



Effect of smoking history on outcome of patients diagnosed with TB and HIV

To the Editor:

Tobacco use, infection with HIV and active tuberculosis (TB) are important public health problems worldwide. Smoking affects susceptibility to TB, with an increased risk of infection, TB disease and TB death [1, 2]. An estimated 1.1 million of the 8.6 million people who developed TB in 2012 were HIV-positive [3]. It has been estimated that smoking could cause 18 million excess cases of TB and 40 million excess deaths between 2010 and 2050 [4], but little is known about the effect of smoking on the outcomes of people receiving care for both HIV and TB.

We performed a secondary analysis of ITART (Integrated Tuberculosis and AntiRetroviral Treatment), a prospective cohort study of integrated TB/HIV care at primary care facilities in Kinshasa, Democratic Republic of Congo [5]. In this study, antiretroviral treatment (ART) was scheduled to start 1 month after TB treatment initiation if baseline CD4 cell count was <100 cells·mm⁻³ or the patient had clinical stage 4 illness other than extrapulmonary TB, and at 2 months if CD4 cell count was between 100 and 350 cells·mm⁻³ or if unavailable (*e.g.* if reagents were out of stock at the national HIV laboratory).

Associations between smoking and outcomes were assessed by multivariate Cox proportional hazard models and expressed as crude and adjusted hazard ratios (HR) and their 95% confidence intervals. The outcomes of interest were uptake of ART during TB treatment and adverse TB treatment outcomes (lost to follow-up (LTFU), death or treatment failure). Follow-up started at TB treatment initiation and was censored at transfer out, adverse outcome or TB treatment completion (and ART initiation for the uptake analysis). Participants were classified as never-smokers or ever-smokers. Ever-smokers included current smokers, recent smokers (age of smoking cessation was the same as age at enrolment) and former smokers (age of smoking cessation was less than the age at enrolment). Among ever-smokers, duration was categorised as either greater or less than 10 years of smoking. The level of significance was set at $p<0.05$. Analyses were carried out using SPSS 19.0.0 (IBM Corp., Armonk, NY, USA).

The study was approved by the ethics boards of the University of North Carolina at Chapel Hill (NC, USA) and the University of Kinshasa (DR Congo). All patients provided written informed consent.

A total of 599 patients diagnosed with TB and HIV were enrolled. Participants were excluded if they were ≤ 18 years-old ($n=31$) or if they were not ART-naïve ($n=36$). Among the 533 participants included in the analysis, the median age was 38 years (IQR 31–45 years) and 61% were female. Overall, 25% (135 out of 533) participants reported having ever smoked. Ever-smokers were older ($p=0.007$) and a larger proportion of males (111 (51%) out of 216) than females (24 (8%) out of 317) reported any smoking ($p<0.001$). Among ever-smokers, 6% (8 out of 135) reported current smoking, 25% (34 out of 135) were recent smokers, and 69% (93 out of 135) were former smokers. Among former smokers, 37% (34 out of 93) stopped smoking ≥ 10 years ago. Duration of smoking differed by sex, with 33% of males and 79% of females smoking for <10 years. Compared with those who never smoked, ever-smokers were less likely to have finished secondary education ($p=0.036$), more likely to experience food insecurity ($p=0.006$), and more likely to report risky behaviours including heavy drinking ($p<0.001$), sexual activity before 13 years of age ($p=0.039$) and multiple sexual partners ($p<0.001$ among females, $p=0.745$ among males). Employment status, underweight, functional status and TB disease location did not differ significantly between ever-smokers and never-smokers.

Baseline CD4 cell count was available in 522 (98%) participants. Median CD4 cell count was higher in current/recent smokers (266 cells·mm⁻³), compared with both never-smokers (166 cells·mm⁻³; $p=0.009$) and former smokers (162 cells·mm⁻³; $p=0.006$). The same proportion (79%) of never-smokers and ever-smokers had a baseline CD4 cell count <350 cells·mm⁻³. Ever-smokers eligible for ART were 30% less likely to start ART during TB treatment (adjusted HR 0.70, 95% CI 0.54–0.90). Among those initiating ART, adherence to ART was similar among ever- and never-smokers (68% *versus* 77%; $p=0.131$).

