

The impact of alcohol on HIV prevention and treatment for South Africans in primary healthcare

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Background: Antiretroviral treatment (ART) has substantially reduced morbidity and mortality for HIV patients. In South Africa, with the largest ART programme globally, attention is needed not only on the further expansion of ART coverage, but also on factors which undermine its effectiveness, such as alcohol use.

Objective: Given the decentralised approach of nurse-initiated and -sustained ART in the South African primary health sector, it is important to document key aspects of alcohol use to be conveyed to HIV-positive individuals and those at risk for HIV.

Method: This study comprised a narrative review of relevant literature.

Results: Alcohol acts through both behavioural and physiological pathways to impact on the acquisition, further transmission and then progression of HIV disease. Besides links to risky sex, alcohol undermines the immune system, raising susceptibility to contracting and then countering HIV and other infections. There are important drug interactions between alcohol and ART, or therapies for opportunistic infections and other co-morbidities. Moreover, alcohol undermines adherence to the medication which is essential for effective ART.

Conclusion: Primary healthcare clinic attendees need evidence-based information on the detrimental effects of alcohol consumption on HIV infection, which ensue throughout the clinical course of HIV. This spans the role of alcohol consumption as a risk factor for HIV infection, HIV replication in infected individuals, a person's response to HIV infection and HIV treatment. Primary healthcare workers, especially nurses and HIV counsellors, require training in order to screen for and provide appropriate interventions for HIV-positive patients, those on treatment and treatment-naïve patients, who will benefit from reduced alcohol consumption or the cessation thereof.

Introduction

Despite HIV prevalence reaching a plateau in South Africa, rates of new infection are still unacceptably high (Department of Health 2012:37). The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that there were 5.6 million HIV-infected people living in South Africa in 2011. This figure, around 11% of the South African population (Doyle & Dorrington 2011), makes up about 17% of the total global number of people living with HIV. Largely as a result of the expanded antiretroviral treatment (ART) programme, the biggest in the world (Shisana *et al.* 2009:viii), there has been a substantial reduction in AIDS-related mortality in South Africa. There were, however, still an estimated 194 000 HIV-related deaths in 2008, down from 388 000 in 2003 (Actuarial Society 2011:1).

South Africans are heavy drinkers, with amongst the highest per capita consumption rates for alcohol in the world, namely, 9.46 litres of pure alcohol per person annually (World Health Organization 2011:276). Alcohol consumption is frequent amongst HIV patients, with some studies showing rates of heavy drinking that are almost twice that of the general population (Galvan *et al.* 2002:179). Alcohol use disorders (AUDs) are common amongst HIV-infected persons, particularly hazardous alcohol consumption, resulting in decreased overall survival in this group (Braithwaite *et al.* 2007:462). Social and psychological aspects, such as the dual stigma of HIV infection and alcohol consumption, hinder health-seeking treatment for HIV and substance abuse (Morojele *et al.* 2010:10).

HIV is not merely a biomedical phenomenon – the disease has a number of interacting socioeconomic, behavioural and psychological components. These, in turn, manifest as risk factors for HIV infection, acting through a myriad of pathways to HIV infection and then its consequences. In a conceptual framework comprising these components and pathways, Shuper *et al.* (2010:160) provide a tool for examining the associations between alcohol consumption and HIV infection. Unsafe sexual intercourse is an essential component for HIV infection. Sexual

transmission of HIV is contingent upon factors such as early sexual debut, the choice of sexual partner, frequency and type of sexual intercourse, the occurrence of sexual violence as well as the number and sequencing of sexual partners (Mah & Halperin 2010:16; Morojele *et al.* 2009:217; Shisana *et al.* 2009:39). There is considerable interaction between each of the above factors and alcohol use.

With ART, as with HIV prevention, cognisance needs to be taken of individual behaviours, as well as the social and structural forces that negate treatment outcomes. This is especially pertinent in the resource-poor South African public health sector (Delva, Pretorius & Temmerman 2009:638).

Pandrea *et al.* (2010) examine the role of alcohol within the natural history of HIV infection, providing a useful framework for analysis. Alcohol consumption can be conceptualised as a pivot around which revolve four domains of the HIV epidemic (Pandrea *et al.* 2010:204). Each domain, with its specific topography and information, constitutes the roadmap needed to traverse this challenging health landscape. In the first, alcohol is linked with HIV acquisition. This encompasses the initial HIV infection, but also possible re-infection. HIV replication in the host, along with the host's immune response, constitute the second and third domain, respectively. A fourth domain is ART and HIV care services, including access to care, HIV testing and counselling, the pharmacology of treatment drugs and adherence to medication. Alcohol consumption impacts negatively on all four domains, which are interlinked. This article discusses each domain, then sums up the key alcohol-related information that health workers need to be aware of in order to discuss this information with patients receiving ART. The article draws on a narrative review of evidence on alcohol-HIV interactions, wherever possible citing systematic reviews on the topic, or empirical evidence where these are not available.

Domain I: Alcohol as a risk factor for HIV transmission

A systematic review and meta-analysis of randomised studies by Rehm *et al.* (2012:51) found that alcohol use was an independent risk factor for the intention to engage in unprotected sex. They noted that an increase in blood alcohol content of 0.1 mg/mL leads to a 2.9% increase (95% CI = 2.0% – 3.9%) in the likelihood of engaging in unprotected sex. Empirical studies demonstrate how HIV and alcohol interconnect and how these interactions amplify negative health outcomes. For example, a study at a sexually-transmitted infection (STI) clinic in Cape Town (Simbayi *et al.* 2004:434) showed alcohol to be a major risk factor for STIs, with heavy drinking being linked with condom failure, a higher number of sexual partners and more STIs.

A meta-analysis by Baliunas *et al.* (2010:162) concluded that alcohol consumption is associated with a 77% higher risk of incident HIV infection. Those drinking alcohol prior to, or

at the time of, sexual relations were at an 87% increased risk of infection. For binge drinkers, the risk of HIV acquisition was twice that of non-binge drinkers. Another meta-analysis also demonstrated that alcohol use was associated with HIV infection in Africa (Fisher, Bang & Kapiga 2007:856). The pooled unadjusted odds ratio from 20 studies was 1.7 (95% CI = 1.5–2.0).

