CLINICAL ASPECTS
Causal Considerations on Alcohol and HIV/AIDS — A Systematic Review

Paul A. Shuper1,2,*, Manuela Neuman3,4, Fotis Kanteres1,5, Dolly Baliunas1,6, Narges Joharchi1,7 and Jürgen Rehm1,6,8

1Centre for Addiction and Mental Health (CAMH), Toronto, Canada, 2Department of Psychology, University of Toronto, Canada, 3In Vitro Drug Safety and Biotechnology, Department of Pharmacology, Institute of Drug Research, University of Toronto, Canada, 4Centre for International Health, University of Toronto, Canada, 5Faculty of Health, Medicine and Life Sciences, Maastricht University, The Netherlands, 6Dalhousie School of Public Health, University of Toronto, Canada, 7Department of Statistics, University of Toronto, Canada and 8Institute for Clinical Psychology and Psychotherapy, TU Dresden, Germany

*Corresponding author: Centre for Addiction and Mental Health, 33 Russell Street, Room T-518, Toronto, Ontario, Canada M5S 2S1. Tel: +1 416 535 8501x4097; Fax: +1 416 595-6899; E-mail: paul.shuper@uconn.edu

(Rceived 17 August 2009; in revised form 5 December 2009; accepted 7 December 2009)

Abstract — Aim: The study aimed to explore the possible causal nature of the association between alcohol consumption and HIV/AIDS.

Methods: A review based on meta-analyses and reviews was conducted according to standard epidemiological criteria to distinguish causality from association, examining (i) the potential impact of alcohol on the incidence of HIV and (ii) alcohol’s impact on worsening the disease course. Results: In terms of incidence of HIV, although we found a consistent and strong association with consumption, there was not enough evidence for a causal connection. In particular, it is not clear whether personality traits such as sensation seeking or sexual compulsivity and psychiatric disorders such as antisocial personality disorder impact both alcohol consumption and risky sex, subsequently creating an association between both behaviors. In terms of worsening the disease course of HIV/AIDS, we found enough evidence for a causal impact of alcohol. Alcohol affects the immune system, thus contributing to a worsened course of HIV/AIDS. In addition, alcohol negatively impacts on behaviors that include support seeking and medication adherence. Conclusions: A randomized controlled clinical trial targeted toward at-risk HIV-negative individuals who live in areas with high HIV prevalence is suggested to test the effects of proven effective alcohol interventions on HIV incidence.

INTRODUCTION

As of 2007, the approximate number of people living with HIV or AIDS (PLWHA) was 33 million, among them 50% women and 2 million children under 15 years of age. This year also saw ~2.7 million new infections, including 370,000 children (UNAIDS, 2007, 2008). AIDS, the fatal progression of HIV, was the fifth leading cause of death worldwide, accounting for more than 2 million deaths, including 1.7 million adults and 330,000 children (UNAIDS, 2007).

Examination of global and regional trends suggests that the pandemic is formed from two broad patterns. Firstly, there are epidemics sustained in the general population of many sub-Saharan African countries, with unsafe sex as the main cause. Secondly, epidemics in the rest of the world are primarily concentrated among populations most at risk, such as men who have sex with men, injection drug users and sex workers and their sexual partners (UNAIDS, 2007). Both of these patterns are associated with risk factors at the more distal level, including behavioral, social, cultural and economic determinants (Cunningham et al., 2005). In order to better understand and possibly prevent the transmission of HIV/AIDS, it is necessary to examine such relevant factors. Alcohol consumption and alcohol abuse have been identified as potential behavioral risk factors for the transmission of HIV/AIDS, in the form of drinking before risky sexual events or frequent binge drinking as associated with HIV incidence (Erbelding et al., 2004; Fisher et al., 2007; Kalichman et al., 2007a; O’Leary & Hatzenbuehler, 2009).

The objective of this paper is to systematically explore and determine whether alcohol consumption has a causal role in this association. A potential causal impact of alcohol consumption is assessed separately for two stages of disease; firstly, for the incidence of HIV and secondly, for the worsening of existing HIV infections. This assessment is based on a systematic review of meta-analyses and review papers covering different dimensions relevant for causal criteria. A conceptual framework developed to guide our assessment for incidence of HIV is displayed in Fig. 1.

