

# Topics in **HIV Medicine**<sup>®</sup>

A publication of the International AIDS Society–USA

## Perspectives

Hepatitis C and B Viruses: The New Opportunists in HIV Infection 78

*Raymond T. Chung, MD*

*Hepatitis C Virus and HIV Coinfection • Hepatitis B Virus and HIV Coinfection*

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*Michael S. Saag, MD*

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The International AIDS Society–USA

## About This Issue

This issue contains 3 *Perspective* articles based on recent presentations at International AIDS Society–USA CME activities and conferences. At the March 2006 course in New York, NY, Raymond T. Chung, MD, discussed hepatitis B and C virus coinfections with HIV. Also at the New York conference, David J. Back, PhD, reviewed important new drug-drug interactions in HIV therapeutics. This issue also offers Steven Shoptaw, PhD's insights about methamphetamine use among gay and bisexual men, initially delivered in February 2006 at the International AIDS Society–USA CME course in Los Angeles.

This issue also marks the start of something new — the *Commentary* column. In the first *Commentary*, International AIDS Society–USA board member Michael S. Saag, MD, has been invited to provide his observations about the Ryan White CARE Act reauthorization, healthcare funding, and the state of HIV and AIDS care delivery in the US. We welcome commentaries from other medical professionals to establish a dialogue about the disease as it moves beyond its 25th year.

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## Topics in HIV Medicine®

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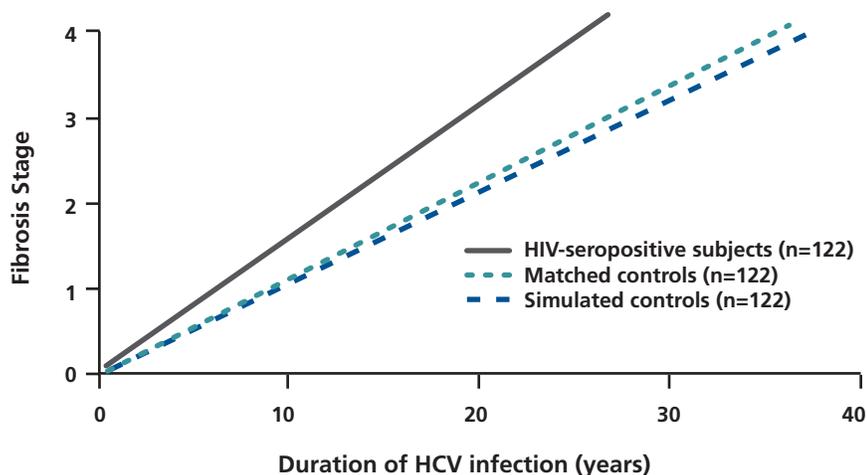


Figure 2. Effect of HIV coinfection on hepatitis C virus (HCV) fibrosis progression. Adapted from Benhamou et al, *Hepatology*, 1999.

response continued in the trial and those without response discontinued treatment. In the international APRICOT trial, patients received: (1) peg-IFN alfa-2a 180 µg weekly plus ribavirin 800 mg daily (n=289); (2) peg-IFN alfa-2a 180 µg weekly alone (n=286); or, (3) IFN –alfa-2a 3 mIU thrice weekly plus ribavirin 800 mg daily (n=285) for 48 weeks. In the French RIBAVIC trial, patients received peg-IFN alfa-2b 1.5 µg/kg/week plus ribavirin 800 mg/day (n=205) or IFN alfa-2b 3 mIU thrice weekly plus ribavirin 800 mg/day (n=207) for 48 weeks. All 3 trials assessed rates of sustained virologic response (SVR) at 72 weeks. The characteristics of the patients are listed in Table 1. Important differences include the fact that ACTG A5071 had a high proportion of African American patients; response rates in African American patients typically are markedly reduced compared with those in white patients, particularly among those with HCV genotype-1 infection. Genotype-1 infection, which is more resistant to treatment than other genotypes, was also more common in this trial. Both ACTG A5071 and the RIBAVIC trials included higher proportions of patients with bridging fibrosis or cirrhosis, factors associated with lower rates of SVR.

In ACTG A5071, SVR occurred in a significantly greater proportion of patients in the peg-IFN alfa plus rib-

avirin arm than in the IFN alfa plus ribavirin arm, 27% versus 12% ( $P = .03$ ). SVR occurred in 14% versus 6% with genotype-1 infection and in 73% versus 33% ( $P < .001$ ) with nongenotype-1 infection (Chung, *N Engl J Med*, 2004). Among virologic nonresponders, 45 of 57 in the IFN alfa plus ribavirin arm had a biopsy at 24 weeks and 16 (36%) showed histologic response. The median changes in HCV RNA were  $-0.61 \log_{10}$  IU/mL in histologic responders and  $-0.58 \log_{10}$  IU/mL in histologic nonresponders. Of 37 virologic nonresponders in the peg-IFN alfa group, 26 had a biopsy and 9 (35%) had a histologic response. The median changes in HCV RNA were  $-1.01 \log_{10}$  IU/mL in histologic responders and  $-0.71 \log_{10}$  IU/mL in histologic

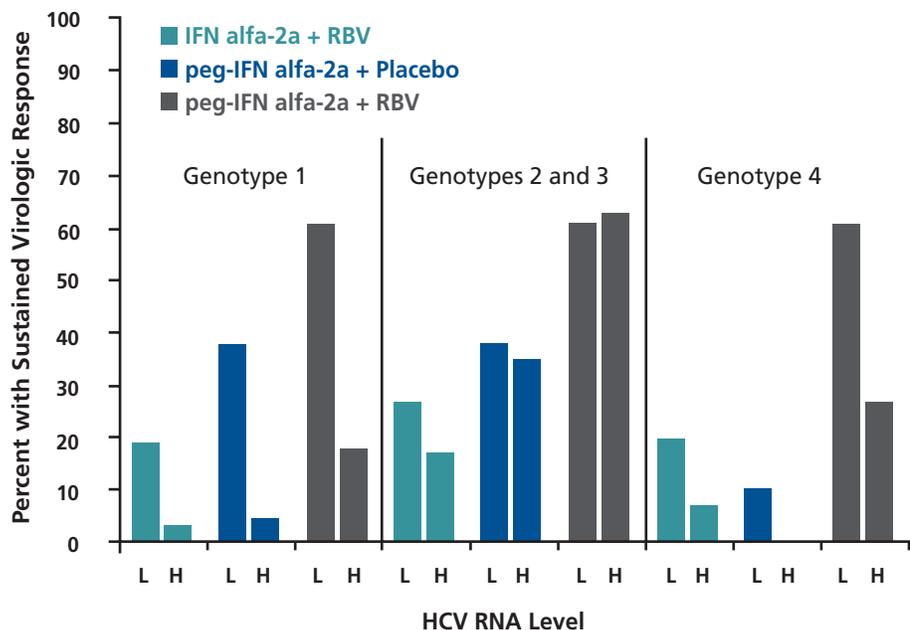
nonresponders. These latter findings suggest that clinical benefit is obtained with treatment despite the absence of SVR in a sizeable proportion of patients. Among 106 patients assessed at week 12, 43 (41%) had early virologic response (a  $2\text{-log}_{10}$  IU/mL or greater decrease in HCV RNA or conversion to HCV-seronegative status). Of these, 21 (49%) did not have SVR at 72 weeks, indicating that early response was not predictive of SVR. Of the 63 patients (59%) without early virologic response at week 12, none had SVR, indicating that absence of early response was highly predictive of absence of SVR.

In the APRICOT trial, SVR occurred in 40% of subjects in the peg-IFN alfa plus ribavirin arm, 20% of the peg-IFN alfa alone arm, and 12% of the IFN alfa plus ribavirin arm ( $P < .05$  for each peg-IFN alfa arm vs IFN alfa arm; Torriani et al, *N Engl J Med*, 2004); SVR rates were 29% ( $P < .05$  vs IFN alfa), 14%, and 7%, respectively, among those with genotype-1 infections, and 62% ( $P < .05$  vs IFN alfa), 36%, and 20%, respectively, in those with nongenotype-1 infections. Figure 3 shows SVR rates by treatment and genotype. A noteworthy finding was that among patients with genotype-1 infection, those with lower HCV RNA level ( $\leq 800,000$  IU/mL) had markedly greater rates of SVR than those with higher viral load ( $> 800,000$  IU/mL). In the peg-IFN alfa plus ribavirin group, SVR was observed in 61% of patients with lower HCV viral load. These find-

Table 1. Baseline characteristics in hepatitis C virus (HCV)/HIV-coinfected patients in 3 HCV treatment studies.

	ACTG A5071	APRICOT	RIBAVIC
White/African American (%)	48/33	79/10	Not reported
Genotype 1 or 4/2 or 3 (%)	78/22	68/32	58/42
Log <sub>10</sub> IU/mL HCV RNA	6.2	6.7	5.9
Bridging fibrosis or cirrhosis (%)	44	16	39
CD4+ count (cells/µL)	444–492	520–542	514
Antiretroviral therapy (%)	86	84	82

ACTG indicates AIDS Clinical Trials Group.



