

Chapter 15

Alcohol and HIV: Experimental and Clinical Evidence of Combined Impact on the Lung

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Abstract Despite antiretroviral therapy, lung disease is a leading cause of death in individuals infected with human immunodeficiency virus type 1 (HIV). Individuals infected with HIV are susceptible to serious bacterial and viral infections, such as pneumococcus and influenza, which are particularly problematic for lung health, resulting in lung injury. Additionally, HIV-infected individuals are susceptible to a number of pulmonary diseases for unknown reasons. Alcohol, the most commonly abused drug in the world, continues to exact an enormous toll on morbidity and mortality in individuals living with HIV. Chronic alcohol abuse has been shown to affect lung immunity, resulting in significant lung injury. There is a paucity of literature on the additive effects of HIV and alcohol, two diseases of immune senescence, in the lung. This chapter begins by discussing the latest literature evaluating the epidemiology of HIV, alcohol use, and lung health focusing on two prevalent infections, tuberculosis and pneumococcal pneumonia. In parallel, we discuss the interactions of alcohol and HIV on the risk for acute lung injury and subsequent morbidity and mortality. We then discuss the pathophysiology of how these two diseases of immune dysfunction affect the lung, with a focus on the oxidative stress, alveolar macrophage host immune capacity, and immunomodulatory role of zinc in the airway. Finally, we review the latest literature on how HIV and alcohol affect other pulmonary disorders including chronic obstructive pulmonary disease, pulmonary hypertension, and lung cancer.

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Overview

HIV/AIDS is a disease that continues to be of paramount global importance. The Centers for Disease Control (CDC) estimate that approximately one million people are living with HIV in the United States and approximately 20 % are unaware that they are infected [1]. Additionally and Prevention, in the past decade the number of people living with HIV has increased considerably. Prior to the widespread use of antiretroviral therapy (ART), pulmonary diseases, especially lung infections, were among the most frequent complications in individuals with HIV and were associated with significant morbidity and mortality [2]. However, even in the era of ART, individuals living with HIV continue to suffer from pulmonary diseases including bacterial pneumonia, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension. Alcohol is the most widely used drug in the world. Chronic alcohol abuse continues to result in increased morbidity and mortality, exacting a tremendous burden on society. Chronic alcohol abuse can affect a number of organ systems including the lung resulting in increased susceptibility to infection and injury. However, there is a paucity of literature examining the compound effects of alcohol and HIV, two diseases of immune senescence, in the lung. This chapter presents epidemiology and pathophysiology of how HIV infection and alcohol use affect lung immunity and discusses other clinical syndromes that are also affected by the interactions of alcohol and HIV.

Part 1: Epidemiology of HIV, Alcohol Abuse, and Lung Health

HIV, Alcohol, and Lung Infection: Tuberculosis

Worldwide, tuberculosis remains one of the most important causes of death from an infectious disease [3]. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis has complicated the efforts at control for this disease. The HIV epidemic has led to an increase in the incidence of tuberculosis globally. At least one-third of HIV-infected persons worldwide are infected with *Mycobacterium tuberculosis*, and 8–10 % of them develop active disease annually [4]. In the United States, there has been a progressive decrease in rates of active tuberculosis and only 10 % of patients are coinfecting with HIV [5]. Coinfection results in difficult issues in diagnosis and

treatment, especially because of drug interactions and complications related to immune reconstitution [6, 7]. Numerous studies have documented the increased risk of TB disease among HIV-infected compared to non-infected persons. Among the HIV-infected population, low CD4 counts and high viral loads have been found to be further risk factors for disease, while treatment with effective ART reduces risk.

The association of alcoholism and TB has been known for decades, but only one systematic review has examined this association [8]. In the 21 studies identified, all forms of TB disease were about three times higher, and pulmonary TB was four times more frequent, in heavy drinkers (>40 g of alcohol per day) than in controls. It is likely that adverse effects of alcohol on the immune system and increased patterns of transmission because of social interactions are both important in this increase. Further, excessive alcohol use complicates (and often decreases) adherence to the TB treatment regimen [9].

