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Pulmonary Tuberculosis in People with HIV: A Cross-sectional Study on the Characteristics Associated with the Negative Result of GeneXpert® MTB/RIF

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Research Article

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Abstract

This is a cross-sectional study which sought to analyze the effectiveness of the GeneXpert® MTB/RIF test and the characteristics of pulmonary tuberculosis (TB) cases associated with the negative test result among people with HIV co-infection. The study was conducted in the state of São Paulo, Brazil, and the data were collected from the Information System in TB. The highest occurrence of negative result among the cases that performed the test was observed among: people aged 60 or older (PR 1.53; CI95% 1.22-1.93); females (PR 1.24; CI95% 1.08-1.41); miliary TB (PR 1.99; CI95% 1.55-2.56); X-ray image suggestive of other pathologies (PR 1.83; CI95% 1.16-2.87); non-smokers (PR 1.20; CI95% 1.03-1.39); non-alcohol users (PR 1.21; CI95% 1.03-1.42); and non-users of illicit drugs (PR 1.33; CI95% 1.15-1.53). Thus, people with these characteristics deserve more attention when they present respiratory symptoms suggestive of TB in healthcare facilities.

Keywords: Tuberculosis, HIV, Diagnosis, Molecular Diagnostic Techniques

INTRODUCTION

According to the World Health Organization (WHO), about 9.9 million people developed tuberculosis (TB) in 2020, among which 800 thousand presented co-infection with the human immunodeficiency virus (HIV). In this scenario, Brazil remains among the 30 countries with the highest TB and TB/HIV co-infection burden, and is considered a priority for control of the disease in the world [1]. According to the Ministry of Health, the country reported 82,680 cases of TB in 2021 and 4,543 deaths from the disease in 2020 [2]. Approximately 25% of the cases notified in Brazil belong to the state of São Paulo [3]. The Sustainable Development Goals (SDG) include ending the global TB endemic (among other goals). The challenge is to reduce 90% of the mortality rates and 80% of the incidence rates by 2030 in order to eliminate the disease by 2050. In this sense, WHO reinforces the need for early and accurate case detection in the End-TB Strategy [4], using faster and more sensitive diagnostic tools to diagnose TB, especially in people with HIV infection [1]. As a result, efforts have been made to boost the development and implementation of new and better diagnostic techniques for TB [5,6].

It is noteworthy that conventional and widely used diagnostic techniques in the country by 2014 consisted of sputum smear microscopy (developed over 125 years ago [5]), culture, and phenotypic susceptibility tests. However, sputum smear microscopy has low sensitivity, especially among TB/HIV co-infection cases. Culture, and phenotypic susceptibility tests have some limitations due to the complexity of these exams which require technical staff, qualified laboratories and an extended time to make their results available. The limitations of these tests corroborate with inadequate and late treatment, thus favoring the increase in TB morbidity and mortality [7]. In recognizing the need for faster, simpler, safer, and effective technologies for the diagnosis of TB, the Rapid Molecular Test for TB (RMT-TB) represented a significant advance to detect the disease [8]. From its approval by WHO in 2010

and its incorporation into the Brazilian Unified Health System (SUS) in 2014, the laboratory confirmation rate of new pulmonary TB cases increased from 73.9% to 83.2% in the state of São Paulo between 2006 and 2020 [3]. GeneXpert® MTB/RIF is the RMT-TB used in Brazil. It is a simple method requiring minimal technical knowledge for its accomplishment, in addition to being sensitive and specific [6], even enabling the detection of resistance to rifampicin and testing unsuccessful sputum samples or samples of extrapulmonary sites [5]. Given this, the WHO has recommended using RMT-TB to replace the sputum smear microscopy, especially in places with high TB multidrug-resistant rates, limited resources, and high prevalence of TB/HIV co-infection [9].

In a literature review [10], it was possible to identify that the sensitivity of GeneXpert® MTB/RIF in diagnosing pulmonary TB in people living with HIV ranged between 68% [11] and 100% [12], being higher when compared to sputum smear microscopy [13,14]. However, the lowest sensitivity found (68%) indicates that many TB/HIV co-infection cases may still have a negative result in the GeneXpert® MTB/RIF due to the lowest chance of cave formation and more interstitial pulmonary involvement, and greater possibility of extrapulmonary forms of the disease in this population [11]. As a result, this study intended to analyze the effectiveness of the GeneXpert® MTB/RIF test and the characteristics of pulmonary tuberculosis cases associated with the negative test result among people with HIV co-infection. Considering the second part of the objective, the study sought to test the hypothesis that there are characteristics associated with the negative result of the GeneXpert® MTB/RIF test among people with HIV co-infection.

