Chapter 23
Alcohol, HIV/AIDS, and Liver Disease

Tamsin A. Knox, Logan Jerger, and Alice M. Tang

Key Points

- Hazardous alcohol use is increased in persons at risk for HIV infection and among those with HIV infection. Alcohol use increases the risk of HIV acquisition through risky sexual practices.
- Alcohol use is associated with decreased adherence to antiretroviral therapy resulting in HIV transmission and in progression of HIV infection to AIDS. In addition, alcohol use may promote progression of HIV disease through deleterious effects on the immune system.
- Alcohol use is associated with complications of HIV infection including cardiovascular and pulmonary conditions. Liver disease, in particular, is exacerbated by alcohol use, which promotes progression to cirrhosis, hepatocellular carcinoma, and death. These effects are more common in persons coinfected with HIV and chronic hepatitis C or B virus.
- Intervention studies to reduce alcohol use in populations with HIV or at risk of HIV are clearly important, but studies have had variable results.
- There may be no safe level of alcohol use in HIV infection.

Keywords  HIV • Liver fibrosis • Sexual transmission of HIV • HIV acquisition • Africa • Men who have sex with men • Antiretroviral therapy for HIV • Adherence to antiretroviral therapy • Immune function • Survival • Hepatitis C virus • Liver disease • Hepatocellular carcinoma • Cardiovascular disease • Intervention studies
Importance of Alcohol Use in HIV/AIDS

Globally, there are over 33 million persons living with HIV/AIDS resulting in 1.8 million deaths annually. While the rate of HIV transmission is slowing, it is estimated that 2.6 million new infections occur yearly [1]. In the United States, there are approximately 1.2 million living with HIV/AIDS, with 50,000 new HIV infections and 17,000 deaths from the disease annually [2]. For those who can obtain effective antiretroviral therapy (ART), HIV/AIDS has become a chronic disease with life expectancies over 30 years [3]. Research in the last 10 years has revealed the importance of alcohol in the HIV/AIDS epidemic. Alcohol use, in moderate or hazardous amounts, has been associated with increased acquisition of HIV infection, progression of HIV infection, deleterious effects on HIV treatment, and acceleration in the comorbidities of HIV infection [4–9]. Yet alcohol remains the “forgotten drug” of the HIV/AIDS epidemic [10].

Alcohol has a complex relationship with HIV acquisition. Risky sexual behaviors, among heterosexuals or among men who have sex with men (MSM), that promote HIV transmission are increased in the setting of alcohol [11, 12]. Attention to the locations and clientele where alcohol is served [13] has led to the development of an “ecological epidemiology” of the interplay of multiple risk factors around HIV transmission [14].

Once infected with HIV, alcohol use is associated with progression of HIV infection from asymptomatic infection, to symptomatic AIDS with declining immune function measured by low CD4 T-cell counts (<200 cells/mm³ [3]) in the blood, to death from wasting or an opportunistic infection. Again, the relationship between alcohol use and progression of HIV infection is multifaceted. Hazardous drinking has been associated with delayed testing and treatment for HIV infection [12, 15, 16], poor adherence to ART therapy [6, 17], and increased HIV viral replication and shedding [18–20]. Simian immunodeficiency virus (SIV) infection in monkey models has confirmed findings that regular intake of alcohol leads to more rapid progression of disease, weight loss, and death [21–24].

Alcohol use also complicates the care of persons with HIV infection. Not only is adherence to ART decreased, but drug interactions between alcohol and specific ART medications may increase the toxicity of therapy [25]. HIV infection has numerous comorbidities including coexisting infections such as chronic viral hepatitis or tuberculosis as well as progressive organ dysfunction involving the liver, cardiovascular system, neurological dysfunction, or pulmonary disease. Concurrent alcohol use may have a deleterious effect on any of these conditions [26–30]. Thus, the management of alcohol misuse is central to control and treatment of HIV/AIDS. This chapter summarizes recent research on the effects of alcohol on HIV infection.

Epidemiology of Alcohol Use in HIV/AIDS

Epidemiologic studies of alcohol use in HIV infection inconsistently define alcohol intake and problematic drinking. Many studies categorize alcohol intake as “none,” “moderate” drinking (ranging from any alcohol intake to daily intake over the period studied), and “hazardous” drinking (including regular daily intake or binge drinking and may or may not include a diagnosed alcohol disorder). In addition, the studies screening for alcohol disorders use different criteria including the CAGE questions, AUDIT questionnaire, self-reported drinking, or a physician’s report of an alcohol disorder [31]. Thus, varying methodology and study population selection will greatly influence the results from studies of alcohol use in HIV.
Acquisition of HIV

Alcohol use, whether moderate or hazardous, daily or binge drinking pattern, increases the risk of acquiring HIV [12, 32]. Drinking alcohol is associated with an increased number of sexual encounters with new, anonymous, or high-risk partners [11, 12, 33]. Alcohol use has also been shown to increase the risk of having unprotected intercourse as well as of acquiring a sexually transmitted disease, which in itself, predisposes to HIV infection through open sores [12, 34–38]. Stein et al. found that hazardous drinkers were 5.6 times more likely to have multiple partners and/or unprotected sex than nonhazardous drinkers [39].

The importance of alcohol as a risk factor for HIV infection has been demonstrated in all at-risk groups including heterosexual men [4], MSM [37, 38, 40, 41], adolescents [34, 40], women [42, 43], and drug users [44–46]. Stueve showed that urban adolescents who use alcohol engage in high-risk sexual behaviors including multiple partners and unprotected sex, predisposing them to HIV infection at an early age [34]. Women may be particularly affected by alcohol use since even if they themselves abstain, they are at increased risk of HIV based on the alcohol intake of their male partner promoting sexual violence and coercion [43, 47].

The association of alcohol use with HIV transmission has been well documented by a number of studies in sub-Saharan Africa [11, 32, 47], which has one of the highest burdens of HIV infection and comprises over half of the persons infected with HIV worldwide [1]. Alcohol use is higher in men and women at risk for HIV and is associated with increased sexual risk practices in Africa [48]. Even low amounts of alcohol use in women (e.g., one drink in the last month) were associated with higher risk of HIV infection [49]. In a meta-analysis of 11 studies from Africa, the odds ratio of having HIV was 1.57 for drinkers and 2.04 for problem drinkers compared to nondrinkers, when controlled for other HIV risk factors [32]. Kalichman has shown that strategies for HIV risk reduction in these settings work best through interventions targeted at decreasing alcohol use [50].

Similarly, in India, risk behaviors favoring the spread of HIV are rare among men in household sampling studies (<4%) but high (70%) among men surveyed in wine shops (street shops selling liquor) [51]. Other studies have confirmed this association, which is particularly important in India where 80% of HIV is ascribed to heterosexual transmission [52]. While few women in India drink alcohol (compared to men), women may be at risk due to their husband’s or male partners’ drinking habits [53, 54]. In the Yunnan province of China, where the epidemiology of HIV has been well studied, spread of HIV has begun to shift from intravenous drug use (IDU) to sexual transmission [55]. This suggests that alcohol use may also play an important role in the spread of HIV in China, but there are no data on this at present.

Social locale where alcohol is served such as bars, gay bars, beer halls, and bath houses may be a nidus of HIV transmission since persons frequenting these establishments may have a higher prevalence of HIV infection and sexually transmitted infections (STI), and sexual encounters occur frequently among the clientele [13]. This may be particularly important in the transmission of HIV among gay men and female sex workers. Scribner et al. developed a model called “ecological epidemiology” that encompasses individual characteristics, social network, and the alcohol neighborhood to understand and study HIV transmission. For example, an individual who frequents a bar will be exposed to a group with multiple interrelated sexual partners and an increased prevalence of sexually transmitted disease and HIV [14].

