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Challenges face clinicians treating HbeAg negative chronic hepatitis B in HIV

A PEER-REVIEWED ARTICLE

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Recent improvements in antiretroviral therapies and medication adherence have resulted in advances in quality of life and decreases in mortality and morbidity rates. In turn, co-morbid infections such as chronic hepatitis B and C have become more prevalent, with co-infection rates of approximately 10% and 30% respectively, representing important aspects of HIV management for caregivers that need to be addressed appropriately to avoid liver complications. Chronic hepatitis B (CHB) is defined as a detectable hepatitis B surface antigen (HBsAg) on two separate checks at least six months apart. Inadequate treatment of both hepatidities

can result in liver cirrhosis and hepatocellular carcinoma (HCC), complications rarely seen previously due to high mortality rates from opportunistic infections. Long-term monotherapy or partial treatment of these infections can lead to development of resistance and may require newer therapies to treat chronic hepatitis B.

In the United States, chronic hepatitis is commonly seen in HIV-infected individuals. Chronic hepatitis B co-infection occurs in 7-15% of the HIV-positive population with 1% of HIV positives infected with both hepatitis B and C.^{1,2} Individuals with hepatitis B co-infection tend to have higher hepatitis viral loads, lower rates of spontaneous seroconversion, more severe liver disease, and increased rates of liver related mortality.^{3,5}

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Food insecurity is health threat to HIV+ patients

Ginger Bouvier, MEd, LDN, RD

Limited access to healthful food and poor nutrition remain major challenges for people living with HIV infection throughout the world.¹ Adequate calorie, protein, and micronutrient intake is essential to the maintenance of healthy immune function and the effect of nutritional status on HIV disease has been well established. Limited access to food and poor nutritional status can increase sus-

ceptibility to co-infections and may hasten progression to HIV-related illnesses.^{1,2}

Food insecurity has been defined by national experts as "limited or uncertain availability of nutritionally adequate and safe foods or limited or uncertain ability to acquire acceptable foods in socially acceptable ways."³ The most recent national U.S. Household Food

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Chronic hepatitis B co-infects 7-15% of HIV-positive patients

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The genetic diversity of hepatitis B plays an important role in determining the progression of hepatitis B viral (HBV) infection. Hepatitis B is a hepadnavirus whose genome is composed of four Open Reading Frames (ORF): the “pre c/c” which encodes the hepatitis B e and hepatitis B core antigens (Ag), the “pre s/s” which encodes the hepatitis B s antigen, the “P ORF” (pol) which encodes the viral polymerase, and the “X ORF” which encodes a protein involved in host and viral gene expression. Genetic diversity may be explained by means of selective or non-selective pressure with genotypic diversity occurring due to the absence of selective pressure in the natural course of evolution. Phenotypic diversity can be explained by selective pressure from host immune responses to HBV infection or from antiviral therapies.⁶

Serotypes are classified based on the composition of amino acids of two mutually exclusive epitopes of HbsAg. HIV co-infection has not been found to correlate with differences in serotype expression. Genotypes are divided into ten categories, labeled A to J. A and D are universally found whereas the other serotypes are distributed regionally throughout the world, such as B and C predominantly in Asia, E in Africa, and F and H in Latin America and Pacific regions. Among patients co-infected with HIV/HBV, serotypes A and D predominate while B and C are infrequently observed. The impact of genotypes on liver disease severity has not been extensively stud-

ied, though one study showed a strong correlation between degree of liver fibrosis and genotype G after adjusting for various factors in HIV/HBV co-infected patients.⁷

Generally, the majority of patients with chronic hepatitis B undergo seroconversion with loss of HBeAg and development of anti-HBe antibody, HBV DNA levels $< 10^5$ copies/ml, normal ALT levels, and lesser risk of progression to cirrhosis and HCC. However, a small proportion of patients undergoing seroconversion experience return of high HBV DNA levels, have persistently or intermittently elevated ALT levels, demonstrate active inflammation on liver biopsy, and have a higher risk of progressing to cirrhosis and HCC, presumably due to mutations in the pre-core and basal core promoter regions that either prevent or decrease HBeAg expression. These patients generally have a poorer long term prognosis compared to HBeAg positive CHB patients. Thirty to 40% of these patients present with persistently high ALT levels (three to four fold) while 45-65% of patients may present with erratic ALT levels with periods of normal ALT levels interspersed with flares.⁸ Spontaneous lifetime remission occurs in less than 15% of these patients.⁸ The prevalence of HBeAg negative chronic hepatitis B varies geographically and is more common in regions where individuals are infected with non-A genotypes.

