

Active tobacco smoking is associated with lower risk of acquiring SARS-CoV-2 infection among people living with HIV

Marta Fernandez-Fuertes

Hospital Universitario de Valme

Anaïs Corma-Gomez

Hospital Universitario de Valme

Elena Rodriguez-Pineda

Hospital Universitario de Valme

Ana Fuentes-Lopez

Hospital Universitario San Cecilio

Pilar Rincon

Hospital Universitario de Valme

Esther Serrano-Conde

Hospital Universitario San Cecilio

Luis M Real

Hospital Universitario de Valme

Federico Garcia

Hospital Universitario San Cecilio

Juan Macias

Hospital Universitario de Valme

Juan A Pineda (✉ japineda@telefonica.net)

Hospital Universitario de Valme

Short Report

Keywords: HIV, SARS-CoV-2, COVID-19, tobacco smoking

Posted Date: December 30th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-129212/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Summary

The relationship between tobacco smoking and SARS-CoV-2 infection is poorly understood. We aimed to assess the impact of current smoking on the risk of COVID-19 acquisition in a well-controlled HIV-infected population. We found that, in this setting, tobacco smoking is associated with a lower risk of acquiring SARS-CoV-2 infection.

Main Text

The current coronavirus disease 2019 (COVID-19) has spread worldwide since starting in China in December 2019, involving over 75 million people by December 2020. Additionally, more than 1.6 million deaths have been reported so far all over the world [1]. The information about the impact of COVID-19 among people living with human immunodeficiency virus (PLWH) is limited. However, preliminary data have shown an incidence of SARS-CoV-2 infection in this subgroup similar as that found among the general population [2].

The impact of smoking on the risk of developing COVID-19 is unclear and has been a matter of controversy. While some studies have observed an association with an increased severity of COVID-19 [3–5], other reports have suggested that the incidence of SARS-CoV-2 infection among current smokers could be lower [6–8].

In the present study, we assessed the incidence of SARS-CoV-2 infection in a cohort of HIV-infected patients followed at a hospital in Spain. Our aim was to evaluate the association of current smoking on the probability of developing SARS-CoV-2 infection in PLWH.

We performed a retrospective nested case-control study within a cohort of HIV infected patients followed at the Unit of Infectious Diseases of a University Hospital in Spain. All individuals were evaluated at least every six months until 30th November 2020 and routinely asked about symptoms consistent with COVID-19. A diagnosis procedure was conducted when any symptom was present. Cases were patients from this cohort with a confirmed diagnosis of COVID-19 between February and October 2020. Control group included the remaining HIV-infected individuals from the cohort without a diagnosis of COVID-19. Diagnosis of COVID-19 was established by the detection of SARS-CoV-2 RNA or antigen in nasopharynx exudate or bronchial-alveolar lavage, by PCR or EIA, respectively, or by presence of plasma SARS-CoV-2 antibodies by ECLIA. Overall, 394 (56%) individuals of this population were tested for plasma SARS-CoV-2 antibodies as a part of a seroincidence study [9]. Variables that were significantly associated with the occurrence of COVID-19 in the bivariate analysis, along with sex and Charlson index, were entered in a logistic regression model, using the enter method. All patients gave informed consent for using their data.

Seven hundred and four individuals were included at the cohort. All patients were receiving antiretroviral therapy by the time of the study. A diagnosis of COVID-19 was established in 23 (3.27%) individuals.

COVID-19 diagnosis was based on PCR in 12 (52.2%) patients, on antigen determination in 8 (34.8%) subjects and on serology in the remaining 3 (13%) individuals. Regarding the clinical spectrum, 3 (13%) patients were asymptomatic, 15 (65.2%) had upper-respiratory tract infections and 3 (13%) had viral pneumonia which required hospital admission with non-invasive mechanical ventilation. One (4.3%) individual showed extra respiratory symptoms which also required hospital admission. One (4.3%) patient developed severe pneumonia and died. Overall, three hundred and sixty-nine (52.4%) individuals were current smokers. A higher proportion subjects who acquired the HIV infection through sexual intercourse were no smokers [214 (65%) vs. 169 (45.8%), $p=0.001$]. Comparative characteristics of COVID-19 cases vs. controls without COVID-19 are depicted in table 1. Likewise, the relationship between several potential risk factors and COVID-19 are shown in table 1. After multivariate analysis, adjusting by sex, HIV infection way of transmission, tobacco smoking and Charlson index, only tobacco smoking was associated with the risk of SARS-CoV2 infection [aOR=5.47 (95% confidence interval 1.81-16.57), $p = 0.003$].