MATERIALS AND METHODS

A cross-sectional study was conducted in the state of São Paulo which has an estimated population of almost 47 million inhabitants. RMT-TB equipment (GeneXpert® MTB/RIF) was implemented in 18 municipalities of the state in 2014 and 2015 (capital: São Paulo; countryside of São Paulo: Araçatuba, Bauru, Bragança Paulista, Campinas, Jundiaí, Marília, Presidente Prudente, Ribeirão Preto, São José do Rio Preto, Sorocaba, Taubaté e Tremembé; metropolitan area of São Paulo: Barueri, Carapicuíba, Guarulhos, Franco da Rocha, Itapecerica da Serra, Santo André e São Bernardo do Campo; coast of São Paulo: Santos. Xpert MTB/RIF Ultra was introduced in these municipalities in 2019. All new cases of pulmonary TB residents in the state of São Paulo notified in the TB-WEB information system from 2014 to 2020 were considered as the study population. Inclusion criteria: individuals with an RMT-TB test result; pulmonary or miliary TB cases; and people with a positive result to the HIV test or with AIDS, or people who have already received antiretroviral therapy (ART). Individuals under the age of 18 were excluded from the study population.

A spreadsheet with data obtained from TB-WEB was made available for research in September 2021 by the São Paulo State Epidemiological Surveillance Center (CVE) “Prof. Alexandre Vranjac". The following variables were used to define the study population: type of case, municipality of residence, municipality of notification, clinical form of TB, HIV, AIDS, ART withdrawal, age, and the RMT-TB result. The following variables were considered to analyze the effectiveness of the GeneXpert® MTB/RIF test: RMT-TB result, sputum smear microscopy result, culture result, and susceptibility test result. Next, the exposure variables were grouped into sociodemographic variables (age group, race, gender, education, occupation) and clinical data (clinical form, X-ray result, diabetes mellitus, mental disorder, smoking, alcoholism, drug use, other immunological disease, no comorbidity) to analyze the characteristics associated with the negative result of the GeneXpert® MTB/RIF test.

The TB cases which initially had an RMT-TB result were characterized according to the year of diagnosis and residence region. Other data were analyzed using descriptive techniques, such as absolute and relative frequency distribution and central trend measures and variability, such as mean and standard deviation (sd).

Then, we compared the agreement of the GeneXpert® MTB/RIF test results with the sputum smear microscopy, culture, and susceptibility test results in order to analyze the test effectivity. Moreover, data analysis included the calculation of prevalence ratio (PR) and confidence intervals (CI95%) to evaluate the association between the outcome (negative RMT-TB result) and exposure variables, adopting a statistical significance level of 5%. In response to the recommendations of the resolution no. 466 of December 12, 2012 of the National Health Council (CNS), the study was approved by the Research Ethics Committee of the Ribeirão Preto College of Nursing, University of São Paulo, according to the decision no. 39861120.3.0000.5393.

RESULTS

A total of 125,738 TB cases who were living in the state of São Paulo were notified on the TB-WEB between 2014 and 2015. Of these, 18,806 cases were excluded because they were exclusively extrapulmonary TB, 88,336 because they had a negative result for HIV test, 9,425 because they did not have an anti-HIV examination, and 185 for being under 18 years old. Thus, a total of 8,986 pulmonary TB cases in people with HIV living in the state of São Paulo during the study period were considered in the study. According to the year of the diagnosis, there was an increase in RMT-TB percentage over the period studied from 5.9% in 2014, the year of the test implementation, to 54.5% in 2020. The municipality of São Paulo performed the most significant number of tests (44.0%), followed by the municipalities of the interior of São Paulo (31.8%) **(Table 1)**.

Table 1 Distribution of Rapid Molecular Tests for tuberculosis performed in the municipalities of the state of São Paulo, according to year of the diagnosis and residence region, 2014 to 2020.

Variables		Total cases	Number of tests conducted (%)
	2014	1,232	73(5.9)
	2015	1,224	414(33.8)
	2016	1,739	528(30.4)

Year of the diagnosis	2017	1,552	659(42.5)
	2018	1,160	568(49.0)
	2019	1,083	571(52.7)
	2020	996	543(54.5)
Residence region	São Paulo (Capital)	4,053	1.782(44.0)
	Countryside of São Paulo	2,730	869(31.8)
	Metropolitan area of São Paulo	1,309	379(29.0)
	Coast of São Paulo	894	326(36.5)

Among the 8,986 cases, 3,356 (37.3%) performed the RMT-TB, of which 17 presented an invalid result. Of the 3,339 cases that presented valid results, 2,529 (75.7%) presented a positive result to the test (2,418 sensitive to rifampicin, 47 with indefinite resistance, and 64 with confirmed resistance by RMT-TB), and 810 (24.3%) presented negative results.

