HIV Infection in the Etiology of Lung Cancer

Confounding, Causality, and Consequences

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Persons infected with HIV have an elevated risk of lung cancer, but whether the increase simply reflects a higher smoking prevalence continues to be debated. This review summarizes existing data on the association of HIV infection and lung cancer, with particular attention to study design and adjustment for cigarette smoking. Potential mechanisms by which HIV infection may lead to lung cancer are discussed. Finally, irrespective of causality and mechanisms, lung cancer represents an important and growing problem confronting HIV-infected patients and their providers. Substantial efforts are needed to promote smoking cessation and to control lung cancer among HIV-infected populations.

Keywords: HIV infection; lung cancer; smoking

With broader uptake of effective antiretroviral therapy (ART), morbidity and mortality attributable to opportunistic infections and AIDS-defining malignancies have declined, and HIV-infected persons are surviving into older ages. Non-AIDS-defining cancers now represent more than half of all malignancies occurring in HIV-infected persons in developed regions. Lung cancer represents the most frequently occurring malignancy in HIV-infected persons. Numerous studies have shown increasing rates and elevated risk for lung cancer among HIV-infected persons; however, HIV-infected persons smoke more than the general population, raising concerns that the association of HIV with lung cancer merely reflects this higher smoking prevalence. Additionally, although there is strong evidence linking AIDS-defining cancers to the degree of HIV-related immunosuppression, the mechanisms for HIV infection in the development of lung cancer remain unclear. The current review describes the burden of smoking among HIV-infected populations and summarizes the epidemiologic data regarding HIV infection and lung cancer, with differentiation of studies that directly accounted for smoking exposure. Data regarding HIV-related immunosuppression in relation to lung cancer risk are assessed to explore potential mechanisms of HIV pathogenesis in lung cancer. Finally, a discussion of potential approaches to reduce the burden of lung cancer among HIV-infected populations is provided.

CIGARETTE SMOKING AMONG HIV-INFECTED PERSONS

Because smoking is the major etiologic agent of lung cancer, heavier smoking exposure among HIV-infected persons results in higher rates of lung cancer compared with the general population. Compared with the 20% prevalence of smoking in the United States general population (1), the prevalence of smoking

has consistently been reported as higher in HIV-infected populations (Table 1) (2–14). In numerous studies of smoking prevalence conducted in varied risk groups from the United States and Europe, more than two thirds of HIV-infected persons have reported being a regular smoker at some time in their life. The prevalence of current smoking in these studies has demonstrated a broader range, with estimates from 25 to 80%. Clinics and cohorts with large representation of injection drug users (IDUs) have often been observed to have the highest smoking prevalence, with almost uniform smoking exposure (14). Several other studies that characterized their HIV-infected population as “lower income” have had estimates of 63 to 86% for ever smoking and 47 to 67% range for current smoking prevalence (6, 9, 12). Among studies largely comprised of men who have sex with men, the prevalence of ever smoking was similar, although current smoking ranged from 31 to 54% (2, 5, 7).

There have been further concerns that even if smoking prevalence is accounted for, differences in smoking behavior (e.g., smoking duration, smoking intensity, or level of addiction) among HIV-infected persons may explain the increased risk of tobacco-related disease. Limited data are available to address this issue. Within the AIDS Linked to the IntraVenous Exposure (ALIVE) study, systematic assessment of HIV-infected and at-risk, HIV-uninfected IDUs did not reveal substantial differences in age at first smoking, smoking duration or intensity, nicotine addiction, or smoking biomarker data (14).

EPIDEMIOLOGIC DATA ON THE ASSOCIATION OF HIV WITH LUNG CANCER

Epidemiologic studies of lung cancer among HIV-infected individuals have generally estimated risk by calculating standardized incidence ratios (SIRs), resulting in comparisons of observed cases occurring among an HIV-infected study population to the expected number of cases estimated from general population rates. The primary methods for identifying lung cancer cases in these studies have involved (1) linkage of HIV/AIDS registries to cancer registries and (2) linkage of observational HIV databases or clinical HIV cohorts to cancer registries (Table 2) (15–39).

