

# HIV screening of tuberculosis patients in Portugal: what are we missing?

L. Ribeiro,\* M. Gomes,<sup>†‡</sup> R. Gaio,<sup>§¶</sup> R. Duarte<sup>#\*\*\*††</sup>

\*Pulmonology Department, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, <sup>†</sup>Occupational Health, Centro Hospitalar de Vila Nova de Gaia/Espinho Entidade Pública Empresarial (EPE), Vila Nova de Gaia, <sup>‡</sup>EPIUnit, Instituto De Saúde Pública Da Universidade Do Porto, Universidade do Porto, Porto, <sup>§</sup>Faculty of Sciences, University of Porto, Porto, <sup>¶</sup>Centre of Mathematics, University of Porto, Porto, <sup>#</sup>Chest Disease Centre, Vila Nova de Gaia, <sup>\*\*</sup>Pulmonology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho EPE, <sup>††</sup>Department of Clinical Epidemiology, Predictive Medicine and Public Health University of Porto Medical School, Porto, Portugal

## SUMMARY

**BACKGROUND:** Knowledge of human immunodeficiency virus (HIV) status is essential to effectively manage both tuberculosis (TB) and HIV infection. This is why the World Health Organization (WHO) recommends routine HIV testing in all TB patients.

**OBJECTIVE:** To determine the number of TB patients with unknown HIV status in Portugal and to identify the factors associated with unknown HIV status.

**METHODS:** A retrospective study of all TB notifications from 2008 to 2014 in Portugal was conducted. A multiple logistic regression model was used to evaluate the association of sociodemographic and clinical factors with unknown HIV status.

**RESULTS:** We examined the records of 18 445 patients with TB notification, 2402 of whom (13%) had

unknown HIV status. Unknown HIV status was positively associated with age  $\geq 65$  years (adjusted odds ratio [aOR] 1.208, 95%CI 1.037–1.408) and extra-pulmonary TB (aOR 1.381, 95%CI 1.252–1.523), but negatively associated with unemployment (aOR 0.755, 95%CI 0.637–0.895), alcohol dependence (aOR 0.809, 95%CI 0.682–0.959) and drug dependence (aOR 0.566, 95%CI 0.449–0.713).

**CONCLUSION:** Risk perception is the most important barrier to complete knowledge of HIV status in TB patients in Portugal. Given the importance of HIV screening in TB patients, every effort should be made to ensure that all TB patients undergo HIV screening.

**KEY WORDS:** TB; human immunodeficiency virus; screening

TUBERCULOSIS (TB) REMAINS a major public health problem, and in 2015 there were an estimated 10.4 million newly infected individuals with TB worldwide. About 11% of these patients were co-infected with the human immunodeficiency virus (HIV), although only 55% had documented HIV test results.<sup>1</sup> Portugal had an estimated TB incidence of 18 per 100 000 population in 2016, the highest incidence in Western Europe. In 2015, HIV was the most common comorbidity of TB in Portugal: 11.8% of all TB patients were HIV-positive, but HIV status was not known in 11.8% of TB patients.<sup>2</sup>

HIV infection is the greatest known risk factor for TB.<sup>3</sup> Patients with TB-HIV co-infection typically present with unique diagnostic and therapeutic challenges. In fact, these two micro-organisms potentiate one another, and together accelerate the deterioration of immunological functions.<sup>4</sup> Patients with HIV infection are more likely to develop active TB, reactive latent tuberculous infection or disseminated TB, present with extra-pulmonary disease and

become re-infected with TB.<sup>5</sup> Multidrug-resistant TB is also associated with HIV infection,<sup>6</sup> and tuberculous infection may accelerate the progression of HIV infection.