Clearly, alcohol-related behavioral and biological factors may both contribute to the incidence of HIV, albeit with an important distinction. Without behavioral factors leading to risky sex, the biological pathway alone can never be sufficient for leading to the incidence of HIV. As such, alcohol-related biological factors such as a weakened immune system may markedly increase the risk of infection from unsafe sex, but they may not, by themselves, lead to incidence of HIV. For worsening the disease course, again, alcohol-related behavioral and biological factors may play a role, including the interaction between these factors.

MATERIALS AND METHODS

This review is based on meta-analyses and reviews that investigated the potential causal impact of alcohol consumption on HIV incidence and on worsening the disease course. Meta-analyses and reviews were obtained through a systematic search of articles on alcohol and HIV, with the keyword search terms of ‘HIV’, ‘alcohol’, ‘review’ and ‘meta’. The search, limited to papers written in English, was carried out in November 2008 on the PubMed, PsycInfo and ETOH databases. The PubMed search resulted in 293 articles, with 43 selected during abstraction, and 20 were used for this paper. The PsychInfo search yielded 81 articles, with 11 selected during abstraction, and 4 were used, none of which overlapped with the other searches. The ETOH search resulted

© The Author 2010. Published by Oxford University Press on behalf of the Medical Council on Alcohol. All rights reserved
in 174 articles, with 50 selected during abstraction, 27 of which were used, 9 overlapping with the PubMed search and 3 appearing twice in this search itself. This was accompanied by a hand search of reference lists of relevant articles. Review articles were also searched for relevant pathways by examining outcomes related to potential causal links between alcohol and HIV/AIDS, such as unsafe sex. Finally, two meta-analyses (Baliunas et al., 2009; Shuper et al., 2009) and one review (Room, 2008) originally prepared for the technical meeting on alcohol and infectious diseases in Cape Town, South Africa were included to further assist in determining the causality of associations (Parry et al., 2009).

In determining causality, an association must first be established between the exposure (alcohol) and disease or condition (HIV). The evidence must then be reviewed to determine whether alternative explanations such as confounding can be ruled out (Mill, 1862). In this paper, the criteria used to judge causality are those identified by English et al. (1995), modeled on a framework used by the International Agency for Research on Cancer (IARC) for the evaluation of carcinogenic risks to humans (IARC, 1992). These criteria, which are a variation of the original Hill criteria (Hill, 1965; Rothman et al., 2008), were originally used for the quantification of alcohol, tobacco and illicit drug-attributable morbidity and mortality in Australia and have since been used in several major studies such as the Comparative Risk Assessment within the Global Burden of Disease Study (e.g. Rehm et al., 2009, 2003; Single et al., 1999). These criteria are as follows:

- Consistency on replication and strength of association (effect size): Consistency of evidence, or lack thereof, regarding diversity in time, place, circumstance and population, where research design strongly supports or detracts from a causal hypothesis. Although stronger effect sizes do not necessarily point to causality, confounding is less likely to explain the association.
- Temporality (time order): Exposure of the effect (alcohol) must precede the disease or injury (i.e. infection, or worsening of HIV/AIDS).
- Dose–response and specificity of effect and/or cause
- Pathways and coherence (theoretical, biological, factual, statistical): Findings plausible in terms of pre-existing theory are supportive, while those in contradiction detract from the evidence. This includes supportive theories on pathways.
- Reversibility of effects: Obviously, there can be no classical reversibility of effects (i.e. a reversal of infection if alcohol consumption ceases). However, one can empirically test the impact of alcohol-related interventions on the reversibility of behaviors leading to HIV infection.

Fig. 1. A conceptual framework for the association between alcohol and HIV infection.
RESULTS

The causal role of alcohol in the incidence of HIV

Consistency on replication and strength of association. Fisher et al. (2007) observed a significant relationship between alcohol and HIV in African studies, in which drinkers had a 70% greater chance of being HIV positive (95% confidence interval (CI) = 45–99%) than non-drinkers in the bivariate case and a 57% (95% CI = 42–72%) increased risk of HIV when potential confounders were controlled in multivariate analysis. This association also remained after adjustment for possible publication bias. Problem drinkers had a slightly higher risk (2.04; 95% CI = 1.61–2.58) than non-problem drinkers (1.57; 95% CI = 1.33–1.86; difference $\delta = 2.08, P < 0.04$). Similarly, Kalichman et al. (2007a), who also reviewed sub-Saharan African studies, provide additional support to these observations by assessing a consistent association between alcohol use and sexual risks for HIV infection.

