Published in final edited form as:

AIDS Educ Prev. 2009 June ; 21(3 Suppl): 28–39. doi:10.1521/aeap.2009.21.3_suppl.28.

Effect of Cigarette Smoking on HIV Acquisition, Progression, and Mortality

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Abstract

Cigarette smoking is more common among those with HIV compared to the general population. However, it remains unclear whether smoking alters the natural history of HIV infection or if unique health consequences related to smoking occur in the context of HIV. In this article, we review the literature on the effect of smoking on acquisition of HIV, progression of HIV to AIDS, and mortality. While there was significant heterogeneity in the study populations evaluated, we found little evidence that cigarette smoking increases the risk for acquiring HIV. Although two studies observed that smoking was associated with more rapid CD4 cell count declines, most data suggest that smoking does not accelerate progression to clinical AIDS. The most consistent finding was an increased risk for respiratory infections in smokers. While no effect of smoking was seen with AIDS-related mortality, findings related to all-cause mortality were inconclusive. Due to an increase in chronic non-AIDS outcomes in the post-HAART era, smoking is likely an increasingly important contributor to morbidity and mortality in HIV-infected populations. Future investigation of the biological and clinical effects of smoking, and of preventive approaches to reduce the heavy burden, in individuals with HIV is warranted.

Keywords

HIV infection; smoking; tobacco; HAART

Introduction

Individuals who are HIV positive are known to have a higher smoking prevalence than the general population (Saves, et al., 2003; Stall, Greenwood, Acree, Paul, & Coates, 1999). In the United States, over half of persons infected with HIV are smokers compared to 20% of the general population (Thompson, Nanny, & Levine, 1996; CDC, 2005). However, available data do not indicate unusually intense tobacco use (e.g., increased quantity of cigarettes smoked) among HIV-infected smokers (Burkhalter, Springer, Chhabra, Ostroff, & Rapkin, 2005; Gritz, Vidrine, Lazev, Amick, & Arduino, 2004), but these data are limited and provide insufficiently detailed comparisons of smoking behaviors by HIV status. Smoking may confer unique health risks in the context of HIV, by enhancing susceptibility to HIV or other infections, by altering the course of HIV infection itself, or by modifying the risk of smoking-related chronic diseases (Webb, Venable, Carey, & Blair, 2007). To begin to address these issues, we performed a review of the literature to examine what evidence exists for the effect of cigarette smoking on three important HIV-related clinical outcomes. Namely, does smoking increase the risk for acquisition of HIV infection, for progression of HIV to AIDS, or for mortality among HIV-

infected populations. Rather than performing a quantitative meta-analysis, our approach was to systematically identify and summarize the important findings within these areas.

Cigarette Smoking as a Risk Factor for HIV Acquisition

Three prospective cohort studies examined the relationship between cigarette smoking and acquisition of HIV infection (Table 1). Each of these studies intended to determine whether cigarette smoking was associated with an increased incidence of HIV. Two of these studies, Burns et al. (1991) and Penkower et al. (1991), assessed the relationship between smoking and HIV seroconversion among men who have sex with men (MSM). In unpublished analyses from the AIDS Linked to Intravenous Experiences (ALIVE) cohort (Mehta et al., 2006), smoking was evaluated as a risk factor for incident HIV infection among intravenous drug users (personal communication, S.H. Mehta). Of these three studies, only one study, Burns, et al. (1991), identified a significant association between cigarette smoking and HIV acquisition.

When comparing men who were HIV seronegative to those who seroconverted, Burns et al. (1991) found that current cigarette smokers accounted for 60 % of HIV seroconverters to only 39 % of HIV seronegatives ($p=0.03$). However, this analysis did not take into account sexual behavior as a risk factor for acquiring HIV. Among men identified as having a high frequency of receptive anal intercourse, 65 % of current smokers seroconverted compared to 42 % of nonsmokers ($p=0.09$), indicating that smoking may be associated with high-risk sexual behavior. In turn, high-risk sexual behavior was strongly associated with HIV seroconversion in this study ($p<0.01$).

