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Clinically Significant Incidental Findings among HIV-Infected Men during Computed Tomography for Determination of Coronary Artery Calcium

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Abstract

HIV-infected persons are at higher risk for cardiovascular disease and may undergo computed tomographic (CT) scans for early detection. Incidental findings on cardiac CT imaging are important components of the benefits and costs of testing. We determined the prevalence and factors associated with incidental findings on CT scans performed for screening for coronary artery calcium (CAC) among HIV-infected men. A clinically significant finding was defined as requiring further work-up or medical referral. A total of 215 HIV-infected men were evaluated with a median age of 43 years, 17% were current tobacco users, median CD4 count was 580 cells/mm³, and 83% were receiving antiretroviral medications. Thirty-four percent had a positive CAC score of >0. An incidental finding was noted among 93 (43%) of participants, with 36 (17%) having at least 1 clinically significant finding. A total of 139 findings were noted, most commonly pulmonary nodules, followed by granulomas, scarring, and hilar adenopathy. The majority of incidental findings were stable on follow-up, and no malignancies were detected. Factors associated with having an incidental finding in the multivariate model included increasing age (OR 1.6 per 10 years, $p < 0.01$), positive CAC score (OR 2.3, $p < 0.01$), and current tobacco use (OR 2.5, $p = 0.02$). In conclusion, incidental findings are common among HIV-infected persons undergoing screening CT imaging for CAC determination. Incidental findings were more common among older patients and those with detectable CAC.

Keywords

HIV; CT scans; CAC scores; coronary artery calcium; heart disease; incidental findings

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This work is original and has not been published elsewhere.

Background

Although several studies have utilized coronary artery calcium (CAC) scores to measure subclinical heart disease in human immunodeficiency virus (HIV)-infected persons [1–3], no study to date has determined the frequency and types of incidental abnormalities found during these tests. Studies evaluating incidental findings detected on coronary computed tomography (CT) imaging (CAC and angiography) in the general population have been published, but did not specifically evaluate HIV-infected subjects [4–18]. HIV-infected persons may be at higher risk for infectious and malignant conditions [19,20], which may have implications for the type and number of incidental findings on imaging studies. Incidental findings are important as they not only impact the clinical usefulness, but also the cost-effectiveness, of screening CT scans. We report the frequency and clinical significance of incidental findings among HIV-infected persons undergoing CT screening for CAC determination.

Methods

We evaluated HIV-infected men who were screened for CAC using non-contrast CT of the heart between December 9, 2008 and March 1, 2010. The primary study objective was to determine the prevalence of subclinical coronary atherosclerosis using the Agatston scoring method [21]. The objectives of this substudy were to: 1) describe the prevalence and types of incidental findings on CT during standard imaging for CAC scores, and 2) compare the characteristics of HIV-infected men with and without incidental findings.

Inclusion criteria for study participation were a positive HIV test (ELISA confirmed by Western Blot) and being a military beneficiary, which included active duty members, retirees, and family members. All participants provided written informed consent; the study was approved by the governing institutional review board; and registered at ClinicalTrials.gov (NCT00889577).

Clinical data collected at the time of the CT scan included demographics, tobacco use history, body mass index (BMI), waist circumference, C-reactive protein (CRP, lower limit of detection <0.5 mg/dl; Particle Enhanced Immunoturbidimetric Assay, Roche), erythrocyte sedimentation rate (ESR, Modified Westergren Method), CD4 cell counts (flow cytometry), plasma HIV RNA levels (Roche Amplicor, undetectable as <50 copies/ml), and antiretroviral therapy use. Diagnoses of hypercholesterolemia (total cholesterol >200 mg/dl), hypertension and diabetes (based on the use of medications for these conditions), and a history of an opportunistic infection were recorded.

Participants underwent non-contrast CT imaging using a multidetector CT machine. Prospectively gated axial 3 mm images were obtained at 120kV on a Siemens Definition Dual Source CT Scanner (Siemens Medical Solutions, Forstheim, Germany). The scanning protocol captured images with a 330-millisecond gantry rotation time, an individual detector width of 0.6 mm with a reconstructed section width of 3 mm and temporal resolution of 165 milliseconds. Contiguous 3 mm thick sections were reconstructed during peak inspiration with a 16–25 cm field of view depending on heart size. Images were processed on an Impax 6.3 workstation (AGFA). Full field of view reconstructions were performed of the entire lungs at the levels from the carina to just below the cardiac apex; CT images also included the mediastinum, hilum, and diaphragm. Abdominal organs were not visualized unless the diaphragm was shifted cranially due to underlying pathology. CAC scoring was performed on an Aquarius workstation (TeraRecon, San Mateo, California) and calculated as the sum of all lesions in each of the coronary arteries using Agatston units, as previously described [21]. A CAC score of >0 was considered positive for detectable calcium.

Images were read by a board-certified radiologist (G.B.) for incidental non-coronary findings at the time of CAC scoring. Any finding requiring further clarification was reread by the same radiologist. Incidental findings were captured only if the finding was not solely age-related (e.g., calcification of the aorta), due to trauma (e.g., old rib fractures), or post-surgical. Incidental findings were classified as clinically significant by the need for further work-up, including imaging, or medical referral. The need for further radiologic imaging was determined using available evidence-based criteria; for example the management of pulmonary nodules was based on the Fleischner guidelines [22]. A pulmonary nodule was defined as a ≤ 3 cm lesion in the lung parenchyma, and a granuloma as a calcified opacity. Cases of emphysema or bronchiectasis were recommended for referral to pulmonary medicine. Medical records of participants with a clinically significant incidental finding were reviewed in August of 2010 for clinical outcomes including data on follow-up imaging.

Statistical analysis included descriptive statistics of the prevalence of incidental findings. Categorical variables were described as numbers with proportions, and continuous variables as medians with interquartile ranges (IQR). Incidental findings were divided into “clinically significant” or “not clinically significant” as defined above. Comparisons of participants with and without incidental findings were performed using Fishers exact and rank-sum testing for categorical and continuous variables, respectively. A multivariate logistic regression model was performed to evaluate factors associated with incidental findings on cardiac CT scan. Variables with a p-value < 0.10 on univariate testing were placed in the full multivariate model and a backward stepwise approach was used to derive the final model. A p-value of < 0.05 was considered statistically significant. All analyses were performed using STATA 10 (College Station, TX).

Results

The study population consisted of 215 HIV-infected men (Table 1). An incidental finding was noted among 93 (43%) of patients with 36 (17%) having a clinically significant finding that required follow-up or medical referral. The number of incidental findings per person ranged from 0 to 5. Of those with an incidental finding, 62 patients had one finding, 19 had two findings, 10 had three findings, 1 had four findings, and 1 had five findings.

The number and type of incidental findings are shown in Table 2. In total, 139 incidental findings were noted; some participants had multiple findings. The most common findings were pulmonary nodules, followed by granulomas and scars. Fifteen patients (7% of the cohort) had findings consistent with emphysema or bronchiectasis. Several extrapulmonary findings were noted including gynecomastia, hiatal hernia, pathologic aortic dilation, and a large (15×13 cm) asymptomatic splenic cyst.

Of all incidental findings, 46 (33%) were deemed clinically significant. Most commonly these were pulmonary nodules (Table 2). On follow-up evaluation (median 15 (range 6–21) months after initial CT for CAC scoring), 15/18 of pulmonary nodules were re-imaged: 13 were unchanged; 1 demonstrated increase in size (7 to 20 mm) and work-up with bronchoscopy with cultures and cytology was negative; and 1 was determined not to be a nodule on reimaging. Three participants with pulmonary nodules failed to undergo the scheduled follow-up imaging. Cases of pneumonia/opacities received antibiotics and were resolved or improving among 4 of the 5 who underwent repeat imaging. Cases of emphysema or bronchiectasis had no changes in management, except in 1 case in which bronchodilators were prescribed. The aortic dilation detected on imaging remained stable. The single patient with the large splenic cyst underwent a splenectomy due to the high risk

of rupture. Only 1 participant died during follow-up; the cause of death was not associated with the incidental finding (i.e., nodule) on CT.

HIV-infected persons with an incidental finding compared to those without were older (48 vs. 41 years, $p<0.01$), current tobacco users (23% vs. 12%, $p=0.04$), diabetic (11% vs. 2%, $p=0.02$), had a higher ESR (13 vs. 10 mm/hour, $p<0.01$), had a positive CAC score (46% vs. 25%, $p<0.01$), and lower current CD4 cell counts (563 vs. 600 cells/mm³, $p=0.02$) (Table 1). Among tobacco users, a longer duration of use was also associated with an incidental finding ($p<0.01$).

In the final multivariate model, increasing age (OR 1.6 per 10 years, $p<0.01$), presence of CAC (OR 2.3, $p<0.01$), and current tobacco use (OR 2.5, $p=0.02$) were associated with the presence of an incidental finding (Table 3). No HIV-specific factor was significant in the final model. The final model had a good fit (likelihood ratio test of 26.7, p -value <0.01).

Discussion

This is the first study to evaluate the prevalence of incidental findings among HIV-infected persons undergoing CT imaging for coronary atherosclerosis screening. We found that 43% of HIV-infected persons undergoing CAC determination had at least 1 incidental finding. In the general population, 5 studies have evaluated the prevalence of incidental findings on CT scans for CAC determination [7–11], with additional studies examining other types of CT cardiac imaging [5,6,12–18], and noted 8–53% had incidental findings, with a mean prevalence of 38% [7,8,10,11]. Our prevalence of incidental findings is similar to these studies and investigations utilizing similar CT imaging techniques (41–56%) [10,12]. However, our study was performed among patients substantially younger (median age of 43 years) than those in the general population (~60 years). Since incidental findings increase with age [5,6], our data suggest that HIV-infected persons may have a higher number of incidental findings. Additionally, our HIV-positive cohort had a higher frequency of incidental findings than HIV-negative military personnel (8%) of similar ages [11].

The reason for the higher rate of incidental findings among HIV-infected persons may be due to their higher risk for pulmonary diseases [19]. Most incidental findings in our study were pulmonary nodules, granulomas, scarring, and bronchiectasis, all suggestive of prior respiratory infections. In addition, HIV-infected persons often have higher rates of tobacco use compared to the general population which may contribute to an increased number of pulmonary findings [10,23]. Finally, HIV-infected persons may have unique incidental findings not typically seen in the general population, including gynecomastia, likely the result of altered fat distribution patterns due to the HIV and/or antiretroviral agents [24,25].

In our study, 17% of HIV patients had a clinically significant finding that required follow-up or medical referral. This compares to a range of 1–52% in general population [4–6]; the reason for the wide variation in rates is due to varying definitions and fields of view used for imaging. We utilized classifications within recent publications and multidetector CT imaging to allow for comparability [4,10]. Similar to the general population, the most common significant findings were pulmonary nodules [4,8–10].

Several of our participants had incidental findings of unquestionable clinical significance including pneumonias treated with antibiotics and a large splenic cyst. The discovery of such findings may result in added value of screening CT scans [4]. On the other hand, detection of findings such as pulmonary nodules, which are often benign or resolve on follow-up imaging [5,17], may have added financial costs, risks (including radiation exposure during repeat imaging), and increase patient anxiety [5]. Most of our incidental findings were stable over time and did not result in changes in management. Also, our study

did not detect any undiagnosed cancers. As such, an assessment of the frequency and medical significance of incidental findings among specific populations are important.

Factors associated with incidental findings included increasing age, current tobacco use, and presence of CAC; no HIV-specific factors were identified. Only 1 other published study evaluated predictors for incidental findings [10]. Age and tobacco use are known to be associated with pulmonary diseases including scarring and nodules. Of particular interest was our finding that HIV-infected participants with a positive CAC score had a >2-fold higher frequency of incidental findings after adjusting for age and smoking. The precise relationship between CAC and incidental findings is unknown. A possible explanation is that increased inflammation associated with prior infections (which leads to incidental pulmonary findings) may contribute to the development of vascular disease [26]; further studies are needed to evaluate this potential association. Other explanations include shared factors between CAC and incidental findings, such as exposures or concurrent conditions, unmeasured in our study. Overall, these data suggest that the benefit of identifying calcified coronary plaques should be balanced against the higher number of incidental findings among these patients.

Our study had potential limitations. As noted in other studies, there is no standard definition for 'clinically significant' incidental findings. Our study did utilize recent classifications [4] and standardized criteria [22]. Second, although our report provides information on outcomes of the initial findings, follow-up is ongoing. Two prior studies with follow-up data showed that a single death in each study was attributed to an incidental finding on screening CT imaging; however, the duration of follow-up was limited [5,16]. Third, we did not enroll an age-matched HIV-negative control group to determine if HIV-infected persons have a higher prevalence of incidental findings, rather utilized historical information. Fourth, our HIV patients had overall low rates of tobacco and illicit drug use; hence, we may have underestimated the prevalence of incidental findings compared with other HIV populations. Finally, since only men were evaluated in our study, future studies examining HIV-infected women are advocated.

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Table 1**Study Population Characteristics by Incidental Findings on Cardiac Computed Tomography Imaging**

Characteristic ^a	Incidental Findings			p-value
	Total Cohort N=215	Yes N=93	No N=122	
Age (years)	43 (36–50)	48 (39–52)	41 (34–47)	<0.01
Ethnicity				0.69
Caucasian	110 (51%)	50 (54%)	60 (49%)	
African American	48 (22%)	21 (22%)	27 (22%)	
Other	57 (27%)	22 (24%)	35 (29%)	
Tobacco Use				
Current	37 (17%)	22 (23%)	15 (12%)	0.04
Ever	109 (51%)	54 (58%)	55 (45%)	0.07
Years of Use ^b	12 (5–20)	17 (8–26)	10 (5–18)	<0.01
Diabetes Mellitus	13 (6%)	10 (11%)	3 (2%)	0.02
Hypertension	64 (30%)	34 (37%)	30 (25%)	0.07
Hypercholesteremia ^c	66 (31%)	27 (29%)	39 (32%)	0.66
Body Mass Index (kg/m ²)	26.7 (24.1–29.5)	26.8 (23.8–29.6)	26.5 (24.4–29.1)	0.86
Waist Circumference (cm)	94 (85–100)	94 (87–103)	93 (85–98)	0.31
C-reactive protein > 0.5 mg/dl	30 (14%)	14 (15%)	16 (13%)	0.70
Erythrocyte Sedimentation Rate (mm/hour)	10 (7–18)	13 (9–23)	10 (7–15)	<0.01
>20 mm/hour	47 (22%)	26 (28%)	21 (17%)	0.07
Presence of Coronary Atherosclerosis (CAC>0)	74 (34%)	43 (46%)	31 (25%)	<0.01
HIV Duration (years)	12 (5–19)	13 (7–21)	9 (5–19)	0.08
Current CD4 Cell Count (cells/mm ³)	580 (386–729)	563 (334–682)	600 (457–754)	0.02
Nadir CD4 Cell Count (cells/mm ³)	260 (138–366)	230 (100–360)	278 (184–367)	0.06
Undetectable HIV RNA level (<50 copies/ml)	150 (70%)	59 (63%)	91 (75%)	0.10
Current Antiretroviral Therapy	178 (83%)	74 (80%)	104 (85%)	0.28
History of Opportunistic Infection	16 (7%)	9 (10%)	7 (6%)	0.30

^a Categorical variables expressed as number (percentage) and continuous variables as median (interquartile range)

^b Among those with a history of tobacco use

^c Hypercholesteremia was defined as a total cholesterol >200 mg/dl

Table 2Number and Type of Incidental Findings by Location among 93 HIV-Infected Men^a

Finding	Number of Incidental Findings	Number of Findings with Clinical Significance
Lung	78	37
Parenchymal/Bronchi		
Nodule	23	18
Granuloma	19	0
Scar	13	0
Emphysema	9	9 ^b
Bronchiectasis	6	6 ^b
Parenchymal Opacity/Consolidation	4	3
Bronchial Opacity	2	1
Bullae	1	0
Pleura		
Pleural Thickening	1	0
Heart	4	2
Cardiac Valves with Significant Calcification	2	2
Papillary Muscle Fat/Calcification	2	0
Mediastinum	9	1
Lymph Nodes	7	0
Mass	2	1
Hilum/Subcarina	18	0
Lymph Node	17	0
Granuloma	1	0
Pericardiac	1	1
Lymph Node	1	1
Other	29	5
Gynecomastia	8	0
Hiatal Hernia	7	0
Axillary Adenopathy	7	0
Aortic Dilation/Aneurysm	1	1
Thymus Mass	1	1
Paralyzed Hemidiaphragm	1	1
Diaphragm Eventration	1	0
Pectus Excavatum	1	0
Enlarged Pulmonary Artery	1	1
Large Splenic Cyst ^c	1	1
Total	139	46

^aSome patients had multiple incidental findings^bMedical referral recommended^cCyst was 15 × 13 cm in diameter

Table 3

Final Multivariate Model for Factors Associated with Incidental Findings on Computed Tomography Imaging for Coronary Artery Calcium Determination

Factor	OR (95% CI)	p-value
Age, per 10 years	1.6 (1.2, 2.2)	<0.01
Positive Coronary CAC score ^I	2.3 (1.3, 4.3)	<0.01
Current Tobacco Use	2.5 (1.3, 4.3)	0.02

^I Defined as a coronary artery calcium score of >0.

CAC, coronary artery calcium; CI, confidence interval; OR, odds ratio.