REVIEW ARTICLE

Lung Cancer Screening with Chest Computed Tomography in People Living with HIV: A Review by the Multidisciplinary CANCERVIH Working Group

Alain Makinson, MD, PhD,[a,*] Vincent Le Moing, MD, PhD,[a] Jacques Reynes, MD, PhD,[a] Tristan Ferry, MD, PhD,[b] Armelle Lavole, MD,[c] Isabelle Poizot-Martin, MD,[d] Jean-Louis Pujol, MD, PhD,[e] Jean-Philippe Spano, MD, PhD,[f] Bernard Milleron, MD[g]

[a]*Department of Infectious and Tropical Diseases, U1175-National Institute of Health and Medical Research/Mixt International Department 233, Development Research Institute, University Montpellier, Montpellier, France*
[b]*Infectious and Tropical Disease Unit, University Hospital de la Croix Rousse, Lyon, France*
[c]*Department of Pneumology and Reanimation, Hôpital Tenon, Public Assistance-Parisian Hospitals, and Faculté de Médecine Pierre and Marie Curie, University Paris VI, Paris, France*
[d]*Clinical Immunohaematology Service, University Aix-Marseille, Public Assistance-Hospitals of Marseille Sainte-Marguerite, National Institute of Health and Medical Research, U912 (Economical and Social Sciences of Health and Treatment of Medical Information), Marseille, France*
[e]*Thoracic Oncology Unit, University Hospital Montpellier, Montpellier, French Cooperative Thoracic Intergroup, Paris, France*
[f]*Department of Medical Oncology, Groupe hospitalier Pitié-Salpêtrière-Charles Foix, Public Assistance-Parisian Hospitals, National Institute of Health and Medical Research, Mixt Research Department_S 1136, Institute Pierre Louis Epidemiology and of Public Health, Sorbonne University, University Pierre Marie Curie University Paris 06, Paris, France*
[g]*Respiratory Disease Department, Tenon Hospital APHP, Paris VI University, French Cooperative Thoracic Intergroup, Paris, France*

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ABSTRACT

A shift in mortality and morbidity has been observed in people living with human immunodeficiency virus (PLWHIV) from acquired immunodeficiency syndrome (AIDS) to non-AIDS diseases. Lung cancer has the highest incidence rates among all the non–AIDS-defining malignancies and is associated with mortality rates that exceed those of other cancers. Strategies to increase lung cancer survival in PLWHIV are needed. Lung cancer screening with chest LDCT has been shown to be efficient in the general population at risk. The objective of this review is to discuss lung cancer screening with chest computed tomography in PLWHIV. Lung cancer screening in PLWHIV is feasible. Whether PLWHIV could benefit from an age threshold for screening that is earlier than the minimum age of 55 years usually required in the general population still needs further investigation. Studies evaluating smoking cessation programs and how they could be articulated with lung cancer screening programs are also needed in PLWHIV.

Keywords: Lung cancer; Computed tomography; Screening; HIV; Smoking

Introduction

Since the advent of combination antiretroviral therapy, a shift in mortality and morbidity has been observed in people living with human immunodeficiency virus (PLWHIV) from AIDS to non-AIDS diseases, a high proportion of which are non–AIDS-defining malignancies.[1–3] In PLWHIV, lung cancer rates are higher than any other non–AIDS-defining malignancy,[3–10] and its mortality rates exceed those due to other AIDS-defining and non–AIDS-defining cancers.[3,11,12] Studies have shown

*Corresponding author.

