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Feasibility and efficacy of early lung cancer diagnosis with chest computed tomography in HIV-infected smokers

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EP48 HIV CHEST study Team

Objective: Lung cancer screening with chest computed tomography (CT) is beneficial in smokers aged 55 to 74 years. We studied the risks, benefits and feasibility of early lung cancer diagnosis with CT in HIV-infected smokers.

Design and setting: French, multicentre, single round chest CT study in France, realized between February 2011 and June 2012.

Participants: Patients were HIV-infected smokers at least 40 years, at least 20 pack-years, with a CD4⁺ T-lymphocyte nadir count below 350 cells/ μ l.

Intervention: Single chest CT with a proposed standardized workup algorithm of positive images.

Main outcome measure: The outcome was the number of histologically proven lung cancers diagnosed by CT with a 2-year follow-up.

Results: Median age of the 442 included patients was 49.8 years, 81.6% were under 55 years, 84% were men, median smoking was 30 pack-years, median nadir and last CD4⁺ cell counts were 168 and 574 cells/ μ l, respectively, and 90% of patients had a plasma HIV RNA below 50 copies/ml. A positive image at baseline was reported in 94 (21%) patients, and 15 (3.4%) patients had 18 invasive procedures with no serious adverse events. Lung cancer was diagnosed in 10 patients (six at early stages), of which nine (2.0%, 95% confidence interval: 0.9–3.8) were CT detected, and eight in patients below 55 years.

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Conclusion: Early lung cancer diagnosis with CT in HIV-infected smokers was feasible, safe, and yielded a significant number of cancers. Lung cancer screening of HIV-infected smokers with an important history of immunodeficiency revealed a substantial number of cancers at younger ages than the targeted range in the general population.

Keywords: computed tomography, HIV, lung cancer, screen, smoking

Introduction

Since the advent of combination antiretroviral therapy (cART), a shift in mortality and morbidity has been observed in people living with HIV (PLWHIV) from AIDS to non-AIDS diseases, amongst which a high proportion of malignancies [1–3]. In this population, lung cancer incidence and mortality rate are the highest among all the non-AIDS-defining malignancies [3–11]. Studies have also found increased standardized incidence ratios (SIR) of lung cancer in the HIV-infected in comparison to the general population [4,5,8,12,13], with increased rates even after adjusting for smoking [14]. However, smoking is the primary trigger of lung oncogenesis in the general [15] and the HIV-infected population, as reflected by nearly 100% smoking prevalence in published case series [14,16–18]. Lung cancers will remain frequent in PLWHIV as long as smoking prevalence in this population remains high.

The randomized National Lung Screening Trial (NLST) showed a significant 20% lung cancer mortality reduction and a 6.7% overall mortality reduction in smokers from the general population aged 55 to 74 years with three annual chest low dose computed tomography (LDCT) versus radiography [19]. Due to higher incidence of lung cancer, lung cancer screening with chest CT in PLWHIV could also be beneficial. However, because of the high prevalence of pulmonary morbidities, such as infectious events, chronic obstructive pulmonary disease (COPD) and emphysema in this population [20–23], chest CT might reveal many false positive nodules or other abnormalities, leading to inappropriate invasive diagnostic procedures with increased risks of complications. Thus, studies are needed to evaluate feasibility, benefits and harms of lung cancer screening in this population. We conducted a lung cancer early diagnosis programme with a single chest CT in PLWHIV in France.

Methods

Study design and participants

This study was a multicentric prospective cohort of PLWHIV at risk for lung cancer followed for 2 years after

assessment of potential lung cancer related images on a single chest CT. To be included, patients had to be infected with HIV and be smokers with a total uptake of at least 20 pack-years (possibly stopped in the last 3 years), be aged at least 40 years, to have a nadir CD4⁺ T-cell count less than 350 cells/ μ l, a current CD4⁺ T-cell count at least 100 cells/ μ l, and a medical insurance coverage. We chose a nadir CD4⁺ T cell count below 350 cells/ μ l to select patients with a history of significant immunodeficiency and a relatively long history of HIV exposure, and a last CD4⁺ value at least 100 cells/ μ l to minimize risk of infectious nodules. Patients were excluded in case of current active cancer or AIDS-classifying disease, lung infection within the previous two months, pregnancy, breastfeeding and contraindication to thoracic surgery. Patients were included in the study by their HIV caring physician during routine visits in 14 clinical centres in France. The study was approved by the Research Ethics Committee of Montpellier Sud-méditerranée IV (No ID-RCB: 2010-A00781-38) prior to data collection and was conducted in accordance with the standards of Ethics Committee and the Helsinki Declaration. All study participants gave written informed consent.

