High Frequency of Early Lung Cancer Diagnosis with Chest CT in HIV-Infected Smokers

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Background and objectives:

Lung cancer is the first incidental and fatal non AIDS defining malignancy in people living with HIV (PLWHIV)[1-9]. Standardized incidence ratios (SIR) of lung cancer is higher in PLWHIV in comparison with the general population[1,6,7,10-12], increased risk still persisting after adjusting for smoking[13-16]. In PLWHIV, smoking is the primary factor of lung oncogenesis, though immunodeficiency also contributes[7, 11, 17]. In the general population, the National Lung Screening Trial (NLST) showed significant reductions in lung cancer and overall mortality of respectively 20% and 6.7% with three annual chest low dose computed tomography (LDCT) versus standard chest radiography in smokers aged 55 to 74 years[18]. We conducted a lung cancer early diagnosis study with chest LDCT in PLWHIV to evaluate feasibility, efficiency, benefits and harms of a screening strategy in this population.

Methods:

- Prospective nationwide cohort from 14 clinical centers in France of PLWHIV followed for two years after a baseline chest LDCT (NCT01207986).
- Main inclusion criteria: age ≥ 40 years, active smoker in the past 3 years with a history of ≥ 20 pack-years, nadir CD4 < 350/µl and current CD4 > 100 cells/µl. Non inclusion criteria: active cancer or AIDS-classifying disease, lung infection within the previous 2 months, pregnancy, breastfeeding or contra-indication to thoracic surgery.
- Multi–detector row scanners scanned the entire chest from apex to posterior recesses at end inspiration in one breath hold according to the low-dose protocol with section thickness ≤1 mm and without contrast enhancement.
- A positive chest LDCT result was either the identification of ≥ 1 solid or partly solid non calcified (SN) pulmonary nodule ≥ 5 mm, ≥ 1 nonsolid non calcified (NSN) pulmonary nodule ≥ 8 mm, a solid endobronchial nodule, or a significant adenopathy.
- Suggested chest LDCT follow up and diagnostic procedures were those of the International Early Lung Cancer Action Program (IELCAP) algorithm[19].
- The predefined primary outcome was the number of proven histological lung cancers.
- With a 2.6 increased risk of lung cancer in PLWHIV, and a 1.06% prevalence of lung cancer after a first round of screening in the IELCAP study of subjects ≥40 years[19], we expected the prevalence of lung cancer to be 3% with a 95% CI of 1.7 to 4.3.

Results:

- 442 subjects had a baseline chest LDCT (figure 1 and table 1). 94 subjects (21%) had positive chest LDCT. Median follow-up was 24.4 months, IQR (22.8; 26.4), and 38 subjects did not have the 24 months visit: 1 abandoned the study, 32 (7.2%) were lost to follow up and 5 subjects died (2 of lung cancer, 1 of sudden death, 1 of a motorbike accident and 1 of lung infection). There were 12 cardiovascular events, 37 infectious complications and 13 incident non lung cancers, of which 6 have a demonstrated link with smoking hazards[20].
- 18 diagnostic procedures induced by significant chest LDCT findings were undertaken in 15 subjects (3.4%). None of these procedures yielded any serious adverse events. Eleven procedures engendered a histological diagnosis: 8 lung cancers, 1 mucosa-associated lymphoid tissue lymphoma, 1 Abrikossoff tumor and 1 *Mycobacterium xenopi* infection.
- In total, 10 lung cancers were diagnosed during follow-up : 8 (all proven) in subjects with significant nodules on baseline chest LDCT, 1 (very probable) in a subject with a significant nodule on baseline chest LDCT but contra-indication to surgery. Thus, proven or very probable lung cancers were evidenced in 9 patients (2.0%, 95% CI: 0.9-3.8). Another patient with no nodule at baseline LDCT was diagnosed with small cell lung cancer during follow-up.
-Characteristics of the 10 proven or very probable lung cancers are shown in table 2.
-At the two year visit, 402 of 404 subjects had available data on smoking: 126 subjects (31%) attempted to quit smoking at least once during the study, with no association between an attempt to quit and results of LDCT.

Discussion and Conclusion:

- Lung cancer early diagnosis with chest LDCT was feasible, with high rates of adherence. Numbers of invasive diagnostic procedures were low, and procedures were efficient and safe.
- Rates of significant images on baseline chest LDCT were in the range of those published in lung cancer screening studies with LDCT in the general population[18,21-23]. Our study showed that most subjects had early lung cancer diagnosis with chest LDCT.
- Our results also supports the hypothesis of an increased incidence of lung cancer in the smoking HIV-infected population.
- Screening HIV-infected subjects at risk for lung cancer with the NLST age criteria would have diagnosed only 2 of the 9 subjects with proven or very probable lung cancers and significant baseline images on chest LDCT.
- As suggested by the incidence of lung cancer, cardiovascular and infectious events, smoking cessation is of upmost importance in the HIV-infected population to reduce hazards of smoking morbidity.
-In conclusion, screening strategy of lung cancer based on chest LDCT should be proposed at younger ages than the general population in PLWHIV that smoke, at least in those with a low CD4 nadir.

