Frequently asked questions on the

WHO treatment guidelines for isoniazid-resistant tuberculosis

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The advice in this document has been prepared by the Global TB Programme of the World Health Organization (WHO) and is to be read alongside the *WHO treatment guidelines for isoniazid-resistant tuberculosis* and its online annexes. See *Further reading* at end for additional resources.

Who are the new WHO treatment guidelines for isoniazid-resistant tuberculosis intended for ?

The *WHO treatment guidelines for isoniazid-resistant tuberculosis* are targeted at health care professionals (doctors, nurses) and other staff involved in TB care in both low and high resource settings. The possibility of drug-resistant disease now needs to be entertained whenever treating TB patients. These guidelines provide technical detail which is helpful in making the best-informed decision in clinical practice and programme management. The answers to the frequently asked questions (FAQ) in this document intend to help implementers with common, practical issues that arise when adopting the new guidance. This document complements the *WHO guidelines* by elaborating further on certain aspects of implementation that were beyond the scope of the guideline itself.

What are the main recommendations of these new guidelines ?

The new guidelines recommend that patients with confirmed isoniazid-resistant and rifampicin susceptible tuberculosis (abbreviated to **Hr-TB**) are treated for 6 months with a regimen composed of rifampicin (R), ethambutol (E), pyrazinamide (Z) and levofloxacin (Lfx). The exclusion of rifampicin resistance ahead of start of this regimen is critical. It is further recommended not to add streptomycin (S) or other injectable agents to the treatment regimen. The recommendations apply both to Hr-TB detected ahead of start and during TB treatment.

Why are the recommendations called "conditional" ?

The recommendations for Hr-TB treatment are conditional (i.e. not strong), which has different implications for the individuals targeted by the guidance. The majority of **patients** would want the suggested course of action, but many would not. **Clinicians** would recognise that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. For **policy-makers,** substantial debate with various stakeholders will be required.

The new guidelines have been produced by experts in the field, using the GRADE approach (www.gradeworkinggroup.org) to collect and analyze relevant evidence and to formulate treatment recommendations on the basis of the quality of the evidence and other considerations. The strength of a recommendation is determined by a number of considerations. These include both the certainty in (quality of) the evidence as well as the various implications of the intervention: the balance between desirable and undesirable effects; values and preferences; resource use; health equity; acceptability and

feasibility (detailed further in the GRADE Evidence to Decision tables published as online annexes to the guidelines document).

Can the recommendations be implemented when the evidence is of very low quality?

Yes. Although the recommendations are not strong and there is important uncertainty on the evidence on which they are based, the Hr-TB regimen can be implemented under programmatic conditions and outside of an operational research framework, within the limits described in this document and the guidelines. This is not an interim policy, although new evidence in future may require the recommendations to be modified, as for all guidance. Programmes can now apply for donor-support to implement the recommendations (see also later).

The recommendations on Hr-TB treatment are based on an analysis of about 5,400 patients treated in 33 observational studies worldwide. These studies were made on patients under treatment and analyzed retrospectively. They were not trials designed to test a particular regimen, and featured no sample size estimations, randomization, blinding, planned controls or other similar processes aimed at minimising bias and increasing generalizability. Nonetheless, efforts were made by the coordinators of the studies to ensure that the data were validated during the studies; moreover, the reviewers collected individual patient data in order that the analysis can be adjusted to reduce certain types of bias. Despite these measures, the potential for bias persists in these studies and as a result the certainty in the evidence is much lower than the one that can be expected from well designed and executed intervention trials. Low or very low certainty in the estimates of effect means that further research is very likely to have an important impact on one's confidence in these estimates and is likely to change the estimate.

Why is it important to find Hr-TB cases and treat them with the new regimen?

Treatment of Hr-TB with the recommended regimen is expected to improve the chances of successful outcome in a patient. Isoniazid is one of the most important components of TB treatment regimens. Patients with Hr-TB strains who are treated with 2HREZ/4HR stand a much higher risk of treatment failure or a relapse, or acquiring additional resistance than those who have drug-susceptible TB. In one recent analysis of published literature, treatment of Hr-TB with the standard regimen for new patients resulted in 11% (95% Confidence limits: 6–17%) treatment failure and 10% (5–15%) relapse; in those with drug-susceptible TB treatment failure was 2% (1–3%) and relapse occurred in 5% (2–7%). Acquired drug resistance was also higher: 8% (3–13%) in Hr-TB and 1% (0–2%) in drug-susceptible TB. The acquisition of additional resistance to rifampicin (termed multidrug-resistant TB or MDR-TB) is a serious consequence of inadequate treatment of Hr-TB, given that it would necessitate a much longer treatment with more second-line agents.

What are the main implications to the programme to implement the new Hr-TB guidelines?

