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Molecular detection of isoniazid monoresistance improves tuberculosis treatment: a retrospective cohort in France

Running title: Interest of early detection of isoniazid resistance

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1 **Abstract (143 words)**

2
3 **Objectives:**

4 Isoniazid-monoresistant tuberculosis (HR-TB) requires early diagnosis and adapted treatment
5 to achieve optimal outcomes. The primary aim of the study was to assess the impact of the
6 implementation of rapid diagnostic tests on HR-TB treatment in France.

7 **Methods:**

8 We designed a retrospective multicentre study including consecutive HR-TB patients
9 diagnosed in 2016 and 2017. Implementation of a molecular assay detecting isoniazid
10 resistance directly on a clinical sample was recorded. The association between early
11 implementation of such assays and adequate treatment was assessed by a multivariable Cox
12 proportional hazards model.

13 **Results:**

14 Overall, 99 HR-TB patients were included from 20 University Hospitals. Among all smear-
15 positive HR-TB patients, only 26% benefited from early molecular HR detection. This
16 detection was independently associated with shorter time to adequate treatment (HR = 2.0
17 [1.1-3.8], $p=0.03$).

18 **Conclusion:**

19 In our study, molecular detection of HR on an initial sample was independently associated
20 with earlier treatment adaptation.

21
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23 **Key words:** *Tuberculosis, Isoniazid, Drug Resistance, Epidemiology, France*

Introduction

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Tuberculosis (TB) remains a major cause of mortality worldwide, causing an estimate of 1.4 million of deaths in 2019 globally (1). During the last decades, the emergence and spread of drug-resistance have threatened the control of this contagious disease. International and national programs have mostly focused their attention on multidrug-resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin, and, more recently, on rifampicin-resistant TB (1–3). Conversely, isoniazid-monoresistant tuberculosis (isoniazid-resistant and rifampicin-susceptible TB, HR-TB), has been often overlooked. However, HR-TB is the most prevalent form of drug-resistant tuberculosis worldwide (besides streptomycin resistance), accounting for 11% (95% CI, 6.5–15%) of all incident cases of TB in 2019 (1). Until recently, HR-TB was thought to have similar treatment outcomes compared to drug-susceptible TB (4), leading to this apparent lack of interest. Nevertheless, many studies have recently shown that HR-TB is associated with higher rates of treatment failure and relapse than drug-susceptible TB (5–11), underlining the importance of early diagnosis and appropriate management of HR-TB. Moreover, poor treatment outcomes seem to be associated with HR-TB regardless of the level of isoniazid resistance (12, 13, 14-16).

Currently, WHO recommends performing early testing for resistance to isoniazid and rifampicin, if possible, or at least to rifampicin, among all suspected TB patients (17).

Recent guidelines for TB management in the European Union recommend the routine implementation of molecular testing to detect resistance to both rifampicin and isoniazid among all microbiologically-confirmed TB patients (18). These guidelines are supported by a modelling study published in 2012, which suggested that performing these tests before treatment is the most cost-effective strategy to avert deaths and prevent acquired MDR-TB (19).

49 With rapid molecular testing, resistance to isoniazid can be detected at an early stage, if tests
50 are performed directly on an initial clinical sample. Mutations in the *katG* gene and the *inhA*
51 gene promoter are frequently involved in isoniazid resistance and can be detected by first-line
52 line-probe assays (FL-LPA), *in situ* hybridization techniques on nitrocellulose strip. The Hain
53 GenoType MTBDR*plus* version 2.0 assay, a last generation FL-LPA, has shown better
54 performance compared to the previous version in the detection of mutations conferring
55 resistance to isoniazid (20). In addition, this test detects mutations in the *rpoB* gene, involved
56 in rifampicin resistance. The GeneXpert MTB/RIF assay (Cepheid, USA) is currently widely
57 used worldwide for rapid molecular identification of *Mycobacterium tuberculosis* and
58 mutations conferring resistance to rifampicin. This assay does not detect mutations associated
59 with resistance to isoniazid, and thus focuses on RR-TB. The new release of the Xpert
60 MTB/XDR assay will help filling this gap, but this was not available at the time of the study.
61 Finally, WGS has the potential to detect resistance to both drugs but is currently rarely
62 implemented in routine.

63 Until 2018, the optimal treatment regimen for HR-TB was still unclearly defined and
64 guidelines were based on low levels of evidence, likely leading to heterogeneous medical
65 practices. In 2014, the WHO recommended a three-drug regimen combining rifampicin,
66 ethambutol, and pyrazinamide for 6 to 9 months, with the possible addition of a
67 fluoroquinolone (21). Due to a lack of data, no further recommendation was made in the 2016
68 WHO guidelines for drug-resistant TB (22). In 2018, the World Health Organization (WHO)
69 published the first evidence-based treatment guidelines for HR-TB, recommending a 6-month
70 regimen including rifampicin, ethambutol, pyrazinamide, and a fluoroquinolone (levofloxacin
71 or moxifloxacin) (23).