Prevalence of Alcohol Use in HIV

In the US population, approximately 4% meet the DSM-IV definition for alcohol abuse and 14% have had an episode of binge drinking in the last 30 days [56, 57]. Table 23.1 contrasts this with the
prevalence of alcohol use among populations with HIV. There are wide apparent differences in rates of alcohol use and hazardous alcohol use due to the populations surveyed, the definitions of “problem” alcohol use even in the same cohort, and the methods used to determine alcohol intake.

In general, the prevalence of alcohol use disorders is several fold higher among populations with HIV infection compared to the general US population. Some of the highest prevalence rates from problem drinking are among US veterans and homeless veterans [6, 58]. Among the Veterans Administration (VA) population, hazardous drinking patterns are found more frequently in African-Americans (26%) than in whites (18%, p <0.001) [59]. Cook et al. determined that the prevalence of moderate and hazardous drinking among women with HIV infection was also higher than in the general US population [42, 56, 57]. Other characteristics were associated with hazardous drinking patterns such as lower education, unemployment, nonwhite race, depression, and drug use. In both this cohort and in a VA cohort, hazardous alcohol use was associated with hepatitis C virus (HCV) infection [42, 60]. Among veterans with HCV infection, 35% were hazardous drinkers compared with 12% hazardous drinkers among matched controls without HCV infection [60]. The increased alcohol use among IDU and the high correlation of IDU and HCV infection likely explain this finding [46, 61].

### Table 23.1 Prevalence of alcohol disorders in HIV

| Demographic group | Prevalence | Reference | Notes |
|-------------------|------------|-----------|-------|
| In general        | 4% alcohol abuse | Grant 2004 [56] |       |
| US population     | 14% binge drinking in last 30 days | Naimi 2001 [57] |       |
| In HIV            | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Galvan 2002 [166] | HCSUS, n=2,864 from 1996 |
|                   | 14% binge drinking in last 30 days | Stein 2005 [39] |       |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Cook 2001 | Providence, RI, n=262 |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Lucas 2002 [167] | Pittsburgh, n=212 from 1998 |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Conen 2009 [64] |       |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Conigliaro 2003 [163] |       |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | and Justice 2006 [164] |       |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Kraemer 2008 [59] | VA, n=16,048 |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Lefevre 1995 [63] | MSM, Michigan, n=111 |
|                   | 53% any alcohol 8% heavy drinkers 28% hazardous drinkers 19% problem drinking 5% heavy drinkers 5% moderate health risk (WHO) 3% severe health risk | Kleeberger 2001 [168] | MSM in MACS, n=539 |
| In men            | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | Gordon 2006 [58] | Homeless veterans, n=881 |
|                   | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | Braithwaite 2005 [6] | VA population, 60% nonwhite |
|                   | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | Goulet 2005 [106] | white |
|                   | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | Conigliaro 2003 [163] | VA, n=25,116 |
|                   | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | and Justice 2006 [164] | VA, n=881 |
|                   | 47% hazardous drinking 46% any alcohol 9% binge drinkers 24% alcohol disorder 20% hazardous drinkers 33% binge drinkers 17% alcohol diagnosis | Kraemer 2008 [59] | VA, n=16,048 |
| MSM               | 41% alcoholism 5% heavy drinkers | Lefevre 1995 [63] | MSM, Michigan, n=111 |
|                   | 41% alcoholism 5% heavy drinkers | Kleeberger 2001 [168] | MSM in MACS, n=539 |
| In women          | 14–24% hazardous drinking 32–48% moderate drinking | Cook 2009 [42] | WIHS, n=2,770 |
| In Africa         | 14% binge drinking | Kalichman 2011 [48] | So.Africa, n=529 men in STD clinic |

*MSM men who have sex with men, WHO world health organization definition of “moderate health risk” from alcohol consumption, VA veteran’s association, MACS multicenter AIDS cohort study, WIHS women’s interagency HIV study, STD sexually transmitted disease*
**Alcohol Use Over Time**

Alcohol intake appears to decline over time in persons with HIV infection as it does in noninfected persons with medical illness [62]. Lefevre et al. examined alcohol intake in a group of 111 HIV-positive patients of a university hospital clinic, mostly MSM. In surveys repeated every 6 months for a mean follow-up of 30 months, the frequency of drinking decreased from 6.4 to 3.9 drinks/week (p<0.001) [63]. In the Swiss HIV Cohort Study, lower alcohol use was found in those who had been on ART for longer periods of time [64]. Cook analyzed data from the Women’s Interagency HIV study (WIHS) on 2,770 HIV-positive women followed for 11 years [42]. There was a slight, approximately 5%, decrease in hazardous drinking over time but no change in the overall amount of drinking, possibly as some switched categories from hazardous to nonhazardous drinking. However, there was a significant decrease in alcohol consumption among women who were coinfected with hepatitis C and HIV from 31% with hazardous drinking patterns in 1995 to 10% in 2006.

**Alcohol and HIV Progression**

Alcohol has been implicated in accelerating the progression of HIV disease through a number of mechanisms. Persons drinking alcohol heavily delay testing for HIV and have less connection with and retention in the health-care system [12, 15, 16], delaying the initiation of ART. Thus, heavy alcohol use predisposes persons to late presentation in the course of infection, with high HIV viral loads, low CD4 counts, and opportunistic infections, and promotes continued spread of HIV [45, 65].

**Adherence**

One of the central ways alcohol intake adversely affects HIV disease is by decreasing adherence to ART. Adherence to ART is key to suppression of HIV replication, prevention of developing drug resistance, and long-term survival [66]. This has been well documented among all subgroups with HIV infection [6, 64, 65, 67–71]. While there are few studies of adherence in developing countries, one study from India confirms the association of alcohol use and risk of nonadherence or discontinuation of ART medications [72]. Convincingly, there is a dose–response relationship between alcohol intake and adherence, with higher amounts of alcohol or more hazardous drinking being associated with poorer measures of adherence. Samet et al. found that the amount of alcohol consumption was the strongest predictor of adherence with highest levels of adherence being found in those abstinent from alcohol compared to moderate use or at-risk use [70]. Chander et al., studying nearly 2,000 HIV-infected persons receiving care at Johns Hopkins Hospital in Baltimore, Maryland, found that adherence was 22% lower in moderate alcohol users and 54% lower in hazardous alcohol users compared to no alcohol use. Adherence was further decreased by 68% with concurrent drug use [65].

There may be several reasons for lower adherence in persons who use alcohol. Drinking pattern affects the likelihood of noncompliance. Braithwaite et al., studying 2,700 members of The Veterans Administration Aging Cohort Study (VACS), found that abstainers missed ART on 2% of days. Non-binge drinkers missed medication on 4% of drinking days and post-drinking days but only on 2% of nondrinking days. Binge drinkers, in contrast, missed ART on 11% of drinking days, 5.5% of post-drinking days, and 4% on nondrinking days [6]. Therefore, while medication adherence was lower on drinking days for binge and non-binge drinkers, missing medications was increased twofold among binge drinkers on days they were either not drinking or post-drinking. This suggests that nonadherence was
also due to factors not directly related to alcohol but related to characteristics common among binge drinkers [6]. Sankar et al. studied beliefs about alcohol and ART medication interactions in a group of African-American patients treated for HIV [71]. Over three quarters of those surveyed felt that “alcohol and ART do not mix”; one-third attributed this to alcohol making ART ineffective and another third felt that alcohol made ART more toxic. In this study, participants reported purposely skipping ART doses when they drank, with light drinkers skipping 64% of the times when they drank and moderate drinkers 55% of the times. However, heavy drinkers skipped ART only 29% of the time when they drank and reported that they felt no ill effects from drinking and taking ART [71]. Thus, medication adherence is determined by amount of alcohol intake, drinking pattern (binge or non-binge drinking), and beliefs about the safety of alcohol combined with ART. Issues of medication adherence and alcohol are further discussed in Chap. 18 and in a meta-analysis by Hendershot [17].

