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MAJOR ARTICLE

Treatment With a Three-Drug Regimen for Pulmonary Tuberculosis Based on Rapid Molecular Detection of Isoniazid Resistance: A Noninferiority Randomized Trial (FAST-TB)

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Background. The rationale behind the use of ethambutol in the standard tuberculosis treatment is to prevent the emergence of resistance to rifampicin in case of primary resistance to isoniazid. We evaluated whether early detection of isoniazid resistance using molecular testing allows the use an ethambutol-free regimen.

Methods. FAST-TB, a phase 4, French, multicenter, open-label, non-inferiority trial, compared 2 strategies: (1) polymerase chain reaction (PCR)-based detection of isoniazid and rifampicin resistance at baseline using Genotype MTBDR*plus* version 2.0 followed by ethambutol discontinuation if no resistance was detected (PCR arm) and (2) a standard 4-drug combination, pending phenotypic drug-susceptibility results (C arm). Adult patients with smear-positive pulmonary tuberculosis were enrolled. The primary endpoint was the proportion of patients with treatment success defined as bacteriological or clinical cure at the end of treatment. A non-inferiority margin of 10% was used.

Results. Two hundred three patients were randomized, 104 in the PCR arm and 99 in the C arm: 26.6% were female, median age was 37 (interquartile range, 28–51) years, 72.4% were born in Africa, and 5.4% were infected with human immunodeficiency virus. Chest x-ray showed cavities in 64.5% of the cases. Overall, 169 patients met criteria of treatment success: 87 of 104 (83.7%) in the PCR arm and 82 of 99 (82.8%) in the C arm with a difference of +0.8% (90% confidence interval, −7.9 to 9.6), meeting the noninferiority criteria in the intention-to-treat population ($P = .02$).

Conclusions. In a setting with low prevalence of primary isoniazid resistance, a 3-drug combination with isoniazid, rifampicin, and pyrazinamide, based on rapid detection of isoniazid resistance using molecular testing, was noninferior to starting the recommended 4-drug regimen.

Keywords. drug-susceptible tuberculosis; ethambutol; nucleic acid amplification.

Bacteriological diagnosis of tuberculosis and detection of *Mycobacterium tuberculosis* resistance has significantly improved with the implementation of nucleic acid amplification tests and the possibility of rapid identification of resistance to rifampicin and isoniazid [1–3]. Whether these tests can be used to personalize tuberculosis (TB) treatment in countries with low TB incidence and low isoniazid resistance is not known. One meta-analysis showed that, when compared with culture positivity, direct testing of sputum smear-positive specimens with the Hain line probe assay Genotype MTBDR*plus* version 2.0 (Hain Lifescience) had an 85.0% sensitivity and 98.8% specificity for detection of isoniazid resistance and a 98.0% sensitivity and a 97.8% specificity for detection of rifampicin resistance [2]. In France, where 5000 cases of TB are reported each year, in 2017 the rates of primary resistance to isoniazid and rifampicin were 6.6% and 1.7%, respectively [4]. Current French guidelines recommend initiating a 4-drug regimen containing isoniazid, rifampicin, pyrazinamide, and ethambutol, pending the results of phenotypic drug-susceptibility testing (DST) on positive cultures. Ethambutol is

Received 26 April 2022; editorial decision 12 July 2022; accepted 21 July 2022; published online 25 July 2022

[a]Presented in part: Journées Nationales d'Infectiologie, Nantes, France, 13–15 June 2018; ECCMID, Paris, France, 18–21 April 2020; Journées Nationales d'Infectiologie, Montpellier, France, 30 August–1 Septembre 2021.

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https://doi.org/10.1093/ofid/ofac353

used as a companion drug to prevent the emergence of rifampicin resistance in case of isoniazid monoresistance [5, 6]. In case of susceptibility to all first-line tuberculosis drugs, it is recommended to discontinue ethambutol, which is in line with other guidelines [5, 6]. This strategy leads to the unnecessary treatment with ethambutol of up to 90% of tuberculosis cases in France, with potential toxicity and increased pill burden because ethambutol is not included in the anti-TB fixed-dose combination used in France (Rifater).

