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# Smoking-associated morbidities on computed tomography lung cancer screens in HIV-infected smokers

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## Introduction

HIV-infected smokers are potentially a suitable target for lung cancer screening, as the smoking prevalence in this population is high, and chronic immunodeficiency significantly increases lung cancer risk [1,2]. Lung cancer screening with chest computed tomography (CT) is an opportunity to evaluate other chest morbidities. The objective of our study was to assess emphysema, bronchiolitis, and coronary artery calcification (CAC) in HIV-infected smokers undergoing chest CT lung cancer screening.

## Methods

This study was a post hoc analysis of the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS) EP48 HIV CHEST study, which evaluated the feasibility of early lung cancer diagnosis with chest CT in HIV-infected subjects in 13 French centres (NCT01207986). Subjects were aged  $\geq 40$  years, and had a history of smoking  $\geq 20$  pack-years, a CD4 T-lymphocyte nadir cell count  $< 350$  cells/ $\mu$ L, and a current CD4 T-cell count  $> 100$  cells/ $\mu$ L. Procedures have been previously described [1]. Two radiologists (SB and IB), blinded to clinical history, read all available baseline CT scans using a standard high-resolution reconstruction filter. The median effective dose was 2.97 mSv [interquartile range (IQR) 1.99 to 4.49 mSv].

The diagnosis of respiratory bronchiolitis was based on centrilobular micronodules or patchy ground-glass opacity presence in the right lung, as follows: absence, presence in the apical segment only, presence in the entire upper lobe or diffuse (scoring 0, 1, 2 and 3, respectively). Focal areas of low attenuation, representative of emphysema, were graded in each lobe of both lungs and the lingula using a five-point scale, as previously described [3]: a score of 0, 1, 2, 3, 4 or 5 indicated emphysema involving, respectively, none,  $< 5\%$ , 5 to  $< 25\%$ , 25 to  $< 50\%$ , 50 to  $< 75\%$  or  $\geq 75\%$  of the lobe. Each coronary artery was identified (main, left anterior descending, circumflex and right) and calcification in each artery was documented as absent, mild (calcification  $< 1/3$  of artery length), moderate (between  $1/3$  and  $2/3$  of length) or severe ( $> 2/3$  of length), corresponding to scores of 0, 1, 2 and 3, respectively, as previously described [4]. Scores were then summed (the score ranging from 0 to 12). Discordant scores were discussed until consensus for CAC only. Factors associated with emphysema on CT were analysed. Analysis of factors associated with CAC was not performed, as important cardiovascular risk factors (e.g. cholesterol level or history of diabetes) were not reported in the primary study.

## Results

Of the 443 participants included in the main study between February 2011 and June 2012, 393 subjects were evaluated for emphysema and bronchiolitis, and 396 for CAC (see Table 1 for subjects' characteristics).

According to the first reader, bronchiolitis and emphysema were reported in 164 (42%) and 292 (74%) subjects, respectively. Fifty-two subjects (13%) had a normal lung phenotype, 44 (11%) had bronchiolitis, 149 (38%) had bronchiolitis and emphysema combined, and 148 (38%)

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\*See Appendix.

**Table 1** Subjects' characteristics in the emphysema and bronchiolitis study and the coronary artery calcification study

Characteristic	All subjects (n = 393)* (em- physema and bronchiolitis study)		All subjects (n = 396) (CAC study)	
Age (years) [median (IQR)]	49.5	46.0–53.7	49.5	46.1–53.7
Female [n (%)]	67	17	67	17
BMI < 18.5 kg/m <sup>2</sup> [n (%)]	34	9	33	8
Last CD4 count (cells/ $\mu$ L) [median (IQR)]	574	416–764	574	415–764
CD4 count nadir (cells/ $\mu$ L) [median (IQR)]	168	80–256	168	76–259
Last viral load < 50 copies/s [n (%)]	353	90	355	90
History of pneumocystis infection [n (%)]	33	8	33	8
HCV coinfection [n (%)]	132	34	133	34
History of cannabis inhalation [n (%)]	141	36	141	36
History of IDU [n (%)]	113	29	114	29
Cigarettes/day [median (IQR)]	20	10–20	20	10–20
Duration of smoking (years) [median (IQR)]	30	28–36	30	28–36
Pack-years [median (IQR)]	30	25–40	30	25–40
FEV <sub>1</sub> /FVC (post-bronchodilator) (%) [median (IQR)] <sup>†</sup>	74	68–80	NA	NA
FEV <sub>1</sub> (% predicted) [median (IQR)]	94	81–104	NA	NA

CAC, coronary artery calcification; IQR, interquartile range; BMI, body mass index; ARV, antiretroviral therapy; HCV, hepatitis C virus; IDU, injecting drug use; NA, not available.

Spirometric data available for 338 subjects.

had emphysema alone. Forty-one (10%), 90 (23%) and 33 (8%) subjects had bronchiolitis scores of 1 (apical segment), 2 (entire upper lobe) and 3 (diffuse), respectively. According to the second reader, bronchiolitis was present in 193 (49%) subjects and emphysema in 297 (76%) subjects. Fifty-six subjects (14%) had a normal lung phenotype, 45 subjects (11%) had bronchiolitis, 173 (44%) had emphysema, and 119 subjects (30%) had bronchiolitis and emphysema. Fifty-three (13%), 55 (14%) and 85 (22%) patients had bronchiolitis scores of 1 (apical segment), 2 (entire upper lobe) and 3 (diffuse), respectively.

Mean scores of the two readers for emphysema were  $1.13 \pm 1.01$  for the upper area (upper lobes),  $0.43 \pm 0.67$  for the middle area (middle lobe and lingula), and  $0.63 \pm 0.82$  for the lower area (inferior lobes). Inter-observer agreement was fair for bronchiolitis and emphysema (kappa coefficient  $k = 0.51$  and  $0.61$ , respectively). Multivariate analysis showed that the only factors associated with emphysema were age ( $P = 0.002$ ), number of cigarettes smoked per day ( $P = 0.044$ ) and history of injecting drug use ( $P < 0.001$ ).

CAC was reported in 266 subjects (67%): 209 subjects (53%) had a score between 1 and 3, and 57 subjects (14%) a score  $\geq 4$ .

## Discussion

Our study was the first to systematically assess emphysema, bronchiolitis and CAC on chest lung cancer CT screens in HIV-infected smokers > 40 years old. Rates were much higher in our study than in lung cancer screening studies in the general population, despite the ages of the subjects being similar [5,6]. However, the lack of a control group in our study precludes direct comparisons. Factors associated with emphysema in our study are factors observed in the general population and, interestingly, did not include any virological or immunological factors.

Early identification and assessment of CAC are important as appropriate preventive strategies could reduce the risk of coronary events. The CAC score used on nongated chest CT in the International Early Lung Cancer Action Program (I-ELCAP) lung cancer screening study, which was identical to our score, showed a significant association with cardiovascular deaths, particularly when scores exceeded 4 (14.5% in our study) [5].

In conclusion, we found that > 85% of HIV-infected smokers over 40 years of age had bronchiolitis, emphysema or both on their chest CT, and that as many as 67% of subjects had some evidence of CAC. Whether systematic assessment and grading of these phenotypes on lung cancer CT screens of HIV-infected smokers could reduce cardiovascular and pulmonary events and mortality still needs to be explored.

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**Conflicts of interest:** All authors declare no conflicts of interest.

## Appendix: the ANRS EP48 HIV CHEST Study Team

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