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Early View

Original article

Computed tomography quantification of emphysema in people living with HIV and uninfected controls

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Title: Computed tomography quantification of emphysema in people living with HIV and uninfected controls

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Take home message: Well-treated HIV infection is not associated with emphysema

ABSTRACT

People living with HIV (PLWH) may be more susceptible to the development of emphysema than uninfected individuals. We assessed prevalence and risk factors for emphysema in PLWH and uninfected controls. Spirometry and chest computed tomography scans were obtained in PLWH from the Copenhagen comorbidity in HIV infection (COCOMO) Study and in uninfected controls from the Copenhagen General Population Study (CGPS) who were aged above 40 years. Emphysema was quantified using low attenuation area below -950 Hounsfield units (%LAA-950), the 15th percentile density index (PD15) and assessed by semi-quantitative visual scales. Of 742 PLWH, 21.2% and 4.7% had emphysema according to the %LAA-950 threshold with cut-offs at 5% and 10%, respectively. Of 470 uninfected controls, these numbers were 24.3% (p=0.23) and 4.0% (p=0.68). HIV was not associated with emphysema (adjusted odds ratio 1.25 [95%CI: 0.68-2.36] for %LAA-950>10%), by PD15, or by visually assessed emphysema. We found no interaction between HIV and cumulative smoking. Breathlessness and sputum production were more common in PLWH with emphysema, and emphysema seemed to be more prevalent in PLWH with airflow limitation. HIV was therefore not independently associated with emphysema but the clinical impact of emphysema was greater in PLWH than in uninfected controls.

Keywords: HIV, emphysema, lung, computed tomography, lung density and lung function

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) related emphysema was first reported in a case series in the late 1980s [1]. Several smaller studies have subsequently suggested that people living with HIV (PLWH) may develop emphysema at an earlier age and independent of tobacco smoking [2-4].

Specific disease mechanisms potentially contributing to destruction of lung parenchyma in PLWH have been recognized, including accumulation of cytotoxic T-cells in the lungs in the absence of combination antiretroviral therapy (cART) [3, 5], and increased oxidant stress in the absence of cART [6, 7]. Even during cART, alveolar macrophages may act as long-lived reservoirs of HIV [8, 9], and induce local inflammation, immune activation and produce proteases [9, 10]. Moreover, since emphysema originates around the small airways, it is noteworthy that HIV binds to human airway progenitor cells [11] and that never-smoking PLWH have evidence of small airway dysfunction [12]. However, while the understanding of emphysema pathogenesis in PLWH has increased, the majority of observational computed tomography (CT) studies in the cART era have not included uninfected controls [3, 13-15], have been restricted to rather small samples [2-4], or have not included quantitative measures of emphysema [3, 4, 16]. Thus, whether HIV infection *per se* is associated with emphysema or severity of emphysema in the current cART era still needs to be determined.

To address this question we performed CT densitometry and visual evaluation of emphysema in a population of PLWH and uninfected controls. A large number of participants enabled us to evaluate emphysema according to different %-low attenuation area thresholds and to perform interaction analyses in order to determine whether the effect of age and smoking is augmented by HIV. Finally, we assessed whether an emphysematous phenotype is more common in PLWH with airflow limitation, and whether the clinical significance of emphysema differs according to HIV status.

METHODS

Study design, study subjects, and ethics

The Copenhagen Comorbidity in HIV infection (COCOMO) study has been described elsewhere [17, 18]. In brief, the COCOMO study is a prospective study evaluating prevalence, incidence, and pathogenesis of non-AIDS comorbidity in PLWH. Chest CT imaging was performed during February 2015 to April 2016 for PLWH and during November 2015 to October 2016 for uninfected controls. Uninfected controls were recruited from the Copenhagen General Population Study (CGPS)[19, 20]. Only individuals above the age of 40 years underwent CT imaging in the CGPS. Thus, in order to obtain comparable samples from the two cohorts, we only included COCOMO participants above the age of 40 for the present study. As females are overrepresented in the CGPS compared to the COCOMO study, we included every fifth women from the CGPS in order to obtain balanced samples. Moreover, as individuals in the CGPS tend to be older we only included every fifth individual above the age of 70. A flow diagram summarizing inclusion has been included as online supplementary material 1. Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (H-15017350; H-KF-01-144/01). Written informed consent was obtained from all participants.

