Cigarette Smoking in the HIV-Infected Population

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As mortality due to AIDS-related causes has decreased with the use of antiretroviral therapy, there has been a rise in deaths related to non–AIDS-defining illnesses. Given the exceedingly high prevalence of cigarette smoking among individuals living with HIV infection, tobacco has been implicated as a major contributor to this paradigm shift. Evidence suggests that smoking-related illnesses, such as cardiovascular disease, respiratory illnesses, and certain malignancies, contribute substantially to morbidity and mortality among HIV-infected persons. In this review, we summarize the adverse health consequences of smoking relevant to HIV-infected individuals and discuss smoking cessation in this unique population, including a discussion of barriers to quitting and a review of studies that have examined smoking cessation interventions.

Keywords: nicotine addiction; smoking cessation; AIDS

Although the prevalence of cigarette smoking among adults in the United States has declined to approximately 20%, studies have consistently indicated that the prevalence of smoking among persons living with HIV infection remains 2- to 3-fold higher than that of the general population (1–6). For example, in 1993, the prospective Pulmonary Complications of HIV Infection Study reported a smoking prevalence of 54% (5). In 2000, a survey of patients receiving HIV ambulatory care from clinics in New England found more than 70% to be current smokers (2). More recently, a questionnaire-based study of New Yorkers living with HIV reported the smoking rate to be 59% (7). As HIV infection is increasingly transformed into a chronic disease, this high prevalence of cigarette smoking has profound health implications for HIV-infected populations (6, 8–11). For example, cigarette smoking is independently associated with lower scores for general health perception, physical functioning, bodily pain, energy, and cognitive functioning (6, 8–10). Furthermore, cigarette smoking has been identified as a significant cofactor in premature development of HIV/antiretroviral-related cardiovascular disease (12–20).

Before the widespread availability and use of combination antiretroviral therapy (ART), the relevance of cigarette smoking as a contributing factor to the development of pulmonary complications was unclear (21–24). Nevertheless, increasing data support that HIV-infected smokers living in the ART era are unusually susceptible to a number of respiratory complications. These include a heightened risk for lower respiratory tract infections (25–28), chronic obstructive pulmonary disease (COPD), and lung cancer.

In this review we summarize the effects of cigarette smoking on a number of health outcomes relevant to the HIV-infected population and focus on issues related to smoking behavior and smoking cessation.

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SMOKING AND HIV-RELATED MORBIDITY

Lower Respiratory Tract Infections

Studies published in the combination ART era demonstrate a clear link between smoking status and the risk of bacterial pneumonia (11, 25, 26). For example, the incidence of bacterial pneumonia was recently reported in SMART (Strategies for the Management of Antiretroviral Therapy), a multicenter study of 5,472 HIV-infected participants randomized to receive continuous or intermittent antiretroviral therapy (25). In both treatment groups, current smoking was a significant risk factor for the development of bacterial pneumonia; in the continuous treatment group, smoking was the single greatest predictor for the development of bacterial pneumonia (hazard ratio, 3.01) (25). Similarly, in a multicenter prospective study of 885 HIV-infected women, the most prominent clinical risk factor for the development of bacterial pneumonia in the ART era was current smoking (26).

Although studies performed in the precombination ART era failed to demonstrate an association between smoking status and the risk for *Pneumocystis carinii* pneumonia (PCP), a recent study suggests that smokers in the modern ART era are more likely to develop PCP than nonsmoking individuals with HIV. Miguez-Barbano and colleagues performed a case-control, cross-sectional analysis of 521 consecutive HIV-infected patients admitted to a New York University hospital and found that HIV-infected smokers were three times as likely as HIV-infected nonsmokers to be hospitalized with PCP (29).

COPD

Evidence supports that the lungs of HIV-infected individuals are especially susceptible to the damaging effects of cigarette smoke (30–38). Using a combination of high-resolution computed tomography of the chest and physiologic criteria to define emphysema, Diaz and colleagues identified emphysema in 17 of 114 HIV-infected participants, compared with 1 of 44 HIV-uninfected control subjects matched for age and smoking history ($P = 0.025$) (37). Although these observations were initially made predominantly in the precombination ART era, recent data suggest that the risk for COPD among those living with HIV infection remains increased even with the widespread availability and use of ART (38). The risk of COPD in HIV is reviewed in detail in this issue by Morris and colleagues.

Malignancy

There are numerous reports demonstrating an increased risk of lung cancer among HIV-infected individuals, with adjusted risk associated with HIV infection ranging from 2.0 to 7.0 (39–43). Given the prevalence of cigarette smoking in the HIV population, it has been difficult to determine whether lung cancer risk is related solely to the increased prevalence of cigarette smoking. Studies examining this question are reviewed in detail in this issue by Kirk and colleagues. Other HIV-associated malignancies, such as anal and cervical cancer, have a higher prevalence in HIV-infected smokers compared with nonsmokers (44, 45). This association has been explained by higher levels of human papilloma

virus (HPV) variants, such as HPV16 and HPV18, found in smokers (46).

