Potential lung cancer screening outcomes using different age and smoking thresholds in the ANRS-CO4 French Hospital Database on HIV cohort

A Makinson, L Tron, Sophie Grabar, B Milleron, J Reynes, V Le Moing, D Morquin, F Lert, D Costagliola, M Guiguet

Lung Cancers Potentially Screened Using Different Age and Smoking Thresholds in the ANRS CO4-French Hospital Database on HIV Cohort

A. Makinson[1], L. Tron[2], S. Grabar[3-4], B. Milleron[5], J. Reynes[1], V. Le Moing[1], D. Morquin[1], F. Lert[6], D. Costagliola[3], M. Guiguet[3], on behalf of the French Hospital Database on HIV (ANRS-CO4)

1 Infectious and Tropical Diseases Department, UMI 233/INSERM U1175, Montpellier University Hospital, France

2 University Hospital of Caen, Caen, France; 'ANTICIPE' U1086 INSERM-UCN, Centre François Baclesse, Caen, France

3 Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP) Paris, France

4- Biostatistic and Epidemiology unit, Cochin hospital, Paris and Paris-Descartes University, Paris France

5 Intergoupe Francophone de Cancérologie Thoracique (IFCT), Paris and University Hospitals of Bichat and Tenon, APHP, France.

6 Department of Epidemiology of Occupational and Social Determinants of Health, Center for Research in Epidemiology and Population Health, INSERM, U1018, Villejuif, France.

Abstract

Introduction: Most lung screening programs condition chest low dose computed tomography to subjects ≥ 55 years and smoking ≥ 30 pack-years. Whether same criteria apply to people living with HIV (PLHIV) is uncertain, given lung cancer susceptibility to immunodeficiency and high rates of smoking. We assessed different outcomes simulating one round lung cancer screening in PLHIV using different age and smoking thresholds for eligibility.

Methods: Data from the French national ANRS CO4-FHDH cohort of PLHIV and a national representative survey of PLHIV in care in 2011 (ANRS-VESPA2 study) were used to estimate the maximum proportion of incident lung cancers between 2012-2016 potentially screened in 2011. Secondary outcomes were numbers of eligible subjects in the cohort and numbers of subjects needed to screen (NNS) to detect one lung cancer.

Results: Among 77819 PLHIV in 2011 (median age 46 years, 66% men), 285 subjects had lung cancer thereafter. The US Preventive Services Task Force (USPSTF) recommendations (55-80 years, ≥30 pack-years) would have detected 31% of lung cancers at most. Lowering the minimal age to 50 and 45 years would have detected 49%, and 60% of cancers, respectively, but would have highly increased eligible subjects and NNS to detect one lung cancer.

Conclusions: USPSTF criteria would have detected only a minority of lung cancers in a large French cohort of PLHIV in 2011. Screening PLHIV at younger ages (45 or 50 years) or lower smoking thresholds (20 pack-years) should be evaluated in future studies, despite implying higher numbers of subjects and NNS to detect one lung cancer.

Introduction

Since the advent of antiretroviral therapy, there has been a shift of morbidity and mortality in resource-rich settings from AIDS to non-AIDS defining diseases in people living with HIV (PLHIV). Lung cancer is now the leading cause of cancer mortality in PLHIV [1,2], with high incidences and increased standardized incident ratio (SIR) in comparison with the general population[3-6], explained in part by higher prevalence of smoking[7]. However, incidence rates remains increased even after accounting for smoking [8-10], and chronic immunodeficiency[11] and recurrent lung infections[12,13] are additional risk contributors. There is evidence in observational studies that lung cancer occurs at slightly younger ages in PLHIV than in the general population: 3.3 years in the French Hospital Database cohort (FHDH) [5] and 4 years in north American registries[6].

Early lung cancer screening is paramount to increase survival. The National Lung Screening Trial (NLST) showed a 20% lung cancer and a 6.7% relative mortality reduction in high risk smokers from the general population for subjects randomized to three annual chest low dose computed tomography (LDCT) versus radiography [14]. Subjects were all smokers of 30 pack-years or more, aged 55 to 74 years, and if former smokers, quit within 15 years. In preliminary results presented at the IASLC 19th World Conference, the NELSON screening study showed a 26 % (9-41%, 95% CI) reduction in male lung cancer deaths at 10 years of study follow-up in the screening arm with LDCT in comparison with no intervention. Volunteers were aged 50 to 75 years, had a smoking history of either 15 cigarettes per day for 25 years or 10 cigarettes for 30 years, active or possibly quit within 10 years. In countries where lung cancer screening is recommended, criteria have been largely adapted from the NLST[15].

Further studies are needed to address how well NLST or other selection criteria perform in HIV-infected populations. Whether PLHIV at risk of lung cancer should be screened at younger ages or at lower smoking thresholds is also an issue [16]. Randomized lung cancer screening studies in PLHIV are not feasible, as they would imply very high numbers of volunteers. In this study, we searched for PLHIV with symptomatic lung cancers diagnosed in the French national cohort (ANRS CO4-FHDH) between 2012 and 2016. We evaluated how many of these cancers could have been detected in 2011 using various age and smoking eligibility cut-offs, assuming that all subjects meeting eligibility would have undergone LDCT and that all lung cancers were present and asymptomatic in 2011. Proportion of lung cancers potentially screened and numbers of subjects needed to screen (NNS) to detect one lung cancer were also assessed.