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Address for correspondence: Alain Makinson, MD, PhD, University Montpellier, Department of Infectious and Tropical Diseases, U1175-INSERM/UMI 233 France. E-mail: a-makinson@chu-montpellier.fr

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that the standardized incidence ratios of lung cancer in PLWHIV are increased in comparison with those in the general population, with ratios varying between 2 and 4.[4,5,8,13–16] Factors implicated in this increased incidence include higher rates of smoking[17,18] and chronic immunodeficiency.[15,19] In a nationally representative cross-sectional survey in the United States, of the estimated 419,945 adults with HIV who were receiving medical care, 42.4% were current cigarette smokers and 20.3% were former smokers.[18] The French Hospital Database on HIV showed a dose-effect increased incidence of lung cancer with declining levels of CD4-positive blood lymphocytes.[19]

The prognosis of lung cancer in PLWHIV is dismal, as it is in the general population.[20] A recent study from the French Hospital Database on HIV showed a 5-year survival rate of 16% in PLWHIV.[11] Some age-, sex-, and stage-adjusted studies have also shown decreased survival rates in comparison with those in the general population.[9,21,22] Thus, strategies to increase lung cancer survival in PLWHIV are needed. Lung cancer screening with chest low-dose computed tomography (CT) has been shown to increase survival in a randomized trial in subjects from the general population at risk for lung cancer.[23] As PLWHIV who smoke are at particular risk for lung cancer, they probably also represent a good target for lung cancer CT screening. The objective of this review is to discuss specificities of lung cancer screening with chest CT in PLWHIV.

Lung Cancer Screening with CT in the General Population

In 2011, the North American randomized National Lung Screening trial (NLST) demonstrated for the first time a mortality reduction of 6.7% (95% confidence interval [CI]: 1.2–13.6) and a lung cancer mortality reduction of 20% (95% CI: 6.8–26.7) with three annual chest LDCT scans versus simple anterior-posterior radiography in a population at high risk for lung cancer.[23–25] More than 50,000 subjects were included, all aged between 55 and 74 years. Subjects had smoked more than 30 pack-years, and if former smokers, they had quit within the previous 15 years. Survival benefits were primarily driven by a shift of cancer diagnosis to earlier stages in the CT arm: 40% of cancers were staged IA versus 21.1% in the radiography arm. Another important result was a high proportion of subjects with false-positive nodules (27.3% of subjects had a positive screen, with more than 96% of the nodules not cancers at the first round), causing unnecessary additional irradiation with diagnostic examinations, additional costs, and risks for occurrence of adverse events due to invasive procedures. In the NLST study, a positive screen was defined as any noncalcified nodule measuring at least 4 mm in any diameter, radiographic images that revealed any noncalcified nodule or mass, and other abnormalities such as adenopathy or effusion.[23] However, despite this, rates of severe complications (0.31%) and mortality (0.06%) were low in the chest CT arm owing to the low number of invasive procedures. In light of the NLST results, several expert groups have recommended routine lung cancer screening in similar populations and settings.[26]

Other randomized screening studies are ongoing in the general population with differing population selection criteria and variable rounds of screening.[27–32] Among these, the Dutch-Belgian NELSON trial[30] has been powered to demonstrate a 25% or more reduction in lung cancer mortality at 10 years with LDCT screening versus in a nonintervention arm.[30] The results of three other European trials were negative, but those trials, which included approximately 4000 people, did not have sufficient power to investigate mortality as their end point.[31–33]

Studies of Lung Cancer Screening with Chest CT in PLWHIV

Up to the submission of this manuscript, only two studies on lung cancer screening with chest CT in the HIV-infected population had been published.[34,35] The first study, which examined a prospective cohort in Baltimore, Maryland, was conducted between 2006 and 2013.[34] The primary objective was to determine the prevalence and incidence of lung cancer in HIV-infected smokers. Eligible participants had no symptoms of lung malignancy, were at least 25 years of age, and had been smokers for at least 20 pack-years, or if former smokers, had quit within the previous 15 years. The median age was 48 years, 89% of the subjects were current smokers, 40% had a history of marijuana use, and the median smoking history was 34 pack-years. The median CD4 nadir was 179 cells per μL and the median last CD4 value was 400 cells per μL; only 60% of subjects had a viral load less than 400 copies per mL. During 678 person-years, one lung cancer was found on an incident screening, and none of the 18 deaths were lung cancer related. According to the study protocol, of 224 participants (all of whom could have received five scans), 18 (8%) received only one scan, 103 (46%) had two scans, 44 (20%) had three scans, 39 (17%) had four scans, and 20 (9%) received all five scans, reflecting low adherence. Thirty-two positive screens at baseline (14% of subjects) were detected.