Penkower et al. (1991) examined the relationship of cigarette smoking and HIV seroconversion among homosexual men engaging in high-risk sexual behavior in the Multi-Center AIDS Cohort Study (MACS). With an odds ratio of 1.22 (95 % CI 0.99 to 1.55), this study suggested but failed to significantly associate smoking with HIV acquisition in a comparison of current smokers who seroconverted to those that remained HIV-seronegative. Nelson et al. (2002) and Mehta et al. (2006) identified several independent risk factors for HIV seroconversion within the ALIVE study. Controlling for these risk factors, no association between cigarette smoking and HIV acquisition was detected (Mehta SH, Personal Communication 2008).

Cigarette Smoking as a Risk Factor for HIV Disease Progression

Sixteen prospective cohort or case-control studies evaluated the relationship between cigarette smoking and HIV progression with a variety of endpoints, including CD4 cell counts, time to AIDS, incidence of AIDS, and incidence of opportunistic infections and HIV-related clinical events (Table 2). Although sometimes not the primary objective, each of these studies examined whether cigarette smoking was associated with an increased progression of HIV disease among infected individuals.

Eight studies used CD4 cell counts as the outcome of interest with the objective of determining if cigarette smoking influences CD4 cell count declines. Of these eight studies, only two studies, Royce & Winkelstein (1990) and Feldman et al. (2006), identified an association between cigarette smoking and CD4 cell count decline among HIV-infected individuals. Previous studies have concluded that in the absence of HIV infection, cigarette smoking leads to an increase in CD4 cell counts; however this relationship may change when comparing light to moderate to heavy smoking (Arcavi & Benowitz, 2004). Royce & Winkelstein (1990) found that the positive dose-response relationship between packs smoked per day and CD4 counts observed for HIV-uninfected smokers was substantially decreased in HIV-infected smokers ($p<0.01$). This study further suggested in a subgroup analysis that CD4 cell counts of cigarette smokers decreased faster than those for non-smokers. In the Women's Interagency HIV Study (WIHS), Feldman et al. (2006) also confirmed that cigarette smoking leads to increased CD4

counts in HIV-uninfected individuals. Following HIV seroconversion, this study found that the initially higher CD4 cell counts in smokers decreased to below the mean CD4 cell count for nonsmokers over a five-year period, after adjusting for age and race ($p=0.01$). Among MSM seroconverters, Park et al. (1992) demonstrated that the somewhat higher CD4 cell counts observed prior to seroconversion among smokers was probably related primarily to an increase in the total white blood cell count and further, that this effect disappeared within three years following seroconversion. In addition to Park et al. (1992), the remaining five studies, Burns et al. (1991), Craib et al. (1992), Conley et al. (1996), Miguez-Burbano et al. (2003), and Webber et al. (1999), all found no relation between cigarette smoking and CD4 cell count decline among HIV-infected individuals.

Ten studies assessed whether cigarette smoking was an independent risk factor for AIDS incidence or increased time to AIDS and only 2 studies identified a significant relationship (Table 2). Feldman et al. (2006) found that HIV-positive cigarette smokers had a higher risk of developing AIDS when compared to nonsmokers ($HR=1.36$, 95% CI 1.07-1.72). In a study conducted by Nieman et al. (1993) in the pre-HAART era, the median time to AIDS among current HIV-infected cigarette smokers was 8.17 months compared to 14.50 months for nonsmokers ($p=0.003$). Both of these studies periodically evaluated smoking habits and change of smoking status among individuals. The remaining eight studies, Craib et al. (1992), Coates et al. (1990), Conley et al. (1996), Eskild & Petersen (1994), Galai et al. (1997), MRC Study Group for the Collaboration Study of HIV-infection in Women (1999), and Webber et al. (1999) all concluded that cigarette smoking did not increase the risk of incident AIDS or the time to AIDS diagnosis.

