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Expanding Research on the Role of Alcohol Consumption and Related Risks in the Prevention and Treatment of HIV/AIDS

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This article is a review of some of the major epidemiological, behavioral, biological, and integrative prevention research issues and priorities in the area of HIV/AIDS and alcohol consumption. Drinking alcohol increases both the risk for infection with HIV and related illnesses and the morbidity and mortality of patients who progress to AIDS. New and improved measurement procedures have helped in assessment of the complex patterns of alcohol use, identification of intervening explanatory mechanisms for risk behaviors and contexts, and determination of intervention outcomes. Both the direct and indirect effects of alcohol misuse appear to be major contributors to both the risk for infection with HIV and the transmission of HIV/AIDS at the individual and population levels. There is increasing evidence that perhaps no level of alcohol consumption is “safe” for those who are HIV infected and receiving antiretroviral treatment. Interdisciplinary basic behavioral and biomedical research is needed to develop comprehensive culturally appropriate strategies for programs that can be effectively delivered in community contexts in the United States and abroad and that focus on the integration of our understanding of individual behaviors, high-risk group membership, biological mechanisms, and the social and physical environments that place individuals at risk for HIV infection. High-priority topics include improving adherence to antiretroviral medications, prevention of infection in young minority women in the United States, and treatment of HIV+ pregnant women who are alcohol abusers to prevent adverse fetal outcomes, which is an international focus in under-resourced settings in Africa.

Keywords AIDS; alcohol consumption; alcohol misuse; at risk; behavior; CNS; HIV; immune

Overview

Complex patterns of alcohol use—which often result in alcohol use disorders and the need for alcohol user treatment or intervention—are frequently linked with unprotected sex with partners who may be HIV+ or who are injection drug users. These patterns of alcohol use place individuals at risk for contracting HIV. Individuals with alcohol use disorders are more likely than the general public to contract HIV (the virus that causes AIDS.) Similarly, people with HIV are more likely to have serious problems with alcohol use at some time during their life (Petry, 1999). Alcohol consumption likely plays a pivotal, but incompletely defined,
role in HIV viral replication, disease progression, poteniation of comorbid conditions, and increased frequency of adverse medical events from treatment (drug toxicity). There are clear implications for these findings in the prevention and treatment research in those countries that have been regularly using medications for the treatment of AIDS and those that are beginning to develop the capacity to distribute and use these drugs. As has been continually emphasized by major world health organizations both in the United States and abroad, improved prevention strategies should be the primary focus for stopping the spread of HIV, and effective treatment is part of an overall prevention plan.

These complex outcomes among HIV-infected individuals who drink may be especially salient among American veterans. This population represents the largest single population receiving care within a single system of care in the United States. In preliminary work with HIV-positive veterans, 33% report binge drinking, 21% report hazardous drinking, and 32% have diagnosis of alcohol addiction or dependence (Justice et al., 2004). These veterans suffered from an increase in AIDS-related illnesses, including neurological, respiratory, and metabolic disorders. International studies have reported even higher rates of alcohol consumption–related problems in HIV-infected individuals being seen in treatment clinics. Similarly, preliminary work from Kenya has indicated that over 60% of patients seen in clinics receive scores on the AUDIT, a standardized internationally validated alcohol questionnaire (Babor et al., 2001), indicating the presence of alcohol use disorders (Shaffer et al., 2004). Other than alcohol misuse, little other substance misuse is found in many populations in Africa (World Health Organization ([WHO], 2002). Similar levels of alcohol use disorders are being found in HIV+ patients in other African settings (Oyugi et al., 2004; Bangsberg et al., 2004). Delivery of antiretroviral medications, which interact with alcohol use, may severely compromise the effectiveness of these medications and directly lead to increases in mortality (Braithwaite, in press; Samet et al., 2005).

Role of NIAAA: Goals of Behavioral and Biomedical Research

The National Institute on Alcohol Abuse and Alcoholism (NIAAA), an institute within the National Institutes of Health, plays a unique role in coordinating behavioral and biomedical research on the role of alcohol use and misuse in the prevention and treatment of HIV/AIDS. NIAAA is involved in both domestic and international AIDS research activities and facilitates collaboration between institutes and agencies on alcohol consumption and HIV/AIDS relevant research issues. A comprehensive plan for prevention of HIV and AIDS developed by the National Institutes of Health (NIH) directly acknowledges the role of drinking and alcohol misuse in the context of developing comprehensive prevention strategies as demonstrated in the recent testimony to Congress:

“Our prevention research priorities include the development of vaccines, topical microbicides, strategies to prevent mother-to-child transmission, including a better understanding of risk associated with breast-feeding, management of sexually transmitted diseases (STDs), and behavioral research strategies, including interventions related to drug and alcohol use. Efforts continue to identify the most appropriate intervention strategies for different populations and sub-epidemics in the U.S. and around the world.” (Dr. Jack Whitescarver’s Director, Office of AIDS Research NIH, Congressional Appropriations Testimony FY 2006)
Alcohol Consumption–Related Morbidity and Mortality

Alcohol is the most frequently abused substance in the United States. It is estimated that 110 million people age 12 and over are current alcohol users, 32 to 40 million drink hazardedly, and 11 to 14 million are diagnosed as alcohol dependent (Rehm, 2001; Rehm and Gmel, 2000; Rehm et al., 2004). Individuals with hazardous drinking patterns are likely to cause harm to themselves or to others and represent a disproportionate number of primary care and emergency room patients. In the United States, its misuse results in approximately 100,000 deaths each year through accidents and alcohol use-related disease. Alcohol is also one of the most commonly misused drugs in both developed and underdeveloped nations (Saxena, 1997). Drinking directly impacts multiple medical conditions and their treatment. These include developmental disabilities related to fetal alcohol syndrome and other fetal maternal outcomes such as sudden infant death syndrome, cardiovascular disease, and cancer, to name a few. In addition, the social consequences of alcohol misuse must also be identified. These consequences, which are often also associated with HIV/AIDS infection, include unintended pregnancy, sexually transmitted disease (STD) transmission, tuberculosis (TB) and multiple drug resistant versions of TB, liver disease, hepatitis C virus (HCV), and perhaps 60 other medical diseases.

When the measurable impact of alcohol misuse is considered in terms of consequences and medical disabilities throughout the world, including STD transmission and violence, alcohol is ranked as the fourth leading cause of disability-adjusted life years lost, overall; it is the 1st leading cause in developing countries and 11th in the least developed countries. Drinking has been particularly implicated in increased mortality rates and is used in predicting declining populations in Russia and other countries (World Health Report, 1999). In many developing countries where the impact is greatest, poor measurement of alcohol use and related consequences makes it difficult to accurately assess this impact. Expanding our understanding of the accurate measurement of alcohol use in HIV/AIDS prevention and treatment is essential to reducing the rates of HIV infection and expanding the treatment of a range of associated alcohol consumption–related problems.

Defining Alcohol Use and Misuse: Quantity/Frequency, Abuse, and Dependence

Understanding the exact role of alcohol use and misuse in increasing the lifetime risk for HIV/AIDS involves measuring multiple alcohol-specific factors. These factors include alcohol’s pharmacological and psychological action, social and physical contexts for use of alcohol, and environmental and cultural dimensions that determine general access and availability of alcohol. Researchers in the field of alcohol studies have developed a set of processes and definitions that are being applied to the use and misuse of alcohol by individuals. These definitions help to distinguish the many constructs that are available for measuring alcohol misuse: (1) the standardized measurement of alcohol content to identify the role that ethanol has in primarily biological processes such as liver toxicity and neurological degeneration, (2) quantity and frequency of standard measures of a drink to describe patterns of drinking over time, and (3) a definition of alcohol abuse that includes concepts of hazardous and harmful use, and refers to high rates of episodic or situationally dependent drinking (parties) in which individuals drink to excess. This repeated excessive drinking, such as drinking to “blackout,” may have physiological implications such as

1The journal’s style utilizes the category substance abuse as a diagnostic category. Substances are used or misused; living organisms are and can be abused. Editor’s note.
neural damage ("harmful drinking") or environmental consequences such as car accidents, unplanned pregnancy, and acquiring HIV through risky sex ("hazardous drinking").

Most important in the alcohol field is the concept of "alcohol dependence," which is both a diagnosis and the description of a process. The process of dependence (as originally proposed by Edwards et al., 1982) includes physiological, psychological, and social factors that become interdependent and mutually reinforcing. These factors lead to sustained drinking and need for treatment. Individuals who are considered alcohol dependent exhibit physiological processes (withdrawal or tolerance), cognitive preoccupation with seeking and using alcohol, and socially dysfunctional behaviors such as neglect of social role activities (child care, job, etc.) or interruption of daily activities due to withdrawal (such as avoiding work due to hangover). Often, alcohol consumption–related outcomes are referred to as alcohol use disorders, which are identified within medical and substance user treatment settings.

A variety of these characteristics of alcohol use, abuse, and dependence has direct implications for HIV/AIDS research. So, for example, individuals who are infected with HIV may take antiretroviral medications during the week and discontinue their use on weekends to drink. This pattern of alcohol use and discontinuation of AIDS medications may directly contribute to the development of viral resistance to medications and to more rapid disease progression for a number of reasons (Samet, 2005, Braithwaite, in press). These distinctions are important in the treatment, recovery, and relapse of alcohol-dependent HIV+ individuals seeking substance abuse treatment. Although quantity and frequency of alcohol ingestion has been associated to medical outcomes, how much and how often someone drinks can also have implications for other domains of daily activity. These domains might include the amount of daily income used to purchase alcohol instead of meeting other more important family economic needs such as adequate shelter and nutrition and are critical issues among impoverished individuals (Normen et al., 2005).

**HIV/AIDS Incidence and AIDS-Related Mortality**

HIV and STDs are among the most common infectious diseases. There are an estimated 40,000 to 60,000 new cases of HIV infection per year in the United States. The rate of growth in new cases is particularly high among young women (who now account for 47% of new cases) and among young adults aged 13–29 (who now comprise 39% of new cases). New HIV infections also appear to be resurging among young gay and bisexual men nationwide and may be focused within party-going and substance-using cohorts (CDC, 2004d). The U.S. Centers for Disease Control and Prevention (CDC, 2004d) reported that an estimated 850,000–950,000 persons in the United States are living with HIV, including 180,000–280,000 who do not know they are infected. To examine trends of diagnoses for 2000–2003, CDC analyzed HIV and AIDS together as HIV/AIDS (i.e., HIV infection with or without AIDS), counted by the year of earliest reported diagnosis of HIV infection. From 2000 to 2003, in 32 states that used confidential name-based reporting of HIV and AIDS cases for >4 years, the overall annual rate of diagnosis of HIV/AIDS remained stable. However, rates among non-Hispanic Black females were 19 times higher than rates among non-Hispanic White females, underscoring the need for continued emphasis on programs targeting females in racial/ethnic minority populations, their partners, and their families to reduce the number of cases of HIV/AIDS.