In order to implement the new guidelines, diagnostic services need to become more accessible, and to be further strengthened and equipped to face the expected additional demands in laboratory testing (e.g. for resistance to H and R), without compromising the functioning and quality of the diagnostic work. Staff in health care facilities needs to be trained to detect Hr-TB and to treat patients with

appropriate regimens. At the national TB programme level, guidelines and implementation aids (e.g. "test & treat" algorithms and other decision support materials) would need to be revised to align with the new recommendations. Levofloxacin would need to be made available to constitute the regimen.

It is important to confirm Hr-TB with approved laboratory tests ahead of starting treatment. Treatment of Hr-TB without confirmation (termed "empirical treatment") carries the risk of exposing patients without Hr-TB to more medication than is usually needed, particularly to prolonged pyrazinamide and to levofloxacin. Empirical treatment is only to be considered in situations where the certainty of Hr-TB is high (e.g. active TB in a close contact of a confirmed case of Hr-TB) or while awaiting test results.

Before starting Hr-TB regimen, it is important to also rule out rifampicin resistance. This may be done preferably using a rapid molecular test such as Xpert MTB/RIF$^{(R)}$ or LPA according to approved diagnostic algorithms. This is important to avoid the inadvertent treatment of MDR-TB with a regimen which is too weak to protect from the acquisition of resistance to the fluoroquinolone. It is thus emphasised that no fluoroquinolone-containing Hr-TB regimen be given unless MDR-TB has been reliably excluded. Ideally, testing for resistance to fluoroquinolones and if possible to pyrazinamide is also done before starting treatment. Current tests for ethambutol susceptibility are not useful for clinical decision making and means to determine pyrazinamide resistance or susceptibility may not be universally available.

What has been the recommended practice in the treatment of patients with Hr-TB prior to the new guidelines?

Previous WHO treatment guidelines for Hr-TB were based largely on expert opinion. They recommended 6-9 months of REZ for Hr-TB, with the addition of fluoroquinolones, injectable agents or other second-line TB medicines when the regimen needed strengthening (e.g. Z resistance) or in the presence of extensive disease. Prolongation of the regimen to up to 18 months was also recommended in case of polydrug resistance. The implementation of these regimens varied widely by country, as can be attested by the treatment given in the patient data analyzed in preparation of the *WHO treatment guidelines for isoniazid-resistant tuberculosis*. In actual fact, many countries still face limitations to test patients for drug susceptibility ahead of start of treatment. As a result, many patients with Hr-TB are not detected and they are treated with the 6-month first-line TB regimen (2HREZ/4HR). These regimens are less effective than the ones recommended in the current guidelines, increasing the risk of unfavourable outcomes in these patients.

Can isoniazid be added to the regimen if the strain is resistant to it?

Despite being resistant to isoniazid on *in vitro* tests some strains may still respond better when regimens include this medicine as part of the regimen. Where possible, isoniazid resistance testing should also provide genotype information (mutations in *kat*G or in the *inh*A promoter area; see also next question). In addition, knowledge about overall host acetylator status at country or regional level may help decide upon which dose of isoniazid to use (decreased efficacy and toxicity of isoniazid has been related to its increased metabolism (acetylation) in certain individuals, as determined by mutations in the N-acetyltransferase type 2 (NAT2) gene). Finally, and in the absence of fixed-dose combinations (FDC) of REZ alone, it may be more convenient for the patient and programmes to dispense treatment using the

HREZ FDC tablet than composing the regimen with single-dose formulations. In settings where only the HRZ FDC is available, ethambutol has to be administered separately along with the levofloxacin.

Does it matter to identify the mutation or level of resistance associated with isoniazid resistance?

If Hr-TB has been detected using molecular tests such as line probe assay (LPA) or whole genome sequencing then the laboratory can distinguish whether it is associated with mutations in *kat*G or in the *inh*A promoter area. This is relevant to the clinician. Presence of mutations in both *kat*G and *inh*A usually signify a "high-level" resistance. By large the most common mutations in Hr-TB strains are in *kat*G and a number of these also confer "high-level" resistance by themselves, even in the absence of a *inh*A mutation. In this situation, inclusion of isoniazid in the regimen, even at high dose, is unlikely to increase its effectiveness. A mutation limited only to the *inh*A promoter area is usually associated with "low-level" resistance and a higher dose of isoniazid (10-15mg/kg/day), instead of the usual dose in first-line regimens (4-6mg/kg/day), is likely to add benefit. A decision to treat with this higher dose has to be balanced with the logistical downside of adding isoniazid tablets to the HREZ FDC to achieve the required dose and the added risk of adverse reactions to isoniazid (see also further down).

Should isoniazid resistance be detected using phenotypic drug-susceptibility tests then information on the minimum inhibitory concentration (MIC) of the strain is also useful. At higher dose, isoniazid is still likely to increase the effectiveness of the Hr-TB regimen when TB strains have an isoniazid MIC up to 0.1mg/L on solid media (or 0.4mg/L in liquid culture (MGIT)). As the MIC increases to 1mg/L (on solid media) and beyond, the added value of isoniazid in the regimen, even when used at the higher dose, declines.