Cardiovascular Disease

Cardiovascular complications have become a major source of morbidity for HIV-infected individuals living in the ART era (47–53). Although HIV-infected persons have a higher risk of diabetes, hyperlipidema, and hypertension than HIV-negative individuals (50–52), the high prevalence of cigarette smoking is clearly an important contributor to cardiovascular morbidity. In a prospective, observational study by Barbaro and colleagues (54), previously untreated and asymptomatic HIV-infected patients were placed on an ART regimen with a protease inhibitor or without a protease inhibitor. The cumulative annual incidence of cardiovascular-related events was higher in the protease inhibitor group ($P < 0.001$), with a significantly higher annual incidence of myocardial infarction and metabolic alterations. This acceleration in cardiovascular-related events was greater among men and among those who smoked more than 20 cigarettes per day.

Although protease inhibitors and smoking both contribute to the increased risk of cardiovascular morbidity and mortality, results from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD Study Group) show that current smoking is associated with greater risk of myocardial infarction (relative risk, 2.83; 95% confidence interval [CI], 2.04–3.93) than protease inhibitor therapy (relative risk, 1.16; 95% CI, 1.10–1.23) (47). The increased risk of cardiovascular-related illness also translates into an increased risk of cardiovascular mortality in HIV-infected individuals. De Socio and colleagues (55) compared 403 HIV-infected subjects free from overt cardiovascular disease with 96 control subjects and found that the 10-year estimated risk for cardiovascular mortality was 1.23 ± 2.3% versus 0.83 ± 0.9%, respectively ($P = 0.01$).

Quality of Life and Mortality

Smoking in the HIV-infected population not only contributes to the comorbid illnesses mentioned previously, but it also has an impact on quality of life and survival. Turner and colleagues (10) studied 585 HIV-infected persons and found that smoking was associated significantly with decreasing scores in all dimensions of health-related quality of life. Using multivariate regression analysis, smoking was significantly associated with decreases in general health perception, physical functioning, bodily pain, energy, role functioning, and cognitive functioning. In the ART era, Crothers and colleagues (56) examined the impact of smoking on quality of life and mortality in subjects enrolled in the Veterans Aging Cohort 3 Site Study. Out of the 867 subjects in the study, 63% were current smokers, and 22% were former smokers. After adjusting for race, age, viral load, CD4 count, and illegal drug and alcohol use, current smoking was associated with a significantly lower quality of life and with a significantly higher mortality compared with never smokers (hazard ratio [HR] 1.99; 95% CI, 1.03–3.86). A subsequent study in the Veterans Aging Cohort 5 Site Study comparing HIV-infected and non–HIV-infected veterans found that smoking was associated with increased comorbid disease and mortality in the HIV-infected group (57).

The recent prospective study by Lifson and colleagues highlights the excess morbidity and mortality attributable to smoking in the HIV-infected population (11). Using data from the SMART trial, these investigators found that, compared with nonsmokers, current smokers had a significantly greater adjusted hazard ratio (HR) for major cardiovascular disease (HR, 2.0), non-AIDS malignancy (HR, 1.8), bacterial pneumonia (HR, 2.3), and all-cause mortality (HR, 2.4). Current smokers also had a significantly greater HR for these complications compared with former smokers, underscoring the potential significance of smoking cessation in this population (11).

Immune Function

Evidence demonstrates that cigarette smoking adversely affects the immunologic response to ART. In a longitudinal study of a large HIV-infected cohort, Feldman and coworkers (58) found that, compared with nonsmokers, smokers receiving ART had poorer viral responses (HR, 0.79; 95% CI, 0.67–0.93), poorer immunologic response (HR, 0.85; 95% CI, 0.73–0.99), greater risk of virologic rebound (HR, 1.39; 95% CI, 1.06–1.69), and more frequent immunologic failure (HR, 1.52; 95% CI, 1.18–1.96).

SMOKING CESSATION IN HIV

Barriers to Smoking Cessation

Given the high prevalence of cigarette smoking and its impact on comorbidities among HIV-infected populations, it is imperative that smoking cessation becomes a priority in the care of HIV-infected individuals. There are a number of barriers and complicating factors that compromise the success of smoking cessation in this unique population. For example, HIV care providers are less likely to identify current smokers and to report less confidence in influencing smoking cessation than non-HIV care providers (59). Managing complications of HIV infection may overshadow smoking cessation discussions and therapies. In addition, HIV-infected individuals may feel that they will ultimately die from HIV, making smoking cessation less of a priority (60). They may also use tobacco to manage HIV-related symptoms and pain (61, 62).

Body image may contribute to fears of smoking cessation in the HIV-infected population because smoking may serve as a means to manage the physical changes accompanying lipodystrophy-associated antiretroviral use (63). Indeed, recent data suggest that HIV-infected smokers may have a greater change in body mass index (BMI) with smoking cessation than would be expected for the general population (64). Among 28 quitters involved in a specialized smoking cessation program at our institution, the increase in mean BMI 3 months after smoking cessation was 2.3 kg/m^2 (64), substantially greater than average changes in BMI reported in the general population after smoking cessation (1.1–1.6 kg/m^2) (65, 66).

