to the assistant to the study coordinator as soon as the Xpert® MTB/RIF test results become available. Upon receipt the study coordinator will confirm the reception of the reports by e-mail to thomas.bodmer@ifik.unibe.ch.

In addition to molecular testing culturing of the sediments targeted DST will be initiated (see figure 3).

In Sykhiv the reports are forwarded to the attending physician by the local study coordinator. The latter is responsible for adherence to, and documentation of, the study guidelines for subsequent categorization of the patients and the adaptation of drug regimens when indicated (see figures 2 & 4).

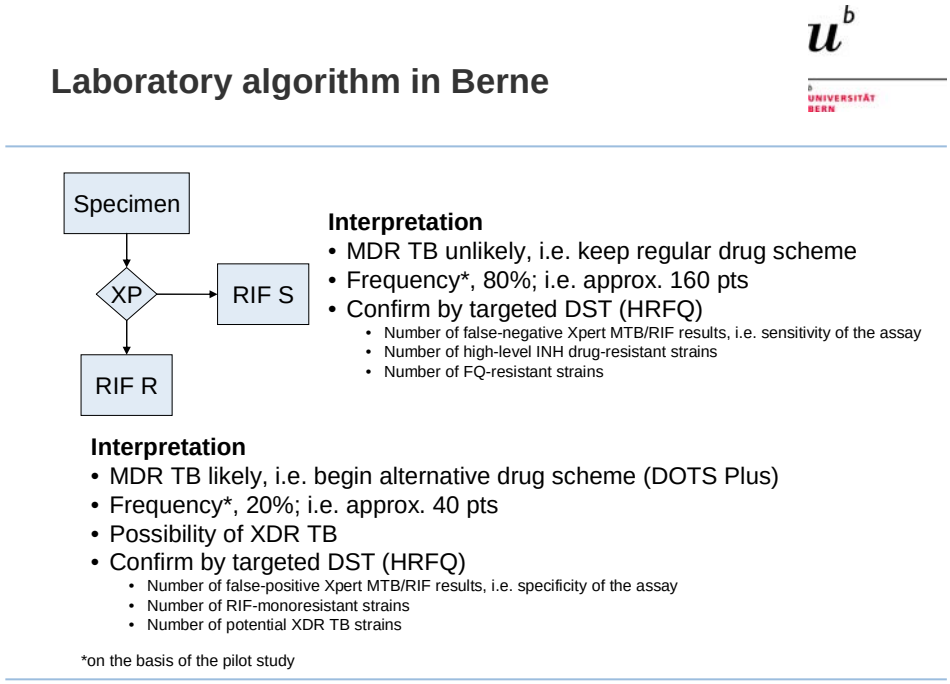


Figure 3: Molecular detection of RIF resistance

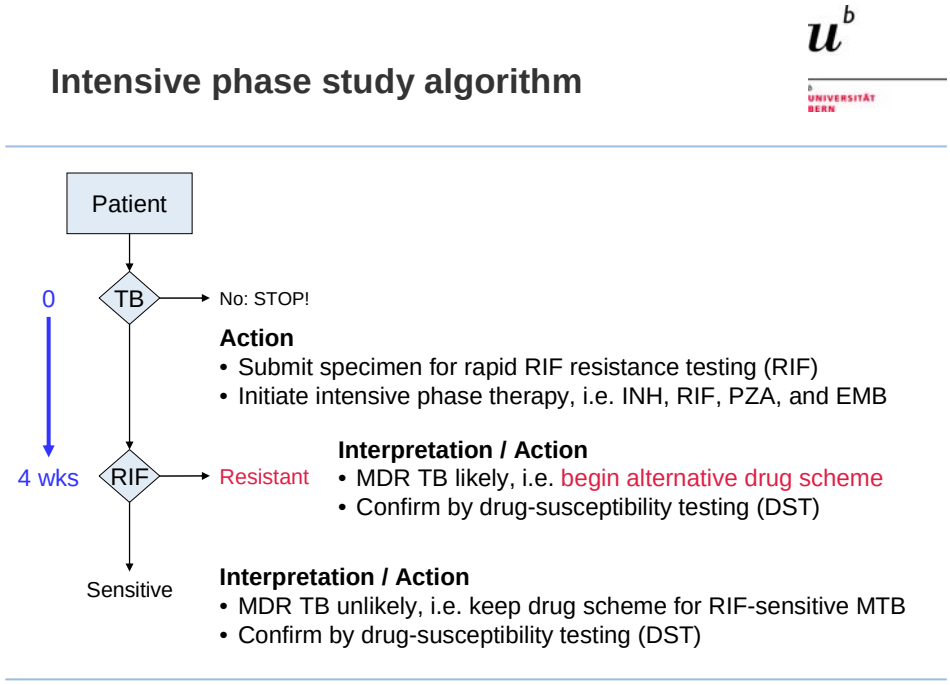


Figure 4: Intensive phase study algorithm

Conventional drug-susceptibility testing

The findings of the rapid RIF resistance testing will be confirmed by conventional drug-susceptibility testing (DST) of cultured *Mycobacterium tuberculosis* by the Bactec® MGIT 960 system. The results should be available by the end of the intensive phase, i.e. within two months after initiation of therapy. DST results will guide the therapeutic decisions with regard to the continuation phase in cases of RIF-susceptible, mono- or poly-resistant MTB (see figure 1).

In case of discrepant results between the Xpert® MTB/RIF assay and the results of DST, the latter will serve as the reference for guiding drug therapy.

Standardised treatment regimens

Figure 2 gives a synopsis of the diverse treatment tracks of the RAPIDOT study. Tracks are based on the results of the molecular detection of RIF resistance, conventional DST and the HIV status of the patient.

All study patients will be hospitalized and intensive phase drug therapy (intensive phase; 0 to 8 weeks) will be initiated according to the WHO recommendations with Isoniazid (INH; H), Rifampicin (RIF; R), Pyrazinamide (PZA; Z), and Ethambutol (EMB; E). Recommended doses for adults are given in table 1.