The second study was a French France REcherche Nord and Sud Sida-HIV Hépatites (ANRS)-sponsored study that evaluated the feasibility and efficacy of early lung cancer diagnosis with low- to moderate-dose chest

CT in HIV-infected smokers in France (median dose of 2.96 mSV).[35] Between 2011 and 2012, 442 subjects from 13 French clinical centers underwent a single baseline chest CT scan. Subjects were at least 40 years, had smoked for at least 20 pack-years, had possibly stopped within 3 years, and had a CD4 cell count of 100 cells per μL or higher and a nadir CD4 cell count of 350 cells per μL or less. A solid nodule was considered positive if the largest diameter was at least 5 mm (or at least 8 mm if nonsolid) or if the radiologists described an endobronchial image or a suspicious lymph node. Median age was 49.8 years, (95% CI: 46.3–53.9), 84% of subjects were men, the median CD4 level was 574 cells per μL, the median nadir CD4 level was 168 cells per μL, and the median smoking history was 30 pack-years (95% CI: 25–40). Subjects were followed for a median of 24.4 months. In this study, 94 subjects (21%) had positive screens. Only 18 diagnostic procedures were realized in 15 subjects, with only four procedures not yielding any diagnosis. Nine screen-detected lung cancers were diagnosed, and an incident SCLC developed in an additional subject 88 weeks after admission. Eight of the 10 lung cancers occurred in subjects younger than 55 years, and six lung cancers were early-stage lung cancers. The number of subjects needed to detect one lung cancer with the CT procedure was 49 (95% CI: 26–111), which is to be considered low from the perspective of studies in the general population (one in 108 screens in the first round of the NELSON study for instance[36]).

In a retrospective evaluation of standardized chest baseline CT scans from 160 HIV-infected and 139 non–HIV-infected veterans enrolled between 2009 and 2012 in the EXHALE study, there was no significant difference by HIV status in the proportion of CT scans classified as positive by NLST criteria (29% of HIV-infected and 24% of non–HIV-uninfected veterans, $p = 0.3$).[37] In this study, HIV-infected outpatients were block-matched to HIV-negative patients by current smoking status to achieve a sample with similar prevalence of current smoking; 85% of HIV-infected subjects had been or were smokers, and 84% of subjects were receiving antiretroviral therapy. However, participants with CD4 cell counts less than 200 cells per mL had significantly higher odds of positive scans, a finding that persisted in multivariable analysis.

The French ANRS study showed the feasibility of lung cancer screening in PLWHIV in a resource rich-setting with free medical care, thus contrasting with the Baltimore study.[34] Adherence to a lung cancer screening program depends more on types of populations selected and health care systems rather than on being HIV-infected per se. In resource-rich settings with free medical care, HIV-infected patients are usually cared for as outpatients in well-structured multidisciplinary hospital settings, which may enhance subjects' adherence to a lung cancer screening program, and respect for positive screens follow-up and biopsy recommendations. Another important result was that the number of false-positive screens was within the range of those in lung cancer studies in the general population with similar definitions.[23,38] One of the presumed caveats of lung cancer screening in PLWHIV was the risk of high numbers of false-positive nodules on CT scans, which induce invasive and costly explorations.

Lung Cancer Screening in PLWHIV: Areas of Uncertainty

The uncertainty and the ongoing debates on lung cancer screening in the general population also apply to PLWHIV, although some specific points exist in the HIV-infected population. It is still unknown whether lung cancer screening has an impact on overall and lung cancer survival in the HIV-infected population. Randomized studies in the HIV-infected population are nonexistent and would necessitate the inclusion of several thousands of subjects. Data on 5-year survival rates are also absent in PLWHIV.