Precore, core, and basal core promoter (BCP) mutations are mainly found to affect pre-c/c

regions and are more commonly found in HBeAg negative CHB patients. In the United States, the prevalence of precore and basal core mutations are 27% and 44% respectively.⁹ Pre C mutations are found to completely abolish HbeAg expression and are linked to genotype and to BCP mutations. Patients with advanced age and infected with BCP mutants tend to have increased risk for the development of liver cirrhosis and HCC. Although BCP mutations were more common in genotype C than genotype B in Taiwan, there was no difference in genotype B to genotype C ratio in HBeAg negative CHB patients with liver cirrhosis and HCC.¹⁰

MANAGEMENT

Therapy in HBeAg positive patients is indicated when serum HBV DNA levels are above 2×10^4 copies/ml in addition to other factors such as likelihood of response, severity of disease, and likelihood of adverse reactions. However, anti-HBV therapy in HBeAg negative chronic hepatitis B patients is indicated when serum HBV DNA levels are above 2×10^3 copies/ml and is initiated earlier in co-infected patients due to faster progression. Baseline liver biopsies may be indicated when serum HBV DNA levels of $\geq 10^5$ copies/mL exist. Patients with HBeAg negative CHB have fluctuating HBV DNA levels and may drop down below 10^4 copies/ml. Hence, patients presenting with HBV DNA levels $\leq 10^4$ copies/ml with normal ALT levels are generally presumed to be either HBeAg negative CHB



patients in a quiescent phase or inactive HBsAg carriers. In these situations, either histologic evaluation of a liver biopsy or serial monitoring for elevated ALT or HBV DNA levels is warranted to determine need to initiate therapy. Patients with mono-infection with HBeAg negative CHB generally have lower response rates, experience longer duration of therapy, and have higher relapse rates than HBeAg positive CHB patients. In addition, treatment endpoint for HBeAg negative CHB is not clearly defined since there is no seroconversion from HBeAg positivity to HBeAg negativity and hence has to be based on suppression of HBV DNA and normalization of ALT levels with or without histological improvement.¹¹

In the HIV/HBV co-infected patient, for those needing treatment for the CHB it is not recommended that treatment should be given only aimed at the hepatitis B by agents that have activity for HIV also. Instead three-drug highly active antiretroviral therapy containing one or two active agents against both HIV and hepatitis B should be started regardless of CD4 count to prevent the development of resistance by the HIV to the agents.

(1) Adefovir

Adefovir dipivoxil is an analogue of adenosine monophosphate and its active metabolite, adefovir diphosphate, inhibits hepatitis B DNA polymerase. At low doses, adefovir suppresses hepatitis B virus replication and is associated with lower rate of resistance compared to lamivudine. Since adefovir is nephrotoxic, especially at the levels needed for HIV suppression, low

doses are typically used to suppress HBV levels. Benhamou *et al.* showed that after 144 weeks of adding adefovir to lamivudine, 45% of patients experienced a decrease in serum HBV-DNA levels while 5-10% of CHB patients did not respond to ADV either due to cross-resistance, genetic polymorphisms, or low dose therapy.¹² Resistance mutations to adefovir have been described, such as substitution of asparagine with threonine (N236T) and alanine to valine or threonine A181V/T. There is also concern about the K65R mutation developing in co-infected patients not taking anti-retroviral drugs although this has not been shown in recent studies; the K65R mutation influences the HIV sensitivity to reverse transcriptase inhibitors such as tenofovir, abacavir, and didanosine. In a trial comprising a total of 184 patients, fifty-five and seventy patients with HBeAg negative chronic hepatitis B treated for four and five years showed undetectable levels of HBV DNA in 65% and 67%. Addition of adefovir to lamivudine in the presence of lamivudine resistance did not confer any additional benefit according to the Gilead 461 trial, though experts recommend administration of at least three months of combined therapy before discontinuing lamivudine after adefovir has achieved HBV suppression.

(2) Tenofovir

Tenofovir disoproxil fumarate is also a nucleotide analogue, similar to adefovir. Tenofovir is one of the few drugs that demonstrates potent activity against HBV in patients with and without lamivudine resistance and has also proven superior to adefovir. Although tenofovir is similar to

adefovir, the incidence of nephrotoxicity is lower with tenofovir than with adefovir at the levels used for HIV treatment and hence the dose of tenofovir can be raised to 300mg/day. Few studies have detected selection of A194T mutation wherein there was ten fold loss in susceptibility, though others have not confirmed this as a source of tenofovir resistance. Snow-Lampart *et al.* showed that after four years of treatment, 93% of HBeAg negative patients and 76% of HBeAg positive patients achieved complete viral load suppression (≤ 400 copies/mL).¹³ At week 144, no participants developed amino acid substitutions (mutations) known to be associated with resistance to tenofovir. There have also been other prospective studies showing higher efficacy of tenofovir compared to adefovir. Rare side effects include Fanconi's syndrome, renal insufficiency, and osteopenia due to hyperphosphaturia.

(3) Lamivudine

Lamivudine is an oral cytosine analogue with both anti-HIV and anti-HBV activities. In treating co-infected patients, the recommended dose of lamivudine is 300 mg/day and the drug should always be given with at least two other anti-HIV agents. HBV resistance mutations can be recognized in 70% of HBV viremic patients with HIV infection who have received lamivudine for over four years. One of the main concerns with lamivudine treatment is the development of YMDD mutations where methionine is substituted for valine or isoleucine in the tyrosine-methionine-aspartate-aspartate

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Genetic diversity plays role in progression of HBV infection

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(YMDD) motif and is usually accompanied by leucine to methionine substitution in an upstream region. This resistance can be detected in about 14-32% after one year of treatment and significantly increases to 60-70% after about four to five years of treatment and develops more rapidly in co-infected patients, appearing in about 50% patients after two years of lamivudine therapy and rising to 90% after four years of therapy.¹⁴ In HbeAg negative CHB, lamivudine was shown to suppress HBV DNA in 60-70% of patients, but the majority relapsed. An increase in duration of therapy led to a progressive increase in the development of YMDD mutations. Also, there is no known treatment endpoint for HbeAg negative CHB with lamivudine treatment. Hence, lamivudine is not typically used as first line therapy for HbeAg negative chronic hepatitis B.