Data collection

Information related to respiratory risk factors and self-reported respiratory morbidity was obtained through identical questionnaires used in the COCOMO study and the CGPS. Breathlessness was defined by the modified medical research council (mMRC) scale with ≥2 signifying more breathlessness [21]. Chronic cough was defined as a cough lasting for 8 weeks or longer. Sputum was defined by duration of 3 months per year. HIV-related variables were extracted from patient records.

Spirometry

The procedure was previously described [17, 18]. An EasyOne® spirometer (ndd Medical, Zürich, Switzerland) was used in accordance with American Thoracic Society/European Respiratory Society guidelines [22]. Predicted values and their lower limit of normal (LLN, i.e. the fifth percentile of the reference population) were calculated using multiethnic prediction equations

provided by the Global Lung Function Initiative [23]. Airflow limitation was defined as either FEV_1/FVC<LLN or FEV_1/FVC<70% with FEV_1<80% predicted.

CT scanning procedure

PLWH and uninfected controls underwent a chest CT scan using the same two scanners on the same location (Department of Radiology, University Hospital of Copenhagen). Details regarding the scan protocol have previously been described [17, 24]. In brief, an Aquillion One Vision Edition scanner (Toshiba Medical Systems, Otawara-shi, Japan) was used for image acquisitions with the following settings: 120 kVp, automated exposure control (SD15), and reconstruction with filtered back projection and a soft tissue kernel (1 mm slice thickness and 1 mm increment). Scans were acquired during a deep inspiratory breath-hold using spiral image acquisition including the entire lungs.

Quantitative and visual emphysema assessment

Lung emphysema was quantified by densitometry using low attenuation area (%LAA) below -950 Hounsfield units (HU)[25-27]. %LAA-950 is defined as the proportion of lung voxels of low density below a threshold of -950 HU and *increases* with worsening emphysema. Various cutoffs have been used to define emphysema [28, 29]. We primarily defined emphysema as %LAA-950>10% but additionally used a threshold of 5%. We also used the 15^{th} percentile density index (PD15) approach for lung density quantification [25]. PD15 is defined as the cut off value in Hounsfield units (HU) below which 15% of all voxels are distributed and *decreases* with worsening emphysema. Images were scored using a dedicated lung density program (Vitrea Vital Images, Minnetonka, MN, US).

One board-certified radiologist (Author: TK) scored all scans un-blinded to HIV status but blinded to any other clinical information including results from quantitative CT analyses. A semi-quantitative score was used [4, 30]; i.e., 0 (no emphysema, 0%), 1 (trace emphysema, 1–10%), 2 (mild, 11–25%), 3 (moderate, 26–50%), 4 (severe, 51–75%), and 5 (very severe, >75%) visual emphysema.

Statistical analysis

Differences in clinical characteristics and emphysema outcomes were assessed using *t*-tests and Mann-Whitney comparisons for continuous data and Chi-square Tests or Fisher's Exact Test for categorical data. Logistic regression analyses were performed to determine risk factors associated with emphysema defined by %LAA-950 according to a 5% and a 10% threshold. As secondary outcome we assessed emphysema visually using a threshold of ≥1 and ≥2 [4]. Crude and adjusted odds-ratios (OR/aOR) with 95% CIs were computed for these analyses. We additionally evaluated %LAA-950 and PD15 as continuous outcomes and performed multiple linear regression analyses. For this purpose we log-transformed %LAA-950 (due to a right skewed distribution) to approximate normality while the explanatory variables were kept in their original metrics. The interpretation for such a model is on the relative scale. For all regression analyses we considered models adjusted for age, sex, ethnicity, and pack-years smoked and tested interactions between cumulative smoking and HIV status as well as interaction between age and HIV status. We performed similar analyses using smoking status (defined as current, former, never or unknown) as a predictor, rather than pack-years, to avoid the potential collinearity between cumulative smoking and age. We finally evaluated PLWH separately and assessed whether various HIV associated factors were each associated with emphysema. Statistical analyses were performed using R software version 3.3.2 [31].

RESULTS

Clinical characteristics

A total of 742 PLWH and 470 uninfected controls with quantitative and visual CT assessment were included in the study (Table 1). Transmission mode for PLWH was primarily men having sex with men (517; 70.4%) and heterosexual (164; 22.3%). Most PLWH were receiving cART at the time of inclusion (730; 98.6%) and had suppressed viral replication (703; 95.4%). Few were intravenous drug users (12; 1.6%) or were hepatitis-C coinfected (38; 5.1%). Current mean (SD) CD4 count was 712 (288) and few had CD4 count below 200 cells/mm^3 (13; 1.8%). CD4 nadir count was 235 (178) with a total number of 346 (47.5%) having nadir CD4 count below 200 cells/mm^3.

