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# Present-day treatment of tuberculosis and latent tuberculosis infection

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ABSTRACT

The major objectives of tuberculosis (TB) control are to reduce morbidity and mortality via an early and appropriate treatment of the disease, to prevent carriers of the *Mycobacterium tuberculosis* bacillus from transmitting it to others, and to prevent latent tuberculosis infection (LTB) sufferers from progressing to the disease. To achieve these objectives, it is imperative to start an appropriate, effective antituberculosis treatment as early as possible, as well as identify contacts of the infected TB patient and others at risk of LTB progressing to TB, in order to establish an appropriate treatment for them. Here we review the bases for treating TB and LTB infections, including those produced by strains resistant to anti-TB drugs.



## Tratamiento actual de la infección y la enfermedad tuberculosas

*Palabras clave:*
Tuberculosis
Infección latente tuberculosa
Tuberculosis extensamente resistente
Tuberculosis multirresistente
Tratamiento antituberculoso

RESUMEN

El objetivo del control de la tuberculosis (TB) es reducir su morbilidad y mortalidad mediante el tratamiento precoz y adecuado de la enfermedad, la prevención de la transmisión de *Mycobacterium tuberculosis* desde personas bacilíferas y la prevención de la progresión a enfermedad de personas con infección latente tuberculosa (ILT). Para alcanzar estos objetivos se requieren el inicio precoz y la correcta cumplimentación de un tratamiento antituberculoso efectivo, y la identificación de contactos de pacientes con TB infectante y de otras personas con ILT con riesgo de progresar a enfermedad tuberculosa para establecer el tratamiento adecuado de estas personas. Revisamos las bases del tratamiento de la TB y de la ILT, incluyendo las producidas por cepas resistentes a los fármacos antituberculosos.



## Introduction

Early treatment of tuberculosis (TB) and preventing latent tuberculosis infection (LTB) from progressing to disease are two fundamental strategies of the objective of TB control. In this monograph chapter, we deal with both aspects which are essential for reducing morbidity and mortality due to TB.

## Antituberculosis drugs

Antituberculosis drugs (ATD) have traditionally been classified in terms of first-line, second-line and third-line drugs. The objective of this classification is to identify which ATDs —on the basis of their effectiveness, strength, toxicity or tolerance— should be used preferentially in the initial treatment of TB, and to distinguish them from others that should only be used in situations of intolerance or resistance to the previous drugs.[1-3] In addition, this classification is of particular interest currently in the treatment of in multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), since it provides a framework for taking decisions when designing a treatment regimen.[1-3]

## General principles of antituberculosis treatment

The major objectives of anti-TB therapy are: to eliminate the TB bacillus as rapidly as possible; to prevent the emergence of ATD-resistance; and to avoid relapses by eliminating persistent bacilli from their reservoirs[2] To achieve these objectives, an ATD combination should be employed for an extended period of time.[1,2] *Mycobacterium tuberculosis* has a long generation time and the ability to enter periods of dormancy with slow metabolic activity when antimicrobial penetration is difficult.[4] In TB patients, most of the bacillary population is made up of rapidly multiplying extracellular bacilli, located fundamentally in the tuberculous cavitary walls and the caseum, where the number of microorganisms may reach $10^9$ and $10^5$/mL, respectively. This population, because of its size, is the one

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which most often gives rise to the appearance of ATD-resistant mutations. The second of these populations is made up of slow growing bacilli, located at the periphery of the cavities in necrotic tissue in an acid-fast medium, and the third would consist of sporadically replicating dormant bacilli. The two latter populations are responsible for the appearance of TB relapse. In order to eradicate them properly, extended treatment is fundamental, using ATDs with a sterilizing effect.[1,2,4]

*M. tuberculosis* has the ability to spontaneously mutate, and this may give rise to the development of ATD-resistance. The bacillary population necessary to generate an ATD-resistant mutant varies according to the drug: $10^6$ for isoniazid (H), $10^8$ for rifampicin (R), $10^5$ for ethambutol (E), $10^6$ for streptomycin (S) and $10^3$ for pyrazinamide (Z). The bacillary population necessary to develop a mutation resistant to more than one ATD is calculated by adding together the exponents of the bacillary population needed to develop resistance to each individual drug; so, a bacillary population of $10^{21}$ would be needed to acquire resistance to a regimen containing H, R and Z. In the absence of pre-existing mutations, an appropriate three drug combination therapy would make resistance development impossible.[1,2,4,5]