Procedures

All chest CT were acquired in 13 radiologic departments, all from French university-hospital centres, using multi-detector row scanners without contrast material enhancement. The entire chest from apex to posterior recesses was included at end inspiration in one breath hold according to the protocol of the study (100 kVp, automated tube current modulation) with section thickness not greater than 1 mm. The median effective dose derived from the product of Dose Length Product and a conversion coefficient ($k = 0.014 \text{ mSv}\cdot\text{mGy}^{-1}\cdot\text{cm}^{-1}$) [24] was 2.97 mSv, interquartile range (IQR) of 1.99 to 4.49 mSv. Though there is no standardized definition of low dose in CT for lung cancer screening, actual irradiation goal is less than 2 mSv (1.5 mSv average effective dose in the NLST trial for instance [19]), to be put in perspective with a 8 mSv or higher effective dose in diagnostic CT. The effective dose in our study was thus low to moderate according to cases. One radiologist from each centre read the CT and completed a standardized report.

In case of a positive image on chest CT, a standardized diagnostic workup and follow-up were suggested, adapted from the International Early Lung Cancer Action Program (IELCAP) algorithm (as detailed in efigure 1 and text in the online-only supplement, <http://links.lww.com/QAD/A819>) [25]. Final decision of invasive procedures (biopsy) was left to the panel of physicians in charge of the patient. A positive chest CT result was defined as the identification of at least one solid or partly solid noncalcified pulmonary nodule not less than 5 mm in diameter (maximal length of the cross-sectional area of the nodule), at least one nonsolid noncalcified pulmonary nodule not less than 8 mm in diameter, a solid endobronchial nodule or a significant adenopathy. All patients had a planned clinical evaluation 2 years after study entry. Diagnosis of lung cancer was made by histological analysis of biopsy specimens. In case of lung cancer diagnosis, patients were referred to thoracic oncologists and surgeons for standard of care. Stage classifications followed the seventh edition of the classification of malignant tumours [26].

Baseline chest CT was realized after a clinical evaluation on the same day assessed that no condition (i.e. lung infection) should postpone the exam. Investigators were advised to give information to the patient on benefits of smoking cessation. At baseline visit, demographical and immuno-virological characteristics were recorded. At the 24 months visit, numbers and types of procedures and smoking status were recorded. We also collected all interval cardiovascular morbidity, cancer diagnosis and infectious complications.

Outcomes

The predefined primary outcome was the number of histologically proven lung cancers diagnosed by the single chest CT. Secondary outcomes were the stages at diagnosis of these lung cancers, the number of diagnostic procedures realized and the description of severe adverse events related to procedures, and a description of characteristics in patients diagnosed with lung cancers.

Statistical analysis

To calculate the number of patients needed in the study, we used results from the first screening round with chest LDCT from the I-ELCAP cohort [25], in which a lung cancer prevalence of 1.07%, confidence interval (CI) 95% (0.95–1.20), was found in the year following baseline LDCT in patients aged 40 to 69 years. With a two to three increased risk of lung cancer in PLWHIV in comparison with patients from the general population [4,12,13,27], we hypothesized lung cancer prevalence in our study to be about 3%. Thus, with an α and a β risk of respectively 5 and 80%, the inclusion and follow-up of 2 years of 400 patients would be sufficient to detect 12 lung cancers (95% CI: 5–19 lung cancers). With an anticipated loss to follow-up of 10%, we planned to include 450 PLWHIV.

The study is registered with ClinicalTrials.gov, number NCT01207986.