In this study, we assessed whether detection of resistance within the first week of tuberculosis treatment using a nucleic acid amplification test would allow personalized and simplified treatment of fully susceptible tuberculosis. The objective of the trial was to assess, in patients initiating treatment for pulmonary tuberculosis in a low-incidence setting, the noninferiority of adapting tuberculosis treatment derived from polymerase chain reaction (PCR)-based early detection of isoniazid and rifampicin resistance (Genotype MTBDR*plus* version 2.0), compared with continuing the conventional standard 4-drug combinations while waiting for phenotypic drug-susceptibility testing on culture-positive specimens.

METHODS

FAST-TB, a phase 4, multicenter, open-label, noninferiority, randomized trial, was conducted in 32 clinical centers in France (Supplementary Material). We enrolled adult patients (aged 18 to 85 years old) with suspicion of active pulmonary tuberculosis and a smear-positive respiratory sample on microscopic examination for acid-fast bacilli and were therefore eligible for a standard tuberculosis treatment. In France, tuberculosis treatment consists of fixed-dose combination (Rifater) of isoniazid (3–5 mg/kg per day), rifampicin (8–12 mg/kg per day), and pyrazinamide (25–30 mg/kg per day) with separate additional tablets of ethambutol (15–20 mg/kg per day). The main exclusion criteria were as follows: prior history of tuberculosis treatment, pregnancy or breastfeeding, patient without national healthcare insurance (as required by the French regulation), and tuberculosis treatment started more than 3 days before inclusion or if results of cultures were available at enrollment (for full eligibility and noneligibility criteria, see the full protocol in the Supplementary Materials).

Participants starting tuberculosis treatment were randomly assigned (1:1) to either the PCR-based treatment (PCR group) or the conventional treatment (C group). The randomization was stratified by center and by human immunodeficiency virus (HIV) status. After completing the electronic Case Report Form (e-CRF) inclusion module, patients were randomized and their allocated group was communicated to the investigator (C or PCR group). There was no masking in this study (Supplementary Materials).

In the PCR-based treatment, within the first 7 days of tuberculosis treatment, the line probe assay Genotype MTBDR*plus* version 2.0 was used to detect isoniazid and rifampicin resistance directly on a smear-positive respiratory sample, and patients discontinued ethambutol if no resistance was detected. If the test was not contributive (indeterminate result or test not performed), patients would continue ethambutol until phenotypic drug-susceptibility testing was available. Phenotypic drug-resistance testing was performed on all samples in the PCR arm, regardless of result of line probe assay. In the C group, clinicians waited for the results of phenotypic drug-resistance testing for first-line tuberculosis drugs on cultures (liquid or solid media) as per national guidelines.

Patient Consent Statement

All participants provided signed informed consent before enrollment. The protocol was approved by the National Ethics committee (Comité de Protection des Personnes Ile de France I on May 5, 2014, IDRCB2013-A01406-39). The study is registered in ClinicalTrials.gov (Identifier NCT02231229).

Outcomes

The primary outcome was the proportion of participants with treatment success at the end of tuberculosis treatment or at the latest at 12 months after inclusion in the study. Treatment success was defined as either bacteriological cure (a patient with bacteriologically confirmed tuberculosis at the beginning of treatment who became smear or culture negative in the last month of treatment and on at least 1 previous occasion) or clinical cure (a patient with clinical response who completed treatment but did not meet the criteria of bacteriological cure). (See the full protocol in the Supplementary Material.)

The main secondary outcomes were as follows: proportion of patients with bacteriological cure or clinical cure, proportion of bacteriological and clinical cure among patients with cavities, proportion of treatment failure or relapse within 12 months after treatment completion, response to treatment without ethambutol compared with standard treatment for drug-susceptible tuberculosis, and incidence of grade 3 or 4 adverse events and deaths. Tuberculosis treatment outcomes were adapted from World Health Organization definitions [7].

Statistical Analysis

The proportion of patients with treatment success in the C arm was estimated to be approximately 80% in the intention-to-treat population (taking into account nonevaluable patients). We set a noninferiority margin of 10% in terms of difference of proportion of treatment success between both arms. Thus, the sample size of 198 patients per group was needed in a noninferiority trial with a 5% type I error and a power of 80%. We did not take into account resistance levels for sample size calculation because resistance was not our primary outcome. Proportions of treatment success were compared between the 2 arms using a 1-sided score test (Farrington-Manning) with a 5% type I error [8].