AIDS is one of the leading causes of death among men and women between the ages of 25 and 44, many of whom became infected as young adults. Although deaths
from AIDS are beginning to decline, the characteristics of these deaths are shifting in response to chronic disease management practices using highly active antiretrovirals (and their toxic interactions with alcohol and other drugs). In 2004 in the United States an estimated 14,000 deaths were directly attributed to AIDS-related diseases as compared with approximately 40,000 in 1996. However, individuals now live longer with effective treatment of AIDS, and mortality is attributed to other non–AIDS–related diseases such as liver failure. Internationally, the scope and impact of the AIDS epidemic is growing rapidly. Limited epidemiological information makes it difficult to accurately estimate incidence and prevalence rates in developing countries. However, the overall level of infection is currently estimated at approximately 45 million and will surpass 65 million by 2010 (WHO, 2002). Increased incident rates can be found in some of the countries with the highest per capita drinking rates and in specific heavy drinking populations at risk for HIV in these countries (e.g., Russia, India, China, and South Africa).

**Converging Epidemics: Alcohol and HIV/AIDS**

One perspective on understanding the relationship of alcohol use and HIV infection involves an examination at the population level of converging epidemics. Rapid increases in substance abuse (including alcohol) and HIV infection can be conceptualized as separate but converging epidemics embedded in a context of violence (wars, homicides, and domestic abuse). As the two epidemics converge, there are increasing numbers of individuals at risk for alcohol use disorders, HIV infection, and rapid progression to AIDS. Understanding multiple levels of analysis of the relationship between drinking behavior and HIV risk (and treatment for AIDS) provides a basis for developing ecological models with predictive implications for a broad range of population level interventions and health outcomes. In addition, identifying effective alcohol and HIV/AIDS prevention and treatment strategies (a goal of the NIAAA) requires putting this knowledge to use in the settings and situations where individuals can be influenced to reduce their risk for contracting or transmitting AIDS. The settings for interventions include schools, homes, doctors’ offices, bars, alcohol or HIV treatment facilities, and other community venues. Other sources of influence for prevention and treatment include the media and policies, regulating the sale of alcohol, particularly to adolescents and young adults. Research on how these interventions are developed and implemented will help to address the spread of HIV in specific cultural contexts that promote the use and abuse of alcohol and the populations at greatest risk for contracting HIV.

This article addresses the following topics:

1. Behavioral issues: basic behavioral research and prevention
2. Biological issues: basic biological research and treatment
3. Prevention science: integrating behavioral and biological perspectives
4. Continuing priorities for alcohol consumption and HIV-related research

**Behavioral Issues: Basic Behavioral Research and Prevention**

*Developing Comprehensive Models for Alcohol Use and HIV Risk Behaviors*

Although the need for preventing the transmission of HIV in alcohol and substance abuse risk groups is a pressing public health concern, the development and testing of interventions in these groups should be informed by sound scientific research. Systematic reviews of the
relationship between alcohol consumption and STDs (including HIV) has supported an overall association (referred to as a “global association” between drinking behavior and disease outcome) (Leigh and Stall, 1993; Seage et al., 2002). However this association arises primarily in cross-sectional studies where “heavy alcohol use” is a clear marker for multiple risk behaviors among individuals. Although there are limitations in cross-sectional studies to determining the exact nature of these relationships, there are clear implications for prevention planners, clinicians, and individual patients at risk for HIV/STDs. Identification of “heavy drinkers” or those that attend high-risk bar settings often targets a portion of those who are at greatest risk for HIV infection and in need of prevention activities. Many methodological issues make it difficult to clearly identify specific patterns of alcohol consumption with the greatest risk; advanced consideration of methodological issues is needed (Cook and Clark, 2005; Seage et al., 2002; Stall et al., 2001). However, tests for the importance of alcohol–sexual risk relationships may be put in place by the use of interventions that include specific components related to key mediating variables. These mediators include attitudes, beliefs, and behaviors as critical variables that may achieve causal status (Bryant, 1997).

Alcohol use has long been identified as a determinant of risky sexual behavior. Consequently, many intervention campaigns focus on reducing sex under the influence of alcohol or drugs with the expectation that “safer” sex will result. Safer sex has been defined in two domains: increased likelihood of effective condom use and reduction in number of casual partners with unknown HIV status. Within a specific situation, consistent or inconsistent condom use has been difficult to predict from knowledge of alcohol usage within a specific situation. A variety of potential explanations and mediators may limit the role of a single substance use dimension predicting complex behavioral outcomes for opportunistic behaviors such as unprotected sex (Weinhardt and Carey, 2000). The implication of this research is that finding key variables to intervene or to interrupt a causal chain may involve many time frames for understanding the integration of behavioral repertoires into stable patterns of behavior. Simply reducing alcohol consumption in targeted groups of high-risk individuals may not eliminate or change context specific behavior once it has been established.

**Theoretical Perspectives for Individual Alcohol-Related Risk Behavior**

A number of theoretical perspectives have been proposed to explain the relationship between alcohol consumption and sexual risk-taking (alcohol myopia, disinhibition, excusatory behavior, expectancies, individual differences such as impulsivity, stimulus seeking) (see below). Early research on direct causal explanations focused on the disinhibiting properties of alcohol use. However, these psychophysiological explanations have been modified to include cognitive and affective factors such as alcohol use-related sexual expectancies, alterations in risk judgments, memory processes, and, most importantly, the measurement of arousal (Cooper, 2002; Dermen et al., 1998, 2000). Competing theories of the effects of alcohol misuse within specific situations predict different outcomes that are testable within an experimental framework.

These theories include ones focused on alcohol-specific cognitive effects such as alcohol myopia (Steele and Josephs, 1990), disinhibition and risk perception (George and Stoner, 2000; George et al., 2000; Kalichman, 2004; Maisto et al., 2004), excusatory behavior, physiological arousal (Abbey, 2002; George, 2000), personality (Haertzen and Miner, 1965), personal scripts (Duffy et al., 2004), and a variety of other potential
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approaches generally applicable to social and situational determinants of context specific behavior. These approaches used to establish the specific role of alcohol in a particular encounter are further complicated by individuals’ understanding of the potential role of alcohol and their ability to self-monitor their behavior so that sexual intentions for seeking a specific risk level for behavior may mediate their use of alcohol (MacDonald et al., 2000; Stall et al., 2001). Understanding these theoretical relationships will have implications for developing effective preventive interventions. Some of the clearest relationships between alcohol use and cognitive and affective mediators that impact sexual risk taking have been examined in laboratory settings and with high-risk groups. How this experimental research translates into the examination of real-world interactions between individuals and prevention programs is a point of emphasis for implementing a comprehensive prevention science agenda (Bryant et al., 1997).

Basic Behavioral Experimental Research

The use of alcohol myopia perspective has been effective at explaining some of the paradoxical effects on male and female risk perception (Cooper, 2002). However, laboratory approaches provide further evidence for the role of alcohol in sexual decision making. Basic behavioral experimental and psychophysiological research provides some of the strongest support for a direct causal relationship between alcohol use, its psychological and pharmacological effects, and sexual risk taking for both men and women (George and Stoner, 2000; Maisto et al., 2004). Experimental settings may be used to test predictions derived from different theoretical perspectives. A key component to this work is the ability to directly measure physiological characteristics such as arousal as mediators of alcohol use on sexual decision making (George, 2000a,b) in addition to the impact of self-reported alcohol-related “myopia” or sexual expectancies. These findings are consistent with past research showing that alcohol consumption can have detrimental effects on determinants of sexual health behavior and that individual differences are important predictors of risk behavior. However, this work, like all biomedical or behavioral laboratory work, is limited in its generalizability to real-world settings and needs to be further developed in the context of high-risk groups to understand its implications for preventive interventions (Kalichman, 2004).

High-Risk Groups. There is an overlap between individuals “at risk” for alcohol use disorders and individuals at risk for HIV infection. These individuals form so-called dual or multiple-risk groups and often suffer from mental health problems as well. The terms “dual risk” or “multiple risk” refer to an empirically driven epidemiological category, not necessarily one with diagnostic or etiological implications. That is, the terminology may suggest a particular adaptational lifestyle, as supported by evidence of the well-documented “natural recovery” literature. Dual or multiple-risk groups of heterogeneous individuals may share a common etiological problem that places them at highest risk and are often

2The terminology is intended to refer to an empirically driven category without reference to any stereotypes embedded in this terminology. The creation of any taxonomy is a function of the characteristics of criteria used as well as the perspective of the categorizer. In this case we do not mean to create a new diagnostic taxonomy but rather to refer to a particular adaptational lifestyle. These conditions are neither as predictable nor as controllable as intervention agents and other stakeholders tend to believe and communicate, despite evidence cited by the well-documented “natural recovery” literature (Klingemann and Sobell, 2001).
the most socially vulnerable, thus providing a basis to screen for further examination and intervention—while at the same time requiring care to avoid stigmatization.

Within the United States and other countries where antiretroviral drugs are readily available, the AIDS treatment for these dual-risk groups has shifted toward individuals that are often considered “hard to reach.” Their use of these new agents is often ineffective; these individuals often have less access to these agents as a result of being more marginalized or lacking adequate social support for their use (Burnam, 2001; Shapiro, 1999). Studies have been initiated in a variety of medical (e.g., Veterans Aging Cohort Study) and nonmedical settings (e.g., HIV/AIDS Treatment Adherence, Health Outcomes, and Cost Study) to address the treatment of complex comorbidity among HIV+ individuals, particularly those who are homeless or at risk for infection due to homelessness (Ennett et al., 1999). In the context of these studies, funders of HIV, mental health, and substance abuse research are increasingly seeking substantial constituent representation and comments from individuals for whom prevention or treatment interventions are designed to help with sustained delivery of effective interventions (Brown et al., 2000, 2002; Rollet and Winiarski, 2002; Weissman et al., 1995).

