Factors associated with retreatment tuberculosis in Tshwane, South Africa: the role of tobacco smoking

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Keywords: tobacco smoking, recurrent tuberculosis, human immunodeficiency virus, tuberculosis relapse, retreatment tuberculosis

There is evidence from international studies that tobacco smoking increases the risk of tuberculosis recurrence through its effects on the immunological and barrier functions of the airways. In this cross-sectional study, the association between current tobacco smoking and retreatment tuberculosis was studied in a population of 1 926 South African tuberculosis patients with high human immunodeficiency virus (HIV) co-infection rates. Retreatment tuberculosis was more common in male and among HIV-positive participants currently on antiretroviral treatment, or with unknown antiretroviral treatment status. However, we did not find an association between smoking and retreatment tuberculosis. A longitudinal study is needed to confirm these findings.

Ⓟ Peer reviewed. (Submitted: 2014-00-00. Accepted: 2014-00-00.) © SAJID

South Afr J Infect Dis 2014;29(2):87-90

Introduction

South Africa has one of the highest tuberculosis burdens in the world, an epidemic driven largely by high human immunodeficiency virus (HIV) infection rates in the same population.[1] The problem is aggravated by low treatment success rates in patients with active tuberculosis.[1] The main categories of unsuccessful treatment are death during tuberculosis treatment, treatment interruption for two consecutive months or more, and treatment failure.[1] Patients have to take a second course of tuberculosis treatment, classified as "retreatment tuberculosis" for the latter two categories. Retreatment tuberculosis is any tuberculosis treatment occurring in a patient who has received previous antituberculosis treatment, and may be due to either re-activation following suboptimally treated tuberculosis, as explained, or exogenous re-infection. Common risk factors for treatment interruption, failure and/or retreatment tuberculosis in low-HIV prevalence settings include belonging to the male sex, being of an older age, having a low socio-economic status, initial drug resistance, alcohol abuse and tobacco smoking.[2-7] HIV infection is an additional important risk factor for tuberculosis recurrence, in particular in patients not taking antiretroviral treatment (ART) in areas of high HIV prevalence.[8] With regard to tobacco use, smokers are more likely to have poorer intermediate clinical end-points (delayed sputum conversion and treatment interruption),[2,9] and higher failure and recurrence rates.[3,4,6] The pathophysiological mechanisms are complex that underlie the increased risk and severity of tuberculosis in tobacco smokers. Tobacco smoke causes alterations in cellular and humoral immunity, and impairs lung defence mechanisms through suppression of the protective functions of the airway epithelium, all of which may explain higher recurrence rates in smokers.[10]

To our knowledge, an association between smoking and retreatment tuberculosis has not been studied in a high-HIV prevalence setting. We aimed to ascertain whether or not current tobacco smokers were more likely to present with retreatment tuberculosis than non-smokers with regard to patients with high tuberculosis-HIV co-infection rates, adjusted for other important confounders.

Method

This was a cross-sectional analysis of baseline data, collected for a smoking cessation study. The study took place at six large tuberculosis clinics in Tshwane, South Africa's capital city, from September 2011 to April 2013. These clinics provide tuberculosis- and HIV-related care, and use case definitions, disease classification and treatment outcomes based on World Health Organization (WHO) guidelines.[1] Adult patients seeking tuberculosis treatment at these clinics were approached to participate in the study. Patients who were on treatment for over one month, and those who were very ill and unable to understand the language, were excluded from the study. The study was approved by the ethics committee of the University of Pretoria (Protocol 116/2011).

Information on socio-economic and demographic factors, and alcohol and tobacco use was collected through structured interviewer-administered questionnaires. Questions on tobacco use were adapted from the Global Adult Tobacco Survey questionnaire.[11] Current smoking was defined as having smoked tobacco in the past month, while ever having smoked tobacco was defined as currently smoking, or having smoked in the past. Tuberculosis- and HIV-related information was extracted from standardised individual patient tuberculosis records. Information included whether or not this was a first episode of tuberculosis or retreatment, the type of tuberculosis, the patient's HIV

status and whether or not the patient was taking ART. Information on CD4 count was not collected since this information is often missing from tuberculosis records and/or not updated in our setting.[12]

According to the definitions of the WHO, a "new" tuberculosis patient is one who has never received treatment for tuberculosis, or who has taken antituberculosis drugs for less than one month.