**Figure 3.** Sustained virologic response (SVR) rates by treatment, hepatitis C virus (HCV) genotype, and low (L) HCV RNA level ( $\leq 800,000$  IU/mL) or high (H) HCV RNA level ( $> 800,000$  IU/mL) in the APRICOT trial. IFN indicates interferon; peg-IFN, peginterferon; RBV, ribavirin. Adapted from Torriani et al, *N Engl J Med*, 2004.

ings suggest that HCV viral load bears prognostic information for treatment response in patients with genotype-1 infection.

In the RIBAVIC trial, SVR occurred in 27% of subjects in the peg-IFN alfa plus ribavirin arm versus 19% in the IFN alfa plus ribavirin arm ( $P < .05$ ), including rates of 15% versus 5% ( $P < .05$ ) in genotype-1 infections and 43% versus 41% in nongenotype-1 infections (Carrat et al, *JAMA*, 2004).

In all of the studies, peg-IFN alfa with ribavirin was significantly superior to standard IFN alfa with ribavirin in achieving SVR, and all studies showed that absence of early virologic response was highly predictive of absence of SVR. One potential difference among studies was the somewhat lower relapse rate among peg-IFN alfa patients in the APRICOT trial. In APRICOT, the end-of treatment (48-week) virologic response rate was 47% and the SVR rate was 40%, compared with the rates of 41% and 27%, respectively, in the ACTG trial and 37% and 27%, respectively, in the RIBAVIC trial. Differences in virologic outcomes in the trials could be related to the use of

the dose-escalation ribavirin in the ACTG trial versus the flat doses of ribavirin 800 mg used in the other trials. It is possible that patients in the ACTG trial were receiving too little ribavirin at the beginning of treatment, which may be a period crucial to virologic response. In addition, the greater proportion of African American patients in the ACTG trial likely had an impact on response rates in genotype-1 infections. It is also likely that the greater proportions of patients with bridging fibrosis or cirrhosis in the ACTG and RIBAVIC trials were associated with reduced response rates compared with response rates in the APRICOT trial. With regard to safety and tolerability, premature discontinuation rates were 12% in ACTG A5071 and 15% to 16% in the APRICOT trial, rates comparable to those observed in treatment trials in patients without HIV infection. The discontinuation rate of 31% in the RIBAVIC trial was at least partly due to psychiatric adverse effects, particularly depression, and hyperlactatemia, with the relative risk of the latter being extremely high in patients receiving didanosine. In all of the studies, abso-

lute CD4+ cell count decreased, but CD4+ percentage increased. No loss of HIV virologic control or clinical progression of HIV disease was observed. Among patients with detectable HIV RNA at entry in the APRICOT trial, a reduction in plasma HIV RNA level (0.9  $\log_{10}$  copies/mL) was observed in those receiving peg-IFN alfa but not in those receiving standard IFN alfa. In a pharmacokinetics substudy in this trial, ribavirin did not alter intracellular concentrations of the active triphosphate forms of zidovudine or stavudine. Other data reported since completion of these trials indicate that anemia associated with either zidovudine or ribavirin is worsened when the 2 are given together.

Recommendations for treating HIV/HCV coinfection are shown in Figure 4. Among patients without clinically advanced liver disease who do not yet require antiretroviral therapy or in whom HIV infection is controlled with antiretroviral therapy, the goal is to eradicate HCV using a full 48 weeks of peg-IFN alfa/ribavirin treatment. In patients with genotype-1 infection and higher HCV viral load, early discontinuation of treatment may be considered if there is no early virologic response. In patients with bridging fibrosis or cirrhosis, the goal of treatment is to delay progression. Treatment with 24 weeks of peg-IFN alfa/ribavirin or maintenance treatment should be considered. In patients with poorly controlled HIV infection and those with low CD4+ cell counts not yet receiving antiretroviral therapy, control of HIV infection is the primary objective, and anti-HCV treatment can be initiated when HIV infection is stabilized. In patients receiving antiretroviral therapy, didanosine-containing regimens should be avoided or switched, and consideration should be given to avoiding or switching zidovudine-containing regimens. Erythropoietic treatment may be considered to avoid anemia and permit optimizing of ribavirin dosing.

A mental health liaison should be in place before peg-IFN alfa treatment is initiated to assess risk for depression, and very early use of antidepressant treatment with selective serotonin

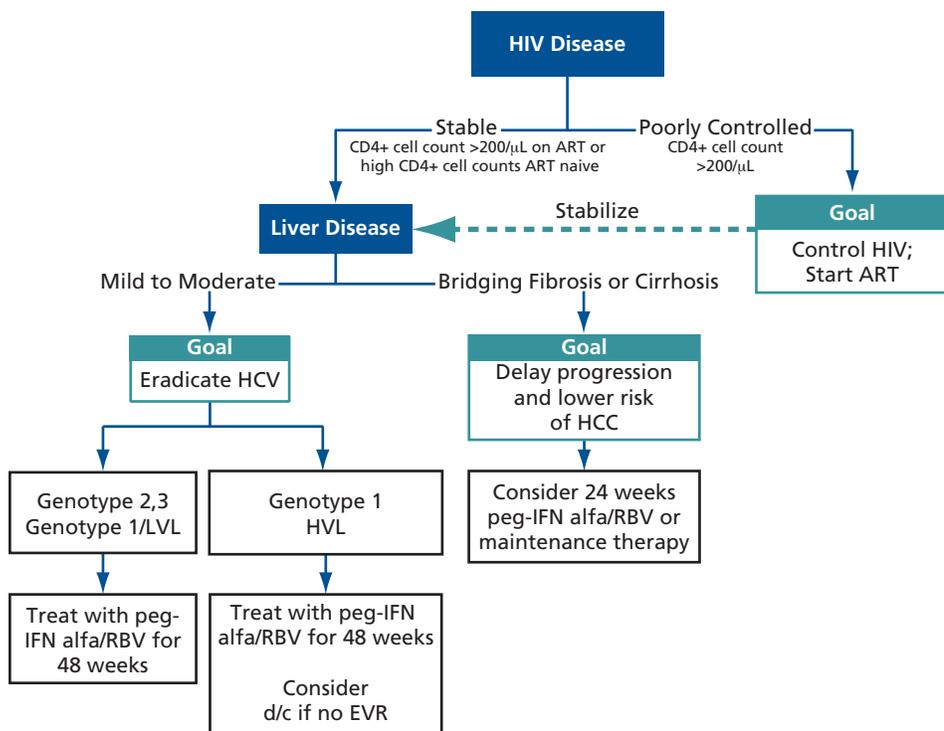


Figure 4. Management of hepatitis C virus (HCV) and HIV coinfection. ART indicates antiretroviral therapy; d/c, discontinuing therapy; EVR, early virologic response; HCC, hepatocellular carcinoma; HVL, high viral load; LVL, low viral load; peg-IFN, peginterferon; RBV, ribavirin.

reuptake inhibitors can be effective in stabilizing patients with symptoms of depression. Improvement of insulin resistance may improve response to anti-HCV therapy, since there are some data indicating that insulin resistance impairs sustained response to IFN alfa. Maintenance therapies are currently being evaluated in the ACTG 5178 trial. The ACTG 5184 trial is examining the effects of antiretroviral therapy on CD4+ and CD8+ T-cell response to HCV and assessing whether improvements in this regard result in improved SVR rates with peg-IFN alfa/ribavirin treatment. Patients include those with high CD4+ cell counts for whom initiation of antiretroviral therapy is not yet required according to current guidelines. Extended duration of treatment is being evaluated among patients in whom there is a failure to achieve early virologic responses.

Investigation of new agents for treating HCV continues, with promising early results being achieved with HCV protease inhibitors. One such agent, an inhibitor of the HCV NS3

serine protease, has been found to decrease HCV RNA by up to 4 log<sub>10</sub> IU/mL in HCV-monoinfected patients.

### Hepatitis B Virus and HIV Coinfection

The course of hepatitis B virus (HBV)-associated liver disease is also accelerated by coinfection with HIV. For example, comparison of outcomes among HIV-monoinfected, HBV-monoinfected, and HBV/HIV-coinfected patients in the Multicenter AIDS Cohort Study (MACS) reported in 2002 showed that liver-attributable mortality rates per 1000 –person-years of observation were 1.7 in HIV-seropositive patients, 0.8 in HBV surface antigen-positive (HBsAg+) patients, and 14.2 (*P* < .0001) in coinfecting patients (Thio et al, *Lancet*, 2002). The relationship between coinfection and risk was strongest in the setting of low CD4+ cell count and with treatment in the post-antiretroviral therapy treatment era.

