International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Study Protocol for the evaluation of the tolerance and effectiveness of a short 9 months treatment for multi-drug resistant tuberculosis patients

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Plan

This will be an observational study that will follow the evolution and treatment outcome of patients with pulmonary multi-drug resistant (MDR) tuberculosis –i.e. with bacilli resistant to at least rifampicin and isoniazid - under a short course treatment of 9 months. Follow-up will be done at 12 and 24 months after the end of treatment to assess the relapse rate.

1 - Rationale

In 2010, Van Deun A & al.[1] have published the results of the regimen of 9 months to treat MDR patients in the part of Bangladesh supported by Damien Foundation: gatifloxacin, clofazimin ethambutol and pyrazinamid throughout supplemented by prothionamid, kanamycin, and high dose isoniazid during the four months of intensive phase (4KmGfxPtoHCfzEZ/5GfxCfzEZ).[2] This treatment resulted in a cure rate without relapse of: 87,9% (IC 95% : 82,7 % - 91,6%) in 206 patients never treated with second line drug (SLD) treatment before.

Since May 2008, in Cameroun and Benin, a standardized regimen of 12 months is used for the treatment of MDR cases never treated before with second line drug treatment : 4KmGfxPtoHCfzEZ /8 GfxPtoCfzEZ. Preliminary results are excellent : in Cameroun, of 90 patients, 84 (93%) were cured and 6 (7%) died during treatment. In Benin, of 23 patients, 22 (96%) cured and one died (4%). In Niger, with the same regimen but without prothionamid during continuation phase, of 65 patients, 58 (89%) were cured, 6 (9%) died and one was lost for follow-up. Till today, in the three countries, there has been no failure and no relapse.

The most recent directives for MDR treatment published by WHO in 2011 recommend using a regimen of minimum 20 months, with 8 months of injections of an aminoglycosid other than streptomycin, for MDR patients not treated before with SLD[3]

The success rate of these regimens is between 55% and 65% ; the proportion of lost to follow-up is high (15-20%), because of the length of treatment and the drugs side effects. Some rarecountries have better success rates , but always lower than those of the shourt course treatment schemes.
The evidence for the WHO recommendation is graded as ‘weak’ and ‘very low quality evidence’ according to the GRADE system of WHO. This means that there are no good scientific data to support it.
The WHO document underlines that the data used to arrive at this recommendation ‘may perhaps not be generalized to all populations with high or low levels of resistance’.

Time has thus come, while respecting the main lines of the WHO recommendations, to promote the use of the short regimens in a larger number of countries where, like in Bangladesh, Benin, Cameroun and Niger, the circulation of second line drugs is limited.
The negativation (conversion) of sputum is so quick that it is desirable to use the same duration as in Bangladesh, i.e. 9 months.

To document the effectiveness of these short regimens unquestionably, it is necessary to collect the information about the follow-up and treatment outcomes in an irreproachable way. For this, it may be necessary to select only those treatment sites in which one will be able to document very precisely the evolution and outcome of the disease according to this protocol. It is for this reason that we launch an international study coordinated by the Union.

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[1] Van Deun A, Maug A K J, Hamid Salim M A, Das P K, Sarker M R, Daru P, Rieder H L. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010 Sep 1;182(5):684-92

[2] Km=Kanamycin, Gfx=Gatifloxacin; Pto=Prothionamid; H=Isoniazid; Cfz=Clofazimin; E=Ethambutol; Z=Pyrazinamid

[3] WHO Guidelines for the programmatic management of drug-resistant tuberculosis. Update 2011. WHO/HTM/TB/2011.6

2 – Countries participating in the study

The countries that desire to participate in this research are : Benin, Burkina Faso, Burundi, Cameroun, Côte d'Ivoire, Niger, République Centrafricaine, République Démocratique du Congo, Rwanda.

The table below summarizes the numbers of MDR cases diagnosed and treated in 2011 and those expected in the first year and in both years of the study

Country	MDR cases diagnosed in 2011	MDR cases treated in 2011	MDR cases expected year 1	Total MDR cases expected
Benin	12	10	10	20
Burkina Faso	41	27	45	90
Burundi	30	30	35	70
Cameroun	63	63	75	150
Côte d'Ivoire	0	21	110	220
Niger	25	22	35	70
RCA	7	0	20	40
RDC	97	128	90	180
Rwanda	85	85	80	160
Total	360	386	500	1000

(Here follow explanations about the particularities of different countries, why not more people were diagnosed and/or treated : lack of DST lab, lack of SLD..)

Recruitment will be done during two years and it is foresees to include 1000 patients in total. We expect a cure rate without relapse at 12 and 24 months higher than 80%. This number is largely sufficient to demonstrate the superiority of the proposed 9 months regimen compared to the 20 months regimen which achieves a cure rate without relapse between 55-65%.
The principal actors in the different countries are in Annex 1, and the role of each one in Annex 2.

3 – Criteria of inclusion and non-inclusion

Among the cases of MDR identified by the national reference laboratory (NRL), will be included in the study :

- those never treated with SLD or for less than one month
- Patients residing in or near to the treatment site until the end of treatment, or deciding to do so.
- those who sign the consent form

In those with a high probability of MDR, treatment may be started before drug sensitivity test (DST) results are available. Those with a proven MDR strain will be included in the study analysis. The others, including those only resistant to rifampicin, will be analyzed separately.

Will be excluded from the study :
-Minor patient
-XDR patients
-Patients previsouly treated with SLD for more than one month
-Pregnant women (because of Kanamycin)
-Patients with known hypersensitivity to one of the drugs used
-Any patient who, according to the principal investigator (PI), has medical or social problems that make his participation dangerous
-Patients with a baseline ECG with a QT interval >500 ms (moxifloxacin can prolong QT interval)

A form will be filled for all non included MDR patients to clarify the reasons of non inclusion.
These patients will be proposed a treatment according to the National Tuberculosis Programme (NTP) directives or to the WHO directives "WHO Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update.
WHO/HTM/TB/2011.6".

Included as well as non included patients will receive free MDR treatment

This cohort study will be conducted in the context of the activities of each NTP. The final decision to include or not include a patient will be taken by the PI of the study.

4 – Therapeutic regimen (treatment scheme)

The short regimen that is used now in Cameroun and in Benin is similar to the one in Bangladesh, but with two differences:

1) to further diminish the risk of failure, the thioamides are continued during the whole treatment, and not just during intensive phase;
2) to diminish the risk of relapse, the continuation phase is prolonged up to 8 months instead of 5

These changes were decided when the results of Bangladesh were known but not yet published, and there was urgency to propose, for compassionate reasons, an effective regimen that could be approved by the local authorities.
When we now analyze the evolution under treatment and particularly the conversion of cultures, we are confident the regimen can be shortened to 9 months like in Bangladesh (89% have a negative culture at the end of the 2d month, 94% at 3 months). Moreover, as there has not been a single failure, it is useless to keep prothionamid, an anti-tuberculosis drug that is extremely badly tolerated, in the continuation phase

A new element appeared suddenly in 2011 : gatifloxacin was banned from the Indian market and is not produced anymore in this country. Therefore, in the present study, it will be replaced by another 4th generation fluoroquinolone: moxifloxacin (Mfx). Mfx is well studied. Its bactericidal effect is at least as good as that of Gatifloxacin; it has been used more frequently for MDR treatment than gatifloxacin, but not in short regimens. It is a bit more expensive, which is why it was not used in the short regimens till now. We do not expect any differences in results when replacing gatifloxacin by moxifloxacin.

Taking into account the above-mentioned arguments, it was decided to use a 9-month regimen with a 4-month intensive phase (4KmMfxPtoHCfzEZ) followed by th 5-month continuation phase.

The regimen used will be :
4KmMfxPtoHCfzEZ/5MfxCfzEZ

The continuation phase will continue on the fifth month, but only after 2 negative sputum smears. This conversion will be confirmed by culture. If patient is smear positive at the end of the 4th month, the intensive phase will be prolonged for a maximum of 2 months with monthly checks. During this prolongation however, kanamycin will not be given daily but three times a week to avoid toxicity. Continuation phase will always last 5 months, whatever the length of the intensive phase. Patients who fail bacteriologically and who are not clinically improved will be classified as "failure", standardized treatment will be discontinued and they will receive individualized regimen (see 9.1. Definitions)

All drugs used in the therapeutic regimen proposed here are on the list of drugs recommended by WHO for MDR treatment[4] and have been largely used for this in the world

Dosage of each drug according to the weight of the patient is given in the table 2.