(4) Emtricitabine

Emtricitabine is a cytosine analogue with antiviral activity against both HBV and HIV. Emtricitabine should not be used as monotherapy in co-infected persons due to an increased risk of developing M184V resistance in HIV. In a study conducted by Lim *et al.* (2006), HbeAg seroconversion rates were found to be similar in treatment and placebo groups. The recommended dose for emtricitabine is 200 mg/

day and follows the same dosing regimen as for HIV therapy.¹⁵ Emtricitabine should not be prescribed after lamivudine failure due to cross-resistance between the two drugs but both drugs can be interchanged if necessary. They are mainly recommended in patients already on HAART therapy and in HbeAg negative chronic hepatitis B where longer duration of therapy is generally required. Emtricitabine does not have an FDA-approved indication for use in the treatment of hepatitis B.

(5) Entecavir

Entecavir (ETV) is a guanosine analogue that inhibits HBV replication at priming, reverse transcriptase, and positive strand synthesis. In a phase II trial, at 48 weeks, entecavir was found to have significantly higher response rates than lamivudine in HbeAg negative chronic hepatitis B patients. In addition, entecavir was found to be effective in suppressing lamivudine-resistant and adefovir-resistant HBV mutants. Entecavir was found to suppress HIV RNA in co-infected patients but can lead to development of M184V resistance so entecavir is never to be used in the absence of initiation of antiretroviral therapy in co-infected patients and is to be used with caution with other drugs such as abacavir.¹⁶

(6) Telbivudine

Telbivudine is a thymidine L-analogue with greater efficacy

than lamivudine or adefovir but has no activity against HIV. Telbivudine selects for mutation M204I and has cross-resistance with lamivudine and hence cannot be used following lamivudine resistance. In addition, patients treated with telbivudine alone were found to have greater seroconversion rates and a higher proportion of patients reported normalization of transaminase levels compared to patients treated with both telbivudine and lamivudine. There has been no evidence of activity and efficacy of telbivudine in co-infected patients.

(7) Interferon-alpha

Pegylated-interferon-alpha is the key component of treatment for hepatitis C but has been shown to have less activity than the previously described oral agents against CHB. Therefore this article will not review its use for CHB therapy at this time.

In summary, none of the reviewed medications except telbivudine are to be used as monotherapy in co-infected patients due to possible development of resistance. Tenofovir and adefovir are effective in patients with lamivudine-resistant virus. Tenofovir and emtricitabine are frequently used for treatment of CHB in HIV-infected patients, although emtricitabine is not FDA-approved for treatment of CHB. When a co-infected patient requires therapy for the CHB, a

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HAART regimen should be identified containing agents active against both diseases and monotherapy or dual-therapy against CHB should not be used to prevent resistance development by HIV towards the agents. In addition, when HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless there is evidence of HBeAg seroconversion and an adequate course of consolidation treatment has been completed. In the event that the hepatitis B medicines are discontinued, patient may experience acute flares of hepatitis, more likely when seroconversion has not occurred, and hence have to be immediately put back on therapy. ❖

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In Delta region, food insecurity is twice that of U.S. as a whole

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Security Survey documented that 14.7 percent of American households were food insecure at least some time during 2009, including 5.7 percent with very low food security. Very low food security occurs when “at times during the year, eating patterns of one or more household members were disrupted and food intake reduced because the household lacked money and other resources for food.” Rates of food insecurity are substantially higher than the national average among households with incomes below the federal poverty level, among households with children headed by single parents, and among black and Hispanic households.⁴ The Lower Mississippi Delta region of Arkansas, Mississippi, and Louisiana has high prevalence rates of poverty, and the prevalence of food insecurity in this region is estimated to be twice that of the United States.⁵ In addition, food insecurity appears highly prevalent among HIV-infected individuals in North America,⁶ and is a significant health threat to people living with HIV.

Adequate food and good nutrition are essential in order for HIV-infected individuals to fully benefit from antiretroviral therapy. Studies indicate that food insecure HIV-infected individuals are less likely to be adherent to antiretroviral therapy, and food insecurity has been

associated with incomplete HIV viral load suppression;^{8,9} therefore food insecurity may actually undermine HIV treatment. Researchers found that food insecurity independently increases the risk of incomplete viral suppression.⁹ Food insecurity should be assessed as part of comprehensive HIV care, and additionally, medication adherence interventions should address access to food.

The U.S. Department of Agriculture (USDA) has implemented several nutrition assistance programs targeted at different populations to improve food security.¹⁰ Additionally, there are food assistance programs, such as the NO/AIDS Food For Friends program in the New Orleans area, which are specifically for low income individuals infected with HIV. It is important for health care providers to know about nutrition assistance programs in their community and help eligible individuals to access these resources.

Supplemental Nutrition Assistance Program (SNAP)

SNAP (formerly the Food Stamp Program) puts food within reach for low income people each month via an electronic benefits transfer (EBT) card used to purchase food at most grocery stores. Applications for SNAP are available at any Social Security Office. Household members must meet certain conditions to be eligible

for SNAP benefits. A pre-screening eligibility tool is available at <http://www.snap-step1.usda.gov/fns>. Many households receiving SNAP benefits still need emergency food at the end of the month since the benefits rarely last an entire month.