Eight studies assessed whether cigarette smoking was an independent risk factor for opportunistic infections or HIV-related clinical events. Six of these studies investigated *Pneumocystis carinii* pneumonia (PCP) outcomes in HIV-infected individuals. Miguez-Burbano et al. (2003) found that cigarette smoking was associated with an increased risk for PCP ($RR=1.56$; $p=0.02$). In a later publication from these authors (Miguez-Burbano et al., 2005), they again reported that cigarette smoking was associated with an increased risk of hospitalization due to PCP ($OR=2.55$, 95% CI 1.27-4.77; $p=0.004$). Similarly, Nieman et al. (1993) identified cigarette smoking as an independent risk factor for incident PCP infection ($p=0.002$). In contrast, Conley et al. (1996), Craib et al. (1992), and Galai et al. (1997) found no association between cigarette smoking and PCP.

Two studies evaluated the relationship between smoking and tuberculosis (TB) infection among HIV-positive individuals. Miguez-Burbano et al. (2003) found that long-term cigarette smokers (20 years or greater) had a three-fold increased risk of incident TB infection when compared to smokers of less than 20 years ($p=0.04$). However, in a second study, Miguez-Burbano et al. (2005) did not find a significant association between cigarette smoking and hospitalization due to TB among HIV-infected individuals.

Four studies assessed whether cigarette smoking was an independent risk factor for bacterial pneumonia. Burns et al. (1996) ($HR=1.57$, 95% CI 1.14-2.15), Conley et al. (1996) ($RR=2.62$, 95% CI 1.30-5.27), and Crothers et al. (2005) ($HR=2.84$, 95% CI 1.48-5.45), identified a significant relationship between cigarette smoking and bacterial pneumonia among HIV-positive individuals. Also, Miguez-Burbano et al. (2005) found that smokers had an increased risk of hospitalization due to bacterial pneumonia compared to nonsmokers ($OR=1.80$, 95% CI 1.16-2.79; $p=0.005$).

Cigarette Smoking as a Risk Factor for Mortality among HIV-Infected Persons

Five studies assessed the relationship between cigarette smoking and mortality (Table 3). For most of these studies, the primary analysis was to determine if cigarette smoking leads to

increased all-cause mortality in HIV-infected patients; only one study specifically evaluated AIDS-related mortality. Of the five studies, two identified smoking as an independent risk factor for death. Crothers et al. (2005) and Feldman et al. (2006) found that HIV-positive cigarette smokers had a higher risk of all-cause mortality when compared with never smokers (HR=1.99, 95% CI 1.03-3.86 and HR=1.53, 95% CI 1.08-2.19, respectively), after adjusting for known risk factors such as age, race/ethnicity, baseline CD4 cell count, HIV RNA level, illegal drug and alcohol use, previous AIDS, and previous antiretroviral use. When looking specifically at death due to AIDS, Feldman et al. (2006) failed to identify cigarette smoking as a risk factor. The three other studies, Burns et al. (1996), Galai et al. (1997), and the MRC Study Group for the Collaboration Study of HIV-infection in Women (1999), found no significant association between cigarette smoking and all-cause mortality.

Importantly, both studies demonstrating a significant effect of smoking on mortality included follow-up almost entirely during the time period in which highly active anti-retroviral therapy (HAART) was the standard of care (Crothers et al., 2005; Feldman et al., 2006). This is in direct contrast to the other three studies, which were conducted earlier prior to the widespread availability of HAART. HAART has dramatically altered the HIV/AIDS epidemic, producing virologic suppression and immunologic improvement accompanied by lower rates of HIV-related morbidity and mortality (Sterne, Hernan, & Ledergerber, 2005). With prolonged duration of disease, growing numbers of infected persons in the U.S. are surviving into older ages (Mack & Ory, 2003) and a changing spectrum of diseases is being observed. Increases in the absolute numbers and proportional mortality from non-AIDS-defining conditions, including cardiovascular, respiratory, liver and malignant diseases have been documented in the post-HAART compared to the pre-HAART era, and these trends are expected to continue (Lewden et al., 2005; d'Arminio et al., 2005; Braithwaite et al., 2005).