There is still active research in the general population on how to select subjects to increase screening efficiency. The best criteria would select subjects who are at high risk for lung cancer, have few negative screens, and are not too "frail" to be able to endure invasive biopsies and/or thoracic surgery. In countries where lung cancer screening is a reality, selection criteria have largely followed the NLST criteria for eligibility.[26] However, recent data from registries between 2007–2008 in the United States estimated that the NLST criteria have a low sensitivity, as they only cover 26.7% of lung cancers diagnosed in subjects aged 40 years or older while still implying screening 6.2% of the total American population.[39] Adding ever-smokers aged 50 to 79 years would cover 68% of registered lung cancers while increasing the necessity of screening 30% of the population aged 40 years or more. One study found that the best criteria for screening in the general population[40] would be subjects between the ages of 50 and 80 years who smoked more than 30 pack-years and ex smokers who quit within the previous 15 years.

Whether HIV-infected subjects should be screened at younger ages is speculative and should be further assessed. The epidemiological arguments for earlier screening in PLWHIV are the relatively younger median age of lung cancer incidence in PLWHIV after standardization[41] and an excessive rate of lung cancer in PLWHIV from the age of 40 years onward compared with in the general population[42] in two studies comparing HIV and cancer registries in North America (Figs. 1 and 2). In the French ANRS screening study most cancers were