Methods

Participants and follow-up

The ANRS CO4-FHDH cohort is a French nationwide, open, prospective cohort of HIV-infected adults managed in more than 130 public hospitals[17]. All volunteers gave written informed consent to participate to the cohort. We counted all lung cancers diagnosed between the first of January 2012 and the 31st of December 2016. Subjects followed in 2011 were excluded if they had a lung cancer diagnosed in or prior to 2011, or had less than 5 years of follow-up (2012-2016), except in the event of death. We followed up subjects until death, lung cancer diagnosis or the 31st of December 2016, whatever occurred first.

We grouped subjects in 18 scenarios of different age ranges and smoking thresholds. Nine age ranges were created with a minimum age of either 45, 50 or 55 years combined with a maximum age of either 70, 75 or 80 years, with two smoking minimal thresholds of 30 or 20 pack-years, possibly quit within the last 15 or 10 years respectively. We added 2 additional scenarios: one based on the NLST criteria, which assessed subjects aged 55 to 74 years with a smoking history of at least 30 pack-years possibly quit within 15 years- and a second based on the USPSTF criteria - with similar thresholds for smoking history but a higher maximum age limit of 80 years

Data collection and smoking imputation

All participants' clinical and biological data were collected prospectively at each HIV-motivated visit. For this study, data collected in 2011 included demographic characteristics and sexual preference, smoking hazards, immunovirological data, and lung cancer events or deaths starting on the 1st of January 2012 up to the 31st of December 2016.

Smoking behavior was poorly recorded in the ANRS CO4-FHDH cohort but for subjects with a lung cancer diagnosis. For lung cancer-free subjects, we used smoking data recorded in a national representative survey of 3016 HIV-infected people (ANRS-VESPA2 study)[7]. This survey was conducted between 2011 and January 2012 in 73 randomly selected hospital departments in metropolitan France and was conceived to be representative of PLHIV followed in public hospitals. In the ANRS-VESPA2 study, a sample of patients, randomly selected according to the order of their appointment, were invited to participate by their physician. The ANRS-VESPA2 study showed different smoking prevalence in PLHIV according to age and demographic characteristics. There were more smokers among intravenous drug users (IDU), men who have sex with men (MSM), French-native women, and heterosexual French-native men, and less in HIV-infected sub-Saharan African migrants[7]. Lung cancer was not recorded in VESPA2. We

inferred smoking rates and smoking pack-years in 2011 of lung cancer-free participants in the ANRS CO4-FHDH cohort from values reported in the ANRS-Vespa2 study according to 49 strata defined by age, gender, geographic origin, and HIV transmission group. For lung cancer cases, we used smoking information and pack-years of smoking recorded in the ANRS CO4-FHDH cohort in 2011. Smoking information was missing for 108 (38%) lung cancer cases. We assumed that all lung cancer cases were smokers and we used the multiple imputation procedure in SAS statistical software. We imputed smoking pack-years based on known smoking behavior of lung cancer cases according to categories of age, gender, geographic origin, HIV transmission group and the year of HIV diagnosis.

Outcomes of lung cancer screening strategies

Assumptions

Lung cancer screening is not recommended in France, so we assumed that all lung cancers diagnosed between 1st of January 2012 and 31st of December 2016 were clinically motivated (primarily by symptoms in relation to cancers) and would have been screened with a single LDCT in 2011. This assumption is based on a preclinical window of 3 to 6 years according to gender and histology during which lung cancers can be detected on screening scans [18]. We also assumed that the benefits of screening subjects in 2011 with a cancer diagnosed in 2011 would be nil or minimal, justifying their exclusion, and that all eligible subjects would have been fully adherent to the screening invitation and diagnosis work-up in case of a positive screen.

Evaluating different screening scenarios according to age and smoking thresholds

We used different outcomes according to each of the 20 scenarios. The primary outcome was the maximum proportion of lung cancers that would have been detected if the scenario had been fully implemented in 2011. Secondary outcomes were the number of NNS to detect one lung cancer, and the number and proportion of eligible subjects for screening. NNS to detect one lung cancer is the ratio between the numbers eligible to screening to the number of lung cancers potentially diagnosed in each scenario.

We first calculated the primary and secondary outcomes applying the NLST and the USPSTF lung cancer screening criteria to the cohort's population in 2011, then evaluated these outcomes with all the other screening scenarios. The number of eligible subjects for screening and the NNS to detect one lung cancer were expressed as absolute numbers as well as relative fraction of the numbers estimated based on the USPSTF criteria (55-80 years, > 30 pack-years, possibly quit<15 years).

Sensitivity analyses

Additional analyses were performed on PLHIV known to have both CD4>200/mm3 and HIV viral load <=50 copies/ml in 2011, as a subject with poorly controlled HIV (viral replication or low CD4) would be unlikely to benefit from a lung cancer screening program due to competing death and potential increased screening harms.