HIV/AIDS registry linkage studies of lung cancer outcomes have primarily been conducted in the United States and Europe, with one study reported from Africa. Other than the large, nationwide AIDS/Cancer match conducted under the leadership of the National Cancer Institute (18, 23), all studies were based on fewer than 60 HIV-infected lung cancer cases, and four studies had fewer than 10 cases. With the exception of one early study from a single county in Texas (17), 12 other HIV/AIDS registry linkage studies have reported an increased risk for lung cancer among persons with HIV infection (Figure 1). SIRs were generally in the range of a 2- to 5-fold increase associated with HIV, and a clear majority of studies achieved statistical significance; however, there was substantial heterogeneity in the risk estimates and in the numbers of cases included.

Observational cohorts of HIV-infected persons derived from databases of single clinics to large geographically defined areas or of administrative databases from hospital networks and large

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TABLE 1. SMOKING PREVALENCE AMONG SELECTED HIV-INFECTED ADULT POPULATIONS

Study	Publication Yr	Site	Population	N	Current Smokers, %	Ever Smokers, %
Conley et al (2)	1996	San Francisco, Denver & Chicago	MSM	345	31	63
Sigel et al (3)	2010	Multi-site US	Veterans	3,707	32	79
Silverberg et al (4)	2010	Northern California	HMO participants	20,277	39	n/a
Royce & Winkelstein (5)	1990	San Francisco, CA	High-risk men	384	46	n/a
Gritz et al (6)	2004	Houston, TX	Multiethnic lower-income	348	47	63
Mamary et al (7)	2002	San Francisco, CA	Clinic	228	54	n/a
Shuter & Bernstein (8)	2008	New York City, NY	Clinic	64	56	89
Feldman et al (9)	2006	Multi-site US	Lower-income women	924	56	72
Saves et al (10)	2003	France	Clinic	274	57	n/a
Crothers et al (11)	2005	Multi-site US	Veterans	867	63	85
Burkhalter et al (12)	2005	New York State Medicaid	Medicaid recipients	428	67	86
Webb et al (13)	2007	Upstate New York	Clinic	212	74	n/a
Marshall et al (14)	2010	Baltimore, MD	IDUs	312	84	94

Definition of abbreviations: MSM, men who have sex with men; HMO, health maintenance organization.

health insurance plans have been used to evaluate the association of HIV infection with lung cancer (Table 2). With the exception of a few studies (23, 32), cancer outcomes in these studies were determined by linkage to cancer registries. Six of the 10 studies had identified fewer than 15 HIV-associated lung cancer cases, and two had more than 100 cases. All 10 studies reported increased risk for lung cancer associated with HIV infection (Figure 1); in two studies, the estimated risk did not achieve statistical significance. SIRs were generally in the range of a 2- to 3-fold increased risk; two studies reported notably higher risk estimates (29, 31). A recent study of HIV-infected and at-risk women reported elevated lung cancer risk in both groups compared with population estimates (37); the unadjusted incidence rate ratio for HIV-infected compared with uninfected women was increased 2-fold, although, with only 14 cases, this estimate was imprecise (95% confidence interval [CI], 0.44–18). Although fewer HIV-infected than uninfected

women were current smokers, lifetime smoking was higher among HIV-uninfected women. However, HIV-infected lung cancer cases tended to have lower lifetime smoking exposure compared with the HIV-uninfected lung cancer cases.

There have been two recent meta-analyses that assessed risk for lung cancer with HIV infection (Table 2). Grulich and colleagues analyzed data from six registry linkage and one cohort study and estimated an overall risk of 2.7 (95% CI, 1.9–3.9) for lung cancer associated with HIV infection (38). Shiels and colleagues incorporated data from six of the studies in the Grulich meta-analysis as well as an additional 12 studies (39); the risk for lung cancer associated with HIV infection was estimated to be increased 2.6-fold (95% CI, 2.1–3.1). Formal testing revealed significant heterogeneity in the data in both meta-analyses.

These studies have several limitations. Although lung cancer is a relatively frequent cancer outcome, most of these studies had substantial sample size constraints with limited power to