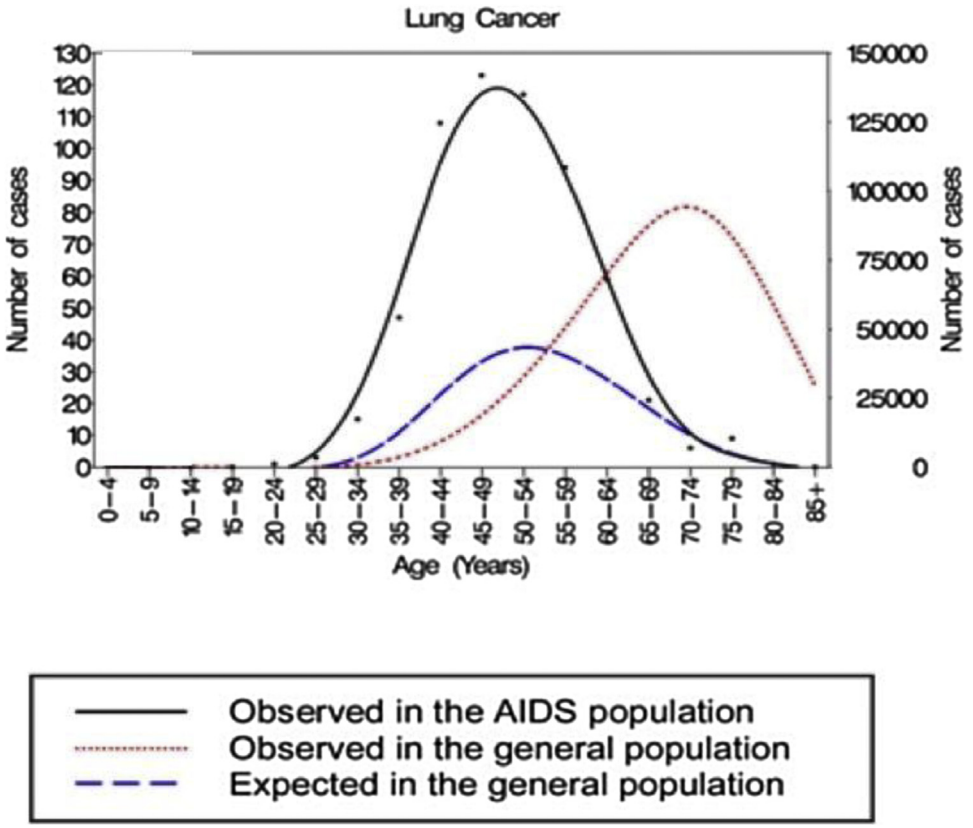

Figure 1. A representation of the number of lung cancers observed in the acquired immunodeficiency syndrome (AIDS) population (*solid line*), observed in the general population (*dotted line*), and expected in the general population (*broken line*). The expected numbers of cases in the general population are the numbers of lung cancers that would be observed in the general population if the composition of the general population had age and sex distributions identical to those in the AIDS population. Thus, according to this figure, advancing age for lung cancer screening with chest computed tomography is justified by the slightly advanced median age of lung cancer and the increased number of cases per age strata in the AIDS population in comparison with the expected numbers and median incidence if both populations were comparable (*broken line*). However, screening too early may miss most lung cancers in the AIDS population too. Adapted with permission from Shiels et al.[41]

diagnosed in subjects younger than 55 years, a finding that could also be explained by a history of marked immunosuppression (all subjects had a CD4 nadir value of $\leq$350 cells per μL) and persistent active smoking or a very recent history of quitting in a minority of subjects. However, in subjects with CD4 levels higher than 500 cells per μL, one study showed that lung cancer incidence was similar to that in the general population,[8] suggesting that screening criteria in this subpopulation should be identical to those in the general population.

Studies evaluating the best lung cancer risk prediction models in HIV-infected populations are needed, and these models could include traditional risk factors from the general population, as well as specific factors such as last TCD4 levels or nadir measures. In models derived from two lung cancer screening studies in at-risk subjects from the general population (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial and NLST studies), use of a lung cancer predictor model increased sensitivity (83% versus 71.1%) and positive predictive value (4.0% versus 3.4%) of screens, without loss of specificity in comparison with the NLST criteria. Also, 41.3% fewer lung cancers were missed.[43]

There is also a debate on the smoking exposure levels necessary to qualify for inclusion in a lung cancer screening program. Data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, a lung cancer screening randomized study with anterior-posterior annual simple chest radiography in the general population, showed that former smokers with a smoking history of 30 or more pack-years and aged 55 to 74 years had lung cancer rates similar to those of current smokers with a smoking history of 20 to 29 pack-years.[44] Screening should probably be extended to current smokers who have smoked for 20 to 29 pack-years. Whether a lower threshold of smoking should apply for HIV-infected individuals to be included in a screening program, as they seem at higher risk for lung cancer than their HIV-negative counterparts, needs to be further evaluated.

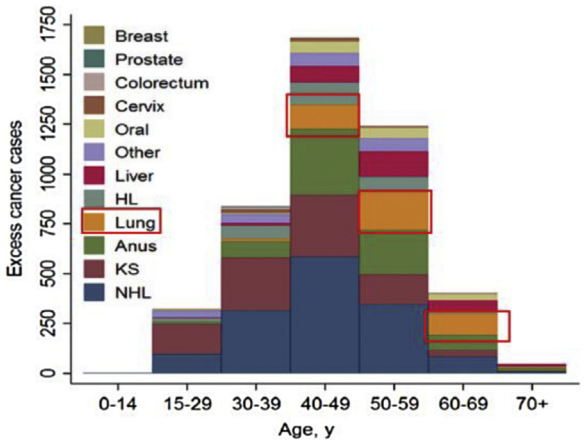

Figure 2. Excess cancer cases in persons living with human immunodeficiency virus (HIV) compared with in the general population from studies comparing HIV and cancer registries in the United States. A significant excess rate in persons living with HIV was revealed as from the 40- to 50-years age group. These results argue for a possible earlier lung cancer screening than that reserved for the general population at risk if the clinical numbers of excess lung cancers as from the 40- to 50-years age group are significant. HL, Hodgkin's lymphoma; KS, Kaposi's sarcoma; NHL, non-Hodgkin's lymphoma. Adapted with permission from Robbins et al.[42]