72 France is a low-incidence country regarding TB. TB diagnosis and care is largely
73 decentralized and TB patients can be managed in general or university referral healthcare

74 centres or in the private sector. A National Reference Centre for Mycobacteria is available to
75 provide advice on diagnosis and treatment of TB patients, whenever necessary. According to
76 data provided by this National Reference Centre, around 5% of all TB patients are HR-TB,
77 three times as prevalent as MDR-TB (24). Yet, the last French guidelines for TB diagnosis
78 and treatment, published by the High Committee of Public Health in 2014, did not provide
79 any specific recommendation concerning HR-TB treatment (25). To date, no data is available
80 concerning the management of HR-TB in France.

81 The primary objective of this study was to assess the consequences of diagnostic method of
82 HR-TB in France on the management of antituberculosis drug regimens. The secondary
83 objectives were to describe the diagnostic methods used for HR-TB management, to evaluate
84 the compliance of HR-TB treatment regimens with international guidelines and to assess their
85 impact on treatment outcomes. For this purpose, we reanalyzed data of a study performed
86 recently to identify characteristics and risk factors for HR-TB in France (26).

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88

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Methods

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91 *1. Study design*

92 **Population**

93 A retrospective, multicentre cohort study included all consecutive HR-TB patients diagnosed
94 by laboratories members of the AZAY-mycobacteria network from January 1, 2016, to
95 December 31, 2017, in the Ile-de-France region (Paris and its suburbs), and the cities of Caen,
96 Lille, and Strasbourg (26, 27). All patients had microbiologically confirmed TB with
97 phenotypic resistance to isoniazid and susceptibility to rifampicin.

98

99 **Data collection**

100 Demographic, clinical, radiological, and microbiological characteristics at baseline were
101 extracted from medical files. Microbiological tests and time to HR-TB diagnosis, as well as
102 treatment regimens were recorded. Among molecular tests, we reported the implementation of
103 FL-LPA and *katG* and *inhA* genes sequencing on clinical sample or strain. We also reported
104 GeneXpert tests performed, although not relevant to detect isoniazid resistance, because of its
105 wide use in France. Collected data was collated using *Epidata v.4.4.3.1*.

106

107 **Definitions**

108 Isoniazid resistance was defined as phenotypic resistance with a minimal inhibitory
109 concentration (MIC) ≥ 0.2 $\mu\text{g/mL}$ on Lowenstein-Jensen medium or ≥ 0.1 $\mu\text{g/mL}$ on MGIT
110 liquid medium. All tests performed at the local laboratory for identification of drug
111 susceptibility were recorded. In addition, some isolates were sent to the French National
112 Reference Centre for mycobacteria for additional testing.

113 Adequate treatment for HR-TB patients was defined as the prolongation of ethambutol and
114 pyrazinamide during the continuation phase, as recommended by WHO in 2014 (21), or as the

115 addition of a fluoroquinolone for >30 days according to 2018 WHO guidelines (23). Time to
116 adequate treatment was calculated starting from the diagnosis of TB. Treatment outcomes
117 were defined as per 2021 WHO definitions (28).

118

119 2. *Statistical analysis*

120 Fisher's exact test and Wilcoxon-Mann-Whitney test were used to compare categorical and
121 quantitative variables between patients who benefited from a rapid molecular test for HR-
122 TB on the initial sample and those who did not. A Cox proportional hazards model was
123 performed to compare time to adequate treatment between the aforementioned groups and to
124 adjust for confounding factors. Explanatory variables were included in the initial Cox model
125 if $p < 0.20$ in univariate analysis. Redundant variables were removed. Similarly, some variables
126 were added to the model when considered clinically relevant and potentially confounding.
127 Missing data was considered as missing at random and managed with multiple imputation
128 using the *Mice* function on RStudio. A stepwise regression was used with the *Step* function.
129 The proportional hazard hypothesis was verified with Schoenfeld residuals. Survival analysis
130 was performed and Kaplan-Meier curves were plotted to describe time to adequate treatment;
131 patients who performed a rapid molecular test for HR-TB on the initial sample and those who
132 did not were compared using a log-rank test. A logistic regression was performed to identify
133 factors associated with a favorable treatment outcome. Explanatory variables were chosen as
134 explained above. All statistical analysis were performed using RStudio version 1.2.5. All
135 statistical tests were bilateral, and significance was determined as $p \leq 0.05$.

136

137

138 **3. Ethics**

139 The study was approved by the ethic committee of the Bligny Hospital (Briis-sous-Forges,
140 France) in October 2018 and registered in the treatment register of Assistance Publique des
141 Hôpitaux de Paris under the following registration number: 20190822142246.

Results

1. Descriptive analysis of the population

Overall, 99 HR-TB patients were included in the study. Almost 70% were male and aged less than 45 years. More than 80% were foreign-born, mostly living in France for less than a decade. Overall, 82% of the patients had pulmonary tuberculosis, 10% had been treated previously for TB, and less than 10% were HIV-positive or immunosuppressed (table 1).