Goals of anti-HBV treatment in both mono- and coinfection consist primari-

ly of virologic suppression, rather than clearance. All clinical improvements in the form of improved liver biochemistry, delay of cirrhosis and hepatocellular carcinoma, and reversal of histopathology, have been achieved with viral suppression alone in trials in HBV-monoinfected patients. Viral clearance in the form of conversion to HBV surface antigen-negative (HBsAg-) status, is a rare event in coinfecting patients; conversion to HBV envelope antigen-negative (HBeAg-) status is rare even in HBV-monoinfected patients. Anti-HBV therapy can also be used to prevent HBV disease flares in patients with immune reconstitution syndrome after initiating antiretroviral therapy for HIV. In addition to the original standard of lamivudine monotherapy (100 mg/d po), approved therapies for HBV monoinfection include IFN alfa-2b (5 mIU sq qd or 10 mIU tiw for 16 weeks), peg-IFN alfa-2a (180 µg/week for 48 weeks), and the newer agents adefovir dipivoxil (10 mg/d po) and entecavir (0.5-1.0 mg/d po). Factors complicating HBV therapy in coinfecting patients include the fact that lamivudine experience is nearly universal in this population, resulting in a very high rate of lamivudine resistance in HBV (approximately 90% by 4 years) accompanied by increases in HBV viral load. The high resistance rates also raise concerns about cross-resistance with other nucleoside analogue reverse transcriptase inhibitors (nRTIs) in this population. Durable beneficial outcomes of lamivudine monotherapy treatment are rarely observed in the coinfecting population, in whom treatment of lamivudine for HIV duration is often indefinite. IFN alfa is generally poorly tolerated in the coinfecting population and has limited efficacy in this setting.

The nucleotide analogues adefovir and tenofovir and the nucleoside analogue entecavir exhibit activity against both wild-type HBV and the YMDD variants resistant to lamivudine. In a study in 35 lamivudine-experienced coinfecting patients, adefovir 10 mg resulted in reductions of HBV DNA of 4.68 log<sub>10</sub> IU/mL at week 48, 5.24 log<sub>10</sub> IU/mL at week 96, and 5.90 log<sub>10</sub> IU/mL at week 144. HBeAg serocon-

version occurred in 6% of patients. Histologic improvement was observed in all 14 patients undergoing biopsy. The study dose was well tolerated; discontinuation occurred in 1 patient, due to increased serum creatinine level, with the increase resolving off treatment. A low frequency of major adefovir resistance in HBV was observed at 144 weeks; in addition, no HIV reverse transcriptase mutations were observed, a concern given the anti-HIV activity of adefovir at higher doses. These latter findings provide some hope that long-term use with this agent may be possible without prohibitive resistance (Benhamou, *J Hepatol*, 2006; Delaugerre et al, *Antimicrob Agents Chemother*, 2002). However, recent data from HBV mono-infected patients indicate that primary adefovir resistance rates increase to 18% at year 4 and to 28% at year 5 (Hadziyannis et al, AASLD 2005).

An analysis of outcome in 10 HBV/HIV-coinfected patients showed that tenofovir 300 mg/day added to pre-existing antiretroviral therapy for HIV resulted in a 4.9 log<sub>10</sub> IU/mL decrease in HBV DNA at week 24. Another analysis in 11 antiretroviral-naive coinfecting patients showed that the addition of tenofovir 300 mg to the backbone of lamivudine/efavirenz produced a 4.7-log<sub>10</sub> IU/mL decrease in HBV DNA at 48 weeks in 5 patients, compared with a 3.0-log<sub>10</sub> IU/mL decrease and development of YMDD mutants in 4 of 6 patients in whom stavudine was combined with lamivudine/efavirenz. The ACTG 5127 trial showed that tenofovir was noninferior to adefovir in the treatment of lamivudine-resistant HBV in coinfecting patients, with HBV DNA being reduced by 4.4 log<sub>10</sub> IU/mL in the tenofovir group and 3.2 log<sub>10</sub> IU/mL in the adefovir group. In a study in France in a coinfecting population, 80% of whom had received lamivudine, tenofovir reduced HBV DNA by 4.56 log<sub>10</sub> IU/mL in 52 HBeAg+ patients, with 30% having undetectable levels (<200 IU/mL), and by 2.53 log<sub>10</sub> IU/mL in 13 HBeAg- patients, with 82% having undetectable levels (Dore et al, *J Infect Dis*,

2004; Peters et al, CROI 2005; Benhamou et al, *Hepatology*, 2006).

Entecavir is approved for treatment of HBeAg+, HBeAg-, and lamivudine-resistant HBV infection, and has no activity against HIV reverse transcriptase. In a study in patients with HBV mono-infection, entecavir 0.5 mg reduced HBV DNA by 6.98 log<sub>10</sub> IU/mL at 48 weeks, compared with a 5.48-log<sub>10</sub> IU/mL reduction with lamivudine 100 mg. In a randomized trial in lamivudine-experienced coinfecting patients, the addition of entecavir 1.0 mg to lamivudine produced a 3.66 log<sub>10</sub> IU/mL decrease in HBV DNA at week 24 compared with no change in patients with placebo added to lamivudine. There is a lower threshold for entecavir resistance in patients with pre-existing lamivudine resistance; in the current study, mutations associated with entecavir resistance were found in 2 (4%) of 48 patients but no phenotypic evidence of resistance was observed at 48 weeks (Pessoa et al, CROI, 2005; Colonna et al, CROI, 2006. See also Chang et al, *N Engl J Med*, 2006 and Lai et al, *N Engl J Med*, 2006).

Management of HBV/HIV coinfection should include assessment of HBV status in all patients prior to the initiation of antiretroviral therapy for HIV. For patients on antiretroviral therapy for HIV that includes lamivudine, a reasonable approach is the addition of an anti-HBV agent with robust activity, such as tenofovir 300 mg. In patients who have not started antiretroviral therapy for HIV and who have replicative HBV, institution of antiretroviral therapy containing tenofovir plus lamivudine or emtricitabine is a recommended approach to provide coverage for both HBV and HIV. For those in whom antiretroviral therapy for HIV can be deferred, use of agents without crossover anti-HIV activity or that pose less risk for the emergence of HIV resistance is preferable, with adefovir 10 mg and entecavir 1 mg being reasonable choices. Development of effective combination therapies will be necessary to minimize development of resistance during longer-term therapy.

Presented by Raymond T. Chung, MD, in March 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Chung in June 2006.

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## Suggested Reading

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**Perspective****Methamphetamine Use in Urban Gay and Bisexual Populations**

*It is estimated that the use of methamphetamine is 5- to 10-times more common in urban gay and bisexual men than in the general US population. Given its effects in stimulating energy, confidence, and libido, as well as its relative inexpensiveness, the drug can efficiently address serious problems in functioning among HIV-infected men, who may suffer significant symptoms of depression or fatigue associated with chronic illness and HIV-related drug treatments. Long-term methamphetamine use is associated with physical, psychologic, and social adverse effects. Increased use of the drug associates with more frequent sexual risk behaviors and increased risks for HIV transmission. Behavioral therapies, notably the approach of contingency management, are being investigated for reducing methamphetamine use and risk behaviors in the urban gay population. This article summarizes a presentation made by Steven Shoptaw, PhD, at the International AIDS Society–USA course in Los Angeles in February, 2006.*

Methamphetamine is a long-acting stimulant. It goes by various street names, including crystal, tina, speed, and crank. It can be injected, insufflated (snorted), smoked (eg, by heating on aluminum foil and inhaling the vapor through a pen or straw), taken orally, or taken via “booty-bump” (anal insertion). Methamphetamine comes in forms that can range from a powder that can be white, yellow, orange, pink, or brown (depending on the chemicals used in processing and the expertise of the “cook”) to an “ice” form consisting of high-purity methamphetamine crystals or coarse powder that is translucent to white, sometimes with a green, blue, or pink tinge. In general, the purity of methamphetamine on the street is very high, with coloring having little to do with potency of the drug.

Methamphetamine has a half-life of 9 to 12 hours, is inexpensive (approximately \$25–\$50 per gram), and is used by many different groups, including gay and bisexual men, blue-collar heterosexuals, and youth. There is an especially high prevalence of use in urban gay and bisexual men, estimated at 5- to 10-times that in the general

population. Data from San Francisco and Los Angeles indicate methamphetamine use within the prior 6 months in 13% and 11%, respectively, of gay men (Stall et al, *Addiction*, 2001).

**Physical and Psychologic Effects of Methamphetamine**

Acute physical and psychologic effects and chronic physical effects of methamphetamine use are listed in Table 1. Medical complications associated with use include: tachycardia, hypertension, tachypnea, hyperthermia, and central nervous system (CNS) excitation; rhabdomyolysis and cardiovascular events, including myocardial infarction and stroke, especially in young patients (29–45 years of age); impairment of CD8+ T-lymphocyte function; and acute pulmonary hypertension associated with smoking the drug. Methamphetamine use is also associated with “meth mouth;” this rotting of the teeth around the gums is related to neglect, xerostomia, decreased fluid intake and intake of high-sugar drinks, characteristics of the drug itself that result in shrinking of the gingival tissue, and bruxism.