Alcohol-use disorders have been related to the acquisition and progression of HIV disease as well as to the adherence and immunologic response to ART [10–14]. A systematic review and meta-analysis of African studies documented a similar association between HIV and alcohol use [15]. Lower CD4 counts have been associated with alcohol consumption, especially in patients not on ART [16]. In addition, a recent model demonstrated that alcohol is a modifiable risk factor for poor survival among individuals with HIV [17]. These effects can be attributed biologically to the alcohol itself and not simply to related factors such as malnutrition, as chronic binge alcohol consumption accelerates progression of simian immunodeficiency virus disease in a primate model [18].

The risks of bacterial pneumonia and COPD are elevated among those with HIV infection compared to uninfected individuals, even after adjustment for smoking exposure [19, 20]. Alcohol impacts both innate and adaptive immune responses leading to immunosuppression [21], so it would be likely that the association of alcohol and HIV would increase the risk of tuberculosis.

Limited clinical data are available to define the interactions of alcohol, HIV, and tuberculosis. Patients diagnosed with TB have higher alcohol intake than persons without TB [8, 22–24]. HIV-infected patients have higher alcohol consumption than non-HIV-infected patients, and patients coinfecting with TB and HIV have higher alcohol consumption than either TB- or HIV-infected patients [25–27]. A study in Botswana found that patients with MDR-TB had high rates of alcohol use and abuse. Further, among TB patients alcohol abuse was associated with a diagnosis of MDR-TB [28]. Recently, alcohol abuse was found to be an independent risk factor for poor outcomes in patients treated for MDR-TB [29].

Overall, there is convincing evidence that HIV and alcohol independently affect lung function and response to infection. These interactions appear to be complex and have yet to be sorted out completely, but it is clear that they contribute to an increased incidence of TB infection, a decreased response to therapy, and, as a consequence, an apparent increase in TB mortality.

HIV, Alcohol, and Lung Infection: Streptococcus Pneumoniae (Pneumococcus)

Community-acquired pneumonia (CAP) is a leading cause of overall death worldwide [30–34]. *Streptococcus pneumoniae* (*pneumococcus*) is associated with more severe forms of pneumonia and is one of the main organisms leading to hospitalization in all groups [35]. However, pneumococcal disease has been shown to be higher in persons with underlying medical conditions (such as HIV), with low socioeconomic status, or who engage in high-risk behaviors such as cigarette smoking, intravenous drug use, and alcohol abuse [36–40]. In fact, recurrent bacterial pneumonia has been considered an AIDS-defining illness since the expanded European definition was adopted in 1993 [41].