**Immune Function**

Alcoholics have increased susceptibility to bacterial infections including tuberculosis, pneumonia, and sepsis [73]. In vitro studies have shown that alcohol impacts several areas of immune function, acting largely as an immunosuppressant. Alcohol decreases T-cell proliferation reducing CD4, CD8, and natural killer (NK) cell numbers [7] and reduces CD8 cell responses to bacteria [74]. Cell-mediated immune responses are decreased [75], and myeloid dendritic cells, which are involved in antigen presentation to the immune system, are decreased in number and function with chronic alcohol ingestion [76, 77]. Alcohol increases expression of pro-inflammatory cytokines such as TNF-alpha [78] which may enhance immune dysfunction.

Experiments by Bagasra et al. on human peripheral blood mononuclear cells (PBMC) have shown that cells from healthy persons who are infected in vitro with HIV-1 have higher levels of HIV replication when harvested after alcohol consumption [19]. Enhanced HIV replication was associated with a concurrent inhibition of CD8 cells by alcohol [18].

SIV infection, a macaque model for HIV, has produced evidence of the effect of alcohol on immune function and HIV replication. In rhesus macaques inoculated with SIV infection, SIV replication was 31- to 85-fold higher in monkeys with chronic alcohol ingestion compared to controls [21]. SIV replication persisted in the central nervous system of alcohol-fed monkeys but was undetectable in control monkeys. Poonia et al. proposed that the mechanism of alcohol’s effect on SIV replication is through its effect on intestinal lymphocytes since the small intestine is one of the most lymphocyte-rich organs. Alcohol-fed monkeys had lower numbers of CD8 cells (before and after SIV infection) and higher numbers of CD4 cells in the small intestine after SIV infection. They suggested that the $1–2 \log_{10}$ increase in SIV replication in alcohol-fed monkeys occurs because of the increase in number of CD4 cells susceptible to SIV infection in the small intestine and reduction in CD8 cells which may control SIV replication [22]. Chronic alcohol ingestion also altered the course of HIV infection with alcohol-fed monkeys having lower CD4 cell counts, lower caloric intake, higher TNF-alpha expression, and a more rapid progression to end-stage SIV disease (mean 374 days compared to 900 days in controls) [23, 24].

**HIV Progression and Survival**

Alcohol use has been shown to affect HIV progression and survival. In the pre-HAART era, alcohol use was not associated with progression to AIDS [79–81]. However, two well-controlled, longitudinal
studies since the introduction of combination ART have shown that alcohol is associated with HIV disease progression. Samet et al. studied alcohol use in 595 participants in the MACS cohort over 7 years [82]. Heavy alcohol use was associated with a lower mean CD4 cell count (by ~50 cells/mL) but not a decline in CD4 percentage or HIV viral load when adjusted for adherence. Baum et al. studied 231 HIV-positive persons followed for 2.5 years [5]. Frequent alcohol users of ≥2 drinks/day were almost 3 times more likely to develop a CD4 count ≤200 cells/mL, which is an AIDS-defining event. This effect was particularly marked in alcohol users not on ART whose risk of developing a CD4 count ≤200 cells/mL was nearly 8 times nondrinkers. In this study, alcohol use was associated with higher HIV viral load in those on ART but not in those without ART. These results suggest that the effect of alcohol on HIV viral load is mediated through adherence. However, the effect of alcohol in lowering absolute CD4 count rather than percentage could be influenced by the splenomegaly and secondary lymphopenia seen with alcoholism and chronic viral hepatitis [83]. Moderate to heavy alcohol use has also been associated with increased HIV viral shedding in the female genital tract after controlling for plasma viral load [20] suggesting that alcohol may affect HIV transmission by physiological as well as behavioral risk factors.

The VACS study has provided models for estimating the effect of alcohol on survival in HIV infection. Using data on ART adherence in the VACS cohort, Braithwaite et al. developed a model simulating survival based on levels of alcohol consumption (nondrinkers, hazardous drinkers consuming ≥5 drinks on drinking days, and nonhazardous drinkers) [84]. The model predicted decreased survival by >1 year in nonhazardous drinkers drinking at least once a week, 3.3 years in nonhazardous drinkers drinking daily, and up to 6.4 years in hazardous drinkers drinking daily. However, the VACS index, subsequently developed to predict decreases in life expectancy based on HIV and non-HIV characteristics, does not include a separate variable for alcohol or drug abuse beyond adjusting for severity of liver disease and coexisting HCV infection [85]. In addition, a longitudinal study of changes in physical function with age in the same cohort did not show an effect of alcohol [86]. Further longitudinal studies in this cohort and others should define the impact of alcohol use on survival in HIV.

Liver Disease and Other Harmful Sequelae of Alcohol in HIV

Persons with HIV infection are particularly vulnerable to the effects of alcohol. The detrimental effects of alcohol on the immune system have been covered above, and the effects of alcohol on general health and nutrition are covered in other chapters in this book. Persons with HIV infection are at risk of poor nutritional status, and even a 3% weight loss has been associated with increased mortality [87–90]. Thus, further changes in nutritional status due to alcohol use, particularly lower body weight or micronutrient deficiencies, would exacerbate the nutritional effects of HIV [91, 92].

Liver Disease

Approximately one-third of persons with HIV infection are coinfected with HCV, and approximately 10% have evidence of chronic hepatitis B virus (HBV) infection [93]. The prevalence of HCV coinfection increases to almost 90% in those who acquired HIV from IDU. Persons with coinfection with chronic hepatitis have accelerated liver fibrosis leading to cirrhosis [9, 94]. In a study of liver histology of IDU who had acquired HCV infection, those with concurrent HIV infection developed cirrhosis in a mean of 6.9 years after infection compared to 23.2 years among HCV
mono-infected persons ($p<0.001$) [95]. Persons with coinfection also have an increased risk of death from end-stage liver disease [96–99]. They are also at higher risk for drug-induced hepatotoxicity from ART [100, 101] which may be related to altered cytochrome metabolism with progressive liver disease [102]. Other metabolic abnormalities are more common in coinfected persons including hyperglycemia, diabetes, and bacterial translocation from the small intestine to the portal system, predisposing coinfected chronic inflammation and progressive liver disease [103–105].

Hazardous alcohol use is increased in some populations with coinfection, particularly IDUs [64, 106]. Alcohol use further exacerbates the effect of coinfection on liver disease. Alcohol use of >50 g/day is associated with increased HCV replication [107, 108] and progressive liver fibrosis assessed by serum markers [109], transient elastometry [110] or by liver biopsy [9, 111–113]. Death from end-stage liver disease is also more common in coinfected persons who use alcohol [29, 30, 114, 115]. The incidence of, as well as deaths related to, hepatocellular carcinoma is also increased in those with coinfection who drink alcohol [30, 116]. Only one study did not find an association of alcohol use and an HCV-related severe event (including decompensated cirrhosis, hepatocellular carcinoma, or death) [117], but in this cohort, only 10% consumed >30 g of alcohol daily.

Alcohol use also contributes to metabolic abnormalities in coinfected persons. It is associated with higher rates of liver steatosis [110] and drug-induced liver disease [25, 118]. The association of alcohol use with hepatocellular carcinoma is also discussed in Chap. 32.

The adverse effects of alcohol in coinfection argue strongly for intervention. Hazardous alcohol use is a common reason for coinfected persons not receiving treatment for HCV infection, where treatment rates may be as low as 7% [106, 119–122]. Fortunately, alcohol use seems to decrease with interventions after HCV diagnosis in some populations [123, 124]. Treatment of chronic viral hepatitis whether due to HCV or HBV infection slows the progression of liver fibrosis [125, 126] and reduces the incidence of drug-induced liver disease [127]. Treatment outcomes with pegylated interferon and ribavirin [128, 129] and with the new protease inhibitors for HCV infection should continue to improve as more coinfected persons are being enrolled in treatment [130].