Addiction to drugs and alcohol perpetuates tobacco use (67–69), and the high prevalence of concomitant substance abuse represents a major barrier to smoking cessation in the HIV-infected population (61, 70–72). In a cross-sectional study by Cofrancesco and colleagues (71), the prevalence of illicit drug use was investigated in a cohort of 1,163 HIV-infected individuals compared with 294 control subjects. Eighty-six percent of the HIV-infected participants, versus 67% of the control subjects, reported ever using illicit drugs ($P < 0.0001$), and 28% of the HIV-infected participants, compared with 16% of the control subjects, reported current illicit drug use ($P = 0.0001$). Another cross-sectional analysis of 384 HIV-infected individuals found that heavy alcohol drinkers were more likely to smoke (73). Humfleet and colleagues (70) recruited 184 HIV-infected smokers from two outpatient clinics to undergo self-administration of multiple questionnaires measuring their level of nicotine dependence by the Fagerström Test for Nicotine Dependence, desire and readiness to quit, and the characteristics of their social support network. Forty percent of the participants reported alcohol use, 39.7% reported marijuana use, 19.6% reported opiate use, 9.8% reported cocaine use, and 8.7% reported amphetamine use.

A large percentage had a history of undergoing treatment for alcohol (33.7%) and for drug abuse (54.9%). The lifetime prevalence of illicit drug use in HIV-infected individuals has been reported to be as high as 84%, with the highest percentage in current and former smokers (61). In a cross-sectional study by Benard and coworkers (74), 509 HIV-infected patients completed self-administered questionnaires about tobacco, alcohol, and illicit drug use as well as nicotine dependence, motivation level, and depression level. Half of the participants were found to be smokers, and there was a significant association between smoking status and excessive alcohol use ($P = 0.01$) and excessive cannabis consumption ($P < 0.001$).

Psychiatric disorders also play a strong role in smoking cessation failure. In the general population, over 40% of the cigarettes smoked in the United States are by people with mental illness (75), and comorbid psychiatric disorders have also been associated with lower successful smoking cessation rates (76). This finding has implications for HIV-infected populations because the prevalence of psychiatric disorders in HIV-infected individuals is between 17 and 63% (72, 77–79). HIV-infected smokers have reported higher symptoms of depression and higher consumption of alcohol and illicit drugs than nonsmokers (80). Depression, in particular, has been associated with higher nicotine dependence and lower readiness to quit in HIV (61, 74).

Low socioeconomic status and lack of strong support systems contribute to low success rates in smoking cessation. Socioeconomically disadvantaged people may be less likely to receive smoking cessation advice and treatment (81, 82). Lower education level and lower income and employment status appear to be associated with smoking in HIV-infected individuals (80, 83, 84). In the study by Humfle and colleagues (70), 66.5% of HIV-infected smokers were unemployed, 43.8% had an annual income below $10,000, and 37.4% had unstable housing. Over 40% of the HIV-infected smokers had a social support network comprised predominantly of smokers.

As part of the Lung HIV project, our group has begun to investigate the effects of a specialized smoking cessation intervention on quit rates as well as clinical and biological outcomes in HIV-infected current cigarette smokers. Baseline demographic and psychosocial characteristics of our study population recruited thus far are detailed in Table 1 and demonstrate potential barriers to quitting. For example, nearly 50% have a score of ⩾10 on the Beck Depression Inventory, meeting criteria for depression. In addition, a large percentage is unemployed and has low household income.

TABLE 1. BASELINE CHARACTERISTICS OF HIV-INFECTED INDIVIDUALS ENROLLED IN A SMOKING CESSATION INTERVENTION STUDY AS PART OF LUNG HIV (n = 215)

Demographics	Mean ± SD	Percentage
Age	42.7 ± 9.2	
Male		85.0
Race/ethnicity		
Hispanic or Latino		2.8
White		53.8
Nonwhite		46.2
Education level		
< High school		16.0
High school or GED		24.4
> High school		59.6
Employment status		
Employed full-time or part-time		27.0
Unemployed or disabled		59.0
Other		7.0
Refused		7.0
Marital status		
Married or member of couple		22.3
Never married		53.6
Divorced/separated/widowed		25.1
Household income		
⩽ $20,000		58.0
> $20,000		33.5
Don't know/refused		8.5
Smoking-related variables		
Age at initiation	17.4 ± 5.2	
Current cigarettes per day	19.4 ± 10.3	
At least one quit attempt in past year	9.5 ± 1.0	51.9
Important to quit smoking*	7.9 ± 1.8	
Confidence in quitting*		
Tobacco dependence		
Fagerström Scale Score	5.0 ± 2.3	
Cotinine concentration, ng/ml	263.8 ± 182.4	
Psychosocial indicators		
Physical Component Score (SF-8)†	46.7 ± 10.1	
Mental Component Score (SF-8)†	45.0 ± 11.1	
Beck Depression Inventory Score	11.0 ± 8.9	
% with Beck Depression Inventory ⩾ 10		49.3

Definition of abbreviations: GED = general equivalency diploma; HS = high school; SF-8 = Short Form 8.

* 0–10 scale, with higher numbers indicating more importance or confidence.

† Norm-based scoring.