Data arising from experimental observations and randomized clinical trials enable us to assert that of all the combinations tried, the one with greatest bactericidal and sterilizing activity is H plus R, and when administered for 9 months, the relapse rate is less than 3%. Reducing the period of this combination to 6 months gives rise to an increase in the incidence of relapses, although adding Z to RH during the first two months is successful in sterilizing the cultures more rapidly without increasing the relapse rate.[1,3,6-9]

## The treatment of tuberculosis disease

### *Indications for start of treatment*

The decision to start anti-TB treatment should be based on epidemiological, clinical, radiological and microbiological data. In the case of clinical forms following a serious, potentially fatal course and where TB is highly suspected, the priority objective should be to initiate empirical anti-TB therapy, even without microbiological confirmation.[1,3,6-8] In such cases it is important, before commencing treatment, to obtain the biological samples needed for the subsequent confirmation of the diagnosis and an ATD sensitivity analysis of the isolated strain. For suspected TB patients in a stable clinical condition, the priority should be to arrive at a microbiological diagnosis before starting treatment, since there is no clinical manifestation or X-ray image —however suggestive it may appear— specific to TB.

### *Recommended therapeutic regimens*

Currently recommended schedules for treating TB last for 6 months. This period is made up of an initial phase of 2 months —during which the basic objective is to eliminate the rapid growth bacilli and reduce the period of infection and contagion— and a maintenance phase of 4 months, during which the objective is to eliminate all intracellular bacilli and prevent a relapse.[1,3,6-8] An extension of the continuation phase to 7 months is indicated in cases where cultures remain positive beyond the first two months of initial therapy, and in special situations.[1,3,6-8] At present, courses of treatment lasting less than 6 months are not recommended, although trial schedules using new drugs are being tested which will enable this possibility to be explored.[9,10]

#### *Guidelines for the initial phase of treatment*

The prescription of choice for the initial phase of TB treatment consists of a daily administration of combinations of H, R and Z for 2 months.[1,3,6-8] Fixed dose preparations of these drug combinations are available, and the use of these formulations confers undoubted benefits, simplifying the complexity of the treatment and making it easier to follow correctly, which, in turn, minimizes the risk of monotherapy and the consequent development of resistance. The replacement of H by moxafloxacin (M) in the initial phase of TB treatment in one randomized clinical trial did not demonstrate greater effectiveness or safety.[11] The addition of a fourth drug to the selected regimen does not increase the bactericidal or sterilizing activities of the regimen but it does supply extra protection against developing resistant mutations. Its use is indicated in patients with suspected baseline resistance to one of the drugs included in the initial treatment plan, or when the primary resistance rate to H exceeds 4% in any particular population, or is unknown.[1,3,6-8] The recommendation for an associated fourth drug has traditionally been one of the first-line drugs (E or S), although it should be borne in mind that in one double-blind randomized clinical trial, the use of M instead of E as the fourth drug was associated with more rapid sterilization of the sputum,[9] and another non-randomized study also demonstrated that adding M to the standard TB treatment with 4 ATDs (RHEZ) was associated with more rapid negative sputum culture conversion.[10] Once the results of the laboratory ATD sensitivity tests are known, treatment can be adjusted accordingly, with the fourth drug in the regimen being suspended in cases where the bacilli are susceptible to all the drugs. There is no evidence arising from randomized clinical trials that enables firm recommendations to be made about the best pattern of treatment in situations where either R or H cannot be used in the initial treatment schedule because of intolerance or because it has been contraindicated. It is however recommended to replace the drug concerned with another first-line ATD and to increase the treatment period to 12-18 months.[3] Nor is there evidence to enable recommendations to be laid down concerning the best treatment option when neither R nor H can be used in the initial treatment because of intolerance, although replacing both drugs by first-line ATDs or M and increasing the treatment period to a minimum of 18-24 months, are recommended.[3]

#### *Guidelines for continuation phase treatment*

After the initial treatment phase, H and R may be continued for 4 months. There is no evidence which permits firm recommendations to be made about the therapeutic strategy or its duration in the maintenance phase when it is impossible to use R or H, either separately or together. However, it seems reasonable to recommend increasing the treatment time in accordance with the indications made in the previous point, and to lay down a sequence for the drugs to be used on an individual basis, depending on the toxicity profile of the drugs used.[1,3,6-8]