**Cardiovascular Disease**

Persons with HIV infection have an increased risk of cardiovascular disease, particularly accelerated atherosclerosis and myocardial infarction [131–133]. Cardiovascular disease is likely due to a combination of additional risk factors found in HIV infection [26] including (1) chronic inflammation from HIV viral replication and subsequent immunodeficiency [134], (2) the effect of chronic inflammation on serum lipid levels [133], (3) the metabolic effects of certain classes of antiretroviral medications [131, 133], (4) increased prevalence of insulin resistance [135], and (5) increased translocation of bacteria across the small intestine into the bloodstream as a result of immunodeficiency [136]. Persons with HIV infection have been shown to have more rapid progression of atherosclerosis measured by intermediate markers such as carotid intima–media thickness, and this has correlated with mortality [134, 137, 138].

Alcohol use further increases the risk of cardiovascular disease in HIV infection. Freiberg et al., studying the VACS Cohort, found that the risk of cardiovascular disease was increased (OR 1.55, 95% CI 1.07–2.23) in HIV-infected men with alcohol abuse or dependence, when controlled for cardiac risk factors, ART use, and CD4 count [8]. Furthermore, HCV infection may have an independent effect in increasing the risk of cardiovascular disease (OR 4.7, 95% CI 1.7–12.7) although alcohol use does not seem to affect this relationship [139]. Chapters 24 and 25 explore further the relationship of alcohol and cardiovascular disease.
**Pulmonary Disease**

Alcohol and HIV infection are both risk factors for pulmonary diseases. Alcoholics have increased prevalence of oropharyngeal colonization by pathogenic bacteria and an increased risk of aspiration [140]. In addition, they have impaired pulmonary immune function leading to a higher incidence of pneumonia [27, 140]. Studies have shown that alcohol use is a risk factor for the development of pneumonia in the absence of HIV, as well as more severe, multilobar pneumonia and more virulent pathogens including *Candida*, gram-negative bacteria, and *Staphylococcus aureus* infections. This, in turn, leads to longer hospitalizations and increased mortality related to alcohol use [141]. The risk for adult respiratory distress syndrome (ARDS), which has a mortality of 40–60% [142], is increased three- to fourfold in those with heavy alcohol intake [143, 144].

Similarly, persons with HIV infection are at an increased risk of community-acquired pneumonias, including unusual pathogens such as *Pseudomonas aeruginosa* [145]. HIV infection is also associated with pulmonary opportunistic infections, such as *Pneumocystis* [146]. While both alcohol use and HIV infection have an increased risk of pneumonia and tuberculosis, there are no studies to date that demonstrate the interaction of these risk factors for acute pulmonary disease [27]. There is suggestive literature that depletions in zinc levels or pulmonary glutathione stores may mediate impaired host defense [27].

Chronic lung disease in alcoholics is largely related to associated tobacco use [27]. However, persons with HIV infection have an increased risk of emphysema, lung cancer, and pulmonary hypertension, independent of smoking, and this is particularly evident in those with poorly controlled HIV infection [147].

**Intervention Studies on Alcohol in HIV**

The adverse effects of alcohol use on HIV are evident, and interventions to mitigate alcohol use among HIV-infected individuals are needed. To date, clinical studies and a few randomized controlled trials (RCTs) assessing the effectiveness of interventions have shown mixed results. In this section, we will briefly review the types of interventions that have been evaluated and discuss results from a few published trials. Interested readers can refer to recent review articles for more complete reviews of the literature [13, 148, 149].

Many types of alcohol interventions have been tested among hazardous alcohol users with and without HIV infection. These include brief interventions as well as more intensive behavioral, social network, and medication interventions. Brief interventions, also referred to as brief motivational interviews, are typically a single session discussing the patients’ alcohol use. Studies employing this type of intervention often involve exploration of the pros and cons of a patient’s alcohol use, self-assessment of the patient’s alcohol consumption severity, and a more formal assessment of the patient’s alcohol consumption as compared to the general population [150]. More extensive behavioral interventions have also been investigated, including cognitive-behavioral therapy, motivation enhancement, or 12-step programs. Each of these behavioral interventions is directly aimed at investigating personal motivation behind alcohol consumption and developing personal behavior modification strategies [151]. These interventions typically require multiple sessions. In addition to individualized plans and programs for those with increased alcohol consumption, social network and structural interventions which target larger populations and communities have also been evaluated. Social network interventions have most commonly focused on employing influential community leaders to change specific behaviors or promote health-conscious decisions. These studies, often referred to as Popular Opinion Leader (POL) or peer-based model interventions, may be particularly effective in communities that are difficult for outside researchers to impact [152]. Alternatively, structural interventions, which may
include political and legal action, may also be effective in altering individuals’ behavior and environment. Lastly, medications, such as disulfiram, naltrexone, and acamprosate, have been shown to decrease alcohol consumption via physiologic effects, including decreasing cravings or causing adverse reactions when alcohol is consumed [149].

In addition to the type of alcohol intervention, there are several other factors to consider when evaluating results from clinical trials of alcohol interventions. The first is the setting in which the interventions are conducted. Interventions have been conducted in various settings including primary care clinics [153, 154], hospital inpatient settings [155], emergent care settings [156], and social settings or drinking venues (places where alcohol is served) [13]. A second important factor to consider is the population being targeted, which may vary depending on severity of alcohol use (dependent vs. nondependent drinkers), geographic region, and cultural practices around drinking. A third factor to consider is the outcome that is being targeted. For example, previous trials have examined the effects of alcohol interventions on decreasing alcohol consumption, improving adherence to antiretroviral medication and/or reducing sexual risk behaviors. The combination of the type of intervention, the setting in which the intervention is implemented, the population that is being targeted, and the expected outcomes of the trial will all contribute to the success or failure of an intervention.

The published literature on RCTs of alcohol interventions among populations affected by HIV reflects the various combinations of factors described above. For example, one study targeting MSM in the USA with alcohol use disorders combined two types of interventions (motivational interviewing and peer-group education/support strategies) and examined the effects on reducing at-risk drinking and sexual risk behaviors [157]. In this study, individuals receiving the combined intervention reported significantly lower number of days of drinking and number of heavy drinking days per 30-day period compared to control participants. Another study tested the effects of a brief theory-based behavioral HIV–alcohol risk-reduction intervention on sexual risk behaviors in men and women recruited from informal drinking establishments in a suburban township of Capetown, South Africa [50]. The authors reported significant reductions in unprotected intercourse, increased use of condoms, and less use of alcohol before sex in the intervention group compared to controls, with the largest impacts among lighter drinkers. These two studies illustrate the success of individual counseling interventions for reducing risk behaviors around alcohol consumption among persons at risk for or living with HIV.

Other interventions among individuals with HIV who consume alcohol have targeted the outcome of antiretroviral medication adherence. In two specific studies [151, 158], motivational interviews and cognitive-behavioral skills training were not effective in improving long-term medication adherence. Given the importance of adherence to ART to controlling HIV infection, more research is needed to develop novel interventions targeting this outcome.

Interventions directed at alcohol-serving establishments have had mixed results. Studies have focused on popular opinion leader (POL) models, in which community-defined opinion leaders are identified and trained to help shift social norms and behaviors toward safer sexual practices [152]. This type of intervention in gay bars in several US cities significantly reduced episodes of risky sexual behavior compared to control bars [152, 159, 160]; however, when this intervention was adapted for testing in several international settings, the findings were negative in that comparable reductions in risky sexual behaviors and incidence of sexually transmitted infections were seen in both intervention and control communities [161]. Another study testing the effects of a peer-based intervention on reducing episodes of unprotected sex with non-wife partners in beer halls in Zimbabwe found no difference compared to controls [162].