Table 2. Dosage according to weight

Product	Weight (en kg)			
	<40	40-54	55-70	>70
Kanamycin[§]	0,5 g	0,750 g	1g	1g
Moxifloxacin (400 mg)	1/2	1	1	1
Prothionamid (250 mg)	2	2	3	4
Isoniazid (300 mg)	1	1,5	2	2
Clofazimin (100 mg)	1/2	1	1	1
Ethambutol (400 mg)	1,5	2	3	3,5
Pyrazinamid (400 mg)	2	3	4	5

§ Patients =>45 years of age will receive maximum 750mg Kanamycin per day. In case of prolongation of the intensive phase of treatment, Kanamycin will be given intermittently (three times a week)

5 – Organization of care and treatment adherence

Because the number of tablets is very high, because side effects, particularly gastro-intestinal ones, are frequent, and because is essential to avoid the development of extensive drug resistance (XDR), the basic rule is that directly observed treatment (DOT) will be mandatory during the whole treatment.
Every month, the research coordinator in charge will see the patient for medical follow-up and refer to the PI if problems which he/she cannot solve.
Each side effect will be precisely documented and treated during this monthly visit, or between visits if necessary.
Social support will be provided to patients on an individual basis. The whole staff of the MDR study as well as the social service will be involved in providing this social support. A specific attention will be given to costs of daily transportation required for the DOT. IN addition, medical staff will be reachable by telephone in case of emergency or unexepected social problem.

The address, place of residence and telephone number of the patient and of a contact person who will act as a guarantor for the patient will be noted on the individual patient treatment file.

Patient's home will be visisted at start of treatment to make sure that the address is correct in order to be able to retrieve it in case it is necessary. Patients not attending one visit will be first contacted by phone, and

[4] WHO Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402

if not reached a home visit will be made in order to know the reason of the absence, to prevent further irregularity and to reinforce adherence.

The following patients follow-up during treatment will be organized:

- Intensive phase : hospitalization if possible
- Continuation phase : ambulatory if possible

6 – Treatment follow up

Table 3 presents all systematic clinical and non-clinical evaluations, including side effect monitoring which should be done at the beginning and during treatment. All evaluations are free of charge for the patient. This pace is essential; if the patient has problems requiring specific examinations outside planned visits, they will be done as needed.
Follow-up will be done monthly by the research coordinator in charge, Every 2 months the PI will supervise this follow-up and discuss individual situations. In case of unexpected problem, the pace of monitoring and supervision visits will be adapted. All supervision visits will be documented.
As shown in Table 3, follow-up will be continued up to 12 and 24 months after the patient is declared 'cured' in order to detect any relapse

Table 3. Follow-up of MDR patients during and after their treatment (M = Month)

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M15	M21	M27	M33
Clinical Evaluation	x	x	x	x	x	x	x	x	x	x	x	X	x	x
Sputum Smear	x	x	x	x	xx	(xx)	x	x	x	xx	x	X	x	x
Sputum Culture	x	x	x	x	x	x	x	x	x	x	x	X	x	x
Audiogram	x				x									
Chest X-ray	x									x				
Hemogram	x													
Serum Creatinin	x	x	x	x	x									
Serum Potassium	x	x	x	x	x									
TSH	x						x							
SGOT, SGTP	x	x	x	x	x		x							
ECG*	xx													
Pregnancy test	x													
HIV test	x													

*** If initial ECG shows QT interval> 500 ms, the patient will not receive moxifloxacin (excluded from study). ECG will be repeated during the first of treatment and again if any heart problem - especially rhythm problem - is suspected during treatment**

The place where bacteriological examinations will take place will be specified for each study side.

MDR patients co-infected with HIV will be referred to the HIV/AIDS department for antiretroviral (ARV) treatment as for all other TB patients according to national directives. A particular attention should be given to side effects of combined ARV / MDR treatment.

7 - Bacteriology

Bacteriological examinations :smear culture, Line Probe Assays (Hain test), Xpert MTB/RIF according to the capacity of each laboratory, will be performed at the National Reference Laboratory.
Morning sputum will be collected at each visit to look for acid fast bacilli, plus an additional spot sample will be taken at the end of the intensive and at the end of the continuation phase as indicated in Table 3.

All strains isolated during this study will be send to the supra-national reference laboratory (SNRL) to confirm the identification of thestrain and the drug sensitivity to all drugs, including second line drugs (especially K and FQ). All strains have to be kept in the SNRL during the whole study duration. In case of failure or relapse, DST will be redone for the initial strain and the failure/relapse strain, with study of minimal inhibitory concentration (MIC) of fluoroquinolones and of injectable SLD. A study of DNA fingerprints will be conducted on the initial and the failure/relapse strain to see is it is the same or a new strain and detect reinfection or identification errors.

Initial strains will be kept in alcohol final concentration +/-70°.

8 - Identification and management of side effects :

The monitoring of side effects, including clinical and non-clinical evaluations for all study patients, are described in table 3. Side effects for the different drugs and strategies for their management are indicated in table 4.

Table 4. Strategies of management for the most frequent side-effects

Side effect	**Suspected drug**	**Strategy of management suggested**	**Comments**
Teratogenic effects	**Pto, Km**	Both drugs should be avoided during pregnancy	Capreomycin is ototoxic like Km, but is the injectable of choice if an injectable drug cannot be avoided
Peripheral Neuropathy	**H**	1. Give pyridoxine, (maximum 200mg/day) 2. Diminish dose of isoniazid if it does not compromise the regimen.	
Hearing loss	**Km**	1 Document loss of hearing.	Patients who received amino glycosides before may already have

		Give Km intermittently if negativation has not yet been achieved Consider to stop Km if negativation of smears has been achieved	hearing loss before start of MDR treatment
Psychotic symptoms	**H**, Mfx, Pto	1.Stop the suspected drug for a short time (1-4wks) until symptoms subside 2.Start antipsychotic treatment 3.Lower the dose of the suspected treatment if you can without compromising the regimen except for Mfx: Never lower the dose	Some patients will have to continue antipsychotic treatment throughout MDR treatment
Depression	Pto	Individual counseling Lower the dose of the suspected treatment if you can without compromising the regimen.	
Hypothyroidism	Pto	Start thyroxin treatment.	
Nausea and vomiting	**Pto**, **Cfz**, H, E, Z	Evaluate dehydratation, rehydrate if necessary Initiate anti-emetic treatment Lower the dose of the suspected treatment if you can without compromising the regimen. Stop Pto in case of very high intolerance	In case of acute abdomen, Clofazimin has to be stopped
Gastritis	**Pto**	Antacids. Stop Pto for a short period (e.g.1-7 days) Lower the dose of the suspected treatment if you can without compromising the regimen. Stop it if this occursduring continuation phase.	Give antacids 2h before or 3h after antiTB drugsin order not to interfere with their absorption
Hepatitis	**Z, H**, Pto, E, Mfx	Stop all medications while waiting for problem to resolve Eliminate other possible causes of hepatitis Reintroduce drugs one by one : Order : Mfx,E,Pto,H and Z	Take good history of hepatic problems to find the causal agent

		While monitoringhepatic function 4. Think about possibility of suspending causal agent for ever	
Renal toxicity	**Km**	1. Stop Km Consider possibility of intermittent treatment 2-3 times per week with Km is patient can tolerate (monitor serum 2. creatinin) Adjust all drugs in function of Creatinin 3.clearance	
Heart problem (see ECG above	**Mfx**	Stop moxifloxacin and replace by 1. levofloxacin at high dose	
Tendinitis	**Mfx**	Stop moxifloxacin and replace by 1. levofloxacin at high dose	
Optic neuritis	**E**	1. Stop E 2. Refer patient to ophthalmologist	
Arthralgia	**Z**	Treat with nonsteroidal anti- 1. inflammatory drugs (NSAID) Lower dose of suspected drug if it does 2. not compromise the regimen	- Arthralgias improve with time, even without specific treatment. Uric acid can be elevated due to Z,
Itching	Cfz	Stop Cfz if itching is severe	

For moxifloxacin, the following recommendations are particularly important :

- If initial ECG shows QT > 500 ms, the patient will not receive moxifloxacin. (excluded from study)
- If that is not the case, ECG will be repeated during the first week of treatment and again if any heart problem, especially rhythm problem, is suspected during treatment. If then QT is > 450 ms, a 24h heart monitoring (Holter monitoring) will be done if possible before taking a decision. If not, treatment will be changed : moxifloxacinwill be replaced by high dose levofloxacin.

