

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

A publication of the International AIDS Society—USA

## Perspectives

HIV and Hepatitis C Virus Coinfection: Bad Bedfellows 112

*Robert T. Schooley, MD*

*Effect of HIV Infection on HCV Disease • Effect of HCV Infection on HIV Disease • Issues in Treatment of HCV Infection • Approaches in Development*

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Selected Primary-Care Issues in HIV Disease 117

*David H. Spach, MD*

*Hepatitis B and A Virus Vaccinations • Screening for Cervical Abnormalities • Renal Disease*

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Medicare Part D and Antiretroviral Therapy:  
Issues for HIV Clinicians 122

*Laura W. Cheever, MD, and Mary R. Vienna, RN*

*Medicare Part D Basics • Illustrative Cases • Help With Costs • Provider Actions*

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## Special Contribution

Drug Resistance Mutations in HIV-1 125

*International AIDS Society—USA Drug Resistance Mutations Group*

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The International AIDS Society–USA

## About This Issue

This issue features 3 *Perspectives* articles based on recent presentations at CME activities and conferences. At the 13th annual International AIDS Society–USA CME course in San Francisco in June 2005, Robert T. Schooley, MD, discussed how to manage hepatitis C virus (HCV) and HIV coinfection using state-of-the-art therapy, given complicating factors like drug-drug interactions and hepatotoxicity, in order to achieve the highest rates of end-of-treatment and sustained virologic response. He cited small-molecule inhibitors of HCV and combination therapy as future possibilities for slowing HCV replication and improving treatment. At the 8th annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005, David H. Spach, MD, spoke on selected issues in HIV primary preventive and treatment care, including guidelines for providing hepatitis B and A vaccines and regular screening for cervical abnormalities and renal disease. At the same conference, Laura W. Cheever, MD, outlined the new Medicare prescription drug program, Medicare Part D, explaining how it will impact low-income patients' access to HIV and AIDS medication and what clinicians can do to smooth this transition. In a special contribution, this issue includes the IAS–USA Drug Resistance Mutations Group's most current list of HIV-1 mutations associated with resistance to antiretroviral drugs.

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Issues for HIV Clinicians 122

*Laura W. Cheever, MD, and Mary R. Vienna, RN*

## Special Contribution

Drug Resistance Mutations in HIV-1 125

*International AIDS Society–USA Drug Resistance Mutations Group*

## Announcements

Guidelines for Authors and Contributors 132

Subscription Request 133

Educational Programs of the International AIDS Society–USA 135

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## Perspective

# HIV and Hepatitis C Virus Coinfection: Bad Bedfellows

*Hepatitis C virus (HCV) infection is common in HIV-infected individuals and is responsible for increasing morbidity in these patients. HIV infection increases HCV replication and accelerates progression of HCV disease. HCV infection increases the risk of antiretroviral-associated hepatotoxicity and the likelihood of withdrawal of antiretroviral treatment. HCV genotype 1 is the predominant genotype in HCV/HIV-coinfected individuals living in the United States. State-of-the-art treatment with peginterferon alfa plus ribavirin results in lower sustained HCV virologic response rates in patients with genotype 1 infection than in those infected with other genotypes. Data from studies of HCV infection treatment in coinfecting patients are discussed, as are prospects for future therapy. This article summarizes a presentation on HIV/HCV coinfection by Robert T. Schooley, MD, at the International AIDS Society–USA course in San Francisco in June 2005.*

In recent years hospitalizations associated with liver complications and injection drug use (IDU)-related complications among HIV-infected patients have increased. Much of the increased morbidity is associated with concurrent hepatitis C virus (HCV) infection. Recent estimates suggest that HCV infection is present in 30% of HIV-infected patients in the United States, 50% in Spain, 33% in Western Europe, and 50% in Thailand. In a cohort of 1955 patients in Baltimore, MD, HCV infection was present in 45% of HIV-infected patients, including 85% of those who acquired HIV through IDU, 14% of those infected through heterosexual sex, and 10% of those infected through male homosexual sex (Sulkowski, *Ann Intern Med*, 2003). HCV/HIV coinfection complicates management of both diseases.

### Effect of HIV Infection on HCV Disease

Studies of stored blood samples from HCV-infected patients with hemophilia who subsequently acquired HIV infection have shown a substantial increase in HCV RNA following HIV antibody seroconversion, suggesting a

marked effect of HIV in increasing HCV replication (Eyster, *Blood*, 1994). Other data indicate a dramatic effect of HIV infection in accelerating HCV disease. In one study in 413 HIV-seronegative patients and 116 HIV-infected patients with HCV infection, the 10-year incidence of cirrhosis was 2.6% in the former group versus 14.9% in the latter ( $P < .01$ ) and the mean time to cirrhosis was 23.2 years versus 6.9 years ( $P < .001$ ; Soto, *J Hepatol*, 1997). In a recent study by Sulkowski and colleagues in Baltimore (12th CROI, 2005), 67 HIV/HCV-coinfecting patients had paired biopsies scored using Ishak criteria. With a median time between biopsies of 2.8 years, an increase in fibrosis of 2 or more stages was observed in 17 patients (28%), whereas only 4 patients (7%), all with stage 1 fibrosis at baseline, had a decrease of 1 stage. A 2001 meta-analysis of 7 studies on the effect of HIV infection on HCV disease progression indicated a relative risk of progression to cirrhosis of 2.92 with coinfection versus HCV infection alone (Graham, *Clin Infect Dis*, 2001).

### Effect of HCV Infection on HIV Disease

There are some data to indicate that HCV coinfection somewhat blunts the CD4+ cell increase observed in HIV-

infected patients receiving potent antiretroviral therapy (Greub, *Lancet*, 2000), although there are conflicting findings in this regard. Further, the relatively small blunting effect that has been observed may not substantially affect the overall immunologic benefits of antiretroviral therapy. More important from the perspective of HIV treatment is the finding that coinfection with HCV increases the risk of antiretroviral-associated hepatotoxicity (Figure 1, top; Sulkowski, *Hepatology*, 2002). Antiretroviral therapy discontinuation rates have been found to be greater in coinfecting patients than in patients without HCV infection (Figure 1, bottom; Melvin, *AIDS*, 2000).

### Issues in Treatment of HCV Infection

An important factor to consider in treating and developing therapies for HCV infection is the high replication rate of HCV, which is 10- to 100-fold greater than that of HIV. Replication occurs via an RNA-dependent RNA polymerase that, like HIV reverse transcriptase, is prone to error in the genetic copying process. As a result, HCV generates great genetic diversity both in terms of viral subtypes and in terms of variants within the host. Indeed, the genetic variation between the closest related HCV viral subtypes is greater than that between the most distantly related HIV subtypes identified. Although these characteristics make the evolution of antiviral-resistant strains of HCV very likely, it is also the case that the virus, unlike HIV, does not replicate via a DNA intermediate inserted into the host-cell genome. Thus, resistance is not likely to be “archived” within host cells, and the response to subsequent use of the same antiviral(s) may not be jeopardized to the same extent as in the case of antiretroviral therapy.

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Dr Schooley is a Professor of Medicine at the University of California San Diego.

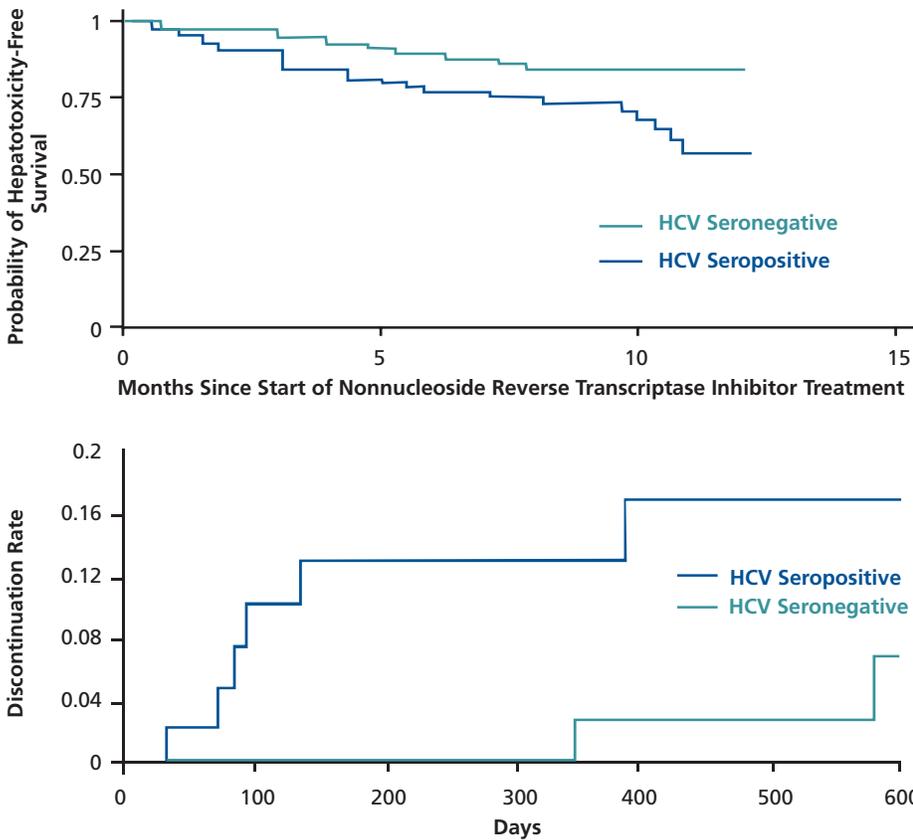


Figure 1. Top: Risk of associated hepatotoxicity in patients with or without hepatitis C virus (HCV) infection. Adapted from Sulkowski et al, *Hepatology*, 2002. Bottom: Rate of discontinuation of antiretroviral therapy due to hepatotoxicity in HCV-infected patients and in patients without HCV infection. Adapted from Melvin et al, *AIDS*, 2000.

Concentrations of anti-HCV drugs in the liver are key to achieving response.