Commodity Supplemental Food Program (CSFP)

The CSFP is a direct food distribution program intended to improve the nutritional status of low income pregnant women and new mothers up to one year postpartum, infants, children up to age six, and older adults at least 60 years of age. All food packages contain high protein, nutrient dense foods, and are available on a monthly basis to participants. These foods are provided to states by the USDA and are very similar to foods found in grocery stores. For example, in Louisiana the local distribution agency for the CSFP is Food for Families/Food for Seniors. Food for Families/Food for Seniors currently holds food box distributions throughout 64 Louisiana parishes, with more than 18 sites in Orleans and Jefferson parishes.

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)

WIC is a supplemental nutrition program for pregnant and postpartum women, infants, and children under 5 years old. WIC provides nutritious foods, nutrition information, and refer-



rals to other health and social services. Clients must fall at or below 185 percent of the U.S. Poverty Income Guidelines, and have medically-based or diet-based nutrition risk as determined by a health professional. Participants receive vouchers to purchase specific foods each month that are designed to supplement their diets with specific nutrients that benefit WIC's target population.

The Emergency Food Assistance Program (TEFAP)

TEFAP is a federal program that provides food at no cost to low-income Americans in need of short-term hunger relief. The USDA makes food products (commodities) as well as storage and distribution grants available to state agencies and Indian Tribal Governments. The state agencies that manage TEFAP distribute the product to qualifying emergency food organizations, including food banks, church pantries, soup kitchens, and emergency shelters, which distribute the food directly to those in need or use it to prepare meals. In most instances,

local food banks combine TEFAP food with privately donated food for food package distribution at food pantries, food shelves, and other local charities.

Nutrition assistance programs, along with innovative interventions such as community gardens and urban farming, are nutrition safety nets for impoverished populations. Addressing basic needs such as access to healthful food should be an integral part of HIV programs.❖

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Brief screening for alcohol use disorders in HIV primary care

A PEER-REVIEWED ARTICLE

Julia M. Hormes, PhD, Kelly R. Gerhardstein, PsyD, and Phillip T. Griffin, PhD

In spite of multiple adverse consequences, including accelerated disease progression and increased risk for further disease transmission, alcohol use is common among individuals living with HIV/AIDS. There is an urgent need for widespread implementation of brief screening for alcohol use problems in HIV primary care settings. More work is needed to identify the screening measures that may be most useful in this patient population and setting.

In this article we briefly discuss some of the ways in which drinking negatively impacts outcomes in individuals living with HIV/AIDS and the prevalence of alcohol abuse and dependence among HIV-positive patients. We review formal diagnostic criteria for alcohol use disorders and present two of the briefest screening instruments for alcohol abuse and dependence that have been developed and validated. Both are available for use in the public domain and may be helpful in identifying HIV-positive patients in need of further assessment and referral for substance use treatment. Finally, we briefly review current research on screening for problem drinking in primary care settings and discuss ways in which findings may be applied to HIV primary care.

Contribution of alcohol to the HIV/AIDS epidemic

The relationship between alcohol use and HIV/AIDS is complex and involves a variety of mechanisms that remain to be fully elucidated. As of now, at least three ways in which alcohol use contributes to the HIV epidemic have been identified:

(1) Alcohol consumption significantly lowers the likelihood that patients will be adherent to highly active antiretroviral therapies (HAART) (Arnsten, Demas, Grant, Gourevitch, Farzagedan, Howard *et al.*, 2002; Hendershot, Stoner, Pantalone & Simoni, 2009; Lucas, Gebo, Chaisson & Moore, 2002; Parsons, Rosof & Mustanski, 2008; Samet, Horton, Meli, Freedberg & Palepu, 2004). In fact, alcohol use has been shown to be the most significant predictor of non-adherence to HAART (Samet *et al.*, 2004). On days on which patients consume alcohol, odds of medication non-adherence are nine times higher, compared to non-drinking days, and each additional drink consumed increases the odds of skipped or delayed medication doses by an additional 20% (Parsons *et al.*, 2008). HIV-positive patients who use any alcohol, regardless of frequency or quantity of drinking, are only 50-60% as likely to be adherent as abstainers (Hendershot *et al.*, 2009).

The strong association between alcohol use and medication non-adherence in HIV/AIDS is due to accidental as well as intentional skipping or delaying of doses. Many HIV-positive patients who report alcohol-related non-adherence state that they do not take their medication when

drinking out of fear of toxicity or other harmful side effects (Kalichman, Amaral, White, Swetsze, Pope, Kalichman *et al.*, 2009). Thus, at a time when the availability of HAART has significantly decreased overall morbidity and mortality in HIV/AIDS (Amico, Harman & Johnson, 2006), many alcohol-using patients do not achieve the minimum 95% adherence necessary for sustained viral suppression and prevention of the development of a resistant virus (Hecht, Grant, Petropoulos, Dillon, Chesney, Tian *et al.*, 1998; McNabb, Ross, Abriola, Turley, Nightingale & Nicolau, 2001; Paterson, Swindells *et al.* 2000; Race, Dam, Obry, Paulous, & Clavel, 1999; Vervoort, Grypdonck, de Grauwe, Hoepelman & Borleffs, 2009).