For drinkers, it is the quantity of alcohol per occasion, rather than the frequency of drinking, that predicts sexual risk-taking (Kalichman *et al.* 2007:146). The greater the quantity of alcohol consumed, the more likely the sexual risk behaviour. There are also gender differences with regard to alcohol use and sexual risks. Oftentimes, men drink and engage in higher-risk behaviour, whilst women's risks may be associated with their male sex partners' drinking. In the behavioural sphere, alcohol, besides its relationships with unprotected sex and other sexual risk behaviours, is linked to interpersonal violence, which can further increase HIV transmission (Schneider *et al.* 2007:665).

Domain II: HIV replication and Domain III: The immune system response

Clinical and experimental evidence demonstrate that both chronic and acute alcohol use impact negatively on the functioning of the human immune system (Molina *et al.* 2010). This impact is bi-directional, with alcohol both stimulating and reducing the host's immune response. In an HIV-infected patient, alcohol may increase inflammation and immune response, thus raising the pool of HIV target cells at key transmission sites and throughout the body. This heightens HIV infectivity, for example, alcohol consumption may raise viral concentration in the semen and in the vagina, thereby enhancing the chances of onward HIV transmission (Pandrea *et al.* 2010:204). Even moderate alcohol ingestion enhances HIV replication in peripheral blood mononuclear cells in culture (Bagasra *et al.* 1996:550). By impacting on individual components of the immune system, however, alcohol consumption also suppresses the immune response, weakening the patient's defences against HIV infection and opportunistic infections (both in resistance to them and in recovery from infection) (Pandrea *et al.* 2010:206).

Evidence that alcohol use hastens the progression of HIV disease is not conclusive (Baum *et al.* 2010:511). However, amongst those with HIV infection, the presence of alcohol use disorders was associated with increased plasma viral loads in five studies and decreased CD4 counts in four studies (Azar *et al.* 2010:185). For persons receiving ART, frequent alcohol use (≥ 2 drinks/day) resulted in a nearly three times higher risk of CD4 cell count decline to $\leq 200/\mu\text{L}$ compared with moderate alcohol use and abstinence in one study (Baum *et al.* 2010:514). Moderate alcohol use (< 1 drink/day over 6 months) did not, however, increase rate of CD4 decline to $\leq 200/\mu\text{L}$ compared with abstainers. For ART-naïve HIV-positive persons, frequent alcohol

use also increased their risk for CD4 decline to $\leq 200/\mu\text{L}$. Furthermore (Baum *et al.* 2010:511) reported that CD4 decline was faster in frequent alcohol users who were not receiving ART than in those who were. Not all findings on the effects of alcohol on disease progression are consistent, however. A longitudinal study of American women with HIV by Ghebremichael *et al.* (2009:834) found no association between alcohol consumption and CD4 cell count, whether or not the participants were receiving ART.

Domain IV: HIV treatment and care

The Annual Performance Plan 2012/13–2014/15 of the Department of Health states that the total number of patients receiving ART in 2009 was 1.1 million and the target for 2014 is 2.5 million (Advocacy Aid 2012). Adam and Johnson (2009:661) estimated that of those South Africans receiving ART, almost 80% receive treatment in the public sector. This is notable, given that 79% of medical doctors work in the private sector in the country (Lawn & Kinney 2009:4). Notwithstanding the expansion of ART coverage, there remains a considerable unmet demand for ART, especially with the raising of the threshold for eligibility for ART from 200 CD4 cells/ μL to 350 cells/ μL (Colvin *et al.* 2010:210; Health Systems Trust 2011:1).

To facilitate treatment scale-up in the public sector, ART service delivery was decentralised in 2010, with the introduction of nurse-initiated ART as a strategy to secure the sustainability of services in the long run (Colvin *et al.* 2010:210). In April 2012, there were 10 000 nurses certified to initiate ART in South Africa, a massive rise from the 250 in February 2010 (Parliamentary Monitoring Group 2012). A randomised trial in urban clinics of Johannesburg and Cape Town demonstrated that nurse-managed ART was not inferior to doctor-managed ART (Sanne *et al.* 2010:33). Both groups had similar outcomes of viral suppression, adherence, toxicity and death. Moreover, nurses at primary care level are well placed to deal with the intersecting epidemics of HIV and alcohol abuse, ensuring effective treatment and patient management.

Nurse-led ART and related interventions can also address the dual stigma surrounding HIV and alcohol use (Nyasulu *et al.* 2012:235). Stigma surrounding HIV and alcohol consumption may manifest in several ways: people may delay testing for HIV if they have a drinking problem or may not attend scheduled follow-up visits if inebriated or recovering from recent alcohol use. Also, patients who abuse alcohol and suspect they may be HIV-positive may elect not to attend HIV clinics based on the mistaken belief that ART will be withheld because of their alcohol consumption. In one study, men reported self-imposed delays in ART enrolment as a result of alcohol use (Fitzgerald, Collumbien & Hosegood 2010:355). Alcohol consumption reduces ART efficacy through several mechanisms. Besides impacting on adherence to ARV drugs, effects include adverse drug reactions (ADRs), drug–drug interactions, direct liver toxicity and other physiological and biological aberrations,

with the result that ARVs are processed improperly, with diminished effectiveness. Also, it is important that ART is taken correctly, as this reduces further HIV transmission by reducing levels of infectivity.

Adherence to antiretroviral medication

ART works suboptimally in a non-adherent patient; resistance to antiretroviral (ARV) drugs can develop, HIV viral load increases and CD4 counts decline, with concomitant poor health (NAM 2009). Furthermore, extended treatment interruptions have a greater impact on treatment failure than occasional missed ARV doses (Kalichman *et al.* 2012a:512). Substantial and consistent associations have been found between alcohol use and ARV non-adherence. Alcohol drinkers are up to 50% – 60% less likely to be classified as adherent to HIV medications, compared with abstainers. The largest effect was for problem drinkers, who were 47% less likely to be adherent compared with those who drank relatively less (Hendershot *et al.* 2009:180). A finding by Braithwaite *et al.* (2008:1651), which is of relevance to HIV-positive individuals, is that hazardous episodic drinking rather than high average daily drinking was associated with non-adherence.