A retreatment patient is one who was previously treated for tuberculosis, and who is started on a retreatment regimen:

- After previous treatment has failed.
- After having previously defaulted.
- After previously being declared cured, or having completed treatment, and who is diagnosed again with bacteriologically positive tuberculosis.[1]

Data were double entered in Microsoft® Excel® by experienced data capturers and exported into Stata® release 12 for comparison, data cleaning and analysis.[13] Analysis consisted of descriptive statistics, followed by an exploratory analysis of variables associated with smoking, since these could confound the relationship between smoking and retreatment tuberculosis. In the next step, we performed univariate and multivariate logistic regression for predictors of retreatment tuberculosis. Co-variates known to be associated with retreatment tuberculosis from a literature review, and/or those identified during univariate analysis at the 25% level, were included in the initial multivariate mode, as well as interaction variables. Co-variates were then removed one by one using backward elimination with a liberal retention criterion (p-value < 0.2), as recommended for models designed to evaluate a predictor of primary interest.[14] Standard errors were adjusted for clustering by facility. Current smoking was the primary predictor of interest. However, an alternative model, with ever smoked as the main predictor, was also run.

Results

The baseline characteristics of the 1 926 interviewed patients (485 exclusions) are presented in Table I, according to smoking status. Roughly one in five respondents was a current smoker (420/1 924, 21.8%) and 13% of respondents had previously had tuberculosis (245/1 879). The retreatment status was missing for 47 patients. The median daily number of cigarettes smoked was 8 for daily smokers (interquartile range 5-12.5, n = 352). Only 1.8% (35/1 918) of respondents were past smokers. (The results for the number of cigarettes and past smoking status are not presented in Table I). Following univariate analysis of potential confounders of the relationship between smoking and retreatment tuberculosis, several variables were significantly associated with current smoking, including being male, not receiving ART while HIV-positive, having an alcohol problem, living in a household with a low monthly income, not being well educated, going hungry in the past month and carrying out occasional work (Table I).

Factors associated with retreatment tuberculosis are presented in Table II. The small group of 35 past smokers were included in the group of non-smokers for the purpose of this analysis. After adjustment for other

Table I: Characteristics of tuberculosis patients, by smoking status

Variable	All participants n = 1 926* n (%)**	Non-smoker n = 1 504 n (%)**	Current smoker n = 420 n (%)**	p-value***
Retreatment tuberculosis (n = 1 879)	245 (13)	53 (13)	192 (13.1)	0.949
HIV status and ART				
HIV-negative	233 (12.9)	178 (12.6)	55 (14.3)	< 0.001
HIV-positive and on ART	359 (19.9)	303 (21.4)	56 (14.5)	
HIV-positive and ART unknown	496 (27.5)	405 (28.6)	91 (23.6)	
HIV-positive and not on ART	715 (39.7)	539 (37.4)	184 (47.7)	
Alcohol problem** (n = 1 895)	367 (19.4)	164 (11.1)	203 (49.5)	< 0.001
Female (n = 1 926)	919 (47.7)	877 (58.3)	42 (10)	< 0.001
Age groups				
18-29	409 (21.2)	354 (23.5)	55 (13.1)	< 0.001
30-39	713 (37)	568 (37.8)	144 (34.3)	
40-49	503 (26.1)	357 (23.7)	135 (34.5)	
50-59	216 (11.2)	158 (10.5)	58 (13.8)	
≥ 60	85 (4.4)	67 (4.5)	18 (4.3)	
Household income				
ZAR***** 1-500	523 (27.5)	379 (25.5)	143 (34.5)	< 0.001
ZAR 501-2 500	992 (52.1)	784 (52.7)	207 (50)	
> ZAR 2 500	389 (20.4)	325 (21.8)	64 (15.5)	
Education				
Primary schooling or less	533 (27.8)	377 (25.1)	156 (37.6)	< 0.001
Some high school	844 (44.5)	654 (43.5)	198 (47.7)	
Completed high school or higher	532 (27.7)	471 (31.4)	61 (14.7)	
Employment status				
Not working******	190 (10)	166 (11.2)	24 (5.8)	< 0.001
Unemployed	666 (35.1)	547 (36.8)	118 (28.7)	
Occasional work	218 (11.5)	138 (9.3)	80 (19.5)	
Working full-time or part-time	826 (43.5)	636 (42.8)	189 (46)	
≥ 1 day hunger***** (n = 1 920)	222 (11.6)	157 (10.5)	65 (15.6)	0.004