Table 3.1 RECOMMENDED DOSES OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS

Drug	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin[a]	15 (12–18)		15 (12–18)	1000

[a] Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group (*2*). Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (*WHO Model Formulary 2008*, www.who.int/selection_medicines/list/en/).

Table 1: Recommended doses of first-line anti-tuberculosis drugs.

RAPIDOT treatment tracks

Patients with confirmed (on the basis of the phenotypic DST results) RIF-susceptible TB are eligible for ambulatory directly observed therapy (DOT). All treatment will be given on a daily basis. Individual drug regimens are adapted according to the results of the DST results when indicated (see tracks), and the patients will be discharged from the hospital. Below, the most frequent therapeutic situations and their respective standardised drug regimens, i.e. treatment tracks, are defined. For less common therapeutic situations written instructions are given in table 2. More complex therapeutic situations can be discussed with the Study Coordinator and the Swiss partners.

Track A: pan-sensitive MTB

After completion of the intensive phase of two months HREZ, patients with pan-sensitive MTB will receive a daily, supervised therapy with HR for an additional 4 months, i.e. for a total treatment period of 6 months.

Track B: INH-resistant or INH-/SM-resistant MTB

After completion of the intensive phase of two months HREZ, patients with INH-resistant MTB will receive a daily, supervised therapy with RZE for an additional 4 months, i.e. for a total treatment period of 6 months.

Track C: MDR TB

Patients with suspected RIF-resistant MTB (on the basis of the Xpert® MTB/RIF test) should be considered MDR TB patients until proven otherwise. These patients are separated and a fluoro-quinolone (FQ), preferably levofloxacin (LVX), and amikacin (AMK) are added to the HREZ treatment regimen until the results of the targeted DST become available. Then, individualised drug therapy is initiated on the basis of the DST results.