Response to antiviral treatment for HCV infection is typically assessed in terms of end-of-treatment response (ETR)-HCV RNA levels below assay detection limits at the end of therapy, and sustained virologic response (SVR)-HCV RNA levels below the limit of assay detection at 24 weeks after the end of treatment. An SVR usually indicates a low risk of recurrence—that is, a high probability of virologic cure. Rates of ETR and SVR reported in the literature as of 2001 with interferon alfa, peginterferon alfa-2a, or peginterferon alfa-2b, with or without ribavirin, in patients without HIV infection are shown in Figure 2 (Shiffman, *Clin Liver Dis*, 2001). Although interpretation of these data must be qualified by the fact that there were differences in the study populations providing the data, they do pro-

vide some idea of the overall ability to achieve response with different regimens and the degree to which ETR is followed by either recurrence or SVR. The current state-of-the-art anti-HCV therapy treatment is peginterferon alfa plus ribavirin, which may be associated with an ETR rate of 60% or more and an SVR rate of approximately 50% in patients infected with HCV subtype 1 without HIV coinfection.

Factors that can affect response rates are shown in Figure 3. HCV genotype 1, the predominant type in the United States, is associated with lower response rates than are genotypes 2 and 3, which predominate in Europe. Other factors affecting response include pretreatment plasma HCV RNA level, age, race, weight (likely reflecting differences in drug exposure with standard dosing), alanine aminotransferase level (activated enzymes are a favorable sign), histol-

ogy, dose of ribavirin, and sex (also likely reflecting differences in drug exposure via body size). Among these factors, several are of particular concern in treating HIV-coinfected patients. Patients with coinfection are more likely to have infection with HCV genotype 1, higher pretreatment plasma HCV RNA levels, and more advanced liver histology, and they are less likely to tolerate full doses of ribavirin because of drug interactions with antiretroviral agents.

Results of APRICOT, a trial of HCV infection treatment in HIV-coinfected patients, have recently been reported (Torriani, *N Engl J Med*, 2004). In this trial, coinfecting patients received interferon alfa 3 MIU 3 times weekly plus ribavirin 800 mg daily (n = 285); peginterferon alfa 180 µg once weekly (n = 286); or peginterferon alfa 180 µg once weekly plus ribavirin 800 mg daily (n = 289) for 48 weeks and were

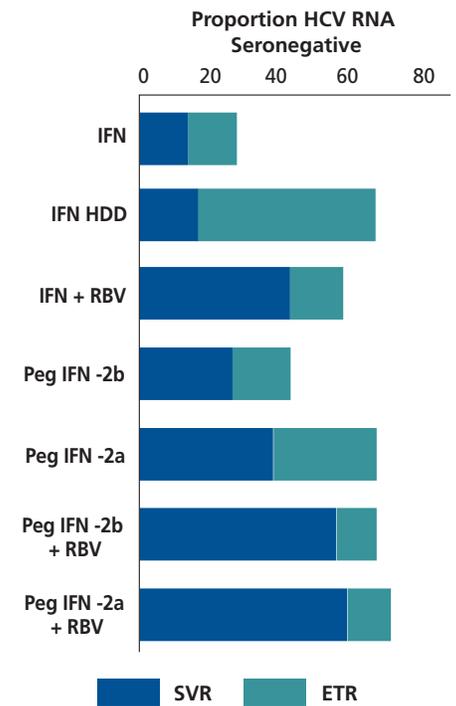
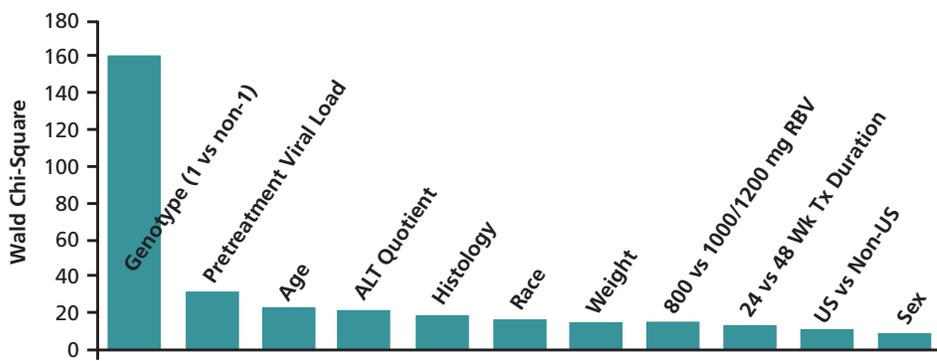


Figure 2. End-of-treatment response (ETR) and sustained virologic response (SVR) rates in hepatitis C virus (HCV)-infected patients without HIV infection, according to treatment. IFN indicates interferon alfa; HDD, high dose daily; RBV, ribavirin; Peg IFN, peginterferon alfa. Adapted from Shiffman, *Clin Liver Dis*, 2001.



**Figure 3.** Factors associated with sustained virologic response to treatment with peginterferon alfa plus ribavirin (RBV) according to a multiple logistic model in 1737 hepatitis C virus monoinfected patients. The Wald chi-square is proportional to the square of the risk associated with each factor noted on the x-axis. ALT indicates alanine aminotransferase; RBV, ribavirin. Adapted from FDA Antiviral Drugs Advisory Committee Proceedings, 2002.

observed to week 72. Patients had to have stable HIV disease, with or without antiretroviral treatment, and they had to have a CD4+ cell count of at least 100/ $\mu$ L. Those with CD4+ cell counts of 100/ $\mu$ L to 200/ $\mu$ L were also required to have a plasma HIV RNA level below 5000 copies/mL. On intent-to-treat analysis, SVR defined as HCV RNA below 50 IU/mL at week 72 occurred in 12% of the interferon alfa plus ribavirin group, 20% of the peginterferon alfa group, and 40% of the peginterferon alfa plus ribavirin group ( $P < .001$  versus both other groups). ETR and SVR rates were lower in patients with HCV genotype 1 infection than in those with genotype 2 or 3 infection (Figure 4).

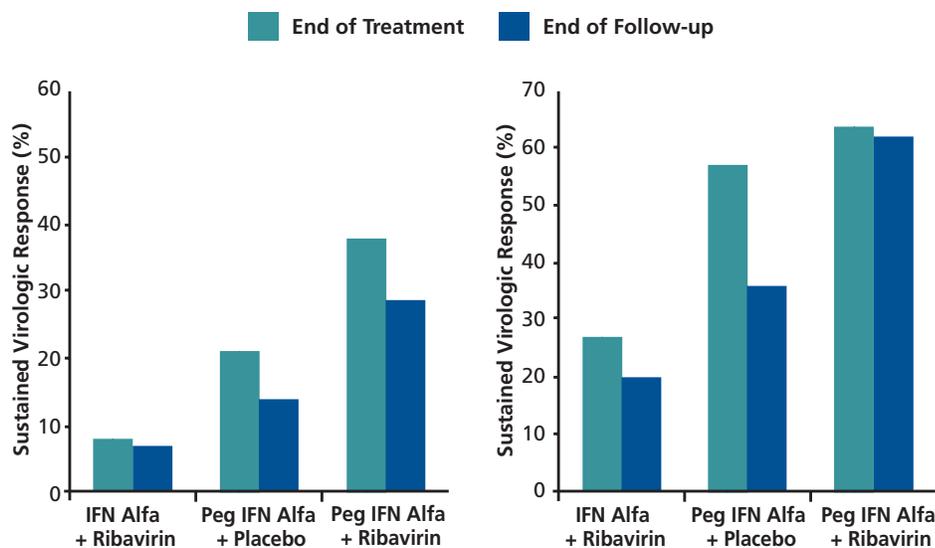
A number of studies have shown the value of early virologic response in predicting long-term response. In APRICOT, reduction of HCV RNA to undetectable levels or by at least 2  $\log_{10}$  copies/mL at 12 weeks occurred in 71% of patients receiving peginterferon alfa-2a plus ribavirin; of these, 56% had an SVR. Of the 29% of patients without such early virologic response, 98% had no SVR. This negative predictive value of 98% was similar to that observed in other trials of antiviral therapy for HCV infection and suggests that the absence of response at 12 weeks may permit sparing the patient the remainder of the treatment course if the patient is experiencing significant toxic effects.

However, even partial response to treatment can improve HCV infection course, so the absence of full suppression of HCV replication should not routinely prompt cessation of therapy.

It is recognized that CD4+ cell counts decrease during interferon alfa treatment, and decreases were observed in all treatment groups in APRICOT (Figure 5). These decreases are usually not accompanied by changes in CD4+ cell percentage, however, and levels in the treatment groups in APRICOT increased at the

end of the treatment period. It is also known that interferon alfa has anti-HIV activity, and decreases in HIV RNA of up to 1  $\log_{10}$  copies/mL were observed in the trial.

Treatment of HCV infection in coinfecting patients also has been examined in the AIDS Clinical Trials Group (ACTG) 5071 study. In this trial, 132 patients received interferon alfa plus ribavirin ( $n = 66$ ) or peginterferon alfa plus ribavirin for 48 weeks, and were followed up for 72 weeks. Ribavirin was started at 600 mg daily and the dose was increased by 200 mg each month to a maximum of 1000 mg daily, if tolerated. Patients were on stable antiretroviral therapy and had CD4+ cell counts above 100/ $\mu$ L and plasma HIV RNA levels below 10,000 copies/mL, or they were antiretroviral-naive and had CD4+ cell counts above 300/ $\mu$ L. This trial was conducted in the United States and thus had a greater proportion of patients with HCV genotype 1. The trial also had more African-American patients, a group that has lower rates of response to interferon alfa-based treatment. Among patients with genotype 1 infection, ETR occurred in 6% of the interferon alfa/ribavirin group and



**Figure 4.** Virologic response at the end of 48 weeks of treatment and at the end of 72 weeks of follow-up in HIV/hepatitis C virus (HCV) coinfecting patients with HCV genotype 1 infection (left) or genotypes 2 and 3 infection (right) according to treatment in the APRICOT trial. Virologic response is defined as an HCV RNA level below 50 IU/mL. IFN indicates interferon; Peg IFN, peginterferon. Adapted from Torriani et al, *N Engl J Med*, 2004.