Methamphetamine use in gay men is rarely casual, and the Diagnostic

**Table 1.** Acute Physical and Psychologic Effects and Chronic Physical Effects of Methamphetamine Use (see Peck et al, *J Addict Dis*, 2005).

**Acute physical effects***Increases*

- Heart rate
- Blood pressure
- Pupil size
- Respiration
- Sensory acuity
- Energy

*Decreases*

- Appetite
- Sleep
- Reaction time

**Acute psychologic effects***Increases*

- Confidence
- Alertness
- Mood
- Sex drive
- Energy
- Talkativeness

*Decreases*

- Boredom
- Loneliness
- Timidity

**Chronic physical effects**

- Tremor
- Weakness
- Dry mouth
- Weight loss
- Cough
- Sinus infection
- Sweating
- Burned lips; sore nose
- Oily skin/complexion
- Headaches
- Diarrhea
- Anorexia

and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for dependence or abuse should be applied to determine the extent of the use problem once it is identified (Table 2). The acute physical

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and psychologic effects of methamphetamine, as well as its relative inaccessibility and availability, make it easy to understand why this drug has practical value for addressing serious problems in functioning among HIV-infected men. Increased energy, confidence, and libido and improved mood are desirable, particularly among individuals who may be wrestling with the consequences of having a chronic illness such as HIV disease and who may therefore be socially withdrawn or depressed, or those who are suffering from drug treatment-related fatigue or other adverse effects of HIV drug therapy. However, there is often a high price exacted for these “benefits.” In addition to the chronic physical effects and complications noted above, the dangers of use include significant risk for psychosis (risk that may persist for years after drug use has stopped), depression, violence, family and social disruptions, and criminal activity. Among men who have sex with men (MSM), methamphetamine abuse increases the likelihood of infection with HIV; in those infected with HIV, it may exacerbate neurotoxicity and other pathologic processes common to HIV infection and complicate the treatment of infection. Methamphetamine use, HIV infection, and HCV infection are each associated with neurocognitive functioning deficits, with additive deficits being found when the conditions are present together. Methamphetamine use also frequently occurs in tandem with the use of poppers (amyl nitrite), which has been independently implicated as a risk factor for transmission of sexually transmitted infections, such as HIV (including resistant virus) and HCV.

Methamphetamine is metabolized by the cytochrome P450 (CYP) 2D6 isoenzyme. It needs to be emphasized that the effect of the HIV protease inhibitor (PI) ritonavir on prolonging the methamphetamine high is well recognized on the street. PIs generally are metabolized via CYP3A4, but ritonavir also affects CYP2D6 and has been shown to increase levels of both methamphetamine and 3,4-methylenedioxy-N-methylamphetamine (MDMA, or ecstasy) by 3- to

**Table 2. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Criteria for Drug Abuse and Dependence**

**Abuse**

Maladaptive pattern of use, clinically significant impairment or distress, and more than 1 of the following in the same 12-month period:

1. Failure to fulfill major role obligations
2. Use in physically hazardous situations
3. Recurrent legal problems
4. Continued use despite social and interpersonal problems

**Dependence**

Maladaptive pattern of use, clinically significant impairment or distress, and more than 3 of the following in the same 12-month period:

1. Tolerance
2. Withdrawal
3. Used for longer periods than intended
4. Inability to cut down or quit
5. Time spent getting, using, or recovering from drug
6. Decreased involvement in social, work, or recreation activities
7. Continued use despite knowledge of negative consequences

*Adapted from the Diagnostic and Statistical Manual of Mental Disorders, 2000.*

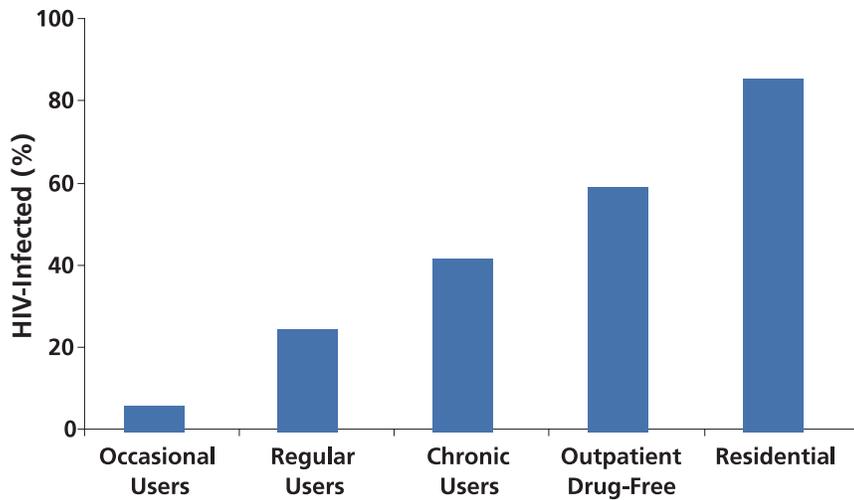
10-fold. A few overdose deaths have been reported in HIV-infected patients using methamphetamine or MDMA, and all have occurred in patients taking ritonavir. The nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) delavirdine also is partially metabolized via CYP2D6, and would be expected to slow metabolism of methamphetamine and MDMA. The risk of methamphetamine toxicity is increased in the approximately 3% to 10% of the white population that has a polymorphism in the CYP2D6 gene.

**Methamphetamine Use and HIV Risk**

Data on methamphetamine use and prevalence of HIV infection among gay men suggest a time-to-response phenomenon, in which the longer or more heavily involved individuals are in using methamphetamine, the more likely they are to be HIV infected. As shown in Figure 1, a study in the Los Angeles area shows that the prevalence of HIV infection increases in a stepwise fashion from approximately 10% in occasional methamphetamine users, to more than 20% of regular users, more than 40% of chronic users,

60% of men in outpatient drug-free treatment, and 86% of men in a gay-specific social model recovery house (Reback, Report from the City of Los Angeles, AIDS Coordinator, 1997; Shoptaw et al, *Drug Alcohol Depend*, 2005). The increased risk of HIV infection with methamphetamine use is attributable to increased sexual risk behaviors. Some idea of the sexual disinhibition associated with methamphetamine use is provided by a study in a population of methamphetamine-abusing heterosexual men and women in San Diego (Semple et al, *Addict Behav*, 2004). In this population, the average number of episodes of vaginal sex within the past 30 days was 20, compared with a national average of 6 to 7 in the general population, and the average number of sex partners in the past 60 days was 11, compared with 1 to 2 in the general population.

Project EXPLORE in San Francisco found that at baseline among 736 initially HIV-seronegative gay men followed up for risk behaviors, approximately 35% had used poppers, approximately 20% cocaine, and approximately 25% methamphetamine within the prior 60 days (Colfax et al, *Curr HIV/AIDS*, 2005). Logistic regression analysis among 386



**Figure 1.** Prevalence of HIV infection in different samples of men who have sex with men who report levels of methamphetamine use that range from occasional use to severe addiction. Data provided by S. Shoptaw.

participants, yielded odds ratios (ORs) for HIV-serodiscordant unprotected anal sex of 1.5 (95% confidence interval [CI], 1.1–1.9) for those using 1 of these drugs less than 1 week out of the month, 3.2 (CI, 2.2–4.7) for 2 drugs less than 1 week out of the month, 2.8 (CI, 1.6–4.9) for 3 drugs less than 1 week in the month, and 2.2 (CI, 1.5–3.4) for at least 1 drug used weekly. In a treatment study in methamphetamine-abusing MSM in Los Angeles, significant univariate predictors of HIV-seropositive status included prior treatment for methamphetamine use (OR, 4.3;  $P = .0006$ ), as well as unprotected receptive anal intercourse (OR, 3.5;  $P = .0046$ ), history of sexually transmitted diseases (OR, 1.5;  $P = .0047$ ), suicidal or homicidal ideation at admission (OR, 6.5;  $P = .0057$ ), and positive health insurance status (OR, 3.0;  $P = .0060$ ; Peck et al, *Addict Dis*, 2005).

### Intervention in Methamphetamine Use

Given the high prevalence of methamphetamine use in urban gay men, any clinical practice in such a setting should establish a routine for assessing methamphetamine use. Use of the 5 “A”s—Ask, Assess, Advise, Assist, and Arrange—is part of good practice in helping patients to stop any kind of

substance abuse. For methamphetamine use, in particular, it is useful to ask *all* patients in such a setting the question: “How much methamphetamine have you used since your last visit?”