Adverse TB treatment outcomes were experienced by 19% of participants: 11% (56 out of 533) were LTFU, 9% (46 out of 533) died during TB treatment and none experienced TB treatment failure. The proportion of individuals who experienced adverse TB treatment outcomes was higher in those who did not initiate

TABLE 1 TB treatment outcomes in relation to smoking history of HIV patients in Kinshasa, the Democratic Republic of Congo

	All patients (n=533)	ART during TB treatment [#] (n=367)	No ART during TB treatment [#] (n=166)
All ever smokers[¶] (n=135)			
Crude HR for LTFU	2.43 (1.43–4.13)	2.05 (0.86–4.88)	2.17 (1.11–4.26)
Adjusted HR for LTFU	2.40 (1.13–5.11)	2.77 (0.95–8.08)	1.67 (0.70–3.97)
Crude HR for death	2.00 (1.10–3.63)	2.37 (0.92–6.10)	1.49 (0.69–3.22)
Adjusted HR for death	0.87 (0.38–1.98)	1.50 (0.48–4.67)	1.08 (0.19–6.33)
Crude HR for adverse outcome ⁺	2.15 (1.45–3.20)	2.14 (1.13–4.06)	1.73 (1.05–2.87)
Adjusted HR for adverse outcome ⁺	1.57 (1.00–2.47)	2.21 (1.16–4.22)	1.15 (0.46–2.88)
Duration of smoking			
Smoked >10 years [¶] (n=79)			
Crude HR for LTFU	2.89 (1.58–5.26)	2.46 (0.89–6.84)	2.29 (1.08–4.84)
Adjusted HR for LTFU	2.71 (1.01–7.28)	5.11 (0.96–27.06)	1.37 (0.52–3.60)
Crude HR for death	2.93 (1.55–5.54)	4.55 (1.76–11.73)	1.62 (0.68–3.88)
Adjusted HR for death	1.64 (0.63–4.26)	3.81 (0.99–14.58)	0.80 (0.11–5.53)
Crude HR for adverse outcome ⁺	2.79 (1.80–4.31)	3.28 (1.65–6.52)	1.84 (1.05–3.25)
Adjusted HR for adverse outcome ⁺	2.39 (1.36–4.22)	4.62 (2.09–10.21)	1.04 (0.39–2.73)
Smoked <10 years [¶] (n=56)			
Crude HR for LTFU	1.84 (0.85–4.00)	1.58 (0.46–5.51)	1.98 (0.74–5.34)
Adjusted HR for LTFU	3.04 (1.23–7.53)	1.74 (0.44–6.95)	§
Crude HR for death	0.72 (0.25–2.65)	0.04 (0.00–143.00)	1.24 (0.37–4.22)
Adjusted HR for death	0.41 (0.09–1.75)	§	0.38 (0.04–3.69)
Crude HR for adverse outcome ⁺	1.33 (0.70–2.52)	0.89 (0.27–2.96)	1.52 (0.71–3.28)
Adjusted HR for adverse outcome ⁺	1.28 (0.67–2.44)	0.87 (0.25–3.00)	1.45 (0.66–3.15)
Duration since exposure			
Current and recent smokers [¶] (n=42)			
Crude HR for LTFU	2.70 (1.24–5.85)	2.07 (0.47–9.12)	1.96 (0.78–4.94)
Adjusted HR for LTFU	3.09 (1.01–9.39)	3.70 (0.47–29.21)	1.51 (0.30–7.62)
Crude HR for death	3.15 (1.44–6.89)	4.11 (1.15–14.73)	1.81 (0.67–4.87)
Adjusted HR for death	2.03 (0.70–5.93)	3.93 (0.63–24.33)	1.27 (0.18–9.28)
Crude HR for adverse outcome ⁺	2.77 (1.60–4.81)	2.87 (1.10–7.50)	1.77 (0.90–3.49)
Adjusted HR for adverse outcome ⁺	2.71 (1.42–5.16)	3.75 (1.00–14.10)	1.48 (0.49–4.52)
Former smokers [¶] (n=93)			
Crude HR for LTFU	2.32 (1.27–4.22)	2.03 (0.78–5.29)	2.34 (1.08–5.06)
Adjusted HR for LTFU	2.62 (1.19–5.75)	2.09 (0.70–6.18)	1.77 (0.47–6.66)
Crude HR for death	1.50 (0.71–3.18)	1.79 (0.57–5.62)	1.26 (0.47–3.38)
Adjusted HR for death	0.53 (0.19–1.48)	1.22 (0.33–4.48)	0.16 (0.02–1.31)
Crude HR for adverse outcome ⁺	1.88 (1.18–2.99)	1.89 (0.91–3.94)	1.70 (0.93–3.10)
Adjusted HR for adverse outcome ⁺	1.25 (0.74–2.12)	1.92 (0.92–3.99)	0.92 (0.34–2.50)