TABLE 2. STUDIES OF LUNG CANCER RISK ASSOCIATED WITH HIV INFECTION

Study	Publication Yr	Study Population	Yrs of Study	N HIV+ in f/u	N HIV+ LC cases
<i>HIV/AIDS registry linkage studies:</i>					
Parker et al* (15)	1998	Texas	1990–1995	26,181	36
Grulich et al* (16)	1999	NSW, Australia	1980–1993	3,616	6
Cooksley et al (17)	1999	Harris Co., Texas	1975–1994	14,986	18
Frisch et al* (18)	2001	U.S.	1978–1996	302,834	808
Grulich et al (19)	2002	Australia	1980–1999	13,067	17
Allardice et al (20)	2003	Scotland	1981–1996	2,574	5
Dal Maso et al* (21)	2003	Italy	1985–1998	12,104	22
Newnham et al (22)	2005	England	1985–2001	33,190	38
Engels et al* (23)	2006	U.S.	1980–2002	375,933	393
Mbulaitye et al (24)	2006	Uganda	1989–2002	12,607	4
Galceran et al* (25)	2007	Catalonia, Spain	1981–1999	1,659	4
Dal Maso et al* (26)	2009	Italy	1986–2005	21,951	42
Polesel et al* (27)	2010	Italy	1986–2004	21,951	59
<i>Cohort/database studies:</i>					
Serraino et al (28)	2000	France, Italy	1982–1998	5,281	4
Phelps et al (29)	2001	Multi-site US	1993–2000	1,310	4
Herida et al (30)	2003	France	1992–1999	77,025	99
Bower et al (31)	2003	London HIV clinic	1986–2001	8,400	11
Clifford et al (32)	2005	Switzerland	1985–2003	7,304	14
Engels et al (33)	2006	Baltimore HIV clinic	1989–2003	5,238	33
Serraino et al (34)	2007	France, Italy	1985–2005	8,074	14
Patel et al (35)	2008	Multi-site US	1992–2003	54,780	140
Guiguet et al (36)	2009	France	1998–2006	52,278	207
Levine et al (37)	2010	Multi-site US	1994–2004	2,651	12
<i>Meta-analyses:</i>					
Grulich et al (38)	2007	Multi-site	Varied	444,172	1016
Shiels et al (39)	2009	Multi-site	Varied	625,716	847

Definition of abbreviations: f/u, follow-up; LC, lung cancer; NSW, New South Wales.

* Studies included only persons with AIDS diagnoses.

Figure 1. Estimates of lung cancer risk associated with HIV infection, by study design.

detect an association with HIV. Despite this, the individual studies consistently displayed increased risk, and generally their findings were statistically significant. Further, these studies have lacked appropriate comparison groups of similar risk, instead relying on comparisons to lung cancer rates derived from the general population. Perhaps most importantly, these findings may be influenced by uncontrolled confounding for smoking, the dominant risk factor for lung cancer. Because HIV-infected persons typically have heavier tobacco use compared with the general population (Table 1), inadequate control for this powerful risk factor could lead to an apparent independent association of HIV infection with lung cancer (40). Although there is a clear and consistent demonstration of elevated lung cancer risk among HIV-infected persons compared with the general population (Figure 1), it cannot be fully determined whether this elevated risk is due solely to heavy smoking in the HIV-infected population.

In contrast, five studies have directly accounted for individual smoking exposure among HIV-infected persons and an epidemiologically appropriate comparison population (Table 3) (3, 4, 29, 41, 42). In these studies, the risk for lung cancer associated with HIV infection after adjusting for smoking ranged from a 1.2- to 3.6-fold increase (Figure 2). In a study of HIV-infected and high-risk, uninfected women followed in the same cohort (29), five lung cancer cases were identified. Smoking history was considered only at baseline, and a 3.3-fold non-significant increased risk of lung cancer was observed with HIV infection. In this study, SIRs for the HIV-infected and uninfected groups compared with the general population were of similar magnitude.

There have been two published studies on HIV and lung cancer based on data from the ALIVE study of IDUs in Baltimore, Maryland. In the first study, lung cancer mortality was the outcome, and a 3.6-fold increased risk (95% CI, 1.6–7.9)

associated with HIV infection was observed after adjusting for age, gender, calendar period, and for individual smoking exposure (41). The elevated risk with HIV infection was consistently observed despite using multiple approaches to adjust for individual smoking exposure. In the follow-up study, ALIVE cohort participants were linked to the Maryland Cancer Registry. After accounting for smoking and other factors, HIV infection was independently associated with a 2.3-fold increased risk (95% CI, 1.1–5.1) for incident lung cancer (42). The reduction in risk observed with lung cancer incidence compared with lung cancer mortality may be partly explained by HIV infection being associated with reduced survival after diagnosis even after accounting for disease stage at diagnosis (42).