Drinking alcohol impacts on cognitive functioning, leading to missed doses of drugs. However, a study by Sankar *et al.* (2007:195) demonstrated non-compliance with ARV medication as being not the result of being inebriated, but rather a deliberate decision not to drink alcohol and take ARV medication simultaneously. A prospective study in the United States found a positive relationship between the belief that mixing alcohol and ART is toxic (interactive toxicity beliefs) and intentional non-adherence. During drinking episodes, people thus often intentionally interrupt ART based on these beliefs (Kalichman *et al.* 2012b:399).

Adverse drug reactions

An ADR caused by alcohol is defined as the clinical consequence of alcohol intake before, concomitant with or immediately after taking ARV drugs. Both alcohol and ARVs are metabolised by CYP450 enzymes. ARVs may inhibit or induce the enzymes within this system. The non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, for example, induces these enzymes. This hastens the drug-clearing processes in the liver and other organs, such as the stomach. This may cause HIV drugs to be cleared too quickly, undermining their effectiveness and facilitating viral resistance. It should be noted that not just HIV drugs, but several other medications may be cleared faster. On the other hand, some protease inhibitor drugs (PIs), particularly ritonavir, inhibit CYP450 enzyme function (BioPortfolio 2010). This slows down how the liver clears medications, leading to higher concentrations of these medications, which often reach toxic levels (Potochnic 2002).

The pattern of alcohol consumption plays a role here too, determining the effect on liver enzymes. Acute ingestion of

alcohol with ART results in the inhibition of the liver enzymes (CYP2E1 and 3A4). However, chronic alcohol ingestion leads to enzyme induction, which may result in subtherapeutic levels of PIs and NNRTIs (Pujol 2003).

Organ damage: The liver

Alcohol use, in particular hazardous drinking, can lead to liver pathology (Szabo & Mandrekar 2010). Similarly, some ARV drugs, used over an extended period, may induce liver damage. The liver metabolises both alcohol and ARVs; and a diseased liver can process neither effectively. Hepatitis viruses and alcohol act synergistically, hastening the progression of liver disease (Neuman *et al.* 2012:4).

Wyles and Gerber (2005:181) conclude that liver dysfunction has a considerable impact on PI metabolism, but, on the whole, processing of NNRTIs and nucleoside reverse transcriptase inhibitors (NRTIs) are affected minimally. Liver toxicity is a common side effect with the use of nevirapine or lopinavir/ritonavir. Liver problems only occur rarely with efavirenz. The altered drug metabolism in people with liver damage can be managed by adjusting drug doses (Highleyman 2005).

The South African Medicines Formulary (Rossiter 2012) suggests prescribing stavudine or lopinavir/ritonavir with caution in patients with a history of hepatic disease. For lamivudine and nevirapine, the caution is liver impairment, whilst for didanosine, the caution is alcoholism. People taking the latter drug should avoid all kinds of drinking, because of the potential for increased risk of pancreatitis (Manfredi & Calza 2008:99).

Co-morbid conditions and effects on other systems

Alcohol also has the potential to impact negatively on medicines used to treat HIV-related opportunistic infections, specifically those for treating tuberculosis (TB), hepatitis B virus and hepatitis C (Neuman, Monteiro & Rehm 2006:1395). For example, alcohol reduces the efficacy of rifampicin, which is used to treat HIV/TB co-infection (Moreno *et al.* 2001:1185). ARVs, furthermore, counteract some pharmacotherapies to treat alcoholism, for example, lopinavir and/or ritonavir is contraindicated with the use of disulfiram (Cvetkovic & Goa 2003:769).

Some ARVs raise blood lipids levels (such as cholesterol and triglycerides) and heavy alcohol consumption may exacerbate this (Míguez-Burbano, Lewis & Malow 2009b:176). Resulting dyslipidaemias enhance risk for cardiovascular disease, which is also associated with alcohol use. Also, peripheral neuropathies from dideoxyinosine (LeLacheur & Simon 1991:538) may be worsened by the neurotoxic effects of alcohol.

Alcohol use for persons living with HIV

There are differing views regarding whether moderate use of alcohol is harmful for persons living with HIV (PLWH),

although there is widespread lay and medical professional agreement that use of alcohol and HIV treatment do not mix well (Kalichman *et al.* 2009:449). Bryant (2006:1465), for example, states that current research supports the conclusion that 'perhaps no level of alcohol consumption is "safe" once individuals are infected with HIV'. On the other hand, a British publication maintains that there is no evidence that moderate alcohol consumption is harmful for HIV-infected people (Carter 2011). Alcohol consumption may help allay anxiety and the moderate consumption of alcohol may serve as a coping mechanism for individuals struggling to come to terms with the disease. Furthermore, certain alcoholic beverages such as red wine are considered to have health benefits. A glass of wine can serve as an appetite stimulant, which may benefit some HIV-positive individuals with appetite loss. Conigliaro *et al.* (2006:S1) state that the quantity and frequency of alcohol consumption that constitutes a measurable harm for HIV patients has not yet been established, but is likely to be less than that recommended for the general population. Ellison (2002:6) observes that, unlike other populations, it has not been demonstrated that alcohol has beneficial health effects for HIV-positive people. Notably, in HIV-infected individuals, the threshold level of cognitive impairment that affected non-adherence occurred at moderate, not at high, levels of alcohol consumption. This lower tolerance level results from the effect of the virus, ART and, possibly, ageing (Braithwaite *et al.* 2008:1651). Importantly, it is ill-advised for an individual to reduce or suddenly discontinue alcohol consumption after a long period of excessive intake as this might precipitate alcohol withdrawal syndrome.