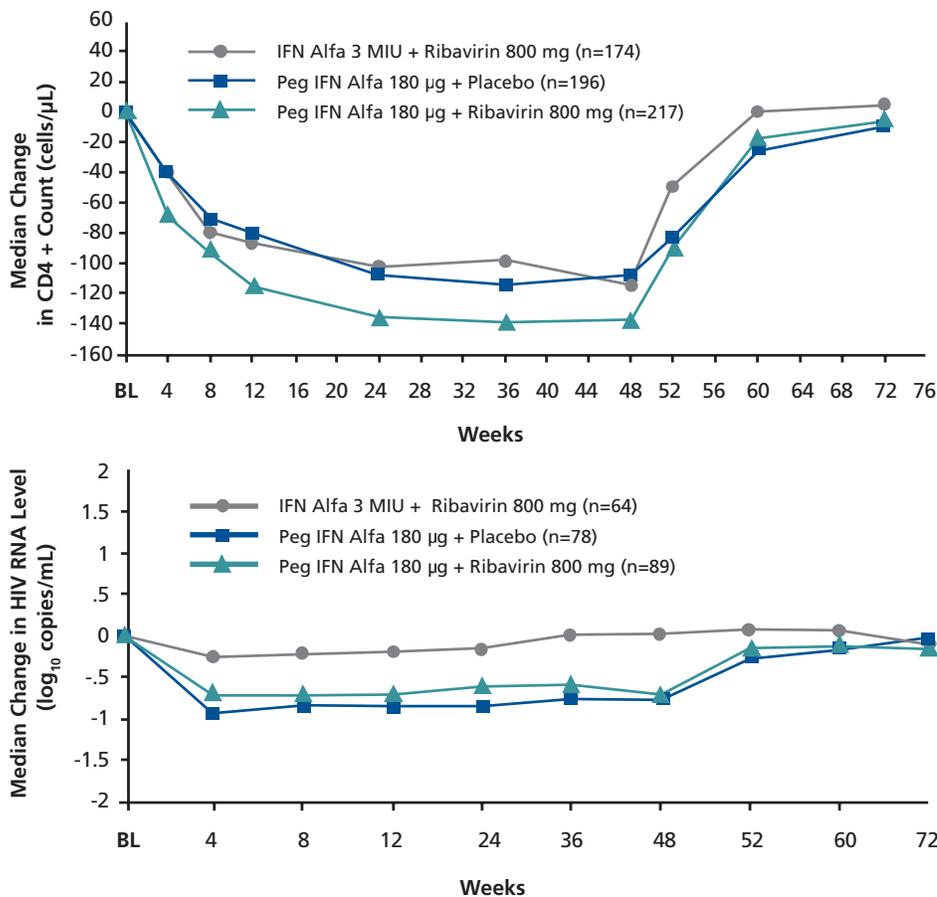


Figure 5. Median change from baseline in CD4+ cell count (top) and mean change from baseline in plasma HIV RNA (bottom) in HIV/hepatitis C virus coinfecting patients, according to treatment in the APRICOT trial. IFN indicates interferon; Peg IFN, peginterferon. Subjects received 48 weeks of treatment. Data are from Torriani et al, *N Engl J Med*, 2004.

29% of the peginterferon alfa/ribavirin group, and SVR occurred in 6% and 14%, respectively (Chung, *N Engl J Med*, 2004). The lower SVR rate in patients with HCV genotype 1 infection in this study than in the APRICOT trial may also be related to the more cautious use of ribavirin in the ACTG 5071 trial.

Pegylated interferon alfa and ribavirin therapy is not without significant toxic effects. Successful therapy requires ongoing support of the patient and anticipatory management of toxicities. Virtually every patient can be expected to experience flu-like symptoms including fatigue, headaches, and myalgias with interferon alfa-based therapies (Aspinall et al, *Aliment Pharmacol Ther*, 2004). These symptoms are manageable in most patients if patients are adequately prepared for

them in advance, and few patients must cease therapy solely because of flu-like symptomatology. The most frequent causes of discontinuation of therapy stem from depression and bone marrow suppression. Patients who are otherwise candidates for interferon alfa-based therapies should be assessed for depression prior to therapy. Depression occurs during therapy in 35% to 40% of patients and can usually be managed with antidepressants. Selective serotonin reuptake inhibitors and tricyclic antidepressants have each been used with excellent success in this setting. Bone marrow suppression from interferon alfa-based therapy may cause granulocytopenia, thrombocytopenia, or anemia. Ribavirin therapy exacerbates the anemia since it causes hemolysis of red blood cells. Although these hematologic

complications are readily reversible with dose reduction of the interferon alfa or ribavirin, reductions in doses of either medication significantly reduce rates of SVR (Fried et al, *N Engl Med*, 2002). Thus, practitioners should not be hesitant to use granulocyte colony-stimulating factor and erythropoietin in the management of granulocytopenia and anemia, respectively.

Based on current knowledge, it generally can be recommended that patients with early HIV infection be considered for HCV treatment to obtain virologic cure prior to the initiation of antiretroviral therapy. In later HIV infection, the potential for obtaining an SVR is lower, but treatment of HCV infection should be considered in order to reduce the HCV disease progression risk and to permit the initiation of antiretroviral therapy. Overall, factors favoring the institution of anti-HCV therapy include infection with genotypes other than genotype 1, earlier HIV disease, and the presence of fibrosis on liver biopsy. Factors complicating therapy include infection with HCV genotype 1, ongoing substance abuse, psychiatric disorders, later HIV disease, the toxic effects of interferon alfa and ribavirin, and current antiretroviral therapy.

### Approaches in Development

The future will bring improved therapies for HCV infection. Potential targets for drug development include the HCV protease and polymerase enzymes. Development of inhibitors of the HCV protease enzyme has proven difficult because of the long and shallow enzyme-binding site on the protein to which it cleaves. Investigation of the protease inhibitor BILN 261 compound showed that inhibition is possible, with treatment producing up to 3 log<sub>10</sub> copies/mL decreases in HCV RNA in patients with HCV genotype 1 infection and generally smaller and less consistent reductions in those with non-genotype 1 infection over short-term administration (Lamarre, *Nature*, 2003; Reiser, *Hepatology*, 2005); however, the molecule is difficult to synthesize. The

protease inhibitor VX-950 is easier to synthesize and appears to exhibit greater activity. In a phase Ib dose-ranging study, a median HCV RNA reduction of 4.4 log<sub>10</sub> copies/mL was achieved at a dose of 750 mg every 8 hours after 14 days of treatment. At the highest dose, 4 of 8 patients had undetectable HCV RNA levels, whereas viral rebound was observed at lower dose levels in some patients. The polymerase inhibitor NM283 (valopicitabine) was found to produce small reductions in HCV genotype 1 RNA levels, with the greatest reduction being somewhat more than 1 log<sub>10</sub> copies/mL when the highest dose tested was administered with an antiemetic. In a phase IIa trial, valopicitabine produced a 1.9-log<sub>10</sub>-copy/mL reduction in HCV RNA when used alone, and the combination of valopicitabine and peginterferon alfa produced a reduction of 4.5 log<sub>10</sub> copies/mL over 24 weeks of treatment.

## Summary

Increased morbidity from HCV infection in HIV-infected patients, with increasing numbers of patients requiring treatment, is expected. It is hoped that effective small-molecule inhibitors of HCV can be developed that will permit a reduced reliance on interferon alfa and ribavirin as primary components of anti-HCV therapy. Given the high replication rate of HCV and its ability to generate wide genetic variation, combination therapy will likely be required for predictable effective suppression of the virus.

*Presented by Robert T. Schooley, MD, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Schooley in September 2005.*

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## Suggested Reading

Aspinall RJ, Pockros PJ. The management of side-effects during therapy for hepatitis C. *Aliment Pharmacol Ther.* 2004;20:917-929.

Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med.* 2004;351:451-459.

Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to HIV infection and liver disease. *Blood.* 1994;84:1020-1023.

Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002;347:975-982.

Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis.* 2001;33:562-569.

Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet.* 2000;356:1800-1805.

Lamarre D, Anderson PC, Bailey M, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature.* 2003;426:186-189.

Melvin DC, Lee JK, Belsey E, Arnold J, Murphy RL. The impact of co-infection with hepatitis C virus and HIV on the tolerability of antiretroviral therapy. *AIDS.* 2000;14:463-465.

Reiser M, Hinrichsen H, Benhamou Y, et al. Antiviral efficacy of NS3-serine protease inhibitor BILN-2061 in patients with chronic genotype 2 and 3 hepatitis C. *Hepatology.* 2005;41:832-835.

Shiffman ML. Management of interferon therapy nonresponders. *Clin Liver Dis.* 2001;5:1025-1043.

Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol.* 1997;26:1-5.

Sulkowski M. The natural history of hepatic steatosis among HIV/HCV co-infected patients with paired liver biopsy. [Abstract 831.] 12th Conference on Retroviruses and Opportunistic Infections. 2005; Boston, MA.

Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med.* 2003; 138:197-207.

Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology.* 2002;35:182-189.

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med.* 2004; 351:438-450.

US Food and Drug Administration Antiviral Drugs Advisory Committee. BLA 125061, peginterferon alfa-2a in combination with ribavirin, NDA 21-511, Hoffmann-La Roche, Inc, proposed for treatment of chronic hepatitis C. November 14, 2002; Bethesda, MD.

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Perspective

# Selected Primary-Care Issues in HIV Disease

Primary care for HIV-infected patients includes ensuring that eligible patients receive hepatitis B and A virus vaccinations, all women undergo appropriate screening and follow-up for cervical cytologic abnormalities, and all patients undergo routine screening for renal function abnormalities. Current guidelines in these specific areas of HIV primary care are reviewed. This article summarizes a presentation on issues in primary care for HIV-infected patients by David H. Spach, MD, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005.

## Hepatitis B and A Virus Vaccinations

Current data indicate that most HIV-infected patients eligible for hepatitis B virus (HBV) and hepatitis A virus (HAV) vaccines are not receiving appropriate immunization. In a recent retrospective study of 1071 ambulatory HIV-infected patients at 9 HIV Outpatient Study clinics, 82% of patients were screened for eligibility for HBV vaccine (no prior receipt of HBV vaccine, seronegative for HB surface antibody [anti-HBs], seronegative for HB core antibody [anti-HBc], and seronegative for HB surface antigen [HBsAg]) and 57% were screened for HAV vaccine eligibility (had risk factor for acquiring HAV, no prior receipt of HAV vaccine, and HAV antibody-seronegative status; Tedalid, *Clin Infect Dis*, 2004). Among the 57% of patients eligible for HBV vaccine, only 32% received at least 1 dose and only 17% received the recommended vaccination series. Among the 67% of patients eligible for HAV vaccine, only 23% received at least 1 dose and only 13% received the recommended series. Health care providers in the study cited the following reasons for not vaccinating patients: (1) the patient did not regularly attend the clinic; (2) the patient was not consid-

ered to be at high risk for infection; (3) the patient's CD4+ cell count was too low; and (4) insurance did not cover the immunization.