Role of the funding source

The study sponsor was the ANRS (France REcherche Nord&Sud Sida-hiv Hépatites). The funder of the study had contributed to the study design. All authors had full access to the study data and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between February 2011 and June 2012, 476 patients were screened for the study, and 442 patients had a CT (Fig. 1). Briefly, patients had a median age of 49.8 years, median CD4⁺ T-cell nadir and current counts of 168 and 574 cells/ μ l, respectively, 84% were men, 98% on cART, for a median duration of 13.8 years, 90% had a HIV viral load less than 50 copies/ml, median smoking was 30 pack-years and 35% had a history of cannabis use (Table 1). Median follow-up time after CT was 24.4 months (IQR of 22.8 to 26.4 months).

A total of 10 lung cancers were diagnosed (Table 2), amongst which nine had been visualized as positive nodules on baseline CT. Of these nine patients, eight had histologically proven lung cancers (seven of which were adenocarcinomas, and one a squamous cell carcinoma), and an additional female patient had a highly probable lung cancer suspected on a 10-mm nodule. She underwent a negative bronchoscopy but no further biopsies as a preinvestigation diagnosis of severe arterial pulmonary hypertension precluded surgical thoracoscopy. She was treated for lung cancer with stereotaxic radiotherapy. Of the nine CT detected lung cancers, four were stage IA, one stage IB, one stage IIA, and three were stage IV. Two of the three patients with stage IV lung cancers had delayed diagnosis procedures after detection of a positive nodule on their CT (see online-only supplement for clinical details, <http://links.lww.com/QAD/A819>). The prevalence of CT detected lung cancer in our population of HIV infected smokers was 2.03% (95% CI: 0.90–3.80), and the number of patients needed to detect one lung cancer with the CT procedure was 49 (95% CI: 26–111). One additional patient was diagnosed with an extended small cell lung cancer 88 weeks after his baseline CT had not identified any nodule. None of these lung cancer patients had a history of AIDS classifying disease involving the lung.

As shown in Fig. 1, 94 patients (21%) had at least one positive image on baseline chest CT (see supplementary details on nodules in online-only supplement, <http://links.lww.com/QAD/A819>). Thirty-eight patients