In light of the increase in non-AIDS mortality in the HAART era, the association seen between cigarette smoking and mortality in the two studies described above may be due to the fact that as HIV-infected persons live longer, tobacco-related diseases (e.g., cardiovascular or chronic lung disease, lung cancer) will be increasingly observed as a cause of death in this population. However, in addition to the HAART effect of simply prolonging survival long enough to observe smoking-related disease, preliminary data raise concerns that smoking may more directly influence HAART responses. Miguez-Burbano et al. (2003) found that smoking was associated with a 40% reduction in immunologic and virologic responses to HAART. Although no biological explanation for reduced HAART responses has been identified, several studies associated cigarette smoking with reduced adherence to HAART. Shuter & Bernstein (2008) found that current cigarette smokers had a lower mean adherence rate to HAART compared to both former and never smokers ($p < 0.001$). In combined data from the MACS and WIHS cohort studies of MSM and women respectively, Lazo et al., (2007) found that cigarette smoking in the past six months was associated with increased self-report of non-adherence to HAART among HIV-infected women (OR=1.19, 95% CI 1.00-1.42) but not among the men. Drawing from this same cohort of women, Feldman et al. (2006) again reported that adherence to HAART was substantially lower among smokers compared to nonsmokers ($p = 0.001$).

Summary of Cigarette Smoking Effects on HIV Infection

We found little evidence that cigarette smoking increases risk for HIV acquisition, nor does there seem to be an obvious biological mechanism. Instead, any association between cigarette smoking and HIV acquisition most likely represents increased smoking among persons with other risk behaviors (e.g., high risk sexual or drug use behavior). There are conflicting data on whether cigarette smoking is associated with HIV progression. Despite higher baseline CD4 cell counts observed among cigarette smokers compared to nonsmokers, some evidence suggests that CD4 cell counts of smokers may decline at a faster rate than that of nonsmokers.

However, most studies have not demonstrated progression to clinical AIDS to be higher among smokers. The variation in populations explored by these studies (e.g., studies of only women, MSM, or injection drug users) may explain differences in results.

The mortality data regarding effects of cigarette smoking is also inconclusive; this may be explained by the lack of effect of cigarette smoking when the primary cause of mortality is AIDS. As HAART has increasingly become available, chronic diseases are notably increasingly as causes of morbidity and mortality among HIV-infected persons. Tobacco-related diseases subsequently would be also expected to increase. One of the most consistent findings in our review was that cigarette smoking was associated with increased respiratory infections, particularly PCP and bacterial pneumonia. Recent data from our and other groups suggests that non-infectious lung disease also is increased in HIV-infected persons (Kirk et al., 2007; Crothers et al, 2005). Similarly, our review suggests that cigarette smoking effects on all-cause mortality have only recently been observed in studies conducted in the HAART era. Interestingly, due to cigarette smoking influences on HAART adherence and responses, smoking actually appears more likely to impact HIV-related morbidity and mortality as effective HIV treatment becomes more widespread.

Directions for Future Research

As a first step, more data are needed regarding the prevalence, patterns, and intensity of cigarette smoking within HIV-infected and at risk populations. Longitudinal studies will be important to identify trajectories of smoking over time and in particular, what changes occur in smoking behavior in relation to HIV seroconversion, HAART initiation, or changes in use of illicit substances. The association of smoking with diminished HAART adherence needs to be replicated in other populations; both behavioral and biological mechanisms underlying this observation need to be explored. As survival increases among those infected with HIV, it will be important to determine the susceptibility of HIV-infected persons to chronic diseases associated with smoking.

In order to fully elucidate the potential effects and interactions between smoking and HIV infection, rigorous attention to the design, analysis and interpretation of epidemiological and clinical studies will be required. Repeatedly in our review, significant concerns regarding confounding were apparent in evaluating associations of smoking with HIV outcomes. Because smoking may be highly correlated with other high risk sexual or drug use behavior, future studies should attempt to include epidemiologically-appropriate comparison groups with similar risk profiles. For example, an optimal approach would be to evaluate smoking behavior and the subsequent development of tobacco-related diseases in both HIV-infected and uninfected persons within specific risk groups, such as MSM or IDUs.