The 2004-2005 Advisory Committee on Immunization Practices (ACIP) guidelines recommend that HBV vaccination be provided for all HIV-infected patients who do not have evidence of prior HBV infection. Thus, assessment of risk of acquisition of HBV infection should not enter into the decision whether to provide vaccination. Similarly, although vaccination is less likely to generate an adequate antibody response in patients with lower CD4+ cell counts, low CD4+ cell count is not a contraindication to vaccination. The schedules for each of

the 3 approved products (Enerix-B, Recombivax HB, and the combined HBV/HAV vaccine Twinrix) consist of 3 doses, with the second and third doses given at 1 and 6 months after the first (Table 1). Postvaccination testing should be performed at 1 to 6 months after the series is completed to assess whether the antibody to the HBV surface antigen (anti-HBs) has achieved the presumed protective titer of at least 10 IU/L.

An issue in determining eligibility for HBV vaccine arises in the frequently encountered situation in which serologic testing shows a patient is seropositive for anti-HBc but seronegative for anti-HBs and HBsAg. Such a finding has been thought to indicate a history of prior infection and presence of immunity, with waning of anti-HBs over time to undetectable levels. One recent study assessed whether patients with isolated anti-HBc on serologic testing exhibited an anamnestic response to HBV vaccine (Gandhi et al, *J Infect Dis*, 2005). Patients with some existing immunity to HBV typically exhibit a large increase in anti-HBs titer within

**Table 1. Recommended Dose, Route, and Schedule for Hepatitis A and B Vaccines in HIV-Infected Persons.**

Vaccine	Dose and Route	No. Doses	Schedule
<b>Hepatitis B Vaccines</b>			
Enerix-B	20 µg (1 mL IM)	3	0, 1, 6 months
Recombivax HB	10 µg (1 mL IM)	3	0, 1, 6 months
<b>Hepatitis A Vaccines</b>			
Havrix	1440 EL U (1 mL IM)	2	0, 6-12 months
Vaqta	50 U (1 mL IM)	2	0, 6-12 months
<b>Combined Hepatitis A and B Vaccine</b>			
Twinrix	Havrix 720 EL U plus Enerix 20 µg (1 mL IM)	3	0, 1, 6 months

EL U indicates enzyme-linked immunosorbent assay units; IM, intramuscular.

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1 to 4 weeks of the first dose of vaccine (anamnestic response), whereas patients who are naive to HBV infection exhibit stepwise increases in antibody with each dose of vaccine (normal vaccine response). Among 69 HIV-infected, anti-HBs–seronegative and HBsAg–seronegative adults evaluated in the study, 29 (42%) were anti-HBc–seropositive. The finding of isolated anti-HBc was significantly associated with hepatitis C virus infection.

Anamnestic response, defined as an increase in anti-HBs titer to greater than 10 IU/L within 4 weeks of HBV vaccination, occurred in 10% of anti-HBc–seronegative patients and in 24% of anti-HBc–seropositive patients. Approximately half of the anti-HBc–seropositive patients also were seropositive for the antibody to hepatitis Be antigen (anti-HBe). Anamnestic response was observed in 43% of anti-HBe–seropositive patients, compared with only 7% of anti-HBe–seronegative patients (Figure 1). Overall, these findings suggest that most patients in the study who had a positive anti-HBe test and a positive anamnestic response probably had prior HBV infection, with anti-HBs titers that gradually diminished over time. On the contrary, most patients who had a negative anti-HBe test and a negative anamnestic response probably did not

have prior HBV infection and their positive anti-HBc test may actually represent a false-positive result. It is also possible that some patients with isolated anti-HBc have ongoing occult HBV infection, although prior work would suggest this appears to occur very infrequently. Unfortunately, the optimal approach to patients with isolated anti-HBc remains unclear and further work is needed to determine whether some or all of patients with isolated anti-HBc should undergo HBV vaccination. Ideally, future studies would identify an appropriate subset of patients with isolated anti-HBc who would most likely benefit from the HBV vaccine series.

Another recent study has suggested that doubling the HBV vaccine dose may improve response in HIV-infected patients, at least in those with higher CD4+ cell counts (Fonseca et al, *Vaccine*, 2005). Among 210 HBV antibody–seronegative patients, administration of 3 doses (at 0, 1, and 6 months) of Energix-B vaccine resulted in seroconversion (anti-HBs titer >10 IU/L) in 34% of those receiving the standard 20- $\mu$ g dose versus 47% of those receiving a 40- $\mu$ g dose. This improvement was confined to patients with CD4+ cell counts greater than 350/ $\mu$ L; seroconversion occurred in 64% of such patients at

the 40- $\mu$ g dose and in 39% of such patients at the standard dose, compared with rates of 24% at the 40- $\mu$ g dose and 26% at the standard dose among patients with CD4+ cell counts below 350/ $\mu$ L (Fonseca et al, *Vaccine*, 2005). At this time, however, there are no formal recommendations to use double-dose HBV vaccine in HIV-infected persons.

The current ACIP guidelines recommend giving HAV vaccination for those persons who have 1 or more of the following risk factors: travel to an HAV-endemic region, male-to-male sex, injection drug use, chronic liver disease, or a clotting factor disorder. The currently approved Havrix and Vaqta HAV vaccines are given in 2 doses, with the second given at 6 to 12 months after the first; the combined Twinrix vaccine (Havrix and Energix-B) is given in the 3-dose series as noted in Table 1. Protective antibody titers have been poorly characterized, but titers that have been used in studies to date differ between the products.

Rates of antibody response to HAV vaccine have varied. In a study in 133 HAV–seronegative patients, rates of seroconversion (HAV antibody >33 IU/L) following 2 doses of the Havrix vaccine were much lower in patients with CD4+ cell counts below 200/ $\mu$ L (approximately 10% at 9 months) than in patients with higher CD4+ cell counts (approximately 60% at 9 months in those with CD4+ cell counts greater than 200/ $\mu$ L; Kemper, *J Infect Dis*, 2003). This study, however, was conducted predominantly in an era prior to the widespread use of potent antiretroviral therapy. In a recent study comparing responses in 90 HIV-infected adults and 90 adults without HIV infection, seroconversion (antibody titer >10 IU/L) occurred by 28 weeks after Vaqta vaccination in 94% of the HIV-infected persons and in 100% of HIV–seronegative persons. Among the HIV-infected, stratification of responses based on CD4+ cell count showed 100% response rates in those patients with a CD4+ cell count of 300/ $\mu$ L or higher, compared with a

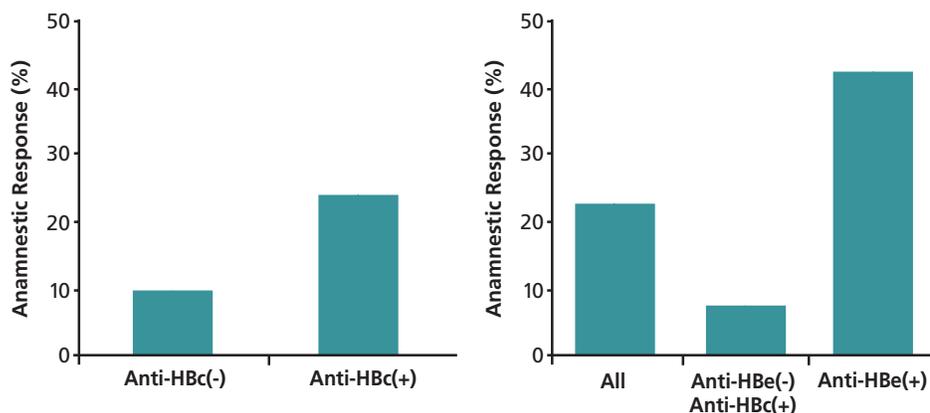


Figure 1. Anamnestic response to hepatitis B virus vaccine in 69 HIV-infected patients testing seronegative for hepatitis B virus surface antibody (anti-HBs) and hepatitis B virus surface antigen. Left figure shows response according to whether patients were seronegative or seropositive for hepatitis B virus core antibody (anti-HBc). Right figure shows response among anti-HBc–seropositive patients according to hepatitis Be virus antibody (anti-HBe) status. Anamnestic response was defined as an anti-HBs titer above 10 IU/L within 4 weeks of vaccination. Adapted from Gandhi et al, *J Infect Dis*, 2005.

response rate of 87% among patients with a CD4+ cell count below 300/ $\mu$ L (Wallace, *Clin Infect Dis*, 2004). The response rates among HIV-infected persons in this study were far better than response rates in prior studies, presumably because more patients in the recent study had received potent antiretroviral therapy and had better immunologic function. In addition, it is unclear whether the use of different vaccine preparations in these studies, or the use of different antibody titer cut-offs to define a vaccine response, may have contributed to the differences in outcome in these studies. In patients who have a CD4+ cell count less than 200/ $\mu$ L and are eligible to receive either hepatitis B or hepatitis A vaccine, many experts would recommend deferring vaccination for at least 6 to 12 months if the patient is starting (or resuming) antiretroviral therapy and will likely have a significant improvement in CD4+ cell count.