In summary, interventions involving varied counseling approaches directed at decreasing alcohol consumption and/or risky sexual behavior appear promising in specific settings. Other areas of investigation, such as interventions aimed at improving ART adherence among alcohol users or use of medications for alcohol dependence (such as naltrexone) in HIV-infected populations, need further research. More intervention studies will help to generalize findings across different contexts and help to improve health outcomes and minimize the effects of alcohol on persons living with HIV.
Is Alcohol Use Harmful in HIV?

In this chapter, we have examined the prevalence of hazardous alcohol use in HIV which is much higher than found in the general US population. Alcohol use and frequenting venues where alcohol is consumed has been shown to be an important risk factor for the acquisition of HIV infection. Understanding the complex interrelationships between individual characteristics and venues should improve our approach to prevention [12, 14]. The effect of alcohol on adherence to ART is well documented. There are also good laboratory models, particularly with SIV infection in macaques, to show that chronic alcohol use accelerates the progression of disease. Finally, alcohol use has deleterious effects on health, particularly related to progression of liver disease in persons with HIV/HCV coinfection.

Health-care providers may underestimate the extent of hazardous drinking among their HIV patients. A study in the VA population showed that the sensitivity for health-care providers’ ability to diagnose hazardous drinking was only 22% [163]. Thus far, trials of interventions to reduce hazardous drinking in populations affected by HIV have shown mixed results. The underdiagnosis of hazardous alcohol use and lack of proven, effective treatment strategies raise the question of whether there is any “safe” level of alcohol intake in HIV. Justice et al. examined the relationship of medical illness related to alcohol use in veterans with HIV infection [164]. For diseases associated with alcohol use (HCV infection, hypertension, diabetes, chronic obstructive lung disease, and certain infections), there was a linear relationship between alcohol intake category (none, moderate, hazardous) and the disease. This suggests that there may be no “safe” level of alcohol intake for HIV-infected persons [165]. More aggressive screening and treatment of alcohol-related disorders is clearly warranted to prevent HIV transmission and to improve treatment and outcomes of persons with HIV infection [84].