Recommended doses and range for levofloxacin and amikacin are listed in table 2:

Drug	**Weight <50 kg**	**Weight >50 kg**
Levofloxacin	750 mg p. o., daily	1000 mg p. o., daily
Amikacin	750 mg i.m., daily (5/7 or 6/7)	1000 mg i.m., daily (5/7 or 6/7)

Table 2: Recommended doses for Levofloxacin and Amikacin.

Patients with confirmed RIF-resistant TB (track C; on the basis of the phenotypic DST results) are not eligible for the RAPIDOT study.

Such patients will be treated according to the existing guidelines for MDR TB treatment, unless alternative MDR TB therapy, such as DOTS *plus*, seems appropriate to the local study coordinator.

Phase 2, Continuation phase, ambulatory drug therapy

The organisation of the drug delivery **must** be clarified **prior to** discharging a patient from the hospital. The direct contact between the patient and the community nurse in charge of the surveillance of the ambulatory phase will generally be established during the patient's hospitalisation. In some cases, facilities for daily clinic visits might be necessary and require consideration (for instance bus tickets).

Following discharge from the hospital, the patients with confirmed RIF-susceptible pulmonary TB will be treated on an outpatient basis, under full supervision of drug intake, until the completion of the treatment. As the usual duration of hospitalization is 2 months or more (intensive phase of treatment with 4 drugs), we can assume that the patients under DOT will receive isoniazid and rifampicin in the continuation phase.

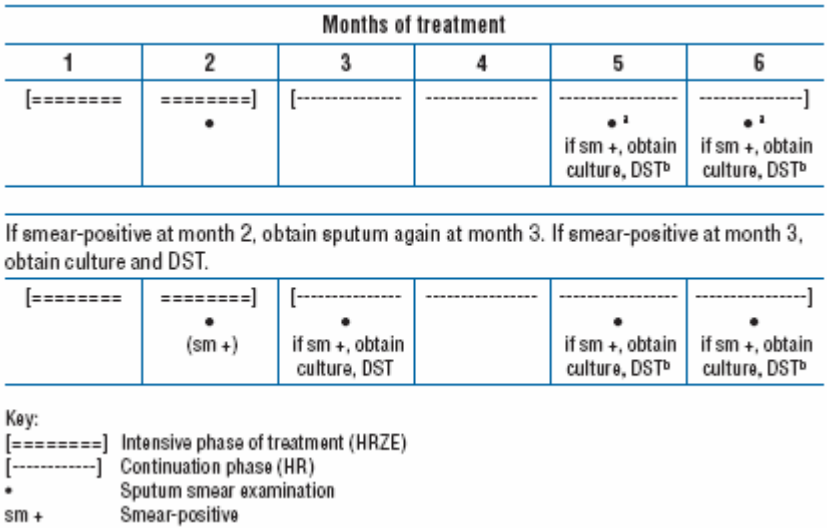
The drugs will be given at least 5 days per week (ideally 6 days) under supervision, by means of the patient visiting the TB dispensary, a local clinic, or a GP, or by a home visit of a community nurse to the patient's home or place of work.

The procedure for tracing patients in case of default should be decided in advance. Both the patient and the community nurse should be able to communicate with each other.

The person in charge of notifying the outcome of treatment (and responsible for action in case of default) should be designated in advance; this is the responsibility of the local study coordinator.

Assessing the treatment response

Note: If a patient is found to harbour a multidrug-resistant strain of MTB at any time during therapy, treatment is declared failure and the patient is re-registered and should be referred to a MDR-TB treatment programme.