The primary noninferiority analysis was performed in the intention-to-treat population, which included all randomized patients. We did not use a modified intention-to-treat population excluding patients with nontuberculous mycobacteria (NTM) because our goal was to evaluate a strategy using direct detection of resistance on smears to adapt treatment and excluding patients with NTM might have favored the PCR arm. The on-treatment (per-protocol) population included all patients who were still on follow up at the end of tuberculosis treatment, with the exclusion of patients with NTM, patients lost-to follow up, patients withdrawing from the study, or patients with resistance not available at baseline in the PCR arm.

The duration of the study was extended from 24 to 42 months, but as of January 2018, only half of the participants had been randomized. The trial Scientific Committee and the sponsor decided to stop the inclusions because the rhythm of patients' enrollment would not allow us to complete recruitment in due time. Ethambutol treatment duration was described in both arms by Kaplan-Meier curves. Patients lost to follow up or who withdrew from the study are censored at the date of first missed visit. The curves were compared by a log-rank test. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

Between July 2014 and January 2018, 203 patients were randomly assigned to the C arm (n = 99) or the PCR arm ($n = 104$), all were included in the intention-to-treat analysis, and 165 patients were included in the per-protocol analysis: 83 in the C arm and 82 in the PCR arm. Various elements explain the low number of patients included: the main reasons were lack of health insurance, refusal to participate, previous tuberculosis treatment, age >85 years, and social vulnerability that might compromise compliance to study procedures (Figure 1). The median duration of follow up in the study was 481 days (interquartile range [IQR], 381–533): 533 days (IQR, 414–548) in the PCR arm and 383 days (IQR, 362–518) in the C arm ($P = .20$).

Overall, patients' baseline characteristics were well balanced across trial arms (Table 1): 26.6% were female, median age was 37 years (IQR, 28–51), and 72.4% originated from sub-Saharan Africa. The most frequent comorbidity was diabetes, present in 10.8% of the participants, and 5.4% were HIV coinfected; 55.9% of the patients were active or former smokers. The type of respiratory samples collected to diagnose tuberculosis was predominantly sputum (88.2%). At tuberculosis presentation, 98.5% of the patients presented with abnormal chest x-ray with 64.5% of cavities and more than one third of bilateral involvement (Table 2).

In the intention-to-treat analysis, at the end of tuberculosis treatment, 82 of 99 (82.8%) in the C arm and 87 of 104 (83.7%) in the PCR arm achieved treatment success. The difference in the proportion of success was 0.8% (90% confidence interval [CI], −7.9% to 9.6%), thus PCR-based treatment strategy was noninferior to conventional treatment strategy ($P = .021$). In the per-protocol analysis, noninferiority of the PCR-based strategy was also demonstrated (Table 3).

In patients with cavities on chest x-ray or computed tomography scan at baseline, noninferiority of the PCR-based strategy was shown with a proportion of treatment success of 48 of 55 (87.3%) in the C arm and 61 of 71 (87.3%) in the PCR arm, with a between-group difference of 0.1% (90% CI, −9.8% to 9.9%; $P = .047$).

One patient interrupted treatment for more than 2 months in the PCR arm (in this patient, nontuberculous mycobacteria was identified). Five patients died while on tuberculosis treatment: 3 of 99 (3.0%) patients of the C arm and 2 of 104 (1.9%) patients of the PCR arm, but no death was considered to be related to tuberculosis. The proportion of patients that could not be evaluated at the end of tuberculosis treatment was similar in both arms: 14 of 99 (14.2%) patients of the C arm and 15 of 104 (14.4%) patients of the PCR arm. For 2 patients in the C arm, after tuberculosis treatment interruption, clinicians decided to resume treatment for suspicion of relapse; no resistance was detected in these 2 cases. Detailed causes of death are reported in Supplementary Table S1, and patients' outcomes are reported in Figure 2 and Supplementary Table 4.

The median duration of tuberculosis treatment was 187 days (IQR, 182–240), with no difference between arms: 189 days (IQR, 183–230) in the C arm and 186.0 days (IQR, 181–255) in the PCR arm ($P = .99$). The median duration of ethambutol treatment was 31 days (IQR, 5–63), but it was significantly longer in the C arm: 61 days (IQR, 33–70) compared with 5 days (IQR, 1–10) in the PCR arm (log rank, $P = <.001$) (Supplementary Figure 1).