Multiple-risk groups include, for example, gay men, runaway and homeless youth, drug users, victims of sexual coercion, and those with other disease such as TB or HCV. These groups are often at risk because of vulnerable lifestyles and share similar ages for onset of “heavy” drinking and HIV/STD infection. The “resiliency” literature may serve to inspire studies to identify possible posited “protective factors” in these multiple-risk populations, whether these factors include individual psychological characteristics (e.g., good intellectual skills or self-efficacy in other realms) or behavioral factors (such as high interpersonal skills), access to beneficial interpersonal relations (such as mentors), participation in other activities, supportive environments, and socioeconomic advantages (Johnson and Wiechelt, 2004; Johnson et al., 2003). Most current research, however, is related to levels of risk and problem identification as a result of group membership (as, e.g., alcohol and drug use among young gay men). Estimates relying on national probability studies of incidence of HIV infection are often cited in support of the need for targeted interventions in specific multiple-risk groups (e.g., African American women) yet do not provide information on whom specifically or by what means individuals within these groups are at risk.

High-Risk Settings and Social Contexts for Group Interactions

Drinking and HIV risk behaviors may often occur together in the same physical location (e.g., high-risk bars) or during a particular activity (e.g., exchange of drugs and alcohol for sex.) Multiple HIV risks are often shared by individuals and the social network to which they belong, and specific types of social networks are associated with specific settings such as bars, bathhouses where liquor is sold and consumed, and specific events such as spring break for college students and social gatherings for specific celebrations (e.g., Mardi Gras, circumcision, or coming of age rituals; Langeni, 2005). It is useful to clarify the implications of membership in substance use/nonuse social networks, particularly in relationship to other social and cultural factors such as rates of STDs (Adimora and Schoenbach, 2005) including networks (of couples) where HIV is present and there is the potential for transmission.

It is helpful to incorporate social network theory, a potentially important tool for intervention planning, implementation, and assessment (Barabási, 2005; Latkin, 2004). Naturally occurring social networks often operate in alcohol use settings which can either
increase or decrease HIV risk behaviors depending on setting and network characteristics. The combination of alcohol setting and network characteristics has been effectively exploited to develop and implement effective interventions (Kelly et al., 1991; Latkin and Knowlton, 2005). An understanding of social network and behavioral settings research can be used to understand and intervene in social behaviors within a larger community context. Methods for geographically mapping these locations and for socially mapping networks of individuals were used in the past for understanding the distribution of HIV infection among gay men (Stall, 2001) and are being used to target preventive interventions among alcohol users (Scribner, 2000).

Setting-Based Interventions

Characteristics of social and personal networks and behavioral settings have been linked to HIV risk behaviors and transmission of HIV and other sexually transmitted infections within alcohol use settings such as bars or bath houses (Latkin et al., 2005). Network analysis can be helpful in delineating population-specific social influences on HIV risk behaviors and behavioral norms that are important for sustaining risk reduction. Interventions developed for these contexts often focus on structural level factors such as social roles, social identities, norms that can be operationalized in network terms, and applied to HIV prevention intervention tailored to drinking contexts. Structural approaches can be utilized to sample high-risk hidden populations (Des Jarlais, 2000). Application of these concepts to network intervention may improve our ability to alter social norms of HIV risk behaviors, and social-level risk reduction through modifications of networks may lead to sustainable intervention outcomes in conjunction with alcohol use behaviors that reinforce both characteristics of the network and risk behaviors (Fritz et al., 2004). Studies among adolescents in their school settings have demonstrated the relationship between the characteristics of individuals in the core and peripheral networks of students and substance abuse and sexual risk behaviors (Rashad and Kaestner, 2004). To be effective and sustainable, HIV-prevention interventions need to be sufficiently powerful to counteract prevailing social norms and diffuse through the targeted community to provide social reinforcement for behavior change. Environmental influences on HIV risk behaviors, social identities, and norms in bar-based contexts remain important targets for HIV-prevention intervention (Kelly et al., 1991). Intervention approaches are being tested in bar-based settings; these approaches offer participants socially meaningful and rewarding behavioral options that are consistent with valued prosocial identities or roles (Fritz et al., 2004).

Alcohol User Treatment Settings

It is necessary to establish the level of risk behaviors in current cohorts of HIV+ individuals in substance user treatment to develop an understanding of effective levels of change among those who are alcohol dependent. The impact of alcohol user treatment on hospitalizations among patients with HIV and alcohol consumption–related problems indicates that these systems of treatment are poorly integrated and that substance user treatment does not impact HIV treatment (Palepu et al., 2005), and this represents a missed opportunity for HIV prevention. These findings are consistent with those that physicians who provide HIV treatment are unaware of individuals drinking problems (Conigliaro et al., 2004). Typically among individuals in alcohol user treatment, over 50% report inconsistent condom use, having multiple sexual partners, trading sex for money, and engaging in intermittent intravenous drug use. Engagement in alcohol user treatment alone may not lead to a
reduction in these behaviors, which differs from much earlier findings by Avins et al. (1997), who found a 30% reduction simply with alcohol user treatment alone. Changing these behaviors may be increasingly difficult with changes in the nature of the HIV epidemic and, in any case, presents a continuing challenge for alcohol use(r) and HIV researchers (Lucas et al., 2002).

Further research is needed to identify issues that compromise access to HIV treatment and adherence to treatment among alcohol-using and -misusing seropositive populations. Special populations of interest include HIV-infected gay men, pregnant women, and underserved minorities. In addition, the impact of treatment settings and services needs to be identified, particularly for alcoholics in institutional (e.g., prisons) and mutual-help (e.g., Alcoholics Anonymous) treatment settings. Research is being designed and interventions tested to the environmental dimensions and “demands” of programs that promote engagement in treatment. Engagement in interventions of at-risk and hard-to-reach groups is a critical issue. Compliance with goals and effective use of techniques minimize and/or prevent the patient and the staff from not becoming therapeutically engaged as well as not maintaining stereotypic “substance abuser roles.”

The relative resources that need to be distributed into making interventions attractive, effective, and sustainable within hard-to-reach populations need to be carefully assessed before implementation (Morganstern, 2003).

**Prevention for HIV-Infected Subjects**

Research is needed to identify how successful alcohol intervention and HIV risk reduction strategies can be modified to become more effective in HIV-infected alcohol-using, -abusing, and -dependent populations. Theoretically grounded, yet practical, multicomponent interventions need to be developed that include accurate assessment of patterns of alcohol use, facilitation of medication with antiretrovirals, changing expectancies for effects of alcohol use on medication efficacy, and tailoring of pill taking to individual patients’ daily living circumstances. Multicomponent interventions are being tested to increase the adherence of individuals to antiretroviral therapy to a level of compliance that ensures therapeutic effectiveness (95%). However, these interventions have met with limited success among alcohol users. Both motivational and cognitive-behavioral multicomponent interventions did not enhance adherence (Morgenstern, 2003; Samet et al., 2005). Alcohol using HIV+ individuals continued to have poor adherence (less than 50%). Further research is needed to identify additional methods to increase adherence, such as supervised medication delivery or very simplified dosing regimens that can be titrated to medically effective levels. This research clearly highlights behavioral difficulties associated with increasing adherence. These difficulties may be enhanced by direct impairment through neurological deterioration of decision-making ability for those who continue to abuse alcohol (Samet et al., 2000, 2005).

In addition, recent pharmacological advances in the treatment of alcohol abuse (e.g., the advent of Naltrexone, bupinorphine for intravenous drug users) suggest that enhanced pharmacotherapies should be tested along with behavioral therapies for treating alcohol users (Bryant et al., 2002; NIAAA, 2004). Programs of research are focusing on prevention

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3Such dimensions include the following: a relationship dimension; a personal development dimension; maintenance and change dimensions; emotional catalyzer dimensions; information catalyzer and processing dimensions; environmental perceptions, attitudes, and values dimensions; problem-solving/adaptational dimensions; and dimension definer-boundary definer (Tuan, 1972; Winters et al., 1974).
for positives (Gerbert et al., 2004) and the need for positives to sustain health promoting behaviors and not “relapse” into risk taking with increased alcohol use (particularly as health is restored through effective antiretroviral use). This research also focuses on medical systems level variables, including physician attitudes and behaviors related to addressing alcohol and HIV risk behaviors in their patients.

**Primary Prevention Among Special Populations: School-Based Interventions**

Many young adults, despite widespread prevention and education efforts that target this age group, engage in behaviors that place them at risk of HIV infection. These behaviors include frequent experimentation with alcohol and other drugs before sex, sexual activity with different partners, and inconsistent safe-sex practices. In combination, these risky behaviors increase the likelihood of contracting HIV still further, raising increased concern about the spread of HIV among young adults. Past research indicates that students exposed to the alcohol education program used alcohol significantly less, gained more knowledge, acquired better attitudes, and reported fewer friends that drank (Perry et al., 1994). Classroom-based research on alcohol use (Perry et al., 1994) and sexual risk taking (Cupp et al., 2006) among adolescents have shown promising results. Hence, for the purposes of delaying and initiating alcohol use and sexual risk-taking behavior, what has been learned both in the United States and abroad should be incorporated into a culturally relevant intervention geared toward the needs of adolescents.

NIAAA has supported a variety of interventions among school-aged young adults that have demonstrated the utility of these interventions. Two examples, one developed early in the HIV epidemic for Native Americans and another developed for high-risk impulsive youth and tested in increasingly risky environments such as housing projects, are now being translated for application in South Africa. These programs of research help illustrate the importance of developing culturally appropriate and theoretically grounded approaches. However, most of this research is based on health behavior theory and the delivery of salient protective health messages and skills. Although research on health behavior theory is being conducted at a rapid pace, the extent to which the field is truly moving forward in understanding health behavior has been questioned (Noar and Zimmerman, 2005).

**HIV School-Based Prevention Curriculum**

*Native American Populations.* Native Americans remain a high priority group for research on alcohol and HIV/AIDS, focusing on behavioral and biomedical activities. In general, after infection with HIV/AIDS, Native Americans are seen later in care, have greater numbers of comorbidities (particularly alcohol-related liver and organ functioning), tolerate and adhere to antiretrovirals at a lower rate, and suffer poorer treatment outcomes in longitudinal cohort studies. Many of the interacting behavioral and biological factors endemic in Native American populations include stigmatization, nonadherence, intermittent patterns of therapeutics use and cessation, viral resistant strains, lack of accessibility to salvage therapeutic regimens for AIDS and AIDS-related diseases, poor integration of treatment into community settings, abundance of drinking venues, and other cultural or interpersonal factors related to health care acceptance (Hoffman-Goetz et al., 2005).