Of note, eliciting information from HIV patients about their alcohol consumption is important, as alcohol abuse or dependence, even in the past, may be an important determinant of the best HIV treatment approach for a patient (Conigliaro *et al.* 2006:S2). For people with HIV infection, not only the amount of alcohol consumed and the patterns of alcohol use are relevant to HIV disease progression, but also perhaps the type of liquor consumed (Míguez-Burbano *et al.* 2009a:366). Patients who drank spirits that included gin, vodka and whiskey, as opposed to consuming wine and beer, had poorer viro-immune outcomes of ART.

Discussion

Heavy, chronic alcohol consumption alters the physiology and biology of every cell in the human body, including the immune system. Despite the well-documented negative effects of alcohol, legislating commensurate alcohol regulation has proven difficult due to powerful economic and social counterforces in play, particularly in South Africa (Parry 2010:1340). Effective interventions to counter the adverse health outcomes of alcohol use are, of necessity, intersectoral and multilevel. The health sector primarily deals with the fallout from hazardous and harmful alcohol use. Most interventions that could target the nexus of alcohol use and unsafe sex lie outside the health sphere. These interventions have been described widely, are considered to

be effective and need to be applied as a matter of urgency (Parry, Rehm & Morojele 2010:86).

In the health sector, alcohol consumption is considered a modifiable health risk, amenable to screening and interventions. Alcohol use varies considerably amongst drinkers and can be categorised by the number of drinks consumed; or whether someone is a binge drinker or not; or by the impact of alcohol consumption on health in terms of responsible, hazardous or harmful use. The National Institute on Alcohol Abuse (NIAAA) defines moderate drinking as no more than four drinks on any single day and under 14 drinks per week for men. For women, the recommendation is no more than three drinks on any single day and less than seven drinks per week (NIAAA 2012a). Hazardous drinking is defined as drinking above these recommended limits and increases one's vulnerability to illness, injury, and social or legal problems (NIAAA 2012b).

The AUDIT tool screens for people who will benefit from reducing or ceasing to drink alcohol (Babor *et al.* 2001:4). This tool is used, commonly, to identify the severity of alcohol problems. It is designed for use in primary healthcare settings, with HIV counsellors and nurses considered to be appropriate screening personnel (Babor *et al.* 2001:9). The AUDIT comprises 10 questions, which are then scored. Based on these scores, patients are stratified from low-risk alcohol consumption to alcohol dependency (Babor *et al.* 2001:19). Low-risk drinkers with an AUDIT score of 0 to 7 require only alcohol education; a score of 8 to 15 necessitates simple advice given to reduce hazardous drinking; scores from 16 to 19 suggest harmful drinking and should prompt provision of counselling with Brief Interventions, as well as continued monitoring; and, finally, a score of 20 or more requires referral to a specialist for full diagnostic evaluation and treatment for alcohol dependence (Babor *et al.* 2001:20). In addition, past alcohol use, as determined from the final two questions of the AUDIT, indicates a need for monitoring, despite the fact that these patients do not currently consume alcohol (Babor *et al.* 2001:19). Furthermore, these guidelines should be considered together with clinical judgement of the patient's HIV disease stage, family history of alcohol problems and the perceived honesty of the patient in responding to the AUDIT questions (Babor *et al.* 2001:20).

Brief Interventions are effective for addressing hazardous and harmful drinking, as are more specialised addiction services for those with alcohol dependence (Kaner *et al.* 2009:301). Typically, Brief Interventions entail one to four short one-on-one counselling sessions. These interventions are delivered via a specific technique of interviewing, namely, motivational interviewing. Patients are encouraged to think about making changes relating to their alcohol consumption behaviours. At a minimum, it seeks to equip them with skills to apply in consuming alcoholic beverages in a safer way.

Two studies demonstrated the effectiveness of group interventions in resource-scarce settings. One by Wechsberg *et al.* (2008:130) utilised a brief behavioural intervention

for a group of high-risk women in the Cape Province, to address HIV issues, substance use and risky sexual practices. Another, by Papas *et al.* (2010:669), applied a cognitive behavioural method to reduce alcohol use amongst HIV-infected outpatients in Kenya.

A key problem for South African health workers at the interface of the dual HIV and alcohol epidemics is the lack of integration of addiction centres and HIV clinics within primary facilities (Parry *et al.* 2010:90). Information on where to refer patients with identified alcohol abuse problems is often unavailable at primary care level. Conversely, staff working at drug and alcohol treatment centres should include HIV prevention, treatment and onward referrals in their scope of work.

Patients with alcohol problems also require screening for alcohol-related HIV risk. This includes ascertaining drinking patterns around sexual intercourse and correct condom usage, as well as choice and number of sexual partners when drinking. Parry *et al.* (2010:90) suggest staff need to be cross-trained in HIV and alcohol problems in order to ensure sufficient capacity. A hospital-based study in HIV care centres in New York City also found that health providers routinely implemented more alcohol intervention components if they had greater exposure to information on the effect of alcohol on HIV (Strauss *et al.* 2009:211). A study by Korthuis *et al.* (2008:301), looking at HIV-infected American adults, found that patient-provider discussions on substance use led to increased utilisation of addiction services. Treatment for substance abuse is linked to reduced HIV-risk behaviour and improved HIV prognosis (increased ARV drug adherence in men, decreased hospitalisation and increased receipt of primary care) (Korthuis *et al.* 2008:295).

Other studies had less assuring findings. Bryant (2006:1486) found that American medical care providers are often uninformed about the interactions of alcohol with HIV progression and treatment, hence do not take this into account when making clinical decisions. A qualitative study of a general patient population in America noted that many providers were uncomfortable about or avoided discussing substance abuse with patients, or gave vague limited advice (McCormick *et al.* 2006:966). A later study in American HIV clinics (Korthuis *et al.* 2011:841) found that the quality of patient-provider communication was worse for HIV-infected patients with unhealthy alcohol use, compared with non-users. Similarly, a cohort study amongst HIV-positive American veterans (Conigliaro *et al.* 2003:523) demonstrated that health providers usually missed alcohol problems in patients with less severe HIV staging or those lacking evidence of liver disease.