References

1. Joint United Nations Programme on HIV/AIDS. UNAIDS Report on the Global AIDS Epidemic 2010. Geneva. 2010. http://www.unaids.org/globalreport/GLOBAL_report.htm. Accessed 28 Sept 2011.
2. Centers for Disease Control and Prevention. HIV Surveillance Report, 2009;21(Feb 2011). http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/. Accessed 28 Sept 2011.
3. Losina E, Schackman BR, Sadownik SN, et al. Racial and sex disparities in life expectancy losses among HIV-infected persons in the United States: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. Clin Infect Dis. 2009;49(10):1570–8.
4. Cook RLMDMPH, McGinnis KAMS, Kraemer KMDM, et al. Intoxication before intercourse and risky sexual behavior in male veterans with and without human immunodeficiency virus infection. Med Care (Alcohol in HIV Infection: Insights from the Veterans Aging Cohort Study and the Veterans Affairs National Health Information System). 2006;44(8):S31–6.
5. Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses. 2010;26(5):511–8.
6. Braithwaite RS, McGinnis KA, Conigliaro J, et al. A temporal and dose–response association between alcohol consumption and medication adherence among veterans in care. Alcoh: Clin Exp Res. 2005;29(7):1190–7.
7. Pandrea I, Happel K, Amedee A, Bagby G, Nelson S. Alcohol’s role in HIV transmission and disease progression. Alcohol Res Health. 2010;33(3):203–18.
8. Freiberg MSMDM, McGinnis KAMS, Kraemer KMDM, et al. The association between alcohol consumption and prevalent cardiovascular diseases among HIV-infected and HIV-uninfected men. JAIDS. 2010;53(2):247–53.
9. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis. 2004;38(1):128–33.
10. Fritz K, Morojele N, Kalichman S. Alcohol: the forgotten drug in HIV/AIDS. Lancet. 2010;376(9739):398–400.
11. Chersich MF, Rees HV. Causal links between binge drinking patterns, unsafe sex and HIV in South Africa: its time to intervene. Int J STD AIDS. 2010;21(1):2–7.
12. Bryant K, Nelson S, Braithwaite RS, Roach D. Integrating HIV/AIDS and alcohol research. Alcohol Res Health. 2010;33(3):167–78.
13. Kalichman SC. Social and structural HIV prevention in alcohol-serving establishments: review of international interventions across populations. Alcohol Res Health. 2010;33(3):184–94.
14. Scribner R, Theall K, Simonsen N, Robinson W. HIV risk and the alcohol environment: advancing an ecological epidemiology for HIV/AIDS. Alcohol Res Health. 2010;33(3):179–83.
15. Hahn JA, Samet JH. Alcohol and HIV disease progression: weighing the evidence. Curr HIV/AIDS Rep. 2010;7(4):226–33.
16. Cunningham WE, Sohler NL, Tobias C, et al. Health services utilization for people with HIV infection: comparison of a population targeted for outreach with the US population in care. Med Care. 2006;44(11):1038–47.
17. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. JAIDS. 2009;52(2):180–202.
18. Bagasra O, Bachman SE, Jew L, et al. Increased human immunodeficiency virus type 1 replication in human peripheral blood mononuclear cells induced by ethanol: potential immunopathogenic mechanisms. J Infect Dis. 1996;173(3):550–8.
19. Bagasra O, Kajdacy-Balla A, Lischner HW, Pomerantz RJ. Alcohol intake increases human immunodeficiency virus type 1 replication in human peripheral blood mononuclear cells. J Infect Dis. 1993;167(4):789–97.
20. Theall KP, Amedee A, Clark RA, Dumestre J, Kissinger P. Alcohol consumption and HIV-1 vaginal RNA shedding among women. J Stud Alcohol Drugs. 2008;69(3):454–8.
21. Kumar R, Perez-Casanova AE, Tirado G, et al. Increased viral replication in simian immunodeficiency virus/simian-HIV-infected macaques with self-administering model of chronic alcohol consumption. JAIDS. 2005;39(4):386–90.
22. Poonia B, Nelson S, Bagby GJ, Zhang P, Quiniton L, Veazey RS. Chronic alcohol consumption results in higher simian immunodeficiency virus replication in mucosally inoculated rhesus macaques. AIDS Res Hum Retroviruses. 2006;22(6):589–94.
23. Bagby GJ, Zhang P, Purcell JE, Didier PJ, Nelson S. Chronic binge ethanol consumption accelerates progression of simian immunodeficiency virus disease. Alcohol Clin Exp Res. 2006;30(10):1781–90.
24. Molina PE, McNurlan M, Rathmacher J, et al. Chronic alcohol accentuates nutritional, metabolic, and immune alterations during asymptomatic simian immunodeficiency virus infection. Alcohol Clin Exp Res. 2006;30(12):2065–78.
25. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. JAIDS. 2001;27(5):426–31.
26. Freiberg MS, Kraemer KL. Focus on the heart: alcohol consumption, HIV infection, and cardiovascular disease. Alcohol Res Health. 2010;33(3):237–46.
27. Quintero D, Guidot D. Modeling HIV and alcohol’s effects: focus on the lung. Alcohol Res Health. 2010;33(3):229–36.
28. Rosenbloom MJ, Sullivan EV, Pefferbaum A. Focus on the brain: HIV infection and alcoholism. Alcohol Res Health. 2010;33(3):247–57.
29. Pineda JA, Gonzalez J, Ortega E, et al. Prevalence factors associated with significant liver fibrosis assessed by transient elastometry in HIV/hepatitis C virus-coinfected patients. J Viral Hepat. 2010;17(10):714–9.
30. Rosenthal E, Salmon-Ceron D, Lewden C, et al. Liver-related deaths in, H. I. V. infected patients between in the French, germivic joint study group network. HIV Med. 2009;10(5):282–9.
31. Samet JH, Phillips SJ, Horton NJ, Traphagen ET, Freedberg KA. Detecting alcohol problems in HIV-infected patients: use of the CAGE questionnaire. AIDS Res Hum Retroviruses. 2004;20(2):151–5.
32. Fisher JC, Bang H, Kapiga SH. The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies. Sex Transm Dis. 2007;34(11):856–63.
33. Shuper PA, Joharchi N, Irving H, Rehm J. Alcohol as a correlate of unprotected sexual behavior among people living with HIV/AIDS: review and meta-analysis. AIDS Behav. 2009;13(6):1021–36.
34. Steuve A, O’Donnell LN. Early alcohol initiation and subsequent sexual and alcohol risk behaviors among urban youths. Am J Public Health. 2005;95(5):887–93.
35. Brown JL, Vanable PA. Alcohol use, partner type, and risky sexual behavior among college students: findings from an event-level study. Addict Behav. 2007;32(12):2940–52.
36. Cohen MS. HIV and sexually transmitted diseases: lethal synergy. Top HIV Med. 2004;12(4):104–7.
37. Irwin TW, Morgenstern J, Parsons JT, Wainberg M, Labouvie E. Alcohol and sexual HIV risk behavior among problem drinking men who have sex with men: an event level analysis of timeline followback data. AIDS Behav. 2006;10(3):299–307.
38. Woolf SE, Maisto SA. Alcohol use and risk of HIV infection among men who have sex with men. AIDS Behav. 2009;13(4):757–82.
39. Stein M, Herman DS, Trisvan E, Pirraglia P, Engler P, Anderson BJ. Alcohol use and sexual risk behavior among human immunodeficiency virus-positive persons. Alcohol Clin Exp Res. 2005;29(5):837–43.
40. Salomon EA, Miniaga MJ, Husnik MJ, et al. Depressive symptoms, utilization of mental health care, substance use and sexual risk among young men who have sex with men in EXPLORE: implications for age-specific interventions. AIDS Behav. 2009;13(4):811–21.
41. Koblin BA, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. AIDS. 2006;20(5):731–9.
42. Cook RL, Zhu F, Belnap BH, et al. Longitudinal trends in hazardous alcohol consumption among women with human immunodeficiency virus infection, 1995–2006. Am J Epidemiol. 2009;169(8):1025–32.
43. Theall KP, Clark RA, Powell A, Smith H, Kissinger P. Alcohol consumption, ART usage and high-risk sex among women infected with HIV. AIDS Behav. 2007;11(2):205–15.
44. Van Tieu H, Koblin BA. HIV, alcohol, and noninjection drug use. Curr Opin HIV AIDS. 2009;4(4):314–8.
45. Lake-Bakaar G, Grimson R. Alcohol abuse and stage of HIV disease in intravenous drug abusers. J R Soc Med. 1996;89(7):389–92.
46. Costenbader EC, Zule WA, Coomes CM. The impact of illicit drug use and harmful drinking on quality of life among injection drug users at high risk for hepatitis C infection. Drug Alcohol Depend. 2007;89(2–3):251–8.
47. Kalichman SC, Simbayi LC, Kaufman M, Cain D, Jooste S. Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings. Prev Sci. 2007;8(2):141–51.
48. Kalichman SC, Cain D, Simbayi LC. Multiple recent sexual partnerships and alcohol use among sexually transmitted infection clinic patients, Cape Town, South Africa. Sex Transm Dis. 2011;38(1):18–23.
49. Hargreaves JR. Socioeconomic status and risk of HIV infection in an urban population in Kenya. Trop Med Int Health. 2002;7(9):793–802.
50. Kalichman SC, Simbayi LC, Vermaak R, et al. Randomized trial of a community-based alcohol-related HIV risk-reduction intervention for men and women in Cape Town South Africa. Ann Behav Med. 2008;36(3):270–9.
51. Go VF, Solomon S, Srikrishnan AK, et al. HIV rates and risk behaviors are low in the general population of men in Southern India but high in alcohol venues: results from 2 probability surveys. JAIDS. 2007;46(4):491–7.
52. Sivaram S, Srikrishnan AK, Latkin C, et al. Male alcohol use and unprotected sex with non-regular partners: evidence from wine shops in Chennai, India. Drug Alcohol Depend. 2008;94(1–3):133–41.
53. Kumar MS, Sharma M. Women and substance use in India and Bangladesh. Subst Use Misuse. 2008;43(8–9):1062–77.
54. Solomon SS, Mehta SH, Latimore A, Srikrishnan AK, Celentano DD. The impact of HIV and high-risk behaviours on the wives of married men who have sex with men and injection drug users: implications for HIV prevention. J Int AIDS Soc. 2010;13(2):S7.
55. Duan S, Shen S, Bulterys M, et al. Estimation of HIV-1 incidence among five focal populations in Dehong, Yunnan: a hard hit area along a major drug trafficking route. BMC Public Health. 2010;10:180.
56. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. Drug Alcohol Depend. 2004;74(3):223–34.
57. Naimi TS, Brewer RD, Mokdad A, Denny C, Serdula MK, Marks JS. Binge drinking among US adults. JAMA. 2003;289(1):70–5.
58. Gordon AJ, McGinnis KA, Conigliaro J, et al. Associations between alcohol use and homelessness with healthcare utilization among human immunodeficiency virus-infected veterans. Med Care. 2006;44(8 (Suppl 2)):S37–43.
59. Kraemer KL, McGinnis KA, Skanderson MMSW, et al. Alcohol problems and health care services use in human immunodeficiency virus (HIV)-infected and HIV-uninfected veterans. Med Care. 2006;44(8 Suppl 2):S44–51.
60. Butt AA, Khan UA, McGinnis KA, Skanderson M, Kent Kwoh C. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. J Viral Hepat. 2007;14(12):890–6.
61. Campbell JV, Hagan H, Latka MH, et al. High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. Drug Alcohol Depend. 2006;81(3):259–65.
62. Liang W, Chikritzhs T. Reduction in alcohol consumption and health status. Addiction. 2011;106(1):75–81.
63. Lefevre F, O’Leary B, Moran M, et al. Alcohol consumption among HIV-infected patients. J Gen Intern Med. 1995;10(8):458–60.
64. Conen A, Fehr J, Glass TR, et al. Self-reported alcohol consumption and its association with adherence and outcome of antiretroviral therapy in the Swiss HIV Cohort Study. Antivir Ther. 2009;14(3):349–57.
65. Chander G, Lau BMHSS, Moore RDMHS. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. JAIDS. 2006;43(4):411–7.
66. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133(1):21–30.
67. Berg KM, Demas PA, Howard AA, Schoenbaum EE, Gourevitch MN, Arnsten JH. Gender differences in factors associated with adherence to antiretroviral therapy. J Gen Intern Med. 2004;19(11):1111–7.
68. Cook RL, Sereika SM, Hunt SC, Woodward WC, Erlen JA, Conigliaro J. Problem drinking and medication adherence among persons with HIV infection. J Gen Intern Med. 2001;16(2):83–8.
69. Palepu A, Tyndall MW, Li K, et al. Alcohol use and incarceration adversely affect HIV-1 RNA suppression among injection drug users starting antiretroviral therapy. J Urban Health. 2003;80(4):667–75.
70. Samet JH, Horton NJ, Meli S, Freedberg KA, Palepu A. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. Alcohol Clin Exp Res. 2004;28(4):572–7.
71. Sankar A, Wunderlich T, Neufeld S, Luborsky M. Sero-positive African Americans’ beliefs about alcohol and their impact on anti-retroviral adherence. AIDS Behav. 2007;11(2):195–203.
72. Sharma M, Singh RR, Laishram P, et al. Access, adherence, quality and impact of ARV provision to current and ex-injecting drug users in Manipur (India): an initial assessment. Ind J Drug Policy. 2007;18:319–25.
73. Cook RT. Alcohol abuse, alcoholism, and damage to the immune system—a review. Alcohol Clin Exp Res. 1998;22(9):1927–42.
74. Gurung P, Young BM, Coleman RA, et al. Chronic ethanol induces inhibition of antigen-specific CD8+ but not CD4+ immunodominant T cell responses following Listeria monocytogenes inoculation. J Leukoc Biol. 2009;85(1):34–43.
75. Szabo G. Consequences of alcohol consumption on host defence. Alcohol Alcohol. 1999;34(6):830–41.
76. Siggins RW, Bagby GJ, Molina P, Dufour J, Nelson S, Zhang P. Alcohol exposure impairs myeloid dendritic cell function in rhesus macaques. Alcohol Clin Exp Res. 2009;33(9):1524–31.
77. Siggins RW, Melvan JN, Welsh DA, Bagby GJ, Nelson S, Zhang P. Alcohol suppresses the granulopoietic response to pulmonary Streptococcus pneumoniae infection with enhancement of STAT3 signaling. J Immunol. 2011;186(7):4306–13.
78. Thakur V, McMullen MR, Pritchard MT, Nagy LE. Regulation of macrophage activation in alcoholic liver disease. J Gastroenterol Hepatol. 2007;22(1):S53–6.
79. Kaslow RA, Blackwelder WC, Ostrow DG, et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. A report from the Multicenter AIDS Cohort Study. JAMA. 1989;261(23):3424–9.
80. Coates RA, Farewell VT, Raboud J, et al. Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with human immunodeficiency virus disease. Am J Epidemiol. 1990;132(4):717–22.
81. Veugelers PJ, Page KA, Tindall B, et al. Determinants of HIV disease progression among homosexual men registered in the Tricontinental Seroconverter Study. Am J Epidemiol. 1994;140(8):747–58.
82. Samet JH, Cheng DM, Libman H, Nunes DP, Alperen JK, Saitz R. Alcohol consumption and HIV disease progression. JAIDS. 2007;46(2):194–9.
83. McGovern BH, Golan Y, Lopez M, et al. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. Clin Infect Dis. 2007;44(3):431–7.
84. Braithwaite RS, Conigliaro J, Roberts MS, et al. Estimating the impact of alcohol consumption on survival for HIV+ individuals. AIDS Care. 2007;19(4):459–66.
85. Justice AC, McGinnis KA, Skanderson M, et al. Towards a combined prognostic index for survival in HIV infection: the role of ‘non-HIV’ biomarkers. HIV Med. 2010;11(2):143–51.
86. Oursler KK, Goulet JL, Crystal S, et al. Association of age and comorbidity with physical function in HIV-infected and uninfected patients: results from the Veterans Aging Cohort Study. AIDS Patient Care STDS. 2011;25(1):13–20.
87. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. JAIDS. 2002;31(2):230–6.
88. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients 10.1016/j.drugalcdep.2011.02.020 (e-publish ahead of print: 18 Mar 2011).
89. Baum M, Cassetti L, Bonvelli P, Shor-Posner G, Lu Y, Saubelrich H. Inadequate dietary intake and altered nutrition status in early HIV-1 infection. Nutrition. 1994;10(1):16–20.
90. Sulkowski MS, Mast EE, Seeff LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. Clin Infect Dis. 2000;30(Suppl 1):S77–84.
91. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33(4):362–9.
92. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol. 1997;26(1):1–5.
96. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;32(3):492–7.

97. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol. 2001;34(5):730–9.

98. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349(9055):825–32.

99. Prasad L, Spicher VM, Negro F, Rickenbach M, Zwahlen M, Swiss Hepatitis C Cohort Study G. Little evidence that hepatitis C virus leads to a higher risk of mortality in the absence of cirrhosis excess alcohol intake: the Swiss Hepatitis C Cohort Study. J viral hepatitis. 2009;16(9):644–649.

100. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA. 2000;283(1):74–80.

101. Inductivo-Yu I, Bonacini M. Highly active antiretroviral therapy-induced liver injury. Curr Drug Saf. 2008;3(1):4–13.

102. Knox TA, Oleson L, von Moltke LL, Kaufman RC, Wanke CA, Greenblatt DJ. Ritonavir greatly impairs CYP3A activity in HIV infection with chronic viral hepatitis. JAIDS. 2008;49(4):358–68.

103. Squillace N, Lapadula G, Torti C, et al. Hepatitis C virus antibody-positive patients with HIV infection have a high risk of insulin resistance: a cross-sectional study. J Hepatol. 2008;9(3):151–9.

104. Mehta SH, Moore RD, Thomas DL, Chaisson RE, Sulkowski MS. The effect of HAART and HCV infection on the development of hyperglycemia among HIV-infected persons. JAIDS. 2003;33(5):577–84.

105. Balagopal A, Philp FH, Astemborski J, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Gastroenterology. 2008;135(1):226–33.

106. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. AIDS. 2005;19(Suppl 3):S99–105.

107. Cooper CL, Cameron DW. Effect of alcohol use and highly active antiretroviral therapy on plasma levels of hepatitis C virus (HCV) in patients coinfected with HIV and HCV. Clin Infect Dis. 2005;41(Suppl 1):S105–9.

108. Cooper CL. An overview of HIV and chronic viral hepatitis co-infection. Dig Dis Sci. 2008;53(4):899–904.

109. Knox TA, Oleson L, von Moltke LL, Kaufman RC, Wanke CA, Greenblatt DJ. Ritonavir greatly impairs CYP3A activity in HIV infection with chronic viral hepatitis. JAIDS. 2008;49(4):358–68.

110. Blanco F, Barreiro P, Ryan P, et al. Risk factors for advanced liver fibrosis in HIV-infected individuals: role of antiretroviral drugs and insulin resistance. J Viral Hepat. 2011;18(1):11–6.

111. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999;30(4):1054–8.

112. Benhamou Y, Di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. Hepatology. 2001;34(2):283–7.

113. Poynard T, Mathurin P, Lai CL, et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol. 2003;38(3):257–65.

114. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34(6):1193–9.

115. Marcellin P, Pequignot F, Delarocque-Astagneau E, et al. Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. J Hepatol. 2008;48(2):200–7.

116. McGinnis KA, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. Hepatocellular carcinoma and non-Hodgkin’s lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. J Clin Oncol. 2006;24(31):5005–9.

117. Loko MA, Salmon D, Carrieri P, et al. The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVII): early findings, 2006–2010. BMC Infect Dis. 2010;10:303.

118. Soriano V, Puoti M, Garcia-Gasco P, et al. Antiretroviral drugs and liver injury. AIDS. 2008;22(1):1–13.

119. Butt AA, Justice AC, Skanderson M, Good C, Kwoh CK. Rates and predictors of hepatitis C virus treatment in HIV/HCV-coinfected subjects. Aliment Pharm Therap. 2006;24(4):585–91.

120. Butt AA, Khan UA, Shaikh OS, et al. Rates of HCV treatment eligibility among HCV-monoinfected and HCV/HIV-coinfected patients in tertiary care referral centers. J Hepatol Clin Trials. 2009;10(1):25–32.

121. Mendes-Correa MC, Martins LG, Tenore S, et al. Barriers to treatment of hepatitis C in HIV/HCV coinfected adults in Brazil. Braz J Infect Dis. 2010;14(3):237–41.

122. Nunes D, Saiz R, Libman H, Cheng DM, Vidaver J, Samet JH. Barriers to treatment of hepatitis C in HIV/HCV-coinfected adults with alcohol problems. Alcohol Clin Exp Res. 2006;30(9):1520–6.

123. Mark KE, Murray PJ, Callahan DB, Gunn RA. Medical care and alcohol use after testing hepatitis C antibody positive at STD clinic and HIV test site screening programs. Public Health Rep. 2007;122(1):37–43.