Results

Baseline characteristics and inferred smoking characteristics (Table 1)

In 2011, 89915 adults (age =>18 years) were followed-up in the ANRS CO4-FHDH cohort. After exclusion of 146 PLHIV who had a previous or a concurrent diagnosis of lung cancer, and 11950 (13.3%) PLHIV who were lost to follow-up before 2016, 77819 PLHIV were included in our analysis (median follow-up post 2011 6.7 years (IQR, 6.4-6.9)), corresponding to 509246 person-years. Patients lost to follow-up were slightly younger than those included in the analysis but the other characteristics were quite similar (data not shown). Moreover, as the minimal age of screening we tested was 45 years, the larger proportion of young people among those not included should not have affected our results. In all, 285 developed lung cancer between 2012 and 2016, giving a lung cancer incidence of 5.6/10000 person-years (95% CI, 5.0 to 6.3). Between 2012 and 2016, there were 1742 deaths, of which 156 were after a diagnosis of lung cancer.

In 2011, median age in the ANRS CO4-FHDH was 46 years, interquartile range (IQR) (39-53), and 66% were men. The 77819 ANRS CO4-FHDH cohort subjects and the 3016 ANRS-Vespa2 participants had similar demographic and immunovirological distributions (table 1). Half of the ANRS-Vespa2 participants were ever smokers, of whom 62% reported current daily smoking. Inferred proportion of smokers or ever smokers in the ANRS-CO4 FHDH participants was 50%, and -amongst smokers- median number of pack-years 17.0 (IQR, 10.2-24.9) and median duration of quitting 9.1 years (IQR, 3.4 – 17.2).

The 285 lung cancer cases had a median age of 52 years (IQR, 47-60) in 2011 and 55 years (IQR, 50-63) at cancer diagnosis. Compared to PLHIV followed in the ANRS-CO4 FHDH cohort, subjects who had a diagnosis of lung cancer were more often men (83% vs 66%) and IDU (28% vs 10%), while Sub-Saharan African (SSA) migrants were almost absent (2% vs 22%). They also had a lower lymphocyte T CD4 nadir count (median, 120 cells/mm3 vs 194 cells/mm3), but lymphocyte T CD4 cell counts in 2011 (median, 514 cells/mm3 vs 552 cells/mm3) and the

percentage with HIV viral load<50 copies/ml (79% vs 79%) were similar. All lung cancers, but four, were diagnosed among smokers or past smokers with a median of 37 pack-years (IQR, 24-49).

Among PLHIV in care in 2011, 7280 (9%) had no CD4 cell count or HIV viral load measurements and 16617 (21%) had either a CD4 cell count <200/mm3 or HIV viral load >50 copies/ml, leaving 53942 PLHIV included in the sensitivity analyses. Of these, 192 developed a lung cancer between 2012 and 2016.

Screening according to NLST and USPSTF criteria.

If screening had been proposed to all PLHIV using the NLST criteria in 2011, 84 lung cancers could have been detected at most, representing 30% of all lung cancers diagnosed in 2012-2016 among current or past smokers in the cohort (primary outcome), and 84/102 (82%) of subsequent lung cancers in the same age range. In all, 1572 subjects (11% of this age class) would have been eligible for screening, and the NNS would have been 19 to detect one lung cancer.

Increasing maximal age limit to 80 years with the same minimal age and smoking threshold than the USPSTF criteria (ie 55-80 years) would have led to screen 88 lung cancers, representing 31% (88/281) of all lung cancers in the cohort (figure 1+Table 2), and 82% (88/107) of lung cancers in the 55-80 years age range. In all, 1595 subjects, thus 10% of subjects from the same age range, would have been eligible (Table 2 +figure 2), and the NNS would have been 18 for one lung cancer.

Modifying minimal and maximal ages on screening outcomes for the other scenarios

In all smoking threshold scenarios, lowering the minimal age increased the proportions of lung cancers screened: 31% with the USPSTF scenario to 49%, and 60%, with a minimal age of 50 and 45 years respectively (figure 1A for age scenarios with > 30 pack-years). Modifying the maximal screening ages from 70 to 80 years old had limited impact on proportions of lung cancers detected (table 2, Figure 1A).

For secondary outcomes, lowering the minimal age had a dramatic impact on the numbers of eligible and the NNS for one lung cancer (Table 2, figure 2). Compared to the USPSTF criteria, reducing minimal age to 50 or 45 years increased the number of eligible subjects by a factor of 2

(from 1595 to 3010 subjects) or 3 (from 1595 to 4674 subjects), respectively (Figure 2A and table 2). It also increased the NNS by a factor of 1.2 or 1.5, that is from 18 to 22 or 28 NNS to detect one lung cancer respectively (Figure 2B and table 2). Modifying the maximal screening ages from 70 to 80 years old had limited impact on numbers of eligible subjects and NNS for one lung cancer (Table 2, figure 2).

Lowering smoking threshold from 30 to 20 pack-years.

Screening smokers with a history of 20 pack-years or more (possibly quit in the last 10 years) instead of 30 pack-years (possibly quit in the last 15 years) could have slightly increased numbers of detected cancer cases in the 55-80 years old range (33% vs 31% of total number of cancers), but potentially had a greater impact if screening was offered in ranges with lower minimal ages, such as 45-80 years old (74% vs 60% of total number of cancers) (Figure 1B).