Does the same regimen apply in all patients with Hr-TB?

It is expected that most Hr-TB patients can be treated with this regimen. The Hr-TB regimen does not need to differ between new and previously treated TB patients, unless there are other reasons (e.g. certain types of polydrug resistance; see also below). Extending the duration from 6 to 9 months was not shown to influence outcomes in the data reviewed ahead of the guideline preparation, but it may be indicated in patients with extensive or extrapulmonary disease, or who take longer to improve while on treatment and have no other cause for non-response, such as resistance to other regimen components or uncontrolled comorbidity. In patients who are still sputum smear positive at month 5, treatment failure is declared and a change of regimen may be in order even if no additional resistance has been discovered. Prolonging treatment beyond 6 months in Hr-TB patients with HIV may not be indicated; the overarching priority in these patients is to ensure that effective antiretroviral therapy is given and that HIV-disease markers are monitored.

The addition of levofloxacin to 6(H)REZ is recommended in all patients with Hr-TB, with the exception of the following: (i) resistance to rifampicin cannot be excluded; (ii) known or suspected resistance to levofloxacin; (iii) known intolerance to fluoroquinolones; (iv) known or risk of prolonged QT-interval; and (v) if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

What happens if a fluoroquinolone cannot be used?

If a fluoroquinolone cannot be used then a 6(H)REZ regimen may be given. The 6(H)REZ regimen has been shown to be more effective at treating Hr-TB than a 2HRZE/4HR regimen (see more details in the guidelines document and online annexes).

When is an Hr-TB regimen to be started?

All patients with Hr-TB are expected to benefit if treatment with the recommended regimen is given. The Hr-TB treatment regimen is started in one of two situations:

1) *Hr-TB is confirmed before TB treatment is started*: 6(H)REZ-Lfx is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of drug susceptibility testing are still pending the regimen may be introduced. Should drug susceptibility test results taken at start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen.
2) *Hr-TB is discovered after the start of treatment with 2HREZ/4HR regimen*: this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance is excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

Drug resistance reported into treatment presents the clinician with a challenge on how to proceed. For example if the result arrives five months into treatment with 2HREZ/4HR and the patient is doing well the clinician would need to decide whether to start 6(H)REZ-Lfx at that point or complete the 2HREZ/4HR regimen and monitor for relapse thereafter. The unexpected discovery of resistance to one agent should prompt the clinician to check for additional resistance and therefore repeat DST would be in order. This would limit the danger of "adding a single agent to a failing regimen". The clinician also needs to determine if any DST results available are still a valid reflection of the current bacterial population, given that the initial resistance may have favoured the acquisition of additional resistance in the interval with an inadequate regimen or with a period of one month or more of functional monotherapy.

Patients who were started empirically on an MDR-TB treatment but who were later found to have Hr-TB would need a regimen change. In these situations recourse to a specialist with experience in TB treatment is advised.

The guidelines make a negative recommendation for the use of streptomycin and injectable agents. Does this apply in all situations ?

Injectable agents like streptomycin, amikacin, kanamycin and capreomycin do not show added benefit to the cure or survival of Hr-TB patients. Given the serious and permanent harms that are often caused by these medicines, particularly damage to hearing and kidney function, as well as the inconvenience of

having daily, painful, intramuscular injections their use as part of Hr-TB regimens is generally discouraged. Injectable agents could play a limited role in uncommon situations in which a regimen cannot be composed because of intolerance, other contraindication or resistance to other standard components of Hr-TB treatment (see also next question). Injectable agents should not be used in pregnancy or in situations where adverse reactions associated with their use have emerged or are more likely (e.g. electrolyte imbalances, pre-existing kidney disease).

How do I treat patients who have Hr-TB with additional resistance (polydrug resistance)?

Not all Hr-TB cases will be truly mono-resistant to isoniazid: some may have additional resistance. This resistance may be documented but in many it may be undetected. In most forms of polydrug resistance, such as to Hr+E or Hr+S or Hr+S+E or Hr+Z, treatment can proceed with 6(H)REZ-Lfx. In cases with Hr+Lfx resistance, treatment with 6(H)REZ is proposed. However when there is resistance to three key agents, such as Hr+Z+Lfx, the 6(H)REZ-Lfx may not contain enough agents to ensure relapse-free cure and to avert the acquisition of resistance to the remaining medicines of the regimen.

These situations require decisions on a case-by-case basis and consultation with a clinician experienced in the use of second-line TB medicines. There is very little evidence about the effectiveness and safety in Hr-TB patients of regimens containing medicines other than H, R, Z, E, Lfx and S. In such circumstances, medicines such as linezolid, ethionamide and cycloserine may have to be considered in order to compose a regimen with sufficient effective agents. It is also not clear if prolonging the duration of these individualized regimens has a bearing on the likelihood of cure.