2. Diagnostic methods used for the management of HR-TB

By definition, all 99 patients had phenotypic drug susceptibility testing (DST) concluding to isoniazid resistance. Considering any molecular test to detect isoniazid resistance, 69 (70%) benefited from a molecular test only on a positive culture, 14 (14%) directly on a clinical sample (among which 4 had a test also performed on a positive culture), and 16 (16%) had no test performed. Among the 83 patients who had molecular testing for isoniazid, isoniazid resistance-conferring mutations were found in 73 cases, including mutations in *katG* (n=42, 58%), in the *inhA* gene promoter (n=28, 38%), or in both (n=3, 4%). For 10 patients, molecular testing did not identify any isoniazid resistance-conferring mutation (data not shown).

The TB and DST molecular diagnostic strategy analyzed by smear-test results is presented in Figure 1. Among the 46 smear-positive patients, 11 (24%) FL-LPA and 30 (65%) GeneXpert MTB/RIF were performed on the initial clinical sample, while 5 had no molecular test performed at this stage. FL-LPA identified isoniazid resistance in 9 cases, while in two cases the result was not interpretable. A second FL-LPA performed on positive culture identified isoniazid resistance-conferring mutations for one of the latter and for the second, isoniazid

167 resistance was diagnosed by phenotypic DST. Among the 35 smear-positive patients with no
168 initial isoniazid molecular test (76%), isoniazid resistance was diagnosed by FL-LPA on
169 positive cultures (n=23) or by phenotypic DST (n=12).
170 Among the 53 (54%) smear-negative patients, 3 (6%) FL-LPA and 12 (23%) GeneXpert
171 MTB/RIF were performed on a clinical sample. Results of the three FL-LPA were either non
172 interpretable (n=2) or negative (Figure 1). For 2 of these 3 patients, FL-LPA performed later
173 on positive culture detected isoniazid resistance-conferring mutations. Out of the 50 (94%)
174 smear-negative remaining patients, 41 and 1 had FL-LPA or *katG* plus *inhA* sequencing
175 secondarily on positive cultures (N=41), respectively, and 38 isoniazid-conferring mutations
176 were detected. In the remaining 12 patients, isoniazid resistance was identified by phenotypic
177 DST. **Comparison between molecular and phenotypic drug susceptibility testing regarding**
178 **isoniazid resistance is detailed in the supplementary table 1.**

179

180 3. Treatment regimens and outcomes

181 *Treatment regimens*

182 Overall, the 99 HR-TB patients received a total of 13 different treatment regimens (Table 2).
183 A total of 27 (27%) patients were treated with the standard regimen for drug-susceptible TB,
184 including seven for whom isoniazid was stopped with no further therapeutic adaptation.
185 Among the 72 (73%) patients who were treated adequately, 56 (57%) received a
186 fluoroquinolone for a median duration of 176 days (25 weeks), including moxifloxacin for 45
187 (80%) or levofloxacin for 11 patients (20%). The other 16 patients (16%) received the
188 standard regimen with a prolonged course of ethambutol (172 days - 24 weeks) and
189 pyrazinamide (182 days - 26 weeks) (Supplementary table 2).

190

191 *Impact of the early implementation of FL-LPA on time to adequate treatment*

192 Time from TB diagnosis to initiation of adequate treatment was significantly shorter among
193 HR-TB patients for whom isoniazid resistance was detected by molecular testing on the initial
194 sample compared to the others, with a median of 28.5 [95% confidence interval (CI): 20–90]
195 and 90 [95% CI: 43–90] days, respectively ($p=0.03$, Figure 2). In a multivariable Cox model,
196 after adjustment for immunosuppressive condition and treatment regimens, the
197 implementation of molecular testing on the initial sample was independently associated with a
198 shorter time to adequate treatment (HR 2.0 [95% CI: 1.1–3.8]).

199

200 *Impact of molecular testing and treatment regimens on outcomes*

201 Overall, 75 (76%) of HR-TB patients achieved treatment success: 10 (10%) were cured and
202 65 (66%) completed treatment. Two (2%) HR-TB patients experienced treatment failure
203 among which one acquired an MDR-TB strain. There was a total of four (4%) all-cause
204 deaths. Finally, 16 (16%) patients were lost to follow-up and no data was available for 2 (2%)
205 patients. In multivariable analysis, when adjusting for age, sex, immunosuppression, smoking,
206 prior history of TB treatment, extrapulmonary TB, disseminated TB, radiological
207 characteristics (presence of miliary or cavity), neither the use of a FL-LPA on the initial
208 clinical sample, nor the type of isoniazid resistance-conferring mutation (*katG* or *inhA*), were
209 significantly associated with treatment success (table 3). However, adequate treatment was
210 strongly and independently associated with treatment success (OR=37.5 [95% CI: 7.6–298.5];
211 $p=0.001$). When adequate treatment was differentiated according to the use of a
212 fluoroquinolone or not, both treatment regimens were statistically associated with treatment
213 success (fluoroquinolone-including regimens: OR=46.2 [95% CI: 8.3–415.3]; $p<0.001$;

214 regimens without fluoroquinolone: OR= 32.3 [95% CI: 3.3–648.5]; $p=0.008$) (data not
215 shown).