### *Treating antituberculosis drugs-resistant tuberculosis*

#### *Concepts*

ATD-resistant TB is a worldwide problem of the first order which makes the disease difficult to control and entails an increase in morbidity and mortality rates.[12] The presence of resistance to a single drug is referred to as monoresistance, and resistance to more than one drug, not including the H and R combination, polyresistance. The term MDR-TB is reserved for the presence of resistance to at least H and R,[13] and that of XDR defines resistance to H, R, fluoroquinolones and at least one of the following parenterally-administered drugs: amikacin, kanamycin and capreomycin.[14]

#### *Basic principles for treating resistant tuberculosis cases.*[1,3,6,12-14]

- When it comes to designing a new therapeutic regimen in cases of TB resistance, the possibility should always be considered that the patient may have followed covert monotherapy or bitherapy during the initial treatment phase which may have given rise to the development of resistance to

one of the initially susceptible ATDs that the patient received. This situation is especially likely in scenarios of MDR-TB and XDR-TB.
- In patients with therapeutic failure, the addition of a new ATD to the failing regimen may give rise to covert monotherapy and the acquisition of resistance to the new ATDs introduced, thus compromising the success of future therapy.
- A laboratory report for ATD sensitivity that includes at least R and H should be carried out for every patient diagnosed with TB. The diagnosis of MDR-TB or XDR-TB requires sensitivity testing that extends to second- and third-line ADTs.
- Changing treatment due to therapeutic failure should always be guided by the results of the baseline sensitivity analysis to ATDs, while taking into account the existence of cross-resistances between different ATDs.
- It is not advisable to reduce the number of ATDs in the initial regimen of TB treatment before the baseline sensitivity test is available, especially in patients who do not respond to treatment.
- MDR-TB and XDR-TB treatments should be carried out in consultation with and on the advice of a TB specialist.
- Appropriate therapy for MDR-TB and XDR-TB requires the use of at least 4 active drugs not used previously, and always including as far as possible a drug for parenteral administration.
- There is insufficient evidence of the kind necessary to be able to make firm recommendations concerning the optimal duration of MDR-TB and XDR-TB treatments. Given these limitations, we consider that the minimum period of treatment should be 12-18 months after the sterilization of cultures, with an injectable agent being maintained, whenever possible, for up to 6 months after their negative conversion, and continuing with a minimum of 3 active oral drugs until the end of treatment.

*Treatment of monoresistant and polyresistant tuberculosis*

The existence of baseline *M. tuberculosis* resistance to one or two ATDs requires a change in the initially established therapeutic regimen to be evaluated. How the new regimen should be drawn up will depend on factors such as: the number of ATDs the patient received during the initial regimen, the number of ATDs received to which the infectious strain is resistant, the presence or absence of a response to treatment, and the estimated initial bacillary population in relation to the clinical form of TB. We can distinguish various scenarios:

- The patient is treated initially with 4 ATDs (R, H, Z and E), with baseline resistance to one of them. In this scenario, once the sensitivity test results are known, the drug to which there is resistance will be suspended, while the others are maintained until the initial phase of treatment is complete. During the continuation phase, where the M. tuberculosis strain is susceptible to R and H, treatment with R and H will be maintained until 6 months are up, given that the patient will have undergone an initial treatment phase with 3 active ATDs that include R and H. If the strain is resistant to H or R, the initial phase of treatment can be completed with the remaining 3 active ATDs; in the continuation phase, the drug to which the strain is resistant will be replaced with Z or E and treatment prolonged until 9 months are completed.
- The patient is treated initially with 3 ATDs (R, H and Z), with baseline Z resistance. In this case, Z will be replaced by a new first-line drug, and R and H maintained until the initial phase of treatment is complete. Subsequently, treatment with R and H will continue for a total of 9 months.
- The patient is initially treated with 3 ATDs (R, H and Z) with baseline resistance to R or H. In this scenario, account should be taken of the time that the patient has received treatment with only 2 active drugs and the bacillary population required to develop resistant mutations which, in the cases of resistance to R or H, would be 109 and 1011 respectively. It should be remembered that this bacillary population may be present in cases of cavitary TB, and that there is, therefore, a possibility that new drug resistances may have developed, especially if the treatment time has been prolonged. In this situation the most conservative approach would be to assume that the patient may have developed new ATD resistances. We should therefore suspend the drug to which the strain is resistant, maintain the other ATDs to which the strain is susceptible (in view of the possibility that they might still be active), add at least 3 new active ATDs including first-line drugs wherever possible, and carry out a new ATD sensitivity test when the treatment is changed. After the results are known, the therapeutic regimen and its duration can be optimized.
- The patient is treated initially with 3 ATDs, with baseline resistance to two of them. In this scenario, it should be considered that the patient may have received covert monotherapy during the anti-TB medication and that the probability of developing resistance to this drug is consequently very high. In this case, the drugs to which the strain is resistant should be suspended, the drug to which the strain was susceptible be maintained, and at least 4 active drugs added, always including first-line ATDs wherever possible. A new sensitivity test should be performed at the time the treatment is changed. After the laboratory results are known, the therapeutic regimen and its duration can be optimized.
- The patient is treated initially with 4 ATDs with baseline resistance to two of them. If the isolate is not resistant to H or R, the drugs to which it is resistant should be replaced by a new first-line ATD, and the others maintained until the initial phase of treatment has been completed. Treatment with R and H will be maintained subsequently until a total of 9 months of treatment has been completed. In cases where R or H is one of the drugs to which the strain is resistant, the period during which the patient has received treatment with only 2 active drugs, and the bacillary population necessary for the development of mutations resistant towards them, should be considered (see scenario C, above)