Two recent studies have reported from large administrative databases that have assessed risk for lung cancer among HIV-infected persons while controlling for smoking. Neither study has been published, but both have been presented in abstract form (3, 4). Sigel and colleagues analyzed administrative data on lung cancer outcomes on a virtual cohort of HIV-infected veterans cared for at multiple Veterans Administration sites throughout the country (3). Smoking data were available only for those persons that had also participated in an earlier cross-sectional national health survey of veterans. Adjusting for self-reported smoking as well as demographic factors and obstructive lung disease, HIV infection was associated with a 1.8-fold increased risk for lung cancer (95% CI, 1.3–2.4).

In an analysis of data from more than 19,000 HIV-infected participants and more than 200,000 HIV-uninfected participants with health insurance coverage through Kaiser-Permanente in Northern California, Silverberg and colleagues identified 51 HIV-infected and 342 HIV-uninfected lung cancer cases (4). After adjustment for smoking and other factors, the risk for

TABLE 3. STUDIES OF LUNG CANCER RISK ASSOCIATED WITH HIV INFECTION, WITH DIRECT ADJUSTMENT FOR INDIVIDUAL SMOKING EXPOSURE

Study	Publication Yr	Population	Yrs of Study	N HIV+ in f/u	N HIV+ LC Cases	N HIV-in f/u	N HIV-LC Cases
Phelps et al (29)	2001	Multi-site US	1993–2000	871	4	439	1
Kirk et al (41)	2007	Baltimore IDUs	1988–2005	1,192	14	894	13
Shiels et al (42)	2010	Baltimore IDUs	1988–2006	1,072	13	1,423	16
Sigel et al (3)	2010	U.S. Veterans	1999–n/a	3,707	74	9,980	123
Silverberg et al (4)	2010	California HMO patients	1996–2007	19,280	51	202,313	342

Definition of abbreviations: f/u, follow-up; IDU, intravenous drug user; LC, lung cancer.

lung cancer associated with HIV infection was moderated from crude analysis and was no longer statistically significant (incidence rate ratio, 1.2; 95% CI, 0.9–1.7). This finding differed from an earlier, unadjusted analysis in the same population suggesting that HIV infection increased lung cancer risk (43). Without access to the published data, it is difficult to fully evaluate the reasons for the differences between this study and others (Table 3), but several possibilities exist. First, although the study suggests only a modest increase in risk of lung cancer with HIV infection, the risk did approach statistical significance. Second, the methods for adjusting for smoking differed between the studies. Apparently, Silverberg and colleagues adjusted for current smoking status obtained through electronic medical record review, although it is unclear at what point in the study (baseline, at, or before lung cancer diagnosis) that this smoking assessment was performed. Other studies assessed smoking using standardized questionnaires administered directly to participants and evaluated smoking intensity or estimated pack-years during life-time or study follow-up. Recognizing that smoking status may often change at or before lung cancer diagnosis, the methods and timing of smoking ascertainment need to be clarified. To reflect exposures occurring during biologically relevant time periods, some studies have incorporated a 2- to 3-year lag of exposure data before lung cancer outcomes (41, 42). The Northern California HMO participants included in the Silverberg study may also have differed from participants of other studies in demographic, behavioral, or clinical factors. For example, 80 to 95% of participants in the Veterans and IDU cohorts had ever been smokers, which likely exceeds that observed among the HMO participants. Smoking cessation may have been more aggressively sup-

ported in the prevention-oriented HMO setting. In previous studies that reported lung cancer risk by HIV risk group, higher risk was consistently observed among IDUs than in other groups (18, 28, 30, 32, 36, 37, 44, 45), although one comparative study among IDUs did not demonstrate higher risk (46). The increased risk among IDUs presumably reflects differences in smoking habits (47); the proportion of IDUs among the HMO population was not reported.

The true test of an independent effect of HIV infection on lung cancer risk would be to observe a main effect of HIV infection among nonsmokers. Due to the very low incidence of lung cancer among nonsmokers, the rarity of lung cancer among HIV-infected persons, and the high prevalence of smoking among HIV-infected persons, it is not realistic that such an analysis will be possible. In the absence of these data, findings from the substantive body of work discussed above, in total, do support the independent association of HIV infection with increased lung cancer risk. Future research should determine more precisely the degree of risk associated with HIV infection, define variability in risk between HIV risk groups, and determine the underlying mechanisms that may be involved.