(2) A growing body of research suggests that alcohol consumption accelerates disease progression even if medications are taken correctly, by adversely impacting drug absorption and metabolism (Miguez, Shor-Posner, Morales, Rodriguez & Burbano, 2003). Findings remain mixed to some extent with some studies showing that patients receiving HAART and consuming moderate to at-risk levels of alcohol have lower CD4 counts and higher HIV RNA levels, compared to non-drinking controls (Samet, Horton, Traphagen, Lyon & Freedberg, 2003), while others find that alcohol use negatively impacts CD4 counts only in those patients not receiving antiretroviral medications (Samet, Cheng, Libman, Nunes, Alperen & Saitz, 2007). While more work is needed to establish with some certainty the mechanisms by



which alcohol accelerates disease progression in HIV/AIDS, it is evident that alcohol use, and heavy consumption in particular, has detrimental effects.

(3) There is strong evidence for positive associations between alcohol use and high-risk sexual behavior in individuals living with HIV/AIDS (Hendershot *et al.*, 2009; Raj, Reed, Santana, Walley, Welles, Horsburgh *et al.*, 2009; Shuper, Joharchi, Irving & Rehm, 2009), increasing the risk of further HIV transmission, infection with other sexually transmitted diseases (e.g. Seth, Wingood, DiClemente & Robinson, 2011), “super- or co-infections” (i.e. infection with a new and/or drug-resistant strain of the virus) (Smith, Richman & Little, 2005), and resistance to drug treatments in those consuming risky amounts of alcohol (Little, Holte, Routy, Daar, Markowitz, Collier *et al.*, 2002).

Prevalence of alcohol use, abuse and dependence among HIV-positive patients

In spite of its multiple adverse consequences, alcohol use remains widespread among individuals living with HIV/AIDS. Around half of HIV-positive patients currently in care report consumption of any alcohol (Galvan, Bing, Fleishman, London, Caetano, Burnam *et al.*, 2002; Kalichman *et al.*, 2009). Rates of heavy drinking are thought to be twice as high among HIV-infected individuals, compared to the general population (Galvan *et al.* 2002; Greenfield, Midanik & Rogers, 2000). Studies of HIV-positive patients presenting for treatment at primary care clinics estimate lifetime histories of alcohol abuse or dependence in as many as half of individuals

surveyed (Phillips, Freedberg, Traphagen, Horton & Samet, 2001).

Diagnosing alcohol abuse and dependence

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association [APA], 2000) distinguishes between substance abuse and substance dependence. Both substance abuse and substance dependence are broadly defined as “a maladaptive pattern of substance use leading to clinically significant impairment or distress,” which occurs within a 12-month period (pp. 110, 114). However, substance dependence is identified as a more severe disorder. A pattern of substance *abuse* must be manifested by continued substance use despite the presence of only *one* of the following negative consequences: 1) “Failure to fulfill major role obligations at work, school, or home;” 2) “substance use in situations in which it is physically hazardous;” 3) legal problems related to substance use; and 4) “Persistent or recurrent social or interpersonal problems”(pp. 114-115) related to substance use. Substance *dependence*, as defined by the *DSM-IV-TR*, requires that a person exhibit *three* of the following criteria: 1) tolerance; 2) withdrawal; 3) taking a substance in “larger amounts or over a longer period than was intended;” 4) “unsuccessful efforts to cut down or control substance use;” 5) spending “a great deal of time trying to obtain the substance, using the substance, or recovering from its effects;” 6) giving up or reducing time spent in “important social, occupational,

or recreation activities” due to substance use (p. 110); and 7) continuing substance use despite knowingly having a “persistent or recurrent physical or psychological problem” that is likely related to substance use (p. 111). An individual is said to have developed “tolerance” when he/she needs more of the substance to achieve the desired effect, or fails to achieve the same effect while using the same amount. Withdrawal is exhibited by a set of symptoms that either occur when an individual stops using a substance, or are avoided by continued use of the same or related substance. Withdrawal symptoms are specific to the substance. Withdrawal from alcohol is exhibited by at least two or more of the following symptoms: autonomic hyperactivity, increased hand tremor, insomnia, nausea/vomiting, transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety, and grand mal seizures. These symptoms will develop within several hours to a few days after an individual stops or reduces “heavy and prolonged” alcohol use (p. 121). It should be noted that although tolerance and withdrawal are typically viewed as hallmarks of substance dependence, based on the criteria outlined in the *DSM-IV-TR*, evidence of withdrawal and/or tolerance is neither sufficient nor necessary to diagnose substance dependence.

Brief screening for alcohol abuse and dependence

In many, if not most cases, it is a serious negative consequence of substance abuse that compels the abuser into treatment, i.e. failed relationship,

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Quick screening techniques can be useful for busy HIV clinics

[Alcohol use disorders, from preceding page](#)

lost job, missed appointments, erratic medication compliance, unlawful behavior and more. Identifying persons at risk for these negative consequences is obviously desirable through whatever mechanism possible. A major goal of screening in a primary care setting is to identify the disease at an early stage and initiate an intervention to avoid dire future consequences (Jones, 2011). It has been recommended that such screening instruments should be validated, simple, and acceptable to the population being assessed (National Institute on Alcohol Abuse and Alcoholism guidelines). Brevity is also a concern so we focus here only on very brief instruments. In terms of content, the most effective screening tools for alcohol-related problems tend to inquire about amount typically consumed, evidence for increased tolerance, negative consequences and risks associated with drinking, and emotions related to use (Smith, Herrmann & Bartlett, 2011).