Quantitative and visual emphysema in PLWH and uninfected controls

The prevalence of %LAA-950 above 5% and 10% were comparable in PWLH and uninfected controls (Table 2). Thus, for PLWH the prevalence of emphysema according to >5% and >10% were 21.2% [95%CI: 18.4-24.2] and 4.7% [95%CI: 3.4-6.5], respectively, and for uninfected controls these numbers were 24.3% [95%CI: 20.6-28.3] and 4.0% [95%CI: 2.60-6.2]. Evaluated as a continuous variable %LAA-950 appeared to be slightly lower in PLWH (2.0% [0.9-4.3] vs 2.7% [1.4-4.9], p<0.0001) (Table 2, Figure 1). Similar results were found for never-smokers (Table 2). HIV was not associated with %LAA-950 cutoffs for emphysema in multivariable logistic regression models adjusted for age, sex, ethnicity and pack-years of smoking (Table 3). Moreover, we found no evidence for interaction between smoking and HIV in these models (p-interaction: 0.82 and 0.74) or between age and HIV (p-interaction: 0.10 and 0.60). In models adjusted for smoking status rather than cumulative smoking we also found no association between HIV and emphysema. We also evaluated log-transformed %LAA-950 as outcome in a linear regression model and found HIV to be independently associated with a 29.0% [95%CI: 16.6-39.5, p<0.0001] lower %LDI-950. HIV was not independently associated with PD15 (-1.94 g/L [95%CI: -4.6-0.75], p=0.16).

We also assessed emphysema visually. Individuals with visual emphysema were more likely to have a higher median %LAA-950 compared to individuals without visual emphysema (5.0% [2.5-10.5] vs 2.2% [1.0-4.4], p<0.0001). In univariate analysis, HIV was associated with emphysema (OR 1.87 [95%CI: 1.11-3.27, p=0.02]). However, we were not able to find this association in

multivariate analyses adjusted for age, sex, ethnicity and cumulative smoking (aOR 1.53 [95%CI: 0.85-2.83], p=0.16). We found similar results when smoking exposure was modelled according to smoking status rather than cumulative smoking (aOR 1.48 [95%CI: 0.83-2.73], p=0.19) and when visual emphysema was defined according to grade 1 (1-10%) or higher (aOR 0.88 [95%CI: 0.58-1.33], p=0.54).

Associations with emphysema by HIV status

We subsequently evaluated whether emphysema was more prevalent in PLWH with airflow limitation compared to uninfected controls with airflow limitation. Emphysema (%LAA-950>10%) tended to be more common in PLWH (17/77) with FEV_1/FVC<LLN compared to uninfected controls (4/49) with FEV_1/FVC<LLN, p=0.07.

We also assessed the clinical significance of emphysema by evaluating the distribution of breathlessness (mMRC 2-4) in PLWH and uninfected controls with %LAA-950 >10%. A total of 8/35 PLWH with emphysema had breathlessness and mMRC categories were different in PLWH with and without emphysema (p<0.001). In uninfected controls, 1/19 individuals had breathlessness and mMRC categories did not differ according to emphysema (p=0.18)(Figure 1). Sputum production was present in 12/35 PLWH with %LAA-950>10% and more common than in individuals without emphysema (p<0.01). Sputum was present in 0/19 uninfected controls with emphysema and, thus, not more common in those without emphysema (p=0.24). Chronic cough was not significantly associated with emphysema in PLWH (p=0.07) or uninfected controls (p=0.65) (Figure 1).

HIV related factors and emphysema

Current CD4 count, CD4 nadir count, detectable viral replication, and prior PCP were not associated with either the 5% or 10% cutoff for %LAA-950 after adjusting for age, sex, ethnicity, and pack-years smoked (Table 4). Time living with HIV (per 5 years) was associated with %LAA-950 in univariate analyses but not after multivariate adjustments (Table 5). Although CD4 nadir <200 cells/mm^3 appeared to be associated with visual emphysema (OR 1.70 [95%CI: 0.97-3.02], p<0.07),

this association was not found in multivariate analyses (Table 5). None of the other HIV variables were associated with visual emphysema in uni- or multivariate analyses.