Lowering the smoking threshold would have led screening 18-22% of an age class instead of 11% (Table 2). With a smoking threshold of 20 and 30 pack-years, 2674 and 1595 subjects aged 55-80 (USPSTF scenario) would have been eligible respectively, increasing the number by a 1.7 factor. If screening was proposed to subjects aged 45-80, lowering the smoking threshold would have doubled the number of subjects eligible to screening (9555 and 4674, respectively). Lowering the smoking threshold increased by 65% the NNS whatever the age ranges (Figure 3 and table 2).

Similar results were observed in sensitivity analyses after excluding PLHIV with low CD4 or uncontrolled HIV viral load from screening (table S1, Figures S1-S3).

Discussion

Our study assessed the maximum proportions of lung cancers that could have been detected, the number of eligible subjects and the NNS to detect one lung cancer in the 2011 ANRS-CO4-FHDH cohort, when applying scenarios of different age and smoking thresholds and including all eligible subjects in the program. We found that the NLST and the USPSTF criteria yielded only a third of lung cancers detected, despite low NNS. Reducing smoking thresholds to 20 pack-years or the minimal age limit to 45 or 50 years increased the numbers of cancers screened, but also eligible subjects and the NNS. Modifying the age limit from 75 to 80 years did not have a substantial impact on any outcome.

Our study had several limitations. First, exhaustive data on smoking behaviour were not recorded in the ANRS C04-FHDH cohort. In order to prevent information bias, we inferred smoking data for non-lung cancer cases from the ANRS-VESPA2 study, a national cross-sectional survey of HIV outpatients in French hospitals realized in 2011, conceived to be representative of the HIV-infected population in France at that time. We used smoking parameters of the ANRS-VESPA2 study as a whole without taking into account possible lung cancer diagnosis among participants. However, among the 3016 participants in ANRS VESPA2 study, less than 2 lung cancer cases would have been expected assuming the lung cancer incidence rate observed in the national ANRS CO4 FHDH cohort. Also, the similar demographic, immunological and virologic characteristics of subjects in the ANRS-VESPA2 and the ANRS CO4-FHDH cohort subjects in 2011 (table 1) indicated that our analysed population was representative of the HIV-infected population in France. Second, cannabis inhalation- highly prevalent in HIV-subpopulations- was unaccounted for as a smoking risk, despite being a presumed risk factor of lung cancer[19]. Third, our estimates are based on optimal assumptions of absolute adherence to lung-cancer screening and that all lung cancers diagnosed between 2012 and 2016 would have been screened in 2011. In real-life settings, accrual and adherence to screening programs are probably lower. However the ANRS VESPA-2 survey showed high adherence rates of breast cancer and most importantly cervical cancer screening among women living with HIV in France, the latter being subject of specific screening guidelines in PLHIV [20]. Also, adherence was high in the French lung cancer screening study in PLHIV, with only 1.6% lost to follow-up [21]. Finally, our surrogate outcomes are not directly related to clinical efficacy and improved survival. Unfortunately, lung cancer tumors stages are not recorded in the ANRS CO4-FHDH cohort and we could not detail how many of the potentially screened cancers in 2011 would have been at low stages, which correlate with better survival. NNS to detect one low stage lung cancer was thus not feasible in our study.

If early lung cancer screening is paramount to increase survival, its benefits and harms have to be balanced. Cumulated irradiations due to LDCT on an annual basis[22,23], increased risks of false positive screens (nodules on LDCT that are not cancerous) with undue potentially life-threatening diagnostic procedures[24] and lung cancer over diagnosis[25] have to be taken into account, but also competing death in the HIV infection context. Our study does not apprehend all these benefits and harms in participating in a lung cancer screening program. Interestingly, in a recent study from the Veterans Aging Cohort Study and the Kaiser Permanente Northern California HIV cohorts [16] that modelled lung cancer screening efficacy in PLHIV with more than 500 cells/mm3 and perfect antiretroviral and screening adherence, lung cancer mortality reduction was similar to the mortality reduction of uninfected individuals objectified in the

NLST[14]. We did not include criteria on CD4 cell count in our primary analysis, but results from the sensitivity analysis restricted to PLHIV with CD4 above 200/mm^3 and controlled viral load were very similar for proportions of cancers diagnosed, proportions of eligible subjects or NNS to detect one lung.

Our data discusses age and smoking thresholds for lung cancer screening in PLHIV. If the NLST [14] or USPSTF criteria had been applied to PLHIV in our cohort, about two thirds of lung cancers would have been missed. The higher rates of lung cancers detected when including younger PLHIV at risk may be explained by the increased numbers of observed lung cancers in PLHIV per age strata in comparison with the general population starting at 40 years [26]. Upholding this, the French feasibility screening study, which included 442 PLHIV aged 40 years or more and smoking 20 pack-years or more, detected 9 screen lung cancers, of which 8 were in subjects aged 54 years or less[21]. NLST criteria may not be optimal in the general population as well. Data from cancer registries between 2007–2008 in the United States estimated that the NLST criteria only covered 26.7% of lung cancers diagnosed in subjects aged 40 years or older while still implying screening 6.2% of the total American population [27]. If one sought to detect more than half of lung cancers, decreasing the minimal age limit to 50 years would be necessary with both smoking thresholds. In our study, screening subjects from age 45 years with a low smoking threshold of 20 pack-years would have revealed the highest proportion of lung cancers. However, strategies lowering the minimal age to 45 years implied a 3-fold increase of NNS and absolute numbers of eligible subjects, though rates of eligible subjects in each age range remained stable with each smoking threshold (11% for 30 pack-years, and around 20% for 20 pack-years).