A convergence of risk for infection through the “heavy use” of alcohol and unprotected sexual risk behaviors frequently occurs on multitribal meeting occasions where young
natives come together. Prevention strategies tested in Navajo and Hopi natives in school-based settings and found to be of some success were disseminated through SAMSHA in the mid to late 1990s. These individuals, who are at risk because of alcohol and sexual or drug using risk behaviors, are identified both on and off of native lands and exist in high concentration in urban centers. Individuals often contract HIV infection in urban settings and return to their homes on reservations to receive terminal care. These HIV+ individuals undergo a high degree of stigmatization, and their care places a high burden on these indigenous native peoples, particularly those with limited resources. The quality of care for AIDS and AIDS-related diseases may be substandard depending on the tribe and its resources. There may be increased exposure to infection within the tribe through this mechanism (Simoni et al., 2006; Walters et al., 2002).

Effective culturally appropriate prevention programs were developed and tested through support from NIAAA. The products of these programs were then disseminated through SAMSHA in the form of specific intervention packages and support materials along with training of interventionists. Three processes were critical to program success: (1) selection of integrative theory to address the multidimensional antecedents of HIV/AIDS and substance abuse among Native Americans, (2) use of ethnographic methodology to obtain intensive input from target groups and community members to ensure cultural and developmental sensitivity in the curriculum, and (3) use of process and outcome evaluations of pilot and field trials to develop an optimal curriculum.

Teens in Public Schools in South Africa. Prior research on interventions in the United States indicates that combined classroom and media interventions designed to be novel and participatory are more effective in reaching adolescents—particularly those most likely to engage in sexual risk taking—and in altering a number of their crucial risk behaviors, including increased likelihood of continued abstinence among those who have not yet had sex (Donohew et al., 1999; Kelly and Donohew, 1999). Risky behaviors were successfully changed by adapting classroom interventions and media campaigns to include elements that would more effectively attract, hold the attention of, and persuade higher risk takers to avoid or reduce risky sexual behavior. Perhaps the most important finding thus far has been that in classrooms receiving the adapted curriculum, high-risk-taking adolescents were significantly less likely to initiate sexual activity than those receiving a nonskills-based comparison intervention (Donohew et al., 1999). These differences remained even when we controlled for the effects of socioeconomic status, grade point average, gender, intervention site, and relationship status.

Biological Issues

Research studies are needed to elucidate the influence of alcohol use, “abuse”, and dependence on the systemic biological changes observed during the course of HIV infection and treatment. Data from these studies are of particular clinical significance because “heavy” and sustained alcohol consumption can change the physiology and biology of virtually every cell in the body, thereby modifying the function of components of the digestive tract, immune system, cardiovascular system, endocrine system, reproductive system, brain and central nervous system, and musculoskeletal system (Figure 1).

Thus, the biomedical consequences of alcohol abuse or dependence on HIV infection, transmission, pathogenesis, and treatment are important research priorities. The AIDS Research Center located at the Louisiana State University Health Sciences Center; the Veterans Aging Cohort Study: An NIAAA Cooperative Agreement (Justice et al., 2004);
Viral Replication

In the past, researchers (Bagsara et al., 1996) demonstrated that alcohol could impair white blood cell responses to HIV. A provocative study (Bagsara et al., 1996) that warrants replication found that a single drinking episode depressed certain immune responses of white blood cells taken from healthy volunteers. In addition, white blood cells isolated after this drinking episode were more susceptible to HIV infection than were cells isolated from subjects who did not drink, hinting that even occasional alcohol consumption may increase the likelihood of infection upon exposure to HIV. Subsequently, researchers focused on understanding the role of viral replication in both laboratory cell cultures, including neural cells, and in animal models, which focus on mucosal membrane response (Liu et al., 2003).

The pathologic consequences of HIV are a function of the completion of the life cycle of the virus (NIAAA, 2004). HIV-1 has a complex viral life cycle that uses 15 distinct proteins in specific functions, some of which may interact with alcohol: Gag and Env structural proteins, capsid proteins, nucleocapsid, SU and transmembrane proteins, Pol enzymes, reverse transcriptase, integrase, gene regulatory proteins Tat and Rev, and accessory proteins Nef, Vif, Vpr, and Vpu (Figure 2). Elevated levels of HIV transcription are regulated, among other things, by nuclear factor kappa B (NF-κB), which is functionally dependent on Tat.
activation. Thus, cell activities, unrelated to HIV infection–inducing signal transduction pathways and ultimately up-regulating transcriptions factors, can enhance HIV transcription. Oxidative stress and certain interleukins have been demonstrated to enhance HIV replication through these pathways A specific cell activity unrelated to HIV infection is cell activation via alcohol exposure. As observed in alcoholics, elevated levels of tumor necrosis contribute to the activation of NF-κB (Gonzalez-Quintela et al., 2004; NIAAA, 2004).

The questions for alcohol/HIV researchers are Does alcohol modify expression of HIV proteins or the cellular biology of infected cells to promote or inhibit HIV replication, via NF-K B or any other mechanism? Is alcohol a viral “adapter” that can influence and/or modify cellular functions to enhance the replicative capacity the virus? Conflicting results have been obtained by those studying HIV replication in isolated peripheral blood mononuclear cells. Bagasra and colleagues (1996) reported increased HIV-1 p24 levels in vitro in infected peripheral blood mononuclear cells from individuals after a one-dose acute alcohol infusion or binge drinking. In differing experimental design, no consistent increase in HIV replication after exposure to alcohol was shown (Fitzpatrick, 1995). Further studies have shown that even alcohol concentrations of 0.25% enhance peripheral blood lymphocytes expressing CXCR4 increasing viral entry 5- to 10-fold (Liu et al., 2003). Thus, alcohol may facilitate enhanced viral infection by increasing the availability of HIV-1 co-receptor and the increased intracellular cAMP may also facilitate its replication. Additional studies are needed to solve the controversy in the field (Liu et al., 2003).

Differing research approaches could be used to resolve whether alcohol consumption enhances HIV replication (Pomerantz, 2004a). The first could be a clinical study of alcohol consumption and viral load over time. A positive correlation or direct relationship would provide important clinical data for patient management. Determining the mechanism of a correlation would likely involve molecular studies of the HIV genome to determine the presence of alcohol binding and/or inducible response elements. Such genomic sequences, on exposure to ethanol or its metabolites, could enhance viral replication. This enhancement could be through the NF-κB activation/augmentation of the HIV promoter, LTR, or other regulatory gene (s), such as Tat or Rev (Rampalli et al., 2003). A second approach for alcohol/HIV replication is to address whether HIV replication could be enhanced through the action of alcohol or its metabolites on tissue specific cellular metabolism.
Animal Models

The animal model that most closely resembles the etiology of HIV infection is simian immunodeficiency virus (SIV) infection of rhesus monkeys (Poonia et al., 2006). SIV is a lentivirus that is genetically related to HIV. SIV is T-cell tropic and infects both lymphocytes and macrophages, inducing an immunodeficient state that correlates with the depletion of CD4 + lymphocytes. Infection with SIV results in three stages comparable with HIV human infections: (1) acute infection characteristic of high viremia, fever, lethargy, and dermal rash; (2) asymptomatic stage with anti-SIV antibody and a decline in CD4 cell count and (3) AIDS, characteristic of substantial CD4 cell depletion and opportunistic infections. Beyond these similarities, an additional advantage of the use of the primate animal model is the ability to establish and monitor specific parameters related to alcohol consumption and HIV infection. These include time and route of infection, timing and quantity of alcohol consumption, assessment of nutritional and behavioral variables, and characterization of systemic and organ specific pathogenesis. Limited data are available using this model, and studies are needed to determine the interactions among alcohol, immune function, patent SIV infection, and disease progression in nonhuman primate infection.

A study in the March issue of Alcoholism: Clinical & Experimental Research (Bagby et al., 2003) used SIV infection of rhesus monkeys to examine the combined effects of chronic binge alcohol consumption on the primary stage of SIV/HIV infection. Researchers found that alcohol consumption may increase host susceptibility to SIV/HIV infection. This study had two primary purposes: (1) to develop an animal model to study the interactive effects of alcohol on HIV disease transmission, pathogenesis, progression, and antiviral therapy and (2) to examine the effects of alcohol consumption on what is called the “primary stage” of infection. This stage is extremely difficult to study in humans because it is rare to be able to identify infected people this early.

The investigators adapted the primate model, using SIV, which infects rhesus monkeys in the same way that HIV infects humans and produces a disease that is very similar to the human disease that leads to an immunosuppressed state and AIDS. Approximately 1 week after SIV infection, there was a 64-fold increase of the SIV virus in the blood of the alcohol-treated monkeys compared with the sucrose-treated monkeys. The researchers hypothesized that more cells are infected with virus at this early stage or that infected cells are producing more virus and that alcohol either increased infectivity of cells or increased the number of susceptible cells. Alcohol consumption also enhanced lymphocyte turnover (as assessed by expression of the cell cycle protein marker Ki67) in SIV-infected monkeys during the early stage of infection, which may have contributed to the observed increase of virus in the blood.

Immunosuppressive Effects of Alcohol

Clinical Evidence. The physiochemical characteristics of alcohol allow it to interfere and damage most organ systems. In addition to the well established relationship between alcohol and liver disease, alcohol may increase morbidity and mortality through its impact on immune system function (Cook, 1998; Watson, 1994). The clinical manifestation of immune changes caused by alcohol consumption are evident in drinkers, who exhibit increased susceptibility to infectious diseases, such as respiratory infections or sepsis (Cortese et al., 1992; Esposito, 1984; Jerrels, 1994; Manson, 2004). Infections that may lead to septicemia in the alcoholic include pneumonia, urinary tract infections, and bacterial peritonitis (NIAAA, 2004). Alcoholics have twice as high a risk for pneumonia-related
mortality as nonalcohol users (Cortese et al., 1992; Esposito, 1984). The incidence of TB is also significantly increased by alcohol consumption (Cook, 1998; Schuman et al., 1997; Manson, 2004). In animal models, alcohol-consuming mice not only had significantly higher lung organism burdens, their lymphocyte proliferation and production of gamma interferon were decreased. Researchers from Emory University (Holguin et al., 1998) reported a number of abnormalities among alcohol users, including impaired alveolar type II pneumocyte function, decreased surfactant production, barrier integrity, and increased apoptosis that could increase the risk of lower respiratory infections in alcohol users (Kovacs et al., 2004). Thus, infections in ethanol-consuming individuals who drink large amounts of alcohol are both more frequent and more severe (Cook, 1998), in part because of ethanol-induced dysregulation of the immune system response. Further research is needed in the context of disease susceptibility and HIV infection including alcohol use-related host defense impairment and opportunistic infection caused by pathogens such as *Mycobacterium tuberculosis*, *Streptococcus pneumonia*, *Pneumocystis carinii*, and HCV.