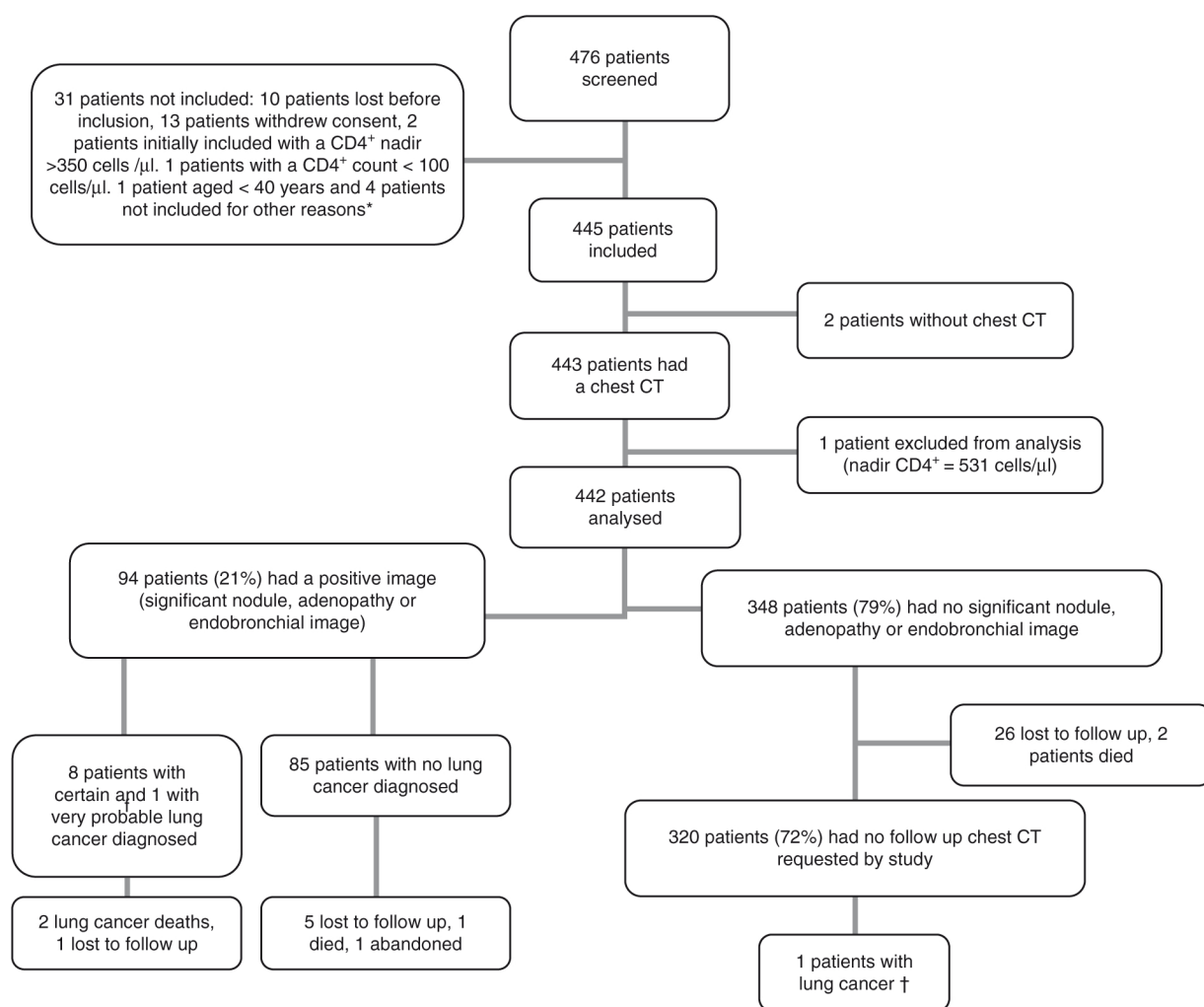


Fig. 1. Study flow chart. CT, computed tomography. *Other reasons for patients not being included were: one chest CT realized with radiological contrast injection (not allowed by study protocol), one patient fractured a bone and could not go to his scheduled CT, and two patients had lung infections (within 2 months of study end). †This patient had a diagnosis of small cell lung cancer 88 weeks after his baseline normal CT, after clinical symptoms appeared.

(8.6%) did not have the last visit at 2 years: five patients died, 32 (7.2%) were lost to follow-up, and one abandoned the study 3 months after inclusion due to anxiety caused by the perspective of invasive diagnostic procedures for a 12-mm solid nodule. Six lost patients had positive baseline images, and one of these six patients had a stage IA lung cancer diagnosed at month 5, and was lost after 1 year of follow-up.

After the 442 baseline CTs, 54 patients (12%) had a second, 22 (5%) a third, 16 (4%) a fourth or fifth, and two (0.5%) a sixth protocol CT for follow-up of positive images. Eighteen diagnostic procedures in 15 patients (3.39% of the total population, 15.96% of the CT positive patients) were undertaken (Table 3). Apart for the eight proven lung cancers, one mucosa-associated lymphoid tissue (MALT) lymphoma, one Abrikossoff tumour, and one *Mycobacterium xenopi* granulomatous infection were

diagnosed. In four patients, invasive diagnostic procedures did not yield any final aetiology to the detected positive chest nodules. None of the diagnostic procedures yielded any serious adverse events.

During follow-up, other events attributable to smoking were cardiovascular in 12 patients (2.7%) [myocardial ischemia ($n=8$), stroke ($n=2$), and symptomatic peripheral arterial disease ($n=2$)], infectious events in 37 patients (8.4%) [pneumonia or COPD exacerbations ($n=15$)], new cancers, other than lung in 13 patients, of which six are associated with smoking [15]: urothelial cancer ($n=2$), hepatocarcinoma, colon cancer, epidermoid carcinoma of the lip, and kidney cancer (one patient each). Five patients died during the study: two of consequences of their stage IV lung cancers diagnosed during the study, one of severe lung infection, one of sudden death and one of a motorbike accident.

Table 1. Study patients' characteristics.