Bedaquiline and delamanid have been developed for use in MDR-TB and extensively drug-resistant TB (XDR-TB) and evaluated for this patient group. They are therefore <u>not</u> recommended for use in other forms of drug resistant TB like Hr-TB and in rifampicin-susceptible polydrug resistant TB.

What dosage schedule is recommended for the Hr-TB regimen?

Hr-TB treatment is given daily and intermittency should be avoided. In contrast to other regimens for drug-susceptible and MDR-TB, the Hr-TB regimen does not have an intensive and a continuation phase (unless the injectable agent is given); this simplifies the delivery and monitoring of treatment. The recommended dosage for the H, R, E and Z in the regimen is generally identical to the one employed in first-line regimens for both adults and children (except when high-dose H may be indicated, see above).

Adult dosage: the Tables below summarize the usual number of FDC tablets to use <u>each day</u> in adults according to body weight band and type of FDC. Ideally the 4-drug FDC (1st Table) is employed to minimize on the need to supplement patient medication with additional pills. If only 3-drug or 2-drug FDCs are available then additional first line medicines are needed (2nd and 3rd Tables). Even with the 4-drug FDC it may still be necessary to add single-dose isoniazid to reach the higher dose range in the presence of “low-level resistance” (see also above). In adults, the dose of levofloxacin to use with 6(H)REZ is 750mg/day for patients weighing less than 49kg, and 1000mg/day for those weighing more.

Dosage schedule with 4-drug FDC (RHZE) - ***Adults***

*Weight bands in **adults***	*4-drug adult FDC RHZE-150/75/400/275**	*Levofloxacin 250mg*	*Isoniazid 300mg*** *(to add only in case of high-dose INH option)*
35-49 kg	3 tablets	3 tablets	1 tablet
50-64 kg	4 tablets	4 tablets	1.5 tablets
65-75 kg	5 tablets	4 tablets	2 tablets

* patients <35 kg may receive 3 tablets/day and patients >75 kg may receive 6 tablets/day if they tolerate this dose

** patients <35 kg may receive ½ tablet/day and patients >75 kg may receive 3 tablets/day if they tolerate this dose

Dosage schedule with 3-drug FDC (RHE) - ***Adults***

*Weight bands in **adults***	*3-drug adult FDC RHE-150/75/275**	*Pyrazinamide 400mg**	*Levofloxacin 250mg*	*Isoniazid 300mg*** *(to add only in case of high-dose INH option)*
35-49 kg	3 tablets	3 tablets	3 tablets	1 tablet
50-64 kg	4 tablets	4 tablets	4 tablets	1.5 tablets
65-75 kg	5 tablets	5 tablets	4 tablets	2 tablets

* patients <35 kg may receive 3 tablets/day and patients >75 kg may receive 6 tablets/day if they tolerate this dose

** patients <35 kg may receive ½ tablet/day and patients >75 kg may receive 3 tablets/day if they tolerate this dose

Dosage schedule with 2-drug FDC (RH) - ***Adults***

*Weight bands in **adults***	*2-drug adult FDC RH-150/75**	*Pyrazinamide 400mg**	*Ethambutol 400mg***	*Levofloxacin 250mg*	*Isoniazid 300mg**** *(to add only in case of high-dose INH option)*
35-49 kg	3 tablets	3 tablets	2 tablets	3 tablets	1 tablet
50-64 kg	4 tablets	4 tablets	3 tablets	4 tablets	1.5 tablets
65-75 kg	5 tablets	5 tablets	4 tablets	4 tablets	2 tablets

* patients <35 kg may receive 3 tablets/day and patients >75 kg may receive 6 tablets/day if they tolerate this dose

** patients <35 kg may receive 2 tablets/day and patients >75 kg may receive 4 tablets/day if they tolerate this dose

*** patients <35 kg may receive ½ tablet/day and patients >75 kg may receive 3 tablets/day if they tolerate this dose

Children: The Table below summarises the usual number of FDC tablets to use each day in children according to body weight band. The new dispersible paediatric preparations of the 3-drug FDC, ethambutol and levofloxacin can facilitate the administration of the Hr-TB regimen in children:

Dosage schedule with 3-drug paediatric FDC (RHZ) ***- Children***

*Weight bands in **children****	*3-drug paediatric FDC RHZ-75/50/150*	*Ethambutol 100mg*	*Levofloxacin 100mg*
4-7 kg	1 tablet	1 tablet	1 tablet
8-11 kg	2 tablets	2 tablets	2 tablets
12-15 kg	3 tablets	3 tablets	3 tablets
16-24 kg	4 tablets	4 tablets	4 tablets

* In children weighing 25 kg or more the adult schedule shown in the previous section is followed.

