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Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives

Review

Special Contribution

Topics in Antiviral Medicine™

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Volume 19 Issue 4 November 2011

Topics in
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Continuing Medical Education

The following article in this issue is associated with CME credit:
Chander G. Addressing alcohol use in HIV-infected persons.
Top Antivir Med. 2011;19(4):143-147

Instructions

This journal-based continuing medical education (CME) activity provides a review of alcohol use and HIV infection. To complete the activity, the learner is instructed to:

- Read the article (see pages 143-147)
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Learning Objectives

Upon completion of this activity, learners will be able to recognize the impact alcohol misuse has on HIV disease outcomes, screen for hazardous alcohol use, and describe pharmacotherapy and brief interventions for alcohol-dependent patients.

Accreditation Statement

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The IAS–USA designates this journal-based CME activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Intended Audience

This activity is intended for physicians involved in the care of patients infected with HIV or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with viral diseases.

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Dr Chander has no relevant financial affiliations to disclose.

Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, CHIMERx, Gen-Probe Inc, Gilead Sciences, Inc, Idenix Pharmaceuticals, Inc, Johnson & Johnson, Merck & Co, Inc, and Monogram Biosciences, Inc; received research grants or contracts from Merck & Co, Inc; and holds stock options in CHIMERx and Idenix Pharmaceuticals, Inc.

Dr Benson has no relevant financial affiliations to disclose.

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Posttest Questions

Check the box next to the single best answer to each of the questions below. To earn CME credit, you must receive a passing score of 80% or more correct.

1. Which statement about alcohol consumption and HIV-infected patients is **correct?**

- ❑ **A.** Hazardous alcohol use is associated with increased likelihood of being on antiretroviral therapy
- ❑ **B.** The rate of hazardous alcohol use in HIV-infected patients is twice that in the general population
- ❑ **C.** Patients presenting for care who screen positive for alcohol use should be screened annually thereafter

2. Which criterion is included in the definition of "at-risk" alcohol use?

- ❑ **A.** More than 7 standard drinks per week in women of any age or men older than 65 years
- ❑ **B.** More than 7 standard drinks per week in women of any age or men of any age
- ❑ **C.** More than 5 drinks per occasion in women of any age or men older than 65 years

3. A female patient regularly consumes 4 drinks every Friday night, but has no other alcohol use during the week and her drinking has no impact on work or interpersonal relationships. How would you classify her drinking pattern?

- ❑ **A.** A moderate drinking pattern that is safe to maintain
- ❑ **B.** An "at-risk" drinking pattern
- ❑ **C.** Alcohol dependence
- ❑ **D.** Not enough information to diagnose

4. Which statement about oral naltrexone treatment is correct?

- ❑ **A.** The starting dose is 10 mg/d and titrates upward to 50 mg/d, with treatment continued for a maximum of 2 months
- ❑ **B.** Patients must be opioid-free for 7 to 10 days and alcohol-free for 5 to 7 days before treatment initiation
- ❑ **C.** Oral naltrexone is safe to use during pregnancy

5. **Chronic** alcohol dependence is differentiated from alcohol dependence (ie, severe alcohol use) by:

- ❑ **A.** The presence of withdrawal symptoms (tremors, sweating, insomnia, etc) on discontinuation of alcohol use
- ❑ **B.** Unsuccessful efforts to cut down on alcohol use
- ❑ **C.** The presence of more alcohol dependence factors than are found in severe alcohol use
- ❑ **D.** Failure to complete an alcohol treatment program

This CME activity is offered from **December 1, 2011**, to **December 1, 2012**. Participants who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.

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Perspective

Central Nervous System Complications in HIV Disease: HIV-Associated Neurocognitive Disorder

HIV-associated neurocognitive disorder (HAND) is the result of neural damage caused by HIV replication and immune activation. Potent antiretroviral therapy has reduced the prevalence of severe HAND but not mild to moderate HAND. Brief symptom questionnaires, screening tests, and neuropsychological tests can be used with relative ease in the clinic to identify cognitive and neurologic deficits and to track patient status. Increasing data on pharmacokinetics of antiretrovirals in cerebrospinal fluid (CSF) have permitted formulation of central nervous system (CNS) penetration-effectiveness (CPE) rankings for single drugs and combinations. Available data indicate that regimens with higher CPE scores are associated with lower HIV RNA levels in CSF and improvement in neurocognitive functioning. This article summarizes a presentation by Scott Letendre, MD, at the IAS–USA live continuing medical education course held in San Francisco in May 2011.

HIV enters the brain primarily by being carried in migrating monocytes and lymphocytes that cross the blood-brain barrier (BBB), a so-called "Trojan horse" mechanism. After crossing the BBB, HIV-infected monocytes can become perivascular macrophages. Activated perivascular macrophages and microglia can replicate HIV and express neurotoxic molecules (eg, soluble immune mediators) that can activate astrocytes and other cells. Astrocytes form an important component of the BBB by surrounding brain microvascular endothelial cells. When activated, astrocytes can lead to increased BBB permeability and monocyte and lymphocyte migration. Although it was once believed that astrocytes produced HIV-encoded proteins but not virus, there is now evidence that infected astrocytes can also produce virus. Eventually, the increase in brain concentrations of glutamate (a neurotransmitter that is an excitatory neurotoxin at high levels) and other neurotoxins results in neuronal injury, the proximal biological event underpinning clinical neurologic and cognitive disease.

The neurobehavioral disturbances resulting from HIV-mediated neural damage include emotional and other behavioral disturbances (eg, depression, anxiety, sleep disorders, mania, and psychosis) and HIV-associated neurocognitive disorder (HAND). HAND consists of 3 subdisorders: (1) asymptomatic neurocognitive impairment (ANI), (2) mild neurocognitive disorder (MND), and (3) HIV-associated dementia (HAD). Secondary neurocognitive disorders consist of cognitive disorders that can accompany coinfections, cerebrovascular disease, malnutrition, and treatment-related disorders. The diagnosis of HAND requires the presence of acquired impairment in at least 2 cognitive abilities. Impairment is marked for a diagnosis of HAD, with the absence of any preexisting causes or strongly confounding conditions. For diagnosis of ANI, impairment does not interfere with daily function, whereas interference is mild for MND and marked for HAD.[1]

Dr Letendre is associate professor of medicine at the University of California San Diego.

HAND in the Current Antiretroviral Therapy Era

Combination (potent) antiretroviral therapy has reduced the prevalence of severe HAND but not the prevalence of mild to moderate HAND. A recent study compared data from the pre–antiretroviral therapy era from University of California San Diego with data from the current era from the CHARTER (CNS [central nervous system] HIV Antiviral Therapy Effects Research) study group. HAND was present in 36% of HIV-infected patients without AIDS in the combination antiretroviral therapy era and in 29% in the pre–potent antiretroviral therapy era (P = .03) and in 43% and 46% (P not significant) of AIDS patients, respectively. Prevalences of similar cognitive impairment in HIV-seronegative subjects were 19% in the pre–potent antiretroviral therapy era and 16% in the current era.[2]

In a study in the Swiss HIV Cohort, 27% of patients had spontaneous complaints about cognitive function and 73% did not, with neuropsychological testing showing neurocognitive impairment in 84% of those with complaints and 64% of those without complaints (69% of the total clinic population). Among those with spontaneous complaints, 24% had ANI, 52% had MND, and 8% had HAD, with 16% not having measurable impairment.[3]

Risk Factors for HAND

The presence of risk factors for HAND should heighten clinical suspicion for the disorder, and include host factors, HIV disease factors, and comorbidities. Host factors include genetic predisposition, metabolic disorders, aging, vascular disease, anemia, and malnutrition. HIV disease factors include AIDS, immune activation, HIV subtype, neuroadaptation, and drug resistance. Comorbidity factors include stimulant use, hepatitis C virus (HCV) infection, and depression. Among the host factors, there is evidence of an association of HAND with apolipoprotein E e4 alleles (as in Alzheimer's disease) and with a polymorphism in a gene encoding the potent chemotactic protein MCP-1.[4] The CHARTER group has performed a genome-wide association study, and it is hoped that a brief testing panel may be available in the foreseeable future.

More important are the associations of HAND with metabolic disorders (eg, insulin resistance), aging, and vascular disease. There is evidence suggesting that vascular disease risk factors are more strongly associated with cogni-

tive impairment than are such HIV disease risk factors as CD4+ count nadir and plasma HIV RNA level.[5] With regard to accelerated aging in HIV disease, there are data on phosphorylated Tau protein and other age-related markers in cerebrospinal fluid (CSF) indicating that HIV-infected patients have levels of these markers comparable to those in noninfected subjects who are 15 years to 20 years older.[6]

With regard to HIV disease factors, data from the CHARTER group indicate that CD4+ cell count nadir is strongly associated with risk for cognitive impairment, providing additional incentive to initiate antiretroviral therapy before CD4+ cell counts drop to below 200/μL.[7] Translocation of bacterial products, such as lipopolysaccharide, and resulting immune activation in people with HIV infection have been the topic of intensive investigation in recent years. Recent data have shown an association between impairment and blood levels of soluble CD14, the solubilized receptor for lipopolysaccharide.[8] This marker can be measured relatively inexpensively by an enzyme-linked immunosorbent assay, and may become a clinically useful biomarker of risk.

In terms of comorbidities, use of such drugs as methamphetamine and cocaine can have persistent adverse effects on the CNS.[9] HCV can infect glial cells. Although only approximately 10% of HCV-infected patients have detectable HCV RNA in the CSF (and typically at low levels), a much larger percentage of patients have relatively high levels of HCV core antigen.[10] The core antigen is highly immunogenic and may be a stimulus for brain injury.