Discussion

216

217

218 In a multicentre retrospective cohort reporting on the management of HR-TB in France, we
219 have shown that performing a molecular test such as FL-LPA on the initial clinical sample
220 shortens the delay to adequate treatment. We also report that this strategy is scarcely
221 implemented in France, precluding the opportunity for early detection of isoniazid resistance
222 and, consequently, early treatment adaptation. To our knowledge, this is the first study to
223 describe the management of HR-TB in France in terms of rapid molecular testing and
224 treatment, and to assess its consistency with international guidelines, as well as the impact on
225 TB treatment outcome.

226 In our study, only one-fourth (24%) of smear-positive HR-TB patients had a molecular test
227 performed on a clinical sample for early detection of isoniazid resistance, and this test
228 allowed detecting isoniazid resistance in most of them. Of interest, a GeneXpert MTB/RIF
229 assay was performed for 2/3rd of smear-positive HR-TB patients, allowing elimination of
230 MDR-TB but overlooking HR-TB. In 2019, Romanowski *et al.* showed in their modelling
231 study that the implementation of rapid molecular testing on initial clinical samples for both
232 isoniazid and rifampicin resistance, compared to GeneXpert MTB/RIF alone, would result in
233 a 50% reduction of acquired MDR-TB strains (29). Similar results were highlighted by an
234 epidemiologic study performed in rural China (30). Hence, the lack of early rapid molecular
235 testing that leads to late diagnosis of HR-TB patients in France may ultimately result in an
236 increased risk of secondary MDR-TB. In addition, we showed that early identification of
237 isoniazid resistance on a clinical sample was independently associated with a shorter time to
238 adequate treatment.

239 Conversely, none of the three patients with smear-negative samples had isoniazid resistance
240 detected by molecular tests at an early stage (one wild-type and two uninterpretable results),

241 suggesting a lack of performance of this test on smear-negative TB samples. These findings
242 confirm previous reports showing an estimate of 44% of interpretable results on smear-
243 negative samples, compared to 89% on smear-positive samples, with an overall sensitivity
244 and specificity of 89.2% (95% CI: 85.8–91.9) and 98.4% (95% CI: 97.5–98.9), respectively,
245 on smear-positive samples (31). Indeed, WHO currently recommends to perform this test on
246 smear-positive samples only (32). The overall implementation of molecular testing to detect
247 HR-TB was disappointingly low in our study. Out of 20 participating centres, only 5
248 performed FL-LPA on initial sample, with most tests being performed in one centre. This may
249 be linked to the priority given to the detection of rifampicin resistance and MDR-TB in the
250 last years, and to the preferential implementation of easy-to-use molecular assays, such as
251 GeneXpert MTB/RIF. The latter molecular assay was performed substantially more often
252 (42% of all patients, 65% of smear-positive samples) than molecular tests for the detection of
253 isoniazid resistance. The issue of the new Xpert MTB/XDR assay including INH testing will
254 make HR-TB detection easier for laboratories already using the geneXpert technique,
255 although the former it is not coupled with the rifampicin assay. In addition, evidence
256 describing the important impact of isoniazid resistance on treatment outcome emerged only
257 recently. The lack of clear French guidelines concerning rapid microbiological diagnosis and
258 management of isoniazid resistance may also have contributed to these findings. **Latest**
259 **national guidelines published by the High Committee for Public Health date from 2014. In**
260 **this document, the use of molecular tests is recommended for the diagnosis of TB and the**
261 **detection of rifampicin resistance; conversely, molecular testing for the diagnosis of isoniazid**
262 **resistance is only encouraged when possible. These national guidelines are now outdated and**
263 **should be replaced in clinical practice by international guidelines.**

264

265 In our cohort, HR-TB treatment was substantially heterogeneous with 13 different treatment
266 regimens reported. Of concern, more than one quarter of patients (27%) were treated
267 inadequately according to 2014 and 2018 WHO guidelines. The great heterogeneity of
268 observed HR-TB treatment regimens reflects the absence of consensual and evidence-based
269 guidelines before 2018, but also the lack of awareness of clinicians and microbiologists on the
270 consequences of isoniazid monoresistance on treatment outcomes. *inhA* mutations, which are
271 usually associated with low level of isoniazid resistance, were identified among more than a
272 quarter of the cohort. This could partly explain why some treatment regimens were not
273 modified after knowledge of isoniazid resistance. Nevertheless, poor treatment outcomes have
274 been associated with HR-TB regardless of the level of isoniazid resistance in several studies
275 (4).