DISCUSSION

Our findings contrast to preART studies, and a limited number of cART era studies evaluating emphysema visually, that found HIV to be independently associated with emphysema. HIV was not independently associated with emphysema and we found no evidence of interaction between age and tobacco smoking with HIV status. We also found no association between factors associated with HIV disease and emphysema. However, emphysema seemed to be more common in PLWH with airflow limitation than in uninfected controls with airflow limitation, and breathlessness was more strongly associated with emphysema in PLWH compared to uninfected controls.

In previous studies radiographic emphysema in PLWH has been semi-quantitatively determined by visual assesement [3, 4, 13, 16]. Emphysema was highly prevalent in these studies ranging from 15% [3] and up to as high as 31% [16]. However, concordance between visual and quantitative CT assessment for the presence or absence of emphysema is only moderate [28]. Each modality has certain strengths and limitation. An advantage of visual scoring is the ability of the radiologist to distinguish whether the low attenuation is caused by emphysematous destruction or hyperinflated regions consistent with gas-trapping caused by small airways disease [32]. Moreover, current smoking status *per se* may be associated with higher lung density (possibly due inflammation and accumulation of soot and tar)[33], which may theoretically cause a lowering of emphysema extent; i.e., a lower %LAA-950, in PLWH. On the other hand, quantitative measurements correlate better with microscopic and macroscopic emphysema than visual scoring [34], may be less prone to over-estimating the extent of emphysema [32], and provide better reproducibility [35]. Few quantitative CT studies have been performed in PLWH [14, 15, 36, 37]. The largest of these studies was the Lung-HIV study from three US centers performing quantitative emphysema determination in 510 PLWH [14]. Although this study included more current smokers, a higher percentage of injection drug users and a higher number of individuals with detectable viral replication than the present study, it found 29.4% and 5.7% with emphysema according to >5% and >10% cutoff of

%LAA-950. Despite the fact that our study consisted of individuals above 40 years of age approximately six years older on average, we found a comparable prevalence of emphysema (21.2% and 4.7%).

Few studies have included uninfected controls. One study compared mean lung density, but not specific %LAA-950 thresholds, in 83 PLWH and 42 uninfected controls, and found HIV to be independently associated with higher lung density [37]. These findings may suggest other underlying disease processes, such as inflammation and fibrosis, but did not indicate an association between HV status and emphysema. HIV was found to be a risk factor for semi-quantitative emphysema (>10%) in the VACS sub-study of 114 PLWH and 89 uninfected controls [4]. We were not able to reproduce this finding in any of our models using quantitative CT measures, and we found no evidence of interaction between HIV status and age or HIV status and cumulative smoking. Thus, although we did not study lung density trajectories, the effect of age and smoking seemed to be equally important in PLWH and uninfected controls in contrast to what was previously suggested [3]. Although earlier findings and the present results differed, they may both be correct and reflect a changing disease pattern for lung diseases in PLWH as a result of better and earlier therapy. Our cohort is unique in that it included individuals from a high-resource setting with a near complete cART coverage, few injection drug users, and individuals with rather high CD4 counts. Thus, other mediators of HIV, such as viral replication, inflammation or immune deficiency in the absence of cART, may potentially be responsible for development of emphysematous destruction. We did not find an association between emphysema (quantitative or visual) and CD4 nadir. However, the VACS sub-study found CD4 nadir below 200 cells/mm^3 to be an independent risk factor for emphysema (OR, 2.98; 95% CI: 1.14-7.81) in a model adjusted for cumulative smoking [4]. Although the VACS cohort tended to have poorer immune status and this association may have been confounded by other factors (e.g. very high rates of smoking and substance abuse), we previously also found CD4 nadir to be associated with measures of pulmonary function in the present cohort [18]. Moreover, a longitudinal study using VACS registry data showed an association between time-updated CD4 counts and lung cancer [38]. Thus, exposure of low CD4 counts before treatment initiation may render the host more susceptible to smoking and other potential insults contributing to emphysema. The discrepancy between our study and the VACS data may reflect the inclusion of different study populations; e.g., the VACS

cohort includes a large proportion of individuals that currently smoke (~60%) and have used intravenous drugs (~30%) or marijuana (~85%). As a consequence, the effect of other risk factors, such as CD4 nadir, may differ.