If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used with 6(H)REZ in children aged 0-14 years, based on a slightly different weight band from the one above:

Weight	*Levofloxacin 250mg*
5 - 6 kg	½ tablet / day
7 - 9 kg	¾ tablet / day
10 – 15 kg	1 tablet / day
16 – 23 kg	1.5 tablets / day
24 – 30 kg	2 tablets / day
31 kg +	Follow adult schedule (up to 1g / day)

Can I use a fluoroquinolone other than levofloxacin? If so, at what dose?

Most of the patients included in the studies reviewed for the *WHO treatment guidelines for isoniazid-resistant tuberculosis* received levofloxacin, at the (adult) dose of 750-1000 mg/day. Moxifloxacin, a later generation fluoroquinolone that is generally reserved for MDR-TB regimens, can replace levofloxacin in Hr-TB regimens (e.g. unavailability). The moxifloxacin dose is 400mg/day in adults and 7.5-10mg/kg/day in children (for children the dose is 0.25 tablet if 10-17 kg and 0.5 tablet if 18-30 kg). Gatifloxacin could probably also replace levofloxacin but there is no known experience in its use in Hr-TB. Ofloxacin is no longer considered a second-line TB medicine.

Rifampicin induces the metabolism of moxifloxacin and studies of pharmacokinetics show that it lowers its exposure in the body by about one third; a similar effect has been described for gatifloxacin (less is known about how rifampicin interacts with levofloxacin but it is likely). In the absence of more data on

the influence of this interaction on regimen effectiveness, no adjustment in the dose of moxifloxacin or other fluoroquinolones in the Hr-TB regimen is advised.

Can I reduce the duration of pyrazinamide if I am using levofloxacin?

This is not recommended at this point. There are too few observations of Hr-TB patients treated with regimens combining a fluoroquinolone with <4 months of pyrazinamide to be able to conclude that such an adaptation may be done without compromising regimen effectiveness. Clinicians may be hesitant to give pyrazinamide for more than two months because of concerns about toxicity. However, the analysis upon which the WHO guidelines have been based, show that use of pyrazinamide for 6 months was associated with better outcomes than 2HRZE/4HR, the WHO-recommended first-line TB regimen in widespread use. This is an area where more research would be of help.

Can I drop ethambutol from the regimen?

This may sound appealing, particularly in children in whom ethambutol needs to be given on top of the 3-drug FDC. However, there are no data on the influence this would have on treatment effectiveness (particularly in cases with polydrug resistance) and therefore this modification cannot be supported on the basis of current knowledge.

What is the safety profile of levofloxacin?

Levofloxacin has a fairly good safety profile in both adults and children when used at the dose recommended in Hr-TB regimens, even when taken for several months as is the case for MDR-TB regimens. The most common adverse reactions attributable to it is common to other fluoroquinolones:
- nausea and bloating
- headache, dizziness, insomnia or tremulousness.
- QT-interval prolongation on electrocardiography
- hypoglycaemia

More rarely, tendon rupture and joint pains can occur.

Many adverse reactions are self-limiting or can be managed by withdrawal of levofloxacin and symptomatic medication. Dosage adjustment is recommended if creatinine clearance is <50 ml/min, in consultation with a specialist.

It is to be remembered that the first-line agents in the Hr-TB regimen may also cause adverse drug reactions, which are mostly mild, not serious and manageable in most cases. TB practitioners are likely to be more familiar with these medicines than with levofloxacin. More details about the adverse drug reactions associated with TB medications and on their prevention and management can be found in the technical annexes of the *WHO companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (see under Further reading at the end of this document).

Are there special precautions to take when prescribing levofloxacin?

Levofloxacin can be taken with food. Good hydration is recommended (tell the patient to drink a lot). The following should be avoided within 2 hours of taking levofloxacin and for 4 hours after: antacids

(especially those containing aluminum), mineral supplements such as iron or magnesium, or multivitamins. The interference of dairy products with the absorption of ciprofloxacin or norfloxacin has not been shown for levofloxacin and moxifloxacin; restriction of milk products on these grounds alone may thus not be justified, particularly in children aged less than 5 years in whom milk is an important source of calcium and magnesium.

Even though levofloxacin is usually well tolerated, the practitioner and patient should be aware of the following associated adverse drug reactions in order to take timely preventive or curative action:
Sun sensitivity: the use of sunscreens is advised.
New, strenuous activities are not advisable.
The patient needs to be advised to inform the caregiver right away if any of the following occurs:
- Pain, swelling or tearing of a tendon (such as at the back of the ankle or elbow)
- Muscle or joint pains
- Rashes, hives, bruising or blistering
- Trouble breathing or tightness in the chest
- Diarrhoea
- Yellow skin or eyes
- Anxiety, confusion or dizziness

What are the main cautions when introducing levofloxacin as part of Hr-TB regimens in a programme?