*Treatment of multi-drug-resistant tuberculosis*

There are many possible combinations of ATD resistance. On a practical level, however, we can distinguish 2 scenarios, based on the number of ATDs used in the initial regimen:

- Patients treated initially with a regimen including 3 ATDs (R, H and Z or E). In this situation, the patient should be considered as having received monotherapy with Z or E, and has most probably developed a resistance to the drug. In this situation, the whole failing regime should be suspended and replaced by a combination of 4 active ATDs, selected in the following order of priority (Table 1): *a)* include, wherever possible, the first-line ATD not used previously (E or Z), because of its profile of baseline resistance; *b)* include a fluoroquinolone (preferably M); *c)* include a parenterally-administered ATD (S, kanamycin, capreomycin or amikacin); *d)* include a second-line ATD (cycloserine, para-aminosalicylic acid [PAS] or ethionamide) until 4 active drugs have been incorporated; and *e)* if it has not been possible to select the desired number of active ATDs in the 4 previous steps, include third-line drugs until this has been achieved (linezolid, clofazimine, amoxicillin-clavulanate, clarithromycin, imipenem).
- Patients treated initially with a regimen that included 4 ATDs (R, H, Z and E). In this situation, the patient should be considered

**Table 1**
Selection of drugs for multi-drug-resistant tuberculosis treatment: order of priority

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Pyrazinamide | Moxifloxacin | Amikacin | Cycloserine | Clofazimine |
| Ethambutol | Levofloxacin | Streptomycin | PAS | Clarithromycin |
| | | Kanamycin | Ethionamide | Amoxicillin-Clavulanate |
| | | Capreomycin | | Linezolid |
| | | | | Imipenem |

PAS: para-aminosalicylic acid.

as having undergone bitherapy with Z plus E. Since the bacillary population necessary to develop mutations resistant to these drugs is $10^8$, it may have triggered off resistance to both, especially if the period of treatment was prolonged and the patient presented with cavitary TB. In this situation, R and H should be suspended and a new regimen designed with 6 active drugs, selected in the following order of priority: if possible, include E and Z because of their profile of baseline resistance and regardless of the risk, already mentioned, of secondary resistance; then, steps 2, 3, 4 and 5 outlined in the previous case should be followed.

*Treatment for extensively drug-resistant-tuberculosis*

The new regimen should consist of a combination of 6 active ATDs, selected in the following order (Table 2): *a)* include E or Z wherever possible because of their profile of baseline resistance; *b)* if the resistance profile permits, include an ATD for parenteral administration (S, kanamycin, capreomycin or amikacin); *c)* include a second-line ATD (cycloserine, PAS or ethionamide); and *d)* include third-line ATDs (linezolid, clofazimine, amoxicillin-clavulanate, clarithromycin, imipenem) until there are 6 active ATDs. The future treatment of patients with MDR and XDR-TB may change substantially as a result of the development of new ATDs, as is explained in a separate chapter of this monograph.

## Treatment of latent tuberculosis infection

After the detection and treatment of active TB cases, the second most pressing measure in the control of TB is the diagnosis and treatment of people with a high risk of developing the disease.