The fact that NLST criteria had the lowest NNS reflects the selection of a very high risk population, as older age and smoking are important risk factors of lung cancer. However our NNS to detect one lung cancer using the NLST criteria was low (19 screened for one lung cancer), and in fact lower than in the NLST study (2001 lung cancers after a follow-up median time of 6.5 years for 53454 subjects at high risk, thus 27 subjects to screen for one cancer).

As the HIV-infected population is aging, and smoking hazards change, lung cancer screening outcomes in each scenario will evolve with time. Reiterative evaluations of scenarios are thus needed to reconsider eligibility lung cancer screening criteria in the HIV-infected population in future years.

In conclusion, our data suggests that lung cancer screening using the NLST or the USPSTF criteria among PLHIV in care in 2011 would have been suboptimal, missing most lung cancers. Whether detecting more lung cancers by screening would result in reducing lung cancer mortality in our population remains speculative, but our study calls for more studies of screening PLHIV at lower smoking thresholds (20 pack-years) and at younger ages (45 or 50 years) than with actual NLST or USPSTF criteria.

Characteristics	ANRS-C04 FHDH (N=77819)	Vespa-2 study (N=3019)
Age (years)		
<40	26%	22%
40-44	17%	16%
45-49	21%	21%
50-54	16%	18%
55-59	9%	10%
60-64	6%	7%
65-69	3%	3%
70-74	1%	2%
75-79	0.7%	0.5%
80-85	0.3%	0.5%
HIV transmission group		
MSM	35%	39%
Male IDU	7%	7%
Female IDU	3%	4%
Heterosexual men SSA	7%	8%
Heterosexual women SSA	15%	16%
Other heterosexual men	17%	13%
Other heterosexual women	16%	13%
Date of HIV diagnosis		
<1996	36%	41%
1996-2000	18%	16%
2000+	46%	43%
Nadir lymphocyte T CD4 °(cells/µL)		
<200	51%	37%
200-349	32%	33%
350+	17%	30%
Last Lymphocyte T CD4 ° (cells/µL)		
<200	6%	5%
200-349	13%	15%
350-499	22%	23%
500+	59%	57%
Controlled HIV viral load °°	79%	76%
Smoking °°°		
Never smokers	50%	51%
Current smokers	32%	31%
Past smokers	18%	19%
Mean (sem) pack-years if smokers or past smokers	18.45 (0.06)	19.62 (0.47)
Mean (sem) duration since quitting if past smokers, years	11.75 (0.09)	11.79 (0.59)

Table 1: main characteristics of PLHIV participants in 2011 in the ANRS-CO4 FHDH cohort (N=77819) and in the ANRS-Vespa-2 study (N=3019).

°Missing for 5326 (6.8%) participants to FHDH. °° Missing for 7013 (9.0%) participants to FHDH. °°° Smoking for the lung cancer-free participants to FHDH were inferred from the ANRS-Vespa-2 study according to 49 strata defined by age, gender, geographic origin, and HIV transmission group (see text for further details).

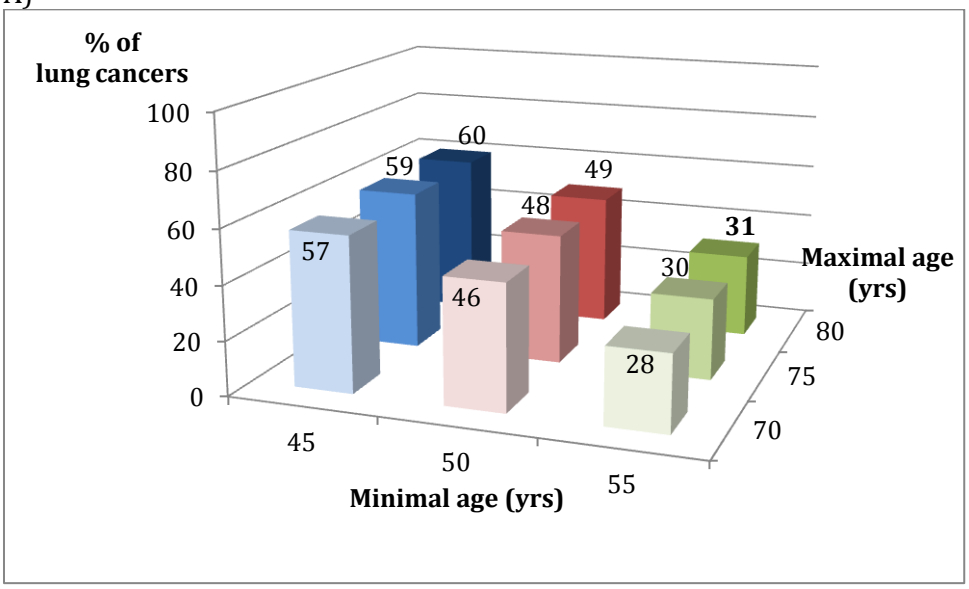
Characteristics/Scenario age ranges	45-70	50-70	55-70	45-75	50-75	55-75	45-80	50-80	*55-80*
Total number of lung cancers	232	167	95	241	176	104	244	179	*107*
Percentage of lung cancers*	83%	59%	34%	86%	63%	37%	87%	64%	*38%*
30 pack-years minimum scenario (possibly quit within 15 years)									
Number of eligible subjects	4622	2958	1543	4656	2992	1577	4674	3010	*1595*
% of eligible subjects in the age range	11%	11%	11%	11%	11%	11%	11%	11%	*10%*
Number of cancers	159	128	78	166	135	85	169	138	*88*
Percentage of lung cancers detected*	57%	46%	28%	59%	48%	30%	60%	49%	*31%*
Number of subjects to screen for one lung cancer	29	23	20	28	22	19	28	22	*18*
20 pack-years minimum scenario (possibly quit within 10 years)									
Number of eligible subjects	9451	5539	2570	9518	5606	2637	9555	5643	2674
% of eligible subjects in the age range	22%	21%	18%	22%	21%	18%	22%	21%	18%
Number of cancers	198	145	82	205	152	89	208	155	92
Percentage of lung cancers detected*	71%	52%	29%	73%	54%	32%	74%	55%	33%
Number of subjects to screen for one lung cancer	48	38	31	46	37	30	46	36	29