A few studies assessing overlap between emphysema and airflow limitation have suggested that emphysema may occur independently of airflow limitation [15, 39]. We found emphysema to be more prevalent in PLWH with airflow limitation (FEV_1/FVC<LLN) compared to uninfected controls with airflow limitation and %FEV_1-predicted correlated better with emphysema in PLWH than in uninfected controls. Moreover, we previously determined FEV_1/FVC<LLN to be equally prevalent in PLWH and uninfected controls, but the degree of airflow limitation was more severe in PLWH [18]. It may therefore be speculated that the emphysematous phenotype is more prevalent in PLWH with airflow limitation and contribute to a more severe degree of airflow limitation.

We also observed that breathlessness and sputum production was more common in PLWH with emphysema than in uninfected controls with emphysema. Similarly, a VACS sub-study found that emphysema only correlated with objective functional impairment (assessed by the 6-minute walking distance) and self-reported chronic cough in PLWH and not uninfected controls [39]. Taken together, these findings suggest that the clinical significance of emphysema may differ according to HIV status, although the mechanism for this differential impact is unknown.

Our study has limitations and strengths. First, uninfected controls were not completely matched on demographic variables and risk factors. Thus, tobacco smoking was more common in PLWH and the two populations were different in regard to ethnicity. Despite accounting for these factors, using several different lung density measures (%LAA-950 according to 5% and 10% thresholds, PD15, and log transformed %LAA-950) and visual assessment, we were not able to show that HIV is associated with emphysema. Second, visual assessment of CT was unblinded to HIV status but was nevertheless consistent with results from the quantitative measures. Finally, we were not able to evaluate the exposure to low CD4 counts longitudinally and had to rely on static measures.

In conclusion, HIV was not independently associated with emphysema in a well-resourced setting where most PLWH had undetectable viral replication and high CD4 counts. Moreover, we were not able to find evidence that the effect of smoking is different according to HIV status. However, the

clinical significance of emphysema was greater in PLWH, and emphysema seemed to be more prevalent in PLWH with airflow limitation than uninfected individuals with airflow limitation.

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ETHICS APPROVAL

The study was approved by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350; CGPS: H-KF-01-144/01). Written informed consent was obtained from all participants.

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COMPETING INTERESTS

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CONTRIBUTORS

AR was responsible for concept, data collection, statistical analysis, and drafted the manuscript. TK was responsible for concept, data collection and edited the manuscript. VSH was responsible for data collection and edited the manuscript. DAK was responsible for data collection and edited the manuscript. TOK: was responsible for concept and edited the manuscript. TB was responsible for concept and edited the manuscript. JG was responsible for concept and edited the manuscript. SA was responsible for concept, data collection, and edited the manuscript BGN was responsible for concept, data collection, and edited the manuscript. JL was responsible for concept and edited the manuscript. JV was responsible for concept and edited the manuscript. KFK was responsible for concept and edited the manuscript. SDN was responsible for concept, data collection and edited the manuscript.

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Table 1. Clinical characteristics in people living with HIV (PLWH) and uninfected controls

	PLWH (n=742)	Uninfected controls (n=470)	p-value
Age, mean (SD)	54.2 (9.2)	57.4 (8.8)	<0.001
Age groups			<0.001
- 40-50 years, n (%)	284 (38.3)	107 (22.8)	<0.001
- >50-60 years, n (%)	253 (34.1)	174 (37.0)	
- >60-70 years, n (%)	156 (21.0)	164 (34.9)	
- >70-80 years, n (%)	46 (6.2)	23 (4.9)	
- >80, n (%)	3 (0.4)	2 (0.4)	
Male, n (%)	636 (85.7)	386 (82.1)	0.11
Scandinavian, n (%)	552 (75.6)	429 (92.1)	<0.001
BMI (kg/m^2), mean (SD)	24.9 (3.7)	26.7 (3.6)	<0.001
Smoking status			<0.001
- Current smokers, n (%)	195 (26.3)	46 (9.8)	
- Ex-smokers, n (%)	288 (38.8)	206 (43.8)	
- Never smokers, n (%)	245 (33.0)	217 (46.2)	
Tobacco consumption in pack-years ‡, median [IQR]	19.5 [7.4-33.0]	18.0 [7.5-32.0]	0.44
mMRC			<0.001
- 0	480 (67.3)	342 (72.9)	
- 1	177 (24.8)	114 (24.3)	
- 2	36 (5.0)	6 (1.3)	
- 3	12 (1.7)	4 (0.9)	
- 4	8 (1.1)	3 (0.6)	
Airflow limitation			
- FEV_1/FVC<LLN, n (%)	77 (10.6)	49 (10.6)	1.00
- FEV_1/FVC<0.7 with FEV_1<80%*, n (%)	69 (9.5)	36 (7.8)	0.37
%FEV_1 predicted			<0.001
- >80%, n (%)	567 (78.0)	408 (88.1)	
- 50-79%, n (%)	146 (20.1)	55 (11.9)	
- 30-49%, n (%)	11 (1.5)	0 (0)	
- <30%, n (%)	3 (0.4)	0 (0)	
Lung volume (L)≠	5.8 (1.4)	5.6 (1.8)	0.03