- Very serious side effects are rare : serious hepatitis, sever skin reactions type Stevens-Johnson or Lyell syndrome.

It is necessary to ensure imputability criteria of the side effects before attributing them to antituberculous drugs. Side effects will be systematically recorded in the patient's file and graded 1 to 4 according the ANRS scale to assess severity of side effects in the adult patient (see Annex 7)

9 – Registration, monitoring et reporting

9.1 Definitions, main judgment criterion

The following definitions will be applied in this study

a) Registration based on former treatment:[5]

New case (N): patient never treated for TB or who has never taken antiTB drugs for more than one month

Relapse (R): patient treated for TB with a first line regimen who has beendeclared 'cured' or 'treatment completed' and is newly diagnosed with TB with apositive smear or culture.

Retreatment Relapse (R2): patient who relapsed after a retreatment regimen

Failure of new case (F): patient who under first line regimen, is smear positive at or after 5 months during treatment.

Retreatment Failure (F2): patient who, under retreatment regimen, is smear positive at or after 5 months of retreatment.

Return after Default (LFU): new smear positive patient, who restarts treatment after interrupting 2 consecutive months or more (i.e. has been declared as 'lost to follow-up')

Other (O): patient who does not enter in any of the above categories.

b) Results of MDR treatment (adapted from[6])

Cured : MDR patient who completed the MDR treatment according to the protocol and who has five negative cultures in the months following the last positive one. But because this treatment is so short, the period following the end of treatment is included in the evaluation. Absence of relapse will be documented at month 6, 12, 18, 24 after end of treatment

Treatment completed: MDR patient who completed his treatment according to protocol, but does not meet the definition of 'cured' or 'Failure' due to lack of bacteriological examination.

Died: MDR patient who dies before the end of the MDR treatment, whatever the cause .

Failure[7] : MDR patient who needs a change of treatment (defined as two or more drugs that need to be

[5] 1 World Health Organization, The Union, KNCV. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis 2001; 5(3): 213-215.

[6] Laserson KF, Thorpe L, Leimane V, Weyer K, Mitnick C, Riekstina V, Zarovska E, Rich ML, Fraser H, Alarcon, E, Cegielski P, Grzemska M, Gupta R, Espinal M Speaking the Same Language: Treatment Outcome Definitions for Multidrug-Resistant Tuberculosis. Int J Tuberc Lung Dis 2005;9(6):640–645

replaced), or for whom the treatment is stopped based on a medical decision for any of the following reasons : 1) Lack of bacteriological (smear or culture) response together with a lack of clinical improvement after 6 months of treatment or: 2) clinical and bacteriological worsening after initial response and at least 6 months of treatment, or:
3) serious side effects.

Loss to follow-up : MDR patient who interrupted his treatment for 2 consecutive months or more, without medical agreement.

Relapse : patient treated for MDR, declared 'cured' or 'treatment completed', and who has at least one positive culture during the post treatment follow-up, unless one can prove by molecular techniques that the strain of the apparent relapse is different from the initial strain.

Transferred out: MDR patient transferred to another treatment unit during treatment and of whom one does not know the treatment result.

c) Main judgment criterion

The success of this treatment will be judged by the percentage of included patients who will be declared 'cured' and who will not haverelapsed 12 months after the end of treatment.

The reasons for non inclusion will be presented.
The results of treatment will be presented separately for patients who failed, were lost to follow-up, died or were transferred out.

9.2 Forms and tools of declaration

Specific treatment cards will be created for MDR-TB patients. An electronic database using EpiData (version 3.1, EpiData Association, Odense, Denmark, http://www.epidata.dk) will be completed based on treatment cards. To avoid entry errors, all fields will be entered twice for validation, and entry possibilities limited to predetermined values

Quarterly monitoring : see annex3

. Recruitment will be reported quarterly
. Results of bacteriology will be reported according to month of treatment (smear and culture separately)
. The results of treatment will be reported in quarterly cohorts
. All side effects will be noted on the treatment card and described in the personal file according to degree of severity (see Annex 7)

[7] 2 Chiang C-Y, A Van Deun, A Trébucq, E Heldal, JA Caminero, N Aït-Khaled Treatment of multidrug-resistant tuberculosis: a proposed definition of the outcome "failure". Accepted for publication in Int J Tuberc Lung Dis

o Degree 1 : minor
o Degree 2 : moderate
o Degree 3 : Severe
o Degree 4 : Life threatening

. Stocks and orders of drugs to be reported in a specific table.

The relapse rate will be calculated 12 months after end of treatment, and if possible also 24 months after end of treatment

10 - National and international technical assistance

10.1 Scientific committees :

a) National Scientific Committee

In each country, a scientific committee composed of national and international members will be in charge of the monitoring of the study, to evaluate the completeness and quality of the data, to respond to all clinical or organizational problem that could compromise the good conduction of the study. The members of the committee are:

. The principal investigator of the country
. The national coordinator of the TB program
. The head of the national reference laboratory
. The research coordinator
. Others..

b) International Scientific Committee

It will be composed of the principal investigators of each country and of the international members listed below:

. Pr. Nadia Aït-Khaled, Pneumologist, Algeria
. Pr. Hans Rieder, Union Consultant
. Dr. Armand Van Deun, ITM Antwerp
. Dr. Muriel Vray, Institut Pasteur, Paris
. Dr Jürgen Noeske, Consultant GIZ
. Dr Alberto Piubello, Consultant Damien Foundation
. Pr Brigitte Gicquel, Institut Pasteur, Paris
. Dr Valérie Schwoebel, Union Consultant
. Dr. Arnaud Trébucq, Union Consultant

The Union will ensure the coordination of the studies. A meeting will be organized at start of the study with all principal investigators to study the study protocol in depth and to specify their role in details. A training will be offered to the research coordinators so they can perfectly fill all forms and fulfill the tasks expected from them. A training will be organized for those in charge of data management in order to train them in the use of the database developed in EpiData. Regular meetings with the main persons in charge of each country will be organized by the Union. Each country will be visited twice by two members of the international scientific committee: one from the north and one from the south but not residing in the visited

country. The quarterly report of each country will be shared to the members of the International Scientific Committee together with the country visit reports.
A meeting of the International Scientific Committee will be organized at least once a year during the International Union Conference.

10.2 Independent external audit

An independent external audit by a team of actors not involved in this work, will be done to verify in a completely independent way the conformity of the actions with the protocol and the accuracy of the data collected. The WHO will be requested to organize and bear the costs of this audit and the auditors will report its results to the International Scientific Committee.

11 – Ethics

The protocol will be submitted to the ethical committee of each country and to ethical committee of the Union.

The protocol will be officially registered with the international organism that records all therapeutic research (http://prsinfo.clinicaltrials.gov/).

Before enrolment, each patient will have been informed about the conditions of the study as in the ‘information sheet for patients’ (ISP), see Annex 4. Patients who can read will be asked to read the ISP. The PI or the nurse will explain the ISP to the other patients, using the locale language of the patient if necessary. Patient will be free to discuss the ISP with his care takers. After everythin is well explained, the patient will be asked to sign the consent form. (Annex 5).

Each country, while remaining the owner of its data and being free to publish them, agrees to share its results for a common publication.