*General principles for treating latent tuberculosis infection*

The therapeutic objective is to avoid progression from latent to active TB. Only 10% of LTB patients are at risk of developing tuberculosis disease. For this reason, and also because treating it may provoke serious adverse and potentially fatal side effects, LTB treatment is only recommended in those individuals who are at greatest risk of progressing to TB.[3] On the other hand it should be remembered that TB may also develop because of the rapid progression of a recent infection, especially in immunocompromised patients (ICP). This possibility should be borne in mind when considering starting prophylactic treatment in IPC who have been in contact with active TB. Some ICP may have a limited ability to respond to the tuberculosis antigen and show negative to the tuberculin test, despite being infected with *M. tuberculosis*; for this reason, starting prophylaxis ought to be considered in ICP following obvious exposure, despite the negative tuberculin test.[12] Finally, the bacillary population in LTB patients is considerably lower than that found in patients with TB, so that the use of combination drug therapy is not necessary to avoid the development of resistant mutations.[3]

**Table 2**
Selection of drugs for treating extensively drug-resistant tuberculosis: order of priority

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Pyrazinamide | Amikacin | Cycloserine | Clofazimine |
| Ethambutol | Streptomycin | PAS | Clarithromycin |
| | Kanamycin | Ethionamide | Amoxicillin-Clavulanate |
| | Capreomycin | | Linezolid |
| | | | Imipenem |

PAS: para-aminosalicylic acid.

*Who should receive preventive therapy?*

Ideally, LTB treatment should be recommended exclusively for those with a significant risk of developing TB and a low risk of toxicity. LTB treatment is recommended for those who have had a recent tuberculin skin test conversion, for people with a positive reaction to tuberculin who may have had significant contact with TB carriers, and for patients with a high risk of developing TB.[3,15]

*Guidelines for treating latent tuberculosis infection*

*Isoniazid*

H has been considered the therapy of choice for LTB since 1965. The earliest randomized clinical trials that evaluated the effectiveness of H in LTB therapy were carried out between 1950 and 1970. Most of these compared H with a placebo for 12 months (12H), and demonstrated 90% effectiveness in reducing TB development.[16] In a clinical trial designed to evaluate the optimum treatment time for LTB using H,[17] a placebo was compared with H regimens for 3 (3H), 6 (6H) and 12 months (12H). In this study, the incidence of TB at 5 years was 1.4% for the placebo and 1.1%, 0.5% and 0.3% for 3H, 6H, and 12H, respectively. Patients in receipt of 6H had a 40% higher risk of TB than those in receipt of 12H. For this reason, 12H is considered the standard for LTB treatment. In a study was observed that the TB rate dropped the longer that H treatment continued, although beyond 9 months, it did not manage to bring down the incidence of TB any further. The study concluded that 9 months treatment could be enough for LTB therapy.[16] Intermittent administration of 9H in LTB treatment has not been studied comparatively, but by analogy with what was demonstrated in the continuation phase of TB treatment —where a twice-weekly dose was equivalent to daily administration— the twice-weekly administration of 9H is an alternative choice for LTB treatment.[15] Likewise, 6H administered daily or intermittently is also recommended as an alternative option in LTB treatment.15 In short, 9H is the preferred regimen recommended at the present time for treating LTB.15), on the grounds that this length of treatment offers maximum benefits, and that an extension to 12 months would bring only minimal extra benefit.

*Rifampicin*

The evidence concerning the effectiveness and safety of R administered daily for 4 months (4R) in LTB treatment is limited. In a placebo-controlled double-blind clinical trial, the effectiveness of 3 regimens of LTB treatment —R for 3 months (3R), 6H, and RH for 3 months (3RH)— was compared with the placebo.[18] After 5 years of follow-up, there was a higher incidence of TB in the placebo group than in the 3 therapeutic regimens, with no differences of effectiveness and safety being found between the 3 regimens evaluated. Available evidence, therefore, suggests that a 4R in LTB treatment achieves higher rates for completion of treatment, with a lower incidence of serious adverse outcomes and at less cost than the standard 9H regimen.[19-22] However, due to the absence of solid evidence concerning its effectiveness, 4R should be regarded as an alternative regimen for treating LTB, although given its low cost and short duration, 4R may be of some therapeutic use for LTB in certain special situations: in areas with a high incidence of H-resistance and in populations where a short treatment program may be indicated.