In the VACS-3 (Veterans Aging 3 Site Cohort Study), a large study of 881 HIV-infected veterans enrolled between 1999 and 2000, there was a significant association between obstructive lung disease and bacterial pneumonia, and these two diseases demonstrated a linear association with the level of alcohol use (OR 1.4 for bacterial pneumonia, $p < 0.001$ for level of alcohol use). In this cohort, approximately 67 % were current users and of these, 41 % drank in moderation, 23 % drank hazardingly, and 35 % carried a diagnosis of abuse or dependence. The degree of alcohol use varied by demographic and HIV-related factors, and antiviral therapy (ART) did not vary significantly by alcohol use. When considering timing of alcohol consumption, past consumption demonstrated an equivalent or a higher prevalence of disease than did current consumption, so the authors concluded that past consumers were somehow different than lifetime abstainers. Associations of medical disease with alcohol use were independent of age, CD4 cell count, viral load, intravenous drug use, smoking, and exercise. Consequently, the authors concluded that there was no evidence of a “safe” level of consumption of alcohol among those with HIV infection [20]. Using 1999 and 2000 data from Active Bacterial Core surveillance and the National Health Interview Survey, Kyaw et al. determined the rates of invasive pneumococcal disease in healthy adults and in adults with high-risk conditions and found that, compared with healthy adults, the risk of invasive pneumococcal disease was 11-fold higher for those that abused alcohol and 23–48-fold higher in adults with HIV/AIDS [42]. The risk also increased with the number of conditions present, suggesting that the combination of HIV/AIDS and alcohol had compounding effects on the risk of pneumonia [42]. Murdoch et al. showed in an observational cohort of 300 HIV-infected individuals receiving care between 1996 and 2005 that a high proportion (60 %) reported prior and/or current alcohol abuse [43]. Multivariate analyses showed that younger age, alcohol use, lack of ART use, lower CD4 counts, and higher HIV RNA were independent predictors of pneumonia. Most recently, Crothers et al. analyzed data from the VACS virtual cohort of 33,420 HIV-infected veterans and 66,840 age-, sex-, race-, and site-matched uninfected control subjects to determine the incidence of pulmonary diseases in HIV-infected persons compared with non-HIV persons. They found that, even in the era of ART, HIV infection increased the risk of bacterial pneumonia ~7-fold (7.5 % vs.

1.1 %, $p < 0.001$) and alcohol disorders were significantly more common among HIV-infected individuals compared to the control subjects ($p < 0.001$) [44].

These studies confirm that although ART has substantially decreased opportunistic infections associated with HIV infection, pneumonias from routine pathogens such as *pneumococcus* continue to be prevalent in these susceptible individuals, and alcohol abuse may have a compounding effect. Additionally, bacterial pneumonia can result in worse outcomes in HIV-infected individuals who abuse alcohol. Large multicenter observational studies have shown that HIV-infected individuals hospitalized with pneumococcal pneumonia have significantly higher 14-day mortality, with a trend for the highest mortality in those with lower CD4 counts, compared to uninfected individuals after controlling for age and severity of illness [45]. Additionally, HIV-infected individuals with cirrhosis and a history of heavy alcohol abuse have increased mortality and increased hospitalizations from community-acquired pneumonia compared to HIV-infected individuals without cirrhosis. In this setting, excessive alcohol intake and hepatitis C coinfection are the most important causes of chronic liver disease in persons living with HIV [46]. These studies suggest that alcohol-use disorders are common in HIV-infected individuals and that the two diseases affect lung function and immunity, resulting in varied responses to infection and therapy.

HIV, Alcohol, and Lung Injury

In the last 10 years, evidence has shown that alcohol abuse significantly increases the risk of a serious life-threatening illness known as acute respiratory distress syndrome (ARDS). Characterized by alveolar cell barrier dysfunction and inflammation, ARDS can cause profound derangements in gas exchange with subsequent severe hypoxemia, respiratory failure, and death. Our group at Emory University first identified an independent association between alcohol abuse and ARDS [47]. Further preclinical studies have confirmed that chronic alcohol ingestion renders the lung susceptible to injury [48, 49]. Critical care outcomes have improved among HIV-infected persons due to advances in HIV therapy. ART has decreased morbidity and mortality [50–52], and overall ICU and hospital mortality associated with critical illness in HIV-infected individuals has decreased [53–57]. However, given the high prevalence of alcohol-use disorders in this population and the likelihood that these individuals will not adhere to ART and other HIV therapies, there is an increased likelihood of worsened outcomes in HIV-infected persons who abuse alcohol. Palepu et al. prospectively analyzed a database of 7,015 index ICU admissions at two teaching hospitals in Canada, of which 4.4 % were HIV infected and 56 % of these patients had a history of drug and alcohol dependence. In contrast, only 7.4 % of the HIV-negative patients had a history of drug and alcohol dependence. Using multivariate regression, the authors found that a history of alcohol dependence, regardless of HIV status, was not associated with hospital mortality after adjusting for age, sex, APACHE II scores (an index of acute and chronic health stresses), and acute overdose diagnosis. In contrast, HIV infection was

strongly associated with increased hospital mortality [58]. Further, other studies have shown that HIV infection independently increased mortality in patients with acute lung injury [59, 60].