276 Among the 72 adequately treated HR-TB patients, 56 received a fluoroquinolone, mainly
277 moxifloxacin. Of interest, among patients treated with fluoroquinolones, DST for
278 fluoroquinolones was performed in less than 50% of patients, in contrast with WHO
279 recommendations (23). In our cohort, unsurprisingly, adequate treatment was associated with
280 better treatment outcomes. Although a recent meta-analysis by Fregonese *et al.* showed better
281 treatment outcomes of HR-TB with fluoroquinolone-including regimens (33), we found no
282 association between the use of fluoroquinolones and treatment outcomes. This result is
283 consistent with the retrospective cohort by Stagg *et al.* which showed similar treatment
284 outcomes between regimens including or not including any fluoroquinolone (34).
285 Nevertheless, our study may not be powered to detect any difference between these groups.

286 Our study has some limitations. First, the retrospective design introduces unavoidable bias.
287 For instance, we could not report the reasons and motivation leading to the clinicians' choice
288 of a specific treatment regimen. Second, the lack of clear and consensual guidelines, in
289 particular at a national level in France, made it complicated to define "adequate treatment".

290 We finally chose a definition based on both 2014 and 2018 WHO guidelines. In our
291 definition, the addition of fluoroquinolone for at least 30 consecutive days was considered
292 adequate; this could lead to a slight overestimation of adequately treated patients. Third, **with**
293 **a few exceptions, most of the cases were diagnosed and treated at University Hospitals or in a**
294 **sanatorium. Consequently,** the results of the study represent **reference-level practices** and may
295 not reflect adequately the situation in the whole country.

296 In conclusion, the diagnosis of HR-TB in France appears to be often delayed due to the lack
297 of implementation of adequate rapid molecular testing on clinical samples. In our study, less
298 than one quarter of smear-positive HR-TB patients had a rapid molecular test performed on
299 the initial sample. As no risk factor have yet clearly been identified to screen TB patients at
300 risk of HR-TB in France (26), we suggest rapid diagnosis of isoniazid resistance to be
301 systematically implemented on smear-positive sample. In addition, disseminating recent
302 guidelines for the management of HR-TB may be necessary to increase awareness of
303 microbiologists and clinicians, and ensure that treatment regimens are designed according to
304 current state-of-the-art. Despite its significant prevalence among resistant TB and its higher
305 risk of treatment failure, HR-TB has been overlooked for a long time. In the era of tailored
306 regimens for tuberculosis, we cannot afford to ignore the relevance of HR-TB anymore (35).

307

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308

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- 338 1. WHO. Global Tuberculosis Report 2020.
 339 <https://www.who.int/publications/i/item/9789240013131>
 340
- 341 2. WHO. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-
 342 Resistant Tuberculosis Treatment. 2020. www.who.int/publications/i/item/9789240007048
 343
- 344 3. Matambo R, Takarinda KC, Thekkur P, Sandy C, Mharakurwa S, Makoni T et al.
 345 Treatment outcomes of multi drug resistant and rifampicin resistant Tuberculosis in
 346 Zimbabwe: A cohort analysis of patients initiated on treatment during 2010 to 2015. PLoS
 347 ONE. 2020;15(4):e0230848.
 348
- 349 4. Stagg HR, Lipman MC, McHugh TD, Jenkins HE. Isoniazid-resistant tuberculosis: a cause
 350 for concern? *Int J Tuberc Lung Dis.* 2017;21(2):129–39.
 351
- 352 5. Gegia M, Cohen T, Kalandadze I, Vashakidze L, Furin J. Outcomes among tuberculosis
 353 patients with isoniazid resistance in Georgia, 2007–2009. *Int J Tuberc Lung Dis.*
 354 2012;16(6):812-6.
 355
- 356 6. Báez-Saldaña R, Delgado-Sánchez G, García-García L, Cruz-Hervert LP, Montesinos-
 357 Castillo M, Ferreyra-Reyes L et al. Isoniazid Mono-Resistant Tuberculosis: Impact on
 358 Treatment Outcome and Survival of Pulmonary Tuberculosis Patients in Southern Mexico
 359 1995-2010. *PLoS ONE.* 2016;11(12):e0168955.
 360
- 361 7. Menzies D, Benedetti A, Paydar A, Royce S, Madhukar P, Burman W et al. Standardized
 362 Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-
 363 resistance to Isoniazid: A Systematic Review and Meta-analysis. *PLoS Med.*
 364 2009;6(9):1000150.
 365
- 366 8. van der Heijden YF, Karim F, Mufamadi G, Zako L, Chinappa T, Shepherd BE et al.
 367 Isoniazid mono-resistant tuberculosis is associated with poor treatment outcomes in Durban,
 368 South Africa. *Int J Tuberc Lung Dis.* 2017;21(6):670–6.
 369
- 370 9. Vinnard C, Winston C, Wileyto EP, Macgregor RR, Bisson GP. Isoniazid Resistance and
 371 Death in Patients With Tuberculous Meningitis: Retrospective Cohort Study. *BMJ.*
 372 2010;341:c4451.
 373
- 374 10. Vinnard C, Winston CA, Wileyto EP, Macgregor RR, Bisson GP. Isoniazid-resistant
 375 tuberculous meningitis, United States, 1993-2005. *Emerging Infect Dis.* 2011;17(3):539–42.
 376
- 377 11. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-
 378 resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet*
 379 *Infect Dis.* 2017;17(2):223–34.
 380
- 381 12. Dominguez J, Boettger EC, Cirillo D, Cobelens F, Eisenach KD, Gagneux S et al. Clinical
 382 implications of molecular drug resistance testing for *Mycobacterium tuberculosis*: a
 383 TBNET/RESIST-TB consensus statement. *Int J Tuberc Lung Dis.* 2016; 20(1):24–42.
 384
-