Among the 203 patients of the study, 198 had at least 1 specimen with a positive culture. Of the 198 positive cultures 188/198 (95.9%) were positive for *M tuberculosis*, 1 for *Mycobacterium bovis*, 1 for *Mycobacterium africanum*, and 8 for nontuberculous mycobacteria. Phenotypic drug resistance testing was available for all 188 specimens with a culture positive for *M tuberculosis* and identified 1 case of rifampicin resistance (in the C arm), 7 cases of isoniazid resistance (5 in the C arm and 2 in the PCR arm that had been detected by Genotype MTBDR*plus* version 2.0 at baseline), 2 cases of ethambutol resistance, and 1 case of pyrazinamide resistance. In the intention-to-treat analysis, 73 of 86 (84.8%) patients with culture-positive multisensitive strains in the C arm and 79 of 91 (86.8%) in the PCR arm achieved treatment success (Supplementary Table S2).

In the PCR arm, Genotype MTBDR*plus* version 2.0 was performed at baseline in 99 of 104 (95.2%) participants according

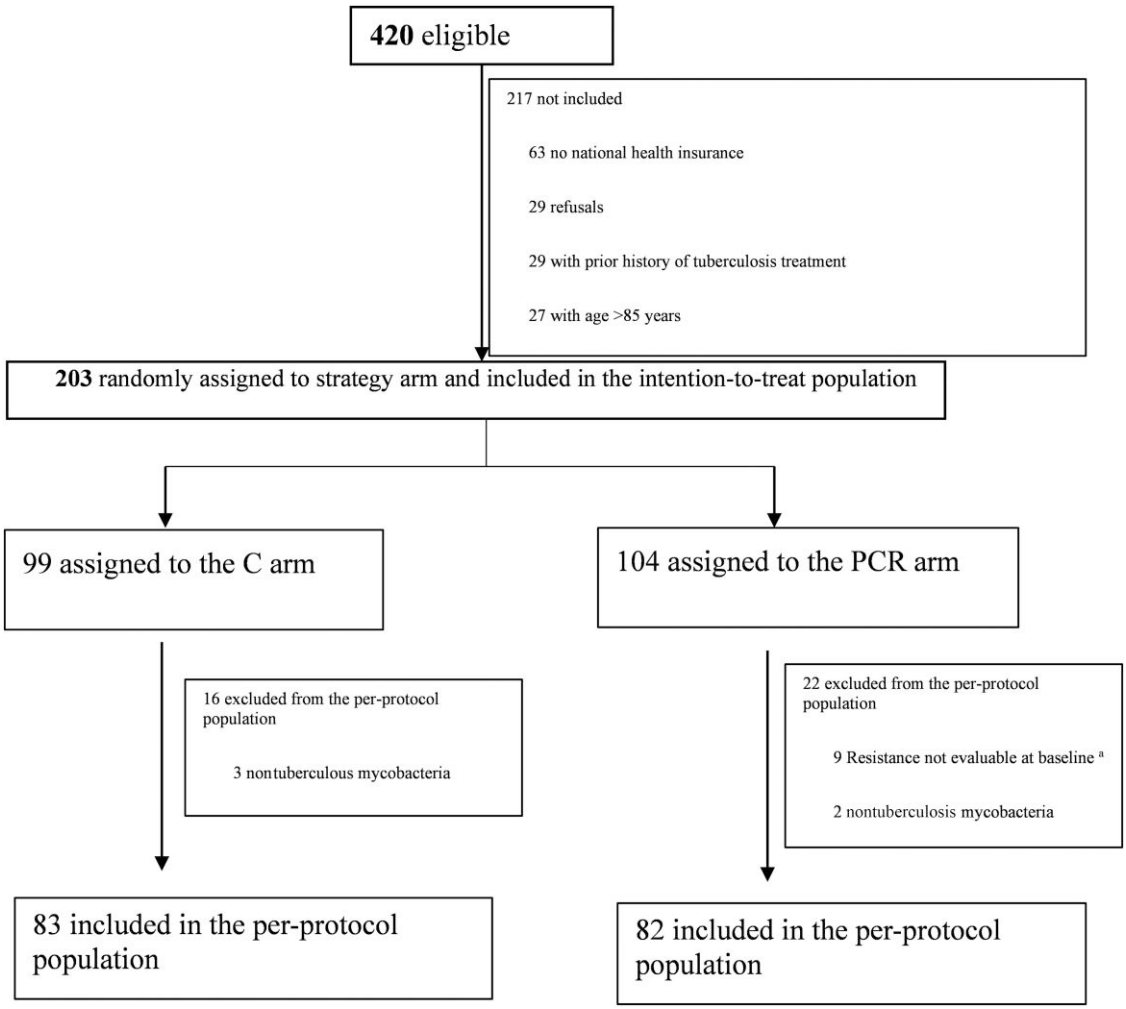

Figure 1. Study flow chart. [a]Protocol violation: polymerase chain reaction (PCR) Genotype MTBDR*plus* not performed or not contributive. C arm: conventional treatment arm.