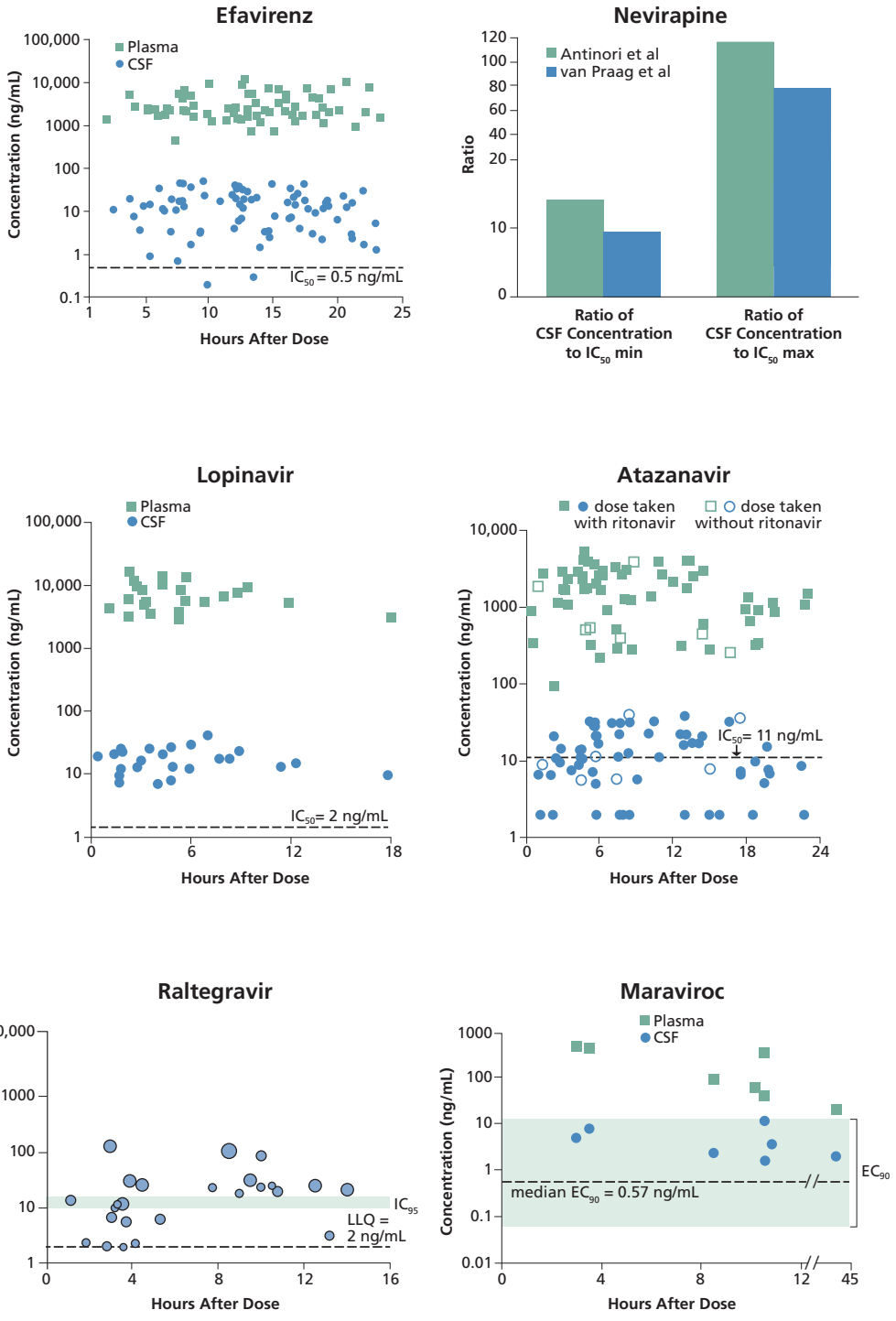

Figure **1**. Results of selected studies of antiretroviral pharmacokinetics in cerebrospinal fluid (CSF). Top left: Efavirenz plasma concentration and CSF concentration over time from dose. Adapted from Best et al.[18] Top right: Ratio of nevirapine CSF concentration to minimum 50% inhibitory concentration (IC_{50} min) and maximum 50% inhibitory concentration (IC_{50} max). Adapted from van Praag et al[19] and Antinori et al.[20] Middle: Plasma concentration and CSF concentraton over time from dose for lopinavir (left, adapted from Capparelli et al[21]) and atazanavir/ritonavir (right, adapted from Best et al[18]). Bottom left: Raltegravir CSF concentration over time from dose. Size of data point indicates ratio of CSF concentration to serum albumin. LLQ indicates lower limit of quantitation; IC_{95}, 95% inhibitory concentration. Adapted from Yilmaz et al.[23] Bottom right: Maraviroc plasma concentration and CSF concentration over time from dose. EC_{90} indicates 90% effective concentration. Adapted from Yilmaz et al.[24]

HAND Assessment in the Clinic

A range of tests are available for use in the clinic to assess neurocognitive function, with many being relatively simple and brief. Symptom questionnaires consist of the Medical Outcomes Study–HIV Health Survey[11] (MOS-HIV) and the somewhat more complex Patient's Assessment of Own Functioning Index[12] (PAOFI). Both are self-administered and can be completed by

the patient in the waiting room before meeting with the physician; results on the questionnaires serve as a baseline for subsequent follow-up.

Brief screening tests include the HIV Dementia Scale (which requires 5 to 10 minutes to complete), the International HIV Dementia Scale[13] (which requires even less time), and the Montreal Cognitive Assessment.[14] HIV clinicians may be reluctant to perform neuropsychologic testing, but brief tests are easy to administer. The ACTG (AIDS Clinical Trials Group) Longitudinal Linked Randomized Trial (ALLRT) Neurocognitive Screen consists of connect-the-dot tests and digit-symbol comparison tests.[15] The Grooved Pegboard test requires purchase of the grooved pegboard and is also not difficult to administer.[16] The Action Fluency test requires patients to name as many verbs as they can within a given time period.[17] Brief computerized tests that can be used in the clinic are also available. More comprehensive neuropsychologic testing requires assessment of at least 5 cognitive abilities, with at least 2 tests per ability.[1]

Antiretrovirals and the Blood-Brain Barrier

The BBB features a number of unique elements that prevent passage of drugs or other substances into the brain. Brain microvascular endothelial cells are joined by tight-junction proteins (forming the "tight junction") and are surrounded by a basement membrane. Abutting the basement membrane are astrocyte foot processes. Both the luminal and abluminal surfaces of the endothelial cells and astrocytes can express molecular drug pumps or transporters (eg, P-glycoprotein and organic anion transporters) that can limit the amount of drug that passes into the brain.

A number of drug characteristics influence penetration across the BBB. Perhaps most important is protein binding: drugs that are more highly bound to plasma proteins are less available to cross the BBB. Nucleoside analogue reverse transcriptase inhibitors (nRTIs) are the least protein-bound, with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) being roughly equally protein-bound and both more highly bound than nRTIs. PIs and NNRTIs exhibit greater fat solubility than nRTIs, a characteristic that favors crossing of the BBB. Low molecular weight also favors crossing of the barrier. Most of the antiretrovirals are relatively small molecules (with the exception of enfuvirtide), with nRTIs being smaller than NNRTIs, which are smaller than PIs. P-glycoprotein inhibits crossing of PIs, maraviroc, and raltegravir, and organic anion transporters inhibit crossing of nRTIs.

In the absence of measuring drug concentrations in the CSF, assessment of ability of antiretroviral drugs to cross the BBB was based on comparisons of the above characteristics, as well as their acid dissociation constants and estimates of the ability of CSF drug concentration to exceed the 50% inhibitory concentration (IC_{50}) (derived by dividing the product of the unbound fraction and the plasma minimum concentration by the IC_{50}). However, data on CSF pharmacokinetics of antiretroviral drugs are becoming increasingly available, in part through population pharmacokinetics studies. These studies involve sparse sampling of a large number of patients (rather than the intensive sampling of a smaller group performed in typical pharmacokinetics studies) to spare patients from having to undergo numerous lumbar punctures.

Examples of data from CSF pharmacokinetics studies are shown in Figure 1. For the NNRTI efavirenz, CSF penetration was 0.5% of plasma concentration, but exceeded the IC_{50} in the majority of measurements.[18] Nevirapine CSF penetration was approximately 29% to 63% of plasma drug concentration.[19,20] For the PI lopinavir, CSF penetration was 0.23% of plasma concentration, but all measured CSF concentrations exceeded the IC_{50}.[21] For atazanavir, CSF levels were 1% of plasma concentration, but only approximately 50% of measurements exceeded the IC_{50}.[22] Further, the variation in CSF levels was wide, and about 15% of patients had atazanavir levels below the limit of detection, as measured by a highly sensitive assay. Among newer agents, maraviroc has exhibited CSF concentrations about 1 $\log_{10}$ lower than expected based on drug characteristics. Figure 1 shows CSF concentrations plotted against a range of 90% effective concentrations.[23] For raltegravir, Figure 1 shows CSF concentrations with the size of the data point indicating the CSF-to-serum albumin ratio, a marker of BBB permeability. Patients with more permeable BBBs generally had higher CSF drug concentrations.[24]

There are fewer data thus far on the pharmacodynamics of antiretrovirals in the CSF. Examples from extant data include the finding of statistically significant reductions in CSF HIV RNA levels in all patients receiving ritonavir-boosted (/r) lopinavir monotherapy for 3 weeks.[25] Other studies have shown CSF viral load greater than 50 copies/mL in 1 of 11 patients with plasma viral load less than 50 copies/mL receiving lopinavir/r monotherapy, and in 3 of 20 patients receiving atazanavir/r monotherapy.[26,27] A study using an assay that detects HIV RNA down to a level of 2 copies/mL showed that in patients with plasma HIV RNA below detection limits, CSF viral load 2 copies/mL or greater was present in 25% of patients receiving lopinavir/r and in 75% of those receiving atazanavir or atazanavir/r.[28]

Using data from a population of approximately 1600 patients, some 80% of whom consented to lumbar puncture, the CHARTER group constructed a CNS Penetration-Effectiveness (CPE) ranking system for antiretrovirals (Table 1).[29,30] Higher numbers indicate better estimated penetration; for combination regimens, the scores for each drug are added. Using CSF viral load data from 615 patients, higher CPE scores were statistically significantly associated with lower CSF viral loads (see Figure 2).[29] Using a highly sensitive assay, a CPE score greater than the median of 7 was associated with a statistically significantly smaller proportion of patients having CSF viral load above 2 copies/mL, compared with a score of 7 or below.[31]

Table **1**. Central Nervous System Penetration-Effectiveness Ranking

Drug Class	CPE Score 4	3	2	1
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Nonnucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Strand Transfer Inhibitors		Raltegravir		

CPE indicates central nervous system penetration effectiveness; /r, ritonavir-boosted. Larger CPE scores reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Adapted from Letendre et al.[30]

Observational and uncontrolled interventional studies support the notion that antiretroviral regimens that better penetrate the CNS better reduce HIV RNA levels in the CSF. Most, but not all, studies also support the notion that antiretroviral regimens that better penetrate the CNS better protect the brain from HIV-related injury. It may be that better-penetrating antiretroviral therapy is a necessary condition for preventing or reducing CNS damage, but use of these regimens may not be sufficient in all individuals. Reducing HIV replication in the brain (through antiretroviral therapy) may not have effects on other processes involved in injury, including ongoing immune activation, comorbidities, and potential toxicities of antiretroviral drugs.