124. Tsui JJ, Saiz R, Cheng DM, et al. Awareness of hepatitis C diagnosis is associated with less alcohol use among persons co-infected with HIV. J Gen Intern Med. 2007;22(6):822–5.
125. Boyd A, Lasnier E, Molina JM, et al. Liver fibrosis changes in HIV-HBV-coinfected patients: clinical, biochemical and histological effect of long-term tenofovir disoproxil fumarate use. Antivir Ther. 2010;15(7):963–74.
126. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol. 2006;44(1):47–55.
127. McGovern BH, Birch C, Zaman MT, et al. Managing symptomatic drug-induced liver injury in HIV-hepatitis C virus-coinfected patients: a role for interferon. Clin Infect Dis. 2007;45(10):1386–92.
128. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus Interferon Alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351(5):451–9.
129. Torriani FJ, Rodriguez-Torres M, Rockstroh J, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351(5):438–50.
130. Cacoub P, Halfon P, Rosenthal E, et al. Care of hepatitis C virus infection in human immunodeficiency virus-infected patients: modifications in three consecutive large surveys between 2004 and 2009. J Hepatol. 2010;53(2):230–7.
131. Holmberg SD, Moorman AC, Greenberg AE. Trends in rates of myocardial infarction among patients with HIV. N Engl J Med. 2004;350(7):730–2.
132. Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation. 2008;118(2):8.
133. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17(8):1179–93.
134. Mangili A, Polak JF, Quach LA, Gerrier J, Wanke CA. Markers of atherosclerosis and inflammation and mortality in patients with HIV infection. Atherosclerosis. 2011;214(2):468–73.
135. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003;349(21):1993–2003.
136. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006;12(12):1365–71.
137. Falcone EL, Mangili A, Skinner S, Alam A, Polak JF, Wanke CA. Framingham risk score and early markers of atherosclerosis in a cohort of adults infected with HIV. Antivir Ther. 2011;16(1):1–8.
138. Hsue PY, Lo JC, Franklin A, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation. 2004;109(13):1603–8.
139. Freiberg MS, Cheng DM, Kraemer KL, Saizt R, Kuller LH, Samet JH. The association between hepatitis C infection and prevalent cardiovascular disease among HIV-infected individuals. AIDS. 2007;21(2):193–7.
140. Happel KI, Nelson S. Alcohol, immunosuppression, and the lung. Proc Am Thorac Soc. 2005;2(5):428–32.
141. Fernandez-Sola J, Junque A, Estruch R, Monforte R, Torres A, Urbano-Marquez A. High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. Arch Intern Med. 1995;155(15):1649–54.
142. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–93.
143. Moss M, Parsons PE, Steinberg KP, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med. 2003;31(3):869–77.
144. Joshi PC, Guidot DM. The alcoholic lung: epidemiology, pathophysiology, and potential therapies. Am J Physiol Lung Cell Mol Physiol. 2007;292(4):L813–23.
145. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the pulmonary complications, ICU support, and prognostic factors of hospitalized patients with HIV (PIP) study. Chest. 2000;117(4):1017–22.
146. Huang L, Crothers K. HIV-associated opportunistic pneumonias. Respir Med. 2009;103(4):474–85.
147. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med. 2011;183(3):388–95.
148. Michielsen K, Chersich MF, Luchters S, De Koker P, Van Rossem R, Temmerman M. Effectiveness of HIV prevention for youth in sub-Saharan Africa: systematic review and meta-analysis of randomized and nonrandomized trials. AIDS. 2010;24(8):1193–202.
149. Samet JH, Walley AY. Interventions targeting HIV-infected risky drinkers: drops in the bottle. Alcohol Res Health. 2010;33(3):267.
150. Daepen JB, Gaume J, Bady P, et al. Brief alcohol intervention and alcohol assessment do not influence alcohol use in injured patients treated in the emergency department: a randomized controlled clinical trial. Addiction. 2007;102(8):1224–33.
151. Parsons JT, Golub SA, Rosof E, et al. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. JAIDS. 2007;46(4):443–50.
152. Kelly JA, Murphy DA, Sikkema KJ, et al. Randomised, controlled, community-level HIV-prevention intervention for sexual-risk behaviour among homosexual men in US cities. Community HIV Prevention Research Collaborative. Lancet. 1997;350(9090):1500–5.
153. Beich A, Thorsen T, Rollnick S, Beich A, Thorsen T, Rollnick S. Screening in brief intervention trials targeting excessive drinkers in general practice: systematic review and meta-analysis. BMJ. 2003;327(7414):536–42.

154. Kaner EF, Beyer F, Dickinson HO, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev. 2007;18(2):CD004148.

155. Emmen MJ, Schippers GM, Bleijenberg G, Wollersheim H. Effectiveness of opportunistic brief interventions for problem drinking in a general hospital setting: systematic review. BMJ. 2004;328(7435):318.

156. D’Onofrio G, Degutis LC. Preventive care in the emergency department: screening and brief intervention for alcohol problems in the emergency department: a systematic review. Acad Emerg Med. 2002;9(6):627–38.

157. Velasquez MM, von Sternberg K, Johnson DH, Green C, Carbonari JP, Parsons JT. Reducing sexual risk behaviors and alcohol use among HIV-positive men who have sex with men: a randomized clinical trial. J Consult Clin Psychol. 2009;77(4):657–67.

158. Samet JH, Horton NJ, Meli S, et al. A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol setting. Antivir Ther. 2005;10(1):83–93.

159. Kelly JA, St Lawrence JS, Stevenson LY, et al. Community AIDS/HIV risk reduction: the effects of endorsements by popular people in three cities. Am J Public Health. 1992;82(11):1483–9.

160. Miller RL, Klotz D, Eckholdt HM. HIV prevention with male prostitutes and patrons of hustler bars: replication of an HIV preventive intervention. Am J Community Psychol. 1998;26(1):97–131.

161. Group NCHSPT. Results of the NIMH collaborative HIV/sexually transmitted disease prevention trial of a community popular opinion leader intervention. JAIDS. 2010;54(2):204–14.

162. Fritz K, McFarland W, Wyrod R, et al. Evaluation of a peer network-based sexual risk reduction intervention for men in beer halls in Zimbabwe: results from a randomized controlled trial. AIDS Behav. 2011;15(8):1732–44.

163. Conigliaro J, Gordon AJ, McGinnis KA, Rabeneck L, Justice AC, Veterans Aging Cohort 3-Site S. How harmful is hazardous alcohol use and abuse in HIV infection: do health care providers know who is at risk? JAIDS. 2003;33(4):521–5.

164. Justice ACMDP, Lasky ERNBSN, McGinnis KAMS, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: a comparison of disease measurement strategies. Med Care (Alcohol in HIV Infection: Insights from the Veterans Aging Cohort Study and the Veterans Affairs National Health Information System). 2006;44(8):S52–60.

165. Conigliaro JMDMPH, Justice ACMDP, Gordon AJMDMPH, Bryant KP, for the VA, Behavior Change Research G. Role of alcohol in determining human immunodeficiency virus (HIV)-relevant outcomes: a conceptual model to guide the implementation of evidence-based interventions into practice. Med Care (Alcohol in HIV Infection: Insights from the Veterans Aging Cohort Study and the Veterans Affairs National Health Information System). 2006;44(8):S1–6.

166. Galvan FH, Bing EG, Fleishman JA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and services utilization study. J Stud Alcohol. 2002;63(2):179–86.

167. Lucas GM, Gebo KA, Chaisson RE, Moore RD. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS. 2002;16(5):767–74.

168. Kleeberger CA, Phair JP, Strathdee SA, Detels R, Kingsley L, Jacobson LP. Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study. JAIDS. 2001;26(1):82–92.