It is important to consider frequency and duration of exposure to alcohol in relation to infection, as well as other host characteristics impacted by alcohol abuse, such as nutritional status, that can influence susceptibility to AIDS-related illnesses. Alcohol-induced malnutrition can further compromise the human immune system (Watzl and Watson, 1993). “Heavy alcohol use” is associated with high caloric intake derived from alcohol and inadequate intake of protein, vitamins, and minerals, creating a malnutrition/wasting-type syndrome (Watzl and Watson, 1993). Thus, alcoholics may not ingest adequate levels of vitamins and trace elements, such as zinc, iron, selenium, and magnesium, necessary for maintaining a competent immune response.

Laboratory Evidence. Chronic, and even acute, alcohol consumption results in significant changes in the immune system of experimental animals and humans (Brodie et al., 1994; Szabo, 1997). A variety of short- and long-term alcohol-induced effects on both cell-mediated and humoral immune response have been described (Miguez et al., 2001; Nair et al., 1994; Petrovick, 1996; Szabo, 1997), with alcohol exposure linked to impaired host defense through a combination of cellular defects, altered cytokine production, and oxidative stress (Dominguez-Santalla et al., 2001; Isaki and Kresina, 2000; Laso et al., 1999; Manso, 1997; Starkenburg et al., 2001; Wang et al., 1997).

Studies in alcohol users have consistently shown decreased lymphocyte numbers accompanied by impaired function (Jerrels et al., 1998; Roselle, 1992). Although the mechanism for an ethanol-induced decrease in lymphoid cell number is yet to be defined, reduced antigen presentation and subsequent decreased antigen-dependent T-cell proliferation may be involved (Brodie et al., 1994; Szabo, 1999). In a chronic alcohol-consuming animal model, defect in antigen presentation occurred during the cognitive phase of the immune response when antigen presenting cells (APC) engage uncommitted T helper CD4\(^+\) cells (Szabo, 1997). This defect, however, could not be reproduced when alcohol exposure occurred after the presentation and recognition steps. Specific to HIV, researchers from the University of Nebraska (Haorah et al., 2004) recently demonstrated that elevated Reactive Oxygen Species (ROS) followed by ethanol exposure decreased proteosome activity and that this impairment could be restored by antioxidant supplementation. The data support the notion that HIV-1 infection and alcohol actions may work in concert to affect antigen presentation (Haorah et al., 2004). An additional suggested mechanism is programmed cell death, known as apoptosis (Zsabo, 1995, 1997).

Alcohol effects on T-cell proliferation are dose dependent and seem to be associated with inhibition of early signaling events of calcium mobilization and/or decreased
interleukin production (Brodie et al., 1994). Even acute alcohol intoxication can suppress inflammatory responses in normal subjects (Dingle and Oei, 1997; Szabo, 1999). Recent findings indicate that the ethanol-suppressed response is mediated through Toll-like receptors (Dai et al., 2005). Current research on cytokine imbalance produced by alcohol is leading to new insights on the regulation of the immune system in alcoholics. The nature of the APC–T helper cell interaction helps to determine the effector response (i.e., cell-mediated [Th1] or humoral [Th2]). Cytokine expression after alcohol exposure of normal human monocytes and murine splenic cells is shifted toward Th2 dominance (Laso et al., 1999; Wang et al., 1997). This polarization to Th2 is further enhanced in alcoholics because levels of pro-oxidants such as glutathione, which play an integral role in determining the Th1/Th2 maturational pathway of an immune response (NIAAA, 2004), are depleted in alcoholics. These experimental observations are of concern in HIV/AIDS, because high levels of TH2 interleukins have been associated with increased oxidative stress-induced damage and increased viral replication and increased prevalence of opportunistic infections (Isaki and Kresina, 2000; Laso et al., 1999; Szabo, 1999). In SIV-infected animals, alcohol has been shown to suppress tumor necrosis factor-α and lead to increased susceptibility to secondary infections (Stoltz et al., 2000).

Alcohol and HIV/AIDS Disease Course Before and After the Era of Highly Active Antiretroviral Therapy (HAART)

Not enough is known about the important factors associated with morbidity and hospitalization rates in HIV-infected men and women or how they compare with rates in HIV-infected subjects with similar CDC stages but without alcohol consumption-related problems. In the current era of declining opportunistic infections and hospitalizations, it would be interesting to determine what factors are predictors of morbidity and mortality in HIV-infected subjects during the HAART era.

Whether alcohol use influences the progression of AIDS in persons already infected with HIV has been explored in past animal and human studies. Findings from experimental animal models clearly indicate that chronic alcohol consumption exacerbates the immunosuppressive effects of the retrovirus, resulting in accelerated progression to clinical illness and decreased resistance to secondary infection in the host. The organisms used in the experiments were Mycobacterium avium complex, Streptococcus pneumoniae, Cryptosporidium parvum, and Giardia muris—all pathogens commonly occurring in patients with AIDS (Dingle and Oei, 1997). Human studies, however, have yielded controversial information. During the pre-HAART era, Watson and colleagues (1994) suggested that alcohol may accelerate the development of AIDS, and case reports have confirmed these data (Fong et al., 1994). Nevertheless, a prospective study by Kaslow et al. (1989) failed to demonstrate a relationship between percentage of CD4 cells, progression to AIDS, and alcohol use. Another study conducted by Chandiwana and colleagues (1999) similarly revealed no significant differences in mean CD4 counts between alcohol users and nonusers; in fact, most of the patients with CD4 < 200 cells did not use alcohol (p = 0.023). Crum and colleagues (1996) confirmed that there were no significant differences in CD4 cell counts nor cell decline among different alcohol categories during 5 years of follow-up. They demonstrated, however, that between 2 to 5 years post-seroconversion there was a statistically significant increase in CD8 cell count among the heaviest drinkers (21 drinks a week). Although Penkower and colleagues confirmed that single measurements of alcohol intake did not predict AIDS-related symptoms and disease progression, the pattern
of drinking over time was significantly associated with several AIDS-related symptoms (Penkower et al., 1995).

Considering that a significant proportion of HIV-infected patients and those under HAART develop liver toxicity, the effect of antiretroviral therapy and alcohol use on liver fibrosis in HIV-infected patients was examined by Benahmou and colleagues. Multivariate analysis identified four independent predictors of progression to cirrhosis: absence of protease inhibitor therapy (relative risk [RR] = 4.74, 95% confidence interval [CI], 1.34–16.67), heavy alcohol consumption (≥50 g daily) (RR = 4.71, 95% CI, 1.92–11.57), low CD4 cell count (<200/µL) (RR = 2.74, 95% CI, 1.17–6.41), and age at HCV contamination (≥20 years) (RR = 2.37, 95% CI, 1.04–5.38). Scientists in Miami (Miguez et al., 2005) reviewed causes of hospitalization in HIV+ patients (n = 538) admitted to Jackson Memorial Hospital from 9/2001 to 9/2002. Their data indicate that independently of HAART use, alcohol users had more central nervous system-related hospitalizations than drug users (15% vs. 4.5%, p = .03) or controls (7.5%, p = .027). In a recent publication a retrospective analyses of medical records from the Adult/Adolescent Spectrum of HIV-Related Diseases study of Public Health-Seattle and King County, a correlation was observed between alcohol use and Kaposi sarcoma. Patients diagnosed with Kaposi sarcoma in the HAART era (n = 40) were significantly more likely to be diagnosed with alcohol consumption-related problems (43% vs. 18%) (Gallafent et al., 2005).

**HAART and Alcohol Use**

Recent advances in antiviral therapies for HIV infection have raised the hope that AIDS can be treated as a chronic disease. This offers the patient a longer potential lifespan, fewer complications, and possibly less social stigmatization, while also reducing the demand on the health care system for “catastrophic event” interventions of a therapeutic or supportive nature. At the same time it may increase the overall burden on the health care system—including caregivers and programs—that may need to provide sophisticated and expensive therapies over a long period of time as patient lifespans increase unless economies of scale and improved technologies develop in parallel. The community-at-large will also need to adapt as the previously catastrophically ill become chronically ill and need to be reintegrated into society as ongoing “more healthy” participants.

Immune reconstitution is observed at some level in patients managed with HAART. To be successful, these HIV treatments require access and strict adherence to drug regimens. Long-term HIV treatment with these new drug therapies is particularly difficult for alcohol-misusing populations. “Heavy alcohol consumption” is known to limit a person’s ability to adhere to HIV treatment, and nonadherence is known to lead to more rapid disease progression (Miguez et al., 2001; Samet et al., 2005; Wagner et al., 2001). Further, alcohol is known to exacerbate common comorbid conditions among those with HIV infection, such as hepatitis C or chronic hepatitis B. Finally, “heavy alcohol consumption” may also lead to increased rates of serious toxicity from antiretroviral therapy as both can be toxic to the liver and bone marrow. Thus, “heavy alcohol consumption” may lead to nonadherence and even complete cessation of antiretroviral therapy through a multitude of behavioral mechanisms.

New research, published by the Miami group (Miguez et al., 2001, 2003, 2005), indicates that HIV-infected patients with a history of alcohol consumption-related problems, who are receiving HAART, and are currently drinking, are twice as likely to have CD4 counts below 500 than light or nondrinkers (95% CI, 1–5.5, p = .03). Moreover, it was
shown that HAART-treated “heavy alcohol users” were four times less likely to achieve a positive virological response (95% CI, 1.2–17, \( p = .04 \)) (Miguez, 2003). These findings were also confirmed by Palepu et al. (2005).

If the main goal of HIV physicians is to recuperate the CD4 population, it needs to be understood that alcohol use may affect thymus-induced immune repletion. Recent findings from the Miami team demonstrate that “hazardous alcohol users,” particularly “heavy alcohol users,” undergoing 6 months of antiretroviral treatment have half of the thymus size of nonhazardous alcohol users (Miguez et al., 2005). A variety of models are being developed for estimating the relative toxicity of the interaction alcohol, HIV, and medication regimens and the impact of nonadherence to these regimens in observational clinical cohort study of U.S. veterans (Braithwaite et al., 2005a,b).