Prospective, uncontrolled, observational studies have assessed the association of antiretroviral regimen CPE score with outcomes on neuropsychological testing. For example, in a study of 37 patients, higher CPE of an antiretroviral regimen was associated with lower CSF viral load; patients were given 6 neuropsychological tests, and those receiving regimens with higher CPE scores performed better than patients on regimens with lower CPE scores.[32] In a study of 185 patients in which CSF viral load was not measured, patients receiving regimens with higher CPE scores performed better on 16 neuropsychological tests given.[33]

In a third example, Ellis and colleagues found that higher CPE score was associated with better outcome on a total of 3 tests in 2636 patients (no measurement of CSF viral load was performed).[34] In a study of 26 patients, CPE score was associated with lower CSF viral load—but in contrast to other studies, patients who were cognitively impaired at baseline and received regimens with higher CPE scores had *less* improvement on a total of 4 tests than those receiving regimens with lower CPE scores.[35] The findings in the latter study raise the issue of potential neurologic toxicity of antiretroviral therapy and highlight the need for careful consideration of implementing treatment strategies based on better CNS penetration.

In addition to these published analyses of CSF viral load and neuropsychological functioning, regimens that appeared to have better distribution into the CNS were associated with better mood in the CHARTER cohort, even after accounting for antidepressant use and neuropsychological performance. Such regimens have also been associated with better survival in studies of nearly 20,000 patients in the United Kingdom,[36] more than 2000 perinatally-infected children,[37] and individuals with CNS opportunistic infections.[38]

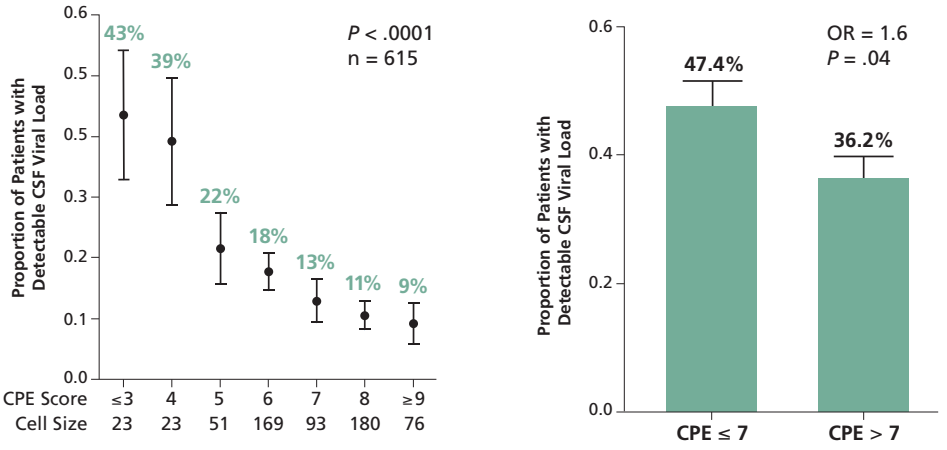

Figure **2**. Left: Association of antiretroviral regimen CNS (central nervous system) Penetration-Effectiveness (CPE) score with proportion of patients with detectable HIV RNA in cerebrospinal fluid (CSF). Adapted from Letendre et al.[29] Right: Proportion of patients with CSF viral load between 2 copies/mL and 50 copies/mL, according to antiretroviral regimen CPE score of ≤ 7 or > 7 (the median value). OR indicates odds ratio. Adapted from Letendre et al.[31]

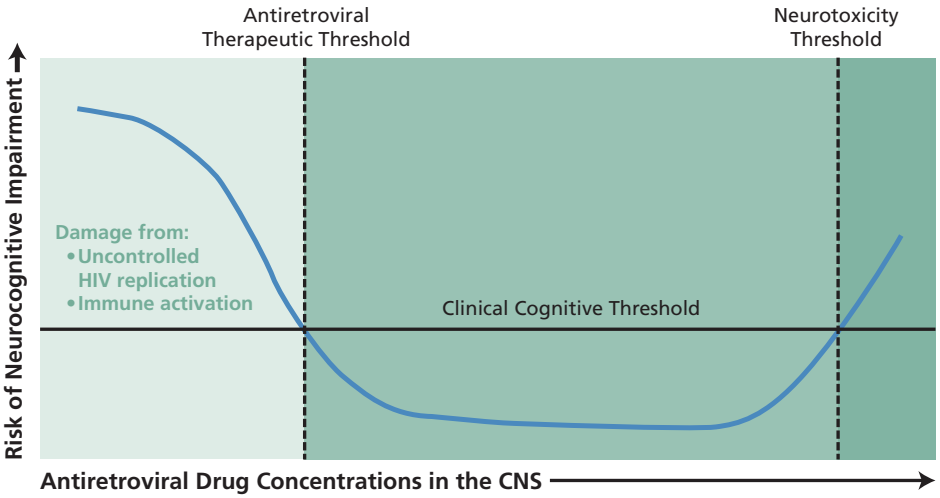

Figure 3. Conceptual therapeutic window for effectiveness of antiretroviral therapy in the central nervous system (CNS).

The goal of antiretroviral therapy, where risk for neurocognitive impairment is concerned, is to achieve adequate drug levels in the CNS without causing drug-related neurotoxic effects (see Figure 3). If drug levels in the CSF are too low, there is greater risk of damage caused by viral replication and ongoing immune activation, as well as a potential risk of drug resistance. However, biomarker and neuroimaging data support that subacute brain injury may continue despite adequate drug levels in the CNS. Such injury may not reach the point at which it is noticeable to the patient; many patients are asymptomatic despite having CNS injury that is detectable on neuropsychological testing. The therapeutic window for antiretroviral therapy in the CNS may thus be defined as the range of CNS drug concentrations that are associated with keeping damage below the clinical cognitive threshold and that do not expose patients to excessive risk of neurotoxicity.

Summary

Patients should be counseled on HAND and on what is known about antiretroviral drug penetration to enable them to make informed treatment choices. Patients should be routinely questioned about cognitive symptoms, particularly at important clinical milestones, such as before initiating antiretroviral therapy. Brief testing improves the ability to correctly identify HAND. Other conditions that can cause CNS complaints (eg, syphilis, substance use, depression) should be screened for and treated. Physicians should consider using better-penetrating antiretroviral therapy, as accumulating data support that it better reduces HIV RNA levels in the CSF and leads to neurocognitive improvements. Patients should be continually monitored, as cognitive impairment might persist or present for the first time during antiretroviral therapy.

Lecture presented by Dr Letendre in May 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Letendre in October 2011.

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Perspective

Addressing Alcohol Use in HIV-Infected Persons

Alcohol use is common among persons with HIV infection and is associated with worse HIV treatment outcomes. Patients with hazardous levels of use are less likely to be receiving antiretroviral therapy, to be adherent to therapy, and to achieve virologic suppression. Screening, intervention, and referral to care for alcohol use disorder is an integral part of clinical care for individuals with HIV infection. Brief screening procedures can identify level of risk and determine whether patients require brief alcohol intervention or should be considered for behavioral therapy and pharmacologic treatment. Identification of concurrent mental health disorders is an important aspect of treating alcohol use disorders in HIV infection and other clinical settings. This article summarizes a presentation by Geetanjali Chander, MD, MPH, at the 14th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in Tampa, Florida, in June 2011. The Clinical Conference is sponsored by the IAS–USA under the Health Resources and Services Administration (HRSA) contract number HHSH250200900010C.

Introduction

Alcohol use is common in HIV-infected persons, with data from national samples indicating that 50% report any alcohol use and that the rate of hazardous use is twice that in the general population.[1] Alcohol use worsens common comorbid conditions in HIV-infected persons, including hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, diabetes, and hypertension. It also increases HIV risk behaviors, including having unprotected sex, multiple sex partners, and high-risk injection behaviors.[2,3] Alcohol use is associated with worse HIV treatment outcomes, and mortality.[4,5]

Hazardous alcohol use is defined as more than 7 drinks per week or more than 3 drinks per occasion for women of any age and for men older than 65 years. In men aged 65 years or younger, hazardous use is defined as more than 14 drinks per week or more than 4 per occasion. Data from a study of approximately 1700 patients at the Johns Hopkins HIV Clinic showed that hazardous alcohol use (in the absence of drug use) was associated with reduced likelihood of being on or being adherent to antiretroviral therapy and reduced likelihood of achieving virologic suppression (Table 1).[4]

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See page 135 for information on CME credit for this article.

Screening for Alcohol Use

In HIV clinical settings, all patients presenting for care should be screened for alcohol use. If screening is negative at baseline, it should be repeated at least annually; if positive, it should be repeated at every visit. Screening is relatively easy and straightforward. The National Institute on Alcohol Abuse and Alcoholism recommends asking a single, validated, screening question, "How often in the last year have you had 4 or more drinks?" (for women) or "5 or more drinks?" (for men).[6] If such consumption has occurred on more than 1 occasion, follow-up questions should be used to identify quantity and frequency of drinking, eg, "How many standard drinks do you have on a typical drinking day?" and "How many days per week do you usually drink?" Instruments for follow-up include the AUDIT-C (Alcohol Use Disorders Test–Consumption) and the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire. Some clues that may prompt screening for alcohol use include changes in medication or appointment adherence, symptoms of depression or anxiety, changes in laboratory measures (eg, an increase in aspartate aminotransferase [AST] on liver function testing [LFT]), changes in blood pressure or diabetes control, or a new sexually transmitted infection.

It is important to note that a "standard" drink is any that contains 14

Table 1. Effects of Alcohol Use or Drug Use on Receipt of Antiretroviral Therapy, Adherence to Antiretroviral Therapy, and Virologic Suppression[a]

Drug Use	Alcohol Use	Antiretroviral Therapy[b]	Adherence[c]	Virologic Suppression[c]
		Adjusted odds ratio (95% confidence interval)		
No	No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	Moderate	1.14 (0.95-1.37)	0.77 (0.62-0.98)	1.00 (0.84-1.20)
	Hazardous	0.57 (0.42-0.77)	0.36 (0.25-0.53)	0.72 (0.52-0.99)
Yes	No	0.54 (0.43-0.68)	0.50 (0.37-0.68)	0.60 (0.46-0.78)
	Moderate	0.68 (0.54-0.88)	0.40 (0.30-0.54)	0.64 (0.50-0.82)
	Hazardous	0.40 (0.29-0.57)	0.32 (0.20-0.51)	0.50 (0.32-0.76)

Adapted from Chander et al.[4]

[a] Adjusted for age, sex, race, CD4+ cell count nadir, and days enrolled in study

[b] Sample includes individuals either receiving antiretroviral therapy or with CD4+ cell count ≤ 350/μL

[c] Adjusted for age, sex, race, CD4+ cell count nadir, and years receiving antiretroviral therapy (days)

grams of alcohol, and that an alcoholic drink includes beer, wine, and liquor. Thus, a standard drink is 12 fluid ounces of regular beer, 8 ounces to 9 ounces of malt liquor, 1 glass of table wine, or 1.5 ounces (1 shot) of 80-proof liquor. Patients may say they have had 2 drinks or "two 40s," referring to two 40-ounce bottles of beer or malt liquor—actually equivalent to approximately 7 standard drinks. They may describe a pint or "a fifth" of vodka as a single drink, actually equivalent to 11 and 17 standard drinks, respectively.