Characteristics	Value
Total numbers	442
Age (median), (IQR)	49.8 (46.3–53.9)
40–44 years	74 (17%)
45–49 years	153 (35%)
50–54 years	134 (30%)
55–59 years	51 (12%)
60 years or more	30 (7%)
Men (%)	370 (84)
Numbers of years of known HIV infection, median (IQR)	17.6 (10.8–22.3)
Nadir CD4 ⁺ (cells/ μ l), (IQR)	168 (75–256)
Nadir CD4 ⁺ < 200 cells/ μ l (%)	266 (60)
Last CD4 ⁺ value, median (cells/ μ l)	574 (408–765)
Last viral load < 50 copies/ml	396 (90)
Antiretroviral use (information for <i>n</i> = 439)	435 (99%)
Duration of ARV treatment, median (years)	13.8 (7.1–16.0)
History of AIDS classifying disease (%)	124 (28)
History of pneumocystis pneumonia (%)	42 (9.5)
History of HCV infection (%)	147 (33)
Cigarettes (per day) (IQR)	20 (15–25)
Duration of smoking (years) (IQR)	30 (28–36)
Cessation of smoking within the last 3 years (%)	37 (8)
Smoking, pack-years (IQR)	30 (25–40)
History of cannabis consumption ^a , <i>n</i> (%)	155 (35)
Asbestos exposure ^a , <i>n</i> (%)	22 (5)
Alcohol intoxication ^a , <i>n</i> (%)	86 (19)
History of IVDU, <i>n</i> (%)	125 (28)
History of cancer, <i>n</i> (%)	40 (9)
History of COPD, <i>n</i> (%)	59 (13)

Details of the 40 cancers: Kaposi sarcoma (*n* = 12), non-Hodgkin Lymphoma (*n* = 8), cervical cancer (*n* = 4), anal cancer (*n* = 3), colorectal cancer (*n* = 2), melanoma (*n* = 2), bladder cancer, hepatocarcinoma, basal-cell carcinoma, lung cancer, testicular cancer, breast cancer, pancreas cancer, Hodgkin disease, head and neck cancer (one patient each). ARV, antiretroviral; COPD, chronic obstructive pulmonary disease (as reported); IQR, interquartile range; IVDU, intravenous drug use.

^aAs assessed by the investigators.

Table 2. Characteristics of patients with lung cancers.

Patient	81 008	67 003	67 029	90 048 ^b	57 017	49 013	75 062	75 006	57 016	67 016
Age	45	46	49	50	50	52	52	54	56	58
Sex	M	F	M	M	F	M	M	M	M	F
Smoking (pack-years)	30	52	45	40	27	35	60	28	34	21
Smoking (years)	30	35	30	32	36	37	34	37	39	42
Cannabis use	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
COPD	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Viral load (copies/ml)	<40	<40	<40	<20	61	<40	43	<20	<40	<40
Nadir CD4 ⁺ (cells/ μ l)	160	132	321	1	60	236	214	71	201	218
CD4 ⁺ value (cells/ μ l)	637	597	378	448	590	568	859	345	480	573
CD4 ⁺ /CD8 ⁺ ratio	0.58	0.84	0.88	0.34	1.02	0.47	2	0.42	1	0.54
Positive LDCT image	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Lung cancer histology	AdenoK	AdenoK	AdenoK	Small cell	AdenoK	AdenoK	AdenoK	Squamous cell	AdenoK	No histology
Lung cancer stage	IA	IV	IIA	Extended	IV	IV	IA	IA	IB	IA ^a
Last LDCT before biopsy (months)	M1	M18	M12	M0	M0	M0	M0	M3	M3	M24
Time till cancer diagnosis (weeks)	23	76	70	88	12	66	7	23	7	NA

AdenoK, adenocarcinoma of the lung; Squamous cell, squamous cell carcinoma of the lung.

^aExtension established with radiological evaluation. COPD, chronic obstructive pulmonary disease (as measured by spirometry or reported); IVDU, intravenous drug use; NA, non-applicable.

^bThis patient had a normal baseline CT, and became symptomatic during follow-up with a diagnosis of small cell lung cancer 88 weeks after inclusion.

Of 404 patients who reached the 2-year visit, complete data on smoking was available for 402 patients (99.5%), of whom 368 (91%) were active smokers at baseline. Seventy-four active smokers (20%) had stopped smoking at their last visit. Positive baseline images were present in 57 (19%) of smokers at baseline and last visit versus 19 (26%) of patients that had ceased smoking at last visit, but distributions were not significantly different (*P* = 0.23).