Table 2 : outcomes of different smoking and age lung cancer screening scenario.

* % relative to the total number of lung cancers among current or past smokers (n=281). In italics, USPSTF scenario.

Figure 1: proportions of lung cancers detected relative to the total number of lung cancer with (A) different minimal and maximal age thresholds in smokers of 30 pack-years or more (possibly quit for less than 15 years), and with (B) the 30 or 20 pack-years smoking thresholds (possibly quit within 15 or 10 years respectively)

A)



B)

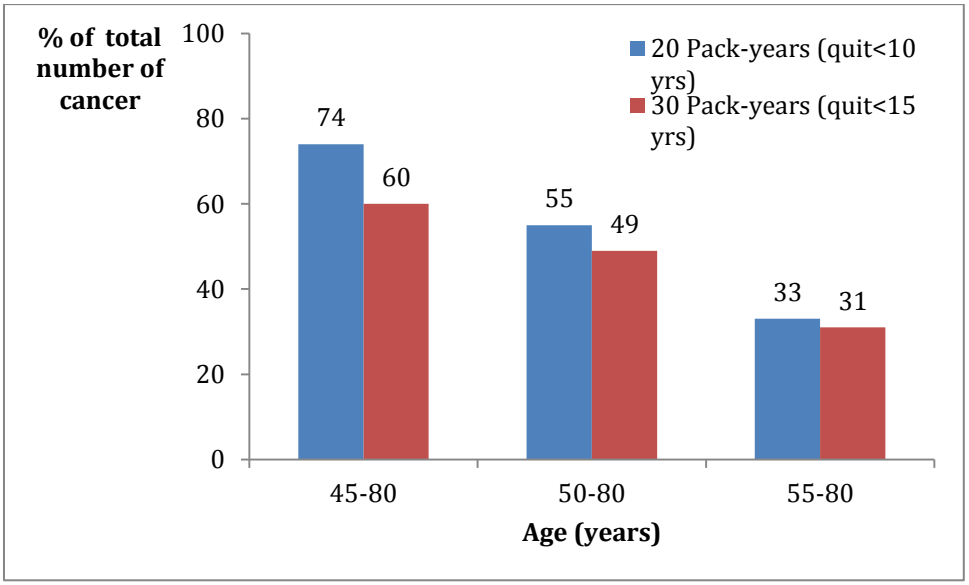
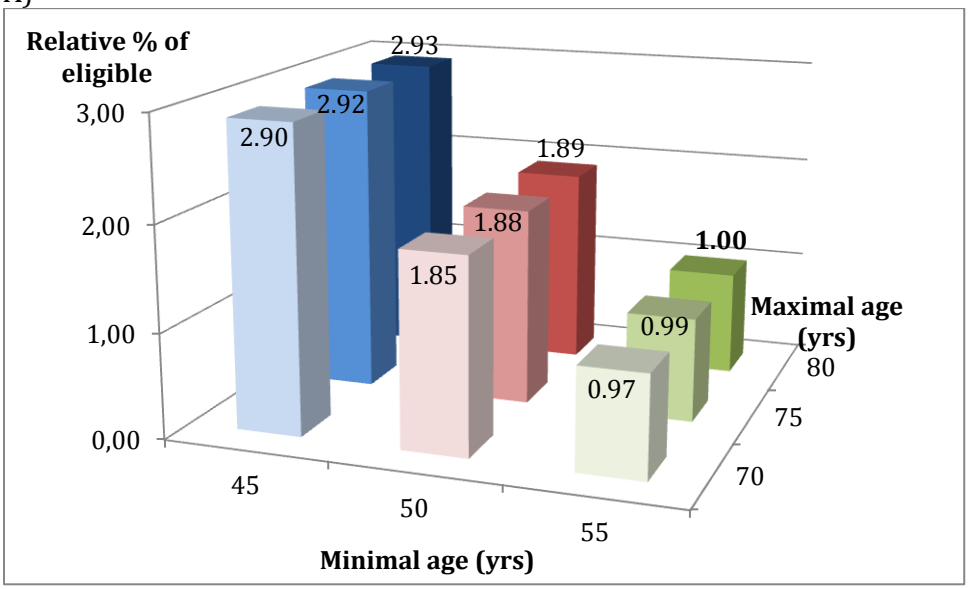