Whereas Fisher et al. (2007) measured the association between alcohol consumption and HIV across studies with varied methodologies (e.g. cross-sectional, prospective), Baliunas et al. (2009) specifically examined the association between alcohol consumption and the risk of ‘incident’ HIV infection, focusing only on prospective studies. Baliunas et al. investigated alcohol consumption in terms of three classifications: any alcohol consumption (i.e. drinking any alcohol yes/no), consumption before/during sex and binge drinking. Across all three classifications, alcohol use was associated with an increased risk of HIV infection (1.98; 95% CI = 1.59–2.47). Those who consumed any alcohol were at 77% higher risk for HIV infection compared to those who did not consume (1.77; 95% CI = 1.43–2.19), and those consuming alcohol before/during sex were at an 87% increased risk (1.87; 95% CI = 1.39–2.50). For those consuming alcohol in binges, the risk of HIV was over double that of non-binge drinkers (2.20; 95% CI = 1.29–3.74). Similar findings were also reported by a recent qualitative review (O’Leary & Hatzenbuehler, 2009), suggesting that alcohol consumption, especially heavy consumption and abuse, was strongly related to incidence of HIV.

Temporality. The evidence of temporality is mainly derived from the meta-analysis of Baliunas et al. (2009) which explicitly included only studies with incident HIV, thus establishing temporality as a precondition for study inclusion. As reported above, the effect of alcohol was equally as strong when examining only incident HIV as the effect reported by Fisher et al. (2007) that was based on a mixed sample of incident and non-incident HIV studies. Additionally, multiple reviews (e.g. Baliunas et al., 2009; Shuper et al., 2009) that investigated drinking alcohol before sexual intercourse found significant links between alcohol and unprotected sex. However, evidence from event-level studies, which control for personality factors by analyzing data from multiple sexual intercourse occasions, is less conclusive (see Leigh et al., 2008 and below). Taken together, results provide support for a temporal link between alcohol and sexual risk behavior as well as alcohol and HIV. Notwithstanding, when more control is applied, the evidence is equivocal.

Dose–response or specificity of effect and/or cause. There is limited evidence regarding dose–response and specificity of effect or cause, as most studies in this area employed dichotomous alcohol consumption categories (e.g. any drinking/no drinking, problem drinking/non-problem drinking) rather than statistically assessing the impact of increasing levels of alcohol use. The few studies that included broader alcohol consumption categorizations tended to have inconsistent definitions, such as moderate or heavy or problem consumption, with different and incomparable operationalizations across studies. Overall, measures of problem drinking tended to yield higher risk estimates than measures of any alcohol use, but these estimates had wide and non-excluding CIs (see above). Therefore, given the state of the literature, substantial conclusions regarding a dose–response effect in this domain cannot be established at this time.

Pathways and coherence: the causal role of alcohol in the acquisition of HIV infection

Biological. There is a well-established biological relationship between addictive drugs, including alcohol, and increased level of infections, including HIV (Friedman et al., 2003, 2006). As indicated in our conceptual framework, alcohol’s impact on biological susceptibility to HIV is proposed to stem from its effects on liver and innate and acquired immune system functioning.

Regarding liver functioning, alcohol (ethanol, EtOH) is a major etiological factor of cirrhosis, and one of the most frequent causes of death and burden of disease in high and medium resourced countries (Levy, 1962; Rehm et al., 2004). EtOH may also be ranked as the most important hepatotoxin to which humans are exposed (Ishak et al., 1991; Leibach, 1975; Lieber, 2000). Long-term consumption of alcohol results in a spectrum of liver abnormalities, ranging from simple fatty liver (steatosis) to inflamed fatty liver (steatohepatitis), cirrhosis and hepatocellular carcinoma (Voiculescu et al., 2009).