to study procedures; for the remaining 5 patients, the test was not performed. Isoniazid resistance was detected in 3 cases at baseline: 2 were confirmed by DST, and for 1 case DST was not contributive (Supplementary Table S3). For these 3 patients, treatment was adapted based on the result at day 4, day 6, and day 8 after the beginning of treatment. The number of patients with at least 1 grade 3 or 4 adverse event was similar in both arms: 19 in the C arm and 18 in the PCR arm, and most of them were not related to tuberculosis treatment (Supplementary Table S5).

Hepatotoxicity was reported in 8 patients (3 in the C arm and 5 in the PCR arm), leading to permanent pyrazinamide discontinuation in most patients (5 cases) and isoniazid discontinuation in 2 patients (subsequently resumed for 1 patient). Ethambutol-related optic toxicity was suspected based on visual tests in 2 patients in the C arm (without clinical visual impairment) and led to ethambutol discontinuation (Supplementary Table S3).

DISCUSSION

In patients with sputum smear-positive tuberculosis without prior history of tuberculosis treatment, we demonstrated that withholding ethambutol during the first week of treatment, based on isoniazid genotypic susceptibility testing, was noninferior to withholding ethambutol based on isoniazid phenotypic susceptibility testing. We found that treatment success was close to 83% in both arms, and the main reason for failure at the end of tuberculosis treatment was nonevaluable patients.

We observed that clinicians apply national guidelines with respect to ethambutol treatment because the median duration of ethambutol therapy in the conventional treatment arm was 61 days. The delay to obtain results of phenotypic drug susceptibility is usually 4 to 8 weeks, which explains why ethambutol is continued for the 2-month duration of the intensive phase. In France, ethambutol is not included in the fixed-drug combination Rifater and is given separately with 2 or 3 supplementary

Table 1. Baseline Characteristics of 203 Patients in the Intention-to-Treat Population

	Total ($n = 203$)	C Arm ($n = 99$)	PCR Arm ($n = 104$)
Female	54/203 (27%)	25/99 (25%)	29/104 (28%)
Age (years)	37.0 [28.0–51.0]	37.0 [28.0–47.0]	39.5 [28.5–53.0]
Region of Origin			
Western Europe	58/203 (28.6%)	23/99 (23%)	35/104 (34%)
Sub-Saharan Africa	105/203 (51.7%)	53/99 (54%)	52/104 (50%)
Asia, Middle East	21/203 (10.3%)	15/99 (15%)	6/104 (6%)
Central/South America	3/203 (1.5%)	1/99 (1%)	2/104 (2%)
Central/Eastern Europe	16/203 (3.9%)	7/99 (7%)	9/104 (8.7%)
Comorbidities			
HIV infection	11/203 (5%)	5/99 (5%)	6/104 (6%)
Positive for hepatitis B virus surface antigen[a]	11/189 (6%)	4/93 (4%)	7/96 (7%)
Positive for hepatitis C virus antibodies[b]	5/190 (3%)	2/94 (2%)	3/96 (3%)
Diabetes	22/203 (11%)	10/99 (10%)	12/104 (12%)
Kidney failure	2/203 (1%)	2/99 (2%)	0/104 (0%)
Cancer	6/203 (3%)	0/99 (0%)	6/104 (6%)
Past or current smoker (1 missing data)	113/202 (56%)	53/98 (54%)	60/104 (58%)
Clinical Presentation			
BMI < 18.5 kg/m²[c]	68/190 (36%)	34/96 (35%)	34/94 (36%)
Cough[d]	186/200 (93%)	89/97 (92%)	97/103 (94%)
Dyspnea	88/203 (44%)	39/99 (40%)	49/103 (48%)
Temperature > 38°C	58/203 (29%)	26/99 (27%)	32/103 (31%)
Type of Sample Smear Positive for Acid-Fast Bacilli			
Sputum	179/203 (88%)	87/99 (88%)	92/104 (89%)
Bronchoaspiration/BAL	13/203 (6%)	6/99 (6%)	7/104 (7%)
Gastric aspirates	11/203 (5%)	6/99 (6%)	5/104 (5%)

Abbreviations: AFB, acid-fast bacilli; BAL, bronchoalveolar lavage; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; PCR, polymerase chain reaction.