Smoking Cessation Interventions

Despite the numerous barriers that HIV-infected smokers face, a substantial portion exhibits a high motivation to quit (Table 1) (4, 61, 74, 85). Nearly half of HIV-infected smokers in one study was in the contemplation stage of the Transtheoretical Model, and the other half was in the preparation stage (70, 86). This group of HIV-infected smokers had moderate levels of nicotine dependence and had made an average of approximately four prior quit attempts (70). In a study by Mamary and colleagues (4), 72% of smokers in an HIV clinic reported that they had tried to quit previously. At the time of the study, 63% were thinking of quitting, 69% were interested in a group cessation program, and 82% were interested in pharmacotherapy to facilitate smoking cessation. One French study showed that 33% of HIV-infected smokers had attempted to quit at least once, and attempts were greater among older patients, those with longer duration of HIV illness, and those with previous quit attempts (87).

The impact of tobacco cessation programs in HIV-infected smokers has been addressed in several, mostly small studies that have primarily involved nicotine replacement therapy (NRT) (Table 2). A study by Elzi and colleagues (88) showed that HIV-infected smokers who participated in a structured cessation program of NRT and counseling had a quit rate of 50%, compared with 15% in a historical control group. At 12 months, self-reported smoking abstinence was 38% in the intervention group and 7% in the control group. One randomized clinical trial comparing a program of NRT, self-help materials, and phone counseling with a usual care program comprised only of self-help materials and NRT found that HIV-infected smokers in the phone counseling group had abstinence rates of 36.8%, compared with 10.3% in the usual care group ($P = 0.0059$) (89). Nevertheless, the largest intervention study to date found no difference in biochemically confirmed quit rate between NRT (n = 232) and motivationally enhanced counseling plus NRT (n = 212) (90). Quit rates in both groups were low (~10%) (90).

Limited data are available regarding pharmacologic therapy other than NRT for smoking cessation in HIV-infected populations. Pedrol-Clotet and colleagues found that of 21 HIV-infected smokers on ART and buproprion, 38% remained abstinent for greater than 1 year, and no clinically significant drug interactions were identified (91). A small Spanish study examining 18 HIV-infected smokers on varenicline and ART revealed five cases of

TABLE 2. SUMMARY OF STUDIES INVESTIGATING NICOTINE REPLACEMENT THERAPY AS PART OF A SMOKING CESSATION INTERVENTION IN HIV-INFECTED POPULATIONS

Study	N	Intervention	Follow-up	Confirmation Method	Quit Rate
Wewers (2000)	15	NRT + counseling + skills training (n = 8) vs. self-help (n = 7)	8 mo	Exhaled CO level	50% in counseling group vs. 0% in standard care
Cummins (2005)	27	NRT + motivational counseling + diary	5 mo	Self-report	22%
Elzi (2006)	34	NRT + counseling (n = 34) vs. historical control	12 mo	Self-report	38% counseling group vs. 7% control group
Vidrine (2006)	95	NRT + cellular phone counseling vs. NRT + self-help materials	3 mo	Exhaled CO level	36.8% in counseling group vs. 10.3% in control group
Ingersoll (2009)	40	NRT + motivational counseling (n = 22) vs. NRT + self-guided learning (n = 18)	3 mo	Exhaled CO level	22.5% for entire group (no difference between groups)
Lloyd-Richardson (2009)	444	NRT + motivational counseling (n = 232) vs. NRT + standard care (n = 212)	6 mo	Exhaled CO level	9% in counseling group vs. 10% in control group

Definition of abbreviations: CO = carbon monoxide; NRT = nicotine replacement therapy.

nausea and six cases of sleep disturbance; none warranted treatment interruption. The abstinence rates after 3 and 6 months were 6 of 18 and 5 of 18, respectively (92). Although such limited data suggest that HIV-infected individuals can tolerate varenicline, the high prevalence of depression and other psychiatric disorders warrant caution when prescribing this agent to HIV-infected patients because varenicline has been linked to increased risk of suicidal ideation and worsening of psychiatric conditions in individuals with underlying disease.

There are several potential interactions between ART and smoking cessation pharmacotherapy. For example, ritonavir, a potent inducer of human cytochrome P4502B6 (CYP2B6) (93), combined with lopinavir can significantly decrease plasma concentrations of buproprion (94). Conversely, *in vitro* studies have shown that several protease inhibitors inhibit CYP2B6 (95) and increase the potential for toxic levels of buproprion, which can manifest as seizures. A case series of 10 patients using buproprion in combination with nelfinavir, ritonavir, or efavirenz for a median duration of 8 months did not identify seizure events in any of the patients (96). However, this was a small study, and none of the patients was on high doses of ritonavir. As such, some precaution should be taken when prescribing buproprion to HIV-infected individuals taking protease inhibitors.

The benefits of smoking cessation in the HIV-infected population have been documented. Vidrine and colleagues enrolled 95 HIV-infected individuals in a smoking cessation study consisting of NRT, counseling, and self-help materials. HIV-related symptom burden and health-related quality of life were assessed 3 months after enrollment in the study. The authors found that the number of abstinent days was associated with lower levels of HIV-related symptom burden (97). Smoking cessation, as part of a therapy of cardiovascular prevention program, has also been shown to reduce cardiovascular risk in HIV-infected individuals (98).