Months of treatment					
1	2	3	4	5	6
[========	========] •	[----------	----------	---------- • [a] if sm +, obtain culture, DST[b]	----------] • [a] if sm +, obtain culture, DST[b]
If smear-positive at month 2, obtain sputum again at month 3. If smear-positive at month 3, obtain culture and DST.					
[========	========] • (sm +)	[---------- • if sm +, obtain culture, DST	----------	---------- • if sm +, obtain culture, DST[b]	----------] • if sm +, obtain culture, DST[b]

Key:
[========] Intensive phase of treatment (HRZE)
[----------] Continuation phase (HR)
• Sputum smear examination
sm + Smear-positive

[a] Omit if patient was smear-negative at the start of treatment and at two months.
[b] Smear- or culture-positivity at the fifth month or later (or detection of MDR TB at any point) is defined as treatment failure and necessitates re-registration and change of treatment.

Figure 5: Sputum monitoring by smear microscopy in new pulmonary TB patients

Additional sputum monitoring is needed for new patients whose sputum smear is positive at the end of the intensive phase:

1. In new patients, if the specimen obtained at the end of the intensive phase (month 2*) is smear-positive, sputum smear microscopy should be obtained at the end of the third month.
   * Sputum should be collected when the patient is given the last dose of the intensive-phase treatment.
2. In new patients, if the specimen obtained at the end of month 3 is smear-positive, sputum culture and drug susceptibility testing (DST) should be performed.

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- the initial phase of therapy was poorly supervised and patient adherence was poor;
- poor quality of anti-TB drugs;
- doses of anti-TB drugs are below the recommended range;
- resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- there are co-morbid conditions that interfere either with adherence or with response;
- the patient may have drug-resistant MTB that is not responding to first-line treatment;
- non-viable bacteria remain visible by microscopy.

Definitions of treatment outcomes

The definitions below are based on the up-dated treatment of tuberculosis guidelines[1] recently published by WHO.

Outcome	Definition [a]
Cure	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion. [b]
Treatment failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
Died	A patient who dies for any reason during the course of treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transfer out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
Treatment success	A sum of cured and completed treatment. [c]

Table 3: Definitions of treatment outcomes

[a] These definitions apply to pulmonary smear-positive and smear-negative patients, and to patients with extra-pulmonary disease. Outcomes in these patients need to be evaluated separately.
[b] The sputum examination may not have been done or the testing results may not be available.
[c] For smear- or culture-positive patients only.

[1] WHO. Treatment of tuberculosis guidelines; 4th edition, 2010

Table 3: Suggested standardized drug regimens

Estimates are based on the results of the STOP TB LVIV Pilot Study[2]. Suggested drug regimens follow published WHO guidelines[3].

Patients with pan-susceptible tuberculosis

Resistant to	Number	Proportion	Drug regimen	Min. duration	Comments
None	120	60%	H, R. Z, and E	6 mo	-

Patients with rifampin-susceptible, mono- or poly-resistant tuberculosis

Resistant to	Number	Proportion	Drug regimen	Min. duration	Comments
INH / INH & SM	40	20%	R. Z, and E	6-9 mo	consider FQ if extensive disease
INH & PZA	0	0%	R, E, and FQ	9-12 mo	adapted (DST results)
INH & EMB	0	0%	R, Z, and FQ	9-12 mo	adapted (DST results)
INH, PZA & EMB	0	0%	R, FQ plus an oral 2nd line drug, plus an injectable agent for the first 2-3 months	18 mo	adapted (DST results)

Patients with rifampin-resistant tuberculosis

Resistant to	Number	Proportion	Drug regimen	Min. duration	Comments
INH & RIF	40	20%	individualized therapy		based on DST results

INH (H), Isoniazid; RIF (R), Rifampin; PZA (Z), Pyrazinamide; EMB (E), Ethambutol; SM (S), Streptomycin; FQ, Fluoroquinolone

[2] Bodmer T., *et al*. Drug resistance of *Mycobacterium tuberculosis* in patients with new pulmonary tuberculosis in Lviv/UA (abstract). IUATLD 2009, Dubrovnik, CRO.
[3] WHO emergency update 2008. Guidelines for the programmatic management of drug-resistant tuberculosis.