Knowledge of the patient's HIV status is essential to effectively manage both TB and HIV infection. It is important to identify HIV-positive TB patients as soon as possible so that appropriate treatment can begin. To reduce excessive TB morbidity and mortality in HIV-positive people, the World Health Organization (WHO) recommends routine HIV testing for individuals with presumptive or confirmed TB. The proportion of TB patients with known HIV status worldwide varies greatly, with the Eastern Mediterranean Region having the lowest documented HIV test results (17%), and Africa and the Americas the highest (81% and 82%, respectively).<sup>1</sup>

Portugal has a policy of mandatory notification of all TB diagnoses, and treatment and follow-up occur in chest disease centres, where all consultations, examinations and treatment are free of charge. The

national directives advise care givers to offer testing for HIV infection at the time of TB diagnosis, although patients have the right to refuse ('opt out').<sup>7</sup>

The aim of the present study was to identify the factors associated with unknown HIV status of TB patients in Portugal.

## MATERIAL AND METHODS

### *Design and patients*

All patients with notified TB in Portugal (continental regions and archipelagos) from 2008 to 2014, with no exclusion criteria, were identified using the Portuguese Tuberculosis Surveillance System (*Sistema de Vigilância da Tuberculose*, the SVIG TB). The SVIG-TB is supervised by the Directorate General of Health, Lisbon, Portugal. To identify the factors associated with unknown HIV status in these patients, the characteristics of those with known and unknown HIV status were compared.

### *Study data*

The sociodemographic and clinical data analysed were age range (<25, 25–44, 45–64 and ≥65 years), country of origin (Portugal or foreign-born), long-term (>24 months) unemployment, main site of TB (pulmonary or extra-pulmonary [pleura, lymph nodes, bones and joints, central nervous system, genitourinary tract, peritoneal or disseminated]), previous treatment episodes (none or at least one), comorbidities (none or at least one), addictions (alcohol abuse, drug abuse or none), incarceration, homelessness or communal living (currently or previously).

### *Statistical analysis*

All descriptive variables are categorical, and are given as absolute or relative frequencies. The crude effect of each variable on knowledge of HIV status was evaluated using a simple (univariate) logistic regression model, with calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs). Multiple logistic regression was then used to evaluate the simultaneous effects of all factors on knowledge of HIV status. The best model was selected based on the Akaike Information Criterion (AIC) and on the statistical significance of the regression predictors. For the final model, the area under the receiver operating characteristic (ROC) curve (AUC) was computed to describe model accuracy. The presented value corresponds to the mean of all AUC values from 100 models, each fitted with a random subsample of 70% of the original sample size, and from 100 predictions, each using the remaining 30% of individuals. All statistical analyses were carried out using R v3.3.0 (R Computing, Vienna, Austria).<sup>8</sup> The significance level was set at 0.05.

### *Ethical approval*

As all patient data were fully anonymised and the

study was retrospective, patient consent and ethical approval were not required.

## RESULTS

Of 18 445 patients with notified TB in Portugal during the study period (2008–2014), 12 115 (65.7%) were males, 15 516 (84.1%) were born in Portugal and the mean age was 47 years ( $\pm$  standard deviation 19). A total of 2402 (13%) of these patients had unknown HIV status.

The Table shows the association of knowledge of HIV status with the different variables. On univariate analysis, patients with unknown HIV status were significantly more likely to be female (38.1% vs. 33.7%,  $P < 0.001$ ), aged ≥65 years (29.5% vs. 18.1%,  $P = 0.015$ ), experience no long-term unemployment (92.1% vs. 85.1%,  $P < 0.001$ ), have extra-pulmonary TB (EPTB) (33% vs. 26.4%,  $P < 0.001$ ), have received no previous anti-tuberculosis treatment (93.3% vs. 90.8%,  $P < 0.001$ ), have lung-related comorbidities (4.5% vs. 3.1%,  $P = 0.027$ ), have no dependencies on alcohol (90.8% vs. 86.1%,  $P < 0.015$ ) or drugs (95.4% vs. 88.7%,  $P < 0.001$ ) and live in a congregate setting (3.9% vs. 3.1%,  $P = 0.047$ ).