The increased risk of bacterial pneumonia in the HIV-infected population appears limited to current and not former smokers. Bernard and colleagues found a 2-fold risk for bacterial pneumonia comparing HIV-infected current smokers with HIV-infected nonsmokers (27). The risk for former smokers, defined as those who have quit for 1 year or more, was nearly identical to that of never smokers. Data from SMART and HIV Epidemiologic Research Study also demonstrate that the association of cigarette smoking with bacterial pneumonia risk is present only in current smokers; both studies found the risk of former smokers to be almost identical to that of nonsmokers (25, 26).

CONCLUSION

Persons infected with HIV are unusually susceptible to the adverse effects of cigarette smoking. These adverse effects include a heightened risk for lower respiratory tract infections, COPD, and lung cancer. In addition, smoking increases the risk for other malignancies, contributes to the burden of cardiovascular disease, decreases quality of life, and adversely affects the immunologic response to ART. Despite the burden of cigarette smoking in this population and the associated public health implications as this group ages, there has been surprisingly little smoking-related investigation in HIV-infected cohorts. In particular, research is needed to determine effective smoking cessation strategies for this vulnerable population. It is essential that tobacco cessation programs, designed to combat the specific challenges that HIV-infected smokers face, be available, accessible, and effective. It is also essential that health care providers recognize the increased susceptibility of HIV-infected individuals to cigarette smoke and make smoking cessation a priority for their patients.

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References

1. 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.
2. Niaura R, Shadel WG, Morrow K, Tashima K, Flanigan T, Abrams DB. Human immunodeficiency virus infection, AIDS, and smoking cessation: the time is now. *Clin Infect Dis* 2000;31:808–812.
3. Stall RD, Greenwood GL, Acree M, Paul J, Coates TJ. Cigarette smoking among gay and bisexual men. *Am J Public Health* 1999;89: 1875–1878.
4. 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.
5. Wallace JM, Rao AV, Glassroth J, Hansen NI, Rosen MJ, Arakaki C, Kvale PA, Reichman LB, Hopewell PC. The Pulmonary Complications of HIV Infection Study Group. Respiratory illness in persons with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993;148:1523–1529.
6. Palacio H, Hilton JF, Canchola AJ, Greenspan D. Effect of cigarette smoking on HIV-related oral lesions. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;14:338–342.
7. Tesoriero JM, Gieryic SM, Carrascal A, Lavigne HE. Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation. *AIDS Behav* 2010;14:824–835.
8. Schuman P, Sobel JD, Ohmit SE, Mayer KH, Carpenter CC, Rompalo A, Duerr A, Smith DK, Warren D, Klein RS. HIV Epidemiology Research Study (HERS) Group. Mucosal candidal colonization and candidiasis in women with or at risk for human immunodeficiency virus infection. *Clin Infect Dis* 1998;27:1161–1167.
9. Shiboski CH, Neuhaus JM, Greenspan D, Greenspan JS. Effect of receptive oral sex and smoking on the incidence of hairy leukoplakia in HIV-positive gay men. *J Acquir Immune Defic Syndr* 1999;21:236–242.
10. Turner J, Page-Shafer K, Chin DP, Osmond D, Mossar M, Markstein L, Huitsing J, Barnes S, Clemente V, Chesney M. Adverse impact of