Figure 2: Effect of minimal and maximal age on (A) numbers of eligible PLHIV (B) numbers to screen to detect one lung cancer relative to the USPSTF criteria (55-80 years, > 30 pack-years, possibly quit<15 years), if screening had been proposed to smokers (possibly quit for less than 15 years), with a history of smoking of 30 pack-years or more. Absolute numbers of eligible subjects are available in table 2.

A)



(B)

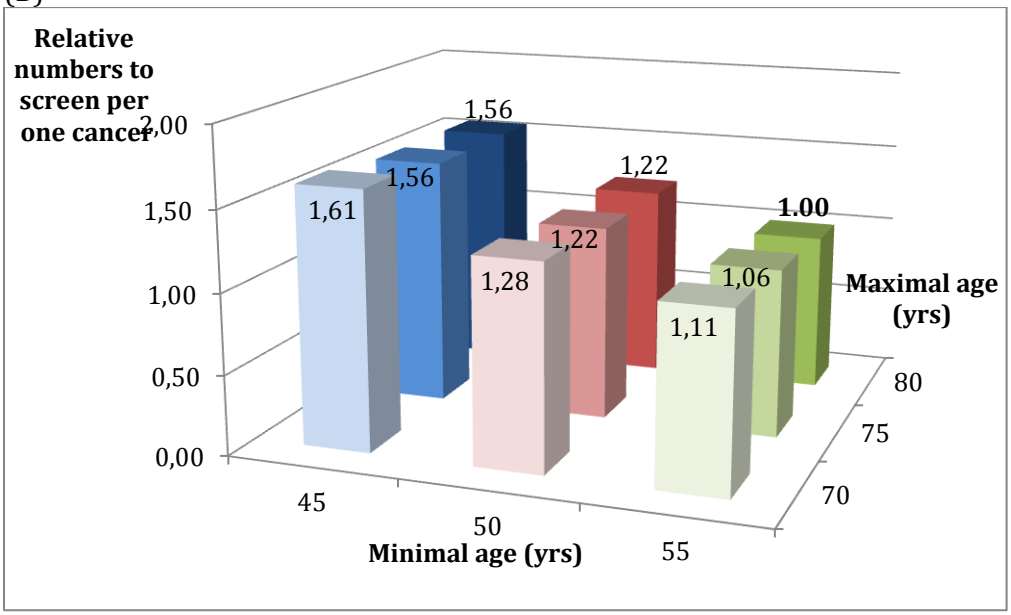
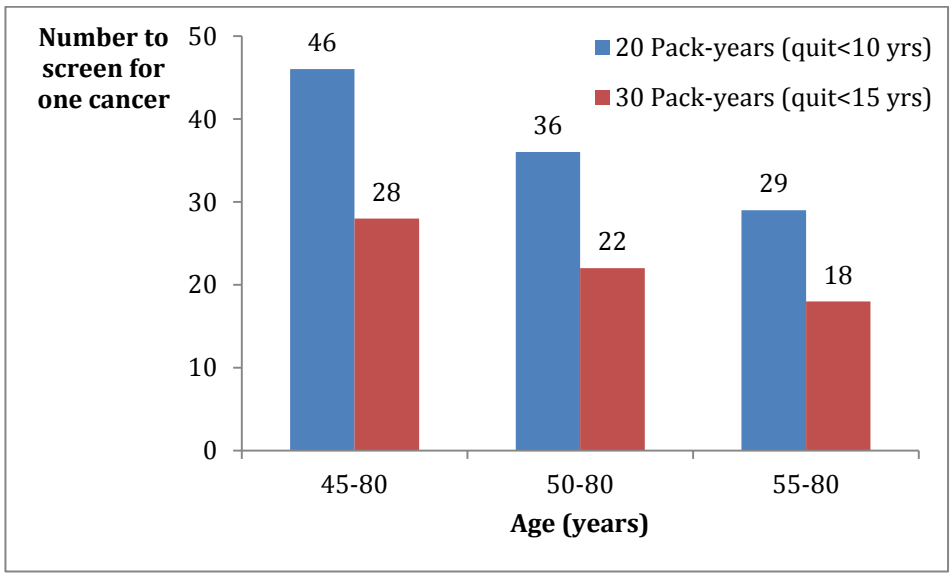
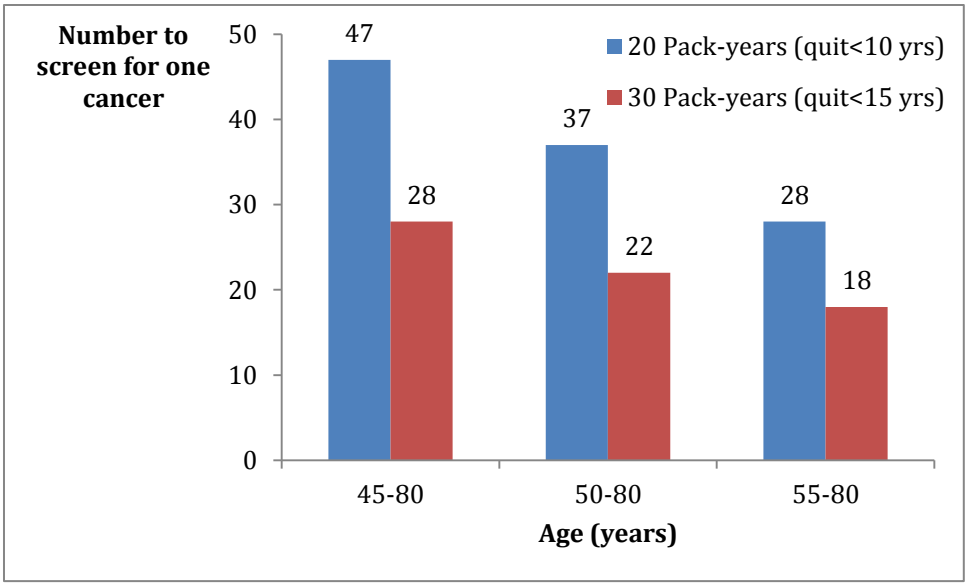