Risk and severity of alcoholic liver disease is related to the amount and duration of alcohol abuse (Leibach, 1975). Cirrhosis is connected with immuno-suppression, as measured by low absolute CD4(+) T cell counts. Also, cirrhosis is associated with low CD4(+) T cell counts in the absence of HIV infection. Data have illustrated that CD4(+) T cell counts are significantly lower among cirrhotic HIV-seronegative individuals than among HIV-seronegative historic controls without liver disease (McGovern et al., 2007). As a result of suppressed ‘innate immunity’, the responses to HIV are low in patients with alcohol-induced liver damage. Consequently, those with alcoholic hepatitis and cirrhosis who are exposed to HIV for the first time do not have the ability to rapidly and efficiently fight the infection by the pathogen.

The adverse effects of alcohol abuse are also directly associated with induction of immune deficiencies and with increased incidence and prevalence of infectious diseases among alcoholics. Alcohol-induced immunomodulation can contribute to heightened susceptibility to infectious pathogens, including HIV. Impaired host defense after alcohol exposure appears to be linked to a combination of decreased inflammatory response, altered cytokine production (lower levels of tumor necrosis factor alpha and interferon gamma) and abnormal reactive oxygen intermediate generation (Friedman et al., 2003, 2006). Alcohol use, both acute and chronic, may thus increase susceptibility to HIV infection (Szabo, 1997, 1999).
Alcohol’s immunomodulatory properties can affect both the primary and secondary lymphoid organs, the innate and adaptive immune systems, as well as the immune barriers of specific organs (e.g., liver, pancreas, vaginal mucosa) (Ben-Eliyahu et al., 1996; Berretta et al., 2008; Bird et al., 1990; Gomaa et al., 2008; Kanagasundram & Leevy, 1981; Molina et al., 2002; Neuman, 2003; Stickel et al., 2002; Trifonova et al., 2007). Brodie et al. (1994) showed that alcohol inhibits early events in T-lymphocyte activation, suggesting a pathway of greater susceptibility to HIV infection.

Chronic and even acute alcohol use can increase host susceptibility to infections caused by bacterial and viral pathogens. Acquired immunity, normally triggered by exposure to antigens and involving an integrated system of host defense and interaction between cells and molecules, can be impaired by alcohol consumption (Cook et al., 1997; Neuman, 1999). Furthermore, cellular immunity, particularly antigen-specific immune response, is impaired by both acute and chronic alcohol use. Moreover, decreased antigen presenting cell function appears to be a key element in the decrease in cell-mediated immunity due to alcohol use (Neuman et al., 2008). The effects of alcohol in HIV acquisition may be quite significant in heavy drinkers and people with alcohol use disorders but negligible in occasional drinkers.

Behavioral. In addition to the possible biological influences of alcohol on HIV susceptibility, alcohol has also been frequently associated with unprotected sexual behavior and subsequent acquisition of HIV. One mechanism proposed to underlie this association involves a direct, disinhibitory behavioral impact of alcohol, where alcohol consumption leads to an impairment of cognitive capacity inhibiting the ability to systematically process risk-relevant information (Dingle & Oei, 1997), and possibly causes ‘alcohol myopia’ (Steele & Josephs, 1990), in which such restricted cognitive faculties allow for prompting cues (e.g. sexual arousal) to be processed while preventing the processing of complex or inhibiting cues (e.g. risk of HIV, fear of pregnancy) (see also MacDonald et al., 2000). Alcohol-related beliefs and expectancies may also in and of themselves impact condom-related attitudes, risk perceptions and condom use skills (Dingle & Oei, 1997; George & Stoner, 2000; Gordon et al., 1997; Maisto et al., 2002), which can provide individuals with ‘social or personal permission’ to engage in what would normally be deemed a socially undesirable behavior (Crowe & George, 1989) and at times can even serve as an excuse to ignore obvious warning signals (Murphy et al., 1998).