The multivariate analysis (Table) indicated that unknown HIV status was independently and positively associated with age ≥65 years (adjusted OR [aOR] 1.208, 95%CI 1.037–1.408) and EPTB (aOR 1.338, 95%CI 1.210–1.480). In contrast, unemployed status (aOR 0.786, 95%CI 0.661–0.935), alcohol dependency (aOR 0.828, 95%CI 0.694–0.988) and drug dependency (aOR 0.566, 95%CI 0.449–0.713) were significantly and negatively associated with unknown HIV status.

## DISCUSSION

We identified the sociodemographic and clinical factors associated with unknown HIV status in TB patients from Portugal by examining the records of all patients with TB notified from 2008 to 2014. Patients with EPTB and those aged ≥65 years were more likely to have unknown HIV status. Conversely, patients who were unemployed, dependent on alcohol or dependent on drugs were less likely to have unknown HIV status.

Patients with HIV infection and advanced immune suppression were more likely to have EPTB than HIV-infected persons with relatively intact immune systems and those without HIV, although HIV infection was frequently associated with concomitant pulmonary TB (PTB).<sup>5</sup> A study in Portugal conducted between 2008 and 2012 reported that HIV-infected patients were more prevalent in the EPTB group than in the PTB group (15.8% vs. 9.2%,  $P = 0.041$ ).<sup>9</sup> In the light of these results, it is difficult to explain why

**Table** Association between knowledge of HIV status and sociodemographic and clinical variables among all patients with notified TB, Portugal, 2008–2014

Variable	Known HIV status ( <i>n</i> = 16 043) <i>n</i> (%)	Unknown HIV status ( <i>n</i> = 2 402) <i>n</i> (%)	OR (95%CI)	<i>P</i> value	aOR (95%CI)	<i>P</i> value
Sex						
Female	5 414 (33.7)	916 (38.1)	Reference			
Male	10 629 (66.3)	1 486 (61.9)	0.826 (0.756–0.903)	<0.001		
Age, years						
<25	1 727 (10.8)	323 (13.5)	Reference		Reference	
25–44	6 513 (40.6)	668 (27.9)	0.548 (0.633–3.619)	<0.001	0.592 (0.508–0.689)	<0.001
45–64	4 883 (30.5)	698 (29.1)	0.764 (0.663–0.882)	<0.001	0.763 (0.655–0.889)	0.001
≥65	2 904 (18.1)	708 (29.5)	1.304 (1.128–1.506)	<0.001	1.208 (1.037–1.408)	0.015
Country of origin						
Portugal	13 502 (84.2)	2 014 (83.8)	Reference			
Foreign-born	2 541 (15.8)	388 (16.2)	1.024 (0.911–1.150)	0.694		
Long-term unemployment						
No	13 651 (85.1)	2 212 (92.1)	Reference		Reference	
Yes	2 392 (14.9)	126 (7.9)	0.490 (0.420–0.572)	<0.001	0.755 (0.637–0.895)	0.015
Site of disease						
Pulmonary	11 776 (73.6)	1 585 (67.0)	Reference		Reference	
Extra-pulmonary	4 220 (26.4)	782 (33.0)	1.377 (1.255–1.510)	<0.001	1.381 (1.252–1.523)	<0.001
Previous treatment						
No	14 565 (90.8)	2 241 (93.3)	Reference			
Yes	1 478 (9.2)	161 (6.7)	0.708 (0.598–0.838)	<0.001		
Comorbidities						
None	13 213 (82.4)	1 972 (82.1)	Reference			
Lung-related	570 (3.1)	108 (4.5)	1.270 (1.028–1.568)	0.027		
Not lung-related	2 260 (12.3)	322 (13.4)	0.955 (0.842–1.083)	0.470		
Behavioural factors						
Alcohol abuse						
No	13 189 (86.1)	1 921 (90.8)	Reference		Reference	
Yes	2 132 (13.9)	194 (9.2)	0.625 (0.532–0.729)	<0.001	0.809 (0.682–0.959)	0.015
Drug abuse						
No	13 657 (88.7)	2 018 (95.4)	Reference		Reference	
Yes	1 733 (11.3)	97 (4.6)	0.379 (0.307–0.467)	<0.001	0.566 (0.449–0.713)	<0.001
Incarceration						
No	15 326 (98.0)	2 083 (97.5)	Reference			
Yes	310 (2.0)	53 (2.5)	1.258 (0.937–1.689)	0.127		
Homelessness						
No	15 379 (98.4)	2 104 (98.9)	Reference			
Yes	246 (1.6)	623 (1.1)	0.683 (0.445–1.050)	0.083		
Communal living						
No	15 086 (96.9)	2 045 (96.1)	Reference			
Yes	475 (3.1)	82 (3.9)	1.274 (1.003–1.617)	0.047		