Figure 3: Impact of smoking thresholds on numbers to screen to detect one lung cancer




Number to screen for one cancer
50
40
30
20
10
0
47
28
37
22
28
18
20 Pack-years (quit<10 yrs)
30 Pack-years (quit<15 yrs)
45-80
50-80
55-80
Age (years)

1. Morlat P, Roussillon C, Henard S, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. *AIDS.* 2014;28(8):1181-1191.
2. Engels EA, Yanik EL, Wheeler W, et al. Cancer-Attributable Mortality Among People With Treated Human Immunodeficiency Virus Infection in North America. *Clin Infect Dis.* 2017;65(4):636-643.
3. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. *AIDS.* 2014;28(6):881-890.
4. Hleyhel M, Belot A, Bouvier AM, et al. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. *Clin Infect Dis.* 2013;57(11):1638-1647.
5. Hleyhel M, Cancer Risk Group of the French Hospital Database on HIV. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. *AIDS.* 2014;28(14):2109-2118.
6. Shiels MS, Althoff KN, Pfeiffer RM, et al. HIV Infection, Immunosuppression, and Age at Diagnosis of Non-AIDS-Defining Cancers. *Clin Infect Dis.* 2017;64(4):468-475.
7. Tron L, Lert F, Spire B, Dray-Spira R, group AN-Vs. Tobacco smoking in HIV-infected versus general population in france: heterogeneity across the various groups of people living with HIV. *PLoS One.* 2014;9(9):e107451.
8. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. *AIDS.* 2012;26(8):1017-1025.
9. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. *Aids.* 2007;21(2):207-213.
10. Kirk GD, Merlo C, P OD, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis.* 2007;45(1):103-110.
11. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol.* 2009;10(12):1152-1159.
12. Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. *J Acquir Immune Defic Syndr.* 2010;55(3):375-379.
13. Hessol NA, Martinez-Maza O, Levine AM, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. *AIDS.* 2015.
14. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
15. Gould MK. Clinical practice. Lung-cancer screening with low-dose computed tomography. *N Engl J Med.* 2014;371(19):1813-1820.
16. Kong CY, Sigel K, Criss SD, et al. Benefits and harms of lung cancer screening in HIV-infected individuals with CD4+ cell count at least 500 cells/mul. *AIDS.* 2018;32(10):1333-1342.
17. Mary-Krause M, Grabar S, Lievre L, et al. Cohort Profile: French hospital database on HIV (FHDH-ANRS CO4). *Int J Epidemiol.* 2014;43(5):1425-1436.
18. Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2015;24(1):154-161.
19. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: a case-control study. *The European respiratory journal.* 2008;31(2):280-286.
20. Tron L, Lert F, Spire B, Dray-Spira R, Agence Nationale de Recherche sur le Sida et les Hepatites Virales -Vespa2 Study G. Levels and determinants of breast and cervical cancer screening uptake in HIV-infected women compared with the general population in France. *HIV Med.* 2017;18(3):181-195.

21. Makinson A, Le Moing V, Reynes J, et al. Lung Cancer Screening with Chest Computed Tomography in People Living with HIV: A Review by the Multidisciplinary CANCERVIH Working Group. *J Thorac Oncol.* 2016;11(10):1644-1652.
22. Christe A, Szucs-Farkas Z, Huber A, et al. Optimal dose levels in screening chest CT for unimpaired detection and volumetry of lung nodules, with and without computer assisted detection at minimal patient radiation. *PLoS One.* 2013;8(12):e82919.
23. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. *Radiology.* 2004;231(2):440-445.
24. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med.* 2013;369(10):910-919.
25. Patz EF, Jr., Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA internal medicine.* 2014;174(2):269-274.
26. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess Cancers Among HIV-Infected People in the United States. *J Natl Cancer Inst.* 2015;107(4).
27. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? *J Med Screen.* 2012;19(3):154-156.