Discussion

We performed a single chest CT study for early lung cancer diagnosis in a multicentre French HIV-infected cohort of smokers and found a 2.03% (95% CI, 0.90–3.80) prevalence of lung cancer and a 21% prevalence of positive images. We also evidenced that six of nine lung cancers with baseline positive images on their CT were diagnosed at early stages. Study adherence was high, and diagnostic procedures were few and safe.

Our result of nine CT detected lung cancers in our HIV-infected smoking population with a CD4⁺ T-cell nadir below 350 cells/ μ l is high. Whether our result reflects increased risk of lung cancer in HIV-infected smokers in comparison with smokers of similar age from the general population is out of the scope of our study in the absence of a control group, but an increased risk is supposedly mediated through persistent decreased tumoural immunovigilance despite cART. Other important mechanisms are chronic lung damage due to clinical or subclinical repeated pulmonary infections and enhanced inflammation [28,29]. In the French Hospital Database on HIV

Table 3. Diagnostic procedures induced by the discovery of a positive image on computed tomography.

Patient	1st invasive procedure	2nd invasive procedure	Lung cancer diagnosis	Alternative histological diagnosis
32007	Thoracic surgery	No	No	MALT lymphoma
32033	Fine-needle CT biopsy	Thoracic surgery	No	<i>Mycobacterium xenopi</i> infection
49013	Bronchoscopy	No	AdenoK	No
57016	Fine-needle CT biopsy	No	AdenoK	No
57017	Fine-needle biopsy	No	AdenoK	No
67003	Fine-needle CT biopsy	Fine needle CT biopsy	AdenoK	No
67016	Bronchoscopy	No	Very probable	No
67029	Thoracic surgery	No	AdenoK	No
75006	Thoracic surgery	No	Squamous cell	No
75039	Thoracic surgery	No	No	AAH
75062	Thoracic surgery	No	AdenoK	No
76032	Bronchoscopy and gastroscopy	No	No	Abrikossoff tumour
81008	Thoracic surgery	No	AdenoK	No
90013	Bronchoscopy	No	No	No
90031	Bronchoscopy	No	No	No

AAH, atypical adenomatous hyperplasia; AdenoK, adenocarcinoma of the lung; MALT, mucosa-associated lymphoid tissue; Squamous cell, squamous cell carcinoma of the lung.

(ANRS CO4 FHDH Study), an association between incidence of lung cancer and chronic immunodeficiency was observed with a dose relationship (i.e. the higher the CD4⁺ cell count, the lower the incidence of cancer) [30]. In another study from the same database, incidence was similar in comparison with the general population only in patients that reached a lymphocyte CD4⁺ cell count above 500 cells/ μ l [8]. Despite high CD4⁺ cell counts at inclusion in our patients, all patients had a long history of immunodeficiency as reflected by the low nadir values, and most patients with lung cancer had a low CD4⁺/CD8⁺ lymphocyte ratio at inclusion, reflecting only partial immune recovery (Table 2).

The number of CT detected lung cancers may have been less than the real numbers of lung cancers in our study. Indeed, we realized a single chest CT and may have not, in some cases, diagnosed asymptomatic cancerous nodules below 5 mm. However, numbers of under diagnosed lung cancers were probably low, as the probability for a patient with a nodule not more than 5 mm of developing lung cancer in the following 2 years was 0.4% [0.2–0.7] in a recent study, not significantly different from the probability of lung cancer in patients without any visible nodule [31].