A total of 482 (59.5%) of the people who presented negative results to the test did not have bacteriological confirmation by sputum smear microscopy and sputum culture. However, 429 (89.0%) performed an X-ray, and 402 (83.4%) presented a suggestive image of TB. The RMT-TB presented an agreement with sputum smear microscopy for 1,614 (71.9%) cases that performed both exams (1,164 positive and 450 negative cases). There was also an agreement with culture for 1,879 (77.8%) cases that performed both exams (1,584 positives and 295 negative cases) and with the susceptibility test in 1,236 (87.8%) cases that performed both exams (17 resistant cases of rifampicin and 1,219 rifampicin-sensitive cases). From positive cases to RMT-TB, 523 (31%) were negative for sputum smear microscopy, and 274 (14.7%) were negative for culture. Regarding negative cases for RMT-TB, 108 (19.3%) were positive for sputum smear microscopy and 262 (47.0%) for culture. There was a disagreement regarding the susceptibility test for the result of RMT-TB in 26 individuals, of which 23 (57.5%) were sensitive in the susceptibility test and resistant in RMT-TB, and 05 (0.4%) were resistant in test susceptibility and sensitive in RMT-TB **(Table 2)**.

Table 2 Distribution of rapid molecular tests performed in the municipalities of the state of São Paulo, according to smear, culture and sensitivity test results.

Variables		Positive RMT-TB n(%)	Negative RMT-TB n(%)
Smear test results	Positive	1,164(69.0)	108(19.3)
	Negative	523(31.0)	450(80.6)
Culture results	Positive	1,584(85.2)	262(47.0)
	Negative	274(14.7)	295(53.0)
Susceptibility test results*	Rifampicin resistent	17(42.5)	05(0.4)
	Rifampicin sensitive	23(57.5)	1,219(99.6)

The mean age of cases that presented a positive result for RMT-TB was 38.4 (sd 11.4) years with a minimum of 18 and a maximum of 87 years of age. The mean age among the cases with negative results was 40.2 (sd 12.4) years (minimum 18 and maximum 89). The highest occurrence of the negative result among the cases that performed RMT-TB was observed among people aged 60 or older (PR 1.53; CI95% 1.22-1.93) and females (PR 1.24; CI95% 1.08-1.41) **(Table 3)**.

Table 3 Distribution of Rapid Molecular Tests for tuberculosis (RMT-TB) performed in the municipalities of the state of São Paulo according to the test result and demographic variables, 2014 to 2020.

Variables		Positive RMT-TB n(%)	Negative RMT-TB n(%)	PR(CI95%)
Gender	Male	1,973(78.0)	589(72.7)	1
	Female	556(22.0)	221(27.3)	1.24(1.08-1.41)
Age group*	18 - 29	621(24.6)	176(21.7)	0.98(0.83-1.17)
	30 - 39	835(33.1)	242(29.9)	1
	40 - 49	635(25.1)	221(27.3)	1.15(0.98-1.35)
	50 - 59	319(12.6)	110(13.6)	1.14(0.94-1.39)
	60 and +	116(4.6)	61(7.5)	1.53(1.22-1.93)
Race*	Brown	998(43.4)	299(40.4)	1
	White	944(41.1)	335(45.3)	1.14(0.99-1.30)
	Black	346(15.1)	101(13.6)	0.98(0.80-1.20)
	Yellow/Indigenous	9(0.4)	5(0.7)	1.55(0.76-3.15)

PR= Prevalence Ratio; CI 95%= 95% Confidence Interval

*Invalid responses (blank/ignored) of the study variables were not considered for the analysis, so the sample size in some analyzes did not correspond to the total population included in the study.

The highest occurrence of the negative result among the cases that performed the RMT-TB was observed among people with the miliary clinical form (PR 1.99; CI95% 1.55-2.56), with a suggestive image of other pathologies to X-ray (PR 1.83; CI95% 1.16-2.87), and among non-smokers (PR 1.20; CI95% 1.03-1.39), non-alcohol users (PR 1.21; CI95% 1.03-1.42) and non-users of illicit drugs (PR 1.33; CI95% 1.15-1.53) **(Table 4)**.

Table 4 Distribution of Rapid Molecular Tests for tuberculosis (RMT-TB) performed in the municipalities of the state of São Paulo, according to the test result and clinical variables, from 2014 to 2020.