ART: antiretroviral therapy, HIV: human immunodeficiency virus
*Includes two patients for whom smoking status was unknown
**Some percentages may not add up to 100% owing to rounding off
***Chi-square test
****CAGE score ≥ 2 (CAGE: Have you ever felt you needed to **C**ut down on your drinking? Have people **A**nnoyed you by criticising your drinking? Have you ever felt **G**uilty about drinking? Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?)
*****1 ZAR ≈ 0.1 US dollar
******Retired, unable to work, a homemaker or a student
*******≥ 1 day hunger in the past month

Table II: Factors associated with retreatment tuberculosis*

Variable	n	Retreatment tuberculosis n (%)	Crude odds ratio	Adjusted odds ratio**
Current smoker				
No	1 468	192 (13.1)	1	1
Yes	409	53 (13)	0.99 (0.71-1.37)	0.98 (0.51-1.90)
HIV status and ART				
HIV-negative	230	24 (10.4)	1	1
HIV-positive/on ART	351	81 (23.1)	2.58 (1.58-4.20)	2.61 (1.69-4.02)***
HIV-positive/ART unknown	488	87 (17.8)	1.86 (1.15-3.02)	1.94 (1.15-3.27)***
HIV-positive/ not on ART	701	41 (5.9)	0.53 (0.31-0.90)	0.53 (0.24-1.18)
Alcohol problem**				-
No	1 493	202 (13.5)	1	
Yes	355	40 (11.3)	0.81 (0.57-1.16)	
Sex				
Male	987	142 (14.4)	1	1
Female	892	103 (11.6)	0.78 (0.59-1.02)	0.69 (0.56-0.85)***
Age groups				
18-29	400	47 (11.8)	1	1
30-39	694	98 (14.1)	1.23 (0.85-1.79)	1.08 (0.74-1.58)
40-49	487	60 (12.3)	1.06 (0.70-1.59)	1.00 (0.67-1.49)
50-59	216	36 (16.7)	1.50 (0.94-2.40)	1.28 (0.65-2.53)
≥ 60	82	4 (4.9)	0.39 (0.13-1.10)	0.48 (0.23-1.02)*****
Household income				
ZAR 1-500	506	80 (15.8)	1	1
ZAR 501-2500	974	117 (12)	0.73 (0.53-0.99)	0.79 (0.59-1.05)*****
> ZAR 2500	378	43 (11.4)	0.68 (0.46-1.02)	0.61 (0.36-1.05)*****
Education				
Primary schooling or less	525	62 (11.8)	1	-
Some high school	829	104 (12.6)	1.07 (0.77-1.50)	-
Completed high school or higher	519	78 (15)	1.32 (0.92-1.89)	-
Employment status				
Not working******	184	27 (14.7)	1	-
Unemployed	649	85 (13.1)	0.88 (0.55-1.40)	-
Occasional work	210	30 (14.3)	0.97 (0.55-1.70)	-
Working full-time or part-time	812	97 (12)	0.79 (0.50-1.25)	-
Hunger in past month				-
0 days	1655	207 (12.5)	1	
≥ 1 day	218	35 (16.1)	1.34 (0.91-1.98)	

ART: antiretroviral therapy, HIV: human immunodeficiency virus
*Variables entered in the initial model: sex, age category, smoking status, a problem drinking, household income, employment category, hunger, educational level, human immunodeficiency virus status, interaction between smoking and human immunodeficiency virus/antiretroviral therapy, smoking and sex, smoking and age category, and smoking and problem drinking (Pearson's goodness of fit test, p-value 0.836)
**Robust standard errors, adjusted for clustering by the facility
***p-value < 0.05
****CAGE score ≥ 2 (CAGE: Have you ever felt you needed to **C**ut down on your drinking? Have people **A**nnoyed you by criticising your drinking? Have you ever felt **G**uilty about drinking? Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?)
*****p-value < 0.10
******Retired, unable to work, a housemaker, student or other