Alternatively, it has also been suggested that the impact of alcohol on sexual risk behavior is mediated by ‘third’ variables, including personality characteristics, psychiatric disorders and situational factors (Dingle & Oei, 1997; Fisher et al., 2007; Stall & Leigh, 1994; Woolf & Maisto, 2009). Individuals possessing a generalized risk-taking personality, and in particular, individuals high on the dimensions of sensation seeking (e.g. Kalichman et al., 1996; Zuckerman, 1994) and sexual compulsion (e.g. Kalichman & Rompa, 1995), may be prone to both problematic drinking and risky sex. Similarly, psychiatric disorders may underlie both substance use and HIV risk behavior, where substance use and diminished impulse control, often associated with personality disorders such as antisocial personality disorder and borderline personality disorder, could result in increased risky sexual behavior (Compton et al., 2005; Disney et al., 2006; Kelley & Petry, 2000; Ladd & Petry, 2003) and subsequent HIV seroconversion (Brooner et al., 1993). Finally, from a situational perspective, the venues at which individuals consume alcohol are very often the same locations where they meet new and/or casual sexual partners (Dingle & Oei, 1997; Fisher et al., 2007), and as such, the combination of the presence of alcohol and available sexual partners in the same settings may contribute to an alcohol–sex association and in turn, an alcohol–risky sex association. That people often go to ‘sexual marketplace’ bars with some intention of finding a sexual partner (Cavan, 1966), and that these are intrinsically drinking places, with drinking assumed by all involved to facilitate making a sexual connection, indicates that the drinking is a cofactor in the risky sexuality. Thus, such third variables could be regarded as explaining away relationships between drinking and high-risk sex; as what was apparently due to alcohol could instead be attributed to these factors.

Despite the direct pathways that have been proposed to underlie the alcohol–protected sex association, given the role of third variables described above, it is perhaps not surprising that a number of systematic reviews and meta-analyses in this area have provided somewhat inconsistent support for an overall behaviorally based alcohol–risky sex association. Global-level alcohol–risky sex associations, which test the relationship between generalized alcohol use or abuse and the occurrence of unprotected sex over an extended time span, have for the most part been supportive of a link between the two behaviors (Halpern-Felsher et al., 1996; Kalichman et al., 2007a; Leigh & Stall, 1993). However, the strength of these global-level associations tends to be modest, indicating potential unmeasured confounding. Further, because these global-level associations focus on alcohol consumption in general rather than alcohol consumption in the context of sexual activity, they do not provide strong evidence concerning the possible causal connection between alcohol and unprotected sex.

Due to these limitations, a substantial literature has instead focused on event-level associations, in which alcohol use is examined in conjunction with specified corresponding sexual acts, often measured through daily diary assessments. An earlier review by Leigh and Stall (1993) found no event-level association between alcohol and risky sex when controlling for personality (e.g. using within-person designs), and these null findings were also mirrored by a number of more recent reviews assessing event-level associations (Room, 2008; Weinhardt & Carey, 2000; Woolf & Maisto, 2009). These results suggest that drinking does not necessarily encourage the intention for risky behavior, which may well be formed before drinking occurs. By failing to show reliable alcohol–risky sex associations, event-level findings raise questions about a causal relationship between drinking and unprotected sex. These questions are serious enough that a causal connection cannot be asserted with any confidence.

Taken as a whole, there is insufficient evidence for a direct behavioral pathway linking alcohol, risky sex and incident HIV. However, based on significant global-level associations, it may be surmised that alcohol consumption is still significant in determining or ‘marking’ characteristics, personality types and psychiatric disorders in terms of risk. As such, there may be individuals who simply have riskier lifestyles, choices, dispositions or disorders that underlie both unprotected sex and drinking heavily. Moreover, these characteristics may also occur without causing each other.
Experimental interventions to reduce the effect of alcohol consumption on risky sexual behavior

Kalichman et al. (2007b, 2008) conducted two randomized clinical trials, where an adapted version of a social cognitive model of health behavior change was used as the theoretical framework for risk-reduction skills interventions either 60 min or 3 h of length. Overall, the interventions showed mixed results, with more behavioral changes in the short (3-month follow-up) versus medium term (6-month follow-up). In addition, in the second trial, heavier drinkers did not respond to the interventions as well as lighter drinkers.

The causal role of alcohol in worsening of HIV infection

Biological. Alcohol’s effects on the immune system not only play a role in higher susceptibility for HIV infection but also in worsening the course of existing infections. Based on increased immunoglobulin levels seen in chronic alcohol users, there is a higher induction of Th2 when compared to Th1 immune response. The effects of chronic and acute alcohol consumption in humans on host defense and immunity can therefore be viewed in the context of the functional abnormalities of T and B lymphocytes, natural killer cells and monocytes/macrophages, that result in the altered immune response after alcohol use (Neuman, 1999). A notable example is a case report of an HIV-1 infected individual who showed rapid progression of HIV-1 infection and development of AIDS upon heavy alcohol use (Fong et al., 1994). Alcohol abuse may also alter the change from the (CD4+CD45RA- to the (CD4+) CD45RA-phenotype selectively as manifested by increased IL-2 production in vitro (Chiappelli et al., 2006).