NOTE: Data are n (%), median [IQR].

[a]14 missing data.

[b]13 missing data.

[c]13 missing data.

[d]3 missing data.

tablets, based on participants weight. Although we were not able to measure the impact of pill burden on adherence and treatment outcomes, ethambutol discontinuation resulted in the reduction in the number of pills taken, which may improve treatment convenience for the patients.

We found a low level of primary resistance to isoniazid and rifampicin detected by drug sensitivity testing on cultures at 3.7% for isoniazid resistance and 0.5% for rifampicin, which was lower than that reported in a recent French study [9]. For the 3 patients with isoniazid resistance detected at baseline in the PCR arm, treatment was adapted within the first week of treatment.

Rapid molecular detection of resistance to isoniazid on smear-positive respiratory samples is not standard of care in most countries. Different nucleic acid amplification tests can be used for the diagnosis of resistance, but data from prospective studies on their clinical performance are lacking [2, 3, 10, 11]. To detect isoniazid resistance, retrospective studies showed that Genotype MTBDR*plus* version 2.0 had only 84% sensitivity but 98% specificity on smear-positive respiratory samples compared with cultures [12]. To our knowledge, only 1 prospective clinical trial confirmed those results with an 86% sensitivity and 97.8% specificity for isoniazid resistance detection. Indeed, Jo et al [13] showed that early testing on respiratory smears or positive cultures with Genotype MTBDR*plus* version 2.0 allowed a reduction in the median duration of ethambutol treatment from 75 to 14 days, with no negative impact on treatment success. Our population was different from this South Korean study given that we only enrolled smear-positive tuberculosis, because our aim was to detect resistance in the very first days after tuberculosis diagnosis to allow us to start an ethambutol-free regimen. We also showed that despite the relative lack of sensitivity of Genotype MTBDR*plus* version 2.0 to detect isoniazid resistance, in the French context of low prevalence of isoniazid monoresistance, adapting the treatment to the results had no negative impact on treatment success. Of note, no isoniazid-resistant case was missed by Genotype MTBDR*plus* version 2.0 in the PCR arm. Moreover, the test identified 1 case of resistance to isoniazid that was missed by the standard DST, which might have prevented subsequent emergence of rifampicin resistance.

Table 2. Tuberculosis Clinical, Radiological, and Bacteriological Description of 203 Patients in the Intention-to-Treat Population

	Total ($n=203$)	C Arm ($n=99$)	PCR Arm ($n=104$)
Pulmonary TB	203/203 (100%)	99/99 (100%)	104/104 (100%)
Other Thoracic Location			
Hilar lymphadenopathy[a]	34/202 (17%)	18/98 (18%)	16/104 (15%)
Pleural	8/203 (4%)	3/99 (3%)	5/104 (5%)
Pericardial	2/203 (1%)	0/99 (0%)	2/104 (2%)
Radiological Presentation			
Abnormal chest x-ray[b]	194/197 (99%)	94/95 (99%)	100/102 (98%)
Cavitations	126/194 (65%)	55/94 (59%)	71/100 (71%)
Bilateral infiltrates/ nodules	65/194 (34%)	34/94 (36%)	31/100 (31%)
Miliary	7/194 (4%)	3/94 (3%)	4/100 (4%)
Pleural effusion	14/194 (7%)	5/94 (5%)	9/100 (9%)
Culture positive for *Mycobacterium tuberculosis*[c]	188/190 (99%)	93/93 (100%)	95/97 (98%)
Drug susceptibility testing (phenotypic)	188/188 (100%)	93/93 (100%)	95/95 (100%)
Rifampicin resistance	1/188 (0.5%)	1/93 (1%)	0/95 (0%)
Isoniazid resistance	7/188 (4%)	5/93 (5%)	2/95 (2%)
Pyrazinamide resistance	1/188 (0.5%)	0/93 (0%)	1/95 (1%)
Ethambutol resistance	3/188 (1.5%)	1/93 (1%)	2/95 (2%)

Abbreviations: PCR, polymerase chain reaction; TB, tuberculosis.

[a]1 missing data.

[b]6 missing data.

[c]Among the 203 patients, 7 had negative cultures culture for mycobacteria (3 in the C arm and 4 in the PCR arm), 5 were positive for non-TB mycobacteria (3 in the C arm and 2 in the PCR arm), and in 1 case culture result was missing (C arm).