Annex 1 Actors in the different countries

Country	Principal Investigator	Research Coordinator	Data manager	Laboratory Referent	Supranational Laboratory
Benin	Martin Gninafon	Ferdinand Kassa	Wilfried Bekou	Dissou Affolabi	Antwerp
Burkina Faso	Martial Ouedraogo	Gisèle Badoum Emile Birba	Tandaogo Saouadogo	Adjima Combary	Milan
Burundi	Thadée Ndikumana	François Ciza Michel Sawadogo	Fulgence Ndayikenguruki ye	Nyandwi Stany	Antwerp
Cameroun	Christopher Kuaban	Petrus Nkamse	Frédéric Bekang	Sara Eyangoh	Antwerp
Côte d'Ivoire	Alimata Bakayoko	Maxime Diangoné Bi Jeremie Akaffou	Attoungbré	Raymond Nguessan	Milan
Niger	Souleymane Hassane	Soumaila Morou et Ibrahim Boukary	Moumouni Kadidja	Saydou Mamadou	Antwerp
RCA	Albert Ignaleamoko	Jean-Pierre Tenegbia	Yvon Ngana	Fanny Minime-Lingoupou	Antwerp
RDC	Zacharie Kashongwe	Serge Bisuta	Georges Kabuya	Michel Kaswa	Antwerp
Rwanda	Michel Gasana	Dr Habimana-Mucyo Yves	Eric Ntanganzwa	Muvunyi Mambo Claude	Antwerp

Annex 2 Description of tasks

A treatment may not be started unless it has been made sure that there is sufficient amount of medications to treat the patient until the end. Drugs for included patients must be separated from the general drug stock.

The director of the NTP and the PI will write down the procedures for:

- collection of sputum samples, particularly the circulation of samples and of results between the periphery and the national reference laboratory (NRL);
- communication with the NRL in order to rapidly obtain all names of patients with resistance to rifampicin newly identified.

They will verify that the word “tolerance” is indeed included in the title of the protocol and rectify it if needed.

Role of the Principal Investigator (PI) :

The PI will monitor the the general conduction of the study and in particular :

1. He/she will confirm the nurse in charge of MDR patients in each site and supervise their activities ensuring that they follow the protocol procedures;
2. He/she will verify that an effective communication system has been estatblished with the NRL to rapidly obtain all names of patients with resistance to rifampicin newly identified; a register of patients resistant to rifampicin (RR) will be established for this purpose in order to help control the inclusion in the study (see Annex 8);
3. He/she will ensure that the system of collection of sputum samples functions properly and that the the circulation of samples and of results between the periphery, the NRL and the data manager is regular;
4. He/she will control the files of each patient at month 0, 2, 4, 6, 9, 15, 18, 21 and 33 and see the patients in case of problem;
5. He/she will verifyi all forms of patients non included in the study
6. He/she will conduct regular meetings with the research coordinator and the nurses to verify their right application of the study procedure;
7. He/she will ensure the regular data entry in the electronic database;
8. He/she will ensure that the quarterly report is distributed to the national Scientific Committee;
9. He/she will contact other members of the ational Scientific Committee;in case of problem;
10. He/she will participate in the six-monthly visit of the members of the International Scientific Committee
11. He/she will participate in the annual meeting of the International Scientific Committee during the global Union conference

Role of the research coordinator (RC) :

At the time of inclusion, he/she will :

1. Ensure that there is sufficient amount of medications to treat the patient for the total duration of treatment;
2. Enrol patients and verify criteria of inclusion and non-inclusion, initating and controlling necessary pre-inclusion examinations
3. Fill in the non-inclusion form for the non included patients
4. Collect signed consent forms
5. Fill in the ‘MDR-TB treatment card’ (address, telephone number, contact,..) and the TB-MDR register. He/she will verify the address of the patient with the help of a health care worker if needed (home visit)
6. ensure that all examinations necessary for inclusion have been prescribed and done;

7. complete the Excel file in which all patients identified as RR or MDR in the laboratory have been properly evaluated for potential inclusion in the study, search for patients loss to follow-up and indicate the status of each patient (included, non included, not treated) in the file with the reasons (see Annex 8).

During treatment, he/she will:

1. Ensure that all patients receive their treatment under direct supervision according to the protocol and that the dose is correct for the patient's weight;
2. Ensure that all patients are regular for their follow-up visits;
3. Ensure that all complementary exams are conducted timely;
4. Fill in treatment cards and MDR-TB register regularly with results of complementary examinations and communicated to the data manager for data entry;
5. Organise the search of the patient at home in case of irregularity in treatment or follow-up visit, the reason of the irregularity will be documented and if possible, solved;
6. manage the financing of transportation, nutritional kits and complementary examinations;
7. contact the PI for decision in case of difficulty in the patient's management (e.g. in case of serious side effect).

For data management, he/she will:

1. Keep all patients results in the patient file and archive them in cardboard boxes in a well-defined location.
2. manage the communication with the data manager and ensure that patient's data are entered in the electronic database at least quarterly
3. Send the anonymised MDR/RR Excel file as well as the quarterly report to the person responsible for the monitoring of the study at the Union (Valérie Schwoebel vschwoebel@theunion.org) at the end of each quarter;
4. validate the correction of data by the data manager if the person responsible for the monitoring of the study in the Union detects any discrepancy and ensure that corrected data are properly sent;
5. in case the patient is followed up outside the study site, make a copy of the patient treatment card and copy all informations in the original card which should stay at the site.

For the monitoring of side effects, he/she will:

1. write down something every month in the part of the treatment card reserved for clinical follow-up and in the table of side effects in the same card, even to say that there has not been any side effect;
2. report any side effect potential linked with the treatment in the table of side effects with its grade (1 to 4 according to the scale in Annex 7) and describe all measures taken to solve the side effect with its result; contact the PI immediately if an event –whether or not linked to the treatment - could probably lead to a change in treatment. The PI will decide for all treatment modification and the RC will document the follow-up in the patient card.

He/whe will also:

1. be available for any evaluation during the study or at the end of the study;
2. participate in the quarterly meeting of the National Scientific Committee and provide the PI will all necessary information for the quarterly monitoring;
3. inform the PI in case of any difficulty in the conduct of the study.

Role of the data manager.
He is in charge of:

1. Entering all data in EpiData at least quarterly according to a standard database, similar for all countries

2. Alert the PI in case of missing data;
3. Control data quality according to a pre-established procedure and correct data if necessary;
4. Send the database quarterly to Valérie Schwoebel using an internet shared space
5. Archive all files once the patient has finished treatment;
6. Perform second data entry of the same quarter one year after the inclusion of the patient (e.g second data entry will be performed on the 4th quarter of 2013 for patients included in the 4th quarter of 2012).

Annex 3 Indicators for the monitoring (to fill each quarter)

1) **Table 1 - Number of tuberculosis cases initiating treatment in this quarter (*Source: MDR-TB Register)***

Quarter		1T13	2T13	3T13	4T13	1T14	2T14	3T14	4T14	1T15	2T15
Enrolled in the study	Confirmed MDR*										
	RR **										
	Drug sensitivity test not yet available***										
Intiating MDR-TB treatment but not enrolled in the study											
Total											

***rifampicin and isoniazid resistant**

****** resistant to rifampicin only (GeneXpert result)**

******* strong presomption of MDR-TB but Drug sensitivity test not yet available (whether based on molecular method or any other method)**

Table 2 – Number of side effects occurring in the quarter among all patients included in the study (Source : MDR-TB patient files)

	Hepatic	Digestive	Auditory	Other	Total
Change in drug dosage					
Permanent discontinuation of a drug					

Table 3 – Drugs for short regimen – stocks and orders (S*ource : NTP pharmacy*)

	In stock	Expiry date	Ordered	Awaited on	To order
Kanamycine				__/__/__	
Moxifloxacine				__/__/__	
Prothionamide				__/__/__	
Isoniazide				__/__/__	
Clofazimine				__/__/__	
Ethambutol				__/__/__	
Pyrazinamide				__/__/__	

From 2014 onwards :

Table 4 – Results of treatment among patients of the study included 12 months before :

Cured	Treatment completed	Failure	Deceased	Lost to follow-up	Transferred	Total number of patients

Date

Name of Principal Investigator/Research coordinator Signature

Annex 4 Information for patient (For countries where the 9 month regimen is not the official regimen)

To be read to each MDR patient requested to enter the study :

Title of the study: Evaluation of the tolerance and the effectiveness of a short treatment of nine months for MDR patients

Name of the PI and contact information so he can be contacted if needed.