Alcohol has been demonstrated to depress levels of CD4 counts. One prospective study evaluated the effect of alcohol use on CD4 T cell counts in 595 HIV-infected patients. In patients not on antiretroviral therapy, heavy alcohol consumption was associated with a lower CD4 cell count compared to patients who had a history of abstinence (Pol et al., 1996).

Results from in vitro experiments show that ingestion or infusion of even a single moderate dose of alcohol (e.g. 0.7–3.1 l of beer or equivalent) by healthy individuals significantly increases HIV replication in peripheral blood mononuclear cells and decreases the ability of lymphocytes to produce interleukin 2 and soluble immune response suppressors (Bagasra et al., 1989, 1996). However, Bagasra and colleagues found that the difference between EtOH-infused and control (saline-infused) blood disappears when cells are depleted of their CD8+ lymphocytes, which may indicate that some portion of the observed increase in HIV-1 replication after EtOH infusion may be the result of the effects of EtOH on CD8+ T-lymphocyte functions (Bagasra et al., 1996). Prospectively analyzing the role of alcohol use and T-lymphocyte subsets among injection drug users with HIV-1 infection, Crum et al. (1996) found the percentage of CD8-positive T cells significantly increased among drinkers (21 drinks/week) between 2 and 5 years post-seroconversion, suggesting the immunomodulatory role of alcohol.

In summary, alcohol has been proposed as a cofactor in spreading the virus within the immune system and can also accelerate the onset of symptoms. The effects of alcohol on the immune system and HIV infection may depend on a person’s drinking habits (i.e. quantities consumed, duration and frequency of consumption and the presence of liver disease), with the most severe effects on worsening the course of HIV infection appearing in heavy drinkers and people with alcohol use disorders.

Behavioral. The behavioral effects of alcohol also play a role in the worsening of the HIV infection, due in large part to its influence on adherence to treatment. Highly Active Antiretroviral Therapy (HAART), the current recommended treatment for HIV, can influence the prolonged suppression of detectable levels of HIV and reduce the patient’s risk of opportunistic infections commonly associated with HIV, significantly improving prognosis (NIH, 1998). Proper adherence to HAART plays a vital role not only in health status but also in avoiding the emergence of drug-resistant virus (Kresina et al., 2002). Given the high viral replication and mutation rate of HIV and the relatively short half-life of current medications, it is possible that missing a few doses, or even adhering at a high but imperfect level, can result in the development of viral resistance, which may adversely impact survival (Gardner et al., 2009). Therefore, for treatment to be most effective, patients should achieve adherence levels of at least 95% (Meyerhoff, 2001; Paterson et al., 2000).

Alcohol consumption, particularly high consumption, has been shown to have a direct influence on adherence to medication in general (Weiss, 2004) and specifically to HIV medication (Cook et al., 2001; Hendershot et al., 2009; Meyerhoff, 2001; Petry, 1999). In a recent comprehensive meta-analysis based on 40 studies with over 25,000 HIV-positive participants, Hendershot and colleagues found that PLWHA who drank alcohol were 50–60% as likely to be adherent (Odds ratio (OR) = 0.55, 95% CI = 0.49–0.61) compared to PLWHA who did not drink or PLWHA who drank at relatively lower levels. Effect sizes for problem drinking were greater (OR = 0.47, 95% CI = 0.41–0.55) than those for any drinking or global alcohol use (OR = 0.60, 95% CI = 0.53–0.69). Braithwaite et al. (2005) found that non-adherence among HIV+ patients was higher among non-binge (OR = 1.8) and binge drinkers (OR = 4.3) compared to abstainers. PLWHA’s HAART adherence also appeared to be more affected by low doses of alcohol than HIV-negative individuals’ adherence to medications in general, indicating a potential interaction between alcohol and specifically HAART, which corresponds with the biological mechanisms outlined above (see additionally Neuman et al., 2006).