### Screening for Cervical Abnormalities

The US Public Health Service (USPHS)/ Infectious Diseases Society of America (IDSA) 2001 opportunistic infection prevention guidelines recommend that HIV-infected women undergo Papanicolaou (Pap) testing for cervical abnormalities twice in the first year after the diagnosis of HIV infection and once annually if Pap tests continue to be normal. In the case of abnormal findings, follow-up approaches differ according to the presence of atypical squamous cells of undetermined significance (ASCUS), the finding of a low-grade squamous intraepithelial lesion (LSIL), or the finding of high-grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma (Table 2). In addition, for patients with ASCUS, the approach varies based on the presence or absence of inflammation and whether a neoplastic process is suspected from the Pap test results. The Health Resources and Services Administration-HIV/AIDS Bureau publication, *A Guide to the Clinical Care of Women With HIV/AIDS*, provides similar screen-

**Table 2. Follow-Up Recommendations for Abnormal Cervical Cytology**

Pap Test Result	Recommendation
ASCUS (with severe inflammation)	Evaluate for infection; if found, treat and recheck Pap test in 2 to 3 months
ASCUS	Follow-up Pap test every 4 to 6 months for 2 years (until 3 consecutive PAP tests are negative)  If another ASCUS, consider colposcopy
ASCUS (neoplastic process suspected)	Follow-up Pap test every 4 to 6 months; OR colposcopy and biopsy if LSIL persists; OR immediate colposcopy
LSIL	Follow-up Pap test every 4 to 6 months; OR colposcopy and biopsy if LSIL persists; OR immediate colposcopy
HSIL (cervical intraepithelial neoplasia 2 or 3, carcinoma in situ) OR Squamous cell carcinoma	Colposcopy and biopsy of abnormal area

Data from 2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infection in Persons with Human Immunodeficiency Virus. Pap indicates Papanicolaou test; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

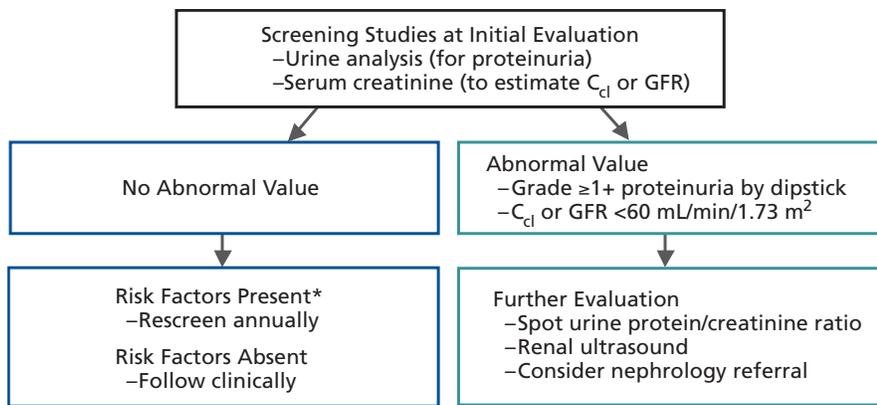
ing recommendations as the USPHS/IDSA guidelines, but also recommends routine twice-yearly screening in women with symptomatic HIV infection and CD4+ cell counts less than 200/ $\mu$ L, owing to increased risk of invasive cervical cancer in such patients.

Very promising results have been obtained thus far in studies of human papilloma virus (HPV) vaccines in the prevention of HPV disease and cervical dysplasia and cancer. In a randomized, double-blind trial of a vaccine directed against HPV-16, the strain accounting for 50% to 60% of cases of cervical cancer, 2392 women aged 16 to 23 years received 3 doses of vaccine or placebo (at 0, 2, and 6 months) and were followed up for a median of 17.4 months (Koutsky et al, *N Engl J Med*, 2002). Rates of persistent HPV-16 infection were 0 and 3.8 cases per 100 person-years of observation ( $P < .001$ ) in the vaccine group and the placebo group, respectively. Nine cases of cervical intraepithelial neoplasia occurred in the placebo group and none occurred in the vaccine group. In a randomized, double-blind trial of a

vaccine directed against both HPV-16 and HPV-18, the latter being the second most common HPV strain in cervical cancer, 1113 women aged 15 to 25 years received 3 doses of vaccine or placebo (each at 0, 1, and 6 months) and were followed up for up to 27 months (Harper et al, *Lancet*, 2004). Persistent HPV-16 and HPV-18 infections occurred in 0% of patients in the vaccine group and in 2.6% of placebo patients on per-protocol analysis ( $P < .001$ ) and in 0.5% versus 4% on intent-to-treat analysis ( $P < .001$ ).

### Renal Disease

Recommendations on screening for renal disease have recently been published by the HIV Medicine Association (HIVMA) of the IDSA (Figure 2; Gupta et al, *Clin Infect Dis*, 2005). Initial evaluation should include urinalysis for proteinuria and a calculation of serum creatinine to estimate creatinine clearance or glomerular filtration rate (GFR). Findings of dipstick proteinuria of grade 1 or higher or creatinine clearance or GFR less than 60



**Figure 2.** HIV Medicine Association of the Infectious Diseases Society of America recommendations for screening for renal disease.  $C_{cl}$  indicates creatinine clearance; GFR, glomerular filtration rate. \*Risk factors for developing proteinuric renal disease: African-American race, CD4+ cell count below 200/ $\mu$ L, plasma HIV RNA level greater than 4000 copies/mL, diabetes, hypertension, or chronic hepatitis C virus infection. Adapted from Gupta et al, *Clin Infect Dis*, 2005.

mL/min/1.73  $m^2$  should prompt further evaluation, including determination of spot urine protein/creatinine ratio, renal ultrasound, nephrology referral, and possibly renal biopsy. Screening should be repeated annually in patients with no abnormalities

**Table 3. Key Recommendations From the HIV Medicine Association of the Infectious Diseases Society of America Guidelines for Management of Nephropathy in HIV Infection**

- Control blood pressure to at or below 125/75 mm Hg
  - Preferential use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers if proteinuria
  - Avoid calcium channel blockers if patient taking protease inhibitor(s)
- Treat HIV-associated nephropathy with antiretroviral therapy at diagnosis
- Use additional therapies for HIV-associated nephropathy refractory to antiretroviral therapy
  - ACE inhibitors, angiotensin II receptor blockers, corticosteroids
- Perform dialysis if indicated
- Consider renal transplant for end-stage renal disease

Data from Gupta et al, *Clin Infect Dis*, 2005.

but with such risk factors as African-American race, CD4+ cell count below 200/ $\mu$ L, plasma HIV RNA level greater than 4000 copies/mL, diabetes, hypertension, or hepatitis C virus infection. Those with no risk factors should be followed up clinically. Recommendations for management of nephropathy are summarized in Table 3. These include control of blood pressure (preferably with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors), institution of antiretroviral therapy to treat HIV-associated nephropathy at the time of diagnosis, and use of corticosteroids in nephropathy refractory to antiretroviral therapy.

### Conclusion

The primary care of HIV-infected individuals includes a wide range of prevention and treatment services. All HIV-infected patients who do not have immunity to HBV should receive the complete hepatitis B vaccine series. Further work is needed to define the optimal approach to patients with isolated anti-HBc. Patients with selected risk factors should receive hepatitis A vaccine; the response rates to this vaccine are good, particularly in patients who have a CD4+ cell count greater than 300/ $\mu$ L. Screening HIV-infected women for cervical abnor-

malities should consist of Pap tests twice in the first year after diagnosis, followed by once-yearly tests as long as the test remains normal. Abnormal Pap tests demand further evaluation, but the evaluation varies based on the specific abnormality. All HIV-infected patients should be screened for renal abnormalities with urinalysis to detect proteinuria and a calculation of serum creatinine to estimate creatinine clearance or glomerular filtration rate.

*Presented by David Spach, MD, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Spach in September 2005.*

*Financial Disclosure: Dr Spach has served on the speakers' bureau of or received honoraria from Gilead, GlaxoSmithKline, and Merck.*

### Suggested Reading

Centers for Disease Control and Prevention. General recommendations of immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Morb Mortal Wkly Rep*. 2002;51:RR-2.

Centers for Disease Control and Prevention. Recommended Adult Immunization Schedule—United States, October 2004–September 2005. *MMWR Morb Mortal Wkly Rep*. 2004;53:Q1-4.

Fonseca MO, Pang LW, de Paula Cavaleiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine*. 2005;23:2902-2908.

Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. *J Infect Dis*. 2005;191:1435-1441.

Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40:1559-1585.

Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle

vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004;364:1757-1765.

Kemper CA, Haubrich R, Frank I, et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis*. 2003; 187:1327-1331.

Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus

type 16 vaccine. *N Engl J Med*. 2002; 347:1645-1651.

US Department of Health and Human Services and Health Resources and Services Administration. *A Guide to the Clinical Care of Women with HIV/AIDS, 2001 First Edition*. Available at: <http://hab.hrsa.gov/publications/womencare.htm>. Accessed: August 10, 2005.

US Department of Health and Human Services and Infectious Diseases Society of America. *2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in*

*Persons Infected With Human Immunodeficiency Virus*. Available at: [http://aidsinfo.nih.gov/guidelines/op\\_infections/OI\\_112801.pdf](http://aidsinfo.nih.gov/guidelines/op_infections/OI_112801.pdf). Accessed: August 10, 2005.

Wallace MR, Brandt CJ, Earhart KC, et al. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis*. 2004;39:1207-1213.

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## Perspective

# Medicare Part D and Antiretroviral Therapy: Issues for HIV Clinicians

*As of January 1, 2006, Medicare Plan D will add a drug benefit to Medicare, potentially affecting antiretroviral therapy for some 60,000 to 80,000 beneficiaries with HIV infection or AIDS. Health care providers should know the basic details of Plan D and how it may affect coverage for Medicare beneficiaries with or without a previous drug benefit under Medicaid. Steps may need to be taken to ensure that there are no lapses in antiretroviral therapy during the transition period from one pharmacy plan to another. This article summarizes a presentation on Medicare Plan D and antiretroviral therapy for patients with HIV or AIDS, given by Laura W. Cheever, MD, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005, and developed by Dr Cheever and Mary R. Vienna, RN.*

With the Medicare Modernization Act, the Centers for Medicare and Medicaid Services (CMS) is adding a drug program to Medicare in the form of Medicare Part D. This drug plan begins on January 1, 2006. Currently, there are approximately 60,000 to 80,000 Medicare beneficiaries with HIV infection or AIDS, most of whom qualify for Medicare benefits by receiving Social Security Disability Insurance (SSDI) for 2 years or more; under current Medicare plans, there is no prescription drug benefit. Of these patients, 70% to 85% are “dually eligible” beneficiaries in that, by receiving Supplemental Security Income (SSI), they also qualify for Medicaid, which does offer prescription drug coverage. Under Medicare Part D, most Medicare beneficiaries must elect the drug benefit and select a drug benefit plan. If this is not done when Part D first comes into force, patients will have to pay penalties for

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later enrollment. Dually eligible individuals will be automatically enrolled in Part D, because prescription drug coverage will switch from Medicaid to Medicare on January 1, 2006. Plan formulations must include all antiretrovirals (they must also include all antidepressant, antipsychotic, anti-convulsant, antineoplastic, and immunosuppressive agents). Patients affected by Medicare Part D are likely to turn to their physicians for help in understanding the changes in their pharmacy plans.