cigarette smoking on dimensions of health-related quality of life in persons with HIV infection. *AIDS Patient Care STDS* 2001;15: 615–624.
11. Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. *Am J Public Health* 2010;100:1896–1903.
12. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;348:702–710.
13. Depairon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, Riesen W, Nicod P, Darioli R, Telenti A, *et al.* Premature atherosclerosis in HIV-infected individuals: focus on protease inhibitor therapy. *AIDS* 2001;15:329–334.
14. Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, Henry WK, Currier JS, Sprecher D, Glesby MJ. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV medical association of the Infectious Disease Society of America and the Adult Aids Clinical Trials Group. *Clin Infect Dis* 2003;37:613–627.
15. Duong M, Buisson M, Cottin Y, Piroth L, Lhuillier I, Grappin M, Chavanet P, Wolff JE, Portier H. Coronary heart disease associated with the use of human immunodeficiency virus (HIV)-1 protease inhibitors: report of four cases and review. *Clin Cardiol* 2001;24:690–694.
16. Heath KV, Hogg RS, Chan KJ, Harris M, Montessori V, O'Shaughnessy MV, Montanera JS. Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 2001;15:231–239.
17. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, Waters DD. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation* 2004;109: 1603–1608.
18. Maggi P, Serio G, Epifani G, Fiorentino G, Saracino A, Fico C, Perilli F, Lillo A, Ferraro S, Gargiulo M, *et al.* Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors. *AIDS* 2000;14:F123–F128.
19. Seminari E, Pan A, Voltini G, Carnevale G, Maserati R, Minoli L, Meneghetti G, Tinelli C, Testa S. Assessment of atherosclerosis using carotid ultrasonography in a cohort of HIV-positive patients treated with protease inhibitors. *Atherosclerosis* 2002;162:433–438.
20. Mooser V. Atherosclerosis and HIV in the highly active antiretroviral therapy era: towards an epidemic of cardiovascular disease? *AIDS* 2003;17:S65–S69.
21. Nieman RB, Fleming J, Coker RJ, Harris JR, Mitchell DM. The effect of cigarette smoking on the development of AIDS in HIV-1-seropositive individuals. *AIDS* 1993;7:705–710.
22. Galai N, Park LP, Wesch J, Visscher B, Riddler S, Margolick JB. Effect of smoking on the clinical progression of HIV-1 infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;14:451–458.
23. Hirschtick RE, Glassroth J, Jordan MC, Wilcosky TC, Wallace JM, Kvale PA, Markowitz N, Rosen MJ, Mangura BT, Hopewell PC. Pulmonary Complications of HIV Infection Study Group. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med* 1995;333:845–851.
24. Study Group for the MRC Collaborative Study of HIV Infection in Women. Survival and progression of HIV disease in women attending gum/HIV clinics in Britain and Ireland. *Sex Transm Infect* 1999;75: 247–252.
25. Gordin FM, Roediger MP, Girard PM, Lundgren JD, Miro JM, Palfreeman A, Rodriguez-Barradas MC, Wolff MJ, Easterbrook PJ, Clezy K, *et al.* Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med* 2008; 178:630–636.
26. Kohli R, Lo Y, Homel P, Flanigan TP, Gardner LI, Howard AA, Rompalo AM, Moskaleva G, Schuman P, Schoenbaum EE. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis* 2006;43:90–98.
27. Benard A, Mercie P, Alioum A, Bonnet F, Lazaro E, Dupon M, Neau D, Dabis F, Chene G. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000–2007. *PLoS ONE* 2010;5:e8896.
28. Le Moing V, Rabaud C, Journot V, Duval X, Cuzin L, Cassuto JP, Al Kaied F, Dellamonica P, Chene G, Raffi F. Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. *HIV Med* 2006;7:261–267.
29. Miguez-Burbano MJ, Ashkin D, Rodriguez A, Duncan R, Pitchenik A, Quintero N, Flores M, Shor-Posner G. Increased risk of pneumocystis carinii and community-acquired pneumonia with tobacco use in HIV disease. *Int J Infect Dis* 2005;9:208–217.
30. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Neal D, Nagaraja HN, Drake J, Clanton TL. The pathophysiology of pulmonary diffusion impairment in human immunodeficiency virus infection. *Am J Respir Crit Care Med* 1999;160:272–277.
31. Mitchell DM, Fleming J, Pinching AJ, Harris JR, Moss FM, Veale D, Shaw RJ. Pulmonary function in human immunodeficiency virus infection: a prospective 18-month study of serial lung function in 474 patients. *Am Rev Respir Dis* 1992;146:745–751.
32. French PD, Cunningham DA, Fleming J, Donegan C, Harris JR, Shaw RJ, Mitchell DM. Low carbon monoxide transfer factor (TLCO) in HIV-infected patients without lung disease. *Respir Med* 1992;86:253–256.
33. Kvale PA, Rosen MJ, Hopewell PC, Markowitz N, Hansen N, Reichman LB, Wallace JM, Glassroth J, Fulkerson W, Meiselman L. Pulmonary Complications of HIV Infection Study Group. A decline in the pulmonary diffusing capacity does not indicate opportunistic lung disease in asymptomatic persons infected with the human immunodeficiency virus. *Am Rev Respir Dis* 1993;148:390–395.
34. Backer V, Nybo Jensen B, Pedersen C, Hertz JB, Jensen TH. Time-related decrease in diffusion capacity in HIV-infected patients with impaired immune function. *Scand J Infect Dis* 1992;24:29–34.
35. Shaw RJ, Roussak C, Forster SM, Harris JR, Pinching AJ, Mitchell DM. Lung function abnormalities in patients infected with the human immunodeficiency virus with and without overt pneumonitis. *Thorax* 1988;43:436–440.
36. Nieman RB, Fleming J, Coker RJ, Harris JR, Mitchell DM. Reduced carbon monoxide transfer factor (TLCO) in human immunodeficiency virus type 1 (HIV-1) infection as a predictor for faster progression to aids. *Thorax* 1993;48:481–485.
37. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Nagaraja HN, Drake J, Clanton TL. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;132:369–372.
38. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* 2006;130:1326–1333.
39. Cadranel J, Garfield D, Lavole A, Wislez M, Milleron B, Mayaud C. Lung cancer in HIV infected patients: facts, questions and challenges. *Thorax* 2006;61:1000–1008.
40. Engels EA. Human immunodeficiency virus infection, aging, and cancer. *J Clin Epidemiol* 2001;54:S29–S34.
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. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies: a prospective cohort study. *Lancet Oncol* 2009;10:1152–1159.
43. Sigel K, Wisnivesky J, Justice A, Brown S, Butt A, Crystal S, Rimland D, Rodriguez-Barradas MC, Gibert C. HIV infection is an independent risk factor for lung cancer. 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA; 2010.
44. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, Young M, Melnick S, Miotti P, Burk R. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *J Natl Cancer Inst* 1999;91:226–236.
45. Palefsky JM, Shiboski S, Moss A. Risk factors for anal human papillomavirus infection and anal cytologic abnormalities in HIV-positive and HIV-negative homosexual men. *J Acquir Immune Defic Syndr* 1994;7:599–606.
46. Brockmeyer N, Kreuter A, Pfister H, Altmeyer P, Wieland U. Elevated anal HPV16 DNA loads in HIV+ men who smoke. 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA; 2007.
47. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte AD, El-Sadr W, De Wit S, Kirk O, Fontas E, Law MG, *et al.* Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;356: 1723–1735.
48. Friis-Moller N, Sabin CA, Weber R, Monforte AD, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De Wit S, Pradier C, *et al.* Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349:1993–2003.