An ongoing issue in lung cancer screening is to diminish the number of false-positive screens. The NELSON group chose to define the positivity of a nodule in a multistep way by estimating the volumetric doubling time of nodules between two chest CT scans, taking into account the time spam between the two examinations. If the doubling time is estimated to be less than 400 days, subjects are eligible to undergo a diagnostic procedure.[36] The NELSON strategy generated a much lower percentage of false-positive images in comparison with the methods used in other lung cancer screening studies: after the first round of screens, only 2.6% of chest LDCT scans were considered positive, with lung cancers present in as many as 35.5% of those patients. Other leads include increasing the threshold of positivity for nodules with the objective to decrease complementary examinations without increasing mortality,[45] to develop scores predictive that a screened nodule is a lung cancer,[46] and to develop tools based on circulating tumoral cells or RNA and DNA material to classify screened positive screens.[47]

Anxiety induced by lung cancer screening has been quite extensively explored in the general population, but not in PLWHIV. Most studies in the general population settings show a transient moderate anxiogenic effect in subjects enduring diagnostic work-ups after positive screens,[48,49] or only in subjects with cancers diagnosed.[50] No evaluation of anxiety relative to participating in screens and the discovery of positive screens has ever been performed in the HIV-infected studies.[34,35]

Another area of insufficient data is the precise risk for development of radiation-induced lung cancers as a result of chest LDCT and the follow-up diagnostic radiological examinations. Chest LDCT uses chest tomography techniques that reduce effective radiation by more than 80% compared with techniques used to perform standard diagnostic CT of the chest.[27] There exists, however, a synergistic effect between smoking and radiographs on the risk for development of radiation-induced lung cancer, with a maximal effect around the age of 50 years.[51] An Italian team estimated that the cumulative individual mean effective dose with 4 years of annual screening with chest LDCT between the ages of 50 and 70 years was between 6.2 and 6.8 mSv (range 1.7–21.5 mSv),[52] leading to a mean estimated cumulative incidence of radiation-induced cancers ranging from 0.12 to 0.33 per 1000 subjects. Whatever the long-term risks for development of radiation-induced lung cancers as a result of chest LDCT screening, they seem insufficient to significantly reverse the benefits in terms of reduction of lung cancer mortality.[53]

There are many other important issues to assess in lung cancer screening programs. Further data are needed on annual or biennial screening strategies and survival equivalence; one small study showed no differential effect.[54] Possible overdiagnosis of lung cancer is of concern. A lung cancer diagnosed by screening that would have otherwise never caused symptoms or death in the screened subject is called overdiagnosis. Two scenarios are possible: either the CT screen reveals a lung cancer with a very slow doubling time or the screened subject dies prematurely of competing morbidities (i.e., cardiovascular risk). An ancillary study from the NLST group estimated that 18.5% (95% CI: 5.4–30.6) of lung cancers in the CT arm were overdiagnosed,[55] although some authors suggest that this may well be an overestimation.[56]

To answer some of these questions, a prospective study is comparing findings of chest LDCT screens in a cohort of HIV-infected smokers to those of matched HIV-negative controls in New York.[57] The study will determine the rate of positive screens, as well as the harm and benefits of annual LDCT lung cancer screening in both populations and the cost-effectiveness of annual LDCT cancer screening in the HIV-infected population. Finally, data from this cohort will also help to create a model of lung cancer risk in the HIV-infected population.

Lung Cancer Screening: An Opportunity to Diagnose Other Smoking-Related Complications

In a recent letter, Mets et al. underscored the potential benefits of evaluating other thoracic morbidities on lung cancer screens without any supplementary radiologic acquisitions.[58] These evaluations should not

replace the accepted standard diagnostic procedures of these conditions, and they may in some cases increase morbidity and mortality on account of unnecessary testing and treatment for conditions that would have never caused harm otherwise. Smoking-associated conditions evaluated in different chest LDCT lung cancer screening studies include coronary artery calcifications,[59–63] emphysema,[64–66] smoking-associated bronchiolitis,[67] and vertebral fractures.[68] In a post hoc analysis of the ANRS EP48 HIV CHEST cohort,[35] coronary artery calcification was found to be highly prevalent (67% of subjects),[69] as were emphysema and bronchiolitis (in more than 85% of subjects [data not published]). A third study evaluated the prevalence of vertebral fractures on 397 reconstructed sagittal spinal planes[70] and found a prevalence of 11.6%.