Eight of the 10 lung cancers occurred in patients younger than 55 years. This result is notable, as these patients would have been missed if NLST guidelines for lung cancer screening had been followed. Performing chest CT in our study in patients over 45 years would not have missed any lung cancers, a result in coherence with epidemiological studies of excess lung cancer risk in PLWHIV in comparison with the general population starting between the ages of 40 and 50 years [32]. However, screening PLWHIV too young is probably not efficient. A study from Baltimore screened with five annual chest LDCT 224 current/former HIV-infected smokers aged 25 years or older (median age 48 years,

IQR [44–53]), and did not detect any lung cancers [33]. Our results are also partly explained by the age distribution of our patients, which reflects HIV epidemiology, as nearly two-thirds were between 45 and 54 years. However, accelerated and accentuated aging in PLWHIV who smoke could have played a significant role in the age distribution of lung cancers in our study. Accelerated aging results from pathways and mechanisms common to the aging process, whilst accentuated aging results from HIV infection behaving as an additional risk factor, thus accentuating the risk of lung cancer at every age in PLWHIV who smoke [34]. A comparison of North American HIV and cancer registries showed that median age of lung cancer diagnosis was 4 years younger in PLWHIV when both populations were standardized on age, suggesting moderate accelerated aging [35]. Data from the VACS cohort showed that mean adjusted-age occurrence of non-AIDS-defining malignancies was similar in HIV-infected versus uninfected patients, but that incidence was significantly increased through all age groups, reflecting accentuated aging [36].

One of the concerns of lung cancer screening in HIV-infected smokers was the possibility of a high number of false positive images identified on chest CT due to former or active lung infections, emphysema or bronchiolitis, leading to subsequent high numbers of CT follow-up scans and invasive diagnostic procedures. Though these rates of false positive images depend on numerous factors including participants' characteristics, positive nodule definition and follow-up algorithms, the 21% prevalence of positive images in our study was in the range (13 to 29%) of most published lung cancer screening studies in the targeted general population settings [19,25,37,38]. Moreover, the number of invasive procedures was low (18 procedures in 15 of patients) in our study and in four cases permitted histological alternative diagnosis.

We did not find any impact of positive CT images on smoking cessation, contrary to some studies in the general population [39–41]. Inclusion in a lung cancer diagnosis programme may have less impact on smoking abstinence in PLWHIV who regularly received counselling on risk reductions, including smoking hazards, by their physicians than in patients included in lung cancer screening programs in the general population [41]. Patients from the general population included in lung cancer screening studies are usually ‘healthy’ smokers, contacted by means of advertisements, direct mailing or use of mass media [38,42,43]. These patients, volunteering to undergo screening, may be more willing to quit smoking and may strongly benefit from their first encounters with health professionals to achieve this goal, further enhanced by the presence of positive images.

As suggested by the numerous smoking-related morbidities in lung cancer screening studies in the general population [19] and in our study, quitting smoking is the most efficient intervention to diminish mortality in smokers, whether HIV-infected or not.

Our study has limitations. First, some characteristics were insufficiently quantified, such as cannabis use. Second, quality of life questionnaires, evaluating the impact on anxiety of positive images, were not administered. Third, as a nonrandomized study, we could not evaluate whether chest CT increased survival and diminished lung cancer mortality in PLWHIV, and follow-up of patients after their baseline chest CT was 2 years only. Fourth, our multicentre study took place in university hospitals, with expertise in CT nodule management, and results may not be generalizable to all clinical settings. Finally, lung cancer induced by radiation is a possible long-term adverse effect that could not be assessed in our study, and would be important to estimate if HIV-infected patients are to be screened at younger ages than patients from the general population, as there is a known interaction between radiation and smoking on lung cancer risk [44]. Upholding this, a substantial number of participants underwent numerous chest CT and additional diagnostic radiological procedures in our study.

Despite these caveats, our study has important implications for lung cancer screening in PLWHIV at high risk. We showed that lung cancer early diagnosis with CT in HIV smokers is feasible. We found an acceptable rate of false positive images and no reported adverse events. Also, adherence to study protocol was high. Finally, lung cancer screening should benefit PLWHIV younger than 55 years who smoke and who have a history of significant immunodeficiency, possibly starting as early as 45 years.

In conclusion, within the 2-year follow-up, we found that chest CT was a safe and effective procedure to detect lung cancer, most of them at early stages, in HIV-infected heavy smokers, aged over 45 years, with history of nadir

CD4⁺ below 350 cells/ μ l and current CD4⁺ above 100 cells/ μ l. Screening of HIV-infected smokers with a significant history of immunodeficiency for lung cancer revealed a substantial number of cancers at younger ages than the targeted age range in the general population.

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Conflicts of interest

The authors report no conflicts of interest.

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