HIV = human immunodeficiency virus; TB = tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR.

our results showed that patients with EPTB were more likely to have unknown HIV status.

We observed that older patients were less likely to undergo HIV testing, possibly due to the mistaken belief that older individuals are at lower risk. In fact, although the proportion of HIV patients aged ≥65 years in Portugal is low (6.8% in 2014),<sup>10</sup> the number of new HIV patients aged ≥65 years has increased in recent years.<sup>11</sup>

We observed that factors widely known to increase the risk of HIV infection, such as long-term unemployment, alcohol dependency and drug dependency, were all associated with known HIV status. However, other behavioural characteristics, such as incarceration and homelessness, were not significantly associated with known HIV status. These results differ from those of a similar study in TB patients in northern Portugal.<sup>12</sup>

In contrast to our study, Kong et al. reported that foreign-born individuals were more likely to have known HIV status.<sup>13</sup> Other studies have reported associations between female sex and unknown HIV status, also due to the belief that females are at lower risk of HIV infection.<sup>13–15</sup> The crude OR for the association between female sex and unknown HIV status was found to be statistically significant; however, this association was not significant on multivariate analysis.

Among all patients with notified TB in our study, 13% had unknown HIV status, a lower rate than that reported in several other geographic regions.<sup>1</sup> The many possible reasons for the low acceptance of HIV testing and counselling in these other regions include the performance of HIV testing separate from TB services, lack of human resources for the implementation of HIV testing, limited access to HIV test kits,

inadequate knowledge among providers about HIV testing policies in TB patients and the stigma of being HIV-positive.<sup>16,17</sup> Some studies have reported that HIV testing was less frequent among patients who only visited private providers than those who only visited public providers; moreover, patients who only visited private providers were more likely to refuse HIV testing because individuals cared for by private providers are believed to have a lower risk of HIV infection.<sup>13–15</sup>

The low proportion of TB patients with unknown HIV status in Portugal relative to other countries is likely due to the availability of HIV testing in TB centres, the widespread availability of HIV test kits, the availability of treatment in public TB services and encouragement to undergo testing by Portuguese national directives. However, the proportion of TB patients with unknown HIV status increased during our study period (10.1% in 2008 to 16% in 2014). Because there were fewer new diagnoses of HIV in Portugal during these years,<sup>2</sup> this might have led to a reduced awareness of the importance of HIV testing in TB patients. The current opt-out approach in Portugal is insufficient, and TB programmes should stress the importance of the rationale and benefits associated with HIV screening among care givers, as patient acceptance of routine HIV testing is higher if care givers encourage testing.<sup>18</sup> TB programmes should also seek to identify worries, doubts and myths regarding HIV testing among care givers and patients so that barriers to HIV screening can be removed.

Our study had some biases. As this was a retrospective study, some information, such as employment status and other behavioural factors, were not available. However, given the large number of patients and the small proportion of missing data, we believe our conclusions to be reliable. Also, we had no information on whether patients were offered HIV testing or whether they refused testing. Based on our clinical practice, we believe that most cases with unknown HIV status were not offered testing by clinicians. Further research is needed to examine how often clinicians offer HIV testing to TB patients.