ROLE OF IMMUNOSUPPRESSION, HIV VIRAL LOAD, AND ART

AIDS-defining malignancies are hypothesized to occur as a direct consequence of HIV-related immune suppression and subsequent decreased immune surveillance. In contrast to the strong relationship between decreasing CD4 cell counts and increased cancer risk in AIDS-defining malignancies, this relationship is less apparent for non-AIDS-defining malignancies, including

Figure 2. Estimates of lung cancer risk associated with HIV infection in studies that directly adjusted for individual smoking exposure.

lung cancer (48). The epidemiologic data are mixed in regard to CD4+ cell count and risk for lung cancer; most individual studies have had limited power to assess relationships between cancer and HIV disease markers. Some studies have not demonstrated an association of AIDS diagnoses or CD4+ cell counts with lung cancer risk, arguing against a major effect of immunosuppression (18, 32, 33, 41, 49). However, several other studies have reported increased lung cancer risk among HIV-infected persons with advanced immune suppression, evaluated as a prior AIDS diagnosis or lower CD4+ cell counts compared with those HIV-infected persons with relatively intact immune function (4, 22, 32). In a recent analysis of a large database of HIV-infected persons cared for in French hospitals (36), a clear dose-response relationship between declining current CD4+ cell counts and lung cancer risk was observed. Importantly, when consideration is given to the biologically relevant time period of exposure, stronger associations of lung cancer with CD4+ cell count nearest to cancer diagnosis (rather than CD4+ nadir or time-weighted markers of immune status) limits interpretation of these data. Many studies of HIV and lung cancer linked AIDS registry data to cancer outcomes, thereby excluding HIV-infected persons before they develop AIDS (*see* Table 2). However, studies comprised only of AIDS patients appear to have similar risks for lung cancer associated with HIV as do studies with representation across HIV disease stage (data not shown). Data from the large US AIDS-Cancer Registry Match indicated increased lung cancer risk among persons with AIDS but no significant association with CD4+ cell counts (50, 51).

Some data have suggested that rates and mortality due to lung cancer and other tobacco-related disease have only increased among HIV-infected populations since the availability of combination ART (52). The mechanism suggested is that, until the competing risks for AIDS-related death have been reduced (due to effective ART), few HIV-infected persons would survive long enough to develop lung cancer. Earlier studies had limited follow-up experience during the ART era, but numerous subsequent studies have suggested that lung cancer risk has increased during the ART era (23, 26, 30, 31, 41, 53). Few of these studies took age into account, and ART era differences in rates in a large Italian study were obviated after age adjustment (27). ART use at the individual level, rather than ART era, should improve CD4 cell counts and suppress HIV RNA levels but has yielded inconsistent associations with lung cancer risk. In one of the largest studies to date, lung cancer risk was lower among persons who had used ART (35); other studies have not shown an association (4, 33, 41, 54).

Several other possible mechanisms might link lung cancer to HIV. HIV itself might have a direct oncogenic role. Although limited experimental data suggest that the HIV *tat* gene product may modulate expression of growth-related genes, amplification of HIV sequences in lung carcinoma tissue has not been demonstrated (55, 56). Further, the limited data on risk for lung cancer associated with HIV RNA levels has not been suggestive of a strong association (4, 36, 41). Another suggested mechanism for HIV in the pathogenesis of lung cancer involves accelerated lung damage associated with HIV-related infections (e.g., bacterial or *Pneumocystis pneumonia*) (57). This model for lung carcinogenesis has substantial merit in HIV-uninfected populations (58, 59). Data related to this hypothesis remain sparse among HIV-infected populations (15, 41). Finally, HIV could mediate an increase in susceptibility to tobacco carcinogens, such as through genomic instability (56); however, the limited epidemiologic data do not suggest a strong effect modification of smoking effects by HIV infection (42). Evidence to evaluate these potential mechanisms remains scarce. Further collaborative research should evaluate epidemiologic and mech-

anistic data to understand how HIV may accelerate the process of lung carcinogenesis.