*Rifampicin with isoniazid*

The first clinical trial in which the effectiveness and safety of this program was evaluated was mentioned earlier.[18] In another randomized open clinical trial including 196 patients, the effectiveness of 3RH turned out to be similar to that of 9H, although the size of the population sample in the study did not permit demonstrate the comparability across the two regimens.[23] The 3RH regimen has been evaluated in various clinical trials in HIV-infected LTB patients. So, in a randomized clinical trial carried out on patients with a positive tuberculin skin test and infected with HIV, 3RH gave a similar level of protection to 6H and reduced the risk of TB compared to the placebo by 60%.[24] In another randomized open trial, 3RH demonstrated a similar effectiveness to 12H; however, the study included both tuberculin reactor and anergic patients, and lacked sufficient power to demonstrate the comparability of the two regimens. In another randomized open clinical trial which evaluated the safety and adherence to 3 short courses of LTB treatment, the TB rate and safety profiles of the 3RH and 6H schedules were similar, although the population sample size did not enable the equivalence of the two regimens to be evaluated.[25] Finally, in a clinical trial carried out on HIV-infected patients with cutaneous anergy, the safety of 3RH was comparable to 6H.[26] In a meta-analysis of randomized clinical trials which included the data of 1926 patients, the effectiveness and incidence of serious adverse outcomes and mortality were equivalent in 3RH and 6-12H.[27]

Therefore, the available data suggest that the safety of 3RH in treating LTB is equivalent to that of 6-12H. However, given that there is currently no solid evidence of its effectiveness, 3RH should be considered an alternative regimen for treating LTB.

*Rifampicin with pyrazinamide*

In a randomized clinical trial performed among HIV-infected patients, it was demonstrated that the effectiveness and safety of 2RZ and 12H were equivalent, although there was a significantly higher rate of compliance with treatment in the former.[28] On the basis of these results, the 2RZ and 12H regimens were regarded as preferential for treating LTB in HIV-infected patients,[29] with 2RZ as an alternative therapeutic course in patients not infected with HIV.[15] However, the description of a higher incidence of hepatotoxicity with 2RZ,[30] the communication of cases of severe hepatitis during LTB therapy in patients not infected with HIV in receipt of 2RZ,[31] and the observation that there was a higher incidence of hepatotoxicity with 2RZ than 6H in a randomized clinical trial carried out on patients not infected by HIV.[32] all served to dissuade use of 2RZ in HIV-negative patients and sowed doubts about the advisability of administering it to HIV-positive ones.[31] The greater risk of hepatotoxicity has been corroborated by other observational studies.[33] In a meta-study comparing the safety and effectiveness of 2RZ with 6-12H, which included clinical trials carried out on HIV-infected and non-infected patients, it was affirmed that 2RZ was equivalent to H for treating LTB in terms of effectiveness and mortality, but that it increased the risk of a serious negative outcome in patients not infected with HIV.[34]

Nevertheless, it is worth mentioning that none of the randomized clinical trials carried out among HIV-infected patients verified a significant increase in hepatotoxicity due to 2RZ.[25,26,28,35,36] In a meta-analysis of randomized clinical trials, designed to compare rates of severe hepatotoxicity in HIV-infected patients using 2RZ against 6H-12H, an increased risk of severe hepatotoxicity due to 2RZ was not demonstrated.[37] However, it should be remembered that the population represented in the clinical trials carried out among HIV-infected patients may not be representative of present-day HIV-infected populations, since all the studies were carried out before powerful antiretroviral treatment was available.

In summary, LTB treatment with 2RZ provokes a higher incidence of adverse outcomes and serious hepatotoxicity than a regimen using H in patients not infected by HIV, so that its use is not advised. Despite the fact that this has not been verified in HIV-infected patients, for reasons already remarked upon, it seems reasonable to advise against its use in these patients too.

*Treatment of latent tuberculosis infection due to antituberculosis drugs-resistant M. tuberculosis strains*

The preferential regimen for LTB treatment in subjects in contact with TB patients brought about by H-resistant strains should be 4R. The treatment of LTB in subjects in contact with MDR-TB has not been evaluated in randomized clinical trials, so that there is insufficient evidence to make firm recommendations about it. In such cases, a careful evaluation should be made of the risk of the LTB patient developing TB. In cases where the risk is high, it seems reasonable to use a combination of two drugs, adjusting the choice of these to the resistance profile of the infecting strain, with a preference —if the resistance profile of the infectious strain permits— for first-line drugs or fluoroquinolones. In cases of XDR-TB, the use of two drugs to which the infecting strain is susceptible is recommended, basing choice on the order set out in Table 2.

## Conflict of interest

The authors declare they have not any conflict of interest.

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