Commonly used screening instruments for alcohol abuse and dependence are the Alcohol Use Disorders Identification Test (AUDIT; Babor, Fuente & Saunders, *et al.*, 1992), which contains ten items, and the Michigan Alcohol Screening Test (MAST; Selzer, 1971), which contains 24 items. Both of these screening instruments have shorter versions available but neither has the research validation of the original versions. Among the briefest of scales, the CAGE (Ewing, 1984)

and the Rapid Alcohol Problems Screen (RAPS4; Cherpitel, 2000) are two of the most widely used screening tools for alcohol use disorders. Both measures consist of four items and are presented in their entirety below. The CAGE assesses perceived need to cut down on alcohol use, experiences of others getting annoyed with one's alcohol use, feelings of guilt about use, and need for alcohol in the morning in order to start the day ("eye opener"). Like the CAGE, the RAPS4 also assesses guilt about alcohol use ("remorse") and need for alcohol in the mornings ("starter/eye opener"); in addition it inquires about episodes of memory loss when drinking ("amnesia") and failure to fulfill major role obligations due to alcohol use ("perform"). Of note, the CAGE and RAPS4 are designed to inquire about lifetime histories of alcohol-related problems; both are easily modified or amended to inquire about current abuse or dependence.

CAGE

1. Have you ever felt you should cut down on your drinking? (Cut down)
2. Have people annoyed you by criticizing your drinking? (Annoyed)
3. Have you ever felt bad or guilty about your drinking? (Guilty)
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? (Eye opener)

Scoring: Each positive response is assigned one point. A score of two points or higher on the CAGE is thought to be indicative of the presence of past or current alcohol abuse or dependence (Ewing 1984).

RAPS4

1. Have you had a feeling of guilt or remorse after drinking? (Remorse)
2. Has a friend or a family member ever told you about things you said or did while you were drinking that you could not remember? (Amnesia)
3. Have you failed to do what was normally expected of you because of drinking? (Perform)
4. Do you sometimes take a drink when you first get up in the morning? (Starter)

Scoring: A positive response to one or more items is considered indicative of the presence of alcohol dependence (Cherpitel, 2000; Cherpitel, 2002).

Both the CAGE and RAPS4 have been shown to be useful in detecting the presence of alcohol use disorders in the general population; however, there is evidence to suggest that the RAPS4 does so with greater sensitivity than the CAGE (Cherpitel, 2002; Fiellin, Reid & O'Connor, 2000). Although both the CAGE and RAPS4 have four items with two items overlapping (remorse about drinking, and morning eye-opener) the RAPS4 requires only one item endorsement to identify problem alcohol consumption;



the CAGE requires two which may be one reason the RAPS4 seems to have the edge in many side-by-side comparisons. Also, the RAPS4 inquires about specific events or incidents, such as amnesia and failed expectations, while CAGE items lean toward the subjective and allow for some interpretative latitude.

Of note, both the CAGE and the RAPS4 have been validated cross culturally. Cremonte, Ledesma, Cherpitel, and Borges (2010) found the scales efficacious as measured against a DSM IV-based clinical interview with American, Mexican and Argentine populations. Cherpitel, Moskalewicz, and Swiatkiewicz (2005) validated both instruments against ICD-10 and DSM IV criteria with a Polish sample. In both studies the RAPS4 performed slightly better than the CAGE in accurately identifying individuals with alcohol abuse or dependence.

Quantity/Frequency

A brief assessment of overall quantity and frequency of alcohol consumption can easily be added to both the CAGE and the RAPS4 brief screening tools. It has been suggested that doing so can increase their specificity and sensitivity in detecting patients with or at risk for hazardous drinking (Cherpitel, 1997; Cherpitel, 2002). The following are examples of questions that can be used to assess quantity and frequency of consumption, developed by the National Institute on Alcohol Abuse and Alcoholism and used widely by physicians and in primary care settings:

1. Typically, on how many days per week do you drink alcohol?

2. On a typical day drinking, how many drinks do you have?
3. What is the maximum number of drinks you had on any given occasion during the past month?

Cutoff points on the quantity/frequency measures that are considered indicators of possible problem drinking are 14+ drinks per week/4+ drinks in one sitting for men and 7+ drinks per week/3+ drinks in one sitting for women (National Institute on Alcohol Abuse and Alcoholism criteria).

The use of brief screening tools in HIV primary care

Screening for alcohol abuse and dependence in primary care settings is encouraged by the National Institute on Alcohol Abuse and Alcoholism, but remains underused in spite of strong evidence supporting its effectiveness in identifying and referring patients in need of services and treatment (Kypri, Langley, Saunders, Cashell-Smith & Herbison, 2008). HIV primary care providers have been shown to be particularly susceptible to missing opportunities to identify patients with alcohol-related problems, especially in the absence of obvious evidence of alcohol abuse and dependence, such as accelerated disease progression or signs of liver disease (Conigliaro, Gordon, McGinnis, Rabeneck & Justice, 2003). The proposed screening tools could easily be incorporated into standard annual (or more frequent) clinical assessments conducted in most HIV outpatient settings.