Drinking Definitions

Alcohol use covers a spectrum from "none" or "never exceeds limit" to "at-risk," where there are not yet major consequences to drinking, through "harmful," "severe" (dependent), and "chronic dependent" (Figure 1).[7] At-risk alcohol use includes hazardous alcohol use, defined as more than 7 standard drinks per week in women and more than 14 standard drinks per week in men, and binge drinking, defined as drinking to a blood alcohol content of 0.08% or greater (roughly 5 or more drinks in 2 hours for men, and 4 or more drinks in 2 hours for women).[8] Problem drinking or harmful alcohol use is defined as drinking above these levels with 1 or more additional social, interpersonal, behavioral, or medical consequences, including risk of bodily harm, relationship trouble, role failure (eg, in school or work), and run-ins with the law.[8]

Alcohol dependence or severe alcohol use is defined as the presence of any 3 of the following within the prior 12 months[9]: (1) Tolerance, defined as (a) need for increased amounts of alcohol to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of same amount. (2) Withdrawal, manifested by (a) tremors, sweating, insomnia, etc, and (b) use of the same (or closely related) substance to avoid or relieve such symptoms. (3) Using the substance in larger amounts or over a longer period than intended. (4) Persistent desire or unsuccessful efforts to cut down or control use. (5) Great expenditure of time in activities necessary to obtain or use the substance or recover from its effects. (6) Withdrawal from or reduced participation in social, occupational, or recreational activities because of substance use. (7) Continued use despite recurrent or persistent physical or psychological problems caused or exacerbated by the substance use. Chronic dependence differs from severe use by the presence of more factors among the criteria for dependence, and is usually exhibited by patients who cycle in and out of treatment programs.[7]

Patients who do not drink or never exceed limits should be screened annually. Those in the at-risk or harmful segment of the spectrum should receive a brief intervention, and those in the harmful to chronic dependent segment are candidates for behavioral therapy and pharmacologic treatment.

Consider a patient who describes her alcohol use as consisting of 4 drinks every Friday night out with friends, with no other alcohol use during the week, no interference with work, no drinking and driving, and no other signs of alcohol abuse or dependence. This patient is actually a hazardous, or "at-risk," drinker, and should receive a brief alcohol intervention.

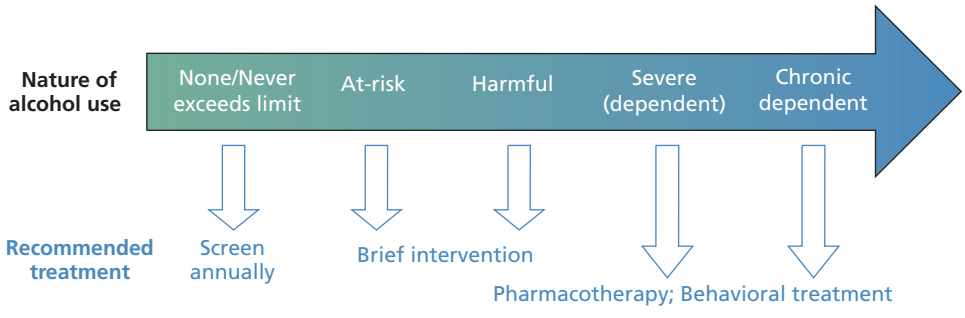

Figure **1**. Spectrum of alcohol use and recommended treatment. Adapted from Willenbring et al[7] and Willenbring.[21]

Brief Alcohol Interventions

A brief alcohol intervention is a short, directed interaction that provides personalized feedback based on alcohol use and related problems (eg, elevated LFTs, depression, increased interpersonal conflicts, poor HIV medication adherence). It offers specific drinking reduction strategies, such as setting goals for safer drinking, alternatives to drinking, and management of risky moods or situations. The brief intervention is a low-cost, cost-effective treatment that promotes reductions in drinking in non–alcohol-dependent persons, as well as facilitates treatment referral in dependent persons.

Components of the brief intervention include the following[8,10]:

- *Ask*: Screen for alcohol use in all patients.
- *Assess*: Assess for risk and consequences, including family history; legal, medical, and social consequences; and alcohol dependence. Assess for readiness to change.
- *Advise*: Provide feedback on drinking and medical, social, and behavioral consequences, and make recommendations for cutting down or quitting alcohol use.
- *Arrange for follow-up*.

Assessing patients' readiness for change can assist in productively advising them on their alcohol use. Readiness to change can be assessed using a question such as: "On a scale of 1 to 10, with 1 being not ready at all and 10 being ready, how ready are you to change your alcohol use?" Patients' confidence in their ability to change can be assessed by asking, "On a scale of 1 to 10, how confident are you that you can change your alcohol use?" If the patient is ambivalent

about changing, a discussion should be initiated about the positive and negative aspects of alcohol use or the "pros" and "cons." A useful technique is to "develop discrepancy"—to have the patient examine alcohol use within the context of their other values and goals and to encourage them to consider how their drinking may conflict with these values and goals. Patients who are ready to change should be helped with goal formulation, guided to resources, and given referrals. Follow-up is imperative for both the ready and the ambivalent.

The basic content of advice for those with drinking problems is as follows:

- *Cut down*: For the hazardous drinker—one with no major consequences from drinking—recommend reducing alcohol use to nonhazardous levels.
- *Cut down or abstain*: For those with harmful alcohol use—eg, no alcohol dependence, but some consequences from drinking—recommend either reduction to nonhazardous levels of alcohol use or abstinence.
- *Abstain*: For those who (a) are alcohol dependent, (b) are pregnant, (c) have HCV infection or other medical conditions in which alcohol use is not recommended, (d) are on medications that interact with alcohol, (e) have blackouts, or (f) are unsuccessful at cutting back on use—recommend abstinence from alcohol.

Treatment for Alcohol-Dependent Patients

Alcohol-dependent patients should be referred to treatment programs. HIV clinicians should be familiar with local resources for substance-abuse treatment and related psychiatric care, including inpatient or residential treatment, outpatient treatment, and support groups such as Alcoholics Anonymous. In addition, clinicians should assess for potential withdrawal symptoms.

Clinicians should also consider the use of pharmacotherapy in dependent individuals. Medications are available that target neurotransmitters involved in the reinforcing effects of alcohol use. Pharmacotherapy for alcohol dependence in combination with behavioral counseling can reduce relapse and help maintain abstinence.

HIV clinics offer a number of advantages as a site for alcohol pharmacotherapy. These clinics are involved in long-term patient care, are generally characterized by integration of a variety of specialty services (eg, psychiatric and ob/gyn services), and have access to funding for prescription medications. Further, many HIV clinics use intensive case management models that promote outreach to and retention of patients who are often challenging to treat. However, currently there are no data on pharmacotherapy for alcohol dependence in patients with HIV infection, although a number of trials are under way. Further, pharmacotherapy for dependence has shown only modest efficacy in clinical trials.

Thus far, US Food and Drug Administration (FDA)-approved treatments for alcohol dependence are naltrexone (oral and injectable forms), acamprosate, and disulfiram.

Naltrexone. Naltrexone blocks opioid receptors and thus lessens the positive reinforcing effects of alcohol consumption. Naltrexone treatment decreases craving, reduces the number of heavy drinking days, and reduces the frequency of relapse to heavy drinking. A Cochrane systematic review of 50 randomized controlled trials of oral naltrexone involving 7793 patients found a 17% reduction in risk of returning to heavy drinking, a 4% reduction in drinking days, and improvement in levels of gamma-glutamyl transferase (GGT, a marker for liver damage).[11]

For oral naltrexone treatment, the patient must be opioid-free for 7 days to 10 days and it is recommended that patients be alcohol-free for at least 5 days to 7 days. The starting dose is 12.5 mg/d to 25 mg/d, increases to 50 mg/d, and treatment is for a minimum of 2 months. Naltrexone is classified by the FDA as pregnancy category C and should not be used during pregnancy. Patients should have LFTs monitored regularly, as naltrexone is associated with hepatitis. Other adverse effects consist mainly of nausea, headache, dizziness, nervousness, insomnia, abdominal pain, and cramping.[12]

Extended-release naltrexone administered via intramuscular (IM) injection is given at a dose of 380 mg monthly, with abstinence required before the start of treatment. Similar to oral naltrexone, individuals should be opioid free before initiating IM naltrexone. Adverse effects include decreased appetite, dizziness, fatigue, vomiting, and injection site reactions including cellulitis, induration, abscess, and necrosis. A randomized, placebo-controlled trial in more than 400 patients showed that monthly IM naltrexone was associated with a 25% reduction in the rate of heavy drinking days.[13]

Acamprosate. Acamprosate affects the glutamate and gamma-aminobutyric acid (GABA) neurostransmitter systems. It has shown moderate efficacy in European trials that has not been replicated in US trials. A Cochrane meta-analysis of 24 randomized, controlled trials involving 6915 patients showed that acamprosate was associated with a statistically significant reduction in risk for any drinking and increased cumulative abstinence duration.[14] A dosage of 666 mg is taken 3 times daily, and alcohol abstinence is required before starting treatment. The drug is categorized as pregnancy category C. Dose adjustment is required with renal insufficency and is contraindicated in individuals with a creatinine clearance of less than 30 mL/min.

Disulfiram. Disulfiram inhibits aldehyde dehydrogenase, increasing levels of acetaldehyde and causing flushing, tachycardia, sweating, nausea, vomiting, and headache if the patient drinks alcohol. Close monitoring of LFTs is necessary, as disulfiram is associated with hepatitis. Neuropathy is also an adverse effect associated with disulfiram. The drug is metabolized by cytochrome P450 3A isoenzymes,

Brief Mental Health Screening Tools for Patients With Alcohol Use

Two-Question Screen for Depression[18]

Over the last 2 weeks, how often have you been bothered by the following problems?

- Have you experienced little interest or pleasure in doing things?
- Have you felt down, depressed, or hopeless?

Generalized Anxiety Disorder 7-Item Scale[19]

How often during the past 2 weeks have you felt bothered by:

- Feeling nervous, anxious, or on edge? _____
- Not being able to stop or control worrying? _____
- Worrying too much about different things? _____
- Trouble relaxing? _____
- Being so restless that it is hard to sit still? _____
- Becoming easily annoyed or irritable _____
- Feeling afraid as if something awful might happen? _____

Total _____

Scoring

0 = not at all 2 = more than half the days

1 = several days 3 = nearly every day

Total score ≥ 10 should prompt further evaluation.

and thus has the potential for interactions with a variety of other drugs that are inhibitors or inducers of these enzymes. Informed consent should be obtained before starting treatment, to ensure that patients are aware of the reactions that occur with alcohol use and that they know to avoid over-the-counter products that contain alcohol. The daily dose is 250 mg. Treatment is best accomplished with monitoring of drug administration, because adherence is low otherwise. Studies of potential pharmacokinetic interactions with antiretroviral agents are under way.