We found that the proportion of patients with extensive pulmonary disease who responded to treatment was also similar in both groups (83%–84%), confirming that adding ethambutol to isoniazid, rifampicin, and pyrazinamide did not provide supplementary bactericidal and sterilizing activities for the treatment of drug-sensitive tuberculosis [14, 15]. However, as a companion drug to rifampicin, previous studies showed that ethambutol prevents relapse and potentially emergence of additional resistance in case of isoniazid resistance when doses used are 30% to 40% higher than the doses currently recommended or with an 8-month duration of ethambutol treatment [16, 17].

Hepatic intolerance of tuberculosis drugs was 4%, in the range of what is expected in such populations, leading to permanent discontinuation of either pyrazinamide or isoniazid [18, 19]. Ethambutol ophthalmologic toxicity was 2%, but the patients in our study were at low risk for ethambutol toxicity with 75% of the patients aged less than 50 years, and patients older than 85 years or with severe renal impairment were not eligible to participate.

Our study has several limitations. Patients without health insurance could not be included in this trial as required by the French health authorities. As a result, slow accrual rate led us to stop inclusions. However, the noninferiority was reached with only half of the participants scheduled. Because isoniazid resistance is low in France, we designed this trial knowing that the risk to miss a resistant case would be minimal given the 85% sensitivity of Genotype MTBDRplus version 2.0 for isoniazid resistance detection. Because it was not standard of care in France due to the lack of evidence, we wanted to demonstrate

Table 3. Primary Endpoint Results for the 203 Participants: Treatment Outcome

	C Arm % [95% CI]	PCR Arm % [95% CI]	Scale Difference % [95% CI]	*P* Value[a]
Intention-to-treat population	n = 99	n = 104		
Primary endpoint: Treatment success[b]	82.8 [75.4–90.3]	83.7 [76.6–90.3]	0.8 [−7.9 to 9.6]	.021
Secondary Endpoints				
Bacteriologically cured[c]	37.4 [27.8–46.9]	38.5 [29.1–47.8]	1.1 [−10.1 to 12.3]	.051
Clinically cured and treatment completed	45.5 [35.4–55.8]	45.2 [35.4–55.3]	−.3 [−11.7 to 11.2]	.081
With cavitation on imaging studies	n = 55	n = 71		
Treatment success	87.3 [75.5–94.7]	87.3 [77.3–94.0]	.1 [−9.8 to 9. 9]	.047
Per protocol population	n = 83	n = 82		
Primary endpoint: Treatment success[b]	97.6 [91.6–99.7]	97.6 [91.5–99.7]	.0 [−6.11 to 6.1]	.004
Secondary endpoints				
Bacteriologically cured[c]	44.6 [33.7–55.9]	46.3 [35.3–57.7]	1.8 [−10.9 to 14.5]	.064
Clinically cured and treatment completed	53.0 [41.7–64.1]	51.2 [39.9–62.4]	−1.8 [−14.5 to 10.9]	.145
With cavitation on imaging studies	n = 48	n = 57		
Treatment success	97.9 [88.9–99.9]	100 [93.7–100.0]	2.1 [−5.1 to 9.2]	.003

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[a]Farrington Manning Non-inferiority test.

[b]Treatment success was defined as clinical cure in a patient who completed treatment or bacteriological cure confirmed by culture conversion as per World Health Organization definition.

[c]Bacteriologically cured (smear and culture negative twice).