HIV, Alcohol, and Outcomes

Alcohol use is well known to have comorbid effects on multiple medical diseases. Since many people living with HIV drink alcohol, it is likely that many comorbid diseases would be more common or worse in patients with both conditions. The Veterans Aging Cohort Study (VACS) has focused on the importance of alcohol use among persons with HIV infection. An early study of 881 HIV-infected subjects with strict definitions of alcohol use documented that hepatitis C, hypertension, diabetes, COPD, candidiasis, and bacterial pneumonia were all associated with alcohol use, and several of these diseases demonstrated a linear association with the degree of alcohol ingestion [20]. In an echocardiographic study of 196 asymptomatic HIV-infected individuals, alcohol use was found to be an independent risk factor of left ventricular diastolic function [61]. In a VACS study examining the incidence and severity of COPD in HIV-infected subjects, alcohol abuse as defined by ICD-9 codes, had an independent elevated odds ratio (1.46), although this did not reach statistical significance.

The rates and causes of mortality among HIV-infected individuals have evolved over the years. Although there are controversies about defining causes of death in HIV-infected persons [62], overall mortality rates have decreased markedly since 1996 with the advent of ART [52], and deaths specifically due to AIDS-defining illnesses and tumors have also declined [63, 64].

The precise influence of alcohol use on these trends in comorbidities and mortality is difficult to quantify. Relatively few studies have examined the independent effect of alcohol use on mortality, but it is likely that excessive alcohol use would affect deaths from liver disease, certain malignancies, pulmonary disease, and violence. An analysis of deaths in the CDC HIV Outpatient Study (HOPS) found a univariate hazard ratio of 1.20 (not statistically significant) for a history of all substance abuse, including alcohol [65]. An early study from VACS found that current or former alcohol use was not associated with increased mortality [66]. In contrast, excess mortality (HR 1.65) was described among HIV-infected patients diagnosed with substance abuse disorders, including alcohol dependence/abuse only, in a large study of deaths in the Kaiser Permanente Northern California health plan [67]. Consistent with those observations, an analysis of deaths in HIV-infected persons in France in 2005 found that alcohol consumption >50 g/day was independently associated with mortality [68].

Several studies from the aforementioned VACS have evaluated the “VACS Index” as a predictor of mortality. The original validation of the index included alcohol use, but this variable did not contribute to discriminatory value. This index now uses HIV biomarkers (CD4, HIV viral load, and AIDS opportunistic infections) and

non-HIV biomarkers (hemoglobin, transaminases, platelets, creatinine, and hepatitis C serology). It is likely that alcohol use is nevertheless a factor, especially in the non-HIV biomarkers, but as currently applied alcohol use does not independently predict mortality in this index [69].

A different approach to assessing causes of premature death is the calculation of expected years of life lost. This was assessed in San Francisco using death registry data and population estimates in 2003–2004. Using this method, the leading causes of premature death among men were HIV/AIDS and alcohol-use disorders [70].