Lung cancer screening in PLWHIV is also an opportunity to screen for other conditions in a highly morbid population. Prevalence of chronic obstructive pulmonary disease (COPD) was assessed using spirometry in 338 subjects from the French ANRS lung cancer screening study[71] and was found to be highly prevalent: 26% of those screened met the diagnostic criteria for COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria.[72] Interestingly, more than three-quarters of these subjects did not know their COPD condition.

Placing Chest LDCT Screening in the Perspective of Other Interventions to Reduce Lung Cancer Incidence in PLWHIV

The most efficient weapon to increase survival of high-risk smokers in a lung screening trial remains smoking cessation, which efficiently reduces all smoking-related morbidities. However, the benefits of smoking cessation and screening are additive: after 7 years of abstinence from smoking, a 20% specific mortality reduction was obtained in participants in the standard arm of NLST; in the experimental CT arm, an additional reduction of 10% was obtained.[73] Similar studies are needed in PLWHIV. Data on mortality induced by smoking in HIV-infected populations underscore the importance of smoking cessation programs. A Danish case-control study showed that PLWHIV lost more years of life on account of smoking rather than on account of their HIV infection and had a threefold to 6.7-fold increased risk of dying in comparison with nonsmoking PLWHIV.[74] The population-attributable risk of death associated with smoking was 61.5% among HIV patients. In an ancillary study of the SMART trial, the population attributable risk in PLWHIV for current smokers was 24.3% for overall mortality, 25.3% for major cardiovascular disease, 30.6% for non-AIDS cancer, and 25.4% for bacterial pneumonia.[75]

How much a lung cancer screening program can affect smoking cessation in the general population is under debate. A study from the NELSON group even showed less smoking cessation in subjects undergoing lung cancer screening.[76] In the French ANRS lung cancer screening study of PLWHIV, subjects with lung images and a CT scan follow-up did not have a significant increase in smoking abstinence versus those who had a "normal" baseline chest CT.[35] However, most studies showed that participation per se in a lung cancer screening program had a beneficial impact on smoking cessation.[77–81] Participation in a screening program by "healthy" smoking volunteers is a key moment to teach, reinforce, or trigger motivation for smoking cessation. The way screen results are communicated to the participants is essential, as abstinence increases when subjects are systematically counseled with scan results.[79,80,82] Lung cancer screening is likely a teachable moment for smoking cessation in PLWHIV. However, PLWHIV have multiple and regular health care contacts with their HIV specialist, and the motivation induced by participation in a lung cancer screening program may thus be attenuated.

There is also a specific need to implement specific codependence cessation programs in PLWHIV, as cointoxications with other substances are frequent. In the Centers for AIDS Research Network of Integrated Clinical Systems in United States, of the 3413 PLWHIV monitored between 2005 and 2010, 24% reported recent use of cannabis,[83] as did 21% of those in a recent survey of men who have sex with men in the United Kingdom.[84] Cannabis could also be an additional risk factor for development of lung cancer that needs to be assessed in specific screening strategies. Despite all these caveats, cessation programs have shown efficacy in HIV-infected populations, as shown in a recent meta-analysis of eight behavioral randomized trials versus standard of care[85] and in a randomized trial evaluating varenicicline versus placebo.[86]

Conclusion

Taken together, the findings of our review underscore that lung cancer screening in PLWHIV with chest CT is feasible. Whether the age limit for screening should be younger in current smokers with a smoking history of 20 or more pack-years than in the general population, particularly when an marked history of immunodeficiency exists, should be further assessed. Improvements in screening strategies in all populations are needed, as well as specific smoking cessation programs in PLWHIV. When screening for lung cancer, one should also assess for multiple thoracic comorbidities, as the prevalence of many of these conditions is very high even in young PLWHIV.

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