49. Sax PE, Kumar P. Tolerability and safety of HIV protease inhibitors in adults. *J Acquir Immune Defic Syndr* 2004;37:1111–1124.
50. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007;92:2506–2512.
51. Palacios R, Santos J, Garcia A, Castells E, Gonzalez M, Ruiz J, Marquez M. Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients: a prospective study in a cohort of naive patients. *HIV Med* 2006;7:10–15.
52. Adeyemi O, Rezai K, Bahk M, Badri S, Thomas-Gossain N. Metabolic syndrome in older HIV-infected patients: data from the core50 cohort. *AIDS Patient Care STDS* 2008;22:941–945.
53. Periard D, Cavassini M, Taffe P, Chevalley M, Senn L, Chapuis-Taillard C, de Valliere S, Hayoz D, Tarr PE. High prevalence of peripheral arterial disease in HIV-infected persons. *Clin Infect Dis* 2008;46:761–767.
54. Barbaro G, Di Lorenzo G, Cirelli A, Grisorio B, Lucchini A, Hazra C, Barbarini G. An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy. *Clin Ther* 2003;25:2405–2418.
55. De Socio GV, Martinelli L, Morosi S, Fiorio M, Roscini AR, Stagni G, Schillaci G. Is estimated cardiovascular risk higher in HIV-infected patients than in the general population? *Scand J Infect Dis* 2007;39: 805–812.
56. 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.
57. Crothers K, Goulet JL, Rodriguez-Barradas MC, Gibert CL, Oursler KA, Goetz MB, Crystal S, Leaf DA, Butt AA, Braithwaite RS, *et al.* Impact of cigarette smoking on mortality in HIV-positive and HIV-negative veterans. *AIDS Educ Prev* 2009;21:40–53.
58. 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.
59. 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.
60. Reynolds NR, Neidig JL, Wewers ME. Illness representation and smoking behavior: a focus group study of HIV-positive men. *J Assoc Nurses AIDS Care* 2004;15:37–47.
61. 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.
62. Nicholas PK, Voss JG, Corless IB, Lindgren TG, Wantland DJ, Kemppainen JK, Canaval GE, Sefcik EF, Nokes KM, Bain CA, *et al.* Unhealthy behaviours for self-management of HIV-related peripheral neuropathy. *AIDS Care* 2007;19:1266–1273.
63. Fingeret MC, Vidrine DJ, Arduino RC, Gritz ER. The association between body image and smoking cessation among individuals living with HIV/AIDS. *Body Image* 2007;4:201–206.
64. Huet JD, Wewers ME, Browning K, Harness J, Habash D, Ferketich A, Khabbaza J, Diaz PT. Body composition changes in HIV+ smokers undergoing smoking cessation. *Am J Respir Crit Care Med* 2010;181: A2649.
65. Munafo MR, Tilling K, Ben-Shlomo Y. Smoking status and body mass index: a longitudinal study. *Nicotine Tob Res* 2009;11:765–771.
66. Kadowaki T, Watanabe M, Okayama A, Hishida K, Okamura T, Miyamatsu N, Hayakawa T, Kita Y, Ueshima H. Continuation of smoking cessation and following weight change after intervention in a healthy population with high smoking prevalence. *J Occup Health* 2006;48:402–406.
67. Barrett SP, Darredeau C, Pihl RO. Patterns of simultaneous polysubstance use in drug using university students. *Hum Psychopharmacol* 2006;21:255–263.
68. Humfleet G, Munoz R, Sees K, Reus V, Hall S. History of alcohol or drug problems, current use of alcohol or marijuana, and success in quitting smoking. *Addict Behav* 1999;24:149–154.
69. Hughes JR. Treatment of smoking cessation in smokers with past alcohol/drug problems. *J Subst Abuse Treat* 1993;10:181–187.
70. Humfleet GL, Delucchi K, Kelley K, Hall SM, Dilley J, Harrison G. Characteristics of HIV-positive cigarette smokers: a sample of smokers facing multiple challenges. *AIDS Educ Prev* 2009;21:54–64.
71. Cofrancesco J Jr, Scherzer R, Tien PC, Gibert CL, Southwell H, Sidney S, Dobs A, Grunfeld C. Illicit drug use and HIV treatment outcomes in a US cohort. *AIDS* 2008;22:357–365.
72. Pence BW, Miller WC, Whetten K, Eron JJ, Gaynes BN. Prevalence of DSM-IV-defined mood, anxiety, and substance use disorders in an HIV clinic in the southeastern United States. *J Acquir Immune Defic Syndr* 2006;42:298–306.
73. Gritz 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.
74. Benard A, Bonnet F, Tessier JF, Fossoux H, Dupon M, Mercie P, Ragnaud JM, Viallard JF, Dabis F, Chene G. Tobacco addiction and HIV infection: toward the implementation of cessation programs. ANRS CO3 Aquitaine Cohort. *AIDS Patient Care STDS* 2007;21: 458–468.
75. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA* 2000;284:2606–2610.