_____

You suffer from a very serious form of tuberculosis : the bacillae responsible for your disease do not respond to the antibiotics usually given for TB : rifampicin and isoniazid. We call this kind of TB 'MDR'.
This is why you need to take medicines which are different from those that are given to other people with TB. You need to understand that this treatment is still new and we need to follow you closely to document the effect and any problem that could come up during treatment. We need your written consent for you to take this treatment which will take 9 months. There are several constraints you need to know:

. you have to reside in a well-identified place in the zone where this treatment is given.
. You need to live there in this zone during the whole course of treatment
. You will be hospitalized for at least 4 months (or for countries where there is no hospitalization: you need to come to your designed treatment centre every day to take your treatment)
. All medicines will be taken under direct supervision of health care personnel during hospitalization AND for another 5 months of the ambulatory phase. That means that you will have to come to the treatment centre every day and take your medicines under direct supervision of health care personnel. In case you do not show up, someone from the centre will call you by telephone and/or will come to your house to look for you and find out what happened.
. You will undergo regular examinations, all of which are free of cost : blood will be taken every month for 6 months (only a tiny quantity), analysis of sputum every month for 9 months and then every 6 months for 2 years, chest X-ray at the start and at the end of treatment
. We hope that after 9 months you will be cured, but we will still ask you to come back for check-up every 6 months for 2 years to be sure you stay cured.

International instances recommend now a treatment of 20 months for your disease, with daily direct supervision of drug taking for the whole duration of this treatment. Some of the drugs of the 9 month regimen are the same than those of the 20 month regimens, while others are different. Both regimens frequently have side effects. During your treatment, whether you take the 9 month one or the 20 month one, we will do our best to help you against those side effects.

If you choose to take the classic 20-month regimen:

- this regimen will be given to you free of charge, like the 9-month regimen;
- you will be hospitalized for 8 months (or for countries where there is no hospitalization: you will need to come to your designed treatment centre every day for 8 months to take your treatment);
- you will have to come to the treatment centre every day for the 12 months of the continuation phase to take your medicines under direct supervision of health care personnel;
- as for the 9-month regimen, you will undergo regular examinations, all of which are free of cost : analysis of sputum every month for 8 months and then on month 14 and 20, chest X-ray at the start and at the end of treatment. Blood examinations will not be done systematically and will be done according to your health condition.

We have already experience with the 9 month regimen in several countries and we propose you to take it because the preliminary results in those countries are excellent and we think it will cure you.

Still, it is a new treatment even if its medicines are known for a long time. You are free to refuse to participate in the study and request to take the 20 month regimen. Among the drugs that are proposed in this regimen, clofazimin has been rarely used to treat MDR-TB. It can cause dryness of the skin, itching. loss of appetite, and orange colour of the skin, of the cornea and of the urine.

If you decide to participate in the study and take this 9-month regimen, you have to sign a consent form. The results of the examinations you undergo will be summed up with those of the other patients and published in a scientific journal. Your name will never be mentioned and your personal data will remain confidential.

If you choose not to participate in the study, the 20-month regimen will be given to you as explained above.

You can now ask all questions you want before signing the consent form.

Note : There are two possibilities to obtain the consent of the patients :
Person capable of reading and signing: each participant reads the information sheet, asks questions he/she wants, and if he/she agrees to enter the study, signs the consent form.
Person not capable of reading and signing: the information sheet is read to him/her. He/she asks the questions he/she wants. If he/she accepts verbally, he/she puts a cross on the consent form which is countersigned by a witness.
Any deviation of this procedure has to be explained and justified and the details of an alternative procedure put in writing.

Annex 5 Consent form

Name of project :
Short treatment of nine months for the treatment of tuberculosis patients with MDR bacilli

Name of the PI and contact information:

_____

"I have read the information sheet regarding this study (or I have been given a clear verbal explanation)
"My questions concerning this study have received satisfying answers by:

……

« I understand now what is expected of me and what can happen to me if I participate.
I understand I can step out of this study at any moment without having to give a reason and that I will still receive habitual care and treatment if I do so.
I accept that my medical data on this disease can be published but that all personal information about my disease and about my treatment must remain confidential : my name will never be mentioned."

« Under these terms, I accept to participate in the study »

Signed…… Date ……..

Name ……..

Witness (if necessary) …… Date…… .

Name …….

Annex 6 Form of non-inclusion

To be filled for every MDR case identified who does not enter the study:

Name : ……..

Given name: ……..

Age : ……. Sex : ……

Address : ……..

……...

Telephone number : …….

Name of the health infrastructure that identified the MDR patient before the final diagnostic of MDR : …….

Reasons of exclusion :

(Reminder: Exclusion criteria are absence of signed consent, non resident, minor patient, XDR case, patient previously treated with SLD, pregnant women, known hypersensitivity to one of the drugs used, QT interval >500 ms, medical or social problem)

…….
…….

…….

…….

…….

…….

Date :

Name of health worker and signature :

Annex 7 ANRS scale for coding the severity of side effects in adults

Note : The last section of the scale concerning vaccine trials has been replaced with a supplementary event – Nbr 67 concerning hearing troubles

This scale of quotation constitutes a working guide meant to :

⇒ **Not to omit to declare a serious undesirable event to the promoter (class 4 in the scale)**

⇒ **Grade the seriousness of a clinical or biological symptom observed in the context of a biomedical research protocol**

⇒ **Harmonize practice of evaluation of symptoms and their quotation in the ANRS protocols**

In practice, the criteria that are evaluated are grouped per body system ; it is a , non-exhaustive table of symptoms (and not a classification of pathologies). We have chosen the clinical and biological signs and symptoms that are most frequently observed and for wich surveillance is imperative to ensure the protection of persons undergoing research.

Some protocols can need supplementary criteria. To evaluate tem, one can refer to the table here under:

1st DEGREE	***Light Anomaly***	Light of transitory symptom, not hampering usual daily activities. Does not need medical intervention or treatment to correct it
2d DEGREE	***Moderate Anomaly***	Partial limitation of usual daily activities. Medical intervention or corrective treatment not obligatory
3d DEGREE	***Serious Anomaly***	Limitation of usual daily activities Medical intervention or corrective treatment not obligatory hospitalization possible.
4th DEGREE	***Life threat***	Very limited activity. Needs medical intervention and corrective treatment, nearly always in hospital

Abbreviations used in the table :

IV : Intravenous

N : Normal superior limit

EMG : Electromyogram

SBP : Systolic Blood Pressure
DBP : Diastolic Blood Pressure
MEVS : Maximal Expiratory Volume per Second

T.A.C. : Time of Activated Cefalin

Prothrombine Rate (%) : Equal to Quick time (sec)

This scale has been made to be used for HIV, HCV or HBV

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Live threatening
			HEMATOLOGY		
1	Hemoglobin (g/dl)	8,0 – 9,40	7,0– 7,99	6,5 – 6,99	< 6,50
2	Leucocytes (/mm3)	3 000 – 3 900	2 000 – 2 999	1 000 – 1 999	< 1 000
3	Neutrophiles (/mm)	1 000 – 1 500	750 – 999	500 – 749	< 500
4	Platelates (/mm3)	75 000 – 99 000	50 000 – 74 999	20 000 – 49 999	<20 000 Or diffuse petechiae
5	Prothrombine rate (%)	/	45 – ≤ 70	20 – < 45	< 20
6	T.A.C	1,0 – 1,66 x N	>1,66 – 2,33 x N	>2,33 – 3,00 x N	> 3,00 x N
			BIOCHEMISTRY		
			Liver and Pancreas		
7	AST (SGOT) (UI/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
8	ALT (SGPT) (UI/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
9	GAMMA GT (UI/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
10	Alcaline Phosphatases (UI/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
11	Hyperbilirubinemia (µmol/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
12	Amylasemia (UI/l) / **Lipasemia** (UI/l)/**Pancreatitis**	1,25 – 2,50 x N	> 2,50 – 5,00 x N	3,00x N with acute abdominal pain or images consistent with acute pancreatitis	> 3,00 x N With abdominal pain and signs of shock
13	CPK (UI/l)	1,25 – 2,50 x N	> 2,50 – 5,00 x N	> 5,00 – 10,00 x N	> 10,00 x N
			Lipids		
14	Hypertriglyceridemia (mmol/l)	/	4,50 – 8,59	8,60 – 13,70	> 13,70
15	Hypercholesterolemia (mmol/l)	>N –7,75	>7,75 – 10,34	>10,34 – 12,92	>12,92