CONSEQUENCES AND CALL TO ACTION

Because of the large numbers of HIV-infected persons with heavy smoking histories who are surviving longer because of ART, lung cancer will become an increasing problem in this population. In fact, an increasing burden of lung cancer is expected even if risk related to HIV infection is not independent of smoking. Close monitoring of lung cancer trends among HIV-infected persons and pooling of HIV cohort data to further examine the risk for lung cancer associated with HIV infection is warranted. However, there is no need to delay dissemination of the fact that tobacco-related disease is a clinical priority in providing comprehensive HIV care. Recent data have suggested that patients with HIV may be recognizing the potential impact of smoking and other chronic diseases on their health and quality of life more promptly than their providers (60). Earlier data have supported the lack of awareness of patients' smoking status by HIV providers (61). In a recent survey of HIV providers (62), although the great majority of clinicians reported asking their HIV-infected patients about smoking, few providers completely followed evidence-based approaches for supporting smoking cessation among their patients. With the recognition that some antiretroviral medicines were associated with lipid abnormalities, HIV providers were very prompt and aggressive in screening and making appropriate interventions. Similarly, improved recognition of the heavy smoking burden and increased risk for lung cancer will likely spur improved counseling for smoking cessation and development of tailored interventions to reduce the effects of tobacco use among HIV-infected populations.

CONCLUSIONS

A review of existing data supports the hypothesis that HIV infection increases lung cancer risk, with substantial evidence that this effect is independent of smoking. The role of immunosuppression in increasing lung cancer risk remains unclear; further investigations should more fully evaluate the timing, duration, and degree of immunosuppression as well as the impact of antiretroviral therapy. With improved life expectancy but heavy smoking history, many HIV-infected patients will be at high risk for developing lung cancer. Targeted education of HIV-infected patients and their providers to improve uptake of evidenced-based smoking cessation approaches should be a priority.

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References

1. CDC. State-specific prevalence of cigarette smoking and quitting among adults: United States, 2004. *MMWR Morb Mortal Wkly Rep* 2005;54: 1124-1127.
2. Conley LJ, Bush TJ, Buchbinder SP, Penley KA, Judson FN, Holmberg SD. The association between cigarette smoking and selected HIV-related medical conditions. *AIDS* 1996;10:1121-1126.
3. Sigel K, Wisnivesky J, Justice A, Brown S, Butt A, Crystal SD, Rimland D, Rodriguez-Barradas M, Gibert C. HIV infection is an independent risk factor for lung cancer. Presented at the 17th Conference on Retroviruses and Opportunistic Infections. February 16-19, 2010, San Francisco, CA.
4. Silverberg M, Xu L, Chao C, Leyden W, Horberg M, Klein D, Towner W, Quesenberry C Jr, Neugebauer R, Abrams D. Immunodeficiency,