Behavioral treatments can have a dramatic effect on methamphetamine use (Shoptaw et al, *Drug Alcohol Depend*, 2005). One such treatment is that of contingency management, a behavioral therapy that shapes behavior change by the provision of immediate reinforcements when the desired behavior is produced. Contingency management strategies validated for use with stimulant abusers typically provide vouchers of increasing value for provision of successive methamphetamine-free urine samples. Vouchers are then exchanged for goods or services that promote a drug-free lifestyle (see Higgins et al, *Am J Psychiatry*, 1993). In an intervention study of 162 treatment-seeking methamphetamine-abusing gay men, contingency management resulted in significantly longer retention in treatment, significantly more drug-free urine samples, and significantly longer stretches of consecutive clean urine samples (Shoptaw et al, *Drug Alcohol Depend*, 2005). The study also showed that provision of this and other behavioral drug-abuse treatments resulted in

prompt and sustained reductions in unprotected receptive and insertive anal intercourse (Figure 2). This type of sustained risk reduction is a rare finding in HIV prevention trials. Based on these results, contingency management was adopted into a San Francisco public health initiative called Positive Reinforcement Opportunity Project in an attempt to extend these benefits into the methamphetamine-abusing population not actively seeking drug-abuse treatment. The program permitted access to the intervention in nontraditional settings and, in effect, allowed individuals who were not necessarily interested in seeking help to nevertheless be linked into treatment. The program found that contingency management helped about half of MSM to reduce or eliminate methamphetamine use.

Currently, there are no effective pharmacologic methods available for treating methamphetamine abuse. Modafinil is a nonamphetamine-type stimulant that has shown some promise in treating fatigue in HIV-infected individuals. The drug has some favorable characteristics, including promoting wakefulness (it is currently approved for treating narcolepsy), improving cognitive function, and being only a mild inducer of CYP; it is a schedule IV drug with what is believed to be a low abuse potential. In a small study in HIV-infected individuals, modafinil reduced fatigue, reduced depression, and improved neuropsychologic functioning (memory, speed of processing, and executive function) and was associated with only mild side effects (Rabkin et al, *J Clin Psychiatry*, 2004). The National Institute on Drug Abuse is interested in assessing this drug as a treatment for methamphetamine abuse in HIV-seropositive patients, and is currently performing a phase II trial of the drug in patients with cocaine dependence. It would also be reasonable to evaluate the drug in the treatment of methamphetamine abuse in HIV-seronegative individuals. Other potential candidates for treating methamphetamine abuse

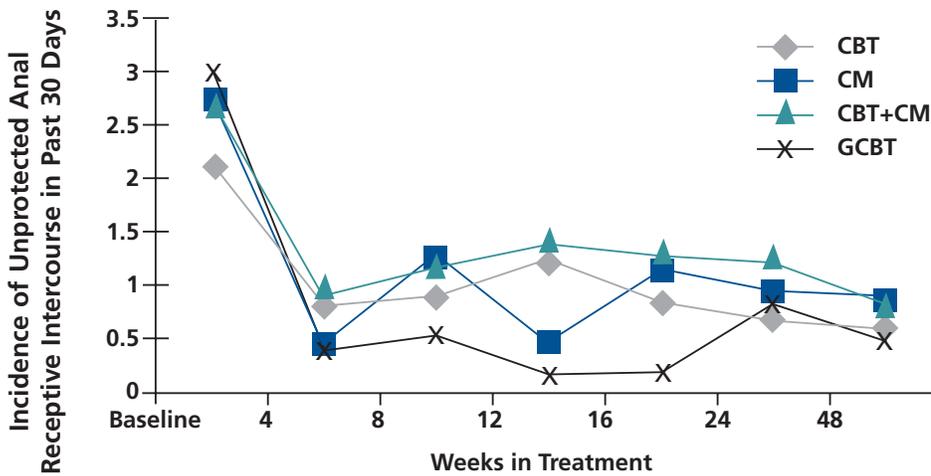


Figure 2. Sustained reduction in unprotected anal receptive intercourse among men who have sex with men receiving treatment for methamphetamine abuse. CBT indicates cognitive behavioral therapy; CM, contingency management; GCBT, group CBT.  $\chi^2_{(3)}=6.75$ ;  $P<.01$ . Adapted from Shoptaw et al, *Drug Alcohol Depend*, 2005.

include bupropion, which showed borderline effectiveness in reducing methamphetamine use in a recent phase II trial (Elkashef, *The Methamphetamine Menace*, 2005).

### Summary

Methamphetamine use is very common in urban populations of MSM, and increased use is associated with increased risks of numerous adverse health consequences and increased prevalence of sexual risk behaviors for HIV transmission. Methamphetamine is a highly functional drug in this population, producing increased energy, confidence, and libido; for those with HIV infection, it helps the individual to temporarily forget about HIV infection, to feel powerful and attractive in his body and to reduce fatigue associated with chronic illness and HIV medications. Given the high prevalence of methamphetamine use among MSM, it is wise to screen all gay and bisexual patients in care settings for methamphetamine use at each clinic visit. At the very least, each contact with MSM should contain a brief intervention that includes a strongly worded message about the need to not start or to discontinue methamphetamine use that includes support and information for not starting or for quitting. Be-

havioral interventions, including contingency management, are successful in producing sustained reduction in methamphetamine use and HIV risk behaviors (Shoptaw et al, *Drug Alcohol Depend*, 2005). Investigation is underway to identify drug treatments that may help in reducing methamphetamine use.

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## Perspective

# Drug-Drug Interactions that Matter

*It is increasingly difficult to keep track of information on drug-drug interactions in HIV therapeutics, and the clinical implications of much of the data reported are not immediately evident. Nevertheless, knowledge of drug-drug interactions is necessary to preserve antiretroviral efficacy and to avoid undue risk of toxicity. The following article reviews important drug-drug interactions and accumulating data on newer antiretroviral agents. The article summarizes a presentation made by David J. Back, PhD, at the International AIDS Society–USA course in New York in March 2006*

Data on drug-drug interactions in HIV therapeutics continue to accumulate at a rapid pace. The clinical significance of such information, however, is not always clear. Some of the reported information is contradictory or counter-intuitive. Further, it is not always easy to determine whether interactions affect the balance between antiretroviral activity and the risk for drug-related adverse effects. The matter is also complicated by the wide inter-individual variability in drug pharmacokinetics; differences between individual patients can depend on such factors as genetic differences, sex, inherent variability in drug formulations, drug-food interactions, and drug-disease interactions. Despite the complexities, potential drug interactions must be considered when starting or changing anti-retroviral therapy. In general, medications with the lowest potential for interactions should be selected for use. Good resources on HIV pharmacology include the following Web sites: [www.hivdruginteractions.org](http://www.hivdruginteractions.org); [www.tthhivclinic.com](http://www.tthhivclinic.com); <http://hivinsite.ucsf.edu>; [www.hivpharmacology.com](http://www.hivpharmacology.com); and <http://clinicaloptions.com>.

### Some Key Antiretroviral Drug Interactions

Some key interactions of protease inhibitors (PIs) with other PIs or non-nucleoside analogue reverse tran-

scriptase inhibitors (NNRTIs) are shown in Table 1. As shown, the combination of tipranavir and lopinavir is not recommended due to a marked decrease in lopinavir exposure. However, a recent small study examined whether increasing lopinavir doses might overcome this effect (Harris et al, CROI, 2006). In this study, 13 HIV-infected patients receiving ritonavir-boosted (r) lopinavir 400 mg/100 mg twice daily and no other PIs or NNRTIs were given tipranavir 500 mg twice daily and either (1) lopinavir/r 400 mg/300 mg twice daily

or (2) lopinavir/r 533 mg/233 mg twice daily. At 14 days, neither group had lopinavir trough concentrations different from those prior to the addition of tipranavir and dose changes; however, there was marked interpatient variability in these concentrations (Figure 1). Such findings suggest that the combination should be considered only if TDM is used to guide dosing in individual patients.

In fact, tipranavir/r is likely to have a somewhat complicated interaction profile because it affects levels of other drugs via more than 1 mechanism. With coadministered PIs, the effect of tipranavir/r is likely mediated to a large extent by an inducing effect on P-glycoprotein and possibly other transporter molecules. With other drugs, the net *in vivo* effect of tipranavir/r is inhibition of cytochrome P450 (CYP) 3A4, as a result of ritonavir inhibiting this enzyme (ie, the inhibition by ritonavir is greater than

**Table 1.** Selected Key Protease Inhibitor-Protease Inhibitor and Protease Inhibitor-Nonnucleoside Analogue Reverse Transcriptase Inhibitor Interactions

Regimen	Drug Concentration		Comment
Lopinavir/r + Saquinavir	Lopinavir ↔	Saquinavir ↔	N
Lopinavir/r + Fosamprenavir	Lopinavir ↓	Fosamprenavir ↓	C
Lopinavir/r + Indinavir	Lopinavir ↔	Indinavir ↔	N
Lopinavir/r + Atazanavir	Lopinavir ↔	Atazanavir ↔	N
Saquinavir/r + Atazanavir	Saquinavir ↑	Atazanavir ↔	N
Saquinavir/r + Fosamprenavir	Saquinavir ↓	Fosamprenavir ↔	D
Tipranavir/r + Lopinavir, Saquinavir or Amprenavir	Lopinavir, Saquinavir, Amprenavir ↓	Tipranavir ↔	C
Lopinavir/r + Nevirapine	Lopinavir ↓	Nevirapine ↔	D
Lopinavir/r + Efavirenz	Lopinavir ↓	Efavirenz ↔	D
Saquinavir/r + Efavirenz	Saquinavir ↔	Efavirenz ↔	N
Atazanavir/r + Efavirenz	Atazanavir ↓	Efavirenz ↔	D

C indicates combination not recommended; D, dose adjustment needed; N, no clinically relevant interactions; r, low-dose ritonavir

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

Dr Back is a Professor of Pharmacology at the University of Liverpool.