76. Piper ME, Smith SS, Schlam TR, Fleming MF, Bittrich AA, Brown JL, Leitzke CJ, Zehner ME, Fiore MC, Baker TB. Psychiatric disorders in smokers seeking treatment for tobacco dependence: relations with tobacco dependence and cessation. *J Consult Clin Psychol* 2010;78: 13–23.
77. Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, Turner BJ, Eggan F, Beckman R, Vitiello B, *et al.* Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the united states. *Arch Gen Psychiatry* 2001;58:721–728.
78. Tegger MK, Crane HM, Tapia KA, Uldall KK, Holte SE, Kitahata MM. The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. *AIDS Patient Care STDS* 2008;22:233–243.
79. Mijch A, Burgess P, Judd F, Grech P, Komiti A, Hoy J, Lloyd JH, Gibbie T, Street A. Increased health care utilization and increased antiretroviral use in HIV-infected individuals with mental health disorders. *HIV Med* 2006;7:205–212.
80. Webb MS, Vanable 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.
81. Browning KK, Ferketich AK, Salsberry PJ, Wewers ME. Socioeconomic disparity in provider-delivered assistance to quit smoking. *Nicotine Tob Res* 2008;10:55–61.
82. Houston TK, Scarinci IC, Person SD, Greene PG. Patient smoking cessation advice by health care providers: the role of ethnicity, socioeconomic status, and health. *Am J Public Health* 2005;95:1056–1061.
83. Diaz T, Chu SY, Buehler JW, Boyd D, Checko PJ, Conti L, Davidson AJ, Hermann P, Herr M, Levy A, *et al.* Socioeconomic differences among people with aids: results from a multistate surveillance project. *Am J Prev Med* 1994;10:217–222.
84. Zierler S, Krieger N, Tang Y, Coady W, Siegfried E, DeMaria A, Auerbach J. Economic deprivation and AIDS incidence in Massachusetts. *Am J Public Health* 2000;90:1064–1073.
85. Fuster M, Estrada V, Fernandez-Pinilla MC, Fuentes-Ferrer ME, Tellez MJ, Vergas J, Serrano-Villar S, Fernandez-Cruz A. Smoking cessation in HIV patients: rate of success and associated factors. *HIV Med* 2009;10:614–619.
86. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot* 1997;12:38–48.
87. Encrenaz G, Rondeau BV, Bonnet F, Lazaro E, Neau D, Dupon M, Dabis F, Mercie P, Chene G. Determinants of smoking cessation attempts among HIV-infected patients results from a hospital-based prospective cohort. *Curr HIV Res* 2010;8:212–217.
88. Elzi L, Spoerl D, Voggensperger J, Nicca D, Simcock M, Bucher HC, Spirig R, Battegay M. A smoking cessation programme in HIV-infected individuals: a pilot study. *Antivir Ther* 2006;11:787–795.
89. Vidrine DJ, Arduino RC, Gritz ER. Impact of a cell phone intervention on mediating mechanisms of smoking cessation in individuals living with HIV/AIDS. *Nicotine Tob Res* 2006;8:S103–S108.
90. Lloyd-Richardson EE, Stanton CA, Papandonatos GD, Shadel WG, Stein M, Tashima K, Flanigan T, Morrow K, Neighbors C, Niaura R. Motivation and patch treatment for HIV+ smokers: a randomized controlled trial. *Addiction* 2009;104:1891–1900.
91. Pedrol-Clotet E, Deig-Comerma E, Ribell-Bachs M, Vidal-Castell I, Garcia-Rodriguez P, Soler A. Bupropion use for smoking cessation in HIV-infected patients receiving antiretroviral therapy. *Enferm Infecc Microbiol Clin* 2006;24:509–511.

92. Tornero C, Mafe C. Varenicline and antiretroviral therapy in patients with HIV. *J Acquir Immune Defic Syndr* 2009;52:656.
93. Kharasch ED, Mitchell D, Coles R, Blanco R. Rapid clinical induction of hepatic cytochrome p4502b6 activity by ritonavir. *Antimicrob Agents Chemother* 2008;52:1663–1669.
94. Hogeland GW, Swindells S, McNabb JC, Kashuba AD, Yee GC, Lindley CM. Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2007;81:69–75.
95. Hesse LM, von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit cyp2b6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001;29:100–102.
96. Park-Wyllie LY, Antoniou T. Concurrent use of bupropion with cyp2b6 inhibitors, nelfinavir, ritonavir and efavirenz: a case series. *AIDS* 2003;17:638–640.
97. Vidrine DJ, Arduino RC, Gritz ER. The effects of smoking abstinence on symptom burden and quality of life among persons living with HIV/aids. *AIDS Patient Care STDS* 2007;21: 659–666.
98. Lima EM, Gualandro DM, Yu PC, Giuliano Ide C, Marques AC, Calderaro D, Caramelli B. Cardiovascular prevention in HIV patients: results from a successful intervention program. *Atherosclerosis* 2009;204:229–232.