On a programmatic level it is important that the provision of levofloxacin to public and private health facilities is accompanied with additional measures to ensure that it is used properly. Hr-TB regimen delivery will be decentralized and most cases will be treated at the same facilities as drug-susceptible TB. Clear instructions need to be provided to frontline health-care workers about good practices in the use of fluoroquinolones, which may be unfamiliar to staff outside MDR-TB treatment facilities. Firstly, levofloxacin should only be used after rifampicin resistance has been definitively excluded (if this is not possible it should not be used; see also below). Secondly, prescribers should clearly understand that levofloxacin monotherapy is forbidden, given that this will induce the rapid development of resistance. Written instructions may reduce mistakes in dosage and in the inadvertent use of partial regimens (e.g. giving Lfx with the RH FDC instead of RHZE). Health care workers should also become conversant with the detection and management of adverse drug reactions. These events should be reported to the local pharmacovigilance authorities as for other drug-related harms. It is not required to follow patients on Hr-TB regimens with active TB drug safety monitoring and management (aDSM) although programmes may wish to do this.

Can I use the 6(H)REZ-Lfx regimen in extrapulmonary TB?

The evidence reviewed for the new guidelines relates to pulmonary TB cases. However, all the components of the regimen are used to treat extrapulmonary TB (including meningeal and central nervous system involvement); there is thus no reason to believe that they will be less active if the causative TB strain in a patient with exclusive extrapulmonary or mixed pulmonary/extrapulmonary disease is Hr-TB. Specialist advice should be sought for the management of extrapulmonary forms which are serious, like disseminated TB, or in which a treatment longer than 6 months may be indicated.

Can I use the Hr-TB regimen in children, people on antiretroviral medicines, and in pregnancy?

The regimen 6(H)REZ-Lfx regimen may be given to children and people living with HIV on antiretroviral therapy. In pregnancy and in breastfeeding mothers levofloxacin may be avoided to reduce the potential of harm to the foetus.

How can the national TB programme expand its capacity to detect Hr-TB?

There is as yet no diagnostic platform approved for the detection of Hr-TB which matches the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance. First line LPA can diagnose isoniazid resistance, complete with genotyping detail of clinical relevance, but requires substantial infrastructure typically available in a provincial or central level facility. The cost of the equipment to perform the test ranges from about USD8,000 to USD40,000, depending on local needs and if results are read automatically. Dedicated rooms in the laboratory would also be necessary. In countries eligible for preferential concessional pricing (138 eligible countries as of March 2018), the cost of a single LPA test strip is USD9.30. However, considering additional laboratory reagents and consumables required to perform the test, the total cost of performing an LPA test is approximately USD20-25. To date, more than 500 laboratories in many low and middle-income countries are known to have established LPA capacity. Typical processing time for an LPA specimen is about 2-3 days due to batching.

Liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory; this option has the disadvantage of an obligatory processing delay of at least 10 days. Testing on solid media is also an option but may take several months to obtain results and is therefore of limited use for baseline testing and monitoring non-response. Nonetheless, a phenotypic or molecular test result confirming Hr-TB is of equal value for clinical purposes once the method used is reliable and quality assured. Increased capacity to undertake phenotypic testing on liquid and solid media also requires substantial investment in infrastructure. Participation in schemes to ensure the quality of testing is critical and collaboration with the supranational TB reference laboratory network is an important step when planning to increase capacity.

High throughput diagnostic platforms are in development as an alternative to LPA. These systems can simultaneously detect TB, and resistance to rifampicin and isoniazid. Evaluation studies of these diagnostics are underway and it is expected that WHO will review their operational and performance characteristics later in 2018.

How do I know who to test for isoniazid susceptibility?

Contacts of documented Hr-TB cases are important to target for testing. In some settings, epidemics of Hr-TB have also been described and this may heighten the priority to test at-risk individuals under such circumstances. However, numerically speaking, very few of the HR-TB cases eligible for treatment in a country will present such manifest risk when they present to treatment.

Current epidemiological data indicate that more than three fourths of the global burden of Hr-TB occurs among previously untreated (“new”) TB cases. Previous TB treatment is thus not a good pointer to risk of Hr-TB - the correlation with previous TB treatment is weaker than it is with MDR-TB. Reserving

isoniazid drug-susceptibility testing to such patients is therefore not likely to yield many Hr-TB cases. Empirical Hr-TB treatment of previously treated TB cases, without prior drug susceptibility testing, increases the risk for drug-related harms from over-treatment, or conversely the inadvertent treatment of MDR-TB with inadequate regimens.