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life Threatening
	Electrolytes / Evaluation of renal function/ Metabolism				
16	Hyponatremia (mEq/l)	130 – 135	123 – 129	116 – 122	<116
17	Hypernatremia (mEq/l)	146 – 150	151 – 157	158 – 165	>165
18	Hypokaliemia (mEq/l)	3,2 – 3,4	2,8 – 3,1	2,5 – 2,7	<2,5
19	Hyperkaliemia (mEq/l)	5,6 – 6,0	6,1 – 6,5	6,6 – 7,0	>7,0
20	Bicarbonate (mEq/l ou mmol/l)	20,00 – 24,00	15,00 – 19,99	10,00 – 14,99	< 10,00
21	Creatininemia (µmol/l)	1,00 – 1,50 x N	> 1,50 – 3,00 x N	> 3,00 – 6,00 x N	6,00 x N or dialysis needed
22	Blood Urea (UI/l)	1,25 – 2,5 x N	2,6 – 5,0 x N	5,1 – 10 x N	> 10 x N
23	Hypocalcemia(mmol/l)	1,95 – 2,10	1,75 – 1,94	1,50 – 1,74	< 1,50
24	Hypercalcemia (mmol/l)	2,65 – 2,87	2,88 – 3,13	3,14 – 3,38	> 3,38
25	Hypophosphatemiea(mg/dl)	2,0 – 2,4	1,5 – 1,9	1,0 – 1,4	<1,0
26	Hyperuricemia (µmol/l)	1,25 – 2,00 x N	> 2,00 – 5,00 x N	> 5,0 – 10,00 x N	> 10,00 x N
27	Hypoglycemia (mmol/l)	3,1 – 3,6	2,2 – 3,0	1,7 – 2,1	< 1,7
28	Hyperglycemia (mmol/l)	6,1 – 7,0	> 7,0 – 16,5	> 16,5 without cetosis.	Cf diabetes Item n°53 (degree 4)
29	Lactate (mmol/l) (Venous blood)	2,0 – 2,99*	3,00 – 3,99**	4,00 – 4,99**	≥ 5,00***
	Urine				
30	Proteinuria (strips)	+	++	≥ +++	Nephrotic Syndrome
31	Hematuria.	≥ 80 hematies/µl On test strip	≥ 200 hematies/µl On test strip	Macroscopic, with or without blood clots	Obstructive or needing a blood transfusion

* *Lactatemia degree 1 : confirm dosing in 8-10 days*
** *Lactatemia degree 2, 3 : confirm dosing the next day*
*** *Lactaeémiae degree 4 : confirm dosing immediately*

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

DEGREES		DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life threatening
Gastro-intestinal / Hepatic / Pancreatic					
32	Nausea. .	Transient, Normal eating	Limited eating <3 days	Limited eating >3 days	Only liquids Hospitalization needed
33	Vomiting.	Transient : 2 – 3 episodes / day or duration ≤ 1 week	Repeatedly : 4 – 5 episodes / day or duration > 1 week.	Vomiting solids/liquids during 24 h. Orthostatic hypotension. Perfusion needed.	Hospitalization for hypovolemic shock
34	Diarrhea.	Transient, 3 – 4 stools / day, diarrhea ≤ 1 week.	Persistent, 5-7 stools / day, diarrhea > 1 week.	> 7 stools / day or Needing perfusion. Blood in stool	Hospitalization, hypovolemic shock, perfusion.
35	Constipation.	/	Moderate abdominal pain. 78 h without stool. Needing treatment	Meteorism. Needs evacuation treatment or other treatment in hospital	Meteorism with vomiting or occlusion.
36	Dysphagia.	Light disconfort when swallowing	Difficulty swallowing but eating possible	Incapable to swallow solids	Incapable to swallow liquid. Perfusion needed
37	Oesophagitis.	Pyrosis < once a week	Pyrosis at least once a week but better with PPI's*	Pyrosis at least once a week but not better with PPI's*	Food Intolerance+Vomiting

**PPI :Proton Pump Inhibiteurs*

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life threatening
			Respiratory troubles		
38	Bronchospasm .	Transient, no treatment MEVS 70 % - < 80 %.	Permanent, Improvement with bronchodilator MEVS 50 % - < 70 %.	Persistent under bronchodilator. VEMS 25 % - < 50 %.	Cyanosis, MEVS < 25 % intubation.
39	Dyspnea.	Dyspnea during effort	Dyspnea during usual activity	Dyspnea in rest.	Dyspnea needing respiratory assistance
			Musculary troubles		
40	Myalgia (outside a point of injection)	Light myalgia during less then 4 weeks and not needing treatment	*Presence of any of the following signs* 1 – light to moderate myalgia > 4 weeks or needing treatment with level I*pain killers	*Presence of any of the following signs* 1. Moderate to severe myalgia > 4 weeks needing pain killers level I/II*	*Presence of any of the following signs* 1. Severe myalgia not related to effort and needing treatment with pain killers level II/III*. 2. Muscular weakness making it impossible to walk without assistance 3. Acute rhabdomyolysis with muscular necrosis and oedema 4. Acute rhabdomyolysis with electrolyte perturbations and renal failure

			2 – Predominance of troubles during effort: difficulty to climb stairs or to get up from sitting position Can walk without assistance. Optional confirmation by looking for biological anomaly (CPK) or anomaly on EMG	2 –Needing aid for walking and daily activities Recommended paraclinical confirmation (CPK, EMG and/or muscular biopsy)	

** Antalgicz level I : paracetamol and/or salicylic acid or NSAID) ;*
** Antalgics level II : Weak Opiods (codeine, dextropropoxyphen), agonists-antagonists of morphins (buprenorphine, nalbuphine) ;*
** Antalgics level III : Morphine.*

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of Septembre 9, 2003***)

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life threatening
			Cardiovascular disorders		
41	Arterial hypertension	Transient or permanent ; BP raised ≤ 20 mmHg et SBP 140-150 or..	Permanent BP raised > 20 mmHg And SBP 160-179 or DBP 100-109.	Permanent. SBP>= 180 or DBP > 110	Malign or malignant arterial hypertension
42	Hypothension	BP lowered≤ 20mmHg in orthostatic position. No treatment needed	SBP lowered > 20 mmHg continuously, but corrected by oral liquids	Perfusion needed.	Hypovolemic shock, needing hospitalization.
43	Cardiac ventricular rhythm disorders	/	Isolated ventricular extrasystoles, no treatment, whether symptomatic or not	Recurrent hearth rhythm disorders, persistent or symptomatic, needing treatment	Arythmia needing hospitalization.
44	QTc interval prolongation	/	Male : >450 et < 500 ms Female : >470 et <500 ms	>500ms	>500 ms with clinical manifestations (ventricular rhythm disorders, syncope, torsade de pointe)
45	Cardiac Ischemia	/	Atypical pain under exploration.	Appearance of effort angor controlled with treatment	Myocardial Infarction Instable angor, Myocardial Preinfarction Syndrome
46	Pericarditis	Chance discovery of a small effusion on echography	Moderate effusion with little symptoms Neither immediate treatment nor intervention considered necessary in the short run	Moderate or large effusion Symptomatic but no tamponade. Treatment needed and hospitalization considered	Tamponade. Hospitalization and intervention

					necessary.
47	Cerebral Vascular accident (stroke)	/	/	Transitory stroke (neurologic focal syndrome regressing within < 24 h).	Stroke not regressing in 24h
48	Peripheral arterial embolisma	/	/	/	Peripheral arterial embolia Hospitalization. Adapted Treatment.
49	Deep venous thrombosis and/or pulmonary embolism	/	/	Deep venous thrombosis. Anticoagulant treatment. Hospitalization to consider	Pulmonary embolism Hospitalization and treatment adapted to the situation