This study shows that tobacco smoking is associated with a lower incidence of SARS-CoV-2 infection among PLWH. Despite of higher risk of infection that would be expected among smokers, because of the frequent face touching during smoking act, the probability of being active smoking among participants diagnosed with COVID-19 was 9-fold lower than that of subjects without such a diagnosis.

The role that tobacco may be playing on the risk of SARS-CoV-2 infection is not entirely understood. On one hand, smoking has been reported to be associated with an increased COVID-19 severity [3]. Tobacco smoke exposure results in inflammatory processes in the lung, increased mucosal inflammation, expression of inflammatory cytokines and tumor necrosis factor α , increased permeability in epithelial cells, mucus overproduction, and impaired mucociliary clearance [10], all of which may prompt a more severe lung damage. On the other hand, there are some data suggesting the risk for COVID-19 among smokers could be lower. Thus, in a study conducted in England, a lower incidence of SARS-CoV-2 infection was observed among smokers. Similarly, in a recent meta-analysis (10), whose aim was to assess the impact of tobacco smoking on the risk of developing SARS-CoV-2 infection, current smoking also appeared to be associated with a lower risk of COVID-19.

The underlying mechanisms involved in the protective effect of tobacco are unclear. Nicotine has a marked impact on regulation of the activity of angiotensin-converting enzyme receptors (ACE) [11], which may interfere SARS-CoV-2 entrance into respiratory epithelial cells, thus reducing the risk of infection. However, Smith *et al* showed a correlation between higher ACE2 mRNA levels and SARS-CoV-2 infection in a study conducted in human lung tissue from current smokers. In addition, the frequent habit mouth-hands of smokers could also boost the risk of infection. Because of all these reasons, a higher risk of infection would be expected [4]. Nevertheless, a recent study performed in mammalian cell culture models has shown that other host molecular factors and pathways can be essential for SARS-CoV-2 infection [12]. Whether the expression of these additional factors is deregulated in current smokers is something that needs to be analyzed, but it might explain the reduced SARS-CoV-2 infection in this population with high levels of ACE2.

This study has some limitations. Given its retrospective design, there might be hidden conditions associated with tobacco use that result in less likelihood of SARS-CoV-2 infection. Thus, a greater proportion of individuals who acquired HIV infection through sexual transmission, particularly MSM (65% vs. 45.8%), were no smokers and COVID-19 might be more common in this specific subset. Nevertheless, the risk factors for HIV-infection were not associated with a higher risk SARS-CoV-2 infection in our study. Similarly, asymptomatic or mild COVID-19 cases may have gone unnoticed among control group. However, in most COVID-19 cases symptoms are present [13]. Moreover, all subjects included in this study were questioned about COVID-19 symptoms and close contact to patients with confirmed COVID-19. Those reporting symptoms or close contact to a COVID-19 confirmed case were tested for SARS-CoV-2 infection. In addition, a majority of participants had undergone a SARS-CoV-2 antibody test. In any case, further prospective cohort studies based on serology determinations should clarify this problem.

The molecular and physiological mechanisms by which tobacco smoking might protect against SARS-CoV-2 infection should be further investigated in order to gain insight into potential targets for the prevention and treatment of COVID-19. In the meanwhile, public-facing messages about a possible protective effect of tobacco smoking on the risk of COVID-19 must be avoided, taking into account the high risk for a wide spectrum of extremely severe health problems associated with tobacco smoking, which counterbalance any protective role of this habit against SARS-CoV-2 infection.

Abbreviations

CI: confidence interval; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus

Declarations

Ethical issues

The Ethics committee of the Hospital Universitario de Valme approved the study. All patients gave written informed to be entered in the cohort.

Funding

This work was funded in part by the Instituto de Salud Carlos III (Project 'PI16/01443'), integrated in the national I+D+I 2013-2016 and co-funded by the European Union (ERDF/ESF, "Investing in your future"), by the Spanish Network for AIDS investigation (RIS) (www.red.es/redes/inicio) (RD16/0025/0010, RD16/0025/0040), as a part of the Nacional I+ D+I, ISCIII Subdirección General de Evaluación and the European Fund for Development of Regions (FEDER). JAP has received a research extension grant from the Programa de Intensificación de la Actividad de Investigación del Servicio Nacional de Salud Carlos III (I3SNS). FG has received a research extension grant from the Programa de Intensificación de la Actividad de Investigación del Servicio Andaluz de Salud.