These findings provide strong support for a direct link between alcohol use and adherence to HAART. Support for a causal relationship between the two behaviors is also demonstrated, in that significant associations were consistently yielded through multivariable models that controlled for a wide range of third variables, including psychological disorders (e.g. depression, anxiety), health status and use of other substances. From a behavioral perspective, the evidence therefore suggests that alcohol may increase the likelihood of suboptimal HAART adherence over time, in turn enabling HIV to progress more rapidly.

CONCLUSIONS

Overall, our review found strong associations between alcohol consumption and both HIV incidence and worsening of the disease condition. However, the evidence regarding causality of these associations seems to differ.
In terms of incidence, although alcohol consumption may lead to a reduction in the strength of the immune system, causing increased biological susceptibility to HIV, biological susceptibility on its own is not causally sufficient for HIV seroconversion to take place. Rather, an active behavioral component is also necessary in order for there to be the possibility that HIV seroconversion will occur. This active behavioral component in most cases consists of the occurrence of unprotected sexual activity, which although linked to alcohol consumption, cannot be conclusively identified as a direct causal consequence of alcohol use. It cannot be excluded that personality factors and psychiatric disorders underlie both alcohol consumption, especially problem drinking or drinking prior to sexual intercourse, and risky sex. Such factors have also been linked to postulated intermediate processes such as expectations (Golding & Perkins, 1996; Kalichman et al., 2002; Kalichman & Cain, 2004). Given this lack of compelling evidence for a causal behavioral association between alcohol and HIV seroconversion, one cannot at this time make unequivocal claims regarding alcohol’s direct causal role in the acquisition of HIV.

The clearest line of evidence in our view regarding the establishment of a causal behavioral connection is through the results of the two trials conducted thus far are mixed and difficult to interpret with respect to the causality of alcohol, as more than one intervention was introduced simultaneously. To clarify causality, alcohol specific interventions should be comprised of one experimental factor to be varied without concomitant variation of other factors. Of course, such a trial can only be conducted in populations where there is high incidence of HIV, for instance, in South Africa (Barnighausen et al., 2008). If suitable samples are selected, such trials could be feasible with relatively small cohorts and short follow-ups.

The potential role of alcohol in worsening the effects of HIV/AIDS appears to be clear, where alcohol, especially heavy drinking, worsens the condition. The causality of this relationship, as demonstrated above, has adequate empirical support from both biological and behavioral pathways. This conclusion is corroborated by the results of the recent technical meeting on alcohol and infectious diseases in Cape Town, South Africa (Parry et al., 2009), where an interdisciplinary group of experts reached the same conclusion.

Establishing causality is only one step towards quantitatively determining the association of alcohol consumption and HIV/AIDS, including incidence, as well as the exact mechanisms of pathways, and thus being able to better estimate alcohol-attributable mortality and burden of disease of HIV/AIDS. In this respect, there is still a lot of work remaining, with more studies needed to provide information for quantifying this relationship. Finally, and most importantly, it would be highly beneficial to develop targeted alcohol-related interventions for reducing the worsening of the HIV/AIDS condition.

On a population level, there are effective treatment interventions for alcohol use disorders, and brief interventions have been shown to significantly reduce heavy drinking (Room, 2005). Furthermore, both alcohol use disorders and heavy drinking can be significantly reduced by policy measures such as increasing taxation on alcoholic beverages (Rehm & Greenfield, 2008). Given the size of the problem in some regions such as sub-Saharan Africa, such interventions should be implemented at this time and carefully studied with respect to their impact on both incidence of HIV/AIDS and disease course including fatal outcome.

Acknowledgements — We thank the attendees of the Alcohol and Infectious Diseases Technical meeting held in Cape Town, South Africa in July 2008 and hosted by the South African Medical Research Council (MRC) in collaboration with the World Health Organization (WHO). We thank the members of the core group for the Comparative Risk Assessment for Alcohol and the Global Burden of Disease collaborators for helpful comments (G. Borges, G. Gmel, K. Graham, B. Grant, R. Norman, C. Parry, V. Poznyak, R. Room, T. Vos; the working group also includes J. Rehm). We would especially thank R. Room for additional help with the first version of the behavioral pathway based on his presentation at the Cape Town Conference, as well as A. Samokhvalov for his insightful contributions to this manuscript.

Funding — This research work was funded by the South African Medical Research Council through a grant received from the US President’s Emergency Fund for AIDS Relief through the US Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

REFERENCES