Cumulative smoking is defined as (average number of cigarettes per day/20) x number of years smoked). Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second, FVC, forced vital capacity; IQR, interquartile range; LLN, lower limit of normal; PLWH, people living with HIV; SD, standard deviation.

‡For current and ex-smokers.

*Prebronchodilatory spirometry.

≠ Total lung volume measured by computed tomography.

Table 2. Quantification of emphysema in people living with HIV (PLWH) and uninfected controls stratified by smoking status

	PLWHV (n=742)	Uninfected controls (n=470)	P-value	PLWH, never smokers (n=245)	Uninfected controls, never smokers (n=217)	P-value
%LAA-950 >5%, n (%)	157 (21.2)	114 (24.3)	0.23	42 (17.1)	47 (21.7)	0.15
%LAA-950 >10%, n (%)	35 (4.7)	19 (4.0)	0.68	3 (1.2)	8 (3.7)	0.15
%LAA-950, median [IQR]	2.0 [0.9-4.3]	2.7 [1.4-4.9]	<0.0001	1.8 [0.8-3.9]	2.5 [1.5-4.6]	<0.0001
%PD15, mean (SD)	109.6 (24.8)	109.1 (19.0)	0.72	112.7 (25.8)	110.2 (19.4)	0.25
Visual emphysema, n (%)	54 (7.3)	19 (4.0)	0.03	1 (0.4)	0 (0)	1.00

Abbreviations: PD15, 15th percentile density index; PLWH, people living with HIV; %LAA, percent low attenuation area.

Table 3. Multivariate logistic regression analyses to determine whether HIV is independently associated with %LAA-950

	OR (95%CI) for %LAA-950>5%	P-value	aOR‡ (95%CI) for %LAA-950>5%	P-value	OR (95%CI) for %LAA-950>10%	P-value	aOR‡ (95%CI) for %LAA-950>10%	P-value
HIV, yes vs. no	0.83 (0.64-1.11)	0.21	0.96 (0.71-1.29)	0.77	1.18 (0.67-2.12)	0.58	1.25 (0.68-2.36)	0.48
Age, per decade	1.69 (1.46-1.97)	<0.0001	1.69 (1.44-1.99)	<0.0001	1.90 (1.42-2.55)	<0.0001	1.85 (1.35-2.55)	<0.001
Pack-years of smoking, per 10 pack years	1.06 (0.99-1.14)	0.09	1.00 (0.92-1.08)	0.99	1.23 (1.09-1.39)	<0.001	1.15 (1.01-1.31)	0.03

Abbreviations: aOR; adjusted odds ratio; %LAA, percent low attenuation area.

‡Multivariate model adjusted for age, sex, ethnicity, pack-years of smoking and HIV.

Table 4. Multivariate logistic regression analyses to determine whether HIV-related factors are independently associated with %LAA-950

	OR (95%CI) for %LAA-950>5%	P-value	aOR‡ (95%CI) for %LAA-950>5%	P-value	OR (95%CI) for %LAA-950>10%	P-value	aOR‡ (95%CI) for %LAA-950>10%	P-value
Current CD4 per 100 cells/mm^3	0.97 (0.91-1.03)	0.38	0.99 (0.93-1.07)	0.98	1.06 (0.95-1.18)	0.28	1.08 (0.96-1.21)	0.16
CD4 nadir < 200 cells/mm^3	1.20 (0.84-1.71)	0.33	0.99 (0.69-1.47)	0.94	0.91 (0.45-1.85)	0.81	0.60 (0.27-1.32)	0.21
HIV viral load > 50 copies/ml	0.96 (0.38-2.12)	0.92	0.84 (0.29-2.07)	0.72	2.03 (0.47-6.08)	0.26	2.43 (0.53-8.07)	0.19
Previous PCP (yes vs. no)	1.26 (0.65.2.33)	0.47	0.85 (0.39-1.71)	0.66	1.63 (0.47-4.31)	0.38	1.49 (0.42-4.14)	0.49
Time living with HIV (per 5 year)	1.18 (1.07-1.31)	<0.01	1.09 (0.97-1.22)	0.15	1.24 (1.02-1.51)	0.03	1.06 (0.86-1.33)	0.57

Abbreviations: aOR; adjusted odds ratio; %LAA, percent low attenuation area.