## Medicare Part D Basics

The basic plans in Part D are shown in Table 1. In general, as poverty level increases, beneficiaries have reduced premiums, reduced deductibles, and reduced coinsurance (amount to be paid by patient). This is because Medicare Part D has low-income subsidies, known as “Extra Help,” for beneficiaries with limited income assets.

Many patients may have income more than 150% of the federal poverty level (FPL) and exceed the asset limit. These beneficiaries will pay the following: a monthly premium that will amount to approximately \$32.20 per month in 2006; a \$250 deductible; 25% coinsurance (the patient pays 25%) up to \$2250 in drug costs for the year; 100% coinsurance (the patient pays all costs) up

to a total of \$3600 in true out-of-pocket expenses and \$5100 in total drug costs for the year; and approximately 5% coinsurance thereafter (at the catastrophic coverage level). Although the plan thus leaves such patients with relatively high out-of-pocket expenses, most Medicare beneficiaries with HIV or AIDS qualify for some type of low-income subsidy. These subsidies count toward out-of-pocket costs and toward reaching the catastrophic coverage level.

Dually eligible beneficiaries, beneficiaries on Supplemental Security Income, and those in a Medicare savings program—Qualified Medicare Beneficiary (QMB), Specified Low-income Medicare Beneficiary (SLMB), and Qualified Individual (QI) programs—are automatically eligible for a subsidy. Other beneficiaries not included in the above groups but who meet income and asset criteria need to apply to Social Security or Medicaid to qualify for a subsidy.

## Illustrative Cases

The following case studies provide some indication of how patients at different income levels will be affected by Plan D. The same antiretroviral regimen is specified in each of the cases only to keep the overall drug cost constant for all the cases discussed.

### Case 1

JM is on SSDI and SSI and receives both Medicare and Medicaid benefits. (She is dually eligible; see Table 1.) Her SSI and SSDI benefits amount to \$780 per month, which puts her at less than 100% of the FPL. Her antiretroviral regimen includes 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) and 2 nucleoside reverse transcriptase inhibitors (nRTIs), which cost \$1300 per month.

Since her income is less than 100% of the FPL and the \$3 brand-name co-pay thus applies, JM pays \$6 in co-pays per month for 2 prescriptions for 3 months. By the fourth month, JM's total drug costs of \$5200 (4 x \$1,300) exceed the \$5100 catastrophic coverage level, and thus she incurs no out-of-pocket costs thereafter. For the year, JM pays a total of \$18 in drug costs (3 months of \$6 co-pays).

**Case 2**

TS receives SSDI and Medicare benefits and a small private disability insurance benefit; his income of \$1100 per month puts him at 138% of the FPL (see Table 1). TS is receiving 1 NNRTI

and 2 nRTIs at a cost of \$1300 per month. TS pays a premium of \$8.00 per month, reflecting a 75% subsidy of the \$32-per-month premium. For month 1, he pays a \$50 deductible, plus \$187.50 reflecting a 15% coinsurance of the \$1250 balance for the monthly drug cost. For months 2 and 3, TS pays \$195 per month in coinsurance (15% coinsurance on \$1300 drug cost). For month 4, he pays \$180 in coinsurance, reflecting 15% of the \$1200 balance before reaching the catastrophic coverage level of \$5100. For months 5 through 12, TS pays \$10 per month, reflecting the \$5 brand name co-pay for 2 prescriptions per month. Thus for the year, TS pays \$983.50, consisting of \$96 in premi-

ums, \$807.50 in deductibles and coinsurance, and \$80 in co-pays.

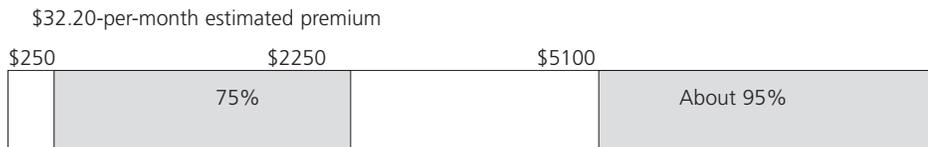
**Case 3**

CJ is a 65-year-old man who aged into Medicare coverage. His income is \$1600 per month, or 200% of the FPL (see Table 1). He is on the same regimen and has the same drug costs as in cases 1 and 2. CJ pays a premium of \$32.20 per month. For month 1, he pays a \$250 deductible plus \$262 reflecting the 25% coinsurance on the balance of \$1050 in drug costs. For month 2, he pays the following: (1) a \$237 coinsurance, reflecting 25% of the balance needed to reach the \$2250 limit on the 25% coinsurance; and (2) \$350, reflecting 100% coinsurance on the balance of the drug costs for the month. For month 3, he pays all of the \$1300 in drug costs out of pocket. For month 4, he pays \$1201, reflecting 100% of the drug cost until he reaches the total of \$3600 in out-of-pocket costs and the \$5100 total drug cost limit. For months 5 through 12, he pays \$65 per month, representing the 5% co-pay. CJ thus pays a total of \$4506.40 for the year, consisting of \$386.40 in premiums, \$3600 in out-of-pocket expenses, and \$520 in co-pays.

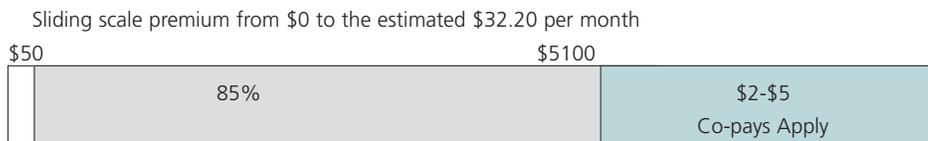
**Table 1. Main Drug Benefit and Low-income Provisions Under Medicare Plan D**

All numbers are for 2006 □ Beneficiary Pays ▒ Plan Pays ■ Co-pays Apply

Main drug benefit for beneficiaries with income more than 150% of the federal poverty level or less than 150% of the federal poverty level but more than the asset limit



Beneficiaries with income less than 150% of the federal poverty level who also meet the asset test (\$11,500 per individual or \$23,000 per couple)



Beneficiaries with income less than 135% of the federal poverty level who also meet the asset test (\$7500 per individual or \$12,000 per couple) SSI recipients, Medicare Saving Programs Groups, and full-benefit dually eligible individuals with income above 100% of the federal poverty level\*



Dually eligible individuals with income at or below 100% of the federal poverty level\*



\*Cost sharing is \$0 if the beneficiary is on Medicaid and institutionalized. SSI indicates Supplemental Security Income. Adapted from the Centers for Medicare and Medicaid Services.

**Help With Costs**

AIDS Drug Assistance Programs (ADAPs) can assist with drug costs, although they must do so in accordance with policies of individual state programs. An ADAP can pay premiums, deductibles, coinsurance (at the 15%, 25%, and 100% levels), and co-pays. However, ADAP contributions do not count toward the \$3600 in true out-of-pocket expenditures needed to reach the catastrophic coverage levels.

**Provider Actions**

Health care practitioners are likely to play a crucial role in ensuring that patients' antiretroviral treatment remains intact during the transition to Medicare Part D. As of June 2005,

dually eligible patients should have received letters from Medicare informing them that they automatically will be enrolled in Medicare Part D. Low-income Medicare beneficiaries may have received letters from Social Security about applying for low-income subsidies. Practitioners can encourage their Medicare patients to apply for the subsidies and inform dually eligible beneficiaries to keep their letters for their records. As of October 2005, a publication entitled “Medicare and You” containing information on Plan D should have been sent to all beneficiaries, and dually eligible beneficiaries should have received letters notifying them of the specific plan in which they have automatically been enrolled. Providers can

encourage Medicare beneficiaries to enroll in Plan D at the first opportunity and inform dually eligible patients that they can enroll in a plan different from the one to which they have been assigned. Patients can also be referred to [www.medicare.gov](http://www.medicare.gov) or 1-800-MEDICARE for additional information. As of January 1, 2006, dually eligible beneficiaries will receive drugs through the Medicare plan. To help with the transition, CMS informed Medicaid that federal matching funds will be provided for early Medicaid refills and 30- to 90-day prescriptions for dually eligible beneficiaries near the end of 2005. Providers should consider the option of prescribing extra antiretroviral medication to their affected patients to help them get

through the transition from one pharmacy plan to the other. During this transition, it is also advisable for providers to routinely ask affected patients about the status of their access to their medications.

*Presentation materials developed by Laura W. Cheever, MD, and Mary R. Vienna, RN, and presented by Dr Cheever in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Cheever in November 2005.*

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# Update of the Drug Resistance Mutations in HIV-1: Fall 2005

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group is marking 5 years as an independent volunteer panel of experts focused on identifying key HIV-1 drug resistance mutations. The goal of the effort is to quickly deliver accurate and unbiased information on these mutations to HIV clinical practitioners.

This October/November 2005 version of the IAS–USA Drug Resistance Mutations Figures replaces the version published in this journal in March/April 2005. The IAS–USA Drug Resistance Mutations Figures are designed for use in identifying mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiologic studies of transmission of drug-resistant virus. A number of amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral 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 most commonly develops to lamivudine or the nonnucleoside reverse transcriptase inhibitors [NNRTIs]).<sup>1–5</sup> This paradox may involve patient nonadherence, laboratory error, 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.

A copy of the current recommendations for antiretroviral resistance testing from the IAS–USA HIV Resistance Testing Guidelines Panel<sup>6</sup> can be found on the IAS–USA Web site at [www.iasusa.org](http://www.iasusa.org).

## Revisions to the Figures for the October/November 2005 Update

### Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

In this October/November 2005 version of the figures and user notes, the zalcitabine bar has been removed because zalcitabine is no longer commercially available. In the previous version, the thymidine analogue-associated mutations (TAMs; M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) as well as the E44D and V118I appeared at the top of the nRTI class on a multi-nRTI resistance bar. The list has been revised to include only TAMs and has been moved to the bottom of the drug class with the other multi-nucleoside reverse

transcriptase inhibitor (nRTI)-resistance pathways. Also, the vertical pink lines previously used to show the nRTI cross-resistance associated with TAMs plus E44D and V118I have been removed from the figures. The changes were made because other mutations may lead to multi-drug resistance within the nRTI class (eg, K65R).