Variables		Positive RMT-TB n(%)	Negative RMT-TB n(%)	PR(CI95%)
Cinical form	Pulmonar	2,491(98.5)	776(95.8)	1
	Miliary	38(1.5)	34(4.2)	1.99(1.55-2.56)
X-ray result*	Normal	125(6.8)	58(9.0)	1.29(0.96-1.74)
	Suggestive of TB	1,483(80.9)	505(78.4)	1.03(0.83-1.29)
	Suggestive of TB with cavity	209(11.5)	68(10.6)	1
	Suggestive of other pathologies	16(1.0)	13(2.0)	1.83(1.16-2.87)
Diabetes mellitus	Yes	78(3.0)	27(3.3)	1
	No	2,451(96.9)	783(96.7)	0.94(0.68-1.31)
Mental disorder	Yes	38(1.5)	13(1.6)	1
	No	2,491(98.5)	797(98.4)	0.95(0.59-1.53)
Smoking	Yes	615(24.3)	164(20.2)	1
	No	1,914(75.7)	646(79.7)	1.20(1.03-1.39)
Alcoholism	Yes	557(22.0)	146(18.0)	1
	No	1,972(78.0)	664(82.0)	1.21(1.03-1.42)
Drug use	Yes	771(30.5)	189(23.3)	1
	No	1,758(69.5)	621(76.7)	1.33(1.15-1.53)
Other immunological diseases	Yes	22(0.9)	8(1.0)	1
	No	2,507(99.1)	802(99.0)	0.91(0.50-1.65)
No comorbidity	Yes	90(3.5)	24(3.0)	0.86(0.60-124)
	No	2,439(96.4)	786(97.0)	1

PR= Prevalence ratio; $CI_{95\%}$= 95% Confidence interval
*Invalid responses (blank/ignored) of the study variables were not considered for the analysis, so the sample size in some analyzes did not correspond to the total population included in the study.

DISCUSSION

A progressive increase in the RMT-TB percentage was observed in the state of São Paulo over the studied period. Early diagnosis of TB is one of the first pillars of the End-TB Strategy, which advocates to an integrated and person-centered treatment and prevention [4]. The laboratory confirmation rate increased after implementing RMT-TB in the state of São Paulo in 2014 and 2015 [3]. The municipality of São Paulo, which concentrates approximately 25% of the state's population, performs the highest percentage of RMT-TB (44.0%), while the interior municipalities performed 31.8% of the tests. The public health system offers free actions focused on the diagnosis and treatment of TB. However, exposure to conditions of higher vulnerabilities to the disease, such as homeless situation, detention, and use of drugs significantly contributes to the increased demand for the case screening actions. This perspective is evident in large population municipalities, such as São Paulo, which together with the floating daily population impacts the number of RMT-TB.

GeneXpert® MTB/RIF represented a significant advance in TB screening, increasing the discovery of cases compared to sputum smear microscopy [15]. A study showed that GeneXpert® MTB/RIF had overcome sputum smear microscopy in case detection, regardless of serological status for HIV [16]. However, only 50% of pulmonary TB cases in the state of São Paulo were tested by RMT-TB, requiring more comprehensive coverage.

The RMT-TB is an additional tool for diagnosing pulmonary TB in developing countries as it has good performance in samples with negative sputum smear microscopy [17]. Sputum smear microscopy has low sensitivity to the diagnosis of TB in people living with HIV, as observed in the study results, in which 31% of negative results by the microscopy were positive for RMT-TB. RMT-TB substantially increases TB detection between cases confirmed by culture and negative for sputum smear microscopy [18]. Another study with adults living with HIV showed that RMT-TB is a precise, easy-to-execute, and reliable alternative to sputum microscopy for pulmonary TB detection [19].

In comparing the results of RMT-TB and sputum culture, which is considered the reference test in detecting pulmonary TB, 22.2% of the results of these exams disagreed; in other words, a positive result was identified in one of the tests, and a negative in the other. This was also observed in other studies in which GeneXpert MTB/RIF detected positive cases for TB among negative culture samples [20, 21]. The sputum culture in people with advanced HIV infection represents a challenge due to the difficulty of obtaining good quality sputum samples in this population, even with induction of the expectoration [22]. It is also worth mentioning the high percentage of negative cases of the RMT-TB which had a positive result in the culture, indicating the need for complementarity of exams for the diagnosis of pulmonary TB in cases of HIV co-infection. In this sense, a literature review [23] corroborates this recommendation, stating that GeneXpert does not eliminate the need for other diagnostic methods, and among them, the traditional ones (sputum smear microscopy, culture, and susceptibility testing).