Encouragingly, a South African study in 2005–2006 (Morojele *et al.* 2010:1) showed that, contrary to expectations, many HIV care and treatment programmes already consider the role of alcohol consumption and HIV in their approach to treatment. However, lack of resources, information and skills hamper the management of HIV clients with harmful drinking

practices. Given the scaling up of the ART rollout, with the twin goals of both high ART coverage and optimal treatment outcomes (Kapp 2009), ineffective ART management at primary healthcare level would be counterproductive in terms of health outcomes, wasted resources and the adverse effects on staff morale. Allocation of resources in South Africa for the additional training of nurses to deal with substance abuse amongst HIV-infected people attending HIV, STI and TB clinics warrants very high priority.

Recommendations for patient care

To minimise the development of hepatic toxicity and retard HIV disease progression, health providers should offer alcohol screening and counselling to HIV-infected patients, as part of routine patient care (Parry *et al.* 2010:91). A minimum requirement is that health workers broach the subject of alcohol use with HIV-positive patients and encourage alcohol reduction and maintenance of ART. Health workers, particularly at primary care level for HIV, need to make patients aware of the detrimental effects of alcohol consumption. Such discussions, both for treatment-naïve HIV patients and those receiving ART, should encompass alcohol use and sexual risk behaviour. This includes emphasising the juncture between alcohol use and sexual violence, which often involves unsafe sex. Patients need information about the fact that alcohol consumption increases viral replication, that is, higher levels of HIV in the body, leading to accelerated disease progression. Alcohol has a negative effect on the immune system, increasing susceptibility to opportunistic infections.

Patients require information on how alcohol interacts with ARVs and other medications used to treat opportunist infections, such as TB. They should not stop taking their ARVs if they have a binge drinking episode. Stopping and starting ART is not a viable treatment option. Damage caused by ART non-adherence likely outweighs that of alcohol and ARV drug interactions (Kalichman *et al.* 2012b). A conservative recommendation is that alcohol should be avoided altogether, both prior to commencing HIV treatment and, thereafter, once on ART. This is particularly valid for people with viral hepatitis co-infection or who are at risk of liver toxicity from their ART medications. For patients on ART, any alcohol consumption is likely inadvisable. Nonetheless, for HIV-positive patients who consume alcohol and need treatment, ART should be initiated and continued, together with efforts to taper off their drinking.

Conclusion

The issue of scarce resources and structural problems within the health sector in South Africa aside, it is of vital importance for primary healthcare workers to be sensitised to and build knowledge of the interconnectedness of HIV and alcohol use. Nurses need to be trained to provide guidance on the interactions between alcohol consumption and HIV across each domain described above. Furthermore,

these health workers need to confront the psychological barriers patients may have, with dual stigmas from alcohol consumption and HIV infection.

The overall cumulative health burden of HIV will increase even further without proactive and effective efforts to address problem drinking in South Africa. In the absence of such interventions, the prevailing levels of alcohol use will hinder further progress in reducing new HIV infections and will further amplify the overall burden of HIV on society in general and on the healthcare system in particular.

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Competing interests

The authors declare that they have no financial or personal relationship which may have inappropriately influenced them in writing this article.

Authors' contributions

M.S. (Medical Research Council) conceptualised, researched, did literature searches for and wrote the article. M.C. (University of Witwatersrand) and C.P. (Medical Research Council) assisted with the writing of the article, information sources as well as editing, in particular the structuring of the article. M.T. (University Ghent) and O.D. (University Ghent) read the final version and provided edits and comments.

References

- Actuarial Society, 2011, *AIDS Committee Newsletter*, September, viewed 12 March 2012, from aids.actuarialsociety.org.za/.../buildfile.asp
- Adam, M.A. & Johnson, L.F., 2009, 'Estimation of adult antiretroviral treatment coverage in South Africa', *South African Medical Journal* 99(9), 661–667.
- Advocacy Aid, 2012, *Annual performance plan 2012/13–2014/15*, viewed 10 June 2014, from <http://www.advocacyaid.com/index.php/health-care/98-department-of-health-publishes-annual-performance-plan>
- Azar, M.M., Springer, S.A., Meyer, J.P. & Altice, F.L., 2010, 'A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization', *Drug and Alcohol Dependence* 112(3), 178–193.
- Babor, T.F., Higgins-Biddle, J.C., Saunders J.B. & Monteiro, M.G., 2001, *AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for use in primary care*, WHO/MSD/MSB/01.6a, 2nd edn., Department of Mental Health and Substance Dependence, World Health Organization, viewed 14 March 2012, from http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf
- Bagasra, O., Bachman, S.E., Jew, L., Tawadros, R., Cater, J., Boden, G. *et al.*, 1996, 'Increased human immunodeficiency virus type 1 replication in human peripheral blood mononuclear cells induced by ethanol: Potential immunopathogenic mechanisms', *Journal of Infectious Diseases* 173(3), 550–558. <http://dx.doi.org/10.1093/infdis/173.3.550>
- Baliunas, D., Rehm, J., Irving, H. & Shuper, P., 2010, 'Alcohol consumption and risk of incident human immunodeficiency virus infection: A meta-analysis', *International Journal of Public Health* 55(3), 159–166. <http://dx.doi.org/10.1007/s00038-009-0095-x>
- Baum, M.K., Rafie, C., Lai, S., Sales, S., Page, J.B. & Campa, A., 2010, 'Alcohol use accelerates HIV disease progression', *AIDS Research and Human Retroviruses* 26(5), 511–518. <http://dx.doi.org/10.1089/aid.2009.0211>