- HIV RNA levels, and risk of non-aids-defining cancers. Presented at the 17th Conference on Retroviruses and Opportunistic Infections. February 16-19, 2010, San Francisco, CA.
5. Royce RA, Winkelstein W Jr. HIV infection, cigarette smoking and CD4+ T-lymphocyte counts: preliminary results from the San Francisco men's health study. *AIDS* 1990;4:327-333.
 6. Griz ER, Vidrine DJ, Lazev AB, Amick BC III, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. *Nicotine Tob Res* 2004;6:71-77.
 7. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care STDS* 2002;16:39-42.
 8. Shuter J, Bernstein SL. Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. *Nicotine Tob Res* 2008;10:731-736.
 9. Feldman JG, Minkoff H, Schneider MF, Gange SJ, Cohen M, Watts DH, Gandhi M, Mocharnuk RS, Anastos K. Association of cigarette smoking with hiv prognosis among women in the haart era: a report from the women's interagency HIV study. *Am J Public Health* 2006;96:1060-1065.
 10. Saves M, Chene G, Ducimetiere P, Leport C, Le Moal G, Amouyel P, Arveiler D, Ruidavets JB, Reynes J, Bingham A, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* 2003;37:292-298.
 11. Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, Gibert CL, Butt AA, Justice AC. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med* 2005;20:1142-1145.
 12. Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine Tob Res* 2005;7:511-522.
 13. Webb MS, Venable PA, Carey MP, Blair DC. Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum. *J Behav Med* 2007;30:371-383.
 14. Marshall MM, Kirk GD, Caporaso NE, McCormack MC, Merlo CA, Hague JC, Mehta SH, Engels EA. Tobacco use and nicotine dependence among HIV-infected and uninfected injection drug users. *Addict Behav* 2011;36:61-67.
 15. Parker MS, Leveno DM, Campbell TJ, Worrell JA, Carozza SE. AIDS-related bronchogenic carcinoma: fact or fiction? *Chest* 1998;113:154-161.
 16. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. *AIDS* 1999;13:839-843.
 17. Cooksley CD, Hwang LY, Waller DK, Ford CE. Hiv-related malignancies: community-based study using linkage of cancer registry and HIV registry data. *Int J STD AIDS* 1999;10:795-802.
 18. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736-1745.
 19. Grulich AE, Li Y, McDonald A, Correll PK, Law MG, Kaldor JM. Rates of non-AIDS-defining cancers in people with HIV infection before and after aids diagnosis. *AIDS* 2002;16:1155-1161.
 20. Allardice GM, Hole DJ, Brewster DH, Boyd J, Goldberg DJ. Incidence of malignant neoplasms among hiv-infected persons in scotland. *Br J Cancer* 2003;89:505-507.
 21. Dal Maso L, Franceschi S, Polesel J, Braga C, Piselli P, Crocetti E, Falcini F, Guzzinati S, Zanetti R, Vercelli M, et al. for the Cancer and AIDS Registry Linkage Study. Risk of cancer in persons with aids in Italy, 1985-1998. *Br J Cancer* 2003;89:94-100.
 22. Newnham A, Harris J, Evans HS, Evans BG, Moller H. The risk of cancer in HIV-infected people in southeast England: a cohort study. *Br J Cancer* 2005;92:194-200.
 23. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ. Trends in cancer risk among people with aids in the United States 1980-2002. *AIDS* 2006;20:1645-1654.
 24. Mbulaitye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, Workneh M, Coutinho A, Engels EA. Spectrum of cancers among HIV-infected persons in Africa: The Uganda AIDS-cancer registry match study. *Int J Cancer* 2006;118:985-990.
 25. Galceran J, Marcos-Gragera R, Soler M, Romaguera A, Ameijide A, Izquierdo A, Borrás J, de Sanjose S, Casabona J. Cancer incidence in AIDS patients in Catalonia, Spain. *Eur J Cancer* 2007;43:1085-1091.
 26. Dal Maso L, Polesel J, Serraino D, Lise M, Piselli P, Falcini F, Russo A, Intrieri T, Vercelli M, Zamboni P, et al. Pattern of cancer risk in persons with AIDS in Italy in the Haart era. *Br J Cancer* 2009;100:840-847.
 27. Polesel J, Franceschi S, Suligoi B, Crocetti E, Falcini F, Guzzinati S, Vercelli M, Zanetti R, Tagliabue G, Russo A, et al. Cancer incidence in people with AIDS in Italy. *Int J Cancer* 2010;127:1437-1445.
 28. Serraino D, Boschini A, Carrieri P, Pradier C, Dorrucci M, Dal Maso L, Ballarini P, Pezzotti P, Smacchia C, Pesce A, et al. Cancer risk among men with, or at risk of, HIV infection in southern Europe. *AIDS* 2000;14:553-559.
 29. Phelps RM, Smith DK, Heilig CM, Gardner LI, Carpenter CC, Klein RS, Jamieson DJ, Vlahov D, Schuman P, Holmberg SD. Cancer incidence in women with or at risk for HIV. *Int J Cancer* 2001;94:753-757.
 30. Herida M, Mary-Krause M, Kaphan R, Cadranet J, Poizot-Martin I, Rabaud C, Plaisance N, Tissot-Dupont H, Boue F, Lang JM, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* 2003;21:3447-3453.
 31. Bower M, Powles T, Nelson M, Shah P, Cox S, Mandelia S, Gazzard B. HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* 2003;17:371-375.
 32. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, et al. Cancer risk in the Swiss HIV cohort study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;97:425-432.
 33. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. *J Clin Oncol* 2006;24:1383-1388.
 34. Serraino D, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, Baccarani U, De Juli E, Pozzetto U, Bellelli S, et al. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer* 2007;43:2117-2123.
 35. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, Holmberg SD, Brooks JT. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008;148:728-736.
 36. Guiguet M, Boue F, Cadranet J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (fhdh-anrs co4): a prospective cohort study. *Lancet Oncol* 2009;10:1152-1159.
 37. Levine AM, Seaberg EC, Hessel NA, Preston-Martin S, Silver S, Cohen MH, Anastos K, Minkoff H, Orenstein J, Dominguez G, et al. HIV as a risk factor for lung cancer in women: data from the women's interagency HIV study. *J Clin Oncol* 2010;28:1514-1519.
 38. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007;370:59-67.
 39. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2009;52:611-622.
 40. Giordano TP, Kramer JR. Does HIV infection independently increase the incidence of lung cancer? *Clin Infect Dis* 2005;40:490-491.
 41. Kirk GD, Merlo C, O'Driscoll P, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007;45:103-110.
 42. Shiels MS, Cole SR, Mehta SH, Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. *J Acquir Immune Defic Syndr* 2010;55:510-515.
 43. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, Klein D, Quesenberry CP Jr, Towner WJ, Abrams DI. HIV infection and the risk of cancers with and without a known infectious cause. *AIDS* 2009;23:2337-2345.
 44. Dal Maso L, Polesel J, Serraino D, Franceschi S. Lung cancer in persons with AIDS in Italy, 1985-1998. *AIDS* 2003;17:2117-2119.
 45. Serraino D, Pezzotti P, Dorrucci M, Alliegro MB, Sinicco A, Rezza G. HIV Italian seroconversion study group. Cancer incidence in a cohort of human immunodeficiency virus seroconverters. *Cancer* 1997;79:1004-1008.
 46. Chan TK, Aranda CP, Rom WN. Bronchogenic carcinoma in young patients at risk for acquired immunodeficiency syndrome. *Chest* 1993;103:862-864.
 47. Benard A, Tessier JF, Rambeloarisoa J, Bonnet F, Fossoux H, Neau D, Dutronc H, Lazaro E, Dabis F, Chene G. HIV infection and tobacco smoking behaviour: prospects for prevention? Anrs co3 aquitaine cohort, 2002. *Int J Tuberc Lung Dis* 2006;10:378-383.

48. Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Curr Opin Oncol* 2007;19:446–451.
49. Lavole A, Wislez M, Antoine M, Mayaud C, Milleron B, Cadranet J. Lung cancer, a new challenge in the HIV-infected population. *Lung Cancer* 2006;51:1–11.
50. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, *et al*. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–194.
51. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. *AIDS* 2007;21:207–213.
52. Marshall MM, McCormack MC, Kirk GD. Effect of cigarette smoking on HIV acquisition, progression, and mortality. *AIDS Educ Prev* 2009; 21(Suppl):28–39.
53. Bonnet F, Lewden C, May T, Heripret L, Jouglu E, Bevilacqua S, Costagliola D, Salmon D, Chene G, Morlat P. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer* 2004;101:317–324.
54. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007;165:1143–1153.
55. el-Solh A, Kumar NM, Nair MP, Schwartz SA, Lwebuga-Mukasa JS. An RGD containing peptide from HIV-1 tat-(65–80) modulates proto-oncogene expression in human bronchoalveolar carcinoma cell line, a549. *Immunol Invest* 1997;26:351–370.
56. Wistuba II, Behrens C, Milchgrub S, Virmani AK, Jagirdar J, Thomas B, Ioachim HL, Litzky LA, Brambilla EM, Minna JD, *et al*. Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. *JAMA* 1998;279:1554–1559.
57. Engels EA. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS* 2009;23:875–885.
58. Alavanja MC, Brownson RC, Boice JD Jr, Hock E. Preexisting lung disease and lung cancer among nonsmoking women. *Am J Epidemiol* 1992;136:623–632.
59. Ramanakumar AV, Parent ME, Menzies D, Siemiatycki J. Risk of lung cancer following nonmalignant respiratory conditions: evidence from two case-control studies in Montreal, Canada. *Lung Cancer* 2006;53: 5–12.
60. Zuniga JM, Solomon S, Sherer R, Schechter M, Rockstroh J, Nachega J. Stigma, isolation, and discrimination and their impact on HIV serostatus disclosure: a global survey of 2035 HIV+ patients. Presented at the XVIII International AIDS Conference. July 18–23, 2010, Vienna, Austria.
61. Crothers K, Goulet JL, Rodriguez-Barradas MC, Gibert CL, Butt AA, Braithwaite RS, Peck R, Justice AC. Decreased awareness of current smoking among health care providers of HIV-positive compared to HIV-negative veterans. *J Gen Intern Med* 2007;22:749–754.
62. Ambrose BK, Westergaard RP, Jonas M, Kirk GD. Provider beliefs and integration of tobacco cessation strategies into the clinical care of HIV-infected patients. Presented at the XVIII International AIDS Conference. July 18–23, 2010, Vienna, Austria.