A possible explanation suggested for the increased risk of lung disease in HIV-infected persons remains that smoking habits may differ in important ways between HIV-infected and uninfected individuals. For instance, HIV-infected persons may have started smoking cigarettes earlier in life, smoked more cigarettes per day, or inhaled more deeply from each cigarette smoked than HIV-uninfected persons. To address these issues, research studies will need to collect much more detailed smoking behavior information and tobacco-related biomarkers may also play an important role.

HIV-infected smokers appear to have an increased risk of chronic obstructive pulmonary disease (COPD) (Sahebji, 1992; Diaz, et al., 2000; Diaz, Clanton, & Pacht, 1992). A recent study that demonstrated an increased number of HIV-infected cells in emphysematous areas compared to the histologically normal areas of lung (Yearsley, Diaz, Knoell, & Nuovo, 2005) suggests that HIV infection could play a direct role in causing emphysema. Studies

investigating the mechanism by which smoking and HIV infection may interact to accelerate lung disease will require significant research investments. Recently, the National Heart, Lung, and Blood Institute has funded several longitudinal studies of pulmonary disease related to HIV infection which are working together to address many of these issues (<http://www.lunghiv.com>).

Beyond understanding the risk for disease or the underlying pathogenesis, it is vitally important to increase preventive measures and develop smoking cessation interventions within HIV-infected populations. To improve cessation rates among HIV positive individuals, it will be important to identify barriers to successful smoking cessation, both on the part of HIV positive patients and their healthcare providers. Specific issues that warrant consideration in tailoring smoking cessation to those with HIV may range from personal characteristics, such as active or prior injection drug use, to more general issues, such as interactions of smoking cessation pharmacotherapy with HAART. Future research targeting smoking cessation interventions for HIV-positive individuals will be necessary to decrease the high prevalence of smoking in this population.

Acknowledgments

Support: This work was supported by NIH grants R01HL090483, R01DA04334 and R01DA12568.

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Table 1

Cigarette Smoking as a Risk Factor for HIV Acquisition

Author, Year	Study Design	Population Under Study	Outcome	Results
Burns et al. (1991)	Prospective Cohort Study	202 MSM from Washington, DC and New York City, NY	HIV seroconversion	Higher % of seroconversion among cigarette smokers compared to nonsmokers ($p=0.03$)
Penkower et al. (1991)	Prospective Cohort Study	1,045 MSM from the Multicenter AIDS Cohort Study (MACS); Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; Pittsburgh, PA	HIV seroconversion	Not significant
Mehta SH (Personal Communication, 2008)	Prospective Cohort Study	1,846 intravenous drug users (78.4% male) from AIDS Linked to the Intravenous Experience (ALIVE) in Baltimore, MD	HIV seroconversion	Not significant