Future pharmacotherapy. Topiramate, ondansetron, and selective serotinin reuptake inhibitors (SSRIs) are currently being investigated for treatment of alcohol dependence, as are combination approaches. Studies with naltrexone, ondansetron, and SSRIs have suggested that treatment response may be correlated with genetic differences at neurotransmitter receptors, raising the possibility of targeted treatment.

Concurrent Substance Use and Mental Health Disorders

Identification and treatment of concurrent mental health disorders is crucial to managing substance use among persons with HIV. Among HIV-infected persons, 13% have been found to have concurrent psychiatric symptoms and either drug dependence or heavy drinking.[15] A study in HIV-infected veterans showed that hazardous drinkers were 2.53 times more likely to meet criteria for depression and binge drinkers were 2.14 times more likely to meet the criteria.[16] Mental health disorders may worsen the negative health and social consequences of drug and alcohol misuse and interfere with treatment of substance use disorders. Substance use among individuals with mental illness can lead to worsening symptoms, increased hospitalizations, and decreased medication or appointment adherence.[17] Concomitant substance-use disorder and mental illness is also associated with a greater financial burden to society. Mental health screening tools that can be used to assess patients with positive screening for alcohol use include a 2-question screen for depression[18] and a 7-item screening instrument for generalized anxiety[19] (see sidebar).

Patients with a triple diagnosis of HIV infection, substance use disorder, and mental health disorder face a number of barriers to care because they must navigate numerous healthcare settings if they are to receive treatment for all disorders. Integrated care in the HIV clinic can greatly facilitate treatment for these individuals. As stated by Soto and colleagues, "Integrated HIV care combines HIV primary care with mental health and substance abuse services into a single coordinated treatment program that simultaneously, rather than in parallel or sequential fashion, addresses the clinical complexities associated with having multiple needs and conditions."[20]

An optimal integrated care system provides such ancillary services as housing and transportation assistance and case management, in addition to providing centralized care for medical, substance use, and mental health issues. Perhaps the most important components of such a system are communication and shared decision making among collaborators involved in patient care.

Lecture presented by Dr Chander in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Chander in October 2011.

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**Dr Chander's recommended curricula, review articles, and websites.*

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Review

Safer Conception Interventions for HIV-Affected Couples: Implications for Resource-Constrained Settings

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Developing and testing safer conception methods that reduce HIV transmission to HIV-seronegative partners in serodiscordant couples and reduce superinfection in HIV-seroconcordant couples is a crucial but often unaddressed component of HIV prevention programs. Most research has focused on developed-world settings, where "high-technology" assisted reproduction techniques are used for HIV-serodiscordant couples in which the male is HIV-infected. There is a dearth of research on safer conception methods for HIV-seropositive women and "low-technology" harm-reduction strategies for HIV-affected couples, including vaginal insemination for HIV-seropositive women and natural conception methods for HIV-seroconcordant and -serodiscordant couples. This review summarizes international studies of safer conception interventions for HIV-affected couples, with a focus on feasibility in public-sector health settings where assisted reproductive technology is not readily available. Given that such low-technology options are feasible in most settings, well-designed, prospective interventions offering low-technology safer conception methods need to be developed and tested.

With the majority of those living with HIV infection being of reproductive age, conception and reproductive options for this population are important issues for health care delivery and research.[1] Despite pronouncements from local and international guideline committees about whether and how those with HIV infection should have children, HIV-seropositive individuals deserve full reproductive rights. The need to develop and test safer conception interventions involving natural conception is underscored by findings that a substantial proportion of HIV-serodiscordant couples engage in unprotected sex, regardless of "safer sex" or "safer conception" messages.

International reproductive guidelines shifted a decade ago from recommending avoidance of pregnancy to recognizing conception and parenting as realistic options for people with HIV infection and their partners.[2] Since 2001, the US Centers for Disease Control and Prevention (CDC) has encouraged information and support for HIV-affected couples who want to explore their reproductive options.[3] HIV advocacy organizations, such as the ATHENA Network and others, have pioneered reproductive rights for people with HIV infection.

No conception methods are 100% risk-free of HIV transmission, other than the use of screened fresh sperm from HIV-seronegative donors (when a woman's male partner is HIV-infected) and adoption. However, several risk-reduction methods for safer conception, in which the HIV-infected partner is on antiretroviral therapy, have been used in the developed world. These include low-technology methods such as timed, unprotected sexual intercourse for HIV-seropositive concordant couples, and vaginal insemination (ie, fresh semen from a condom or sterile cup is inserted into the vagina via a disposable pipette or syringe) for HIV-seropositive women who have HIV-seronegative partners. High-technology methods include sperm washing and intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI) for HIV-seropositive men with HIV-seronegative female partners. The use of antiretroviral drugs by the HIV-infected male partner to lower HIV in the seminal plasma to an undetectable level, and the potential use of preexposure prophylaxis (PrEP) by the HIV-seronegative partner, are other strategies for reducing the risk of HIV transmission in serodiscordant couples.

Aside from recommending expensive technologies to minimize transmission in HIV-affected couples planning to have children, best practices for counseling these couples are only recently being addressed. An increasingly crucial issue, given the high levels of HIV infection in resource-limited areas, is what harm-reduction, safer conception methods are feasible and acceptable. In a pronatal society such as South Africa, being HIV-infected is unlikely to stop people from desiring children.[4-8] Accordingly, the South African HIV Clinicians Society has published safer conception guidelines.[9] These issues are relevant

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not only in resource-limited countries, but in all settings where assisted reproduction is neither widely available nor affordable.

Several reviews on safer conception and HIV have been published,[10-14] but they have tended to focus predominantly on options for HIV-seropositive male and HIV-seronegative female couples, the serodiscordance most common in developed countries.[15] Furthermore, most reviews of safer conception interventions have been based on studies from industrialized-world contexts and do not focus on the feasibility of these interventions in resource-constrained settings. As a result, there are considerable data on the efficacy of sperm washing, but limited data on timed unprotected sex, and no available data on vaginal insemination.

Methods

This review draws on available English-language international studies of safer conception and HIV-affected couples published through October 2010. Relevant material was obtained primarily through a search of key electronic databases, including ScienceDirect, Academic Search Premier, PubMed, MEDLINE, Google Scholar, and TDNet. Key search terms included: safe conception and HIV; safer conception and HIV; HIV and assisted reproduction; and HIV and reproduction. Only articles that dealt specifically with safer conception interventions for HIV-affected couples and that reported on data from such interventions and studies were considered in this review. Commentary pieces and position papers were not included. Reference lists of all articles were also scanned for other relevant studies.

The search yielded 32 published studies that reported on data and findings from safer conception interventions. Given our focus on feasibility in the context of safer conception, in this article we concentrate primarily on reports of low-technology methods that are feasible in resource-constrained settings, including vaginal insemination for HIV-infected women and the use of natural conception methods.

Discussion

Our review of the 32 published safer conception interventions identified certain key themes and issues that recurred throughout. The discussion of these themes, as well as our general conclusions, are detailed below.

Safer Conception: Screening and Preliminary Considerations

Before any safer conception intervention, it is important, to the extent feasible with available resources, to determine that the HIV-infected person has a low viral load, a high CD4+ cell count, and no AIDS-defining symptoms. Both partners should have no sexually transmitted infections (STIs) or should be receiving treatment, and should preferably be in a stable relationship.[12] Where possible, fertility screening is also advisable—for example, semen analysis for HIV-infected men to detect asymptomatic epididymitis or azoospermia and the spinnbarkeit test of vaginal mucus in HIV-seropositive women to detect ovulation. Interventions should also be sensitive to the fact that HIV-infected women are a vulnerable group with unique psychosocial needs[16] who may face considerable pressure from male partners to get pregnant, even if they do not wish to.[17]

Another key factor to bear in mind is the prevalence of infertility problems in people with HIV infection and their concomitant low success rates with assisted reproductive technologies. Tubal infertility, pelvic inflammatory disease, ovarian dysfunction, ovarian resistance to hormonal stimulation, low pregnancy rates, and high rates of fetal death have been reported among HIV-seropositive women,[2,12,18-21] and low sperm counts among HIV-seropositive men.[22] The diminished fertility profile of HIV-seropositive women and men is further complicated by the fact that antiretroviral drug use has been inconsistently linked to fertility problems in women and men.[23] Although HIV infection does not seem to affect the course of pregnancy per se, there is conflicting and thus inconclusive evidence regarding the effects of antiretroviral therapy on obstetrical outcomes such as preterm birth, low birth weight, gestational diabetes and low Apgar score.[11,19]

Safer Conception for HIV-Seropositive Women

Relatively little research on safer conception has focused on HIV-serodiscordant couples in which the woman is HIV-infected. Ethical dilemmas in this context include the possibility of mother-to-child HIV transmission and the risk of HIV transmission to an uninfected partner.[24,25] However, with the success and increasing availability of drug regimens that prevent mother-to-child HIV transmission (PMTCT) (concurrent with safer childbirth and breastfeeding practices), the risk of mother-to-child transmission has been lowered from more than 30% to less than 1% in industrialized countries[12,14,26] and in a study conducted in South Africa was reduced to less than 3%.[27]

Recent trials of combination antiretroviral therapy during pregnancy suggest similar reductions in mother-to-child transmission.[28] Consequently, national medical societies such as the American Society of Reproductive Medicine and the American College of Obstetricians/Gynecologists have argued that it is unethical to refuse to provide safer conception services to HIV-seropositive women and their partners.[10,18] Protection of sexual and reproductive health of all people has been recognized as a fundamental human right and HIV-infected women and men have the right to choose to have children and to access nonjudgmental, high-quality sexual and reproductive health services.[29,30]

Low-technology safer conception options for HIV-seropositive women include vaginal insemination with sperm from a seronegative partner or donated sperm; however, to date, no published studies are available on this method. There are limited data on the use of high-technology assisted reproductive technologies for HIV-seropositive women, including IUI, in vitro fertilization (IVF), and ICSI.[12,20,31-34] Be-

cause of cost and potential problems in using hormone-stimulating drugs in HIV-seropositive women, it is difficult to envision these methods being widely used in any setting.[12]

There are no published studies involving vaginal insemination of HIV-infected women with an uninfected male partner's semen, and data are limited on safer conception methods for HIV-infected women more broadly. Only 6 interventions providing safer conception services for HIV-infected women have been reported to date. These studies focused solely on high-technology assisted reproduction methods and involved multidisciplinary approaches in which HIV-infected women were counseled, provided with comprehensive fertility and health screening, and assigned to high-technology IUI, IVF, or ICSI.[12,20,31-34] The few studies that have been reported were based on small samples, with no studies reporting on a series of more than 50 couples.