Data are presented as estimate [95 % CI], unless otherwise stated. Analysis was performed by Cox proportional hazard modelling using a 10% change in estimate approach for the covariates sex, age (quintiles), underweight, functional status (ambulatory *versus* in bed more than usual), CD4 cell count category (<50, 50–99, 100–350, >350 cells·mm⁻³), ART initiation during TB treatment, extrapulmonary TB, completion of secondary education, employment, food insecurity (hungry in the past week), multiple sexual partners (excluded for the mortality analysis), sexual activity before age 13 years of age (excluded for the mortality analysis), and heavy alcohol consumption (World Health Organisation 2014 definition [6]). ART: antiretroviral treatment; TB: tuberculosis; HR: hazard ratio; LTFU: lost to follow-up.[#]: ART initiated within 6 months following start of TB treatment; [¶]: Compared to patients who never smoked; ⁺: Mortality and loss to follow-up during TB treatment combined; [§]: Number of patients too low to perform this analysis.

ART (62 (37%) out of 166) compared with those who started ART (40 (11%) out of 367; p<0.001). Patients who were eligible for ART but failed to initiate ART were most likely to experience adverse TB treatment outcomes (52 (72%) out of 72). Ever-smokers were about twice as likely to experience adverse TB treatment outcomes compared with never-smokers (crude HR 2.15, 95% CI 1.45–3.20) (table 1). The association was significant after adjustment for covariates among all patients (adjusted HR 1.57, 95% CI 1.00–2.47) and people on ART (adjusted HR 2.21, 95% CI 1.16–4.22), but not among those who did not initiate ART during TB treatment (adjusted HR 1.15, 95% CI 0.46–2.88). When examining the type of adverse TB treatment outcome, LTFU was independently associated with smoking status (adjusted HR 2.40, 95% CI 1.13–5.11), but death was not (adjusted HR 0.87, 95% CI 0.38–1.98).

When stratified by duration of smoking, smoking was independently associated with adverse TB treatment outcome among those reporting smoking for ≥ 10 years (adjusted HR 2.39, 95% CI 1.36–4.22) but not among those smoking for < 10 years (adjusted HR 1.28, 95% CI 0.67–2.44). When further stratifying by ART status during TB treatment, patients who had smoked for ≥ 10 years and initiated ART during TB treatment were five times as likely to be LTFU (adjusted HR 5.11, 95% CI 0.96–27.06) and almost four times as likely to die (adjusted HR 3.81, 95% CI 0.99–14.58) compared with never-smokers who initiated ART.

Finally, those who reported recent or current smoking were nearly three times as likely to experience adverse TB treatment outcomes compared with those who had never smoked (adjusted HR 2.71, 95% CI 1.42–5.16).

Few studies have assessed smoking as a risk factor for adverse care outcomes in people living with TB and HIV. Regarding LTFU, individuals in Brazil [7] who smoked in the 6 months preceding TB treatment were twice as likely to be LTFU (adjusted OR 2.62, 95% CI 1.31–5.26). In Thailand [8], current smoking was also associated with twice the odds of LTFU (adjusted OR 2.3, 95% CI 1.3–4.1). Regarding mortality, a study from Iran [9] reported no effect of smoking, but only included three participants who had never smoked. In Brazil [10], current smokers hospitalised for TB, 71% of whom were HIV infected and were predominantly ART-naïve, were at increased risk of death (adjusted OR 2.14, 95% CI 1.07–4.28), but estimates were not stratified by HIV or ART status.

In summary, we observed that ever-smokers eligible for ART were 30% less likely to initiate ART during TB treatment, and ever-smokers on ART were twice as likely to experience adverse TB treatment outcomes. The effect of smoking was most pronounced among those on ART who were current/recent smokers or those who had smoked for ≥ 10 years. ART was a strong effect modifier, with the absence of an effect of smoking on adverse TB treatment outcomes likely due to the strong effect of the absence of ART on death and LTFU in TB patients. While tobacco smoke has well-known hazardous effects, smokers also have a different psychosocial risk profile, which could contribute to the observed relationship between smoking and adverse TB treatment outcomes. Our estimates were, however, adjusted for many of these psychosocial factors.

In addition to preventing people from smoking, helping smokers to quit and providing ART, the outcome of people living with HIV who develop TB might be improved by increasing support for (former) smokers, such as intensified counselling on the importance of ART.



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Among TB–HIV patients on antiretrovirals those who smoke(d) are more likely to have adverse TB treatment outcomes <http://ow.ly/DyPqW>

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