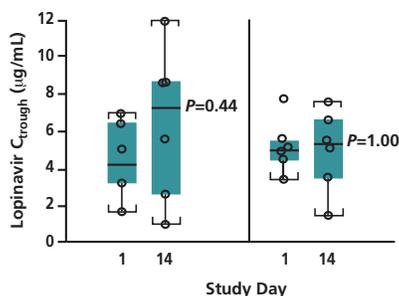


Figure 1. Trough lopinavir concentrations in patients on lopinavir/ritonavir 400 mg/100 mg (and no other protease inhibitors or nonnucleoside reverse transcriptase inhibitors) before (day 1) and after 14 days of tipranavir 500 mg bid and either lopinavir/ritonavir 400 mg/300 mg bid (group A, left) or lopinavir/ritonavir 533 mg/233 mg bid (group B, right). Adapted from data in Harris et al, CROI, 2006.

the effect of tipranavir. As an inhibitor of CYP3A4, tipranavir/r increases rifabutin area under the concentration-time curve (AUC) 2.9-fold, increases the AUC of the rifabutin active metabolite 20-fold, and increases atorvastatin AUC 9-fold (van Heeswijk, ICAAC, 2004; van Heeswijk et al, International Workshop on Clinical Pharmacology in HIV Therapy, 2004). Given the numerous potential drug interactions with tipranavir/r, it should be used with caution when its potential effects in combination are not known.

Effects of tipranavir/r and other boosted PIs on AUCs of other commonly used drugs are shown in Table 2; similar effects among the PIs are highlighted. Differences include the effects of acid-reducing agents on the levels of PIs. It is of interest that the increased AUC of the nucleotide analogue reverse transcriptase inhibitor (nRTI) tenofovir with boosted PIs was an unexpected effect, with the mechanism remaining unclear. Increases in tenofovir AUC or trough concentrations have been observed with saquinavir/r and the PI darunavir (TMC 114; approved by the US Food and Drug Administration in June 2006)/r, but fosamprenavir/r does not appear to affect tenofovir trough levels. The clinical relevance of the increase in tenofovir exposure, and of the apparent differ-

Table 2. Effect of Boosted Protease Inhibitors on Area Under the Curve (AUC) of Other Drugs\*

Drug	Change in AUC in presence of:		
	Lopinavir/r	Tipranavir/r	Atazanavir/r (Atazanavir)
Rifabutin	↑3-fold	↑3-fold	(↑2.5-fold)
Atorvastatin	↑5.9-fold	↑9.4-fold	NR
Tenofovir	↑30%	↑20%	↑45%
Clarithromycin	77%	↑20%	(↑94%)
Abacavir	NR↔	↓40%	(↔)
Zidovudine	NR↔	↓35%	(↔)
Acid Reducing Agents	↔	↓30%	↓80%
Ethinylestradiol	↓42%	↓45%	(↑48%)
Methadone	↓42%	↓50%	(↔)
Loperamide	NR↓	↓50%	↔

\*Acid-reducing agent effect on protease inhibitors. NR, not reported; r, low-dose ritonavir.

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

ences in effect in this regard among PIs, also remains unclear.

In relation to combinations of tipranavir/r with NNRTIs, available data indicate no significant interactions with efavirenz or nevirapine. However, a recent study of tipranavir/r in combination with the investigational NNRTI etravirine (TMC125) in volunteers showed that etravirine exposure was reduced by 76% and tipranavir and ritonavir exposures were increased by 18% and 23%, respectively (Scholler et al, CROI, 2006). These findings suggest that etravirine and tipranavir/r should not be used together.

With regard to some newer agents, the PI darunavir does not appear to have clinically relevant interactions with atazanavir, tenofovir, omeprazole, or ranitidine, but does exhibit a significant interaction with atorvastatin that requires dose modification. (See Table 3.) A study of darunavir and etravirine in combination in HIV-infected subjects with 3-class antiretroviral drug resistance showed no significant pharmacokinetic interaction between the 2 (Boffito et al, CROI, 2006). The investigational CCR5 antagonist maraviroc (UK427,857) is metabolized via CYP3A4. The maraviroc AUC is

increased 4.9-fold with atazanavir/r (3.6-fold with atazanavir), 3.8-fold with lopinavir/r, 2.5-fold with lopinavir/r plus efavirenz, 8.3-fold with saquinavir/r (4.3-fold with saquinavir), 5-fold with saquinavir/r plus efavirenz, 2.6-fold with ritonavir, and 5-fold with ketoconazole. The maraviroc AUC is

Table 3. Drug Interactions with the Protease Inhibitor Darunavir

Drug Concentration	Darunavir	Comment
Atazanavir ↔	Darunavir ↔	N
Tenofovir 22% ↑	Darunavir 21% ↑	N
Atorvastatin Marked Interaction	Darunavir No Data	D
Omeprazole	Darunavir ↔	N
Ranitidine	Darunavir ↔	N

D indicates dose adjustment needed; N, no clinically relevant interactions. Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

**Table 4.** Effects of Various Boosting Agents on Saquinavir, Amprenavir, and Indinavir

Boosting Agent	Change in AUC in presence of:		
	Saquinavir	Amprenavir	Indinavir
Cimetidine	120%↑	ND	↔
Grapefruit juice	50%↑	↔	↔
Ketoconazole	70%↑	31%↑	62%↑
Itraconazole	28%↑	ND	↔
Fluconazole	50%↑	ND	25%↓
Clarithromycin	187%↑	18%↑	20%↑
Erythromycin	100%↑	ND	ND
Delavirdine	120%↑	300%↑	70%↑
Atazanavir	*	80%	ND
Ritonavir	400%-1000%↑	100%-200%↑	270%-400%↑

\*Atazanavir 400 mg gives up to 50% of the boost given by ritonavir 100 mg. ND indicates no data.

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

decreased by 50% with efavirenz alone and by 70% with rifampicin. No change in maraviroc exposure has been observed with coadministration with nevirapine or tipranavir/r.

### Is There An Alternative To Ritonavir For PI Boosting?

None of the other drugs that have been examined as potential PI boosters provides the same magnitude of effect as ritonavir (Table 4). The potential for atazanavir boosting of saquinavir was recently assessed in a crossover trial in which healthy subjects received twice-daily saquinavir/r

1000 mg/100 mg, saquinavir/atazanavir 1000 mg/200 mg, or saquinavir/atazanavir 1500 mg/200 mg (King et al, CROI, 2006). Saquinavir concentrations over 12 hours following dosing on day 10 were markedly higher with ritonavir 100 mg than with atazanavir boosting (Figure 2); it was also found that saquinavir concentrations at the higher atazanavir-boosted saquinavir dose were lower than those at the lower atazanavir-boosted saquinavir dose. Another recently reported crossover trial assessed atazanavir 400 mg, fosamprenavir 1400 mg, and the combination in 21 HIV-seronegative subjects (Clay et al, CROI, 2006). When the drugs were given alone, AUCs were

17.9  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 21.7  $\mu\text{g}\cdot\text{h}/\text{mL}$  for atazanavir and amprenavir, respectively, compared with 11.9  $\mu\text{g}\cdot\text{h}/\text{mL}$  (33% decrease) for atazanavir and 38  $\mu\text{g}\cdot\text{h}/\text{mL}$  (78% increase) for amprenavir when the drugs were given together. Combined treatment decreased atazanavir minimum concentrations by 0.06  $\mu\text{g}/\text{mL}$  to 0.14  $\mu\text{g}/\text{mL}$  and increased amprenavir minimum concentrations by 0.06  $\mu\text{g}/\text{mL}$  to 0.23  $\mu\text{g}/\text{mL}$ .