## CONCLUSIONS

The belief in the low risk of HIV infection is the main barrier to determining HIV status among TB patients in Portugal. Knowledge of a patient's HIV status is essential for the effective management of TB and HIV infections, as early identification of HIV positivity assures prompt and appropriate treatment. Every effort should be made to ensure that all TB patients are screened for HIV.

## Acknowledgements

RG was supported in part by the Centre for Mathematics of the University of Porto, Porto (UID/MAT/00144/2013), which is

funded by Fundação para a Ciência e a Tecnologia, Lisbon, Portugal, with national (Ministério da Educação e Ciência) and European structural funds (*Fonds européen de développement régional*) under the PT2020 partnership agreement.

Conflicts of interest: none declared.

## References

- 1 World Health Organization. Global tuberculosis report, 2016. WHO/HTM/TB/2016.13. Geneva, Switzerland: WHO, 2016.
- 2 Direção-Geral da Saúde, Ministério da Saúde, Portugal. Programa Nacional para a Infecção VIH, SIDA e Tuberculose 2017. Lisbon, Portugal: Ministério da Saúde, 2017. [Portuguese]
- 3 European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2017. Stockholm, Sweden: ECDC, 2017.
- 4 Pawlowski A, Jansson M, Sköld M, Rottenberg M E, Källenius G. Tuberculosis and HIV co-infection. *PLOS Pathog* 2017; 8: e1002464.
- 5 Kwan C K, Ernst J D. HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev* 2011; 24: 351–376.
- 6 Small P M, Shafer R W, Hopewell P C et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV Infection. *N Engl J Med* 1993; 328: 1137–1144.
- 7 Direção-Geral de Saúde. Circular normativa N°19/DSCS/PNT de 17/10/2017. Rastreo de infeção VIH nos doentes com tuberculose. Lisbon, Portugal: Direção-Geral de Saúde, 2017. <https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/circular-normativa-n-19dscspnt-de-17102007.aspx>. Accessed June 2018. [Portuguese]
- 8 Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2008. <http://www.R-project.org>. Accessed June 2018.
- 9 Sanches I, Carvalho A, Duarte R, Who are the patients with extra-pulmonary tuberculosis? *Rev Port Pneumol* 2015; 21: 90–93.
- 10 Direção-Geral da Saúde, Direção de Serviços de Informação e Análise, Ministério da Saúde, Portugal. Infecção VIH, SIDA e Tuberculose em números 2015. Lisbon, Portugal: Ministério da Saúde, 2015. [Portuguese]
- 11 Direção-Geral da Saúde, Direção de Serviços de Informação e Análise, Ministério da Saúde, Portugal. Infecção VIH, SIDA e Tuberculose em números 2013. Lisbon, Portugal: Ministério da Saúde, 2013. [Portuguese]
- 12 Reina S, Silva C, Gaio A R, et al. HIV screening in tuberculosis patients in the northern region of Portugal. *Int J Tuberc Lung Dis* 2015; 19: 1554–1555.
- 13 Kong D G, Watt J P, Marks S, Flood J. HIV status determination among tuberculosis patients from California during 2008. *J Public Health Manag Pract* 2013; 19: 169–177.
- 14 Klein P W, Harris T G, Leone P A, Pettifor A E. HIV testing of tuberculosis patients by public and private providers in New York City. *J Community Health* 2014; 39: 494–502.
- 15 Asch S M, London A S, Barnes P F, Gelberg L. Testing for human immunodeficiency virus infection among tuberculosis patients in Los Angeles. *Am J Respir Crit Care Med* 1997; 155: 378–381.
- 16 Sendagire I, Schreuder I, Mubiru M, et al. Low HIV testing rates among tuberculosis patients in Kampala, Uganda. *BMC Public Health* 2010; 10: 177.
- 17 Bishnu B, Bhaduri S, Kumar A M, et al. What are the reasons for poor uptake of HIV testing among patients with TB in an Eastern India District? *PLOS ONE* 2013; 8: e55229.
- 18 Irwin K L, Valdiserri R O, Holmberg S D. The acceptability of voluntary HIV antibody testing in the United States: a decade of lessons learned. *AIDS* 1996; 10: 1707–1717.