- 385 13. Villegas L, Otero L, Sterling TR, Huaman LA, Van der Stuyft P, Gottuzzo E et al.
386 Prevalence, Risk Factors, and Treatment Outcomes of Isoniazid- and Rifampicin-Mono-
387 Resistant Pulmonary Tuberculosis in Lima, Peru. *PLoS One*. 2016; 11(4):e0152933.
388
- 389 14. Chien JY, Chen YT, Wu SG, Lee JJ, Wang JY, Yu CJ. Treatment outcome of patients
390 with isoniazid mono-resistant tuberculosis. *Clin Microbiol Infect*. 2015; 21(1):59–68.
391
- 392 15. Wang TY, Lin SM, Shie SS, Chou PC, Huang CD, Chung FT et al. Clinical
393 characteristics and treatment outcomes of patients with low- and high-concentration isoniazid-
394 monoresistant tuberculosis. *PLoS One*. 2014; 9(1):e86316.
395
- 396 16. Bang D, Andersen PH, Andersen AB, Thomsen VØ. Isoniazid-resistant tuberculosis in
397 Denmark: mutations, transmission and treatment outcome. *J Infect*. 2010; 60(6):452–7.
398 [PubMed: 20347869]
399
- 400 17. WHO. Technical manual for drug susceptibility testing of medicines used in the treatment
401 of tuberculosis. 2018.
402 www.who.int/tb/publications/2018/WHO_technical_drug_susceptibility_testing/en/
403
- 404 18. European Respiratory Society, Europäisches Zentrum für die Prävention und die
405 Kontrolle von Krankheiten, editors. European Union standards for tuberculosis care. 2017
406 update. Luxembourg: Publications Office; 2018. 20 p.
407
- 408 19. Oxlade O, Falzon D, Menzies D. The impact and cost-effectiveness of strategies to detect
409 drug-resistant tuberculosis. *Eur Respir J* 2012;39(3):626–34.
410
- 411 20. Brossier F, Veziris N, Jarlier V, Sougakoff W. Performance of MTBDR plus for detecting
412 high/low levels of Mycobacterium tuberculosis resistance to isoniazid. *Int J Tuberc Lung Dis*.
413 2009;13(2):260-5.
414
- 415 21. WHO. Companion handbook to the WHO guidelines for the programmatic management
416 of drug-resistant tuberculosis.2014. www.ncbi.nlm.nih.gov/books/NBK247420/
417
- 418 22. WHO. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update.2016.
419 www.who.int/publications/i/item/9789241549639
420
- 421 23. WHO. WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the
422 WHO treatment guidelines for drug-resistant tuberculosis. 2018.
423 www.who.int/tb/publications/2018/WHO_guidelines_isoniazid_resistant_TB/en/
424
- 425 24.CNR-MyRMA. Rapport annuel d'activité. 2018.
426 http://cnrmyctb.free.fr/IMG/pdf/rapport_CNR-MyRMA-2018__final.pdf
427
- 428 25. HCSP. Tuberculoses à bacilles résistants: diagnostic et prise en charge. 2014.
429 www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=484
430
- 431 26. Bachir M, Guglielmetti L, Tunesi S, Billard-Pomares T, Chiesi S, Jaffré J et al. Isoniazid-
432 monoresistant tuberculosis in France: risk factors, treatment outcomes and adverse events. *Int*
433 *J Infect Dis*. 2021. S1201-9712(21)00311-8.
-