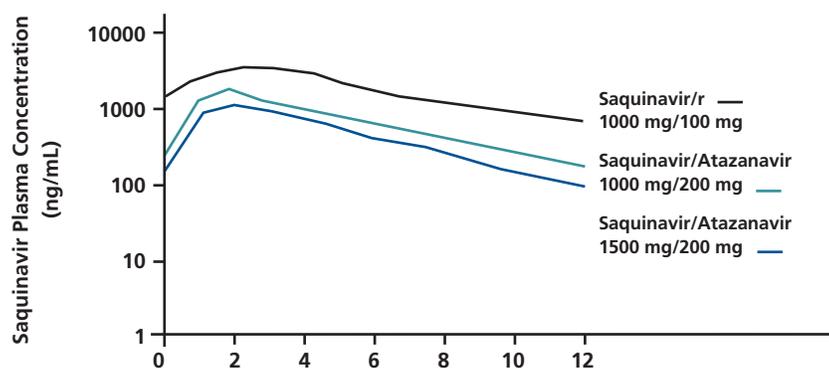
## Other Important Interactions

### Acid-Reducing Agents

Interactions between acid-reducing agents (ARAs) and PIs are shown in Table 5. It should be noted that there may be differences in potency among agents within each class of ARA that can result in different magnitudes of effect on PI exposure. Concomitant use of proton pump inhibitors and indinavir should be avoided. There are data suggesting that concomitant use of atazanavir and H<sub>2</sub> blockers is possible if dosing of the 2 agents is separated by 10 hours. The clinical significance of decreased tipranavir exposure, decreased fosamprenavir exposure, and increased saquinavir exposure with concomitant ARA use currently is uncertain. Further information on ARA interactions with antiretroviral drugs is needed, with attention given to coadministration versus staggered administration, interactions in HIV-infected patients (in addition to HIV-uninfected subjects), effects of different dose levels of individual ARAs, and potential clinical consequences of any identified pharmacokinetic interactions.

### Fluticasone

The potent locally-acting glucocorticoid fluticasone is rapidly metabolized via CYP3A4 after oral dosing. Coadministration with ritonavir or other CYP3A4 inhibitors, however, raises the potential for markedly increased systemic exposure and a marked decrease in endogenous cortisol levels. Consequences can include systemic effects such as adrenal sup-



**Figure 2.** 12-hour concentrations on day 10 of bid dosing of ritonavir-booster (r) saquinavir or saquinavir/atazanavir at mg doses shown in HIV-seronegative subjects. Adapted from data in King et al, CROI, 2006.

Table 5. Effects of Acid-Reducing Agents on Protease Inhibitors

Protease Inhibitor	Antacids	H <sub>2</sub> Blockers	Proton Pump Inhibitors	Significance
Saquinavir/r (1000/100 mg bid)		C <sub>12</sub> ↑ AUC ↑	C <sub>12</sub> AUC 80%	Unclear
Indinavir (800 mg tid)			C <sub>min</sub> 55% AUC 46.7%	+++
Lopinavir/r (400 mg/100 mg bid)	↔	↔	↔	Unlikely
Fosamprenavir (1400 mg bid)	C <sub>min</sub> ↑14% AUC ↓18%	C <sub>min</sub> ↔ AUC ↓30%	↔	Possible
Fosamprenavir/r (700 mg/100 mg bid)			↔	
Atazanavir/r (400 mg qd)		C <sub>min</sub> ↓42% AUC ↓41%	C <sub>min</sub> and AUC ↓80%	+++ (Separate if H <sub>2</sub> blocker)
Atazanavir/r (300 mg /100 mg qd)		C <sub>min</sub> ↓28% AUC ↓18%	C <sub>min</sub> and AUC ↓70%	+++ (Separate if H <sub>2</sub> blocker)
Tipranavir/r (500 mg/200 mg bid)	C <sub>min</sub> ↓29% AUC ↓27%			Possible
Darunavir/r (400 mg/100 mg bid)		↔	↔	Unlikely

AUC indicates area under the concentration-time curve; bid, twice daily; C<sub>12</sub>, concentration at end of 12-hour dosing interval; H<sub>2</sub> blocker, histamine H<sub>2</sub> receptor antagonist; C<sub>min</sub>, minimum concentration; qd, daily; tid, thrice daily. Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

pression and Cushing's syndrome.

### Methadone and Buprenorphine

As listed in Table 6, available data

Table 6. Interactions Between Antiretroviral Drugs and Methadone or Buprenorphine

	Methadone	Buprenorphine
Atazanavir	↔	?↑
Fosamprenavir	13% ↓	?↑
Indinavir	↔	?↑
Lopinavir/r	30%-50% ↓	?↑
Nelfinavir	47% ↓	?
Saquinavir	32% ↓	?↑
Tipranavir	50% ↓	?↑
Efavirenz	52% ↓	50% ↓
Nevirapine	46% ↓	?↓

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

indicate that most PIs and the NNRTIs efavirenz and nevirapine reduce morphine levels. Although there are few substantive data in this regard, buprenorphine levels are believed to be increased by PIs and reduced by efavirenz and nevirapine.

### CYP Genomics

Differences in genes regulating CYP enzymes can have significant effects on drug metabolism and exposure. For example, 1 study of polymorphisms at the 516 position of the CYP2B6 gene has shown that individuals with the 516T/T variant have a 3-fold increase in efavirenz concentrations and markedly increased efavirenz AUC compared with individuals with wild-type 516G/G or the 516T/G variant (Haas et al, *AIDS*, 2004). Data from a study in the Swiss HIV Cohort indicate that most patients with very high efavirenz concentrations on standard doses, some of whom had central nervous system (CNS)-related toxicity,

had single nucleotide polymorphisms in the CYP2B6 gene at both the 516 and 785 positions. In the case of efavirenz, and other drugs for which pharmacogenomic data are accumulating, it is unclear at present whether genotypic testing or TDM should be used to guide dosing. It is likely that most genotypic and phenotypic relationships affecting drug metabolism and exposure reflect the involvement of numerous genes and numerous polymorphisms. As more information in this regard is gained, genotypic testing is likely to be an increasingly used tool in both selecting antiretroviral agents and achieving optimal dosing.

*Presented by Dr Back in March 2006. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Back in June 2006.*

*Financial Disclosure: Dr Back has received grants and research support from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Roche, and Tibotec. He has also served as a consultant to or is on the speakers' bureau of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and GlaxoSmithKline.*

### Suggested Reading

Boffito M, Winston A, Fletcher C, et al. Pharmacokinetics and ART response to TMC114/r and TMC125 combination in patients with high-level viral resistance. [Abstract 575C.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

Clay P, Anderson P, Smith P, Lein D, Glaros A. Pharmacokinetics of once-daily fosamprenavir 1400 mg plus atazanavir 400 mg without ritonavir in HIV-negative subjects. [Abstract 587.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

Harris M, Ramirez S, Joy R, et al. Effect of lopinavir and ritonavir dose adjustments on the pharmacokinetic interaction between LPV/RTV and tipranavir. [Abstract 584.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

King J, Paul Lundy S, Kakuda T, Becker S, Acosta E. Pharmacokinetics of saquinavir with low-dose ritonavir or atazanavir twice daily in seronegative volunteers: ASPIRE II.

[Abstract 586.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

van Heeswijk R, Sabo J, MacGregor T, et al. The pharmacokinetic (PK) interaction between single-dose rifabutin (RFB) and steady-state tipranavir/ritonavir 500/200 mg bid (TPV/r) in healthy volunteers. [Abstract A-456.] 44th Interscience Conference on Antimicrobial Agents and Chemotherapy.

October 30-November 2, 2004; Washington, DC.

van Heeswijk R, Sabo J, MacGregor T, et al. The effect of tipranavir/ritonavir 500/200 mg bid (TPV/r) on the Pharmacokinetics (PK) of clarithromycin (CLR) in healthy volunteers. [Abstract A-457.] 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30-November 2, 2004; Washington, DC.

van Heeswijk R, Sabo JP, Cooper C, et al. The pharmacokinetic interactions between tipranavir/ritonavir 500/200 mg bid (TPV/r) and atorvastatin, antacid, and CYP3A4 in healthy adult volunteers. [Abstract 5.2.] 5th International Workshop on Clinical Pharmacology of HIV Therapy. April 1-3, 2004; Rome, Italy.