Table 2

Cigarette Smoking as a Risk Factor for HIV Progression

Author, Year	Study Design	Population Under Study	Outcome	Results
Coates et al. (1990)	Prospective Cohort Study	249 HIV-positive and negative MSM from Toronto, Ontario, Canada	Incident AIDS	Not significant
Royce & Winkelsstein (1990)	Prospective Cohort Study	989 HIV-positive and negative men from San Francisco, CA	CD4 cell decline	Significant decline ($p<0.01$)
Burns et al. (1991)	Prospective Cohort Study	202 MSM from Washington, DC and New York City, NY	CD4 cell decline Incident AIDS	Not significant; Not significant
Craib et al. (1992)	Prospective Cohort Study	299 HIV-positive and negative MSM from Vancouver, Canada	CD4 cell decline; Incident AIDS; Incident PCP infection	Not significant; Not significant; Not significant
Park et al. (1992)	Prospective Cohort Study	307 HIV-1 seroconverters MSM from the Multicenter AIDS Cohort Study (MACS); Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; Pittsburgh, PA	CD4 cell decline;	Not significant
Nieman et al. (1993)	Case Series/Prospective Cohort Study	84 HIV-infected men (97.6%) and women (2%) from St. Mary's Hospital in London, UK; 96.4% were MSM	Median Time to AIDS; Incident PCP infection	Shorter for smokers ($p=0.003$); Increased in smokers ($p=0.002$)
Eskild & Petersen (1994)	Prospective Cohort Study	80 HIV-infected MSM from Norway	Incident AIDS	Not significant
Burns et al. (1996)	Prospective Cohort Study	3,221 HIV-1 positive men (54.3%) and women (45.7%) from 17 community-based clinical centers in 13 U.S. cities	All opportunistic diseases; Bacterial pneumonia	Not significant; HR=1.57, 95% CI 1.14-2.15;
Conley et al. (1996)	Prospective and Retrospective Cohort Study	232 HIV-infected MSM from San Francisco, Denver, and Chicago	CD4 cell decline; Incident AIDS; Incident PCP infection; Bacterial pneumonia	Not significant; Not significant; Not significant; RR=2.62, 95% CI 1.30-5.27
Galai et al. (1997)	Prospective Cohort Study	2499 HIV-infected MSM from the Multicenter AIDS Cohort Study (MACS); Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; Pittsburgh, PA	Incident AIDS; Incident PCP infection	Not significant; Not significant
MRC Study Group (1999)	Prospective Cohort Study	505 HIV-infected women in Great Britain and Ireland	AIDS defining illness; Incident AIDS	Not significant; Not significant
Webber et al. (1999)	Prospective Cohort Study	524 HIV-infected men (57.6%) and women (42.4%) opiate-addicted drug users from New York, NY	CD4 cell decline; Time to AIDS; AIDS defining illness	Not significant; Not significant; Not significant
Miguez-Burbano et al. (2003)	Case-Control Study	54 HIV-infected men (59.3%) and women (40.7%)	Incident PCP infection; Incident TB infection	RR=1.56, $p=0.02$ Increased risk for long-term smokers ($n=0.04$)
Crothers et al. (2005)	Prospective Cohort Study	867 HIV-positive veterans from 3 Veterans Affairs (VA) medical centers	Bacterial pneumonia	OR=2.84, 95% CI 1.48-5.45
Miguez-Burbano et al. (2005)	Case-Control Study	521 HIV-infected men (58.6%) and women (41.4%) admitted to University of Miami/Jackson Memorial Hospital from Miami, FL	Hospitalization from Incident PCP infection, Bacterial pneumonia, Incident TB infection	OR=2.55, 95% CI 1.27-4.77 OR=1.80, 95% CI 1.16-2.79 Not significant
Feldman et al. (2006)	Prospective Cohort Study	924 HIV-infected women from the Women's Interagency HIV Study (WIHS) from New York, NY; Washington, DC; San Francisco, CA; Los Angeles, CA; Chicago, IL	CD4 cell decline; Incidence of AIDS-defining conditions	Significant decline ($p=0.01$) Significant ($p<0.01$)

Table 3
Cigarette Smoking as a Risk Factor for Mortality among HIV-infected Persons

Author, Year	Study Design	Population Under Study	Outcome	Results
Burns et al. (1996)	Prospective Cohort	3,221 HIV-1 positive men (54.3%) and women (45.7%) from 17 community-based clinical centers in 13 U.S. cities	All-cause mortality	Not significant
Galai et al. (1997)	Prospective Cohort	2,499 HIV-infected MSM from the Multicenter AIDS Cohort Study (MACS); Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; Pittsburgh, PA	All-cause mortality	Not significant
MRC Study Group (1999)	Prospective Cohort	505 HIV-infected women in Great Britain and Ireland	All-cause mortality	Not significant
Crothers et al. (2005)	Prospective Cohort	867 HIV-positive veterans from 3 Veterans Affairs (VA) medical centers	All-cause mortality	HR=1.99, 95% CI 1.03-3.86
Feldman et al. (2006)	Prospective Cohort	924 HIV-infected women from the Women's Interagency HIV Study (WIHS) from New York, NY; Brooklyn, NY; Washington, DC; San Francisco, CA; Los Angeles, CA; Chicago, IL	All-cause mortality AIDS-related mortality	HR=1.53, 95% CI 1.08-2.19 Not significant