### Protease Inhibitors

In the protease inhibitor (PI) category, newer data prompted numerous additions and changes to the list of mutations associated with atazanavir resistance. As described in user note 18, the accumulation of these mutations is associated with high-level resistance to atazanavir. Similarly, various changes have been made with regard to mutations associated with resistance to tipranavir. This drug was approved by the US Food and Drug Administration in July 2005 and data have become available to begin to better describe relevant mutations. The other specific changes in the PI category include: for (fos)amprenavir, the addition of position 82 and the substitutions associated with this new minor mutation; for lopinavir/ritonavir, the designation of mutations at 3 positions—32, 47, and 82—as major; and for ritonavir, the addition of the minor mutation, I50V. The multi-PI resistance bar has now been removed. In general, as major and minor substitutions associated with resistance to drugs within the PI class accumulate, susceptibility to certain PIs may decrease.

(continued, page 130)

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

**Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)<sup>1</sup>**

Abacavir <sup>2</sup>		K		L		Y		M	
		<b>65</b>		<b>74</b>		<b>115</b>		<b>184</b>	
		R		V		F		V	
Didanosine <sup>3,4</sup>		K		L					
		<b>65</b>		<b>74</b>					
		R		V					
Emtricitabine <sup>5,6</sup>		K						M	
		<b>65</b>						<b>184</b>	
		R						V	
Lamivudine <sup>6</sup>		K						M	
		<b>65</b>						<b>184</b>	
		R						V	
Stavudine <sup>6,7,8</sup>	M E		K D	K		V		L T K	
	<b>41 44</b>		<b>65 67</b>	<b>70</b>		118		<b>210 215 219</b>	
	L D		R N	R		I		W Y Q	
								F E	
Tenofovir <sup>9</sup>		K							
		<b>65</b>							
		R							
Zidovudine <sup>6,7,8</sup>	M E		D	K		V		L T K	
	<b>41 44</b>		<b>67 70</b>			118		<b>210 215 219</b>	
	L D		N	R		I		W Y Q	
								F E	

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations<sup>6,10</sup> (TAMs; affect all nRTIs currently approved by the US FDA)

	M		D	K				L T K	
	<b>41</b>		<b>67</b>	<b>70</b>				<b>210 215 219</b>	
	L		N	R				W Y Q	
								F E	

Multi-nRTI Resistance: 69 Insertion Complex<sup>11</sup> (affects all nRTIs currently approved by the US FDA)

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

Multi-nRTI Resistance: 151 Complex<sup>12</sup> (affects all nRTIs currently approved by the US FDA except tenofovir)

	A		V	F		F	Q		
	<b>62</b>		<b>75 77</b>			<b>116</b>	<b>151</b>		
	V		I	L		Y	M		

**Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)<sup>1,13</sup>**

Delavirdine			K	V		Y	Y		P
			<b>103 106</b>			<b>181</b>	<b>188</b>		<b>236</b>
			N	M		C	L		L
Efavirenz		L	K	V	V	Y	Y	G	P
		<b>100 103 106 108</b>				<b>181</b>	<b>188 190</b>		<b>225</b>
		I	N	M	I	C	L	S	H
						I	L	A	
Nevirapine		L	K	V	V	Y	Y	G	
		<b>100 103 106 108</b>				<b>181</b>	<b>188 190</b>		
		I	N	A	I	C	C	A	
				M		I	L	H	

Multi-NNRTI Resistance<sup>14</sup> (affects all NNRTIs currently approved by the US FDA)

		K	V			Y			
		<b>103 106</b>				<b>188</b>			
		N	M			L			

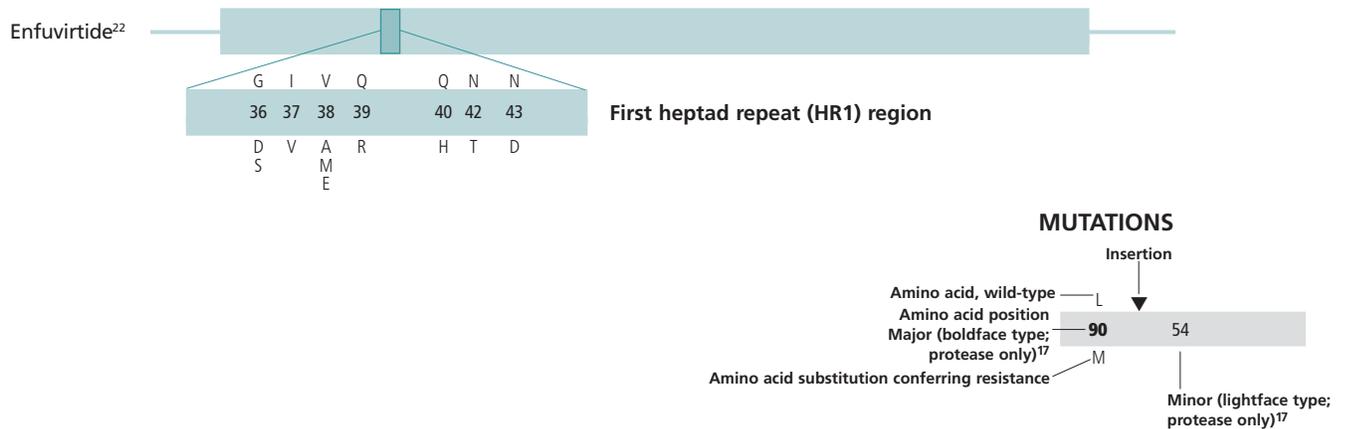
Multi-NNRTI Resistance: Accumulation of Mutations<sup>15</sup> (affects all NNRTIs currently approved by the US FDA)

	L	V		Y	G		M	
	<b>100</b>	<b>106</b>		<b>181</b>	<b>190</b>		<b>230</b>	
	I	A		C	S		L	
				I	A			

**MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS**<sup>16,17</sup>

Atazanavir <sup>18</sup>	L	G	K	L		V	L	M		M	G	I	I	D	I	A	G	V	I	N	L	I
	<b>10</b>	<b>16</b>	<b>20</b>	<b>24</b>		<b>32</b>	<b>33</b>	<b>36</b>		<b>46</b>	<b>48</b>	<b>50</b>	<b>54</b>	<b>60</b>	<b>62</b>	<b>71</b>	<b>73</b>	<b>82</b>	<b>84</b>	<b>85</b>	<b>88</b>	<b>90</b>
(Fos) amprenavir	L					V				M	I	I	I			G	V	I		L		
	<b>10</b>					<b>32</b>				<b>46</b>	<b>47</b>	<b>50</b>	<b>54</b>			<b>73</b>	<b>82</b>	<b>84</b>		<b>90</b>		
Indinavir	L	K	L		V		M		M						A	G	V	V	I		L	
	<b>10</b>	<b>20</b>	<b>24</b>		<b>32</b>		<b>36</b>		<b>46</b>			<b>54</b>			<b>71</b>	<b>73</b>	<b>77</b>	<b>82</b>	<b>84</b>		<b>90</b>	
Lopinavir/ ritonavir <sup>19</sup>	L	K	L		V	L		M	I	I	F	I		L	A	G	V	V	I		L	
	<b>10</b>	<b>20</b>	<b>24</b>		<b>32</b>	<b>33</b>		<b>46</b>	<b>47</b>	<b>50</b>	<b>53</b>	<b>54</b>		<b>63</b>	<b>71</b>	<b>73</b>	<b>82</b>	<b>84</b>		<b>90</b>		
Nelfinavir <sup>20</sup>	L			D			M		M						A	V	V	I	N	L		
	<b>10</b>			<b>30</b>			<b>36</b>		<b>46</b>						<b>71</b>	<b>77</b>	<b>82</b>	<b>84</b>	<b>88</b>	<b>90</b>		
Ritonavir	L	K			V	L	M		M		I	I			A	V	V	I		L		
	<b>10</b>	<b>20</b>			<b>32</b>	<b>33</b>	<b>36</b>		<b>46</b>		<b>50</b>	<b>54</b>			<b>71</b>	<b>77</b>	<b>82</b>	<b>84</b>		<b>90</b>		
Saquinavir	L									G		I			A	G	V	V	I		L	
	<b>10</b>									<b>48</b>		<b>54</b>			<b>71</b>	<b>73</b>	<b>77</b>	<b>82</b>	<b>84</b>		<b>90</b>	
Tipranavir/ ritonavir <sup>21</sup>	L	I	K		L	E	M		K	M	I		I	Q	H	T	V	N	I		L	
	<b>10</b>	<b>13</b>	<b>20</b>		<b>33</b>	<b>35</b>	<b>36</b>		<b>43</b>	<b>46</b>	<b>47</b>		<b>54</b>	<b>58</b>	<b>69</b>	<b>74</b>	<b>82</b>	<b>83</b>	<b>84</b>		<b>90</b>	

**MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS**



*The International AIDS Society–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order 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.*

*The mutations listed 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) genetic 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. In addition, the group only reviews 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 (FDA) or are available through expanded access protocols 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. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.*