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<p><b>Welcome and Introduction</b> Presenter(s): Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 8:15 AM PST Length: 7 Minutes 39 Seconds</p> <p><b>View: Welcome and Introduction</b></p>		<p><b>Demographic Question-and-Answer</b> Presenter(s): Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 9:00 AM PST Length: 4 Minutes 15 Seconds</p> <p><b>View: Demographic Question-and-Answer</b></p>	
<p><b>Resistance Testing Interpretation</b> Presenter(s): Diane V. Havlir, MD Status: Available Air Date: 2/23/2006 Air Time: 9:10 AM PST Length: 46 Minutes 18 Seconds</p> <p><b>View: Resistance Testing Interpretation</b></p>		<p><b>Cases from the Clinic: Initiating Antiretroviral Therapy and Managing Complicated ART Failure</b> Presenter(s): Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 10:20 PM PST Length: 48 Minutes 56 Seconds</p> <p><b>View: Cases from the Clinic: Initiating Antiretroviral Therapy and Managing Complicated ART Failure</b></p>	
<p><b>Drug-Drug Interactions and the Pharmacotherapy of HIV Infection</b> Presenter(s): Courtney V. Fletcher, PharmD Status: Available Air Date: 2/23/2006 Air Time: 11:05 AM PST Length: 35 Minutes 22 Seconds</p> <p><b>View: Drug-Drug Interactions and the Pharmacotherapy of HIV Infection</b></p>		<p><b>Managing Complications of HIV Disease and Antiretroviral Therapy: Case-Based Presentation</b> Presenter(s): Judith A. Aberg, MD Status: Available Air Date: 2/23/2006 Air Time: 11:45 AM PST Length: 34 Minutes 17 Seconds</p> <p><b>View: Managing Complications of HIV Disease and Antiretroviral Therapy: Case-Based Presentation</b></p>	

## Commentary

# Ryan White Care Act Reauthorization: We Need Help

*In this, the first Commentary column for Topics in HIV Medicine, Michael S. Saag, MD, has been invited to share his insights and observations about reauthorization of the Ryan White CARE Act, the healthcare funding crisis, and the changing nature of HIV and AIDS care delivery in the US. His opinion piece heralds a new approach for this publication, which welcomes commentaries on other medical and social issues arising from an epidemic in transition.*

The University of Alabama at Birmingham (UAB) 1917 Clinic is the largest HIV/AIDS clinic in Alabama and one of the largest in the Southeast United States. If it is a ship, it is sinking. If it is a fortress, the walls are breached and falling. If it is a haven, it is burning. We know we are not alone in this failure. Many HIV/AIDS private practices are closing and public clinics across the country are absorbing the additional burdens of care. We are losing devoted and resourceful HIV/AIDS healthcare personnel, who are flaming out while using ridiculously insufficient resources to meet impossible and increasing demands. We need help. Some of this help can come through appropriate reauthorization of the Ryan White CARE Act (RWCA).

The Ryan White CARE Act was created in 1990 with the intent of helping both individual HIV/AIDS patients and a healthcare system stunned by the demands of caring for the growing numbers of these patients. In those early days, we had few therapeutic options and a poorer understanding of the disease. Mostly, we battled opportunistic illnesses and helped patients die with dignity. Political mobilization within the gay community created political and public awareness of the disease and was critical in mounting and maintaining community-based prevention and treatment efforts. This made work for us in the medical community somewhat easier, since a large proportion of our patient population was self-organized and

active in seeking responsive legislation and healthcare.

Over the decade and a half since the CARE Act was first authorized, the nature of the epidemic in the US has changed in a number of important ways. Most importantly, owing to the breathtaking success of prior research and treatment efforts—patients are living. With the advent of potent antiretroviral therapy and improved understanding of the disease, patients are living far longer lives. This gain, however, is not the result of drugs alone; it occurs in the context of successful efforts at timely diagnosis, effective counseling, improved monitoring for viral resistance and virologic response, and skilled management of therapies to address toxicities and resistance—that is, improved overall care. Our patients can now live, they can work and be productive again, but they still require careful vigilance and provision of complex medical care. Narrow focus on increased funding to improve access to drugs is misguided; the primary emphasis should be on providing access to care. Without provision of appropriately sophisticated care the drugs will not be effective and resistant virus will become rampant. Stated another way, what good are drugs if they are not used properly?

Another change is the ongoing shift of growth of the epidemic to disadvantaged populations; the population in which the epidemic is growing fastest is largely poor and underinsured or uninsured and has virtually no political organization or advocacy. These patients typically present with advanced disease, having missed the chance for early diagnosis, timely treatment, and prevention counseling. Patients diagnosed later in the course of disease (CD4+ counts <200 cells/ $\mu$ L) have a substantially higher degree of HIV-related morbidity and mortality. In addition, they have spent greater amounts of time at risk for transmitting disease.

It also costs more to treat sicker

patients. Studies at UAB have shown that annual costs for patients initiating antiretroviral therapy at CD4+ cell counts below 200/ $\mu$ L, who now constitute more than 70% of our patient population, are significantly higher than for those diagnosed with higher CD4+ counts. For the 33% of patients in our clinic who present initially with CD4+ counts below 50 cells/ $\mu$ L, their costs are 2 to 5 times greater than costs in patients diagnosed with more than 50 cells/ $\mu$ L. Of note, medications are mostly responsible for the increases in these costs. Seventy-eight percent of costs were due to medications and not to hospitalization (7%) as might be anticipated. Most of the medication costs in the below 50 CD4+ cells/mL group were due to non-antiretroviral costs; the costs for antiretroviral medications remained constant across all CD4+ strata.

What is most striking in this cost analysis is that payment for physician services represents less than 2% of total expenditures, or \$360 per patient per year. This value assumed that all patients were insured and the collection rate was 100%. In our clinic of 1250 patients, this degree of reimbursement would yield a total of \$450,000. However, typically, 30% of our patients have no insurance and our collection rate is about 45%—yielding annual collection from fee for services of around \$250,000. Collections for provision of infusion therapy average \$240,000 per year. RWCA Title III provided us with \$508,000 for 2005. Together, these sources contribute less than \$1,000,000 to our overall budget of \$2.4 million, with UAB making up the remainder.

Taken together, the current level of funding through RWCA is inadequate to cover the costs of care for patients in 2006. Although most HIV clinics and practices, including ours, have had a 40% to 60% increase in patient volume over the past 5 years, our RWCA funding has been flat for the

past 7 years, with RWCA Title III clinics actually suffering a 2.5% funding reduction in early 2006. And, of course, it gets worse. In 2005, the proportion of new patients referred to the UAB clinic with no insurance whatsoever increased to 46%, in what is likely to be a trend. Staffing has been flat for 5 years despite a 50% increase in patient census. In addition, our social workers now spend 95% of their time exclusively accessing medications for patients, including monitoring compassionate use program eligibility or renewals, performing Medicare plan D counseling, and completing applications and tracking waiting lists for the AIDS Drug Assistance Program (ADAP). Our nurses also spend substantial amounts of their time serving as advocates for medicine access—that is handling prior authorizations and the numerous Medicare Plan D complications, including multiple plans with different rules, multiple formularies, rejection of prescriptions, long forms and long wait times to talk with insurance providers, and absence of means to track prior authorization requests. ADAP itself has spurred a sub-industry at our clinic. None of the more than 200 patients currently on the ADAP waiting list for medications has gone without treatment. Rather, we apply to compassionate use programs of the pharmaceutical companies to obtain the needed drugs. Yet, the majority of discussion on Capitol Hill regarding the reauthorization of the RWCA has focused on the ADAP, and very little attention is being paid to the plight of clinics and care providers.

Rising demands, insufficient fund-

ing, insufficient staffing, and loss of experienced personnel constitute a recipe for disaster. Increased federal funding is urgently needed to bail out failing clinics and practices and to increase staffing to a level sufficient to meet the needs of the patient population. This includes funding directed to accelerate efforts at early diagnosis and treatment among the population in which the epidemic is growing most rapidly. In addition to showing that earlier treatment results in reduced healthcare cost, our studies at UAB have shown that annual costs decline in every category when there is improvement in CD4+ cell counts. Early diagnosis and timely and effective treatment reduce cost, and likely reduce risk of transmission. And although it makes perfect sense to increase policies of widespread HIV testing to reduce costs of care and reduce risk of HIV transmission, how and where will these newly diagnosed patients receive care?

To my colleagues in HIV/AIDS care: Many of you are in similar positions. Discussion of the reauthorization of RWCA is ongoing right now. Write and call your representatives. Go see them if you can. I brought this plea to them in person, and got a favorable reception. One is listened to; less clear that one is heard. We need to speak with one voice.

To policy makers: The HIV/AIDS epidemic continues. The number of infected patients in the US increases annually and clinics do not have sufficient resources to maintain operations without more direct federal assistance. Much of the attention in RWCA reauthorization appears to be focused

on ADAP. Although it is a laudable goal to have this program fully funded and to remove patients from waiting lists, availability of medications means little without personnel and resources to monitor patients, to treat side effects, to provide resistance testing interpretation, to alter drug regimens appropriately, to refer for counseling, to provide counseling, to guide patients through the maze of insurance benefits and claims, and to guide them through the maze of lifelong treatment for an incurable disease. In short, to care for them. Without your attention and help, we will lose clinics, practices, and devoted and knowledgeable personnel, and there will be no one to replace them. Without your attention and help, we will lose health care providers with the required skills, knowledge, and dedication to provide appropriate care to this rapidly growing patient population. And without adequate numbers of such health care providers, we will replace waiting lists with waiting lines and lose patients' lives.

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Dr Michael S. Saag is Professor of Medicine and Director of the Center For AIDS Research at the University of Alabama at Birmingham. He is also a member of the volunteer Board of Directors of the IAS-USA. The remarks in the *Commentary* have been adapted in part from an interview with Dr Saag conducted by Michele Norris for the National Public Radio *All Things Considered* show that aired on April 12, 2006. (see <http://www.npr.org/templates/story/story.php?storyid=5339022>)

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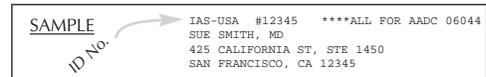
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