Part 2: Pathophysiology of How HIV and Alcohol Affect Lung Immunity

Oxidative Stress

Oxidative stress refers to a disruption in the oxidant/antioxidant balance and is an important component of cell injury in both HIV- and alcohol-related disorders. Oxidative stress can be generated from a number of different mechanisms including relative oxidation of extracellular thiol disulfide pairs such as glutathione/glutathione disulfide (GSH/GSSG) and cysteine/cystine (Cys/CySS) and the generation of reactive oxygen species by enzymes such as NADPH oxidase [71, 72]. Chronic HIV infection alone has been known to cause significant oxidative stress systemically, both in preclinical [73–75] and clinical studies [76–78]. GSH levels were found to be decreased greater than 90 % in HIV transgenic rats compared to wild-type rats, and the GSSG/GSH ratios were increased threefold [75]. In response to endotoxemia induced by intraperitoneal lipopolysaccharide instillation, HIV-infected animals also have decreased GSH, increased nitric oxide metabolites, and increased superoxide anion production [73]. Clinically, plasma cysteine levels were significantly lower in HIV-infected subjects compared to control subjects [78], and several studies have shown that HIV-infected individuals have disturbances in GSH redox balance [79–81]. GSH deficiency has even been associated with impaired survival in HIV-infected subjects [82]. Chronic alcohol consumption is known to cause deleterious effects on host defense and immune responses. Alcohol toxicity has also been associated with oxidative stress and free radical-mediated injury [83, 84] and lipid peroxidation [85]. Additionally, alcoholics have also been shown to have considerably lower levels of other antioxidants, including vitamin E and selenium [86].

The compound effects of HIV infection and alcohol use with respect to oxidant/antioxidant balance have been noted in some studies. Bautista et al. demonstrated in a simian model of simian immunodeficiency virus (SIV) and alcohol intoxication enhanced reactive oxygen species formation by Kupffer cells and endothelial cells [87]. The liver is a major organ for clearance of microbial particles because of the preponderance of tissue Kupffer cells or macrophages. During HIV infection or prolonged alcohol use, Kupffer cells can produce a wide array of inflammatory

substances while also serving as scavenger cells. Alcohol can enhance the body's susceptibility to retrovirus infection, thus increasing the progression to AIDS [88]. Alcohol-induced alterations in signal transduction may also lead to host immune dysregulation. Helper T (Th) cells produce a number of cytokines that modulate the immune system. Retrovirus infection has been known to cause abnormal cytokine production, such as increases in IL-4 and IL-5, which results in a switch from a Th1 to a Th2 response. These changes have resulted in a progression to AIDS, defined by a decline in T-cell production [89]. In a murine model of AIDS, Wang et al. found that elevated levels of Th2 cytokines were further increased by alcohol consumption [90]. Additionally, release of IL-2, normally suppressed in murine AIDS, was further suppressed with alcohol [91]. These results suggest that chronic alcohol consumption could exacerbate the Th1/Th2 imbalance seen in AIDS. The role of antioxidant defense mechanisms to protect against oxidative stress is well characterized in the liver, and the effects of alcohol in altering oxidant/antioxidant systems in the liver are also well known. Although the exact effects of HIV on this system are unknown, there are several antioxidant defense systems that could be altered by both alcohol and HIV, including superoxide dismutase, catalase, and glutathione peroxidase. Chen et al. investigated the effects of chronic alcohol ingestion on antioxidant defenses in mice infected with retrovirus, which causes an AIDS-like disease [92]. They found that alcohol and murine AIDS alone caused specific effects on antioxidant mechanisms, but the combination led to more severe effects with respect to liver GSH levels and superoxide dismutase. The mechanism of this observed synergistic effect of alcohol and HIV infection is unclear at this time. It is possible that the virus leads to higher alcohol concentrations, as was seen in a previous animal study [92], and thereby potentiates alcohol toxicity or that HIV inhibits pathways of alcohol metabolism.