**HAART**

The activity level of CYP3A4 is important in the metabolism of drugs comprising HAART. Orally administered drugs comprising HAART regimens are rapidly converted to inactive metabolites via first-pass oxidative metabolism by the cytochrome P450 system, including CYP3A4 (Ast and Luke, 2004; Rodriguez-Novoa et al., 2005). HIV protease inhibitors amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir and the non-nucleoside reverse transcriptase inhibitors efavirenz, nevirapine, and delavirdine are susceptible to drug–drug interactions, resulting in either enhanced or decreased metabolism. Drugs that are inhibitors of specific cytochromes reduce clearance and extend the serum concentration half-life of drugs. Inducers of cytochromes enhance oxidative metabolism and reduce serum concentrations of drugs (Ast and Luke, 2004; Rodriguez-Novoa et al., 2005). Additional inducers of CYP3A4 modify (reduce) HAART pharmacokinetics. Isopentanol has been shown to be a more potent and effective inducer of CYP3A4 than ethanol in human liver cells in vitro. In animals, the administration of isopentanol/ethanol mixtures results in increases in CYP3A greater than that induced by either agent alone. An elevation in CYP3A4 activity in these individuals may result in enhanced drug metabolism and reduced therapeutic drug levels. Thus, HAART may not be as effective in some individuals who consume alcoholic beverages. Individuals consuming alcoholic beverages may place themselves at risk for developing drug-resistant HIV strains due to subtherapeutic levels of protease inhibitors, as a consequence of enhanced protease inhibitor metabolism. Therapeutic drug monitoring studies, stratified by alcohol consumption levels, are needed in HIV patients who consume any alcoholic beverages to confirm this hypothesis. In addition, the success of emerging treatment strategies needs to be evaluated. New targets for interruption of viral replication need to be identified (Ast and Luke, 2004; Rodriguez-Novoa et al., 2005). The HIV-1 life cycle involves a number of cellular cofactors. Some are essential for HIV-1 replication and thus may serve as targets for therapeutic intervention. An emerging role for cellular DNA repair in HIV-1 infection suggests that inhibition of these repair functions may lead to suppression of viral replication (Daniel and Pomerantz, 2005).

**Additional Host Factors: Pharmacogenomics and Pharmacogenetics**

Two genetic characteristics are relevant when considering a patient’s response to drug therapy and drug metabolism: pharmacogenomics and pharmacogenetics. Pharmacogenomics, a function of the human genome, is the emerging field that uses genetic information to predict a patient’s response to a drug (Ast and Luke, 2004; Rodriguez-Novoa et al.,
Examples of genes that influence a patient’s response are genes regulating the enzymes and proteins involved in drug(s) metabolism and transport genes that code for specific drug targets or genes that influence the expression of a disease (NIAAA, 2004). Pharmacogenetics is the field of science that identifies and characterizes polymorphic expression of genes related to drug metabolism. Most important for alcohol detoxification are alcohol and aldehyde dehydrogenases and the cytochrome P450 systems in phase I biotransformation and glutathione-S-transferase for phase II biotransformation. For the metabolism of drugs used for the control of HIV infection, the cytochrome P450 system and glutathione-S-transferases are important. Polymorphisms in the genes that encode for enzymes in phase I or phase II biotransformation result in differing enzyme kinetics, with relatively slower or faster than normal rates of metabolism (Ast and Luke, 2004; Rodriguez-Novoa et al., 2005). Thus, based on the expression of polymorphic genes, ethanol metabolites and toxic intermediates could build up or be quickly biotransformed based on the nature of the kinetics. This could change the bioavailability of the drug in question and present dosing difficulties for drugs with narrow therapeutic ranges. The question “How do individual patient pharmacokinetic profiles contribute to HIV treatment failure?” is now being addressed through the elucidation of an individual’s pharmacogenetics. Subsequent individualized drug regimens can then be contemplated to include alcohol consumption and metabolism to maximize treatment success.

**Alcohol, HIV Infection, and the Central Nervous System (CNS)**

Higher rates of alcohol use are often reported (Penkower et al., 1995) among HIV+ individuals when compared with the general populations (NIAAA, 2004). The combination of “heavy alcohol use” and HIV infection also are associated with increase neuropsychiatric impairment. Weather alcohol interacts with HIV neuroinvasion to increase synergistic cell death is under investigation. Neuropsychological testing indicates, however, that there is decrease motor and visumotor speed and generally poorer executive functioning. In addition, “heavy alcohol use” and poor executive functioning is associated with poorer adherence, suggesting that planning functions impacted by the synergistic interaction may mediate behaviors such as adherence.

In addition to causing major dysregulation of the immune system, HIV infection profoundly affects the CNS. Viral invasion of the brain has been documented as early as 2 weeks postinfection, a time well before seroconversion can be determined (NIAAA, 2004). Autopsy reports have confirmed neuropathological abnormalities in as many as 90% of patients with AIDS (Meyerhoff, 2001). Consistent with these observations of CNS damage, HIV-associated cognitive/motor complex—characterized by psychomotor slowing, memory deficits, and behavior changes—is thought to afflict between 15% and 40% of AIDS patients and to be the histopathologic correlate of HIV encephalitis.

Despite the widespread recognition of the devastating effects of HIV on neural tissue and brain function, the mechanism(s) underlying these pathologies remains unclear. Penetration of the virus into the CNS arena appears to be critical, however, as neurobehavioral deficits correlate with viral load. Mounting evidence points to the ability of HIV or HIV-infected mononuclear cells to penetrate the blood–brain barrier (BBB) as the means by which the virus gains access to the CNS compartment. The cerebral microvessel endothelium is the major cellular element of the BBB and comprises the primary limitation to passage of substances from the blood to the brain. Brain microvessel endothelial cells possess unique features that distinguish them from cells of peripheral endothelium, and these may significantly limit the paracellular flux through the BBB and
are thought to be a major impediment to invasion of the brain by both microorganisms and circulating leukocytes. The lack of fenestrae in brain microvessel endothelial cells, as well as the presence of specific membrane-associated transport systems, further restricts the transcellular movement of materials from blood to brain (NIAAA, 2004.) It stands to reason that modulation of any of these BBB properties could significantly impact the ability of HIV to enter the CNS and cause neurodestruction.

Although many factors could potentially alter BBB integrity and function— and thus foster HIV access to brain environs— particular attention should be given to alcohol. Alcohol has been linked to increases of the BBB permeability to various tracers. Using proton magnetic resonance imaging Thomsen et al. (1994) demonstrated on humans that alcohol induced transient opening of the BBB. Thus alcohol has the potential to heighten susceptibility to and progression of HIV-related CNS disease. Potential routes by which alcohol might facilitate HIV entry into the brain include augmented expression of pro-inflammatory cytokines, modulation of membrane permeability and inter-endothelial junctions, and stimulation of viral replication (NIAAA, 2004). Alcohol may also act in concert with HIV-1 proteins (gpl20, Tat) and/or cytokines, present in the circulation of HIV-1–infected patients, and the detrimental effect of alcohol on HIV-1 pathogenesis could be exacerbated. In support of this concept, interaction of Tat protein with alcohol has been confirmed in an animal model. Belmadani and colleagues (2001), however, suggested that moderate ethanol consumption is neuroprotective by abrogating excitotoxicity induced by Gp120. The metabolic effects of advanced HIV infection and alcohol use were measured using breakdown products of membrane molecules and magnetic resonance spectroscopy studies and confirmed that chronic alcohol use may exacerbate some metabolic injury in the brains of HIV-infected individuals (Meyerhoff, 2003). Given the widespread use of alcohol and rapidly growing HIV-infected population, the need to delineate the role of alcohol in the development of HIV-related CNS disease has reach urgent status.

Previous alcohol misuse may create a point of “vulnerability” that is exacerbated by the effects of the virus on the brain. In contrast, in the absence of HIV infection, a past history of chronic alcohol abuse, combined with current abstinence from alcohol, appears to cause no significant cognitive impairment. Researchers (Green et al., 2004) hypothesize that there is enough alteration to cognitive function to make the brain more susceptible to the damaging impact of a second independent process. The known risk of cognitive decline in HIV infection has prompted attempts to identify risk factors for this decline. Numerous studies (Ohio State Research, 2004) have reported deficits in memory, learning, slower reaction time, and decreased speed in decision making in HIV-infected patients (Antunes, 2004; McArthur et al., 2003). The most severe cognitive changes, sometimes to the point of dementia, are almost always reported in the latest stages of the illness, but some research (Ohio State Research, 2004) has demonstrated that asymptomatic HIV-positive patients experience subtle cognitive impairments that influence their daily activities.

AIDS Dementia/Cognitive Impairment

Several studies (Fein et al., 1995; Fletcher et al., 1997; Meyerhoff, 1995; Meyerhoff, 2001; Pfefferbaum et al., 2002) have raised the possibility of increased vulnerability for cognitive impairment and HAD development and progression of CNS in patients with HIV and alcohol comorbidity. Durvasula and colleagues reported that alcohol use exacerbated adverse HIV effects on sequential reaction time (Durvasula et al., 2001). Meyerhoff and colleagues (2001) add an additional piece of information by demonstrating synergistic effects of “heavy alcohol use” and HIV infection in both motor and visuomotor speed.
Similar results were obtained by Rothlind and colleagues with the most robust group differences observed between those with comorbidity (HIV+ heavy drinking) and the seronegative control group (light drinking). Heavy drinking showed robust effects on measures of working memory, balance, and executive function.

Neuropathological and neuropsychological studies (Durvasula et al., 2001; Meyerhoff, 2001) have indicated that certain brain regions are affected by both HIV infection and chronic alcohol abuse. There has been little research on how extremely “heavy drinking” affects the clinical outcomes relating to neurological impairment and HIV disease. Initial studies (Pfefferbaum et al., 2002) demonstrated a potentially additive or synergistic effect of alcohol use and HIV disease on cognitive performance. The current studies focus on brain and underlying neural metabolic mechanisms that may interact to lead to cell death in specific regions of the brain. These studies (Durvasula et al., 2001; Meyerhoff, 2001) include subjects who drink “heavily”—on average at least 100 drinks per month over many years—and who are being treated for HIV. Magnetic resonance spectroscopy studies (Meyerhoff, 2001) of both HIV-positive and HIV-negative people who were either heavy or light drinkers found that chronic alcohol abuse exacerbates some metabolic injury in the brains of HIV-infected people, although this effect may be less pronounced in patients receiving effective antiretroviral therapy.5

Prevention Science: Need for Integration

At present, the most effective way to slow the spread of HIV/AIDS is through changing the sexual and injecting drug risk behaviors that transmit HIV from individual to individual. Individual behavior is embedded within a social context, which provides the networks and norms for human behavior and interaction, wherein individuals develop their own biological and behavioral adaptational patterns. Interventions need to address individual and group adaptational patterns. A comprehensive approach to prevention in this context is the basis for what has been proposed (Bryant et al., 1997) and is the focus of future strategies for research and intervention delivery.