Competing Interests

None to declare

References

1. Weekly epidemiological update - 3 November 2020. Available at: <https://www.who.int/publications/m/item/weekly-epidemiological-update-3-november-2020>.
2. Del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy: A Cohort Study. *Ann Intern Med* **2020**; 173:536–541.
3. WHO. Smoking and COVID-19. **2020**. Available at: <https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19>.
4. Smith JC, Sausville EL, Girish V, et al. Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract. *Dev Cell* **2020**; 53:514-529.
5. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur. Respir. J.* **2020**; 55.
6. Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? *Intern Emerg Med* **2020**; 15:845–852.
7. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **2020**; 584:430–436..
8. Ward H, Atchison CJ, Whitaker M, et al. Antibody prevalence for SARS-CoV-2 in England following first peak of the pandemic: REACT2 study in 100,000 adults. *MedRxiv* **2020**. Available at: <https://doi.org/10.1101/2020.08.12.20173690>.
9. Fernandez-Fuertes M, Rodriguez-Pineda E, Macias J. Incidence of COVID-19 among people living with HIV in Southern Spain. *Scientific Square* **2020**. Available at: <https://doi.org/10.21203/rs.3.rs-110312/v1>..
10. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: A mechanistic review. *Int J Environ Res Public Health* **2018**; 15.
11. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* **2018**; 315:895–906.
12. Daniloski Z, Jordan TX, Wessels HH, et al. Identification of Required Host Factors for SARS-CoV-2 Infection in Human Cells. *Cell* **2021**. [Epub ahead of print]. Available at: <http://doi.org/10.1016/j.cell.2020.10.030>.
13. Yanes-Lane M, Winters N, Fregonese F, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. *PLoS One* **2020**; 15.

Table

Table 1. Factors associated with SARS-CoV-2 infection (N=704)

Parameter	Patients with COVID- 19, n (%) N=23	Control Patients, n (%) N=681	P bivariate	Unadjusted Odds Ratio (95% CI)	P multivariate	Adjusted Odds Ratio ^s (95% CI)
Sex						
Male	20 (87)	546 (80.2)	0.425	1.65 (0.48-5.63)	0.390	1.72 (0.50-
Female	3 (13)	135 (19.8)				5.92)
Age, years ^Ω	54 (44-58)	52 (43-57)	0.993	1.00 (0.96-1.04)	-	-
HIV infection way of transmission						
			0.291		0.741	
Sexual	15 (65.2)	367 (54)		1.60 (0.67-3.82)		1.17 (0.46-
Other	8 (34.8)	313 (46)				3.03)
Active tobacco smoking^a						
Yes						
No	4 (17.4)	365 (54.1)	0.002	5.59 (1.88-	0.003	5.47 (1.81-
	19 (82.6)	310 (45.9)		16.61)		16.57)
Alcohol intake^a, g/day						
< 50	22 (95.7)	624 (92.4)	0.570	0.56 (0.07-4.21)	-	-
≥ 50	1 (4.3)	51 (7.6)				
Active opiate use^b						
Yes	1 (4.3)	45 (6.7)	0.601	0.64 (0.08-4.82)	-	-
No	22 (95.7)	629(93.3)				
CD4 cell count ^Ω , cell/mL	705 (522-832)	624 (414-846)	0.502	1.00 (0.99-1.00)	-	-
Plasma HIV viral load^c, copies/mL						
< 50	23 (100)	585 (86.4)	0.997	0.00 (0.00)	-	-
≥ 50	0 (0)	92 (13.6)				

Charlson Index ^Ω	3 (0-3)	2 (0-3)	0.920	0.99 (0.78-1.25)	0.944	0.99 (0.80-1.24)
Active HCV infection						
Yes			1.000	0.00 (0.00)	-	-
No	0 (0)	2 (0.3)				
	23 (100)	676 (99.7)				

[§] Adjusted by sex, tobacco smoking and Charlson index.

^Ω Median (Q1-Q2)

*Age was excluded from the models, because this parameter is included in Charlson index.

^a Available in 697 patients; ^b Available in 696 patients; ^c Available in 700 patients