- BioPortfolio. 2010, *Interaction of alcohol and highly active antiretroviral therapy (HAART) in HIV/AIDS and HIV/AIDS with hepatitis C virus (HCV) co-infection*, viewed 12 April 2012, from <http://www.bioportfolio.com/resources/trial/78003/Interaction-Of-Alcohol-And-Highly-Active-Antiretroviral-Therapy-haart-In-Hiv-aids.html>
- Braithwaite, R.S., Conigliaro, J., McGinnis, K.A., Maisto, S.A., Bryant, K. & Justice, A.C., 2008, 'Adjusting alcohol quantity for mean consumption and intoxication threshold improves prediction of nonadherence in HIV patients and HIV-negative controls', *Alcoholism, Clinical and Experimental Research* 32(9), 1645–1651. <http://dx.doi.org/10.1111/j.1530-0277.2008.00732.x>
- Braithwaite, R.S., Conigliaro, J., Roberts, M.S., Shechter, S., Schaefer, A., McGinnis, K. et al., 2007, Estimating the impact of alcohol consumption on survival for HIV+ individuals. *AIDS Care*, 19(4), 459–466. <http://dx.doi.org/10.1080/09540120601095734>
- Bryant, K.J., 2006, 'Expanding research on the role of alcohol consumption and related risks in the prevention and treatment of HIV/AIDS', *Substance Use & Misuse* 41(10), 1465–1507. <http://dx.doi.org/10.1080/10826080600846250>
- Carter, M., 2011, *Alcohol*, viewed 10 March 2012, from <http://www.aidsmap.com/Alcohol/page/1045082/>
- Colvin, C.J., Fairall, L., Lewin, S., Georgeu, D., Zwarenstein, M., Bachmann, M.O. et al., 2010, 'Expanding access to ART in South Africa: The role of nurse-initiated treatment', *South African Medical Journal* 100(4), 210–212.
- Conigliaro, J., Gordon, A.J., McGinnis, K.A., Rabeneck, L., Justice, A.C.; Veterans Aging Cohort 3-Site Study, 2003, 'How harmful is hazardous alcohol use and abuse in HIV infection: Do health care providers know who is at risk?', *Journal of Acquired Immune Deficiency Syndromes* 33(4), 521–525. <http://dx.doi.org/10.1097/00126334-200308010-00014>
- Conigliaro, J., Justice, A.C., Gordon, A.J., Bryant, K.; VACS Alcohol & Behavior Change Research Group, 2006, 'Role of alcohol in determining human immunodeficiency virus (HIV)-relevant outcomes: A conceptual model to guide the implementation of evidence-based interventions into practice', *Medical Care* 44(8 Suppl 2), S1–S6. <http://dx.doi.org/10.1097/01.mlr.0000223659.36369.cf>
- Cvetkovic, R.S. & Goa, K.L., 2003, 'Lopinavir/ritonavir: A review of its use in the management of HIV infection', *Drugs* 63(8), 769–802. <http://dx.doi.org/10.2165/00003495-200363080-00004>
- Delva, W., Pretorius, C. & Temmerman, M., 2009, 'Is scaling up enough to curb the HIV epidemic in southern Africa?', *South African Medical Journal* 99(9), 638–639.
- Department of Health, 2012, *Annual Report 2012/2013*, viewed 10 June 2014, from <http://africacheck.org/wp-content/uploads/2014/02/131016dohrreport.pdf>
- Doyle, P. & Dorrington, R., 2011, *Expansion of ARV programme in SA slows AIDS mortality rate*, viewed 08 June 2014, from http://sareporter.com/index.php?option=com_content&task=view&id=1946&Itemid=46
- Ellison, R.C., 2002, 'Balancing the risks and benefits of moderate drinking', *Annals of the New York Academy of Sciences* 957, 1–6. <http://dx.doi.org/10.1111/j.1749-6632.2002.tb02900.x>
- Fisher, J.C., Bang, H. & Kapiga, S.H., 2007, 'The association between HIV infection and alcohol use: A systematic review and meta-analysis of African studies', *Sexually Transmitted Diseases* 34(11), 856–863. <http://dx.doi.org/10.1097/OLQ.0b013e318067b4fd>
- Fitzgerald, M., Collumbien, M. & Hosegood, V., 2010, "'No one can ask me 'Why do you take that stuff?': Men's experiences of antiretroviral treatment in South Africa", *AIDS Care* 22(3), 355–360. <http://dx.doi.org/10.1080/09540120903111536>
- Galvan, F.H., Bing, E.G., Fleishman, J.A., London, A.S., Caetano, R., Burnam, M.A. et al., 2002, 'The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: Results from the HIV Cost and Services Utilization Study', *Journal of Studies on Alcohol* 63(2), 179–186.
- Ghebremichael, M., Paintsil, E., Ickovics, J.R., Vlahov, D., Schuman, P., Boland, R. et al., 2009, 'Longitudinal association of alcohol use with HIV disease progression and psychological health of women with HIV', *AIDS Care* 21(7), 834–841. <http://dx.doi.org/10.1080/09540120802537864>
- Health Systems Trust, 2011, *South Africa: Govt moves to earlier HIV treatment*, viewed 15 March 2012, from <http://www.hst.org.za/news/south-africa-govt-moves-earlier-hiv-treatment>
- Hendershot, C.S., Stoner, S.A., Pantalone, D.W. & Simoni, J.M., 2009, 'Alcohol use and antiretroviral adherence: Review and meta-analysis', *Journal of Acquired Immune Deficiency Syndromes* 52(2), 180–202. <http://dx.doi.org/10.1097/QAI.0b013e3181b18b6e>
- Highlyman, L., 2005, *Drug interactions and anti-HIV therapy*, viewed 12 April 2012, from <http://www.thebody.com/content/art2579.html>
- Kalichman, S.C., Amaral, C.M., White, D., Swetsze, C., Kalichman, M.O., Cherry, C. et al., 2012a, 'Alcohol and adherence to antiretroviral medications: interactive toxicity beliefs among people living with HIV', *Journal of the Association of Nurses in AIDS Care* 23(6), 511–520. <http://dx.doi.org/10.1016/j.jana.2011.11.005>
- Kalichman, S.C., Amaral, C.M., White, D., Swetsze, C., Pope, H., Kalichman, M.O. et al., 2009, 'Prevalence and clinical implications of interactive toxicity beliefs regarding mixing alcohol and antiretroviral therapies among people living with HIV/AIDS', *AIDS Patient Care and STDs* 23(6), 449–454. <http://dx.doi.org/10.1089/apc.2008.0184>
- Kalichman, S.C., Grebler, T., Amaral, C.M., McNery, M., White, D., Kalichman, M.O. et al., 2012b, 'Intentional non-adherence to medications among HIV positive alcohol drinkers: Prospective study of interactive toxicity beliefs', *Journal of General Internal Medicine* 28(3), 399–405. <http://dx.doi.org/10.1007/s11606-012-2231-1>
- Kalichman, S.C., Simbayi, L.C., Kaufman, M., Cain, D. & Jooste, S., 2007, 'Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings', *Prevention Science* 8(2), 141–151. <http://dx.doi.org/10.1007/s11121-006-0061-2>