(1) Engels AIDS 2006; (2) Bedimo JAIDS 2009; (3) Shiels Annals Internal Medicine 2010; (4) Shiels J Natl Cancer Inst 2011; (5) Lanoy IJC 2011; (6) Robbins AIDS 2014; (7) Heydhel AIDS 2014; (8) Morlat AIDS 2014; (9) Gotti Plos one 2014; (10) Dal Maso Br J Cancer 2009; (11) Grulich Lancet 2007; (12) Bedimo JAIDS 2009; (13) Sigel AIDS 2012; (14) Chatuverdi AIDS 2007; (15) Shiels JAIDS 2010; (16) Kirk CID 2007; (17) Guiguet Lancet Oncology 2009; (18) NLST Team N Engl J Med 2011; (19) Henschke N Engl J Med 2006; (20) Agudo JCO 2012; (21) Van Klaveren N Engl J Med 2009; (22) Pegna Lung Cancer 2009; (23) Infante Lung Cancer 2008.

Figure 1: Flow chart

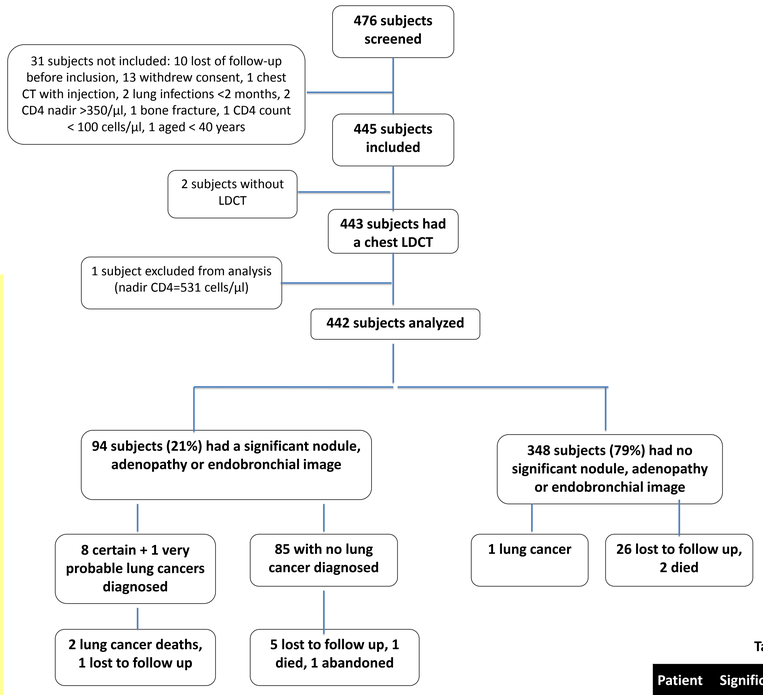

Table 1 : subjects' characteristics (n=442).

Characteristics	Value
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)
Known duration of HIV infection, median (IQR)	17.6 (10.8-22.3)
Nadir CD4, median (cells/µl), (IQR)	168 (75-256)
History of IVDU n (%)	125 (28)
Last CD4 value (median cells/µl)	574 (408-765)
Last viral load < 50 copies/ml (%)	396 (90)
Duration of ARV treatment, median (years)	13.8 (7.2-16.0)
History of AIDS classifying disease (%)	125 (28)
Chronic alcohol intake, n (%)	86 (19)
History of HCV infection (%)	147 (33)
Cigarettes (per day) (IQR)	20 (14-25)
Duration of smoking, (years), (IQR)	30 (28-36)
Cessation of smoking within the last three years (%)	37 (8)
Smoking, pack-years (IQR)	30 (25-40)
History of cannabis consumption n (%)	155 (35)
Asbestosis risk n (%)	23 (5)

IVDU: Intravenous Drug Use; ARV: Antiretroviral Treatment; HCV: hepatitis C virus

Table 2 : characteristics of the 10 proven or very probable lung cancers.

Patient	Significant images on baseline LDCT	Lung cancer histology	TNM stage	Stage	Last chest LDCT	Time (weeks) till cancer diagnosis
81008	Yes	Adenocarcinoma	T1aN0M0	IA	M1	23
67003	Yes	Adenocarcinoma	T2N2M1b	IV	M18	76
67029	Yes	Adenocarcinoma	T2N0M0	IIA	M12	70
57017	Yes	Adenocarcinoma	T1N3M1b	IV	M0	12
49013	Yes	Adenocarcinoma	T4N3M1b	IV	M0	66
75062	Yes	Adenocarcinoma	T1aN0M0	IA	M0	7
75006	Yes	Squamous cell	T1NOM0	IA	M3	23
57016	Yes	Adenocarcinoma	T2N0M0	IB	M3	7
67016	Yes	No histology	T1aNOMO*	IA*	M24	96
90048	No	Small cell	NA	Extended	M0	88

Table 2 (continued) : characteristics of the 10 subjects with proven or very probable lung cancers.

Subject	Age	Sex	Smoking (pack-years)	Smoking duration	Cannabis use	COPD (spirometry)	Asbestosis	Viral load	Nadir CD4	Last CD4	CD4/CD8
81008	45	M	30	30	Yes	No	No	<40	160	637	0,58
67003	46	F	52	35	Yes	No	No	<40	132	597	0.84
67029	49	M	45	30	No	No	No	<40	321	378	0.88
57017	50	F	27	36	No	No	No	61	60	590	1.02
49013	52	M	35	37	Yes	Not done	No	<40	236	568	0.47
75062	52	M	60	34	Yes	Yes	No	43	214	859	2
75006	54	M	28	37	Yes	Yes	No	<20	71	345	0.42
57016	56	M	34	39	No	Yes	No	<40	201	480	1
67016	58	F	21	42	Yes	Yes	Yes	<40	218	573	0.54
90048	50	M	40	32	No	No	No	<20	1	448	0.34

Age : years ; Viral load : copies/mL ; CD4 : cells/µl

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