- 434 27. Khuê PM, Truffot-Pernot C, Texier-Maugein J, Jarlier V, Robert J. A 10-year prospective
435 surveillance of *Mycobacterium tuberculosis* drug resistance in France 1995-2004. *Eur Respir*
436 *J* 2007 ;30 :937-944.
437
- 438 28. WHO. Meeting report of the WHO expert consultation on drug-resistant tuberculosis
439 treatment outcome definitions, 17–19 November 2020. Geneva: World Health Organization;
440 2021.
441
- 442 29. Romanowski K, Campbell JR, Oxlade O, Fregonese F, Menzies D, Johnston JC. The
443 impact of improved detection and treatment of isoniazid resistant tuberculosis on prevalence
444 of multi-drug resistant tuberculosis: A modelling study. *PLOS ONE* 2019;14(1):e0211355.
445
- 446 30. Hu Y, Hoffner S, Jiang W, Wang W, Xu B. Extensive transmission of isoniazid resistant
447 *M. tuberculosis* and its association with increased multidrug-resistant TB in two rural counties
448 of eastern China: A molecular epidemiological study. *BMC Infect Dis* 2010;10(1):43.
449
- 450 31. WHO. The use of molecular line probe assays for the detection of resistance to isoniazid
451 and rifampicin. www.who.int/tb/publications/molecular-test-resistance/en/
452
- 453 32. WHO. Implementing tuberculosis diagnostics: A policy framework. 2016.
454 www.who.int/tb/publications/implementing_TB_diagnostics/en/
455
- 456 33. Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P et al.
457 Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient
458 data meta-analysis. *Lancet Respir Med*. 2018 Jun;6(6):e27.
459
- 460 34. Stagg HR, Bothamley GH, Davidson JA, Kunst H, Lalor MK, Lipman MC et al.
461 Fluoroquinolones and isoniazid-resistant tuberculosis: implications for the 2018 WHO
462 guidance. *Eur Respir J* 2019; 54 (4): 1900982
463
- 464 35. Sulis G, Pai M. Isoniazid-resistant tuberculosis: A problem we can no longer ignore. *PLoS*
465 *Med* 2020;17(1):e1003023.
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Tables

Table 1. Baseline characteristics of isoniazid-resistant tuberculosis patients (N=99).

Baseline characteristics of HR-TB patients	N (%)
Male sex	69 (70)
Age (median), years	35
HIV infection	9 (9)
Immunosuppression	9 (9)
Previous TB treatment	10 (10)
Foreign-born	82 (83)
Length of stay in France for foreign-born patients (years)	
≤5	35 (43)
>5	29 (35)
No data	18 (22)
Extra-pulmonary TB (with or without pulmonary TB)	71 (72)

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475 *Table 2. Treatment regimens of isoniazid-monoresistant tuberculosis patients (N=98).*

Treatment	Treatment details		Total, N (%)	
Adequate treatment	FQ	Addition of a FQ only	35 (35)	52 (53)
		FQ and prolongation of E	3 (3)	
		FQ and prolongation of Z	4 (4)	
		FQ and prolongation of E and Z	10 (10)	
	Prolongation of E and Z		14 (14)	14 (14)
Inadequate treatment	Standard treatment regimen for DS-TB		20 (20)	32 (32)
	Interruption of H		7 (7)	
	Prolongation of E		5 (5)	

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477 *H= isoniazid, FQ= fluoroquinolones, E =ethambutol, Z = pyrazinamide.*

478 *Overall, 13 different regimens were listed when considering treatment changes on isoniazid*
 479 *(continuation or interruption). Treatment data was missing for one patient.*

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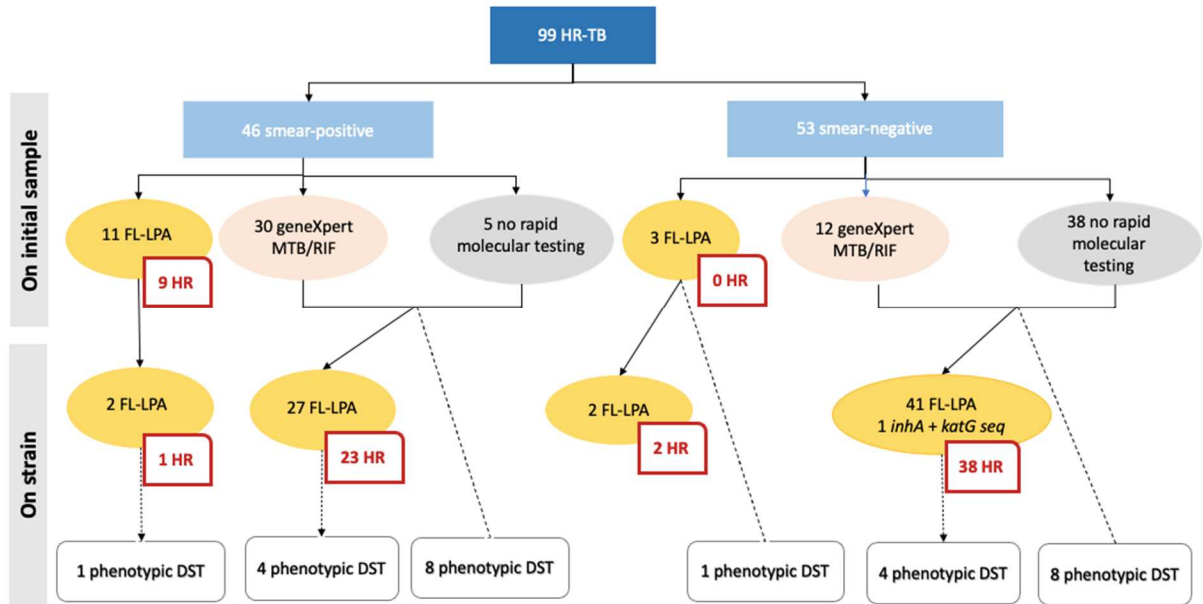
481 Table 3. Characteristics of isoniazid-resistant tuberculosis patients according to treatment
 482 outcomes (N = 99).
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Variable	HR-TB with favourable outcome (N=75)	HR-TB with unfavourable outcome (N=24)	<i>p</i> (univariable)	<i>p</i> (multivariable)	
Median age	31	37	0.39		
Female sex	24 (32%)	6 (25%)	0.61	0.21	
Immunosuppression	5 (7%)	4 (17%)	0.21	0.07	
Smoking history	21(28%)	4 (17%)	0.12	0.02	
Prior history of TB treatment	7 (9%)	3 (13%)	0.70	0.42	
Extrapulmonary TB	51 (68%)	20 (83%)	0.20	0.10	
Disseminated TB	10 (13%)	13 (54%)	0.73	0.29	
Presence of miliary	6 (8%)	5 (21%)	0.21	0.20	
Presence of cavity	30 (40%)	11 (46%)	0.64	0.04	
FL-LPA implementation on sample	10 (13%)	4 (17%)	0.66	0.40	
Genotypic results	<i>inhA</i> mutation	21 (28%)	6 (25%)	1.00	0.20
	<i>katG</i> mutation	32 (43%)	12 (50%)	0.64	0.05
	<i>inhA</i> + <i>katG</i> mutation	3 (4%)	0	1.00	
	NA	19 (25%)	6 (25%)		
Phenotypic level of resistance	Low-level of H resistance	19 (25%)	7 (29%)	0.86	0.15
	High-level of H resistance	50 (67%)	16 (67%)		
	NA	6 (8%)	1 (4%)		
Adequate treatment	With fluoroquinolone	47 (62%)	7 (29%)	0.01	
	Without fluoroquinolone	11 (15%)	3 (13%)	1.00	
Inadequate regimen	treatment	17 (23%)	14 (58%)	0.04	<0.001