predictors, current smoking was not associated with retreatment status [odds ratio (OR) 0.98, 95% confidence interval (CI): 0.51-1.90]. Females (OR 0.69, 95% CI: 0.56-0.85) were less likely to have had more than one episode of tuberculosis. Compared to HIV-negative participants, HIV-positive participants currently on ART, and those for whom ART status was unknown, were more likely to have presented with retreatment tuberculosis (OR 2.61, 95% CI: 1.69-4.02 and OR 1.94, 95% CI: 1.15-3.27, respectively). However, being HIV-positive, but not yet receiving ART, was not significantly associated with retreatment tuberculosis. Being aged 60 or older and with a higher household income was marginally associated with a lower retreatment rate (p-value < 0.10) (Table II). Results were very similar in the model with ever versus never smoked as the main predictor.

Discussion

Somewhat in contrast with the findings of studies that indicated higher relapse, treatment interruption and failure rates among smokers,[2-4,6] we did not find that smoking was independently associated with tuberculosis retreatment in this cross-sectional analysis. However, some of the identified predictors of increased risk of retreatment (being of the male sex, and being HIV positive and on ART) were similar to those of other studies.[5,8] Considering that smokers were found to be significantly more likely to be HIV-positive but not on ART than non-smokers, survival bias would have been introduced if patients who smoked died more often after a first episode of tuberculosis than non-smokers. Another explanation for the lack of association between smoking and tuberculosis retreatment is that the majority of our respondents were light smokers (1-10 cigarettes per day). Therefore, the effect of smoking may have been minimal in the context of the overwhelming influence of HIV on tuberculosis recurrence. Misclassification of retreatment status may have occurred. We did not validate whether or not patients with a self-reported first episode of tuberculosis had been registered with tuberculosis previously, at the same or another facility. Nevertheless, our retreatment rates were similar to those of national statistics based on routinely collected data,[1] but were much lower than the 28% retreatment rate in a recent study undertaken in Cape Town[8] on a population with generally higher smoking, but lower HIV-infection rates. We may also have missed some retreatment cases if retreatment patients who had multidrug-resistant tuberculosis (MDR-TB) were referred directly from a hospital to

a MDR-TB unit. However, unless smokers who developed MDR-TB were more often missed than non-smokers who developed MDR-TB, this should not have affected the OR of the relationship between smoking and retreatment tuberculosis.

The finding that HIV-positive patients on ART, or with unknown ART status, presented more often with retreatment tuberculosis is in accordance with an increased risk of tuberculosis recurrence when a patient is HIV-positive, even when treated with ART.[8] The low retreatment rate in HIV-positive patients not yet on ART may be explained by death during or after the first tuberculosis episode. Also, many tuberculosis patients are diagnosed with HIV when they first present with tuberculosis. Therefore, new tuberculosis patients have often not yet started ART. As a result of this, paradoxically, retreatment tuberculosis may somewhat be less common in this group. Another plausible explanation is that HIV-positive patients on ART were more likely to be screened for tuberculosis than those not on ART since they regularly attend care. Lastly, some patients may not yet have taken ART because of a CD4 count above the threshold. Therefore, they would be at lower risk of retreatment tuberculosis than patients with more advanced disease. The non-availability of CD4 count data limited the interpretability of these results.

This was a cross-sectional study, and therefore true longitudinal relationships between smoking and tuberculosis recurrence could not be determined. A longitudinal analysis of the relationship between smoking and tuberculosis recurrence in the same setting is needed to confirm these findings. Further research is also warranted on whether or not the effects of tobacco smoking on the risk of tuberculosis infection, disease and recurrence differ in HIV-infected populations. Previous studies have demonstrated increased susceptibility to smoking-related mortality and morbidity in HIV-positive populations,[15,16] but data on tuberculosis risks in HIV-positive smokers are limited.[10]

Conflict of interest

The authors declare no competing interests.

Acknowledgments

This project was supported by funding from the KNCV Tuberculosis Foundation (Grant 12.402.2/MvdW/U.10.0696/cal), Global Bridges Health Care Alliance for Tobacco Dependence Treatment, and the National Research Foundation of South Africa. We are grateful to the fieldworkers and to the research assistant, Keabetswe Kodi, for their enthusiastic and hard work. We also wish to thank the tuberculosis nurses at the facilities, and the Tshwane District Health management team. Lastly, we thank Barbara English for language editing.

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