- Kaner, E.F., Beyer, F., Dickinson, H.O., Pienaar, E., Campbell, F., Schlesinger, C. et al., 2009, 'Effectiveness of brief alcohol interventions in primary care populations', *Drug and Alcohol Review* 28(3), 301–323. <http://dx.doi.org/10.1111/j.1465-3362.2009.00071.x>
- Kapp, C., 2009, 'Aaron Motsoaledi: South African Minister of Health', *Lancet* 374(9692), 776. [http://dx.doi.org/10.1016/S0140-6736\(09\)61580-4](http://dx.doi.org/10.1016/S0140-6736(09)61580-4)
- Korthuis, P.T., Josephs, J.S., Fleishman, J.A., Hellinger, J., Himelhoch, S., Chander, G. et al., 2008, 'Substance abuse treatment in human immunodeficiency virus: the role of patient-provider discussions', *Journal of Substance Abuse Treatment* 35(3), 294–303. <http://dx.doi.org/10.1016/j.jsat.2007.11.005>
- Korthuis, P.T., Saha, S., Chander, G., McCarty, D., Moore, R.D., Cohn, J.A. et al., 2011, 'Substance use and the quality of patient-provider communication in HIV clinics', *AIDS and Behavior* 15(4), 832–841. <http://dx.doi.org/10.1007/s10461-010-9779-8>
- Lawn, J.E. & Kinney, M.V., 2009, 'Health in South Africa. An executive summary for *The Lancet Series*', *The Lancet* 347, 1–8.
- LeLacheur, S.F. & Simon, G.L., 1991, 'Exacerbation of dideoxycytidine-induced neuropathy with dideoxyinosine', *Journal of Acquired Immune Deficiency Syndromes* 4(5), 538–539.
- Mah, T.L. & Halperin, D.T., 2010, 'Concurrent sexual partnerships and the HIV epidemics in Africa: Evidence to move forward', *AIDS and Behavior* 14(1), 11–16. <http://dx.doi.org/10.1007/s10461-008-9433-x>
- Manfredi, R. & Calza, L., 2008, 'HIV infection and the pancreas: Risk factors and potential management guidelines', *International Journal of STD & AIDS* 19(2), 99–105. <http://dx.doi.org/10.1258/ijisa.2007.007076>
- McCormick, K.A., Cochran, N.E., Back, A.L., Merrill, J.O., Williams, E.C. & Bradley, K.A., 2006, 'How primary care providers talk to patients about alcohol: a qualitative study', *Journal of General Internal Medicine* 21(9), 966–972. <http://dx.doi.org/10.1007/BF02743146>
- Míguez-Burbano, M.J., Lewis, J.E., Fishman, J., Asthana, D. & Malow, R. M., 2009a, 'The influence of different types of alcoholic beverages on disrupting highly active antiretroviral treatment (HAART) outcome', *Alcohol and Alcoholism* 44(4), 366–371. <http://dx.doi.org/10.1093/alcalc/agg024>
- Míguez-Burbano, M.J., Lewis, J.E. & Malow, R., 2009b, 'Alcohol and race/ethnicity elicit different changes in lipid profiles in HIV-infected individuals receiving highly active antiretroviral therapy', *Journal of the Association of Nurses in AIDS Care* 20(3), 176–183. <http://dx.doi.org/10.1016/j.jana.2009.02.004>
- Molina, P.E., Happel, K.I., Zhang, P., Kolls, J.K. & Nelson, S., 2010, *Focus on: Alcohol and the immune system*, viewed 29 February 2012, from <http://pubs.niaaa.nih.gov/publications/arh40/97-108.htm>
- Moreno, S., Podzamczar, D., Blázquez, R., Iribarren, J.A., Ferrer, E., Reparaz, J. et al., 2001, 'Treatment of tuberculosis in HIV-infected patients: safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin', *AIDS* 15(9), 1185–1187. <http://dx.doi.org/10.1097/00002030-200106150-00018>
- Morojele, N.K., Kachieng'a, M.A., Mokoko, E., Nkoko, M.A., Parry, C.D., Nkwane, A.M. et al., 2009, 'Alcohol use and sexual behaviour among risky drinkers and bar and shebeen patrons in Gauteng province, South Africa', *Social Science & Medicine* 62(1), 217–227. <http://dx.doi.org/10.1016/j.socscimed.2005.05.031>
- Morojele, N.K., Pithey, A.L., Kekwaletswe, C.T., Joubert-Wallis, M., Pule, M. & Parry, C.D.H., 2010, 'South African health care providers' recognition of the links between alcohol and HIV in their daily practice: A pilot study', *African Journal of Drug and Alcohol Studies* 9(1), 1–14. <http://dx.doi.org/10.4314/ajdas.v9i1.61753>
- NAM, 2009, *Adherence*, viewed 10 March 2012, from http://aidsprogramme.ukzn.ac.za/Libraries/HIV_Treatment/adherence.sflb.aspx
- Neuman, M.G., Monteiro, M. & Rehm, J., 2006, 'Drug interactions between psychoactive substances and antiretroviral therapy in individuals infected with human immunodeficiency and hepatitis viruses', *Substance Use & Misuse* 41(10–12), 1395–1463.
- Neuman, M.G., Schneider, M., Nanau, R.M. & Parry, C., 2012, 'Alcohol consumption, progression of disease and other comorbidities, and responses to antiretroviral medication in people living with HIV', *AIDS Research and Treatment* 2012, 14 pages. <http://dx.doi.org/10.1080/10826080600846235>
- National Institute on Alcohol Abuse and Alcoholism, 2012a, *Moderate & binge drinking*, viewed 23 March 2012, from <http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking>
- National Institute on Alcohol Abuse and Alcoholism, 2012b, *Five Year Strategic Plan FY07-11. Alcohol across the lifespan*, viewed 23 March 2012, from <http://pubs.niaaa.nih.gov/publications/StrategicPlan/NIAAASSTRATEGICPLAN.htm>
- Nyasulu, J.C., Muchiri, E., Mazwi, S.L. & Ratshefola, M., 2012, 'NIMART rollout to primary healthcare facilities increases access to antiretrovirals in Johannesburg: An interrupted time series analysis', *South African Medical Journal* 103(4), 232–236.
- Pandrea, I., Happel, K.I., Amedee, A.M., Bagby, G.J. & Nelson, S., 2010, 'Alcohol's role in HIV transmission and disease progression', *Alcohol Research & Health* 33(3), 203–218.
- Papas, R.K., Sidle, J.E., Martino, S., Baliddawa, J.B., Songole, R., Omolo, O.E. et al., 2010, 'Systematic cultural adaptation of cognitive-behavioral therapy to reduce alcohol use among HIV-infected outpatients in western Kenya', *AIDS and Behavior* 14(3), 669–678. <http://dx.doi.org/10.1007/s10461-009-9647-6>
- Parliamentary Monitoring Group, 2012, *Health: Minister's Budget Vote Speech*, viewed 06 March 2012, from <http://www.pmg.org.za/briefing/20120424-minister-health-mr-aaron-motsoaledi-budget-vote-speech-201213>
- Parry, C.D.H., 2010, 'Alcohol policy in South Africa: A review of policy development processes between 1994 and 2009', *Addiction* 105(8), 1340–1345.