Specifically with respect to the lung, HIV infection and chronic alcohol abuse have been individually associated with oxidative stress. Our research group at Emory University has been instrumental in many studies examining the effects of alcohol abuse on lung immune function [48, 93–95]. Specifically, we have shown that chronic alcohol ingestion causes oxidative stress as reflected by GSH deficiency and epithelial barrier dysfunction in both preclinical and clinical studies. With respect to HIV infection, our group identified that chronic HIV transgene expression in animal models causes significant alveolar oxidative stress, as reflected by a greater than 90 % decrease in GSH levels, and a threefold increase in GSSG/GSH ratios [74]. Others have also shown similar results [73, 96]. In clinical studies, the results have been somewhat less conclusive. Pacht et al. reported that the concentration of GSH in the epithelial lining fluid was similar between HIV-infected and non-infected subjects [97]; however, these same authors demonstrated in a small study of 33 HIV-infected subjects that GSH levels in the epithelial lining fluid were significantly decreased over time [98]. Others have also shown that HIV-infected subjects had a deficiency of GSH in the lung [99, 100], but these studies have involved small number of subjects. Our group determined that chronic alcohol ingestion exacerbated defects in alveolar epithelial permeability and lung water clearance in HIV-1 transgenic rats [101]. Additionally, cultured alveolar epithelial cells from alcohol-fed HIV-1 transgenic rats had increased paracellular permeability

to sucrose. This dysfunction correlated with alterations in the expression of tight junction proteins. These effects appeared to be mediated by oxidative stress as alveolar epithelial barrier function and tight junction protein localization were restored by supplementation with procysteine, a GSH precursor.

Taken together, there is now considerable experimental evidence and corresponding circumstantial clinical evidence that dietary alcohol consumption after or prior to HIV infection exacerbates the immune dysfunction already seen in AIDS. Further investigation is necessary to evaluate these effects, particularly within the lung.

The Alveolar Macrophage

As mentioned previously, chronic alcohol abuse often coexists with HIV disease, and therefore, it is important to understand the interaction of these two immunosuppressing conditions. The host immune defense system in the lung against infection and other toxins involves both innate and adaptive immune responses. Our group at Emory University has studied macrophage function in both preclinical and clinical models of HIV and chronic alcohol abuse. We found that both transgenic expression of HIV-related proteins and chronic alcohol ingestion decreased granulocyte/macrophage colony-stimulating factor (GM-CSF) receptor membrane expression, a necessary factor for macrophage function [102, 103]. Further, treatment with recombinant GM-CSF can restore functions of both alveolar macrophages and the epithelium [104]. Alveolar macrophage phagocytosis of microbial pathogens is also decreased by HIV infection [105, 106].

Few studies have evaluated the additive effects of chronic alcohol ingestion and HIV on alveolar macrophage function. Tumor necrosis factor- α (TNF- α) serves as an important mediator in the pro-inflammatory response of the host to an invading pathogen [107]. Numerous studies have shown that neutralization of TNF- α impairs clearance of a variety of microorganisms including *S. pneumoniae* and *M. tuberculosis* [108, 109]. Stoltz et al. conducted a study to determine the effects of alcohol and SIV on alveolar macrophage TNF- α production and found that alveolar macrophages from SIV-infected nonhuman primates had a depressed response and that alcohol ingestion further suppressed the TNF- α response by approximately 50 % [110]. Because of the vital role of TNF- α in generating an effective immune response, these results suggest that alcohol abuse may further impair host immune defense in HIV-infected individuals. Others have also reported decreased TNF- α production by alveolar macrophages from subjects with HIV [111] and alcohol [112]. Nelson et al. utilized the macaque SIV infection model to examine the effect of chronic alcohol feeding on SIV burden during the course of *S. pneumoniae* infection and found that the chronic alcohol-fed macaques showed a prolonged increase in SIV RNA in their lungs [113]. Additionally, alveolar macrophages from these alcohol-fed animals had greater nuclear factor kappa beta (NF-KB) activation. This study suggests that chronic alcohol abuse results in increased SIV replication within the lung and it is possible that increased NF-KB activation is part of the mechanism.