Natural Conception for HIV-Affected Couples: Debates and Studies

Pregnancy via natural conception is increasingly accepted as a strategy for HIV-seroconcordant couples in developed countries. Some opposition still exists in resource-constrained settings, largely because of concerns about HIV superinfection. International literature, however, reports a very low absolute level of superinfection risk, particularly in the context of antiretroviral therapy.[35]

Timed unprotected sex has thus far not been recommended by most practitioners and researchers for HIV-serodiscordant couples. A central concern is that compromising the "safer sex" message for the purpose of conception, even if only during a woman's fertile window, might have deleterious effects on condom use and public health more broadly.[36] Recently, however, there have been calls for more in-depth discussion about natural conception for HIV-serodiscordant couples.[2,11,37] There is little research on the impact of natural conception programs on rates of transmission to the uninfected partner, especially in sub-Saharan Africa where, given high HIV infection rates and high profertility norms, the need is great.

Sexual transmission rates of HIV in stable HIV-serodiscordant couples. Closely related to the debate regarding natural conception and HIV-serodiscordant couples is the question of sexual transmission rates of HIV. It has recently been argued that the risk of sexual transmission of HIV is very low when the infected partner is receiving antiretroviral therapy, has an undetectable plasma viral load, and both partners are currently free of STIs.[38] In a meta-analytic review by Attia and colleagues of 11 cohorts involving 5021 stable, heterosexual, serodiscordant couples, no transmission to the uninfected partner occurred in couples in which the HIV-infected partner was receiving antiretroviral therapy and had a viral load below 400 copies/mL.[39] Although there was zero incidence in the studies reviewed, Attia and colleagues calculate that the data are compatible with 1 transmission per 79 person-years or 1 transmission per 7900 sex acts (taking the yearly average as 100 sexual contacts).

In a study by Castilla and colleagues in which 393 stable, heterosexual, serodiscordant couples in Spain were observed over a 12-year period (1991-2003), HIV prevalence in those with an HIV-infected partner *not* receiving antiretroviral therapy was 8.6%; no cases of HIV transmission occurred in couples in which the infected partner was on antiretroviral therapy.[40] Gray and colleagues observed 174 monogamous HIV-serodiscordant Ugandan couples over a 4-year period (1994-1998) and found a transmission rate of 0.0001 per coital act at viral load below 1700 copies/mL, 0.0023 per coital act at viral load above 38,500 copies/mL, and 0.041 in couples with genital ulceration.[41] In this sample, 93% of couples reported never using condoms and cited a coital frequency of 8.9 acts per month.

A randomized placebo-controlled trial compared HIV transmission rates (over a 24-month follow-up) in heterosexual HIV-serodiscordant couples in which the HIV-infected partner initiated antiretroviral therapy (n = 349) with those who did not (n = 3032) in 7 African countries (South Africa, Botswana, Kenya, Rwanda, Tanzania, Uganda, and Zambia). A transmission rate of 0.37 (95% confidence interval [CI], 0.09-2.04) per 100 person-years for couples in which the HIV-seropositive partner had initiated antiretroviral therapy (effectively 1 HIV transmission) and a transmission rate of 2.24 (95% CI, 1.84-2.72) per 100 person-years for those not on treatment (102 transmissions) were found.[42] For couples in which the infected partner was receiving antiretroviral therapy, this was a 92% reduction in HIV transmission rate. These studies collectively point to a relatively low HIV sexual transmission rate under certain key conditions, namely stable partnerships, low plasma viral loads, the HIV-infected partner on antiretroviral therapy, and the absence of active STIs.

Studies of natural conception in HIV-serodiscordant couples. Only 3 reports have been published outlining the outcome of natural conception in HIV-serodiscordant couples. The first, published by Mandelbrot and colleagues, reviewed natural pregnancies in HIV-serodiscordant couples (in which the male was HIV-infected) at a Paris hospital over a 10-year period in the pre–antiretroviral therapy era (1986-1996).[43] The study reported on 104 pregnancies in 92 couples. Most of the HIV-seropositive men were symptom-free (13% had HIV-related symptoms), and only 21 were on antiretroviral drugs. Couples received preconception counseling and education regarding best practices for timing of sex in the ovulatory window, and genital infections were diagnosed and treated, condom use was strongly advised after pregnancy attainment, and women were tested monthly for HIV antibodies and p24 antigen.

One-third of the couples reported inconsistent or no condom use. Of the 104 pregnancies, 68 occurred as a result of unprotected sex in the ovulation window and 17 resulted from only a single act of sexual intercourse dur-

ing ovulation. Although no seroconversions were reported in the first 6 months postconception, 2 women seroconverted at 7 months of pregnancy and another 2 women seroconverted in the postpartum period. All 4 seroconversions occurred in couples who reported inconsistent condom use after conception had been achieved. According to Mandelbrot and colleagues, these findings are compatible with a seroconversion rate of 1 per 1000 episodes of sexual contact.

Yee and colleagues reported on a small series of British HIV-seropositive men and their partners attaining natural pregnancy before the introduction of potent antiretroviral therapy.[44] In this series, 14 couples achieved 19 pregnancies. One woman seroconverted during her second pregnancy. Interestingly, this study found that the only man who transmitted HIV to his female partner had a high viral load (more than 38,700 copies/mL).

A more recent study conducted by Barreiro and colleagues during the era of potent antiretroviral therapy involved a review of all natural pregnancies attained by HIV-serodiscordant couples seen in 3 clinics in Spain over a 7-year period (1998-2005).[45] Only cases in which the infected partner was on antiretroviral therapy and had an undetectable plasma viral load were included in their review. They reported that 62 serodiscordant couples, of which 22 involved an HIV-seropositive woman and 40 involved an HIV-seropositive man, achieved 76 natural pregnancies—resulting in 68 children—over this time period. No horizontal seroconversions were reported, although 1 case of vertical transmission did occur.

The need to develop feasible safer conception interventions that involve natural conception is heightened by findings that a substantial number of HIV-serodiscordant couples prefer natural conception methods and engage in unprotected sex, regardless of safer conception guidelines. In a study conducted by van der Straten and colleagues, more than two-thirds of 104 American, heterosexual, HIV-serodiscordant couples reported unprotected sex with their partner in the preceding 6 months.[46] Vandermaelen and Englert reported that 14.5% (32/221) of HIV-serodiscordant couples requesting assisted reproduction treatment in Belgium did not use condoms consistently.[37]

Ryder and colleagues studied 178 married HIV-serodiscordant couples in the Democratic Republic of Congo over a 3-year period (1987-1990) in the pre–antiretroviral therapy era, observing pregnancy rates and HIV seroincidence.[47] Couples wanting children frequently engaged in unprotected sex during the woman's perceived fertile time, which resulted in the birth of 24 children and 1 HIV seroconversion (4%; 95% CI, 0.0%-21.6%). Couples who wanted a child and practiced safer sex except during the woman's fertile period were successful in having a child.

A more recent cross-sectional study by Ezeanochie and colleagues involving 55 HIV-seropositive Nigerian women on antiretroviral therapy and married to HIV-seronegative men found that younger women (mean age, 29.8 ± 3.9 years) were statistically significantly more likely than older women (mean age, 33.6 ± 5.1 years) to choose natural conception over assisted reproduction technologies ($P = .02$).[48] Furthermore, 23 (48.9%) women reported inconsistent condom use, and 11 (23.4%) reported never using condoms after initiation of antiretroviral therapy. There was also a statistically significant difference in the consistency of condom use between those who preferred natural conception and those who preferred assisted reproduction technologies (56.8% vs. 20%, respectively; $P = .049$).

An American study reported by Van DeVanter and colleagues observed 71 heterosexual HIV-serodiscordant couples over 2 years (1990-1992) and found that women in serodiscordant relationships had a pregnancy rate (10.7 per 100 person-years) similar to women in the general population.[49] Over the 2-year period, 15 (21%) women achieved pregnancy: 9 HIV-seronegative women with an HIV-infected male partner and 6 HIV-seropositive women with an uninfected male partner. One woman, whose partner was not on antiretroviral therapy and had a CD4+ cell count below 200 cells/μL, seroconverted during the study. Even couples who participated in safer conception programs have been found to engage in natural conception. According to Semprini and colleagues, 50% of couples in whom conception via assisted reproduction fails turn to natural conception methods.[50]

Emphasizing safer sex practices after conception and throughout pregnancy should be underlined as an important component of safer conception programs. It is noteworthy that in Mandelbrot and colleagues' study of natural conception in HIV-serodiscordant couples, all 4 HIV horizontal seroconversions occurred in couples who reported unsafe sex practices during pregnancy.[43]

Using Periconception PrEP to Reduce Sexual Transmission of HIV

An important development in the implementation of safer conception services for HIV-serodiscordant couples is the use of periconception PrEP to lower the risks of HIV transmission to the uninfected partner during conception attempts. The term "PrEP-ception" has recently been coined by American researchers and clinicians to refer to the possibilities of using PrEP for safer conception.[51] Preliminary results from 2 studies reported at the 6th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Rome in July 2011 provide compelling evidence about the efficacy of PrEP in the prevention of heterosexual HIV transmission.[52,53] This adds to the results of the Preexposure Prophylaxis Initiative (IPrEx) trial that found combination tenofovir/emtricitabine to be safe and to reduce acquisition of HIV infection by 44% for HIV-seronegative men who have sex with men.[54]

The Center for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial found that the use of 1% tenofovir topical gel reduced the rate of HIV acquisition by 39% in heterosexual HIV-

seronegative women.[55] The Partners PrEP trial of 4758 HIV-serodiscordant couples in Kenya and Uganda found 62% protective efficacy among HIV-seronegative partners who took a once-daily dose of tenofovir versus placebo, and 73% protective efficacy for those taking daily tenofovir/emtricitabine versus placebo.[52] In the TDF2 PrEP trial of 1219 men and women in Botswana, once-daily tenofovir/emtricitabine had 62.6% protective efficacy compared with a placebo pill, consistent with the findings of the Partners PrEP trial.[53] Results from the HIV Prevention Trials Network (HPTN) 052 study in 9 countries provided proof-of-concept that early antiretroviral treatment of HIV-infected individuals suppressed viral replication and reduced heterosexual transmission to uninfected partners by 96% compared with delayed treatment.[56]

It is thus not surprising that the use of PrEP is rapidly gaining ground as an important component of safer conception programs for HIV-serodiscordant couples.[51,57] Although no formal results on the use of periconception PrEP were available during the period under review, preliminary (unpublished) data are available from an intervention study of periconception PrEP in HIV-serodiscordant couples (in which the male partner is HIV-seropositive), currently underway in Switzerland. These data indicate that 22 couples achieved 11 natural pregnancies (of which 50% occurred after only 3 timed intercourses) and no seroconversions occurred.[23,58] In this series, all HIV-seropositive men were receiving antiretroviral therapy and female partners were provided with a short course of PrEP with 245 mg tenofovir at 36 hours and 12 hours before couples engaged in unprotected sex.[23]

High-Technology Assisted Reproduction Techniques for HIV-Affected Couples

Most of the international research on safer conception for HIV-affected couples has concentrated on options for couples in which the man is HIV-seropositive and the woman is HIV-seronegative. Although the use of screened and confirmed HIV-seronegative donor sperm and adoption remain the only options completely free of HIV transmission risk for these couples, a strong desire for biological children makes these options untenable for many. Risk-reduction strategies for these couples include sperm washing along with IUI or sperm washing along with IVF or ICSI.