Considering that the GeneXpert MTB/RIF reliability to detect bacillus resistance is questionable by some studies [24, 25], the susceptibility test should be prioritized in the initial diagnosis, in line with the End-TB strategy [4,26] with the prerogative of subsidizing the diagnosis confirmation made by GeneXpert MTB/RIF and the proper indication of therapy for cases of TB and TB drug-resistant (TBDR). From an operational point of view, when considering the high demand for resources and the long time to produce results by the susceptibility test, the opportunity to perform and disseminate results through GeneXpert MTB/

RIF within two hours is a vital tool since it has enabled a reduction in time for the diagnosis of drug-resistance, specifically from rifampicin resistance, and for early start of treatment, thus increasing the chances of cure and having an economic impact on health services and society [27]. However, the limitation of the test in identifying resistance to drugs other than rifampicin must be considered, which would reinforce the importance of performing the susceptibility test for cases that do not adequately respond to the treatment scheme.

In the present study, the odds of being female is higher than the odds of being male for those with a negative RMT-TB result; this is in agreement with a study [28], which identified that women probably have more significant difficulties in spitting due to cultural reasons, and thus collecting better quality samples and is more likely to detect bacillus or its genetic material in the sample. However, findings from another study Lawn SD, et al. [29] showed no difference between the sexes regarding the positivity of the sample. Sputum production is more common in younger people than older ones [30], justifying the most significant amount of negative test results between older adults and retirees, which may come from the difficulty of people expectorating when they are in advanced ages.

The miliary TB results from the disease hematogenic spread, most common in immunocompromised people such as those with HIV infection, is a consequence of the immune system failing to contain the dissemination of *Mycobacterium tuberculosis*, and reflects the involvement of pulmonary nodules and often multiple organs (extrapulmonary TB) [31]. Due to these characteristics, miliary TB is usually oligo symptomatic, with dry coughing and scarce sputum [32], which contributes to the test being negative. People with X-rays suggestive of other pathologies were associated with negative RMT-TB results; in other words, the treatment in many cases was empirically performed without bacteriological confirmation of the disease [33]. This fact may have at least two interpretations: the importance of clinical diagnosis even after implementing the Gene Xpert MTB/RIF test; or most likely the wrong diagnosis of the disease that has no confirmation either by microscopy or culture or gene Xpert MTB/RIF. As sputum smear microscopy has low sensitivity in people living with HIV and the culture takes time to produce its results, treatment was only started based on clinical and radiological findings.

The advent of RMT-TB significantly reduced the number of cases in which sputum smear microscopy was unable to detect bacillus, as well as aid in clinical and therapeutic decision making; this is because the culture was not performed in many places or did not have its result available to start TB and TBDR treatment in a convenient time. Despite the increase in positive results, a study conducted in South Africa showed that GeneXpert MTB/RIF did not interfere with reducing the beginning of treatment time, concluding that health system improvements should accompany the test implementation [34]. Diabetes mellitus, mental disorders, and other immunological diseases did not constitute variables associated with the negative result of RMT-TB; however, such a result was higher among those who denied the use of alcohol, tobacco, and illicit drugs. The use of alcohol and other psychoactive drugs is known to constitute a factor associated with the delay in diagnosing TB [35].

As a result, there may be an aggravation of the disease and more bacilli in the sputum samples harvested during the diagnosis of users of these substances, giving more positive results in such situations. Among the limitations of the study, there is a possible bias of information due to the use of secondary data, as well as the impossibility of measuring the accuracy of the GeneXpert MTB/RIF testing by calculating sensitivity, specificity, and other related measures since the information system only allows for recording the confirmed/empirical cases of TB. It is also worth mentioning that some clinical variables, which were not possible to be included in the study, could be associated with the negative result of the test, as found in another study [29].

CONCLUSION

The RMT-TB presented agreement results regarding sputum smear microscopy, culture, and susceptibility testing in about 80% of cases. However, there is a need for complementarity with other usual tests for the diagnosis of TB in people living with HIV. The study also showed that the negative result for the GeneXpert MTB/RIF test in the diagnosis of TB in people with HIV was associated with females, advanced age and retirement, miliary TB, non-smokers, non-alcohol users, and non-users of illicit drugs. Thus, closer attention on the part of health professionals is necessary regarding early identification of respiratory symptoms and suggestive signs of TB, especially when they face patients with these characteristics and the overlap of physiological and behavioral vulnerabilities. Activities focused on education and awareness of health professionals regarding the need for risk stratification of a negative result of RMT-TB could culminate in the use of strategies which favor the use of more complete diagnostic algorithms, and orientations for the collection of more quality sputum samples, thereby favoring the most opportune and accurate diagnosis.

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