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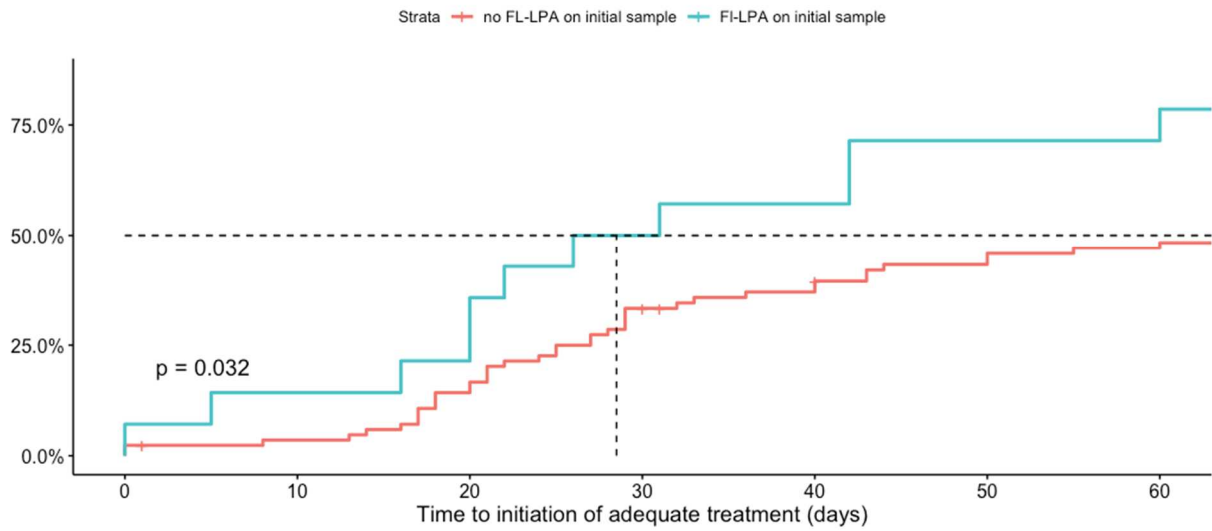
Figures



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Figure 1: Microbiological diagnosis of isoniazid resistance among all isoniazid-monoresistant tuberculosis patients. FL-LPA=First-Line Line Probe Assay (Hain GenoType MTBDRplus). DST: Drug Susceptibility Testing. HR=diagnosis of isoniazid resistance. *inhA* + *katG* seq= *inhA* and *katG* genes sequencing.

Time to adequate treatment according to the implementation of FL-LPA on sample



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49 **Figure 2:** Reversed Kaplan-Meier curve showing time to adequate treatment according to availability of a first-line line probe assay on the initial sample among isoniazid-resistant patients (N=99) ($p=0.032$ with log-rank test). Time to treatment adaptation starts at tuberculosis diagnosis. The blue curve represents patients for whom first-line line probe assay was performed on initial sample (N=14), the red curve those who had no first-line line probe assay performed on initial sample (N=85). Discontinued lines represent median time to adequate treatment for both groups.