Sperm washing with intrauterine insemination. Pioneered by Semprini, clinical application of sperm washing in conjunction with IUI has been offered to HIV-serodiscordant couples in Italy since 1989.[59] Numerous studies have reported on the efficacy of sperm washing in combination with IUI in terms of pregnancy rates, live birth rates, and HIV transmission incidence.[12,22,23,31,60-68] However, evaluation of the efficacy of this safer conception strategy is limited by methodological issues, including small sample sizes, lack of standardized protocols, and nonrigorous study designs—for example, most studies reported only on retrospective data and very few used control groups.

Intracytoplasmic sperm injection. The use of ICSI—a high-technology in vitro fertilization procedure in which a single sperm is injected into an egg—is a popular assisted reproduction technique in the United States for HIV-seropositive men and their partners. Several studies reported that ICSI for HIV-serodiscordant couples in which the man is HIV-seropositive is relatively safe and efficacious.[68-79] However, a number of problems are associated with its use.[72,74] These include high cost, increased risk of multiple pregnancies,[64,68,72,73,75] and the potential use of an HIV-infected gamete.

Summary

It is crucial to introduce harm-reduction methods and safer conception methods for people with HIV infection in settings where assisted reproductive technology cannot be easily obtained. This is particularly urgent in countries like South Africa, which recently showed a decline in AIDS-related deaths from 257,000 in 2005 to 194,000 in 2010,[80] but that continues to have a high prevalence of HIV, largely because of increased longevity associated with antiretroviral therapy.[81] Whereas some studies indicate that HIV-infected individuals on antiretroviral therapy are reluctant to have children,[7] others show that use of antiretroviral therapy may increase fertility intentions and pregnancy rates,[82,83] particularly among younger people who have no biological children.[5,84,85]

Most international research on safer conception in the context of HIV infection has concentrated on options for couples in which the male partner is HIV-infected and the female partner is not, therefore focusing on high-technology methods such as sperm washing with IUI or ICSI in laboratory settings. However, these strategies are not feasible on a widespread basis in resource-constrained settings. Sperm washing with ICSI, in particular, has little, if any, justification for use even in most resource-rich conditions, let alone resource-constrained ones. Its high cost, the invasive nature of the procedure, the high number of cancelled cycles,[72,75] increased risk of multiple pregnancies,[68,72,73,75] and potential danger of using an HIV-infected gamete all mitigate the argument for use of ICSI. Furthermore, in sub-Saharan Africa, more women than men are HIV-seropositive.

The most feasible method in resource-constrained settings for HIV-serodiscordant couples in which the woman is HIV-seropositive (once the couple has been counseled and screened in line with the earlier recommendations regarding viral load, CD4+ cell count, and STIs) is vaginal insemination with an uninfected male partner's sperm during the fertile time of the woman's menstrual cycle. This involves the couple either having intercourse with a condom and then drawing out the semen into a needleless syringe and inserting it as high as possible into the vagina, or the male partner ejaculating into a sterile container and the semen being drawn up in a similar manner.

Given that neither IUI nor ICSI is feasible in resource-constrained settings and that vaginal insemination with the sperm of an HIV-seronegative male partner is highly feasible and has been found to be reasonably acceptable to both men and women,[1] this appears to be the most practical low-technology safer conception option to introduce in limited-resource settings. However, only anecdotal evidence on this method is available from resource-constrained settings, and systematic research is needed to establish pregnancy outcomes, HIV transmission risk to infants, and acceptability for couples and health care providers.

Timed, limited, unprotected sex for HIV-seroconcordant couples, and timed, unprotected sex accompanied by periconception PrEP for the HIV-seronegative female partner in serodisconcordant couples, should form part of a harm-reduction strategy to reduce exposure to HIV when planning conception in resource-limited settings. Little is known, however, about the awareness, understanding, and acceptability of low-technology, safer conception strategies among people with HIV infection. Preliminary data from a South African study demonstrated acceptability of some of these methods among HIV-affected individuals, policy-makers, and providers.[86] More generally, antiretroviral therapy roll-out needs to be enhanced in resource-constrained settings, given the protective benefits of antiretrovirals not only for the HIV-infected person but for decreasing sexual transmission to uninfected partners in serodiscordant couples who want to conceive and do not use condoms.

Conclusion

Most research has looked at the efficacy and safety of sperm washing with IUI and ICSI as assisted reproductive treatments among HIV-serodiscordant couples in which the male partner is HIV-infected. Substantial evidence points to the relative safety of these procedures, although some methodological limitations impede the evaluation and comparison of these studies. That is, most studies report on small sample sizes, use retrospective analysis, and do not include control groups. More rigorous and controlled prospective studies are therefore needed.

With the publication of safer conception guidelines in South Africa,[9] discussion is urgently needed about piloting these guidelines to further assess acceptability, preparedness of public sector health services, and feasibility in implementation. In addition, studies to determine outcomes in terms of pregnancy success rates and HIV transmission would be valuable. Avoiding HIV transmission but enabling HIV-affected couples in resource-limited settings to embark on safer childbearing is crucial in decreasing both mother-to-child HIV transmission and transmission to uninfected partners. Furthermore, failure of the health system to engage HIV-seropositive women and men in fertility management and denying safer conception services to those who want to conceive a child is unethical[1] and deprives them of a fundamental reproductive right. Most importantly, people with HIV infection require the support of health care providers in affirming their rights to make their own reproductive decisions.

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Special Contribution

2011 Update of the Drug Resistance Mutations in HIV-1

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This November 2011 edition of the IAS–USA drug resistance mutations list updates the figures last published in December 2010 (Johnson VA et al, *Top HIV Med*, 2010;18:156-163).

In this update, the format has changed to the use of **bold** type for most gene positions and corresponding amino acid substitutions. However, the substitutions for which data indicate that there is a lesser impact on susceptibility—certain mutations impacting drugs in the protease inhibitor class and those impacting the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) etravirine—are represented in plain (non-bold) type. For the protease inhibitors, the mutations are designated as "major" or "minor" (see user note **q**); for etravirine, see below.

Rilpivirine (formerly TMC278), an NNRTI studied in antiretroviral treatment–naive patients and approved by the US Food and Drug Administration (FDA) this year, has been added. Fifteen mutations in HIV-1 reverse transcriptase have been observed to date from rilpivirine-treated patients with virologic failure: K101E/P; E138A/G/K/Q/R; V179L; Y181C/I/V; H221Y; F227C; and M230I/L. There are few data available on the clinical effectiveness of rilpivirine therapy for patients harboring NNRTI-resistant viruses. As a result, all of these mutations were **bolded**. The E138K mutation, especially with M184I or V, is found most frequently in patients in whom rilpivirine is failing, and is thus marked with an asterisk (*) because the combination of E138K and M184I showed a 6.7-fold reduced phenotypic susceptibility to rilpivirine compared with a 2.8-fold reduction for E138K alone (see user note **o**).

For etravirine, the Q substitution has been added to the E138 position on the reverse transcriptase gene, based on data from updated analyses of patients in the DUET trial (Tambuyzer L et al, *JAIDS,* 2011;58:18-22). Using the etravirine-weighted genotypic scoring system, reverse transcriptase mutations at positions L100I*, K101P*, and Y181C*/I*/V* are noted with an asterisk (*) to reflect that these mutations each have the greatest impact (ie, highest weighted scores) on reduced phenotypic susceptibility and impaired clinical response compared with other etravirine mutations (see user note **n**). For this reason, only those positions with asterisks are in **bold** type.

The S substitution has been added to the K103N mutation, which is associated with clinical resistance to efavirenz and nevirapine. This addition reflects the emerging understanding of substitutions other than N at the 103 position in the reverse transcriptase gene. (Harrigan PR et al, *AIDS*, 2005;19:549-554; Zhang Z et al, *Antimicrob Agents Chemother,* 2007;51:429-437; Tambuyzer L et al, *Antivir Ther,* 2009;14:103-109).

Methods

Mutations Panel

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As with all IAS–USA volunteer panels, members are rotated on a structured, planned basis. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

In addition, the group reviews only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (US FDA) as well as any drugs available in expanded access programs are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Identification of Mutations

The mutations listed are those that have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug.

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The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance develops most commonly to lamivudine or emtricitabine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing (Hirsch MS et al, *Clin Infect Dis*, 2008;47:266-285) and 2010 IAS–USA panel recommendations for antiretroviral therapy (Thompson MA et al, *JAMA*, 2010;304[3]:321-333). Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at **resistance2011"at"iasusa.org** or by fax at 415-544-9401. Please include your name and institution.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and **no alterations in format or the content can be made**.

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which you wish to reprint the material, the funding organization(s), if applicable, and the intended audience of the publication. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of how the adapted version will be changed from the original version and, if possible, a copy of the proposed adaptation. To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted.