Study quality remains an important barrier to understanding the complex relationship of patterns of alcohol use and risk for HIV infection. Few studies use adequate self-report or biological measures to assess patterns of problematic alcohol use. Although a variety of issues remains in establishing the exact causal role of alcohol, future studies should focus on mechanisms by which multiple factors related to alcohol consumption contribute to risk and inform prevention or treatment. Interventions that successfully address these factors and reduce risk behaviors should be accepted as adequate tests of a critical relationship between these underlying constructs. Testing the mediating role of alcohol (consumption and its effects) in HIV/AIDS preventive interventions requires multicomponent interventions with well-measured outcomes (Bryant et al., 2002) and falls within a broader range of prevention science models. Developing new innovative models for intervention can be “bottom up” or “top down.”

Advances in the understanding of alcohol use-related outcomes are dependent on improved measurement of co-occurring alcohol and HIV risk behaviors and the application of alcohol-focused theories. At present, decisions about which interventions to use and in which setting are constrained by incomplete information and decisions must be made in this context of uncertainty. However, the ideal methodological approach to establish the

role of alcohol is to obtain global, situational, and event-specific measures (NIAAA, 2004) of drinking behavior and unsafe sexual behavior in conjunction with partner characteristics, use of other substances, and frequency of these encounters.

Models for intervention could then be built at the individual, dyadic, and social network level for changing difficult or intractable alcohol/sexual risk behaviors. “Top down” models would focus on key components of models including health behavior theory such as individual thought and decision-making processes that can be influenced and tested within an intervention context. “Bottom up” models would be based on a complete understanding of the specific ecology of a risk behavior (e.g., drunken driving, risky sex, bar settings), its stochastic relationship to the physical environment, and points of intervention. These more qualitative approaches are often found within anthropological research orientation. Structural factors for settings and situations in which risk behavior is enacted include the cultural, social, economic, and political contexts within which behavior occurs and set the parameters that delimit our understanding of behavior and potential interventions to reduce harmful consequences.

In general, research on health behavior theory that encompasses many of these “bottom up” and “top down” approaches is being conducted at a rapid pace, the extent to which the field is truly moving forward in understanding health behavior needs to be closely examined. The proliferation of health behavior theory and the role of theory comparison for alcohol-specific theories needs further development and approaches simplified for practical use need to be tested and disseminated (Noar and Zimmerman, 2005). The field might move forward by increased recognition of the similarity of health behavior constructs and the need for empirical comparisons between theoretical frameworks while taking into account such alcohol specific theories such as “cognitive narrowing” or “alcohol-related disinhibition” phenomena. This integrative approach requires improvements in data collection methodologies and their integration with each other to produce important insights into the relationship between alcohol use and unsafe sexual behavior and tailored models for preventive interventions.

Developing combined alcohol/HIV interventions for groups who are at significant risk for both of these problems has been identified as a priority for future research by the Office on AIDS Research, NIH, and in both domestic and international settings. One of these priorities is also to increase the exchange of ideas between behavioral and biological researchers and those carrying out preventive interventions, in particular “prevention for positives.” The goal of these interventions is to more completely integrate biological prevention strategies such as the use of microbicides or vaccines (or therapeutic suppression of virus—reducing infectivity) which are under development with behavioral interventions. Specific areas of integration are suggested in the alcohol and HIV/AIDS area. These include integrative models of adherence in which patient factors including alcohol use can be used to determine suitability of individuals for antiretroviral interventions or course of intervention (with or without successful drinking interventions); the development of protective agents/behaviors for hepatic, neurological, and cardiac functioning; and how patient health behaviors may be changed to help integrate and sustain these interventions in care settings.

Expansion of Integrative Biomedical and Behavioral Research Paradigm

In the area of therapeutics research, current drug regimens have resulted in extended survival and improved quality of life for many HIV-infected individuals in the United States and western Europe. However, a growing proportion of patients receiving therapy are
demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. The increasing incidence of metabolic disorders, cardiovascular complications, major organ dysfunction, and physical changes associated with current antiretroviral drugs underscores the critical need for new and better treatment regimens. Improved regimens also are needed to treat HIV coinfections such as hepatitis B and C, as well as other opportunistic infections, to reduce drug interactions and problems with adherence to complicated treatment regimens. The goal of this research is to develop new, safe, less toxic, less expensive, and more effective therapeutic agents and regimens. Research in this area requires the development and collection of new data sets to implement both prevention and treatment strategy trials. These types of trials are described in the recent Institute of Medicine (IOM) report on poverty and starvation (IOM, Global Strategies for Intervention, 2005) and are contrasted with standard randomized controlled clinical trials. The goal of these trials is to meet the immediate need to address critical disease issues in developing countries in a timely and cost-effective way using appropriate research methods which meet ethical considerations for sustaining critical interventions (Migura, 2000).

One issue that has been raised is how to begin to conceptualize the development and use of informative data for these interventions. Data sets can be conceptualized as minimal patient care data sets or as optimal research data sets. Combining data may greatly increase the prognostic values of patient biomedical information (Siika et al., 2005; Tierney, 2002). Identifying the benefits and trade-offs of these approaches allow for academically supported heath research in patients who need advanced HIV/AIDS care with multiple comorbidities, including alcohol abuse and dependence.

**NIAAA Objectives: Integrative Priorities for Future Research**

The integrative priorities for future research according to NIAAA objectives include

- **Observational studies:** Investigate changing patterns, contexts, and tools of substance use (alcohol and other drugs) and their implications for HIV transmission, including individual and host factors that contribute to specific risks related to combined alcohol and noninjecting drug use, as well as those that link substance use and sexual risk. Use observational cohort studies as the basis for assessing the impact of the direct and indirect effects of preventive interventions and improved strategies for combined alcohol and HIV/AIDS prevention. Expand this understanding gained from these studies to new settings and situations for research and interventions in domestic and international contexts.

- **Integrated AIDS-alcohol User treatment:** Would allow us to better understand and address, through interventions, the biological, psychological, social, economic, and cultural factors that underlie the relationship between alcohol use, abuse, and dependence and AIDS and AIDS/alcohol-related illnesses. In particular, investigate the interaction of behavioral and pharmacologic therapies for alcohol addiction and co-occurring physical and mental health disorders in those already HIV infected and improve short-term and long-term patient outcomes in treatment

- **Structural intervention, implementation, and dissemination:** Would support research to increase the effectiveness, cost-effectiveness, and cost utility of interventions for HIV-related alcoholism prevention and treatment, and the social and structural dynamics to improve access to these treatments and interventions. Understand how multiple interventions can be optimally combined to address community-level prevention and treatment needs.
**Brief Summary of Continuing FY2005 Priorities for NIAAA**

The NIH/NIAAA HIV/AIDS Research Plan is focused on developing and implementing effective prevention strategies. These strategies include both behavioral prevention (reduction in risk behavior and increase in protective health behaviors) and biomedical prevention strategies (vaccines, microbicides, and therapeutics). Developing these prevention strategies requires a foundation of basic behavioral and biomedical research that results in an understanding of specific cultural or environmental constraints for implementing interventions. Research needs to be extended into high-risk populations—particularly those with limited prevention and treatment resources. NIAAA has recently expanded its research in response to the changing characteristics of the epidemic to increase focus on women, international settings, and biological and behavioral aspects of adherence of antiretrovirals to ensure funding for the highest priority research.

**Resource Poor Settings**

Epidemiologic studies on the dynamics of “alcohol abuse” and HIV demonstrate a continual need to reach new and emerging risk groups in diverse geographic settings with effective prevention interventions. Data from the WHO indicate that while alcohol consumption is declining in most of the developed countries, it is rising in many resource-poor countries and the countries of Central and Eastern Europe (Saxena, 1997). Males do most of the drinking in these countries, and evidence available regarding patterns of drinking suggests that “heavy drinking” is prevalent in these countries. The contribution of alcohol to the global burden of disease is significant and growing in some regions, to the point that in parts of Central and Eastern Europe, alcohol use is contributing to an unprecedented decline in male life expectancy. These same parts of the world have seen significant increases in rates of HIV infection over recent years, and there is growing evidence that escalating rates of “alcohol abuse” and HIV infection are closely related. For example, while the epidemic in sub-Saharan Africa, home of two thirds (23.3 million) of the 33.6 million people in the world living with HIV/AIDS in 1999, has been largely driven by heterosexual transmission, there, as elsewhere, alcohol use is becoming increasingly important as rates of alcohol use continue to rise. The vulnerability of “heavy alcohol using” populations can be clearly seen in Russia, which is seeing a rapid migration from injecting drug users to “heavy alcohol users” (Samet et al., 2005). There, the onset of the epidemic is being tracked in distinct drug and alcohol using populations.

Africa and specific subregions in Africa have high rates of both HIV and alcohol abuse identified in patients through the use of electronic medical records coming for treatment (Siika et al., 2005). The predominant mode for HIV transmission in sub-Saharan Africa is heterosexual contact. Although the major risk factors for HIV transmission are now well known and form the basis for preventive public health interventions, special issues arise surrounding alcohol and AIDS research in under resourced countries. Only a few research studies of alcohol and AIDS relationships are being conducted in sub-Saharan Africa, where nearly half of the global epidemic exists, or in other countries (Russia, India) with rapidly increasing rates of infection. Qualitative studies from sub-Saharan Africa demonstrate easy access to and use of alcohol by groups at high risk for HIV infection such as commercial sex workers, truckers, or migrant workers such as miners. These studies need to be expanded to identify a wide range of individual scripts related to alcohol misuse that could potentially be linked to infection. The approach using qualitative and script research has been successfully used with gay men (Parsons et al., 2004) in the United States, and in other domains, such
as with drunk drivers. For example, individuals injured in drunk driving accidents were interviewed and the origin of their drinking and access to their vehicle were identified. Most of these accidents occurred when drivers left bars at closing time. To ameliorate this situation, risk-free rides programs were instituted (with servers calling taxis for inebriated patrons). These programs, which avoid legal liability for the serving establishment (Hingson and Howland, 1988), have proven to be cost effective.