‡Multivariate model adjusted for age, sex, ethnicity, pack-years of smoking and HIV.

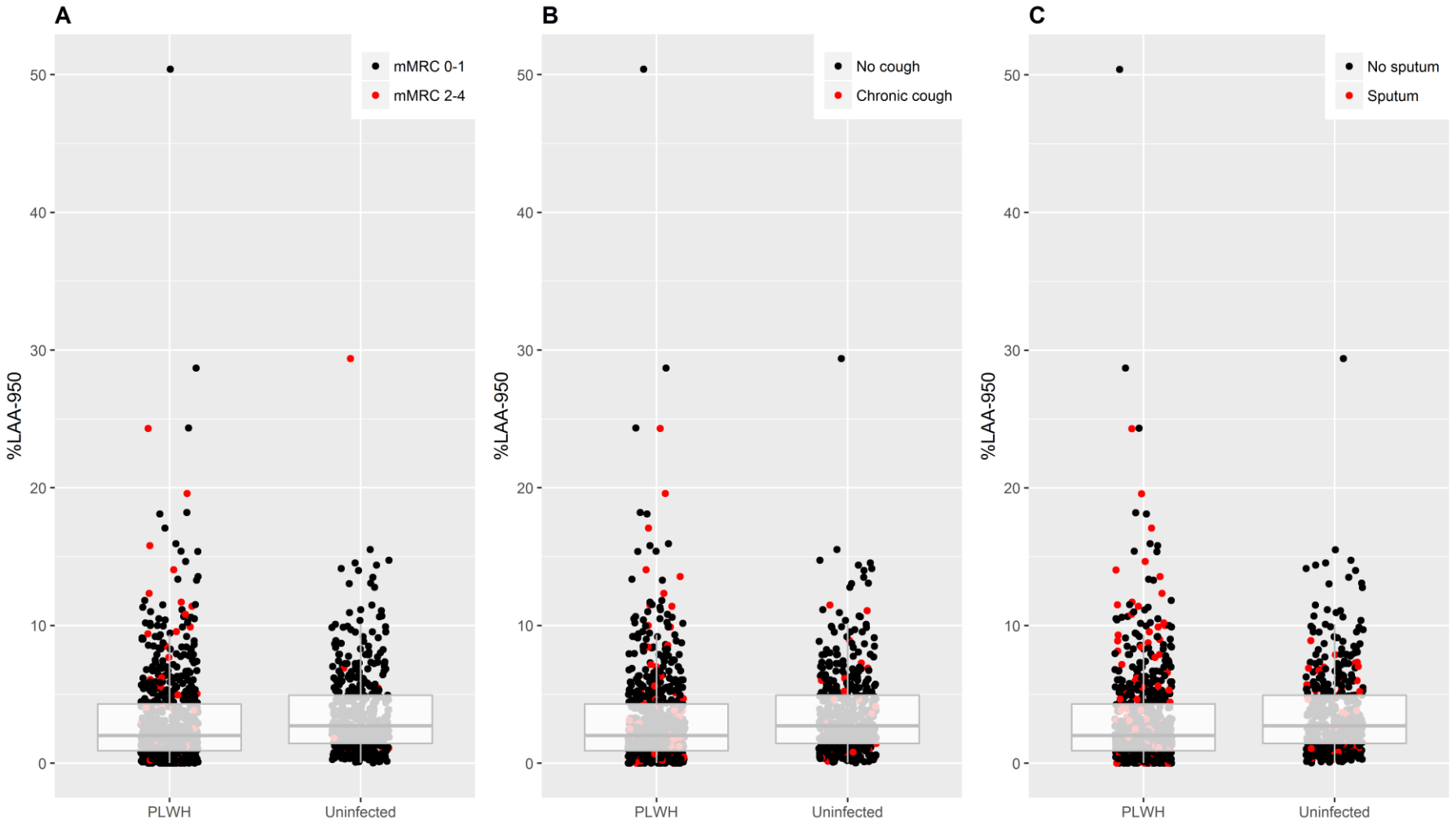
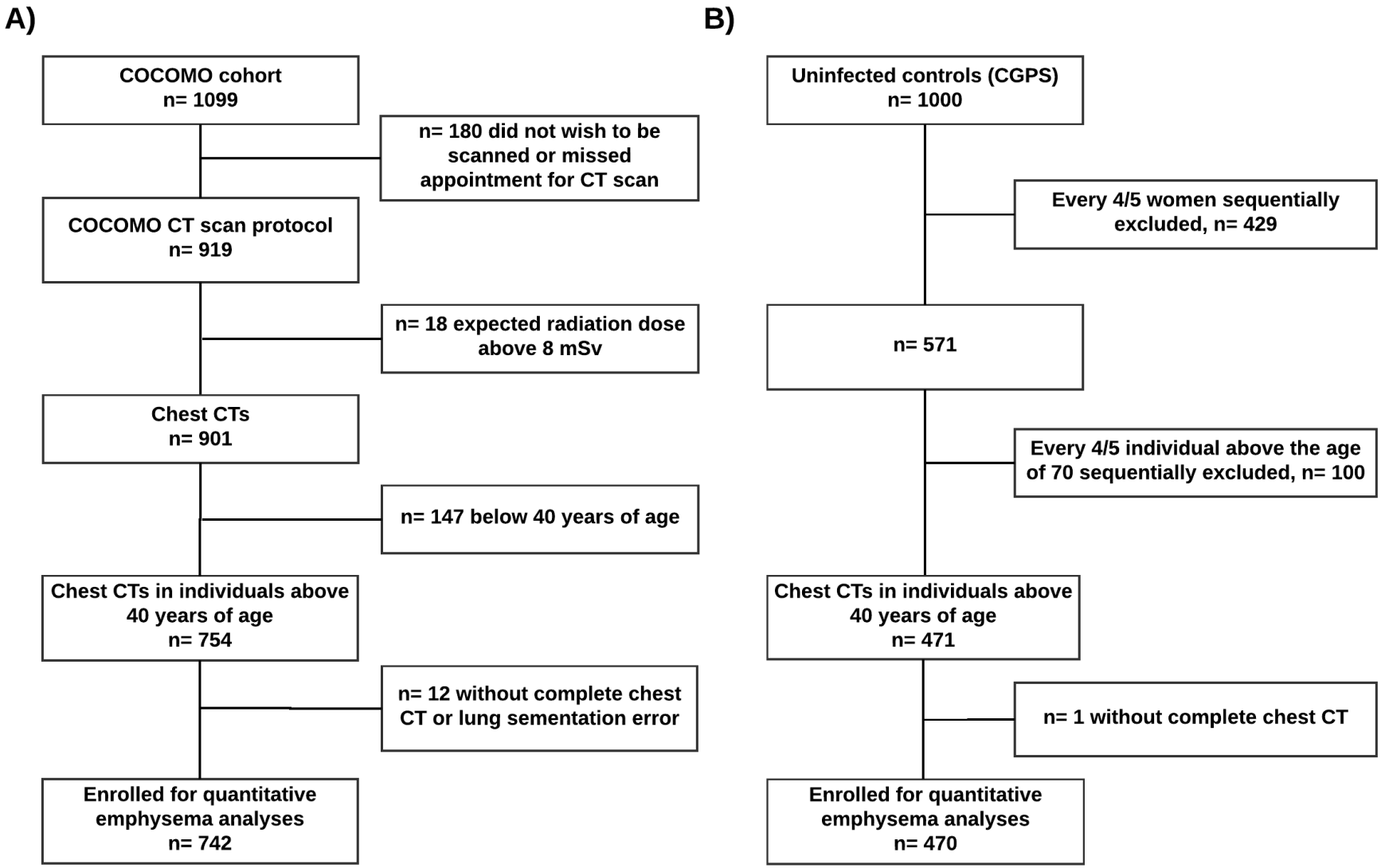


Figure 1. %LAA-950 and self-reported respiratory morbidity in people living with HIV and uninfected controls

P-value for the difference between %LAA-950 in PLWH and uninfected controls ($p<0.001$). Boxplot represents 25th and 75th percentile (lower and upper quartiles, respectively) and 50th percentile (median). Abbreviations: mMRC; modified medical research council dyspnea scale, PLWH, people living with HIV; %LAA, percent low attenuation area.

Online Supplementary Figure 1.



Abbreviations: CGPS, Copenhagen General Population Study; COCOMO, Copenhagen Co-morbidity in HIV infection Study; CT, computed tomography.