In a situation where access to drug susceptibility testing is good, a logical diagnostic algorithm would start with Xpert MTB/RIF as the initial test for all patients evaluated for TB. Cases in whom TB is confirmed and rifampicin-resistance is not detected are further tested with LPA. Even in the absence of a positive sputum smear on direct microscopy, one can expect to achieve an interpretable LPA result on 80% of samples using this testing routine. Liquid culture may replace LPA but the additional delay in getting results is a disadvantage. Past modelling has shown that rapid testing of both isoniazid and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB >1% and Hr-TB >2%).

Isn't it simpler to give an Hr-TB regimen to all retreatment TB patients without any susceptibility testing?

Such a policy would carry a number of concerns. Firstly, it will lead to unnecessary overtreatment with fluoroquinolones and prolongation of pyrazinamide use in many patients. The large majority of retreatment cases will not have Hr-TB and can be cured with a 2HRZE/4HR regimen. Secondly, unless rifampicin resistance is excluded at the baseline, patients with MDR/RR-TB would be exposed to an inadequate regimen with the risk of acquiring additional resistance, including fluoroquinolones. Thirdly, this policy would deflect the focus of the programme from testing new (previously untreated) TB patients who usually harbour the main burden of Hr-TB. Lastly it would risk creating once again a "retreatment regimen", not too different from the situation that prevailed in many settings until recently with the indiscriminate use of streptomycin-containing 8-month "Category 2" regimen in all previously treated TB patients.

How do I monitor patients on treatment for Hr-TB? When should I repeat the drug-susceptibility testing during treatment?

Close monitoring of patients is needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment. Bacteriological monitoring may follow the same schedule as drug-susceptible TB, with direct microscopy of sputum smear at months 2, 5 and 6. It is useful to perform a culture in the last month to check for any emergent resistance - especially to rifampicin. Testing for resistance, preferably with Xpert MTB/RIF or LPA, may need to be done earlier when there are signs of non-response. A positive sputum on microscopy at month 5 or later is an indication of treatment failure and an investigation of drug resistance is urgent in order to revise treatment. Likewise, detection during Hr-TB treatment of additional resistance to the one present at the baseline is a signal for a comprehensive review of the clinical and microbiological status of the patient.

In addition to bacteriology, tests for liver and kidney function and blood indices may be necessary based on clinical manifestations and medications in use. Electrocardiography for patients on 6(H)REZ-Lfx is not usually required unless there are other risks for QT-interval prolongation. Adverse drug reactions should be reported to the spontaneous pharmacovigilance systems required by national regulations, as for

other drug-related harms. Active TB drug safety monitoring and management (aDSM) is not mandatory for patients on Hr-TB regimens.

Is in-person direct observation of treatment (DOT) required for patients on the Hr-TB regimen?

In 2017 WHO issued evidence-based recommendations on support to treatment adherence and delivery (including DOT) within the broader context of patient-centred care. This guidance applies equally to Hr-TB care as other forms of TB.

Community- or home-based DOT is conditionally recommended over health facility-based DOT or unsupervised treatment. DOT administered by trained lay providers or health-care workers is conditionally recommended over DOT administered by family members or unsupervised treatment. Moreover, video observed treatment (VOT) can replace DOT when the technology is available and can be appropriately organized and operated by health-care providers and patients.

Apart from DOT, a number of other interventions were considered helpful to promote treatment adherence. A package of treatment adherence interventions may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option: being defined as material support (e.g. food, financial incentives, and reimbursement of transport fees); psychological support; home visits; use of information technology; medication monitors; and staff education. Moreover, counselling and patient education on the disease and on treatment adherence are strongly recommended.

How many Hr-TB cases do I have in my programme?

Globally, about 8% of TB cases presenting for care have Hr-TB, being higher in retreatment TB cases than in new TB cases (14% and 7% respectively according to most recent WHO estimates). The frequency of Hr-TB varies between regions and countries but in many countries the number of Hr-TB cases is much higher than the caseload of MDR-TB. Only representative drug-resistance surveys can give a reliable estimate of how many Hr-TB cases to expect among TB patients. If specimens used in drug-resistance surveys or surveillance systems test for isoniazid susceptibility independently of rifampicin, it is possible to derive a value for the Hr-TB burden which is sufficiently accurate to contribute to programme planning.

Do I register Hr-TB cases on treatment in the Basic Management Unit TB register (BMU or District TB register) or in the Second-line TB register?

Like any other notifiable TB case, drug-susceptible or drug-resistant, the Hr-TB patient should be registered in the BMU TB register even if treatment is not started or if only a 2HREZ/4HR is given. The case may be retained in the BMU register for the purposes of monitoring treatment response and interim/final outcomes. The Hr-TB cases may be enumerated with the main drug-susceptible TB cases for the purposes of treatment outcome reporting. The case may also be registered in the Second-line TB register if the programme wishes to monitor how many patients are being given regimens containing second-line medicines: however, the Hr-TB cases should <u>not</u> be enumerated with the MDR/RR-TB cohort for outcome monitoring purposes.