**Alcohol Use and Risk for HIV Infection and Transmission Among Women**

Many socioeconomic factors such as availability of treatment for HIV or substance “abuse,” changing social norms, and enforcement of laws around alcohol use and/or spousal rights may influence local variations in HIV prevalence rates and may indirectly influence the rapid rise in infection among minority women in the United States and elsewhere. Rapid increases in HIV infection can occur among women in specific neighborhoods, particularly among alcohol and drug users who have high access to alcohol resulting from increased densities of liquor outlets as documented by high-rates of STDs African American women who are “heavy drinkers” report higher risk sexual encounters and other substance use than those that do not “drink heavily” (Zule et al., 2002) In addition, injection drug users who are “heavy drinkers” are also more likely to share unclean needles (Latkin et al., 2005; Stein et al., 2000). In general, studies revealed that minority women had most frequently placed themselves at risk for HIV infection through drugs and drinking, and they also reported drug and alcohol use as important barriers to practicing safer sex (Essien et al., 2005).

State agencies have concluded that reductions in alcohol and drug “abuse” are critical in controlling rapid changes in HIV infection. They have recommended a significant increase in substance “abuse” interventions as part of comprehensive prevention strategies. However, these recommendations do not take into account differential gender impact.

Researchers need to incorporate what they have learned about problem drinking and alcoholism into interventions among HIV at-risk populations, and improvement is needed in the ongoing inadequate communication between researchers, clinicians, and policymakers in this field to facilitate technology transfer from research to clinical or population-based implementation. Male-oriented intervention models may not be appropriate for female alcohol misusers. A variety of factors needs to be considered. These include understanding women’s perceptions of their susceptibility to AIDS the actual severity of exposure to HIV in women’s lives barriers to enacting safer behaviors with partners, and the perceived benefits of changing high-risk behaviors.

Interventions need to address the interactive role of alcohol use and “abuse” and sexual risk taking in women. Harm reduction strategies may be of particular importance for low-income women who may have limited personal control over decisions that affect their lives. These strategies focus on reducing the negative consequences of alcohol “abuse” by encouraging consistent condom use, reduction of number of sex partners, treatment for STDs, and realistic drinking goals. Women in alcohol user treatment settings may be at particularly high risk for both HIV infection and transmission. Efforts should be made to monitor alcohol-dependent women both in and out of alcohol and substance user treatment settings. Effective interventions need to consider lifestyle issues, such as unavailability and inaccessibility of interventions, child care concerns, family and partner roles, lack of adequate opportunity with formal-informal, institutional based, noninstitutional based needed resources, discriminatory delivery of services, and interfering stakeholder agendas, among the various potential barriers to receiving ongoing health care on a parity level with other groups of fellow citizens and types of ailments and conditions.
Structural Interventions

The general riskiness of the social network may be indexed by alcohol use among its members. The distribution of liquor outlets or enforcement of laws aimed at controlling availability and accessibility of alcohol may also impact the spread of STDs at the community level. Examination of the social and cultural contexts for alcohol use and HIV risk offers another level of understanding of these dual risks. For example, research on gay culture and the development of gay identity poses important behavioral research questions about the relationship between alcohol use and HIV transmission. Male gay bars, which provide opportunities for gay men to socialize, also represent a high-risk context for excessive alcohol use. However, this is a complex, dynamic multidimensional phenomenon, which is often not readily explained by a simple linear cause and effect relationship. Alcohol use is the most frequent precipitant of relapse to unsafe sex among gay and bisexual men, and locations that combine sexual opportunities and alcohol availability pose the greatest risk for populations vulnerable to HIV. Similarly, understanding how acculturation patterns and social norms emerge for drinking among new immigrants, migrant workers, or individuals in new settings such as colleges improves our understanding of how patterns of alcohol and HIV risk coalesce. The linkages between the personal, social, and situational factors are likely to be interrelated in a complex process whose elements may facilitate or impede, directly or indirectly, risky behaviors and their consequences. Further, individuals with problems due to HIV/AIDS and alcohol frequently have a host of co-occurring problems, including psychological, medical, social, legal, and economic difficulties. This group of problems acts additively and synergistically to amplify the effect of risk factors. A multipronged approach is needed to address the organized complexity of psychosocial problems (Rosenberg et al., 2005).

Priorities by Area of Research

The Epidemiology and Natural History of Alcohol Use and HIV/AIDS. Studying the epidemiology of alcohol use and “abuse” in HIV infection and AIDS will help to identify high-risk groups and promote the development of effective HIV prevention and treatment efforts. This knowledge will also improve the medical management of HIV/AIDS disease, once the ongoing challenges of “transfer of technology” from scientific knowledge into real-world action are taken into account. Specific studies are needed to

- Further our understanding of the alcohol consumption–HIV/AIDS intersection through population-based studies, which describe the alcohol consumption patterns of groups at risk for HIV infection.
- Identify and model the net impact of patterns of alcohol consumption on the spread of HIV infection and opportunistic infections over time.
- Describe alcohol use and alcohol use disorders in high-risk groups with HIV/AIDS and co-occurring medical and psychiatric complications.
- More fully describe through quantitative and qualitative studies the role of gender, race/ethnicity, and cultural factors in the intersection of the alcohol and HIV/AIDS epidemics.
- Examine the potential, and actual, role of the cultural understanding of problems, target populations, the types of questions asked (as well as those not asked), and the types of solutions that are perceived to be effective within that context (e.g., stigmatization and treatment access).
Primary Prevention of Alcohol Use–Related AIDS Risk Behaviors. Alcohol consumption prevention and treatment interventions are effective in reducing HIV risk behaviors and preventing HIV infection. Development and testing of new interventions are needed at various levels (e.g., community, dyadic, individual, organizational, and social network). Specific interventions are needed to

- Integrate HIV risk reduction goals into alcohol “user” treatment settings—including psychosocial and pharmacological interventions. In addition, there may be a need to direct our attention to tradition-based as well as ‘alternative-treatment’ interventions.
- Develop community-based interventions (e.g., bar-based server training, alteration of alcohol availability, and improvement of linkage between alcohol and HIV preventive services).
- Target and retain the highest risk drinkers, including difficult-to-reach groups (e.g., runaways, partners of injection drug users, and individuals who are incarcerated or homeless), in HIV/STD prevention and treatment interventions—including trials for prophylactic vaccines.
- Motivate drinkers—including those who perceive themselves to be at low risk for HIV infection (e.g., high school and college students)—to decrease risky sexual and substance use behaviors.
- Create viable new roles that make it possible for alcohol and HIV/AIDS patient/treatment recipients to act as change agents, helping others within the limits of their strengths and limitations given the de facto realities of their contexts and settings.

Basic Alcohol/HIV Behavioral Research. Behavioral, affective, and cognitive factors affect the risk for HIV infection and the efficacy of HIV prevention and treatment among alcohol abusers. Models should be developed for interrelating these individual factors with contextual and social factors that influence alcohol misuse, sexual risk-taking, and other HIV risk behaviors. Models are needed to increase the understanding of

- The relationship of alcohol consumption, alcohol use-related sexual expectancies, social norms, and decision making on HIV risk behaviors for different at-risk groups, generally, as well as in terms of network processes and influences, more specifically.
- The multidimensionality of the relationship between alcohol use and “abuse” and adherence to HIV therapeutic regimens, including delivery and cost of services.
- Social dynamics and environmental characteristics of high-risk alcohol use-related settings (bars, parties, “wet” neighborhoods) and the impact of alcohol regulations and policies on HIV transmission.
- Improvement of methods for assessing and analyzing the dynamic, complex, nonlinear, multidimensional relationships among alcohol use and misuse, specific situations and settings, ongoing historical events, and HIV-related risk behaviors.

Alcohol Use and Treatment Among HIV-Positive Individuals. Alcohol use may be a key determinant in adherence to therapeutic regimens among HIV-infected individuals. Research is needed on interventions to improve treatment adherence and to ameliorate
negative physical, behavioral, affective, cognitive, and social consequences of HIV infection in alcohol-using and -abusing populations. Research efforts are needed to

- Improve medication adherence in alcohol-using and misusing HIV+ patients.
- Prevent alcohol relapse and related HIV risk behaviors among HIV+ individuals.
- Enhance linkage of primary medical care with alcohol misuse prevention and treatment services for HIV-infected alcohol misusers.
- Develop and test interventions to improve quality of life for alcohol-using and abusing HIV-infected persons (e.g., ameliorating the interaction of alcohol use and medical sequelae of AIDS progression).
- Document who have been, currently are, and are likely to be the individual and systemic stakeholders affecting adherence and compliance among the untreated, those seeking and entering treatment, those continuing treatment, as well as the mandated deliverers of needed treatment and other services.

Biomedical Research on Alcohol and HIV/AIDS. Biomedical research on basic, applied, and preclinical studies to address the biological interactions between alcohol and HIV pathogenesis focuses on

- Effects of alcohol on viral burden, immune function, organ pathogenesis, and neuropsychological function in HIV infected individuals.
- Effects of alcohol consumption on seroconversion and progression of disease in defined cohorts including biological endpoints that relate to both alcohol misusing populations (e.g., MCV, CDT, liver function enzymes) and AIDS-specific measures (e.g., viral load, CD4+ and CD8+ levels).
- Mechanism(s) of enhanced progression of liver disease by alcohol consumption in individuals infected with HIV and/or coinfected with HCV–HIV.
- Drug–drug interactions between alcohol and antiretroviral drugs and altered pharmacology due to alcohol consumption.
- Alcohol use-related host defense impairment and opportunistic infection caused by pathogens such as *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Pneumocystis carinii*, and HCV.
- Interaction between alcohol and HIV proteins in neurodegeneration, organ pathogenesis, and immune deficiency in animal models of HIV infection.
- Preventive interventions against tissue injury related to alcohol and HIV-related illnesses including neurological, hepatic, cardiac, and metabolic processes.

Glossary

**Immune Reconstitution Syndrome:** Immune reconstitution is observed at some level in patients managed with HAART. Only specific components of the immune system are reconstituted by HAART, resulting in an exaggerated immune response on exposure to a pathogen or activation of autoimmunity.

**Opportunistic Infections:** May be relatively mild or non-life-threatening in healthy persons but that become severe and potentially fatal in the immunosuppressed such as persons with HIV/AIDS.

**Pharmacogenetics:** The field of science that identifies and characterizes polymorphic expression of genes related to drug metabolism. For example, polymorphisms in the genes that encode for enzymes result in differing enzyme kinetics, with relatively slower or faster than normal rates of metabolism. This could change the bioavailability
of the drug in question and present dosing difficulties for drugs with narrow therapeutic ranges. The elucidation of an individual’s pharmacogenetics could lead to individualized drug regimens to maximize treatment success.

**Pharmacogenomics**: A function of the human genome, The emerging field that uses genetic information to predict a patient’s response to a drug. Examples of genes that influence a patient’s response are genes regulating the enzymes and proteins involved in drug(s) metabolism and transport, genes that code for specific drug targets, or genes that influence the expression of a disease.

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