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life threatening
			Endocrine disorders		
50	Hyperthyroidism	Infraclinical hyperthyroidism Low TSH Free T3 and T4 : normal.	Moderate non complicated thyrotoxicosis Treatment indicated.	Malignant exophtalmia. Cardiac Arythmia Myopathy.	Thyrotoxic crisis and/.or cardiac failure
51	Hypothyroidism	Infraclinical hypothyroidism TSH increased but <12 mU/l. Free T4 : normal.	Frank hypothyroidism without complications. Treatment necessary.	Severe Hypothyroidism with multiple clinical signs. Urgent treatment Hospitalization to be considered.	Myxoedematous coma
52	Diabetes/Hyperglycemia	Moderate hyperglycemia (fasting serum glucose between 6,1 and 7 mmol/l) No immediate treatment.	Fasting serum glycose >7 mmol/l. Diet needed withmaybe oral antidiabetics	Fasting serum glucose >16,5 mmol/l With or without clinical signs. Insulin needed	Acidocetosis or hyperosmolarity (>27,8 mmol/l without acidosis).
			Skin		
53	Skin rash or mucosal lesions	Erythema, Moderate pruritus (itching).	Extended maculopapularrash with or without itching	Extended palpulovesicular or weepy rash Palpable Purpura (consistent with vascularitis). Erythema multiforme Non-extended cutaneous or	Any bullous skin or mucosal lesion (type Lyell ou Stevens-Johnson). Febrile Erythrodermia with or without other signs of hypersensitivity

				Mucosal ulcerations	Skin necrosis
54	Manifestations of immediate hypersensivity With or without cutaneous signs	/	Acute localized urticaria (hives)	Huge urticaria (hives), angioedema.	Anaphylactic shock

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

	DEGREES	DEGREE 1 Light	DEGREE 2 Moderate	DEGREE 3 Severe	DEGREE 4 Life threatening
			Neurological disorders		
55	Awareness, sleep .	Minor attention and concentration difficulties	Daytime sleepiness and/or difficulty falling asleep and/or waking up at night. Reduction of mental activity, Obnubilation.	Modification of wake/sleep rhythm or insomia needing treatment or Modification of dream content Syndrom of confusion with temporal disorientation	Total disorganisation of wake/sleep rythm not responding to treatment Confusioniric syndrom coma and/or convulsions
56	Psychism	Minor anxiety.	Anxiety needing treatment, or moderate depression	Major anxiety or depressive episode needing treatment	Acute Psychosis with Hospitalization, including suicidal ideation, manic phase, delirium, hallucinations
57	Head ache	Episodic, no treatment	Needing level I* pain killers	Needing at least level II* pain killers	Not controlled, even with level III* pain killers
58	Paresthesias	Paresthesia, light pain, no treatment	Paresthesia, permanent pain of moderated intensity, Needing level I* pain killers	Paresthesia, permanent pain of severe intensity Needing level II* pain killers at least.	Unbearable invalidating pain, restricting activity despite level III* pain killers
59	Motor deficit	Sensation of weakness, no objective deficit, no modification of neurological reflexes	Distal motor deficit, impaired functionality or modification of reflexes	Marked motor deficit interfering with usual activity	Confined to bed or wheel chair due to motor deficit

60	Disorders of the movement control	Occasional clumsiness,, light coordination disorders	Tremor or dyskinesia or dysmetria, ou dysarthria, With moderate effect on daily activity .	Ataxia of upper or lower limb or abnormal movements Impact on daily activity .	Unable to stand. Total depedency
61	Deficit of sensitivity	Minor deficit of sensitivity Of any modality or distribution, focal or symmetric .	Moderate deficit of sensitivity.	Severe deficit of sensitivity	Extensive loss of sensitivity Affecting the trunk and the four limbs

ANRS scale for coding the severity of side effects in adults

(***version n° 6 of September 9, 2003***)

DEGREES		DEGREE 1 Light	DEGRE 2 Moderate	DEGRE 3 Severe	DEGRE 4 Life threatening
			Divers		
62	Temperature (oral) persisting >12 h (°C).	37,7 – 38,9	39 – 39,5	39,6 – 40,5	> 40,5
63	Renal colic	Spontaneous regression of symptoms Pain not needing treatment	Renal colic needing medical treatment .	Obstructive syndrom not disappearing spontaneously .	/
64	Fatigue	Limitation of usual daily activity < 25 % <48 h.	Limitation of usual daily activity 25-50 % > 48 h.	Limitation of usual daily activity >50% Cannot work >48h	Unable to take care of oneself. Needing help for daily activities
65	Arthritis / Arthralgia.	Arthralgia.	Arthralgia with or withoutarticular effusion and with moderate functional limitation	Frank Arthritis with or without effusion, or with severe functional limitation	/
66	Eye disorder	Conjunctival hyperemia	Moderate pain Conjunctivitis.	Diminished visual acuity Uveitis.	/

				Severe pain. Glaucoma.	
67	Hearing disorders	**Light hearing deficiency** : 20 - 40 dB hearing loss; difficulty to perceive soft sounds, complexe noises and words spoken in a low or distantvoice .	**Moderate hearing deficiency:** 40 - 70 dB loss Words are perceived but ill understood or only understood when looking at the speaker (lip reading)	**Severe hearing deficiency:** 70 - 90 dB loss. Words are only understood from a strong voice near the ear	**Profound hearing deficiency** > 90 dB Words are not perceived

Annex 8 Management and Statistical Analysis

Data Management

1. Data on eligible patients :

A datafile including all patients found resistant to rifampicin (RR) in the lab will be made by the research assistant in each country using a table software (like Excel®). He will enter all RR cases, whether MDR or not, with or without other resistances associated, extracting them from the lab registers. The file will be updated weekly and completed with the help of the forms of non inclusion for patients treated but not included in the study. It will contain the following data: number in lab register, date of test that defined the case as RR, resistance to INH, name and surname, sex, age, and status according to the following categories:

- Case « included » in the study (whether MDR or only RR);
- Case treated for MDR-TB with whatever regimen but « not included », with the reason for non inclusion (see Exclusion criteria p.6 of the Protocol) ;
- Case « not treated » with the reasons (refusal, no drugs, not resident, died before start of treatment, loss of follow-up,…).

The data of this file will be regularly confronted by the RC with the registers of MDR patients kept in each treatment centre (model: TB-MDR register of the UNION) to verify that elegible patients have all been evaluated for inclusion into the study.

Each quarter, the number of cases in each category will be counted by the RC to fill the quaterly table for the study monitoring (Annex 3). A copy of the file will made anonymous (columns with patient IDs will be suppressed) and transmitted to the following person, in charge of follow-up of the study, at the UNION:
Valérie Schwoebel (vschwoebel@theunion.org).

2. Data on included patients

An electronic database EpiData version 3.1 (EpiData Association, Odense, Denmark, 85 http://www.epidata.dk) including the information needed for analysis, will be made according to the specifications of common data, with a dictionary of variables and automatic controls for entry which will be common to all countries.The data will be extracted from the registers of MDR-TB patients. They willconcern all patients verifying inclusion criteria and having started treatment according to the study protocol. This database will be totally anonymous. The only data identifying the patient will be his age, sex, and an identification number unique for the country. Data entry will be done by the DM (Data Manager) at least quarterly. The data will be regularly validated by the RC of the country according to a pre-established procedure
At the end of each quarter, the data files will be put in a securized shared space likeDropbox (http://www.dropbox.com). The person in charge of follow-up at theUNION : Valérie Schwoebel (vschwoebel@theunion.org) will conduct a second validation of the data. Any error or inconsistency will lead to an exchange with the RC or the PI of the country. The errors will be corrected and the corrections will be confirmed by mail from the CR to Valérie Schwoebel one month after the end of the quarter at the latest (1st of May, 1st of August, 1st of Novembe, 1st of February).

The quarterly monitoring tables (seeAnnexe 3) will be completed by the RC and sent to Valérie Schwoebel by email at the same time as the validation confirmation of quarterly data.

At the end of the study, the data will be entered a second time in an empty database sent by the Union. Once entered, the database will be put in a shared space and compared to the initial

database. Discrepancies between the two databases will be noted in a report that will be sent to the RC for correction.