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(continued on page 164)

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

Multi-nRTI Resistance: 69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

M	A	▼	K	L	T	K
41	**62**	**69**	**70**	**210**	**215**	**219**
L	**V**	**Insert**	**R**	**W**	**Y** F	**Q** E

Multi-nRTI Resistance: 151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

A	V	F		F	Q
62	**75**	**77**		**116**	**151**
V	**I**	**L**		**Y**	**M**

Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	**N**	**R**	**W**	**Y** F	**Q** E

	K	L	Y	M
Abacavir[f,g]	**65**	**74**	**115**	**184**
	R	**V**	**F**	**V**
Didanosine[g,h]	**65**	**74**		
	R	**V**		
Emtricitabine	**65**			**184**
	R			**V** I
Lamivudine	**65**			**184**
	R			**V** I

	M	K	D	K	L	T	K
Stavudine[d,e,g,i,j,k]	**41**	**65**	**67**	**70**	**210**	**215**	**219**
	L	**R**	**N**	**R**	**W**	**Y** F	**Q** E

	K	K
Tenofovir[l]	**65**	**70**
	R	**E**

	M	D	K	L	T	K
Zidovudine[d,e,j,k]	**41**	**67**	**70**	**210**	**215**	**219**
	L	**N**	**R**	**W**	**Y** F	**Q** E

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,m]

	L	K	K	V	V	Y	Y	G	P
Efavirenz	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**225**
	I	**P**	**N** S	**M**	**I**	**C** I	**L**	**S** A	**H**

	V	A	L	K		V		E	V	Y		G		M
Etravirine[n]	90	98	**100**	**101**		106		138	179	**181**		190		230
	I	G	**I***	E H **P***		I		A G K Q	D F T	**C* I* V***		S A		L

	L	K	K	V	V	Y	Y	G
Nevirapine	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**
	I	**P**	**N** S	**A** M	**I**	**C** I	**C** L H	**A**

	K	E	V	Y	H	F	M
Rilpivirine[o]	**101**	**138**	**179**	**181**	**221**	**227**	**230**
	E P	**A** G **K*** Q R	**L**	**C** I V	**Y**	**C**	**I** L

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[p,q,r]

	L	G	K	L		V	L	E	M		M		G	I	F	I	D	I	I	A	G			V	I	I	N	L	I
Atazanavir +/– ritonavir[s]	10	16	20	24		32	33	34	36		46		48	**50**	53	54	60	62	64	71	73			82	**84**	85	**88**	90	93
	I	E	R	I		I	I	Q	I		I		V	L	L	L	E	V	L	V	C			A	V	V	S	M	L
	F		M				F		L		L				Y	V			M	I	S			T					M
	V		I				V		V							M			V	T	T			F					
	C		V													T				L	A			I					
																A													

	V					V	L							I			I							T	L			I		L		
Darunavir/ ritonavir[t]	11					32	33							**47**			**50**		**54**					74	**76**			**84**		89		
	I					I	F							V			V		M					P	V			V		V		
																			L													

	L					V					M	I		I			I						G		L		V		I		L		
Fosamprenavir/ ritonavir	10					32					46	47		**50**			54						73		76		82		**84**		90		
	F					I					I	V		V			L						S		V		A		V		M		
	I										L						V										F						
	R																M										S						
	V																										T						

	L		K	L		V			M		M						I				A	G	L	V	V	I			L		
Indinavir/ ritonavir[u]	10		20	24		32			36		**46**						54				71	73	76	77	**82**		**84**		90		
	I		M	I		I			I		I						V				V	S	V	I	A		V		M		
	R		R								L										T	A			F						
	V																								T						

	L		K	L		V	L				M	I		I	F	I		L		A	G	L	V	V	I			L		
Lopinavir/ ritonavir[v]	10		20	24		**32**	33				46	**47**		50	53	54		63		71	73	**76**		**82**		84		90		
	F		M	I		I	F				I	V		V	L	V		P		V	S	V		A		V		M		
	I		R								L	A				L				T				F							
	R															A								T							
	V															M								S							
																T															
																S															

	L			D			M		M								A			V	V	I	N	L
Nelfinavir[u,w]	10			**30**			36		46								71			77	82	84	88	**90**
	F			N			I		I								V			I	A	V	D	M
	I								L								T				F		S	
																					T			
																					S			

	L			L								G		I		I		A	G		V	V	I		L
Saquinavir/ ritonavir[u]	10			24								**48**		54		62		71	73		77	82	84		**90**
	I			I								V		V		V		V	S		I	A	V		M
	R													L				T				F			
	V																					S			

	L				L		M		K		M	I			I	Q		H		T			V	N	I		L	
Tipranavir/ ritonavir[x]	10				33		36		43		46	**47**			54	**58**		69		**74**			**82**	83	**84**		89	
	V				F		I		T		L	V			A	E		K		P			L	D	V		I	
							L								M			R					T					M	
							V								V													V	

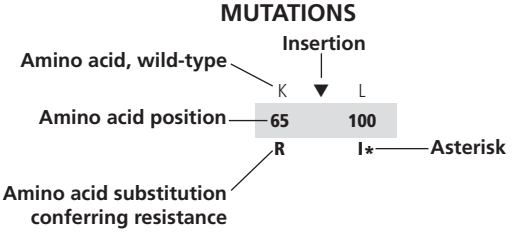
MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G	I	V	Q	Q	N	N
Enfuvirtide[y]	**36**	**37**	**38**	**39**	**40**	**42**	**43**
	D	**V**	**A**	**R**	**H**	**T**	**D**
	S		**M**				
			E				

Maraviroc[z]	See User Note

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

	E	Y	Q	N
Raltegravir[aa]	**92**	**143**	**148**	**155**
	Q	**R**	**H**	**H**
		H	**K**	
		C	**R**	



Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

User Notes

a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,[1] may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,[2] in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals,[3-7] although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals.

b. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more thymidine analogue–associated mutations (TAMs) at codons 41, 210, or 215.[8] Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

c. Tenofovir retains activity against the Q151M complex of mutations.[8]

d. Mutations known to be selected by thymidine analogues (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, termed TAMs) also confer reduced susceptibility to all approved nRTIs.[9] The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[10-13] Mutations at the C-terminal reverse transcriptase domains (amino acids 293-560) outside of regions depicted on the figure bars may prove to be important for HIV-1 drug resistance. However, to date clinical relevance of these in vitro findings has not been established[14] because the connection domain mutations arise mostly in conjunction with TAMs and M184V and do not seem to have major independent effects.[15]

e. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.[16-18]

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo.[19,20] When associated with TAMs, M184V increases abacavir resistance.[19,20]

g. As with tenofovir, the K65R mutation may be selected by didanosine, abacavir, or stavudine (particularly in patients with nonsubtype-B clades) and is associated with decreased viral susceptibility to these drugs.[19,21,22] Data are lacking on the potential negative impact of K65R on clinical response to didanosine.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[23] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[24]

i. K65R is selected frequently (4%–11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.[25,26]

j. The presence of M184V appears to delay or prevent emergence of TAMs.[27] This effect may be overcome by an accumulation of TAMs or other mutations.

k. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.[28-30] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[31,32]

l. The presence of K65R is associated with a reduced virologic response to tenofovir.[8] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[8] The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.[33-35]

m. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.[36]

n. Resistance to etravirine has been extensively studied only in the context of coadministration with darunavir/ritonavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.[37-39] Asterisks (*) are used to emphasize higher relative weights with regard to reduced susceptibility and reduced clinical response compared with other etravirine mutations.[40] The single mutations L100I*, K101P*, and Y181C*/I*/V* reduce clinical utility. The presence of K103N alone does not affect etravirine response.[41] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[42-44]

o. A total of 15 mutations (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, and M230I/L) associated with decreased susceptibility to rilpivirine have been described by in vitro studies and in patients in whom rilpivirine was failing.[45-53] These mutations differ quantitatively in their impact on resistance. E138K, especially with M184I/V, is found most frequently in patients in whom rilpivirine is failing, and is thus marked with an asterisk (*) because the combination of E138K and M184I showed 6.7-fold reduced phenotypic susceptibility to rilpivirine compared with 2.8-fold reduction for E138K alone.[45,53] The K103N substitution alone was not associated with reduced susceptibility to rilpivirine.[52,53]

p. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[54] In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

q. Resistance mutations in the protease gene are classified as "major" or "minor."

> Major mutations in the protease gene (positions in **bold** type) are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. These mutations tend to be the primary contact residues for drug binding.
>
> Minor mutations generally emerge later than major mutations and by themselves do not have a substantial effect on phenotype. They may improve replication of viruses containing major mutations. Some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades.

r. Ritonavir is not listed separately, as it is currently used only at low dose as a pharmacologic booster of other PIs.

s. Many mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I plus L76V might increase susceptibility to atazanavir when no other related mutations are present.[55]

t. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. The negative impact of the protease mutations I47V, I54M, T74P, and I84V and the positive impact of the protease mutation V82A on virologic response to darunavir/ritonavir were shown in 2 data sets independently.[56,57] Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). A median darunavir phenotypic fold-change greater than 10 (low clinical cutoff) occurs

with 3 or more of the 2007 IAS–USA mutations listed for darunavir[58] and is associated with a diminished virologic response.[59]

u. The mutations depicted on the figure bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

v. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to lopinavir/ritonavir.[60,61] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[62] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[63-65] The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to lopinavir/ritonavir.[55]

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.[66]

x. Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. The available genotypic scores have not been validated on large, diverse patient populations. The presence of mutations L24I, I50L/V, F53Y/L/W, I54L, and L76V have been associated with improved virologic response to tipranavir in some studies.[67-69]

y. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.[70-72]

z. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXC chemokine receptor 4 (CXCR4; termed dual/mixed [D/M]) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs frequently is associated with outgrowth of D/M or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism. There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted in the figure. Some CCR5 antagonist-resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3; the clinical significance of such mutations is not yet known.

aa. Raltegravir failure is associated with integrase mutations in at least 3 distinct genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/K/R, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M plus E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H plus G140S, which also confers the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this major mutation plus either L74M, E92Q, T97A, E92Q plus T97A, Y143H, G163K/R, V151I, or D232N.[73] The Y143R/H/C mutation is uncommon.[74-78] Another major mutation, E92Q, has also been described.[79-81]

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NEW HIV and Pain

Jessica S. Merlin, MD, MBA, and Rodney Tucker, MD, MMM
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Patients with HIV infection now have near-normal life expectancies, but 40% to 55% still report pain. Various comorbid conditions, including cardiovascular disease, frailty, and non–AIDS-defining malignancies, are prevalent in the HIV-infected population, which also has high rates of substance abuse. For this reason, HIV medical practitioners have become HIV primary care doctors who must address all of these issues. Dr Jessica Merlin and Dr Rodney Tucker present an approach to the treatment of pain, an underdiagnosed and undertreated condition in HIV-infected patients.

Quality Measures in HIV Care

Kathleen Clanon, MD, and Steven Bromer, MD
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Choosing a set of quality of care measures and a strategy for using them is an investment in time and resources—the resulting information can be either a powerful tool for improving care or a useless paper exercise. Dr Kathleen Clanon and Dr Steven Bromer provide guidelines and advice on selecting performance measures, determining data collection methods, and using and leveraging the eventual results to improve care.

Initiation of Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients

Greer A. Burkholder, MD
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What impact does the timing of antiretroviral therapy (ART) initiation have on the prognosis of HIV-infected patients? Dr Greer Burkholder discusses the influence of CD4+ cell count, plasma HIV RNA level, AIDS-related and non–AIDS-related comorbidities, pregnancy, and patient willingness to take lifelong medications. Because of the evolving nature of guidelines and evidence regarding timing of ART, HIV practitioners need to update their knowledge on this topic regularly.

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Dr Melissa Osborn explains how the 2 new HCV protease inhibitors, telaprevir and boceprevir—direct-acting antiviral agents that inhibit viral replication—will affect therapy for treatment-naive and treatment-experienced patients with HCV infection. Her presentation describes the effects of telaprevir and boceprevir on sustained virologic response (SVR) rates, and includes response-guided treatment algorithms.

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Steven A. Schroeder, MD and Margaret Meriwether, PhD
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