If an electronic case-based database is used to register TB patient data then it is easier for the programme manager to monitor Hr-TB patients separately as an additional cohort for the purpose of outcome monitoring. Programmes are encouraged to follow good practices when collecting these data and to participate in collaborative initiatives to share individual patient records for pooled reviews of global TB patient series. Such data could be useful to guide future policy on the optimization of TB treatment regimens for these conditions.

Which definitions do I use to assign treatment outcomes in Hr-TB cases?

The definitions to use when assigning outcomes are the same ones as for drug-susceptible TB. No new outcome definitions (or registration categories) are warranted.

How do I budget ahead of introducing a treatment component for Hr-TB in my national TB programme?

Based on the price of medicines supplied by the Global Drug Facility (GDF) in March 2018, a full course of treatment for an average adult with 6(H)REZ-Lfx using in part FDCs amounts to about USD69 and 6(H)REZ using FDCs costs USD48 (in contrast a first-line 2HREZ/4HR adult regimen in FDC kits amounts to USD22). These amounts do not take in account additional costs, such as inspection and shipment. The treatment is therefore affordable and feasible even in low income settings. Use of FDCs simplifies treatment and lowers costs. As for the treatment of other forms of TB, the expenses associated with the proper delivery of care (e.g. DST, adherence support, monitoring of microbiology, blood indices, liver function) would dominate the overall programme costs when compared with cost of medicines.

Can I apply for a donor grant to expand services for Hr-TB treatment?

Yes. The recommendations in the *WHO treatment guidelines for isoniazid-resistant tuberculosis* apply with immediate effect and can be used for programme planning. It is thus justified to prepare funding proposals to implement this treatment component at large scale (e.g. to the Global Fund).

Can the Global Drug Facility (GDF) provide all the medications, laboratory equipment and consumables needed to expand Hr-TB treatment services?

Yes. All the medications required to compose the Hr-TB regimen, including adult and paediatric FDCs, single dose formulations and levofloxacin, are currently available on the GDF product catalogue. Programmes can also procure laboratory equipment and consumables for LPA and culture from GDF, and benefit from preferential concessional prices if the country is eligible. It is thus justified to quantify programme needs and to place orders with GDF to implement this treatment component at a large scale. GDF also provides comprehensive technical assistance and capacity-building to countries on quantification, forecasting, procurement and supply chain management of TB medicines and diagnostics.

Further reading

A listing of selected resources relevant to the *WHO treatment guidelines for isoniazid-resistant tuberculosis*.

WHO TB treatment guidelines and implementation aids for drug-resistant TB

- WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis (WHO/CDS/TB/2018.7). Geneva, World Health Organization. 2018. Available from: http://apps.who.int/iris/bitstream/10665/260494/1/9789241550079-eng.pdf
- Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization, 2015. Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf
- Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. UNICEF and World Health Organization, 2017. Available from: http://www.who.int/tb/areas-of-work/children/WHO_UNICEFchildhoodTBFDCs_Statement.pdf
- Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. (WHO/HTM/TB/2017.05). Geneva, World Health Organization, 2017. Available from: http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf
- Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children: second edition. Geneva, World Health Organization, 2014. Available from: http://www.who.int/tb/publications/childtb_guidelines/en/
- Compendium of WHO Guidelines and Associated Standards: Ensuring Optimum Delivery of the Cascade of Care for Patients with Tuberculosis (WHO/HTM/TB/2017.13). Geneva, World Health Organization, 2017. Available from: http://apps.who.int/iris/bitstream/10665/259180/1/9789241512572-eng.pdf

WHO & GLI TB diagnostic guidelines and implementation aids

- GLI Model TB Diagnostic Algorithms. Geneva, Stop TB Partnership, 2017. Available from: http://www.stoptb.org/wg/gli/assets/documents/GLI_algorithms.pdf
- Implementing Tuberculosis Diagnostics: A Policy Framework (WHO/HTM/TB/2015.11). Geneva, World Health Organization, 2015. Available from: http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf
- The Use of Molecular Line Probe Assays for the Detection of Resistance to Second-Line Anti-Tuberculosis Drugs. Policy Guidance. (WHO/HTM/TB/2016.07). Geneva, World Health Organization, 2016. Available from: http://www.who.int/tb/publications/lpa-mdr-diagnostics/en/

Evidence reviews of Hr-TB treatment (study level meta-analyses)

- Stagg HR, Harris RJ, Hatherell H-A, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016 Oct;71(10):940–9.
- Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Feb;17(2):223–34.

Other resources (estimates, surveillance, procurement)

- Global tuberculosis report 2017 (WHO/HTM/TB/2017.23). Geneva, World Health Organization, 2017. Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf
- Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Geneva, World Health Organization, 2013. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
- Stop TB Partnership | Global Drug Facility (GDF) - GDF Products List. Available from: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp