Lung Cancer With HIV
Big 3 Lung Cancer Risk Factors with HIV
When to Screen
Disparities in Lung Cancer Mortality and Treatment

Interview
Keith M. Sigel, MD, PhD, MPH
Lung cancer risk and screening with HIV—and an intriguing new treatment opportunity
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Perspectives
Mark Mascolini

Lung Cancer With HIV
prevalence, incidence, age at diagnosis

Big 3 Lung Cancer Risk Factors
with HIV: smoking, low CD4s, lung infection

When to Screen
for lung cancer in people with HIV

Disparities in Lung Cancer
mortality and treatment with HIV infection
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ABSTRACT: Lung cancer kills more people in the United States than any other malignancy. Among people with HIV, lung cancer develops at a twice-higer rate than in the general population. Compared with the general population, people with HIV are younger at lung cancer diagnosis, get diagnosed with more advanced lung cancer, and die faster. In Denmark and France, lung cancer prevalence in people with HIV stands at about 3%. If that rate applies to the United States, about 33,700 people with HIV have lung cancer. Median age at lung cancer diagnosis in a North American HIV cohort was 54 years, compared with 58 in the general population. Ten recent studies of lung cancer found consistently higher incidence with HIV than in the general population. In these studies incidence ranges from 79 to 204 cases per 100,000 person-years. Standardized incidence ratios comparing lung cancer incidence with and without HIV range from 2.7 to 6.3. Five of 7 recent studies found declining or flat lung cancer incidence in HIV populations.

Lung cancer ranks as the most common cancer worldwide and has for several decades. In the United States lung cancer takes second place in prevalence tallies, following prostate cancer in men and breast cancer in women. But lung cancer kills more people in the United States than any other cancer—more than prostate, breast, colon, and ovarian cancer combined—accounting for about one quarter of all cancer deaths (Figure 1). The American Cancer Society estimates that 155,870 people died of lung cancer in the United States in 2017, a tally equivalent to the population of Eugene, Oregon or Springfield, Massachusetts. Lung cancer kills so many people—about 90% of those diagnosed—because most people have advanced disease by the time it’s found.

Lung cancer numbers are just as bad—or worse—for people with HIV, partly because smoking prevalence in HIV groups doubles that in the general population. A population-based US study found that lung cancer develops in people with HIV at a twice-higher rate than in everyone else. And North Americans with HIV are about 4 years younger when they get diagnosed with lung cancer than people in the general population.7

Among non-AIDS cancers, lung cancer has the highest incidence in the multinational DAD study of people with HIV, accounting for 16% of all non-AIDS cancers diagnosed and out-ranking Hodgkin lymphoma and anal cancer. In the same analysis, lung cancer (versus other non-AIDS cancers) predicted shorter survival after diagnosis of non-AIDS cancer. A 6-state US study figured that HIV infection independently boosts the risk of dying from lung cancer by 28%. In California’s huge Kaiser

Figure 1. In the United States lung cancer kills more people than prostate, breast, colon, and ovarian cancer combined. (Illustration from Servier PowerPoint Image Bank, http://smart.servier.com/).
Permanente healthcare system, 5-year survival was significantly lower with than without HIV for lung cancer but not for Hodgkin lymphoma, anal cancer, colorectal cancer, or prostate cancer. Analysis of 4.5 million US cancer cases linked HIV infection to higher odds of diagnosis with advanced versus local lung cancer, independently of age, sex, race, and year. The same association did not hold in immunosuppressed transplant recipients. A US study of more than 2.2 million people diagnosed with cancer determined that people with HIV had almost 2.5 times higher odds of not getting treated for lung cancer.

Ominous early signals
In 1983, the year Françoise Barré-Sinoussi isolated HIV-1, US National Cancer Institute researchers noted autopsy findings in AIDS patients including Kaposi sarcoma (KS) of the lung, apparently the first indexed mention of any lung-invading malignancy in people with HIV. But not until 1988 did researchers note a single case of lung cancer other than KS in GICAT, the AIDS and cancer cohort in Italy. A year later GICAT investigators tallied 8 lung cancers in their HIV group, including 4 adenocarcinomas, 2 small-cell carcinomas, 1 epidermoid carcinoma, and 1 mesothelioma. Everyone with non-small-cell lung cancer got diagnosed with stage 3 disease, and 7 of these 8 people died by the time of the report.

Evidence soon emerged that lung cancer poses greater threats in people with than without HIV. A 1993 review article noted a 1983-1991 prospective comparison of 7 HIV-positive people with lung cancer (all drug injectors) and 14 HIV-negative lung cancer patients. The HIV group was significantly younger (median 38 versus 60.5 years, \(P = 0.0006\)). Everyone with HIV versus 4 (29%) without HIV had stage 4 cancer at diagnosis. Median survival measured 4 weeks in the HIV group and 25.5 weeks in the group without HIV. All these variables—younger age at diagnosis, more advanced cancer, and shorter survival—hold true with HIV to this day.

Two US studies published before people started taking stronger antiretroviral combinations could not establish greater lung cancer incidence with HIV infection, possibly because many people with HIV died from AIDS before lung cancer could be diagnosed. But as soon as dual and triple antiretroviral regimens started helping people with HIV live longer, research began charting higher lung cancer incidence in people with than without HIV. A September 1997 report set lung cancer incidence at 180 per 100,000 person-years in people with HIV in the US, more than 3-fold higher than the incidence of 55.8 per 100,000 in the general US population. A year later a statewide case-control comparison in Texas figured that primary lung cancer incidence with HIV exceeded general-population incidence 6.5-fold. In the more recent US HER study, with follow-up extending 4 years into the triple-antiretroviral era, lung cancer incidence proved 6.4-fold higher in women with HIV than in age- and race-matched women in the general population.

Lung cancer incidence remains higher with than without HIV, though some research indicates flat or even falling lung cancer incidence with HIV. The next sections of this article scrutinize these studies.

Lung cancer prevalence and age at diagnosis
How many people with HIV have lung cancer? Recent national studies of histologically confirmed lung cancer in Denmark and France—countries with HIV epidemics similar to the
US epidemic—give some idea. Both studies used low-dose computed tomography (LDCT) to screen for lung cancer. The Danish analysis focused on an overall HIV cohort of 901 people and a 113-person high-risk HIV cohort (older than 50 years, more than 30 pack-years smoking). Median age of the whole group stood at 50.4 years. In the overall group 3% had histologically confirmed lung cancer, and in the high-risk group 10% had lung cancer. The French study included 442 HIV-positive smokers with a median age of 49.8 years, and 3% had lung cancer.

The CDC estimates that 1,122,900 adults and adolescents in the United States had diagnosed or undiagnosed HIV infection in 2015. If Denmark’s overall HIV-lung cancer prevalence of 3% applies to the United States, about 33,700 people in the US with HIV have lung cancer.

CDC investigators calculate that 42% of HIV-positive people in the United States smoke, an estimate that would yield about 471,618 smokers with HIV based on the 2015 CDC prevalence estimate. Current and former smokers make up 63% of the US HIV population. Combining these populations yields 707,427 HIV-positive current and former smokers. Applying the 3% French lung cancer prevalence to the number of current US smokers with HIV yields a lung cancer prevalence of 14,149. Applying the 3% estimate to current and former US smokers with HIV would yield a lung cancer prevalence of 21,223.

The Danish and French HIV study groups both had median ages around 50. In 2015 in the United States, people 50 to 54 years old accounted for the biggest percentage of diagnosed HIV cases, almost 1 in 5.

Age 50 may be something of a watershed year for lung cancer in people with HIV. An international database of 75 HIV-positive people with primary lung cancer figured a median age of 50 years at diagnosis, compared with 68 years at lung cancer diagnosis in the general-population SEER program. A much larger analysis compared age at lung cancer diagnosis in 88,018 HIV-positive people in the North American NA-ACCORD cohort and SEER. The researchers used statistical weighting to ensure that the general-population SEER group and the NA-ACCORD group had an identical distribution of age, race, and calendar period. After these adjustments, the age-at-diagnosis difference came to 4 years—median age 54 in the HIV group versus 58 years in the general population, a still highly significant gap ($P < 0.0001$).

**Lung cancer incidence consistently higher with HIV**

Table 1 summarizes 11 studies of lung cancer incidence in people with HIV published after 2003 and arranged chronologically by year of publication. They estimate incidence as standardized incidence ratio (SIR), incidence rate ratio (IRR) (both comparing HIV incidence with general-population incidence), as diagnoses per 100,000 person-years (p-y), or as 5-year cumulative incidence.

All studies found higher lung cancer incidence in HIV groups than in the general population, whether figured as SIR (from 2.7 to 6.3) or IRR (from 1.4 to 1.79). A 2013 systematic review tabulated SIRs ranging from 0.7 to 6.9 with HIV in US studies and from 1.5 to 3.4 with HIV in European studies. In HIV populations lung cancer incidence ranged from a low of 79 per 100,000 p-y in a 42,000-person study in Europe, the US, and Australia to a high of 204 per 100,000 p-y in 37,000 US veterans. In contrast, in the general US population, lung and bronchus cancer incidence stands at about 56 per 100,000 p-y.
In the Veterans Aging Cohort Study (VACS), lung cancer incidence in 1997-2008 was almost twice higher in veterans with than without HIV (204 versus 119 per 100,000 p-y, IRR 1.7). But in a 1994-2001 comparison of HIV-positive women and behaviorally similar HIV-negative women in the Women’s Interagency HIV Study (WIHS), SIR versus general-population SEER data proved slightly higher in HIV-negative than positive women (6.9 and 6.3, Table 1).27

Numerous other clinical nuggets emerge from the 11 studies of lung cancer incidence with HIV, many summarized in the “Other details” column of Table 1. The 2004-2010 analysis of HIV populations in Europe, the US, and Australia found that lung cancer incidence was higher than incidence of any other non-AIDS cancer.8 Comparison of HIV-positive and negative members of MACS and WIHS cohorts charted more than a twice-higher lung cancer incidence in the HIV groups (119 versus 45 per 100,000 p-y).35 Even MACS and WIHS cohort members who never had AIDS had almost a twice higher lung cancer incidence than HIV-negative cohort members (IRR 1.79).35

In a nationwide French study, the difference in lung cancer incidence with versus without HIV disappeared in an analysis of HIV-positive people who maintained a CD4 count above 500 cells/mm³ on ART.33 A 1997-2008 analysis of 113,000 US veterans with or without HIV independently linked HIV infection to a 70% higher risk of lung cancer.30

<table>
<thead>
<tr>
<th>Author; pub y; study y; type</th>
<th>n, study group, comparison group</th>
<th>Population data</th>
<th>Incidence</th>
<th>Other details</th>
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<tbody>
<tr>
<td>Hessol;27 2004; 1994-2001; Prospective, comparative</td>
<td>1554 HIV+, 391 HIV–; WIHS; SEER</td>
<td>All women; about one third &lt;40 y old; about 80% black or Latina</td>
<td>For HIV+, SIR vs SEER 6.3; for HIV-, SIR vs SEER 6.9</td>
<td>SIR vs SEER dipped nonsignificantly from 1994-1996 to 1997-2001 (6.8 to 6.2)</td>
</tr>
<tr>
<td>Engels;26 2006; 1989-2003; Retrospective</td>
<td>5238 HIV+; Baltimore HIV clinic</td>
<td>170 per 100,000 p-y; SIR vs general population 4.7; SIR 2.5 after adjustment for smoking</td>
<td>Incidence tended to rise with calendar year (P = 0.09); incidence rose with age, but did not differ by sex, race, or CD4 count</td>
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<td>Simard;29 2011; 1980-2006; Population-based record linkage</td>
<td>472,378 with AIDS in 15 US states and cities</td>
<td>About 80% men; about 12% &lt;50 y; about 40% black, 40% white</td>
<td>Cumulative incidence 5 y after AIDS diagnosis 0.14%, 0.32%, 0.33% in 1980-9, 1990-5, 1996-2005</td>
<td>Over the same periods, incidence of two AIDS cancers—Kaposi sarcoma and non-Hodgkin lymphoma—dropped sharply</td>
</tr>
<tr>
<td>Sigel;30 2012; 1997-2008; Retrospective, comparative</td>
<td>37,294 HIV+, 75,750 HIV- veterans in VACS</td>
<td>Median age 46; 2% women; 48% black, 39% white</td>
<td>204 per 100,000 HIV+, 119 per 100,000 HIV-; IRR vs HIV- 1.7 after adjustment</td>
<td>Lung cancer risk independently linked to HIV (IRR 1.7), COPD (IRR 1.9), and bacterial pneumonia (IRR 1.5)</td>
</tr>
<tr>
<td>Worm;8 2013; 2004-2010; Prospective</td>
<td>41,746 HIV+; DAD Study Group (Europe, US, Australia)</td>
<td>73% men; median age 39; 50% black, 41% unknown</td>
<td>79 per 100,000 p-y</td>
<td>Incidence higher for lung cancer than any other non-AIDS cancer; lung cancer incidence flat 2004-2010</td>
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<tr>
<td>Hou;31 2013; Systematic review</td>
<td>Review of 65 publications of HIV population-based lung cancer incidence studies</td>
<td>SIR or adjusted IRR 0.7-6.9 in USA, 1.5-3.4 in Europe, 5.0 in Africa</td>
<td>In most studies incidence did not change between pre-cART and cART eras; no significant trend in lung cancer risk by CD4 count</td>
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ART, antiretroviral therapy; IRR, incidence rate ratio; MACS, Multicenter AIDS Cohort Study; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; SEER, US Surveillance, Epidemiology, and End Results registry; SIR, standardized incidence ratio; VACS, Veterans Aging Cohort Study; WIHS, US Women’s Interagency HIV Study.
Table 1b. Lung cancer incidence in US and other HIV populations

<table>
<thead>
<tr>
<th>Author; pub y; study y; type</th>
<th>n, study group, comparison group</th>
<th>Population data</th>
<th>Incidence</th>
<th>Other details</th>
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</thead>
<tbody>
<tr>
<td>Robbins;23 2014; 1996-2010; analysis of US HIV/AIDS Cancer Match Study</td>
<td>275,975 HIV+ vs expected cancers in general population</td>
<td>About 74% men; about 47% black, 34% white; 12.9%, 13.7%, 27.3% &gt;50 y in 1996-2000, 2001-5, 2006-10</td>
<td>Annual percentage change –2.8%; SIR trend –4.4%</td>
<td>General population annual percentage change –3.2%; aging and other demographic shifts masked what would have been steeper incidence decline in the HIV population</td>
</tr>
<tr>
<td>Hleyhel;24 2014; 1997-2009; French HIV population vs general population</td>
<td>84,504 HIV+ in French national database vs expected cancers in French general population</td>
<td>In 2005-2009, 68.3% men; median age 40.9; 15.5% sub-Saharan African</td>
<td>SIR 4.7 in 1997-2000, 3.8 in 2001-2004, 2.8 in 2005-2009</td>
<td>Equivalent lung cancer incidence with vs without HIV if CD4 count above 500 for at least 2 years on ART</td>
</tr>
<tr>
<td>Silverberg;25 2015; 1996-2006; Prospective, comparative</td>
<td>86,620 HIV+, 196,987 HIV-; NA-ACCORD for HIV+ and demographically similar HIV-</td>
<td>In 1996-9, 2000-4, 2005-9 median ages of HIV+ 42, 44, 47; 85% men; about 44% white, 40% black</td>
<td>129.3 and 45.4 per 100,000 for HIV+ and HIV-</td>
<td>Cause-specific annual trend –4% for lung cancer in HIV+ (P &lt; 0.001), –6% in HIV- (P &lt; 0.001)</td>
</tr>
<tr>
<td>Hessol;26 2015; MACS 1984-2011, WIHS 1994-2011; Prospective, comparative</td>
<td>1860 HIV+, 2414 HIV-; MACS (men); 1875 HIV+, 674 HIV-; WIHS (women); all past or current smokers</td>
<td>75% in MACS, 68% in WIHS &lt;40 y; blacks 20% 58%, whites 70% 17% MACS/WIHS</td>
<td>119/45 per 100,000 p-y HIV+/HIV-; IRR HIV+ AIDS-free vs HIV+ 1.79</td>
<td>IRR 3.5 with pneumonia in 1984-2011 (MACS) and 1995-2011 (WIHS)</td>
</tr>
<tr>
<td>Marcus;27 2017; 1996-2011; Retrospective, comparative</td>
<td>24,768 HIV+, 257,600 HIV- in same California healthcare system</td>
<td>About 90% men; age averaged about 40 years; 56% HIV+ white, 44% HIV- white</td>
<td>Rate ratio vs HIV- 2.0, rate ratio 1.4 after adjustment for demographics and cancer risk factors</td>
<td>Rate ratio for HIV+ vs HIV- no longer significant after adjustment for pneumonia; CD4 count &lt;200 did not affect risk</td>
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A 1996-2011 comparison of HIV-positive and negative patients in California’s Kaiser Permanente healthcare system figured that HIV conferred a higher lung cancer risk after adjustment for demographics and cancer risk factors (rate ratio 1.4, 95% confidence interval [CI] 1.1 to 1.7) but not after additional adjustment for pneumonia (rate ratio 1.2, 95% CI 0.9 to 1.6).26

Is lung cancer incidence with HIV changing?

Seven large studies published since 2004 chart HIV-related lung cancer incidence over time to assess incidence trends.28-31,33 Together, these analyses generally show slowly falling or stable lung cancer incidence in diverse HIV populations (Table 1). Caution in interpreting all these data makes sense since none of the studies extends beyond 2010.

The exceptions were (1) a 1989-2003 retrospective analysis of 5238 HIV-positive people at a single Baltimore clinic in which incidence tended to rise with calendar year, but not significantly ($P = 0.09$)28 and (2) a 1980-2006 population-based record linkage that calculated cumulative incidence 5 years after AIDS diagnosis over three calendar periods, two of them before the dawn of triple therapy: 1980-1989, 1990-1995, and 1996-200629 (Table 1).

In a 65-study systematic review, lung cancer incidence did not change from the era before combination ART to the combination ART epoch.31 Researchers working with the WIHS cohort,27 US residents in 15 states or cities,29...
and the European-US-Australian DAD group tracked nonsignificant drops in incidence, an initial decline then stable incidence, and no change in incidence (Table 1).

Analyzing 1996-2010 data from the US HIV/AIDS Cancer Match Study, National Cancer Institute researchers figured a rising annual percentage change in rates of anal (+3.8%), liver (+8.5%), and prostate (+9.8) cancer (Figure 2). In contrast, annual percentage change fell for the three AIDS cancers, for lung cancer (-2.8%), and for Hodgkin lymphoma (-4.0%). Across the study period, SIR comparing lung cancer incidence in people with HIV and the general population fell for the AIDS cancers, lung cancer (-4.4%), and Hodgkin lymphoma (-3.2%).

The National Cancer Institute team cites evidence that the fall in lung cancer incidence with HIV would have been steeper if not masked by aging and other demographic shifts in the population. They suggest that dwindling lung cancer SIR may reflect (1) a bigger drop in smoking prevalence among people with HIV than in the general population or (2) the positive impact of ART on immune suppression and inflammation, which research ties to development of lung cancer.

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<th>Increasing</th>
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<td>• Anus</td>
<td>• Kaposi sarcoma</td>
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<td>• Liver</td>
<td>• Non-Hodgkin lymphoma</td>
<td>• Colorectum</td>
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<td>• Prostate</td>
<td>• Cervix</td>
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Figure 2. A 1996-2010 US National Cancer Institute analysis of people with HIV charted increasing incidence for three cancers, decreasing incidence for five (including lung cancer), and no change for two.

REFERENCES
Lung cancer risk and screening with HIV—and an intriguing new treatment opportunity

An interview with Keith M. Sigel, MD, PhD, MPH

Mount Sinai Medical Center – New York, New York
Assistant Professor of Medicine
Division of General Internal Medicine
Division of Infectious Diseases

Highly regarded for his contributions to cancer research in people with HIV, Dr. Sigel is Assistant Professor of Medicine in the Division of General Internal Medicine and the Division of Infectious Diseases at the Icahn School of Medicine at Mount Sinai in New York City. With a focus on two non-AIDS-defining malignancies—lung cancer and anal cancer—Dr. Sigel has led numerous innovative studies on these conditions and others in people with HIV. His work addresses unique aspects of HIV-related malignancy, including risk, prevention, treatment, and prognosis. He cochairs the Cancer Core of the Veterans Aging Cohort Study, a large longitudinal comparison of HIV-positive and -negative veterans with equivalent access to care and a high lung cancer burden. With an MD and a Masters in Public Health from the University of North Carolina and a PhD from Mount Sinai, Dr. Sigel devotes time to the primary care of people with HIV infection and hepatitis C infection. His many speaking invitations include talks at Yale University, the University of Massachusetts, and the University of North Carolina.

Mark Mascolini: Is suspicion of lung cancer high enough among HIV clinicians?

Keith Sigel: In general I think many HIV clinicians are aware of the prominence of non-AIDS-defining cancers in the HIV population. Several large cohort studies have shown that non-AIDS-defining cancers have become a leading source of morbidity and mortality in the HIV population.1-3 And it’s hard for any HIV clinician to ignore the persistently high rates of smoking in the US HIV population.

I’m not aware of any literature that specifically addresses HIV clinicians’ awareness of the higher risk of lung cancer with HIV, but my suspicion is that clinicians across the country have become highly aware of this risk. When I go to national meetings, lung cancer gets good coverage in well-attended sessions. Because HIV clinicians function in a specialty area with lots of intragroup communication, I do think they tend to be aware of the threat of lung cancer.

Lung cancer incidence and risk

Mascolini: Is lung cancer incidence flat or falling in people with HIV, and what are the factors determining this trend?

Sigel: A study from the Kaiser Permanente healthcare system a few years ago looked at trends in lung cancer incidence over the antiretroviral era and found essentially a flat curve as we’ve had more time in the antiretroviral era.4 That being said, the HIV cohort in the United States is aging, so much of the
current incidence trend reflects the graying of the HIV population and the increasing lung cancer risk with aging.

But lung cancer incidence rates are still high in relation to the general population,⁴ ⁶ and I haven’t seen any data to refute that. There’s been some interesting data showing that, particularly in the early combination antiretroviral therapy era, immunosuppression with HIV was driving some portion of the excess in lung cancer incidence seen in people with HIV. I think the impact of immunosuppression has lessened and aging has become a big factor.

Mascolini: Smoking and prior lung disease are clear risk factors for lung cancer in people with HIV. But evidence on nadir or current CD4 count seems more complicated. How do you interpret those data?

Sigel: This is something I’ve spent a lot of time looking at, and there’s a decent amount of data out of Europe addressing this question as well.⁵ ⁷ ⁸ The relationship between CD4 count and lung cancer risk is complicated because looking at a single CD4 measurement in time can lead to the conclusion that CD4 count is not related to lung cancer risk or is very weakly related. It does seem that longitudinal trends—long periods of low CD4 count or low CD4/CD8 ratio—appear to have a much stronger association with lung cancer risk.

I published a paper from the Veterans Aging Cohort Study (VACS) in the US that showed a much stronger relationship between long periods of low CD4 count and lung cancer risk,⁹ and research on the large French HIV cohort found similar effects.⁵ ⁷ These findings are not a big surprise because the immune system is responsible for immune surveillance for lung cancer. We always suspected that some degree of immunosuppression was going to be related to some portion of the excess lung cancer risk with HIV. So I do believe, based on the larger published studies, that longer periods with low CD4 count do play a role in lung cancer risk. It would be great to create an HIV-specific lung cancer risk index using some of that information. But such an index has not emerged yet.

Mascolini: In that VACS study you found an independent association between lower CD4/CD8 ratio and lung cancer risk.⁹ What’s driving that particular association?

Sigel: CD4/CD8 ratio is an interesting measure. The ratio was used a lot more clinically earlier in the HIV epidemic. But it’s gotten much more attention in the past few years because it does appear to be a strong marker of continued immune dysfunction during HIV suppression. You can have patients who are reasonably adherent to antiretroviral therapy and who may even return to a normal CD4 count. But some people nevertheless maintain a low CD4/CD8 ratio, and it’s not clear why.

There’s some suggestion that a persistently low CD4/CD8 ratio reflects later initiation of antiretroviral therapy. But it certainly seems to be a marker of many poor outcomes. Several studies show that low CD4/CD8 ratio is associated with mortality in general as well as with non-AIDS-defining cancer risk.¹⁰ ¹¹ In the Veterans cohort we were able to look at it specifically with lung cancer because we have so many lung cancer cases.⁹ We found a lower CD4/CD8 ratio was actually the strongest
immunologic predictor of lung cancer incidence. That finding is really interesting because it underlines the possibility that overall immune dysfunction—not just immunodeficiency—plays a role in lung cancer development. Whether the CD4/CD8 ratio could be a biomarker included in lung cancer risk assessments is still not clear. We still have this issue of whether or not a single measurement in time (as opposed to a longitudinal average) is an effective lung cancer predictor.

**Mascolini:** Why are prior pneumonia and chronic obstructive pulmonary disease (COPD) risk factors for lung cancer in people with HIV?

**Sigel:** COPD is an acknowledged risk factor for lung cancer in the general population because it signifies an inflammatory state in the lung that lies on the pathway to the local dysfunction required to create the mutations that drive lung cancer. So it’s not a surprise that COPD emerged as an independent lung cancer risk factor in HIV-infected patients.

We also have data suggesting that HIV is associated with a higher risk of COPD. And one thing that we’ve been trying to determine with spirometry data in the VACS is whether COPD is associated with excess lung cancer risk in people with HIV. We’re presenting a study at the American Thoracic Society in a few months looking at that issue. We found that COPD seems to be an equal-magnitude risk factor for lung cancer in both HIV-infected and uninfected veterans. So it appears to be an independent risk factor with HIV but doesn’t seem to be a stronger risk factor with HIV, which is something that hadn’t been assessed before.

Prior pneumonia also has some association with lung cancer in the general population. It’s a difficult exposure to untangle epidemiologically because sometimes pneumonia is the initial presenting factor for lung cancer. But our VACS study and others assessed the impact of pneumonias much more distant to the cancer diagnosis and did find a positive association. The suspicion has been that pneumonia may trigger a strong inflammatory injury that then spurs oncogenic mutations as one of the hits needed to cause cancer.

**Lung cancer screening advice in HIV patients**

**Mascolini:** There are lung cancer screening guidelines for the general population but not specifically for people with HIV. When do you consider screening people with HIV?

**Sigel:** I generally stick to the National Lung Screening Trial (NLST) inclusion criteria, which informed the Preventive Services Task Force guidelines and Centers for Medicare and Medicaid Services (CMS) guidelines. Those low-dose CT criteria are to start screening at age 55 in persons with a 30 pack-year smoking history. This includes current smokers or former smokers who quit within 15 years. With HIV infection, deciding on screening gets complicated because it’s hard to get your screening scan covered by insurance if you don’t meet these national guidelines. Clinicians will have trouble if they try to screen outside of those guidelines.

“Until we have stronger evidence, I think it’s difficult to make a strong suggestion that we veer from those [general-population lung cancer screening] criteria.”
guidelines just because there’s such limited data on screening HIV-infected patients.

One common complicating issue is that we have consistent epidemiologic evidence suggesting lung cancer emerges at an earlier age in people with HIV—on average about 3 to 5 years earlier. More limited evidence suggests that lung cancer develops with less smoking in people with HIV. This has prompted researchers and clinicians to ask whether we should be screening HIV patients with a little bit less than a 30-pack-year history and at an earlier age.

I don’t think we have a great answer to that question yet. We have a study coming out in AIDS in which we used a highly validated lung cancer simulation—the Lung Cancer Policy Model—to try to determine appropriate criteria for screening for lung cancer in people with HIV. What we came up with is that the most efficient solution based on available data is the NLST criteria—yearly screening starting at age 55, 30 pack-years, current and former smokers within 15 years. Until we have stronger evidence, I think it’s difficult to make a strong suggestion that we veer from those criteria.

Lung cancer treatment and survival disparities

Mascolini: Should clinicians use the same criteria to determine whether people should get treated for lung cancer regardless of HIV status?

Sigel: This is an area that has even less data than the screening question we just considered. We know there are lung cancer treatment disparities in people with HIV. Several large national studies suggest lower receipt of stage-appropriate treatment in HIV populations.

Our own recent analysis of practice within the Veterans Administration system—where care is accessible regardless of HIV status—found very limited lung cancer treatment disparities by HIV status, suggesting that a lot of these treatment disparities are probably structural. Gita Suneja from Duke did an interesting study a few years ago in which she surveyed US oncologists nationally about their perspective on treating HIV-infected patients with non-AIDS-defining cancer, and 20% of respondents said they do change practice when treating HIV-infected patients. So we do need more information in this area.

Table 1. Two studies of chemotherapy and surgery for lung cancer with HIV

<table>
<thead>
<tr>
<th>Chemotherapy study: Makinson et al.21</th>
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<tbody>
<tr>
<td>• Design: Retrospective analysis of non-small-cell lung cancer patients in large French HIV cohort</td>
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<tr>
<td>• Study period: 1996-2008</td>
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<tr>
<td>• Participants: 52 people, 81% men, median age 48; 40 in toxicity substudy, 78% men, median age 50</td>
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<tr>
<td>• Toxicity: 14 of 68 chemotherapeutic combinations (21%) complicated by grade 4 hematologic toxicity in 13 people (33%); 6 deaths (15%) due to hematologic toxicity</td>
</tr>
<tr>
<td>• Toxicity factor: Protease inhibitor therapy associated with 5-fold higher odds of grade 4 hematologic toxicity</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Surgery study: Sigel et al.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Design: Linkage of VACS cancer data to Veterans Administration surgical database</td>
</tr>
<tr>
<td>• Study period: 2000-2016</td>
</tr>
<tr>
<td>• Participants: 424 early-stage lung resection patients, 151 with HIV, 273 without HIV; mean age 60 in both groups; no differences by sex, race, year of surgery/cancer diagnosis, surgical risk class, cancer stage or histologic type</td>
</tr>
<tr>
<td>• Outcomes: Frequency of any complication did not differ by HIV status; no difference in 30-day mortality (2% with HIV); 180-day mortality nonsignificantly higher with HIV (11% versus 6%, ( P = 0.07 ))</td>
</tr>
</tbody>
</table>
Randomized controlled trial data on lung cancer therapy specific to HIV-infected patients are very limited. What data there are suggest lung cancer treatment is well tolerated and does not seem to cause excess harm in people with HIV. But there are some observational data from Alain Makinson in France on a large series of HIV-infected patients who received chemotherapy, and there was a high rate of serious complications in that HIV cohort (Table 1). So the question about appropriate lung cancer therapy for people with HIV is difficult to answer. My personal feeling is that in patients with well-controlled HIV, if you pay attention to potential antineoplastic drug interactions with antiretroviral therapy and other medications, you should be able to treat lung cancer as you ordinarily would.

In 2017 we presented data at the International Conference on Malignancies in HIV/AIDS looking at HIV-infected and uninfected patients with early-stage lung cancer who were undergoing surgery for their early-stage lung cancers. We found that the rate of surgical complications was identical by HIV status (Table 1), suggesting that lung-cancer surgery is very well tolerated in this group. So in terms of surgical treatment, in this era there should be little reluctance to treat, almost as if the HIV wasn’t there. We need more information on chemotherapy.

Mascolini: Is antiretroviral therapy improving the lung cancer survival disadvantage reported in people with HIV?

Sigel: I do think so. The association of HIV with poorer lung cancer survival has been complicated for a few reasons. Number one, a lot of the data is still from the early 2000s, when people were not having HIV-related outcomes as good as they do now. So competing risks were influencing the poor prognosis we saw in many of the bigger studies. I also think that treatment disparities, which can be difficult to measure, were playing a role in survival outcomes. Some HIV-infected patients were not getting optimal lung cancer treatment and that led to the appearance of worse lung cancer outcomes. I presented survival data last year at CROI looking within the Veterans Administration, where there are many fewer lung cancer treatment disparities by HIV status than in the general population. In the latest study period, 2009-2015, we found no difference in lung cancer survival by HIV status in a large group of lung cancer patients, almost 600 with HIV and almost 900 without HIV. So I think antiretroviral therapy does mitigate the poorer-prognosis issues identified in some older studies.

### Lung cancer pitfalls and opportunities

**Mascolini:** What’s the biggest mistake HIV clinicians make in lung cancer management?

**Sigel:** I think it’s reluctance to offer stage-appropriate treatment. Based on our data, I definitely think there should be very limited reluctance to refer for surgery, which for early-stage lung cancer can be curative. Make that referral—don’t let the HIV stand in your way. In terms of prevention, the two big potential areas of benefit are focusing on smoking cessation and screening patients who meet national screening guidelines.

**Mascolini:** Are there other issues we haven’t addressed that you would like to raise?

“In patients with well-controlled HIV, if you pay attention to potential antineoplastic drug interactions . . . you should be able to treat lung cancer as you ordinarily would.”
Sigel: There’s a big one: the role of immuno-therapy. The question is whether immunotherapy is appropriate for HIV-infected patients with lung cancer. I’m not an oncologist, I’m an HIV clinician and infectious disease specialist. So I don’t treat cancer. But I’ve followed the immunotherapy story closely because it’s very interesting in relationship to lung cancer with HIV.

The checkpoint inhibitors are becoming very important tools, particularly in certain advanced lung cancer cases. They target PD-1, which has been an important immune exhaustion marker in HIV for a long time. It manifests itself prominently in patients with HIV. A small study in Japan suggested that HIV-infected lung cancer patients with higher PD-1 expression have worse outcomes.

There has been some question about whether checkpoint inhibitors and other new immunotherapies are safe in HIV patients. Very preliminary case-study data—including a retrospective review of veterans with HIV and cancer—suggest checkpoint inhibitors do appear safe. But these early results need confirmation. An ongoing National Cancer Institute-sponsored trial is evaluating checkpoint inhibitors in HIV-infected patients.

There’s another large question beyond safety of checkpoint inhibitors. We think immune dysregulation plays at least a small role in driving the excess lung cancer incidence in people with HIV. Is it possible that checkpoint inhibitors may be even more effective than current therapies or that this might be a group of tumors that particularly exhibits local immune exhaustion? These are important and interesting areas to explore as we continue to learn more about the role of the immune system in managing lung cancer.

Finally, I should reiterate something we discussed before: Another big area that needs clarification is whether and how we should modify lung cancer screening recommendations to be more inclusive when it comes to people with HIV infection.

“In terms of surgical treatment, in this era there should be little reluctance to treat, almost as if the HIV wasn’t there.”

REFERENCES


Big 3 lung cancer risk factors with HIV: smoking, low CD4s, lung infection

By Mark Mascolini

ABSTRACT: All the lung cancer risk factors that apply to the general population also apply to people with HIV infection. Smoking is by far the top lung cancer risk factor for people with and without HIV. In HIV populations smoking may account for 94% of lung cancers. A simulation model predicts that HIV-positive men and women who quit smoking at age 40 dramatically cut their risk of dying from lung cancer through age 80. Two other factors inflate lung cancer risk in people with HIV—compromised immunity indicated by various CD4-cell measures and prior lung disease. Although low CD4 count did not predict lung cancer in models adjusted for most major risk factors, a low CD4/CD8 ratio did remain an independent predictor in a study of US veterans. Prior bacterial pneumonia also predicted lung cancer in the fully adjusted model. Prior *Pneumocystis* pneumonia or chronic obstructive pulmonary disease also boosts lung cancer risk in some analyses.

SMOKING. It so dominates the lung cancer risk list that other factors struggle for a small slice of the spotlight. That sounds like hyperbole, but NA-ACCORD researchers recently produced compelling data to back it up. If no one with HIV ever smoked, they figured 94% of all lung cancers would be prevented in people with HIV. Smoking is by far the top lung cancer risk factor for people with and without HIV. In HIV populations smoking may account for 94% of lung cancers. A simulation model predicts that HIV-positive men and women who quit smoking at age 40 dramatically cut their risk of dying from lung cancer through age 80.

Two other factors inflate lung cancer risk in people with HIV—compromised immunity indicated by various CD4-cell measures and prior lung disease. Although low CD4 count did not predict lung cancer in models adjusted for most major risk factors, a low CD4/CD8 ratio did remain an independent predictor in a study of US veterans. Prior bacterial pneumonia also predicted lung cancer in the fully adjusted model. Prior *Pneumocystis* pneumonia or chronic obstructive pulmonary disease also boosts lung cancer risk in some analyses.

Adjusted population-attributable fraction analysis showed that never smoking would prevent 19% of all cancers, 50% of smoking-related cancers, and a whopping 94% of lung cancers. If one accepts the estimate that about 33,700 HIV-positive people in the United States have lung cancer (see page 6), never smoking would slice prevalence to 2022.

Because available data dictated that NA-ACCORD researchers compare ever-smokers with never-smoker, they could not estimate lung cancer risk in HIV-positive people who quit smoking. But other researchers have scrutinized how quitting affects lung cancer mortality. For the general population, quitting for 10 years halves the risk of dying from lung cancer.

Boston collaborators used a simulation model to make a similar analysis in HIV-positive people in care in the United States. Among 40-year-old men who continued to smoke, estimated cumulative mortality from lung cancer by age 80 stood at 28.9% in heavy smokers, 23.0% in moderate smokers, and 18.8% in light smokers. Among men who quit smoking at age 40, cumulative lung cancer mortality by age 80 plunged to 7.9% in heavy smokers.
smokers, 6.1% in moderate smokers, and 4.3% in light smokers. For 40-year-old women who kept smoking, cumulative lung cancer mortality at age 80 measured 27.8% in heavy smokers, 20.9% in moderate smokers, and 16.6% in light smokers. Among women who quit at age 40, those death rates swooned to 7.5%, 5.2%, and 3.7%. Men who never smoked had a cumulative lung cancer mortality of 1.6% at age 80, while women who never smoked had a cumulative 1.2% lung cancer death rate at age 80. If smokers among an estimated 644,240 HIV-positive US residents between ages 20 and 64 do not quit smoking, the authors project that 59,900 (9.3%) will die from lung cancer.

Smoking tops American Cancer Society and CDC lists of lung cancer risk factors in the general population, followed by several other factors that all apply to people with HIV (Table 1). Researchers believe smoking can trigger lung cancer in two ways, (1) by suppressing pulmonary immunologic defenses, and (2) by torqueing up systemic immune activation. Two other portentous lung cancer risk factors specific to people with HIV also work by upsetting the immune system—low CD4 count and previous lung disease.

**Impact of low CD4 count on lung cancer risk**

Studies of nonlung cancers in people with HIV suggest that prolonged periods at a low CD4 count heighten cancer risk. But similar lung cancer studies in HIV populations yield diverse results impossible to summarize in a neat declarative sentence.

National Cancer Institute (NCI) researchers offered an early analysis of immunosuppression and lung cancer risk in early antiretroviral days (1978 to 1996). Matching 302,834 adults with AIDS to cancer registry data, they found that lung cancer met all 3 criteria they had set for potential association with immunosuppression: (1) elevated overall relative risk (RR) from 60 months before to 27 months after AIDS diagnosis; (2) elevated RR in the 4- to 27-month post-AIDS period; and (3) increasing trend in RR from before to after AIDS onset.

Three large longitudinal cohort studies in the United States and France link poor immune control—measured various ways—to incident lung cancer. The US study involves 21,666 HIV-positive Veterans Aging Cohort Study (VACS) members tracked for at least 3 years in a period spanning January 1998 through December 2012. During a median follow-up of 7.4 years, lung cancer developed in 277 veterans (1.3%).

Cox regression models adjusted for age, race/ethnicity, smoking, HCV infection, alcohol or drug use, and history of chronic obstructive pulmonary disease (COPD) or occupational lung disease identified three

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**Table 1. Lung cancer risk factors in the general population**

- Smoking
- Second-hand smoke
- Older age
- Personal or family history of lung cancer
- Radiation therapy to chest
- Air pollution
- Exposure to radon
- Arsenic in drinking water
- Exposure to workplace substances including diesel exhaust, silica, and chromium
- Beta carotene supplements in smokers

immune predictors of incident lung cancers in 12-month time-lagged analyses: low CD4 count, low CD4/CD8 ratio, and high viral load (HIV RNA) (Table 2). These analyses were time-lagged for 12 months to account for the possibility that falling CD4 counts could reflect undiagnosed lung cancer. More cumulative bacterial pneumonia episodes also predicted incident lung cancer, as discussed in the following section. In an additional analysis that adjusted for all these factors, low CD4/CD8 ratio and bacterial pneumonia remained independent predictors of lung cancer.

Keith Sigel, principal investigator of the VACS study, suggested two interesting implications of linking a low CD4/CD8 ratio to higher lung cancer risk: (1) low CD4/CD8 ratio may indicate “a persistent immune disturbance that contributes to inflammation or abnormal cancer surveillance” and (2) the CD4/CD8 ratio may be a useful lung cancer risk factor even in people with an apparently normal CD4 count.

A study of 52,278 members of the French Hospital Database on HIV through a median follow-up of 4.9 years in 1998-2006 tested 78 different models to estimate the impact of current CD4 count on lung cancer risk. Compared with a current count above 500 cells/mm³, a CD4 tally between 350 and 499 cells/mm³ inflated lung cancer risk from 2.2 to 8.5 times, depending on the model (rate ratio [RR] 2.2, 95% CI 1.3 to 3.6, to 8.5, 95% CI 4.3 to 16.7, \( P < 0.0001 \)).

More recently some of these same French investigators compared incidence of four non-AIDS cancers in 84,504 people with HIV and the general population by calculating standardized incidence ratios (SIRs) in three periods: early combination ART (1997-2000), intermediate ART (2001-2004), and late ART (2005-2009). Through an average 6.8 years of follow-up for each person with HIV, lung cancer incidence remained higher with HIV across the three study periods, though the difference diminished with time:

- 1997-2000 SIR 4.7 (95% CI 4.1 to 5.5)
- 2001-2004 SIR 3.8 (95% CI 3.3 to 4.3)
- 2005-2009 SIR 2.8 (95% CI 2.5 to 3.1)

### Table 2. Independent predictors of lung cancer in US veterans, 1998-2012*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% confidence interval)</th>
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<tbody>
<tr>
<td>CD4 count 100 to 199 (vs over 500)</td>
<td>2.3 (1.6 to 3.4)</td>
</tr>
<tr>
<td>CD4 count 200 to 500 (vs over 500)</td>
<td>1.2 (1.2 to 2.1)</td>
</tr>
<tr>
<td>CD8 count over 1000 (vs under 600)</td>
<td>1.5 (0.9 to 2.1)</td>
</tr>
<tr>
<td>CD8 count 600 to 1000 (vs under 600)</td>
<td>1.4 (1.0 to 2.3)</td>
</tr>
<tr>
<td>CD4/CD8 ratio below 0.4 (vs above 1.0)</td>
<td>2.6 (1.6 to 4.1)</td>
</tr>
<tr>
<td>CD4/CD8 ratio 0.4 to 1.0 (vs above 1.0)</td>
<td>1.9 (1.2 to 3.0)</td>
</tr>
<tr>
<td>Viral load above 500 (vs under 500)</td>
<td>1.4 (1.1 to 1.9)</td>
</tr>
<tr>
<td>Bacterial pneumonia, 2 of more episodes (vs 0)</td>
<td>1.8 (1.0 to 2.5)</td>
</tr>
<tr>
<td>Bacterial pneumonia, 1 episode (vs 0)</td>
<td>1.7 (1.2 to 2.4)</td>
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</table>

Among people who reached a CD4 count above 500 cells/mm³ for at least 2 years on ART, lung cancer incidence became nearly equivalent in people with and without HIV (SIR 0.9, 95% CI 0.6 to 1.3) but not in people with two other non-AIDS cancers, Hodgkin lymphoma (SIR 9.4, 95% CI 7.9 to 16.8) and liver cancer (SIR 2.4, 95% CI 1.4 to 4.1). Together these findings suggest that gaining CD4 cells with stronger antiretroviral regimens trims lung cancer risk. Besides reduced pulmonary inflammation with immune recovery, the authors note that decreased incidence of recurrent pneumonia probably contributed to falling lung cancer incidence (2.4 pneumonia cases per 1000 person-years in 1997 to 0.9 per 1000 in 2009).

A comparison of 24,768 HIV-positive people and 257,600 HIV-negatives in California’s Kaiser Permanente healthcare system during 1996-2011 also marks low CD4 count as a lung cancer predictor, but not after adjustment for pneumonia.

The Kaiser team offers three layers of adjustment for lung cancer risk: (1) demographics (age, sex, race/ethnicity, calendar period), (2) cancer risk factors (smoking, drug/alcohol abuse, overweight/obesity), and (3) any history of pneumonia (Pneumocystis pneumonia or at least two episodes of bacterial or other pneumonia). Lung cancer incidence measured 66 per 100,000 person-years in people with HIV and 33 per 100,000 in the HIV-negative group. Poisson regression models linked HIV to higher lung cancer risk after adjustment for demographics (RR 1.9, 95% CI 1.5 to 2.4) and demographics plus cancer risk factors (RR 1.4, 95% CI 1.1 to 1.7) but not after additional adjustment for pneumonia (RR 1.1, 95% CI 0.9 to 1.5).

In a CD4-stratified analysis with 12-month time lagging, as in the VACS study, after adjustment for demographics a CD4 count below 200 cells/mm³ almost tripled lung cancer risk compared with HIV-negative controls (RR 2.7, 95% CI 1.5 to 4.8) and a CD4 count between 200 and 499 cells/mm³ almost doubled the risk (RR 1.7, 95% CI 1.2 to 2.5). But neither low CD4 bracket boosted lung cancer risk after further adjustment for cancer risk factors and pneumonia. As in the French study, however, people with a recent CD4 count above 500 cells/mm³ did not run a higher lung cancer risk in unadjusted or adjusted models.

The Kaiser team concludes that excess lung cancer risk in these people with HIV can be traced to differences in demographics, cancer risk factors like smoking, and higher pneumonia risk—but not to low CD4 counts. A Swiss HIV Cohort Study (SHCS) analysis pinpointed only smoking as a lung-factor risk factor in a case-control comparison of 68 cohort members with lung cancer and 337 HIV-positive matched controls (Table 3). Current versus never smoking inflated odds of lung cancer more than 14-fold (odds ratio 14.4, 95% CI 3.36 to 62.1). But recent CD4 count, earlier CD4 count, use of combination antiretroviral therapy, and a history of AIDS did not predict lung cancer.

Why do the Kaiser and SHCS results appear to differ from the VACS and French analyses? Comparison of the four study populations, methods, and risk variables suggests the results actually differ less than they first seem to (Table 3).

Alone among the four studies, the SHCS found no hint of a CD4-count impact on lung cancer risk in any adjusted analysis. This study also differs most from the other three, with a case-control design involving (1) only 68 lung cancer patients with HIV and 337 HIV-positive
controls with no cancer, (2) a largely white study population, (3) 96% smoking prevalence in the lung cancer group, and (4) an observation period stretching 10 years back into the pre-combination ART era (*Table 3*).

The other three studies all involve 21,000 or more people with HIV and hundreds of lung cancer cases (*Table 3*).\(^6,8,10\) In these three studies follow-up began with the dawn of combination ART and reached 2009, 2010, or 2011. All three studies found tenuous ties between low CD4 count and lung cancer risk. In the VACS\(^6\) and Kaiser\(^10\) studies, significant ties disappeared in fully adjusted models including pneumonia history. In the VACS study a fully adjusted model linked lower (worse) CD4/CD8 ratio to lung-cancer risk;\(^6\) none of the other studies evaluated this variable. In the French\(^8\) and Kaiser\(^10\) studies, people who reached a CD4 count above 500 cells/mm\(^3\) had a lung cancer risk equivalent to the general population, a finding suggesting that maintaining or regaining a robust CD4 tally helps shield people from lung cancer.

Faulty immune function has other possibly baneful effects related to lung cancer—younger age at lung cancer diagnosis and shorter survival with lung cancer. NA-ACCORD researchers compared median age at cancer diagnosis in 88,018 North Americans treated

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**Table 3.** Four studies with varying findings on how CD4 tallies affect lung cancer risk

<table>
<thead>
<tr>
<th></th>
<th>Low CD4 or CD4/CD8 raises risk</th>
<th>Little or no CD4 impact on risk</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>VACS(^6)</td>
<td>France(^8)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>50 lung ca+/45 lung ca-</td>
<td>35.5 1997-2000; 38.3 2001-2004; 40.9 2005-2009</td>
</tr>
<tr>
<td><strong>Male/female (%)</strong></td>
<td>99/1</td>
<td>~70/30</td>
</tr>
<tr>
<td><strong>Comparison group</strong></td>
<td>HIV+ VACS members without lung ca</td>
<td>General population of France</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>46% white, 48% black, 4% Hispanic</td>
<td>~13% African</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>73% current, 15% former</td>
<td>22% current (unknown for 52%)</td>
</tr>
<tr>
<td><strong>Adjustment variables</strong></td>
<td>Age, race, smoking, HCV, alcohol/drug use, COPD, occupational lung disease</td>
<td>Age, sex</td>
</tr>
<tr>
<td><strong>CD4 outcome</strong></td>
<td>CD4, CD8, CD4/CD8 ratio</td>
<td>At least 500 CD4s after 2 y ART</td>
</tr>
</tbody>
</table>

\(^a\)Matched by age, sex, HIV transmission route, calendar period, and SHCS center to HIV-positive cohort members without lung cancer.

\(^b\)Age at lung cancer diagnosis. \(^c\)SHCS. \(\text{http://www.shcs.ch/226-1-demographical-characteristics}\). \(^d\)Smoking status known for about 75% of participants.

ART, antiretroviral therapy; ca, cancer; COPD, chronic obstructive pulmonary disease; Kaiser, Kaiser Permanente healthcare system; NR, not reported; SHCS, Swiss HIV Cohort Study; VACS, Veterans Aging Cohort Study.
for HIV and the general population represented by the Surveillance, Epidemiology and End Results (SEER) Program. An analysis weighted to yield groups equivalent in age, race, and calendar period linked a recent CD4 count below 200 cells/mm$^3$ to a 4-year younger age at lung cancer diagnosis (51 versus 55 years) when compared with either a recent CD4 count of 200 to 499 cells/mm$^3$ or a recent count of 500 cells/mm$^3$ or more.

In a 1984-2011 study of 2549 women in the Women’s Interagency HIV Study (WIHS) and 4274 men in the Multicenter AIDS Cohort Study (MACS), all participants had a history of smoking. In an analysis limited to 42 lung cancer patients with HIV, a Cox model adjusted for ART use, AIDS diagnosis, prior AIDS pneumonia, viral load, and CD4 count identified only one predictor of shorter survival—a nadir CD4 count below 200 cells/mm$^3$.

**Lung cancer risk posed by previous pulmonary disease**

Several studies tie prior episodes of pneumonia or other lung disease to heightened lung cancer risk—and people with HIV run a higher risk of pneumonia. In the 21,666-veteran analysis described in the preceding section, 1 or more episodes of bacterial pneumonia nearly doubled the risk of incident lung cancer in a 12-month time-lagged analysis (Table 1). Lung cancer risk was even higher in analyses lagged 24 months, 36 months, or 48 months. And that association remained significant in the final adjusted model (HR 1.3, 95% CI 1.1 to 2.3 for 1 versus 0 episodes). A previous VACS analysis of 37,294 veterans with HIV and 75,750 without HIV figured that bacterial pneumonia upped the risk of lung cancer 50% (incidence rate ratio [IRR] 1.5, 95% CI 1.1 to 2.0), while COPD nearly doubled the risk (IRR 1.9, 95% CI 1.5 to 2.3).

A National Cancer Institute (NCI) study involved 322,675 people with HIV in 11 US regions in 1997-2002. Linking AIDS patients to cancer registries allowed the NCI team to estimate risk of incident lung cancer in analyses adjusted for age, race, sex, HIV acquisition route, CD4 count, and AIDS diagnosis year. Recurrent pneumonia (2 or more episodes in 1 year) boosted lung cancer risk more than 60% in the overall study group (HR 1.63, 95% CI 1.08 to 2.46) for 10 years after AIDS began and doubled the risk in people younger than 50 (HR 1.99, 95% CI 1.26 to 3.16). These risks with recurrent pneumonia remained elevated, but nonsignificantly, after indirect adjustment for smoking. The analysis found no link between *Pneumocystis* pneumonia or tuberculosis and incident lung cancer.

The combined MACS and WIHS analysis discussed above involved 4274 men (1860 with HIV) and 2549 women (1875 with HIV), all of them current or prior smokers. In a multiple regression model prior *Pneumocystis* pneumonia or recurrent bacterial pneumonia more than tripled lung cancer risk in the combined MACS and WIHS groups for all study years (1984-2011) (IRR 3.56, 95% CI 1.67 to 7.61) and for the combination ART era (1995-2011) (IRR 3.51, 95% CI 1.61 to 7.67). These associations held true when the researchers lagged the pneumonia diagnosis up to 5 years.

Table 4. Five key factors to identify HIV-positive people with high lung-cancer risk

- Smoking
- Older age
- Low CD4/CD8 ratio
- Bacterial pneumonia history
- COPD history

Source: Sigel K, et al.
In the already-noted Kaiser study involving 24,768 people with HIV and 257,600 HIV-negative Kaiser patients, HIV infection and lower CD4 counts boosted lung-cancer risk in some multivariable models, but not after adjustment for pneumonia (Pneumocystis pneumonia or at least two episodes of bacterial or other pneumonia). This statistical impact of pneumonia underlines its strength as a lung-cancer predictor. Researchers who conducted the VACS analysis propose that pneumonia-induced inflammatory injury could heighten lung cancer risk and “dysfunctional immune activation could lead to more deleterious inflammatory responses to bacterial pneumonia in patients with HIV than in those without HIV.” Putting all the risk pieces together, they suggest clinicians can identify HIV-positive people with a high lung cancer risk by looking for the 5 risk factors listed in Table 4.

REFERENCES
When to screen for lung cancer in people with HIV

By Mark Mascolini

ABSTRACT: Results of a large randomized trial informed lung cancer screening guidelines for the general population: Heavy current or former smokers 55 to 80 years old able and willing to undergo curative surgery are prime candidates for annual low-dose computed tomography (LDCT). Despite a fair amount of LDCT research in HIV populations, data accrued so far cannot support definitive guidelines for smokers with HIV. Nonrandomized studies of LDCT in HIV-positive smokers found lung cancer detection rates not far below those recorded in the general-population trial, and at a younger age. These HIV studies partly allay concerns that LDCT may prompt overly aggressive use of potentially dangerous invasive procedures in people with HIV, who have high rates of prior lung disease that may leave nodules suggesting cancer. Some HIV cancer experts advise that, for now, clinicians follow general-population lung cancer screening guidelines.

Lung cancer often gets diagnosed late—when it rarely responds to treatment—in people with and without HIV. Yet HIV-positive people have a doubled risk of lung cancer compared with the general population, and they have more than a 25% higher risk of dying from lung cancer than people without HIV, even after adjustment for cancer treatment. So routine screening of HIV-positive people seems to make sense. But data supporting this assumption remain scant, while good reasons for caution about aggressive screening abound. Expert opinion varies on when or how aggressively to screen high-risk HIV-positive people for lung cancer.

The US Preventive Services Task Force (USPSTF) has formulated lung cancer screening guidelines for the general population. They recommend annual low-dose chest computed tomography (LDCT) for people with the following characteristics:

- Age 55 to 80 years
- 30 pack-year* smoking history
- Current smoker or quit within 15 years
- “Ability and willingness to have curative lung surgery”

Annual LDCT should stop when a person passes 80 years of age or has quit smoking for more than 15 years.

These recommendations rest on data from the 2002-2004 National Lung Screening Trial (NLST), which randomized 53,454 US smokers from 55 to 74 years old to annual LDCT or chest x-ray. The trial stopped early when reviewers noted a 20% lower lung cancer death rate and a 6.7% lower all-cause death rate in the LDCT arm. The researchers figured the study population needed 320 LDCTs to prevent 1 death.

Should this advice apply to people with HIV? Or should screening be even more aggressive in HIV populations because of their doubled lung cancer risk—starting at a younger age or targeting people with a lower pack-year history? The studies needed to answer those questions have not been done and may never be done: a randomized trial of LDCT in people with HIV would require thousands of participants. And the risks of annual LDCT in an HIV population cannot be dismissed lightly; so opinion remains divided.

*Pack-years equal the number of packs smoked daily times the number of years a person has smoked. So 30 pack-years could be 3 packs daily for 10 years, 1.5 packs daily for 20 years, and so on.
Factors that matter in lung cancer screening for HIV patients

In a review article on lung cancer with HIV, Keith Sigel (Icahn School of Medicine at Mount Sinai) and colleagues list four factors clinicians and oncologists should weigh in considering LDCT for HIV-positive people at high risk for lung cancer: Researchers from the University of Washington suggest a fifth factor.

1. Survival with HIV still lags that of the general population, so the benefit of earlier lung cancer detection may be limited.

2. People with HIV may have more false-positive LDCT results (for example, because of calcified tuberculous or fungal-related nodules). Those false-positives may lead to unnecessary and potentially dangerous procedures, such as biopsy, bronchoscopy, or surgical resection.

3. Clinicians aware of higher lung cancer risk with HIV may be more aggressive in evaluating possibly abnormal LDCT findings.

4. Morbidity from diagnostic tests may be greater in people with HIV infection.

5. The cumulative impact of radiation from annual LDCT may itself pose a health risk.

The last point would be especially cogent for an at-risk HIV-positive person starting annual LDCT at age 55 and continuing for 2 decades or longer. That scenario may be rare, however, when one considers current longevity with HIV and competing risks that pose a greater mortality threat than lung cancer and so could curtail the need for annual LDCT. Italian investigators figured that 4 years of LDCT exposure between ages 50 and 70 would yield a radiation-induced lung cancer incidence of 0.12 to 0.33 per 1000 person-years. But “whatever the long-term risks for development of radiation-induced lung cancers as a result of chest LDCT screening,” write French HIV-lung experts, “they seem insufficient to significantly reverse the benefits in terms of reduction of lung cancer mortality.”

How great are those benefits? Several recent studies compare suspicious nodule detection rates and lung cancer diagnoses with LDCT in HIV populations versus results in the 53,454-person general-population NLST trial (Table 1). The general-population group was a median 7 years older than the US veterans HIV group and a dozen years older than the other HIV groups. All study groups consisted entirely of current or former smokers or had high proportions of smokers, and most smokers smoked heavily. The general-population group undoubtedly had better overall immune function than the HIV groups, some of which had low nadir CD4 counts. The NLST general-population group had the lowest proportion of men, 59%, compared with 68% to 98% of the HIV groups. Substantial proportions of the HIV groups had previous lung disease that might leave lung nodules. For example, in the US veterans study 20% of veterans with HIV had asthma, 19% had prior pneumonia, and 14% had chronic obstructive pulmonary disease (COPD). NLST researchers did not report prior lung disease in participants.

Despite the lung disease history in the HIV groups studied, detection of suspicious nodules was usually lower in the HIV groups, perhaps partly because the HIV cohorts generally had fewer LDCT scans than the general-population group, which had three rounds of annual screening. And the HIV groups were younger than the general-population group. Still, the usually lower nodule rate in the HIV
groups should allay concerns that their history of pulmonary disease will litter the lungs with nodules mistakenly interpreted as cancer. The oldest HIV group, the VACS veterans, had a nodule detection rate comparable to the NLST general-population group (29% VACS and 24% NLST), and HIV-negative veterans in the VACS study had a similar nodule prevalence (24%). When the VACS researchers stratified HIV-positive people by CD4 count, however, they found a much higher nodule detection rate in HIV-positive veterans with a CD4 count below 200 cells/mm$^3$ (55%) than in HIV-positive veterans with a CD4 count above 200 cells/mm$^3$ (25%).

LDCT yielded lung cancer diagnoses in 3.6% of the general population studied (Table 1). Diagnosis rates always proved lower in the HIV groups, which were all younger than the general-population group, and which had fewer scans and less follow-up. Even so, lung cancer diagnosis rates reached 2% in HIV-positive veterans, 2% in the French single-round LDCT study, and 2.7% in the high-risk HIV group in Denmark. Lower lung cancer diagnosis rates in the other two HIV studies at least partly reflect their younger age. These findings suggest LDCT provides a reasonable diagnostic yield in high-risk HIV populations.

<table>
<thead>
<tr>
<th>Author; pub y; study years; site(s)</th>
<th>n, type of study</th>
<th>Age (range); CD4 count; prior lung disease</th>
<th>Other patient traits</th>
<th>Positive baseline screening tests, lung cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberle (National Lung Screening Trial); 2011, 2002-2009, US</td>
<td>26,722 LDCT, 26,732 x-ray (not tested for HIV), randomized trial</td>
<td>62 (55-74)</td>
<td>Smoked at least 30 p-y; current smoker or quit within 15 y; 59% men; 90.9% white</td>
<td>24%, 3.6%</td>
</tr>
<tr>
<td>Sigel, 2014, 2009-2012, US VACS</td>
<td>160 HIV+/139 HIV-, retrospective</td>
<td>In HIV+, 55 (IQR 50-59); 14% &lt;200; 20% asthma, 19% pneumonia, 14% COPD</td>
<td>US veterans, 98% men, 64% current smoker, 21% former, median 26 p-y, 72% black, 12% white</td>
<td>In HIV+ 29%, 2.0%</td>
</tr>
<tr>
<td>Hulbert, 2014, 2006-2013, Baltimore</td>
<td>224 HIV+, single-arm trial</td>
<td>48 (IQR 44-53); CD4 nadir 179, current CD4 400; 37% pneumonia, 37% emphysema</td>
<td>72% men, 89% current smoker, 11% former, median 34 p-y, 58% IDU</td>
<td>5%, 0.4%</td>
</tr>
<tr>
<td>Clausen, 2014, Pittsburgh</td>
<td>121 HIV+, cross-sectional</td>
<td>45 (range 21-72); current CD4 537; 23% pneumonia, 9% TB</td>
<td>68% men, 80% ever smokers</td>
<td>17%, 0.8%</td>
</tr>
<tr>
<td>Makinson, 2016, 2011-2012, France multicenter</td>
<td>442 HIV+, single-round LDCT study</td>
<td>50 (IQR 46-54); nadir CD4 168, current CD4 574; 13% COPD, 9.5% PCP</td>
<td>84% men, 100% smokers, median 30 y smoking, median 30 p-y</td>
<td>21%, 2.0%</td>
</tr>
<tr>
<td>Ronit, 2017, Copenhagen</td>
<td>901 HIV+, 113 HIV+ at high risk,* single-round LDCT study</td>
<td>50 (IQR 43.5-59); in high-risk group 60.3 (IQR 53.8-65.2); nadir CD4 373, current CD4 77% &gt;500; 6.5% PCP</td>
<td>87% men, 86% white, 28% current smoker, 56% former, median 18 p-y</td>
<td>Overall group: 3.1%, 0</td>
</tr>
</tbody>
</table>

Table modeled after Sigel et al. *High risk means 50 to 74 years old, current or former smokers, more than 30 p-y. COPD, chronic obstructive pulmonary disease; IDU, injection drug user; IQR, interquartile range; PCP, Pneumocystis pneumonia; p-y, pack-years; VACS, US Veterans Aging Cohort Study.
Insights from two big LDCT studies in HIV groups

Two large and recent LDCT studies in HIV populations in France and Denmark provide further screening insights. Both studies scrutinized the impact of a single LDCT scan in groups consisting largely of white men in later middle age (median 50 years in both studies) (Table 1). Both research teams aimed to determine proportions of positive scans (suspicious nodules) and histologically proven lung cancer diagnoses following positive scans.

The French analysis focused on 442 HIV-positive people seen in 2011 and 2012 at age 45 or older (median 49.8 years, IQR 46.3 to 53.9). Most participants, 84%, were men, and median nadir and current CD4 counts stood at 168 and 574 cells/mm³. Almost everyone was taking antiretroviral therapy for a median duration of 13.8 years. Everyone smoked currently (91%) or in the past for a median of 30 years and a median of 30 pack-years. While 13% had a history of COPD, 5% reported asbestos exposure.

Ninety-four participants (21.3%) had at least one positive LDCT, a rate similar to the US general-population trial (Table 1). Through 2 years of follow-up in people with positive LDCTs, 8 people had histologically proven lung cancer and 1 had highly probable lung cancer for a diagnosis rate of 2.0%, about half that in the much older US general population. Five cancers were stage 1, 1 stage 2, and 3 stage 4. Two people died with stage 4 lung cancer. Only 15 people (3.4%) had 18 invasive procedures and none of these procedures led to serious adverse events. The investigators figured 49 people would need LDCT to detect 1 lung cancer, a low number compared with findings in the general population.

Among the 9 people with lung cancer, age ranged from 45 to 56, nadir CD4 count from 1 to 236 cells/mm³, current CD4 count from 345 to 637 cells/mm³, and pack-years from 27 to 60. The researchers observe that 8 lung cancers arose in people younger than 55; these cancers would be missed if clinicians adhered to general-population guidelines calling for LDCT in heavy smokers starting at age 55. An NA-ACCORD analysis of North Americans with HIV found a median lung cancer diagnosis age of 54 in the HIV group versus 58 in the general population. That means half of the NA-ACCORD HIV group got diagnosed with lung cancer at age 54 or younger. But finding an LDCT starting age for HIV populations won’t be easy. The 2006-2013 Baltimore study that included HIV-positive heavy smokers 25 years or older (median 48, IQR 44-53) diagnosed only a single case of lung cancer with LDCT (0.4%).

Danish investigators enrolled 901 people from the Copenhagen HIV cohort, including 113 judged at high risk of lung cancer because they were older than 50 and smoked more than 30 pack-years. Among all participants, median age stood at 50.4 years (IQR 43.5 to 59.0), compared with 60.3 (IQR 53.8 to 65.2) in the high-risk group. In the whole group, 87% were men, 86% white, 28% current smokers, 36% former smokers, and 34% never-smokers. While 41% had a nadir CD4 count below 200 cells/mm³, 77% had a current count above 500 cells/mm³. Median pack-years stood at 18 in the whole group, and 6.5% had a history of Pneumocystis pneumonia.

LDCT proved positive in 28 people (3.1%) of the whole group, including 11 people (9.7%) in the high-risk group. Through a median follow-up of 14.6 months, lung cancer developed in 3 people, all in the high-risk group (2.7%)
of 113). These 3 people represented 10.7% of the 28 with a positive LDCT. At lung cancer diagnosis they were 50, 59, and 60 years old, so the diagnosis would have been missed in 1 of 3 people if clinicians had followed US general-population guidelines to start screening at age 55. The researchers calculated that it took 38 LDCTs to detect 1 case of lung cancer, an estimate even lower than the 49 scans reckoned by the French. Nine people had invasive diagnostic procedures, 3 of which led to localized and self-resolving pneumothorax.

Statistical analysis adjusted for age and cumulative smoking identified 3 independent predictors of a positive LDCT in the Danish study: current CD4 count below 500 cells/mm³ (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.01 to 5.13), nadir CD4 count below 200 cells/mm³ (OR 2.63, 95% CI 1.13 to 6.66), and prior Pneumocystis pneumonia (OR 4.32, 95% CI 1.34 to 11.9). In the already-discussed US veterans study, a baseline CD4 count below 200 cells/mm³ independently tripled odds of a positive scan (OR 3.1, 95% CI 1.2 to 8.2) compared with HIV-negative veterans.

The Danish team observes that their positive scan and diagnosis rates are comparable to those in the Danish general population. The diagnosis rate in the Danish high-risk group is similar to that of the French study and three quarters of that in the general-population trial (Table 1). All 3 detected cancers were resected with no signs of relapse during follow-up.

**Whether and when to screen HIV patients for lung cancer**

Three just-reviewed studies found LDCT detects lung cancer in HIV-positive people at rates approaching that in a large US general-population trial—even though the HIV populations were younger (Table 1). And LDCT scanning did not prompt an undue flurry of potentially risky invasive procedures in these HIV studies. So should HIV clinicians order annual LDCT scans for HIV patients at high risk for lung cancer—heavy smokers in their 50s, 60s, or 70s?

No expert panel has made a formal proposal, mainly because research in people with HIV has not yielded the critical finding that emerged from the US general-population NLSC trial—that screening high-risk people with LDCT saves lives. And such a trial randomizing HIV patients to LDCT or chest x-ray seems unlikely because it would require thousands of participants and would be ethically dubious after NLSC showed such a decided advantage for LDCT.

Two ongoing analyses of LDCT in people with HIV could provide a sharper focus on the potential value of these scans. First, a prospective cohort study at Baltimore’s Sidney Kimmel Comprehensive Cancer Center and Johns Hopkins University is testing the diagnostic value of 5 annual LDCTs in 200 HIV-positive people at least 26 years old and with a smoking history of more than 20 pack-years. Participants can be current smokers or people who quit within the past 15 years. Researchers will compare lung cancer stage in people diagnosed with LDCT and historical controls.

Second, Keith Sigel and colleagues at New York’s Mount Sinai are studying the cost-effectiveness of lung cancer screening with LDCT in people with HIV. The investigators will compare the rate of positive LDCT screens in HIV-positive smokers and a cohort of previously screened HIV-negative smokers. With these and other data, the researchers aim to create a simulation model of lung cancer screening in people with HIV. With that model...
they will estimate the harms, benefits, and cost-effectiveness of annual LDCT screening in HIV populations.

But neither of these studies will provide a definitive answer on when to screen HIV-positive smokers for lung cancer. And in the meantime, HIV guideline-writing bodies remain largely silent on lung cancer screening. US Department of Health and Human Services antiretroviral guidelines and advice from the HIVMA and Europe’s EACS say nothing on the issue. The British HIV Association (BHIVA) seems to be the only conclave that takes a position, and that position is negative: “We suggest there is currently no role for screening for lung cancer [with either x-ray or CT] in people with HIV.”

In a review article National Cancer Institute HIV experts advise following screening advice for the general population in people with HIV, “pending additional studies in younger and moderate-smoker [people living with HIV] to assess sensitivity, specificity, and complication rates from follow-up procedures.” (See bullet list at the top of this article for general-population guidelines.) A review by University of Washington researchers takes a similar stance, suggesting that “clinicians with access to high-volume, high-quality lung cancer screening and treatment centers initiate a discussion about screening with apparently healthy PLWHA aged 55-74 years who have at least a 30-pack-year smoking history and who currently smoke or have quit smoking within the past 15 years.”

French HIV malignancy experts hint that they believe screening might start at an earlier age in people with HIV because their study of LDCT in HIV-positive smokers and other research found that CT scanning can spot lung cancer at an earlier stage in younger people with HIV. But they stress that they did not design their study to address this question. And in a review article they say the value of screening HIV-positive smokers at an age younger than 55 “still needs further investigation.”

In a review of cancer screening in people with HIV, Sigel and colleagues spell out the essentials clinicians should consider when screening for any cancer: “an assessment of individualized risk for the particular cancer, life expectancy, and the harms and benefits associated with the screening test and its potential outcome.” In the interview in this issue of RITA, Sigel observes that providers will face difficulty getting insurers to cover lung scans for people who fall outside the general-population guidelines. And a simulation analysis he conducted integrating the Veterans Aging Cohort Study (VACS) Index with the Lung Cancer Policy Model indicated that following general-population screening criteria is “the most efficient solution” in people with HIV.

French experts remind clinicians that, if they do order LDCT, they should use the scan to check for other thoracic complications prevalent in people with HIV, including coronary artery calcification, emphysema, smoking-associated bronchiolitis, and vertebral fractures. But they stress that LDCT “should not replace the accepted standard diagnostic procedures of these conditions.”
REFERENCES
Disparities in lung cancer mortality and treatment with HIV infection

By Mark Mascolini

ABSTRACT: Lung cancer accounts for almost one third of all US cancer deaths in people with HIV and about 10% of all non-HIV deaths. In some HIV populations lung cancer explains a growing proportion of all deaths through the first decade of this millennium. A 2006-2010 analysis determined that lung cancer is the most frequent non-AIDS cancer cause of death in HIV-positive people in the United States. Most (but not all) recent studies found shorter overall survival in non-small cell lung cancer patients with versus without HIV, even after statistical adjustment for confounders. Some work confirms that higher CD4 count and antiretroviral therapy promote longer survival with lung cancer. But other research indicates that antiretroviral therapy has not erased the survival disadvantage seen with HIV infection.

If you add up all the people who die yearly in the United States from prostate, breast, colon, and ovarian cancer, they would not equal the number who die from lung cancer.1 Lung cancer kills about 9 in 10 US people diagnosed with the malignancy, mainly because it often gets diagnosed at a late stage.2 And some research shows worse lung cancer mortality in people with than without HIV.

High and growing lung cancer mortality with HIV

National Cancer Institute (NCI) researchers report that lung cancer accounts for about 30% of all cancer deaths in US people with HIV—and about 10% of all non-HIV deaths.3 In some places lung cancer has killed growing proportions of HIV-positive people as the combination antiretroviral therapy (ART) era goes on. A nationwide study in France, for example, found that lung cancer accounted for a growing proportion of all deaths in people with HIV from 2000 (4.6%) to 2005 (5.1%) to 2010 (8.4%) (P = 0.04) (Figure 1).4 By 2010 lung cancer explained 61 of 262 cancer deaths in HIV-positive people in France (23%), outstripping non-Hodgkin lymphoma (53 of 262 cancer deaths, 20%) and hepatitis-virus cancer (31 of 262 cancer deaths, 12%).

Lung cancer deaths as proportion of all deaths with HIV in France

In a 2006-2010 analysis, NCI investigators figured that lung cancer ranks as the most common non-AIDS cancer cause of death in people with AIDS the United States, explaining 21% of cancer-related deaths. A 6-state 1996-2010 NCI analysis used Cox regression analysis adjusting for age, sex, race/ethnicity, year of cancer diagnosis, and cancer stage to explore

Figure 1. From 2000 to 2010 lung cancer explained a significantly growing proportion of all deaths in HIV-positive people in France (P = 0.04).4
the impact of HIV infection on death resulting from 14 cancers. HIV and cancer data came from linkage of cancer and HIV/AIDS registries. HIV infection independently predicted death from 7 non-AIDS cancers, including lung cancer (adjusted hazard ratio [aHR] 1.28, 95% confidence interval [CI] 1.17 to 1.39). That association remained constant after further adjustment for receiving cancer treatment (HR 1.28, 95% CI 1.14 to 1.44).

Compared with other cancers, lung cancer independently predicted shorter survival in a 41,746-person 2004-2010 DAD Study analysis. Lung cancer proved the most frequent non-AIDS cancer in this international HIV cohort (0.79 cases per 1000 person-years), more frequent than Hodgkin lymphoma and anal cancer. More than half of the 140 people diagnosed with lung cancer (57%) had died from any cause after 1 year of follow-up, and 77% had died after 2.5 years. A multivariable Cox model determined that lung cancer more than doubled the risk of death from any cause when compared with other non-AIDS cancers (relative hazard 2.43, 95% CI 1.84 to 3.21, P = 0.0001).

A 1996-2010 NCI analysis figured that overall mortality in people with both HIV and lung cancer exceeds expected mortality with each disease separately. In this analysis covering the same years as the Kaiser Permanente California study, the NCI team explored data from the HIV/AIDS Cancer Match Study and the National Center for Health Statistics. Poisson regression models including the terms HIV, cancer, and an interaction for their combined effect on mortality (stratified by age, sex, and race) identified large mortality excesses with HIV and lung cancer for 30- to 49-year-old white men (excess 573 per 1000 person-years) and nonwhite men (excess 503 per 1000 person-years).

**Shorter non-small cell lung cancer survival with HIV**

Recent studies generally found shorter survival with non-small cell lung cancer (NSCLC) in people with HIV than in HIV-negative comparison groups. But a study of US veterans found equivalent survival with and without HIV in the most recent study period, 2009-2015. NSCLC is the most frequent type of lung cancer, accounting for 80% or more cases. If diagnosed early enough, NSCLC can be cured.2

A single-center retrospective study found shorter overall survival in people with HIV after surgery for NSCLC at Baltimore’s Johns Hopkins Hospital from 1985 through 2009. The analysis involved 22 HIV-positive people with NSCLC and 2430 NSCLC patients with unspecified HIV status. Survival in the two groups proved equivalent in the 30 days after surgery, but over the long term overall survival was significantly shorter in people with HIV (median 26 versus 48 months, P = 0.001). Higher rates of postoperative pulmonary and infectious complications in the HIV group probably contributed to higher
mortality with HIV. Statistical analysis adjusted for confounders figured a 3-fold higher death risk in the HIV group (aHR 3.08, 95% CI 1.85 to 5.13). After additional adjustment for surgical characteristics, HIV still more than doubled the risk of death (aHR 2.31, 95% CI 1.11 to 4.81).

A population-based NSCLC study found shorter overall survival with HIV in an analysis linking the US Surveillance, Epidemiology and End Results (SEER) registry to Medicare claims. Researchers identified 267 HIV-positive people diagnosed with NSCLC between 1996 and 2007 and 1428 similar NSCLC patients without HIV. The two groups did not differ by lung cancer stage at presentation or use of stage-appropriate lung cancer treatment, but median overall survival was 6 months in the HIV group (95% CI 5 to 8) and 20 months in the HIV-negative group (95% CI 17 to 23). Multivariable regression analysis adjusting for potential confounders determined that people with HIV had almost a doubled risk of dying from any cause (aHR 1.9, 95% CI 1.6 to 2.2). Analysis accounting for a higher noncancer death risk with HIV and other confounders figured that HIV infection boosted chances of lung cancer-specific death 70% in NSCLC patients (adjusted odds ratio [aOR] 1.7, 95% CI 1.1 to 2.3).

Another SEER-Medicare analysis limited to a shorter period (2000-2005) and including more participants found equivalent overall survival with and without HIV. This study included 322 HIV-positive NSCLC patients—all taking antiretroviral therapy—and 71,976 without HIV. Median age stood at 75 years in both groups, two decades older than the 55 years in the other SEER-Medicare analysis. Median overall survival did not differ between the HIV and no-HIV groups for NSCLC stages 1, 2 or 4. Among people with stage 3 cancer, median survival was shorter in the HIV group (3 versus 7 months, \( P = 0.051 \)). But after propensity score adjustment, that difference disappeared (HR 0.88, 95% CI 0.71 to 1.09). Among people who had surgical resection for stage 1 or 2 NSCLC, median survival was similar with and without HIV (50 and 58 months, \( P = 0.88 \)).

Besides the marked age difference in these two studies, researchers who conducted the 1996-2007 analysis note that the two teams used different algorithms to identify people with HIV. The 1996-2007 team argues that the 2000-2005 investigators used a less strict algorithm that may have resulted in misclassification of HIV-negative people as HIV-positive. The similar overall survival with and without HIV in the 2000-2005 study, the other team maintains, “in itself suggests contamination of the HIV-infected group by HIV-uninfected persons because a higher death rate from causes other than lung cancer would be expected in the HIV-infected group.” They add that the median age of 75 in the other study also suggests that analysis counted some HIV-negative people as HIV-positive because most other research shows median ages in the 50s in HIV-positive people with lung cancer.

A study in British Columbia found equivalent NSCLC mortality with and without HIV but greater all-cause mortality with HIV. This comparison of 71 HIV-positive adults with NSCLC and a 10% sample of the British Columbia population with NSCLC (2463 people) reached farther into the combination ART era that the other three studies, covering 2000-2013, but did not reach as far as the following veterans study. People with HIV got diagnosed with NSCLC at a significantly younger age than the comparison group (57 versus 71 years, \( P < 0.01 \)). NSCLC-specific mortality did not
differ significantly between the groups with and without HIV. But an analysis adjusted for age, gender, cancer stage, and comorbidities determined that people with HIV had a 44% higher risk of death from any cause (aHR 1.44, 95% CI 1.08 to 1.90). Median survival came to 4 months in the HIV group and 10 months in the HIV-negative controls.

A US veterans study found similar NSCLC survival in veterans with and without HIV in the latest study period, 2009-2015, and similar survival with stage 1 NSCLC in the entire study period, 2002-2015. This study offers the most recent survival analysis of the 5 studies considered and has another potential advantage over some of the other studies—equal access to cancer care with and without HIV. Linking Veterans Health Administration cancer registry data to Veterans Aging Cohort Study data, the researchers found 581 NSCLC cases in veterans with HIV and 875 in HIV-negative veterans. Kaplan-Meier analysis saw no difference in overall survival by HIV status with stage 1 NSCLC in 2002-2015 ($P = 0.3$) and no difference in overall survival regardless of stage or HIV status in 2009-2015 ($P = 0.2$). The researchers found limited treatment disparities by HIV status, a result that could contribute to the similar survival findings.

Impact of HIV status and ART on survival

Research confirms the intuitive ideas that antiretroviral therapy (ART), higher CD4 count, and earlier cancer stage predict longer survival with lung cancer in people with HIV. But other work shows that ART has not erased the survival disadvantage conferred by HIV infection.

Researchers at two Paris hospitals tracked people with HIV for non-small cell lung cancer diagnosed between June 1996 and March 2007. In that span clinicians diagnosed NSCLC in 49 people at a young median age of 46 years, and 84% had advanced disease. Survival after diagnosis ranged from 5 to 10 months. Multivariate analysis picked out 4 independent predictors of longer survival: performance status at or below 1 (HR 0.2, 95% CI 0.09 to 0.46, $P = 0.0001$), stage 1 or 2 cancer (HR 0.15, 95% CI 0.04 to 0.53, $P = 0.003$), and use of antiretroviral therapy (HR 0.4, 95% CI 0.2 to 0.9, $P = 0.027$). (Lower performance status is better: [http://ecog-acrin.org/resources/ecog-performance-status](http://ecog-acrin.org/resources/ecog-performance-status).)

Another French analysis involved 52 HIV-positive people diagnosed with NSCLC by November 2008 while in the national Dat’Aids cohort. All but 1 of these people smoked, and median pack-years stood at a hefty 30. They had a median CD4 count of 300 cells/mm$^3$ when diagnosed with lung cancer at a young median age of 48 years. Median survival reached 12 months. A multivariable Cox model identified 3 independent predictors of longer survival: CD4 count at or above 200 cells/mm$^3$ at NSCLC diagnosis (HR 0.29, 95% CI 0.10 to 0.89), taking ART (HR 0.26, 95% CI 0.09 to 0.74), and performance status below 2 (HR 0.32, 95% CI 0.15 to 0.68). A 40-person substudy linked 14 of 68 antiretroviral combinations to grade 4 hematologic toxicity. Protease inhibitors raised chances of toxicity more than 5-fold (odds ratio 5.22, 95% CI 1.07 to 25.38).

But US researchers figured that people with HIV may run up to a 13 times higher risk of dying from lung cancer than from AIDS diseases, despite good adherence to antiretroviral therapy. A simulation model devised by a Boston team used standard demographic data and recent HIV epidemiology statistics to predict lung cancer mortality by age 80 in 40-year-old HIV-positive smokers who did or did not quit...
smoking. Current moderate smokers had a 24-fold higher chance of dying from lung cancer than people who never smoked. For people who quit at age 40, the lung cancer death risk compared with never-smokers dwindled to about 4.5-fold. Even among people with good antiretroviral adherence, continuing to smoke at age 40 conferred a 6- to 13-fold higher risk of death from lung cancer than from AIDS, depending on sex and smoking level. Among 644,200 HIV-positive US residents 20 to 64 years old in the United States, the model predicted that 59,900 (9.3%) will die from lung cancer if smokers do not quit.

Combination ART, at least in its early years, did not improve 5-year lung cancer survival among HIV-positive people in France. The analysis focused on survival with the most frequent cancers in people with HIV—including 446 lung cancers—in the years before combination ART (1992-1996) and in early ART periods (1997-2000, 2001-2004, and 2005-2009) in the national French Hospital Database on HIV. For these periods, the French investigators estimated 5-year Kaplan-Meier survival rates; they used Cox proportional hazards models to compare survival across periods.

The arrival of combination ART and subsequent development of stronger regimens did not improve lung cancer survival in the first decade of combination therapy in this French study. Five-year survival with lung cancer remained uniformly low across the four study periods: 13.2% in 1992-1996, 9.9% in 1997-2000, 16.7% in 2001-2004, and 16.4% in 2005-2009 (P = 0.36) (Figure 2). The Cox model adjusted for age, sex, and other variables found no change in lung cancer death risk when comparing 1997-2000 to the other three periods. Nor did the death risk differ by year of lung cancer diagnosis after 1997. In these same analyses, survival did improve across the years with 2 AIDS cancers (Kaposi sarcoma and non-Hodgkin lymphoma) and 2 non-AIDS cancers (anal and Hodgkin lymphoma).

**Figure 2.** Despite the arrival of combination antiretroviral therapy and stronger combinations over the years, 5-year survival with lung-cancer did not improve among HIV-positive people in France through 2009 (P = 0.36).

**Lung cancer treatment disparities in HIV populations**

A few just-reviewed studies found worse lung cancer mortality in HIV-positive people even after adjustment for cancer treatment. But other research suggests people with HIV get treated for lung cancer less often than their HIV-negative counterparts, which would certainly inflate lung cancer mortality.

Two studies by US National Cancer Institute (NCI) investigators found that HIV-positive people ran more than a twice higher risk of going untreated for lung cancer than the general population. The first analysis involved 3045 adults with cancer and HIV and 1,087,648 with cancer but without HIV in Connecticut, Michigan, and Texas. Participants got diagnosed with lung cancer (581 with HIV,
260,652 without HIV) or other cancers from 1996 through 2010—just as the combination ART era began. Logistic regression analysis adjusted for cancer stage and demographics determined that having HIV more than doubled the odds of not getting treated for lung cancer (aOR 2.18, 95% CI 1.80 to 2.64). And having HIV more than doubled chances of not getting standard treatment for non-small cell lung cancer (aOR 2.43, 95% CI 1.46 to 4.03). Five factors independently predicted lack of therapy for any of the cancers studied: low CD4 count, male sex with injection drug use as HIV exposure, age 45 to 64 years, black race, and distant (disseminated) or unknown cancer stage.

The second study by NCI researchers involved nonelderly adults diagnosed with cancer from 2003 through 2011. The NCI team assessed insurance status and other variables as predictors of cancer treatment with versus without HIV. They used the National Cancer Data Base to identify people with cancer across the United States. This analysis focused on 10,265 HIV-positive people with cancer and 2,219,232 HIV-negative people with cancer—including 1420 with HIV and lung cancer and 353,156 without HIV with lung cancer. Ages ranged from 18 to 64.

As in the previous 3-state analysis, having HIV more than doubled chances of going untreated for lung cancer (aOR 2.46, 95% CI 2.19 to 2.76, \( P < 0.001 \)). These odds for lack of lung cancer treatment persisted among privately insurance people (aOR 2.47, 95% CI 1.89 to 3.22, \( P < 0.001 \)). Yet for all solid tumors (including lung cancers), having no insurance or using Medicaid or Medicare (versus private insurance) independently boosted odds of nontreatment. Stage 4 versus stage 1 cancer more than doubled odds of nontreatment for solid tumors, and black versus white race inflated odds of nontreatment about 40%. Notably, though, lung cancer stage at diagnosis did not differ significantly by HIV status in a 2012 study of 113,044 US veterans or in a 2013 Medicare case-control study of 267 people with HIV and lung cancer and 1428 HIV-negative controls with lung cancer. In a study of 15 cancer types diagnosed from 1996 through 2010 in the United States, HIV-positive people were slightly but nonsignificantly more likely to get diagnosed with advanced versus local lung cancer than were immunocompetent people (aOR 1.13, 95% CI 0.98 to 1.29, \( P = 0.08 \)). In contrast another immunosuppressed group, solid organ transplant recipients, proved less likely to get diagnosed with advanced lung cancer than immunocompetent people (aOR 0.54, 95% CI 0.48 to 0.61, \( P < 0.001 \)).

In a 2016 review of lung cancer with HIV, Mount Sinai’s Keith Sigel and collaborators review 7 case series of 236 people with HIV who had surgical resection, chemotherapy, and/or radiotherapy for lung cancer (Table 1 in reference 23). As one can expect in people being treated for lung cancer, complications did arise and sometimes proved more frequent in people with than without HIV. In a French study 6 of 52 people with HIV receiving chemotherapy died with grade 4 hematologic toxicity, often associated with protease inhibitor therapy.

But other case series revealed no perioperative complications or evidence of poor treatment tolerance in people with HIV. For example, Sigel and colleagues compared early-stage lung resection results in 151 veterans with HIV and 273 without HIV (see Table 1 on page 14). Complication frequency and 30-day mortality did not differ by HIV status; 180-day mortality was nonsignificantly higher in the HIV group.
Sigel and colleagues suggest that “disparities in lung cancer treatment in HIV-infected patients compared to uninfected patients may be partly due to real or perceived treatment intolerance in this population.” Given the lack of guidelines for lung cancer management in people with HIV, Sigel and coauthors call for further research addressing these issues.

REFERENCES
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