As of now, few studies have systematically examined the use of brief screening tools for alcohol abuse and dependence

specifically in HIV-positive patients. The measures most frequently used to assess alcohol use in HIV-positive patients are the CAGE, AUDIT and DSM-IV criteria (Hendershot et al. 2009). Two studies that used the CAGE to screen for alcohol abuse in HIV-positive patients in primary care found that it performed well in this population, yielding a positive predictive value of 95% for lifetime diagnoses of alcohol abuse or dependence (Phillips et al. 2001; Samet *et al.*, 2004). The RAPS4 has been used in studies of HIV-positive patients (e.g. Wagner, Bogart, Galvan, Banks & Klein, 2011); however, its sensitivity and specificity in detecting possible alcohol abuse and dependence in HIV primary care settings has yet to be evaluated systematically. The focus of the RAPS4 on functional impairment may render it particularly suitable for use in HIV-positive patients who might be over-pathologized by the reliance of the CAGE on assessing more subjective experiences (i.e., guilt regarding use and feeling that one would benefit from cutting back on consumption). Patients who are aware of the negative effects of any alcohol use on HIV disease progression may give positive responses to these items, even in the absence of any formal diagnostic criteria for alcohol use disorders. The RAPS4 may also be particularly suitable for use with HIV-positive patients because the question about role obligations can help start a conversation between providers and patients about responsibilities when it comes to disclosing a seropositive status to sex partners. The possibility that the RAPS4 may perform particularly well in

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One session of a brief intervention can reduce problem drinking

Alcohol use disorders, from preceding page

HIV primary care should be assessed in future research.

Of note, screening for alcohol abuse and dependence in primary care has been shown to be easily and effectively combined with brief interventions and referral to treatment (SBIRT), providing an evidence-based, cost-effective approach to addictions treatment outside of specialty settings (Ballesteros, Duffy, Querejeta, Arino & Gonzales-Pinto, 2004; Ballesteros, Gonzales-Pinto, Querejeta & Arino, 2004). As little as a single session of a brief intervention following a positive screen, administered via web in a primary care setting, was shown to effectively reduce hazardous drinking for up to a year (Kypri, Langley, Saunders, Cashell-Smith & Herbison, 2008). An evaluation of the extent to which SBIRT for alcohol use disorders can be translated into HIV primary care has been called for in the literature (Conigliaro, Gordon, McGinnis, Rabeneck & Justice, 2003) and should be a major focus of future research.

With high rates of problem drinking in HIV-positive patients and considering its multiple adverse consequences, implementing regular screening procedures in primary care HIV clinics is critical in order to ensure that individuals in need of substance abuse treatment can be identified and referred for services. Due to time constraints in these types of settings, conducting lengthy clinical interviews is oftentimes not feasible and the use of brief screening tools may be prefer-

able. We hope that the tools and references provided here will contribute to a more widespread adoption of routine screening for alcohol abuse and dependence in HIV primary care. ❖

Helpful online resources and references

National Institute on Alcohol Abuse and Alcoholism: "A Pocket Guide for Alcohol Screening and Brief Intervention" (online publication): http://pubs.niaaa.nih.gov/publications/practitioner/pocketguide/pocket_guide.htm

"Screening Tests" (online publication): <http://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm> "Alcohol Research and Health" (NIAAA's quarterly peer-reviewed journal)

Issue on Alcohol & HIV/AIDS: http://pubs.niaaa.nih.gov/publications/arh333/toc33_3.htm

Issue on Brief Screening and Intervention: <http://pubs.niaaa.nih.gov/publications/arh28-1/toc28-1.htm> and <http://pubs.niaaa.nih.gov/publications/arh28-2/toc28-2.htm>

Center for Disease Control and Prevention Resources on Alcohol Screening (including a step-by-step guide for implementing SBIRT): <http://www.cdc.gov/InjuryResponse/alcohol-screening/resources.html>

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HIV research is alive and well at Louisiana's HOP Clinic

Rebecca Clark, MD, PhD

Research is active at the HIV Outpatient Program (HOP) Clinic of the Interim Louisiana Hospital and several studies are ongoing as described below.

The Centers for Disease Control is funding a study in the HOP clinic to look at a food safety intervention and has been ongoing for the last year. Persons living with AIDS are highly vulnerable to food-borne enteric infections and at risk of substantially increased morbidity and mortality. Compared to the general population, the incidence rates of gram-negative bacterial enteric infections (such as *Salmonella* and *Campylobacter*) in the HIV-infected population are 20 to 100 fold higher. AIDS patients are particularly susceptible to food-borne diseases due to their immune suppression resulting from a decrease in the number of CD4 cells. Additional factors that increase susceptibility include lack of gastric acidity and recent use of antimicrobials, which may kill organisms that naturally compete with pathogens living in the intestine. To mitigate the risk of food-borne disease in persons with AIDS, evidence-based educational materials that are brief and targeted to gaps in food-safety knowledge are being evaluated in the study. Several patients who have reviewed the educational materials are currently being assessed on the impact of the educational materials to increase their knowledge of food safety.