Statistic Analysis

1. Plan of analysis

1.1. Descriptive Analysis

- Description of the study population: The number and distribution of included patients will be calculated in total and per :
  - o quarter of inclusion
  - o participating country
  - o results of initial DST (MDR, RR),
  - o age group 18-34 yrs, 35-54 yrs, >=55 yrs)
  - o sex
  - o HIV status (P, N, unknown).
- Representativeness **:** number, distribution of eligible patients not included and the proportion included (number of patients included / number of patients eligible) will be calculated per quarter, country, sex, age group. Reasons for non inclusion will be described.
- Treatment results **:** the proportions of treatment results according to the predefined categories (Cured, Completed, Died, Failed, Loss of follow-up, Relapse) 6, 12, 18 and 24 months after end of treatment will be calculated for the whole group of patients and described according to the following variables

1.2. Analysis of the main judgement criterion

The main objective of the study is to show that the proportion of MDR patients cured without relapse within 12 months is over 80%. The analysis of the main judgement criterion will be conducted separately on confirmed MDR patients and on RR-only patients.
The analysis will include the following steps:

- Proportion of cure : The proportion of patients cured at 12 months, i.e. having completed their treatment, with at least 5 negative cultures after their last positive culture, and a negative culture 12 months after finishing treatment (absence of relapse) will be calculated according to initial resistance (MDR/RR), country, age group, sex and HIV status

☐ Survival Analysis : The cure (5 negative cultures) and the negativation of the culture will be analysed in function of time, by the Kaplan Meier method. A multivariate analysis will be conducted according to the Cox model taking into account the variables here above and the side effects of treatment and the resistance to second line drugs.

1.3. Analysis of side effects

Description : The side effects will be described by degree of severity(1 à 4) according the ANRS scale (see Annex 7), imputability to a certain drugnumber and delay of occurrence during treatment

- Proportion of significant side effects: The following proportions will be calculated for the total number of included patients, per country and according to patient characteristics:
  - The proportion of patients having had at least one side effect considered as potentially related to treatment and that caused a modification of treatment, independently of the severityof the side effect
  - The proportion of patients having has a serious side effect (degree 3 or 4)
- Survival Analysis : The occurrence of a side effect leading to a modification of treatment will be analysed delay of occurrence during treatment, drug used and characteristics of the patient

2. Number of patients required

The expected number of patients included in all participating countries together is 1000.
With this number, the lower limit of the 95% confidence interval for the proportion of cure will be 80% if the observed proportion is equal or above 82,4%.

The table below shows, according to the number of subjects included, the minimal proportion of cure for which the lower limit of the 95% confidence interval would be over 80%:

Number of patients included	Proportion of patients cured
100	86,7%
150	85,6%
200	85,0%
300	84,1%
500	83,3%
1000	82,4%

Annex 9 Protocol for X-ray reading

A standard anteroposterior chest X-ray will be made for each patient at the start of treatment and at the end of treatment. This X-ray will be verified and repeated if of low quality (underexposed, wrong position or any other problem making it un-interpretable). The correct identification of the X-ray will be checked : name and surname, date the film was taken.
All X-rays will be kept in the file of the patient. The reading will be done by the clinician in charge of the patient.

Definition of the extension of the lesions

The extension of the lesions is defined by the number of zones affected in each lung. Each lung is divided in three zones (superior, middle, inferior). These zones are defined by dividing the space between apex and hemi-diaphragm into three.

Registration of reading of X-ray on the treatment card

At start of treatment, the person in charge to fill in the file of the MDR patient in the country (this person has to be clearly identified in each country : it can be the RC or the PI) will write in the file the extension of the lesions in each lung in the space reserved for this purpose

For each lung he/she will put a cross in the box corresponding to the extension of the lesions : 0 (no lesions) ; 1 (one zone affected) ; 2 (2 zones affected) or 3 (3 zones affected).

	Zones affected	
	Left lung	Right lung
0		
1		
2		
3		

Note : There is an error in the 'File of MDR patient' : 5 zones are shown while only 3 exist. Please do not take into account zones 4 and 5. These should be eliminated

Annex 10 Laboratory Protocol

1. Diagnosis of MDR or at least RR tuberculosis

This concerns the patients suspected of MDR-TB according to the definition of the country

Diagnosis should be rapid, preferably by a molecular method. The best test, if available, is GeneXpert® (rapid, rifampicin sensitivity).

- If the result of the test is undetermined, it has to be repeated on a second sputum.
- For each case found resistant to rifampicina by molecular method, a culture and DST will be requested immediately

2. Procedure according to the results of the molecular test

Rifampicin sensitive case

Put the patient on retreatment regimen with first line drugs

Case resistant to rifampicin who has never been treated with second line drugs for more than a month

- Accept the result of resistance to rifampicin, whatever the method used by a lab considered competent, without waiting for confirmation.
- Put the patient on short MDR treatment without waiting for culture results.
- Finish the treatment according to study protocol, whatever the results of initial DST.

Case resistant to rifampicin who has already been treated with second line drugs for more than a month

The procedure has to be discussed at least with the PI. Depending on the clinical status of the patient and the relationships with the Supranational reference lab (SRL), either start treatment or wait for the results of second line DST and other examinations performed by this SRL.

3. Culture and DST in National Reference Laboratory (NLR)

Culture will be systematically performed for all cases found resistant to rifampicin by molecular method. In case the initial culture is too poor, reculture will be done from the initial culture.

Once the culture is positive :

- Test sensitivity (if possible) according to the method used in the lab
- Prepare tubes for conservation and for sending to the SRL according to the following protocol :

If freezing is possible in an environment where the freezer temperature is sufficiently stable to avoid repeated unfreezing/refreezing

- Prepare 4 tubes for freezing (2mL) per strain to conserve
    - One tube containing 70% ethanol / sterile distilled water (+/- 1 ml) to be

conserved at room temperature. This tube will be sent to SRL

- 3 tubes containing 20% of glycerine / sterile distilled water (+/- 1 ml) to freeze at – 80°C or – 20°C
  2 of these tubes will be sent to SRL

  1 of these tubes is to conserve the strain in NRL

- Suspend a loop full of recent colonies in each of these 4 tubes.

If freezing is not possible in an environment where temperature is sufficiently stable

- Prepare 1 « tube for freezing » (2ml) per strain to conserve
- Distribute 1 ml of 70% ethanol / sterile distilled water in this tube
- Suspend a loop full of recent colonies in this tube
- Conserve at room temperature

4. Sending of strains to SRL

One needs to group sendings
In all cases, tubes will be sent at room temperature

For strains in an environment where the freezer temperature is sufficiently stable, minimum once a year :

- Unfreeze one of the 3 tubes containing 20% glycerine / sterile distilled water
- Add CPC (cetylpyridinium chloride) to the tube until a final concentration of 0.5% (+/- 1 ml of CPC 1% if the tube has already 1 ml of liquid)
- Add nothing to the 2d tube out of the freezer, let it unfreeze.
- Send, at room temperature, both unfrozen tubes plus the one containing 70% of ethanol / sterile distilled water
- Use UN 6.02 packaging for infectious material Class A for sending and respect the IATA rules for this material

If freezing is not possible, send each quarter

- Only tubes with ethanol 70% ;
- Use ordinary packaging

5. ***Tasks of the SRL***

1) Support to the NRLs for the logistics of sending of tubes according the IATA rules if they contain life cultures
2) Realize at least the following analysis :
    a. **Whatever the sample** :
        i. Identification of *M. tuberculosis* complex
        ii. DST (MGIT or proportion method)
            - Streptomycin, Isoniazid, Rifampicin, Ethambutol
            - Kanamycin, Capreomycin
            - Fluoroquinolon - ofloxacin 2 mg/l or moxifloxacin 0,25 mg/l
        iii. Analysis of sequence of mutation for resistance against pyrazinamid
    b. For cultures found positives after at least 6 months of treatment and for relapses
        i. Same tests as above, including pyrazinamid
        ii. Genotypic Analysis on initial and ulterior strains in order to classify the case as failure, relapse, reinfection or lab error
            - MIRU or genome sequence
            - Spoligotyping is sufficient if profiles are different; other methods to be added if spoligo profiles are identical
        iii. Optional, in function of available funds and needs for management of the patient :
            - MIC (MGIT or proportion method) on initial and ulterior samples
                - Fluoroquinolon- ofloxacin or moxifloxacin
                - Clofazimin
                - Prothionamid, PAS
            - GyrA/B sequencing
            - DST for all drugs that seem interesting