## User Notes

- Numerous nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) mutations, such as the M41L, L210W, and T215Y mutations, may lead to viral hypersusceptibility to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens in NNRTI treatment-naive individuals (Shulman et al, *AIDS*, 2004; Demeter et al, 11<sup>th</sup> CROI, 2004; Haubrich et al, 11<sup>th</sup> CROI, 2004; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003).
- The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000; Lanier et al, *Antivir Ther*, 2004). When present with 2 or 3 thymidine analogue-associated mutations (TAMs), M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo (Lanier et al, *Antivir Ther*, 2004). The M184V plus 4 or more TAMs resulted in no virologic response to abacavir in vivo (Lanier et al, *Antivir Ther*, 2004).
- The K65R mutation may be selected by didanosine and is associated in vitro with decreased susceptibility to the drug (Winters et al, *Antimicrob Agents Chemother*, 1997). The impact of the K65R in vivo is unclear.
- The presence of 3 of the following—M41L, D67N, L210W, T215Y/F, and K219Q/E—has been associated with resistance to didanosine (Marcelin et al, *Antimicrob Agents Chemother*, 2005). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).
- There are limited data on the effects of emtricitabine mutations in vivo. It is assumed that if resistance to emtricitabine emerges, the virus will also be resistant to lamivudine, and vice versa. New mutations that confer resistance or cross-resistance to emtricitabine may exist, but have not yet been described.
- The E44D and the V118I increase the level of resistance to zidovudine and stavudine in the setting of TAMs, and correspondingly increase cross-resistance to the other nRTIs. The significance of E44D or V118I when each occurs in isolation is unknown, and therefore these mutations are not in bold type on the figure (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).
- The presence of the M184V mutation appears to delay or prevent emergence of TAMs (Kuritzkes et al, *AIDS*, 1996). This effect may be overcome by an accumulation of TAMs or other mutations. The clinical significance of this effect of M184V is not known.
- The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215, conferring increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients (Riva et al, *Antivir Ther*, 2002; Chappey et al, *Antivir Ther*, 2003; Violin et al, *AIDS*, 2004). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *J Virol*, 2004; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).
- The K65R is associated with a reduced virologic response to tenofovir in vivo (Miller et al, *J Infect Dis*, 2004). A reduced response occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W (Miller et al, *J Infect Dis*, 2004). Slightly increased treatment responses to tenofovir in vivo were observed if M184V was present (Miller et al, *J Infect Dis*, 2004).
- Multi-nRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as TAMs. TAMs are a subset of NAMs that are selected by the thymidine analogues zidovudine and stavudine and are associated with cross-resistance to all nRTIs currently approved by the US FDA (Larder et al, *Science*, 1989; Kellam et al, *Proc Natl Acad Sci USA*, 1992; Calvez et al, *Antivir Ther*, 2002; Kuritzkes et al, *J Acquir Immune Defic Syndr*, 2004).
- 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 TAMs at codons 41, 210, or 215 (Miller et al, *J Infect Dis*, 2004). Some other amino acid changes from the wild-type T at codon 69 without the insertion may also be associated with broad nRTI resistance.
- Tenofovir retains activity against the Q151M complex of mutations (Miller et al, *J Infect Dis*, 2004).

13. The long-term virologic response to sequential NNRTI use is poor, particularly when 2 or more mutations are present (Antinori et al, *AIDS Res Hum Retroviruses*, 2002; Lecossier et al, *J Acquir Immune Defic Syndr*, 2005).

14. The K103N or Y188L mutation alone prevents the clinical utility of all NNRTIs currently approved by the US FDA (Antinori et al, *AIDS Res Human Retroviruses*, 2002). The V106M mutation is more common in HIV-1 subtype C than in subtype B, and confers cross-resistance to all currently approved NNRTIs (Brenner et al, *AIDS*, 2003; Cane et al, *J Clin Micro*, 2001).

15. Accumulation of 2 or more of these mutations substantially reduces the clinical utility of all NNRTIs currently approved by the US FDA.

16. In general, the same mutations emerge whether or not the protease inhibitors (PIs) are boosted with low-dose ritonavir, although there is some difference in the relative frequency of various mutations. However, with regimens that include boosted PIs, multiple mutations may be required to result in less virologic activity. More data are needed to make specific comparisons between a particular boosted PI and a non-boosted PI.

17. Resistance mutations in the protease gene are classified as either "major" or "minor," if data are available.

Major mutations in the protease gene are defined in general either as those selected first in the presence of the drug; or those shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. Major mutations have an effect on drug susceptibility phenotype. In general, 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 significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus containing major mutations. However, some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype B clades, such as K201/R and M36I in protease.

18. In most patients in whom an atazanavir/ritonavir-containing regimen was failing virologically, accumulations of the following 13 mutations were found (L10F/I/V, G16E, L33F/I/V, M46I/L, I54L/V/M/T, D60E, I62V, A71I/T/L, V82A/T, I84V, I85V, L90M, and I93L). Seven mutations were retained in an atazanavir score (L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V); the presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M was present (Vora, et al, *Antivir Ther* 2005).

19. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the bar is associated with a reduced virologic response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002; Kempf et al, *J. Virol*, 2001). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. In contrast, in those in whom lopinavir/ritonavir is their first PI used, resistance to this drug at the time of virologic rebound is rare. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance (Mo et al, *J. Virol*, 2001; Friend et al, *AIDS* 2004; Kagen et al, *Protein Sci*, 2005).

20. In some nonsubtype-B HIV-1, D30N is selected less frequently than other PI mutations (Gonzalez et al, *Antivir Ther*, 2004).

21. In PI-experienced patients, early studies of tipranavir/ritonavir suggested an accumulation of mutations at positions 33, 82, 84, and 90 correlated with virologic response. Responses were greater when fewer than 3 of these mutations were present, but larger data sets did not confirm an independent role for L90M in tipranavir resistance. Subsequent analyses of data from phase II and III studies in PI-experienced patients identified mutations associated with reduced susceptibility or reduced virologic response. These include: L10V, I13V, K20M/R, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Accumulation of these mutations leads to reduced tipranavir response. These data must be considered preliminary, and require further confirmation and validation before their clinical utility can be considered (Schapiro et al, 12th

CROI, 2005; Kohlbrenner et al, DART, 2004; Mayers et al, *Antivir Ther*, 2004; Kohlbrenner et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003; Valdez, *Antivir Ther*, 2005; Muzammil, *Antivir Ther*, 2005).

22. Although resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene, wild-type viruses in the depicted HR1 region vary 500-fold in susceptibility. Such pretreatment susceptibility differences were not associated with differences in clinical responses (Labrosse et al, *J Virol*, 2003). Furthermore, mutations or polymorphisms in other regions in the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *Proc Natl Acad Sci USA*, 2002; Reeves et al, *J Virol*, 2004; Xu et al, *Antimicrob Agents Chemother*, 2005). Thus, testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure (Reeves et al, *J Virol*, 2004; Menzo et al, *Antimicrob Agents Chemother*, 2004; Poveda et al, *J Med Virol*, 2004; Sista et al, *AIDS*, 2004; Su et al, *Antivir Ther*, 2004).

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**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.

(continued from page 125)

### Fusion Inhibitors

The E substitution at position 38 and the Q40H have been added to the list of mutations conferring resistance to enfuvirtide.<sup>12</sup>

### Future Revisions of the Figures

As part of the recent revisions to the user notes, the IAS–USA Drug Resistance Mutations Group is developing a table for the IAS–USA Web site ([www.iasusa.org](http://www.iasusa.org)) on emerging issues in HIV-1 resistance and available resistance data for investigational drugs for which phase II trial data are available.

### Acknowledgments

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### Comments?

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes. Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at **resistance2005“at”iasusa** (this will change to **resistance2006“at”iasusa** as of January 1, 2006) or by fax at 415-544-9401. Please include your name and institution.

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### References

- Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team. *JAMA*. 2000;283:205-211.
- Havir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. 2000;283:229-234.
- Maguire M, Gartland M, Moore S, et al. Absence of zidovudine resistance in antiretroviral-naïve patients following zidovudine/lamivudine/protease inhibitor combination therapy: virological evaluation of the AVANTI 2 and AVANTI 3 studies. *AIDS*. 2000;14:1195-1201.
- Galleo O, Ruiz L, Vallejo A, et al. Changes in the rate of genotypic resistance to antiretroviral drugs in Spain. *AIDS*. 2001;15:1894-1896.

5. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346:2039-2046.
6. Hirsch MS, Brun-Vézinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of the International AIDS Society-USA panel. *Clin Infect Dis*. 2003;37:113-128.
7. Vora S, Marcelin AG, Gunthard H, et al. Clinical validation of atazanavir/ritonavir genotypic resistance score in PI-experienced patients. *Antivir Ther*. 2005;10:S9.
8. Mo H, King MS, King K, Molla A, Brun S, Kempf DJ. Selection of resistance in protease inhibitor-experienced, human immunodeficiency virus type 1-infected subjects failing lopinavir- and ritonavir-based therapy: mutation patterns and baseline correlates. *J Virol*. 2005;79:3329-3338.
9. Friend J, Parkin N, Liegler T, Martin JN, Deeks SG. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. *AIDS*. 2004;18:1965-1966.
10. Kagan RM, Shenderovich MD, Heseltine PN, Ramnarayan K. Structural analysis of an HIV-1 protease I47A mutant resistant to the protease inhibitor lopinavir. *Protein Sci*. 2005;14:1870-1878.
11. Boehringer Ingelheim. Aptivus [package insert]. Germany: Boehringer Ingelheim; 2005.
12. Stanfield-Oakley SA, Mosier SM, Davison DK, Medinas R, Heilek-Snyder G, Cammack N, Greenberg ML. Impact of Mutations in HR2 of HIV-1 env gp41 on susceptibility to enfuvirtide. *Antivir Ther*. 2005;10:S75.

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#### Atlanta, GA

Monday, March 6, 2006  
Westin Peachtree Plaza  
Chair: Michael S. Saag, MD  
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#### New York, NY

Wednesday, March 15, 2006  
New York Marriott Marquis  
Chair: Gerald H. Friedland, MD  
Vice-Chair: Paul A. Volberding, MD

#### San Francisco, CA

Tuesday, April 4, 2006  
San Francisco Grand Hyatt  
Chair: Robert T. Schooley, MD  
Vice-Chair: Stephen E. Follansbee, MD

#### Chicago, IL

Monday, May 8, 2006  
Marriott Chicago Downtown  
Chair: John P. Phair, MD  
Vice-Chair: Harold A. Kessler, MD

#### Washington, DC

Friday, May 19, 2006  
JW Marriott Pennsylvania Avenue  
Chair: Henry Masur, MD  
Vice-Chair: Michael S. Saag, MD

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The International AIDS Society–USA co-sponsors sessions at the annual Infectious Diseases Society of America (IDSA) meeting and at the annual *Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC). The agendas feature current clinical issues and controversies presented in interactive formats, with expert faculty using clinical decision points as springboards for discussion of new data and updates in diagnostic and therapeutic issues in HIV management.

#### ICAAC 2005

Washington, DC

#### *Current Issues and Controversies in HIV Infection Management: Session 182*

Sunday, December 18, 2005, 2:00pm - 4:30 pm  
Washington, DC, Convention Center, Room 146  
Chair: Judith S. Currier, MD

Due to Hurricane Katrina and its devastating effect on New Orleans, the ICAAC organizers have rescheduled the conference for December 16-19, 2005, in Washington, DC. Please visit [www.icaac.org](http://www.icaac.org) or [www.iasusa.org](http://www.iasusa.org) for updated information about this interactive session.

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