A second study supported by a technology company is testing

a new diagnostic device to assess HIV RNA in HOP patients. Assessment of HIV RNA levels is one of the best predictors of clinical progression, as well as the main parameter to assess treatment response. Reproducible and sensitive assays based on real-time PCR technology have been developed to quantify HIV in the bloodstream. This study evaluates an enhanced method to produce results faster with larger dynamic ranges and is applicable to all HIV subtypes. Up to 500 HOP adult volunteers who have a viral load of at least 1,000 copies will be recruited for this study.

The only pharmaceutical-sponsored study ongoing at HOP is a five-year long-term epidemiological study of the safety of maraviroc use in treatment-experienced patients with HIV. There is limited information about the safety of long-term treatment with maraviroc especially concerning the theoretical risks of hepatotoxicity, malignancy, myocardial ischemia, rhabdomyolysis, or infection rates in patients who use this class of drug. The study will enroll 2,000 patients who have been prescribed maraviroc. The comparator group will consist of 1,000 patients receiving a regimen who were not prescribed maraviroc. The study will enroll from approximately 300 sites in 13 countries with approximately 10 from the HOP clinic.

Michael Hagensee, MD, is studying the risk factors associated with the development of cervical or anal cancer in HIV-infected individuals. More specifically, he has an ongoing

longitudinal study of about 90 HIV-infected women examining a co-factor role of Epstein-Barr virus (EBV) being shed from the cervix or anus and how this virus may interact with the human papillomavirus (HPV), the known cause of cervical cancer. Preliminary studies have shown a 2-3 fold increase in the rate of cervical dysplasia in those shedding both HPV and EBV from their cervix. In addition, he is initiating screening in HPV-infected men for anal cancer by instituting anal Pap smear for high-risk individuals and has initiated a high-resolution anoscopy clinic to follow up those individuals with an abnormal anal Pap smear. Studies to date have shown over 50% of HIV-infected individuals have an abnormal anal pap smear but fortunately, only a handful of anal cancers have developed. Finally, Dr. Hagensee has been also studying the impact of antiretroviral therapy (ART) on the rates of oral HPV infection in HIV-infected individuals. Surprisingly, ART has led to an increase in oral HPV infection and may be related to the development of oral warts as well as oral HPV-related cancers.

Tulane is actively recruiting for the START Study (Strategic Timing of AntiRetroviral Treatment). This NIH-supported study is considered the definitive study to determine whether immediate initiation of ART is superior to deferral of ART until the CD4 declines below 350 in terms of morbidity and mortality in HIV-infected persons who are ART naïve with a CD4 count above 500, any viral load. Patients are randomly assigned to Early ART Group or Deferred ART Group. The treat-



ing clinician chooses the HAART regimen and the study provides most of the ARVs for free.

Finally, two retrospective chart reviews are ongoing at HOP. The first is evaluating the frequency of gonorrhea and chlamydia infections among adults who do not have risk factors for sexually transmitted infections. The chart review will also collect symptomatology on any persons with positive testing. The objective of the study is to determine the practicability of universal screening for these STDs in a relatively low-risk population as opposed to targeted screening based on symptomatology. The second

chart review evaluates healthy HOP patients who have achieved adequate viral suppression and immunologic competence at low risk for medical or psychosocial complications. The review will determine the cumulative risk for adverse outcomes in this population if clinic visits are expanded to biannual clinic encounters.

We encourage clinicians to refer to any of these studies. If you have any questions, please call Alison Fleury, the HOP Research Coordinator, at 504-826-2189. ❖

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▲ **The mediating role of pain in substance use and depressive symptoms among Multicenter AIDS Cohort Study (MACS) participants.** Tsao JC, Stein JA, Ostrow D, Stall RD, Plankey MW. *Pain*. 2011 Sep 29.

▲ **Health Care Transition for Youth Living With HIV/AIDS.** Dowshen N, D'Angelo L. *Pediatrics*. 2011 Oct;128(4):762-71.

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Make plans now to attend HIV/AIDS conferences

▲ November 10-13, 2011
United States Conference on AIDS
Chicago, Illinois

▲ November 17-21, 2011
Annual ANAC Conference
Baltimore, Maryland

▲ December 4-8, 2011
American Society of Health-System Pharmacists Midyear Clinical Meeting
New Orleans, Louisiana

▲ March 21, 2012
Keystone Symposia: HIV Vaccines
Keystone, Colorado

▲ May 23, 2012
International Symposium on HIV and Emerging Infectious Diseases
Marseille, France

▲ July 22-27, 2012
XIX International AIDS Conference
Washington, DC

▲ November 11, 2012
International Congress on Drug Therapy in HIV Infection
Glasgow, UK



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Clinical preceptorship for nurses and clinical service providers: Comprehensive Management of the Patient with HIV Disease—November 7-8, 2011. 11 contact hours. Contact Danielle Pierce, 504-903-0788 or dpierce@lsuhsc.edu.

Clinical preceptorship for physicians, nurse practitioners, physician assistants: Care and Management of the Patient with HIV Disease—March 12-13, 2012. 15.5 CMEs. Contact Danielle Pierce, 504-903-0788 or dpierce@lsuhsc.edu.

JACKSON, MISSISSIPPI

Course for physicians, physician assistants, nurse practitioners, nurses, pharmacists, case managers, social workers: Care and Management Overview of HIV Infection—March 21-23, 2012. Discipline-specific CEUs. Contact Joan Bounds, 601-984-1300 or jbounds2@umsmed.edu.

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