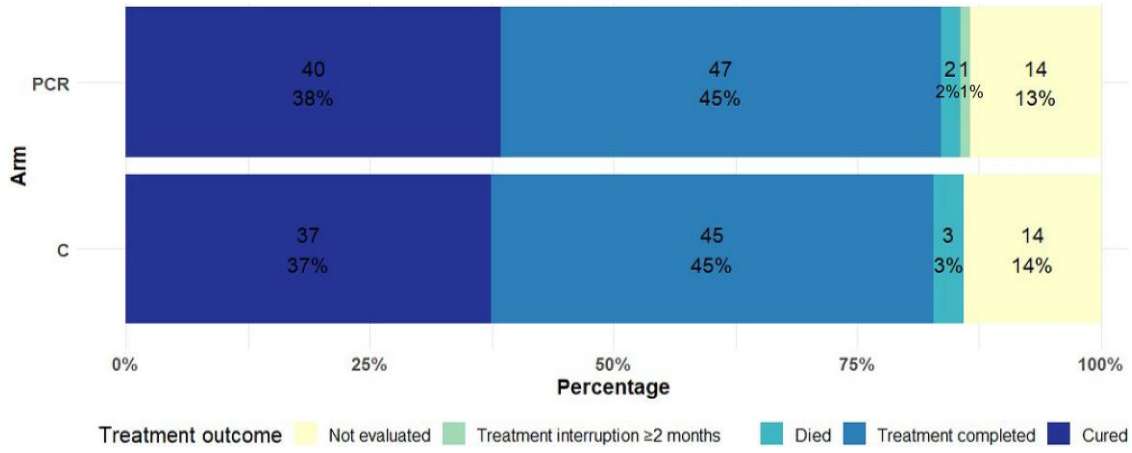

Figure 2. Tuberculosis treatment outcomes according to World Health Organization criteria (intent-to-treat population). C arm: conventional treatment arm. PCR, polymerase chain reaction.

that it was feasible in this context to perform the test directly on smear samples without impairing treatment outcomes. The participants of our study had no history of prior tuberculosis treatment, and the clinicians could choose not to enroll patients with suspicion of resistance or severely ill patients for whom they were willing to start a standard 4-drug combination. We also excluded patients who might be more difficult to treat due to treatment-related toxicities such as participants older than 85 years. Our results may thus be difficult to extrapolate to patients who are at higher risk for resistance to isoniazid and/or rifampicin and more severe patients. A previous French study showed that during tuberculosis treatment in the Paris area, the proportion of nonevaluable patients could be as high as 20% and increases with the vulnerability of the patients [20]. Although it was lower than the expected rate of lost to follow up, the rate of nonevaluable patients in our study was 15%, and relapse rates after the end of tuberculosis treatment might therefore be underestimated.

CONCLUSIONS

In conclusion, our study demonstrated that early detection of isoniazid resistance is feasible in real-life conditions to personalize treatment and start an ethambutol-free regimen in patients at low risk for isoniazid resistance. This strategy was noninferior to the standard 4-drug combination and ethambutol discontinuation based on phenotypic DST results. Our findings might not be generalizable to other areas with higher levels of resistant tuberculosis, but we showed that clinical decision can be guided by the results of nucleic acid amplification tests before patients are discharged from the hospital. The conduct of clinical trials in countries with low incidence of tuberculosis is challenging but remains necessary to address the specificities of the vulnerable populations affected by tuberculosis in these settings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We thank all the participants of this trial for their commitment. We also thank the members of Coordinating Clinical Trials Unit (Unité de Recherche Clinique Paris Nord Val de Seine, Assistance Publique-Hôpitaux de Paris Hôpital Bichat, Paris): Khadidja Amrani, Tristan Delory, Candice Estellat, Sonia Makhlouf, Yohan Maurer, Ophélie Rogier, Marion Schneider. Finally, we thank the members of the independent data and safety monitoring committee and the FAST-TB study group (members listed in the Supplementary Appendix).

Author contributions. N. D. C., Y. Y., C. L., D. B., P. T., N. V., and J. M. M. conceived and designed the study. N. D. C., Y. Y., C. L., D. B., P. T., N. V., and N. G. contributed to the interpretation of the results. F. M., A. C., V. J., N. D. C., M. V., D. Bo., J. M. M., and M. K. implemented the study in the centers and enrolled participants. D. Ba. performed statistical analysis. D. Ba. and C. L. prepared the report. N. D. C. wrote the first draft, and all authors reviewed and approved the final version of the report and the manuscript. N. D. C., C. L., and Y. Y. had full access to all the data during the study and had the final responsibility for the decision to submit for publication.

Disclaimer. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Financial support. This work was funded by the French Ministry of Health (PHRC n°P 120130/N°AOM12317). The sponsor of the study was Assistance Publique-Hôpitaux de Paris and its clinical research department (Département de la Recherche Clinique et du Développement).

Potential conflicts of interest. N. D. C. received a research Grant from Gilead in 2015, unrelated to the present work. N. V. works in a laboratory that received a grant from Janssen outside the scope of this work. N. V. provided consultation service to Insmed outside the scope of this work. N. V. received speaker honoraria from Insmed outside the scope of this work. N. V. provided expert testimony to Insmed outside the scope of this work. N. V. provided expert advice for Becton-Dickinson on in vitro diagnostic tests for tuberculosis. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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