## RÉSUMÉ

**CONTEXTE :** La connaissance du statut du virus de l'immunodéficience humaine (VIH) est essentielle pour prendre en charge de façon efficace à la fois la tuberculose (TB) et les infections à VIH, raison pour laquelle l'Organisation Mondiale de la Santé recommande un test VIH en routine chez tous les patients TB.

**OBJECTIF :** Déterminer le nombre de patients TB ne connaissant pas leur statut VIH au Portugal et identifier les facteurs associés à une non connaissance du statut VIH.

**MÉTHODE :** Une étude rétrospective de toutes les notifications de TB au Portugal de 2008 à 2014 a été réalisée. Un modèle de régression logistique multiple a été utilisé pour évaluer l'association de facteurs sociodémographiques et cliniques avec un statut VIH inconnu.

**RÉSULTATS :** Nous avons examiné les dossiers de

18 445 patients dont la TB a été notifiée ; 2402 d'entre eux (13%) avaient un statut VIH inconnu. Ce statut inconnu a été positivement associé avec un âge de  $\geq 65$  ans (odds ratio ajusté [ORa] 1,208 ; IC95% 1,037–1,408) et une TB extra-pulmonaire (ORa 1,381 ; IC95% 1,252–1,523), mais négativement associé avec l'absence d'emploi (ORa 0,755 ; IC95% 0,637–0,895), la dépendance à l'alcool (ORa 0,809 ; IC95% 0,682–0,959) et la dépendance aux drogues (ORa 0,566 ; IC95% 0,449–0,713).

**CONCLUSION :** La perception du risque est la contrainte la plus importante à la connaissance complète du statut VIH des patients TB au Portugal. Sachant l'importance du dépistage du VIH chez les patients TB, tous les efforts doivent être faits pour assurer que tous les patients TB bénéficient d'un dépistage du VIH.

## RESUMEN

**MARCO DE REFERENCIA:** Conocer la situación frente al virus de la inmunodeficiencia humana (VIH) es primordial para la eficacia del tratamiento de la tuberculosis (TB) y también de la infección por el VIH, y por esta razón la Organización Mundial de la Salud recomienda que se practique de manera sistemática la prueba del VIH en todos los pacientes con TB.

**OBJETIVO:** Determinar el número de pacientes con TB que desconocen su situación frente al VIH en Portugal y reconocer los factores que se asocian con este desconocimiento.

**MÉTODOS:** Se llevó a cabo un estudio retrospectivo de todos los casos de TB notificados del 2008 al 2014 en Portugal. Mediante un modelo de regresión logística múltiple se evaluó la asociación de los factores sociodemográficos y clínicos con el desconocimiento de la situación frente al VIH.

**RESULTADOS:** Se examinaron las historias clínicas de 18 445 pacientes con TB notificada, 2402 de los cuales

(13%) desconocía su situación frente al VIH. El hecho de desconocer su situación frente al VIH exhibió una asociación positiva con la edad  $\geq 65$  años (aOR 1,208; IC95% 1,037–1,408) y la TB extrapulmonar (aOR 1,381; IC95% 1,252–1,523), pero una relación negativa con el desempleo (aOR 0,755; IC95% 0,637–0,895), la dependencia del alcohol (aOR 0,809; IC95% 0,2–0,959) y la dependencia a las drogas (aOR 0,566; IC95% 0,449–0,713).

**CONCLUSIÓN:** La percepción del riesgo constituye el principal obstáculo al conocimiento de la situación frente al VIH en los pacientes con TB en Portugal. Habida cuenta de la importancia de la detección sistemática del VIH en los pacientes con TB, es necesario emprender todos los esfuerzos necesarios que contribuyan a que se practique la detección sistemática de la infección por el VIH en todos los pacientes con diagnóstico de TB.