- Parry, C.D.H., Rehm, J. & Morojele, N., 2010, 'Is there a causal relationship between alcohol and HIV? Implications for policy, practice and future research', *African Journal of Drug and Alcohol Studies* 9(2), 81–91. <http://dx.doi.org/10.1111/j.1360-0443.2010.03003.x>
- Potochnic, M.A., 2002, *Cocktails and party favors*, viewed 14 March 2012, from <http://www.thebody.com/content/art1891.html>
- Pujol, G., 2003, *Risky cocktails. Interactions between street drugs and HIV medications*, viewed 12 April 2012, from <http://www.thebody.com/content/art32513.html>
- Rehm, J., Shield, K.D., Joharchi, N. & Shuper, P.A., 2012, 'Alcohol consumption and the intention to engage in unprotected sex: Systematic review and meta-analysis of experimental studies', *Addiction* 107(1), 51–59.
- Rossiter, D. (ed.), 2012, *The South African Medicines Formulary*, viewed 05 June 2014, from <http://www.hst.org.za/links/south-african-medicines-formulary>
- Sankar, A., Wunderlich, T., Neufeld, S. & Luborsky, M., 2007, 'Sero-positive African Americans' beliefs about alcohol and their impact on anti-retroviral adherence', *AIDS and Behavior* 11(2), 195–203. <http://dx.doi.org/10.1007/s10461-006-9144-0>
- Sanne, I., Orrell, C., Fox, M., Conradie, F., Ive, P., Zeinecker, J. et al., 2010, 'Nurse management is not inferior to doctor management of ARV patients: The CIPRA South Africa randomised trial', *Lancet* 376(9734), 33–40. [http://dx.doi.org/10.1016/S0140-6736\(10\)60894-X](http://dx.doi.org/10.1016/S0140-6736(10)60894-X)
- Schneider, M., Norman, R., Parry, C., Bradshaw, D. & Plüddemann, A., 2007, 'Estimating the burden of disease attributable to alcohol use in South Africa in 2000', *South African Medical Journal* 97(8 Pt 2), 664–672.
- Shisana, O., Rehle, T., Simbayi, L., Zuma, K., Jooste, S., Pillay-van-Wyk, V. et al., 2009, *South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers?*, HSRC Press, Cape Town.
- Shuper, P.A., Neuman, M., Kanteres, F., Baliunas, D., Joharchi, N. & Rehm, J., 2010, 'Causal considerations on alcohol and HIV/AIDS – a systematic review', *Alcohol and Alcoholism* 45(2), 159–166. <http://dx.doi.org/10.1093/alcalc/aggp091>
- Simbayi, L.C., Kalichman, S.C., Jooste, S., Mathiti, V., Cain, D. & Cherry, C., 2004, 'Alcohol use and sexual risks for HIV infection among men and women receiving sexually transmitted infection clinic services in Cape Town, South Africa', *Journal of Studies on Alcohol* 65(4), 434–442.
- Strauss, S.M., Tiburcio, N.J., Munoz-Plaza, C., Gwadz, M., Luniewicz, J., Osborne, A. et al., 2009, 'HIV care providers' implementation of routine alcohol reduction support for their patients', *AIDS Patient Care and STDs* 23(3), 211–218. <http://dx.doi.org/10.1089/apc.2008.0008>
- Szabo, G. & Mandrekar, P., 2010, 'Focus on: Alcohol and the liver', viewed 10 April 2012, from <http://pubs.niaaa.nih.gov/publications/arh40/87-96.htm>
- The Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012, *HIV and AIDS estimates*, viewed 10 September 2013, from <http://www.unaids.org/en/regionscountries/countries/southafrica/>
- Wechsberg, W.M., Luseno, W.K., Karg, R.S., Young, S., Rodman, N., Myers, B. et al., 2008, 'Alcohol, cannabis, and methamphetamine use and other risk behaviours among Black and Coloured South African women: a small randomized trial in the Western Cape', *International Journal on Drug Policy* 19(2), 130–139. <http://dx.doi.org/10.1016/j.drugpo.2007.11.018>
- World Health Organization, 2011, *Global Status Report on Alcohol and Health 2011*, viewed 25 March 2012, from http://www.who.int/substance_abuse/publications/global_alcohol_report/en/index.html [now links to 2014 update].
- Wyles, D.L. & Gerber, J.G., 2005, 'Antiretroviral drug pharmacokinetics in hepatitis with hepatic dysfunction', *Clinical Infectious Diseases* 40(1), 174–181.