Zinc

Zinc is an essential micronutrient that plays an important role in numerous biological processes and is the focus of an earlier chapter in this book. Specifically, zinc is crucial for immune function and the catalytic functions of ~300 enzymes, and its deficiency is an important driver of oxidative stress [114]. Studies have shown that alcoholism causes systemic alterations in zinc metabolism [115, 116]. Further, there is evidence that chronic alcoholism alters zinc bioavailability in the lung and may be an important mechanism by which chronic alcohol exposure predisposes individuals to pulmonary infection and acute lung injury [117, 118]. Recent experimental evidence has demonstrated that the HIV phenotype is characterized by a similar state of zinc deficiency and immune dysfunction within the alveolar space [119, 120]. This zinc-depleted state contributes to further immune dysfunction in a host that is already compromised by HIV. While there have been no studies to determine the combined effect of alcohol and HIV, it stands to reason that zinc deficiency and its consequences would be much more severe among HIV-infected individuals who suffer from alcohol-use disorders.

Part 3: HIV and Other Pulmonary Syndromes

Chronic Obstructive Pulmonary Disease

COPD is one of the most prevalent comorbid diseases in HIV-infected individuals and is diagnosed in 12–15 % under medical care [20]. As mentioned previously, COPD is more common in HIV-infected compared to non-infected persons, and this association is linearly associated with the degree of alcohol use. COPD presents at an earlier age, with fewer pack-years of smoking, and is more prevalent in HIV-infected individuals than in uninfected individuals [19]. In addition, a high HIV viral load and a low CD4 cell count were associated with an increased prevalence of spirometry-defined obstructive lung disease in a cohort at risk for COPD and HIV infection [121]. Unfortunately, no assessment of alcohol use was reported in this study. In parallel, other studies have suggested that HIV may also be associated with an increased risk for several different manifestations of airway and obstructive lung disease, including features of emphysema [122, 123], chronic bronchitis [124], non-specific airway disease or bronchial hyper-responsiveness (such as is seen in asthma) [125, 126], and bronchiectasis [127]; nonspecific focal air trapping with decreased expiratory flow rates [128] and bronchial dilatation [129] have also been described. Taken together, the evidence suggests that HIV exacerbates the effects of smoking on the development of COPD, but at present there is no evidence that alcohol abuse adds to this risk.

Pulmonary Hypertension

Primary pulmonary hypertension was first described in HIV-infected persons in 1990 [130], and it has been found to be more common in HIV-infected compared to uninfected persons [131]. Improved hemodynamics and survival from pulmonary hypertension have been described in patients on ART [132]. In a cross-sectional study of 116 HIV-infected outpatients, echocardiographic manifestations of pulmonary hypertension were common and associated with respiratory symptoms, more advanced HIV disease, airway obstruction, abnormal diffusion capacity, and systemic and pulmonary inflammation [133].

Lung Cancer

Compared with the general population, lung cancer risk was found to be elevated in a cohort of almost 400,000 persons with HIV from 11 US regions [134]. This increased risk was found to be independent of smoking [135]. In a large VA study comparing HIV-infected to uninfected veterans, HIV infection was found to be an independent risk factor for lung cancer after controlling for potential confounders including smoking [136]. In this study, alcohol abuse, defined by ICD9 codes, was not independently associated with lung cancer. Outcomes for patients with lung cancer were initially found to be poor and related to low CD4 counts [137]. In the large Swiss cohort study, lung cancer was not clearly associated with immunodeficiency but was attributable mainly to heavy smoking [138]. A recent report found no significant difference in clinical outcome between patients with HIV and uninfected controls with non-small-cell lung cancer, including those with curative surgical resection in early-stage disease [139]. These data suggested that HIV status should not affect therapeutic decision making.

Summary

Alcohol abuse is a common problem among individuals living with HIV, and there is considerable experimental and clinical evidence showing that chronic alcohol use accelerates HIV progression and increases the risk of opportunistic and non-opportunistic infections. Alcohol abuse also decreases adherence to medical regimens including the consistent use of ART, which only further exacerbates the HIV infection. Alcohol abuse and HIV each imposes oxidative stress and zinc deficiency within the lung and together cause severe lung epithelial and macrophage dysfunction. Therefore, it is critically important that alcohol-use disorders be identified and treated whenever possible in the care of an individual living with HIV.

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