Experts Issue Early Guide for Hep C Protease Inhibitor Therapy in People Living with HIV

January 3, 2012

A small but influential group of hepatitis C virus (HCV) experts has published provisional guidelines on the use of HCV protease inhibitors (PIs) in people living with HIV. The guidelines, published ahead of print by Clinical Infectious Diseases, are based in part on recommendations made to the Maryland AIDS Drug Assistance Program (ADAP) to help guide the use of these drugs in people coinfected with both viruses in the absence of official approvals from the U.S. Food and Drug Administration (FDA) and complete clinical trial results. [See editor's note at end of article.]

"Until additional data or alternative treatments are available," David Thomas, MD, of the Johns Hopkins Schoolf Medicine and his colleagues write, "some experts believe that HCV PIs should be used in combination with peginterferon and ribavirin in certain HIV/HCV-coinfected persons."

Merck's Victrelis (boceprevir) and Vertex's Incivek (telaprevir) were approved by the FDA in May 2011 for use in combination with pegylated interferon and ribavirin in people with genotype 1 HCV infection. These approvals were based on clinical trial data indicating improved sustained virologic response (SVR) responses—viral cures—by 25 to 31 percent, over pegylated interferon and ribavirin alone, in HIV-negative people living with chronic HCV infection.

Though they are not yet approved for people coinfected with both HIV and HCV, there is a great deal of interest in prescribing the HCV PIs for those living with both viruses. The authors note that liver disease progression is more rapid and pegylated interferon and ribavirin is less effective in coinfected individuals, compared with those without HIV, and liver transplantation is neither widely available nor highly successful in those living with HIV and HCV.

But prescribing the HCV PIs for people living with HIV is not without challenges. As Thomas and his colleagues explain, "the safety and efficacy of HCV PIs are largely unproven in HIV/HCV-coinfected persons, data regarding drug-drug interactions are limited, additional anti-HCV medications are being developed, and the price of HCV PIs may add to the cost of the peginterferon and treatment regimen."

Yet some early data from clinical trials are available, the authors note, which do allow for provisional guidelines, notably for state ADAP programs which "will need to consider the provision of HCV PIs alongside other competing priorities." These guidelines, Thomas and his colleagues add, will likely be of interest to other groups as well.

A series of general treatment recommendations, along with guidelines specific to each HCV PI, were offered by Thomas's group, which included three other Johns Hopkins coinfection experts, as well as Marion Peters, MD, of the University of California, San Francisco, and Kenneth Sherman, MD, of the University of Cincinnati School of Medicine.

Among the general recommendations, Thomas and his colleagues note that pegylated interferon and ribavirin—without either Victrelis or Incivek—remains the standard treatment for coinfected patients with HCV genotype 2, 3 or 4. Additionally, pegylated interferon and ribavirin alone should be used when important drug-drug interactions, including those between the HCV PIs and HIV antiretrovirals, cannot be confidently eliminated or managed.

If either Victrelis or Incivek are prescribed for people living with HIV and genotype 1 HCV, the authors warn that using either drug alone—without pegylated interferon and ribavirin—is contraindicated, given that rapid resistance to the drugs can occur. In turn, people who are unable to use pegylated interferon plus ribavirin—notably women who are pregnant, are using Videx EC (didanosine) or have severe, uncontrolled psychiatric issues—should also avoid HCV PI treatment.

The authors also point out that the benefits of Victrelis or Incivek therapy outweigh the potential risks when started by those with significant liver fibrosis, as opposed to earlier disease. "Although HIV/HCV-coinfected persons have more rapid progression of liver disease than HIV-uninfected persons and HCV treatment is more efficacious at lower disease stage," they write, "some experts believe that it is safer to monitor patients with little or no fibrosis for evidence of progression while awaiting additional safety and efficacy data in HIV/HCV-coinfected persons, as well as additional new antiviral agents."

Thomas and his colleagues also recommend that HIV should be well controlled before HCV treatment is started—either a CD4 counts above 500 and a viral load below 20,000 copies in the absence of ARV treatment or a viral load below 50 copies while on HIV therapy.

In addition, it is recommended that prescribing physicians continually monitor HCV PI package inserts for specific drug interactions, including antiretrovirals that should not be combined with either Victrelis or Incivek.

Specific recommendations for each drug are also provided. These include:

Incivek

- Incivek should be combined with pegylated interferon and ribavirin for the first 12 weeks of therapy, followed by pegylated interferon and ribavirin alone for an additional 36 weeks—a total of 48 weeks of treatment.
- The following antiretroviral regimens are considered by Thomas's group to be safe in combination with Incivek: Norvir (ritonavir)-boosted Reyataz (atazanavir) plus Truvada (tenofovir plus emtricitabine), Isentress (raltegravir) plus Truvada, and Atripla (efavirenz plus tenofovir and emtricitabine). With either Norvir-boosted Reyataz or Isentress, standard doses of

Incivek—750 mg every seven to nine hours—should be used, though it is important to take it with food containing at least 20 grams of fat. If Atripla is used, the Incivek dose should be increased to 1,125 mg every seven to nine hours, in order to circumvent the interaction between the efavirenz in Atripla and Incivek.

- Incivek, pegylated interferon and ribavirin treatment should be stopped if HCV viral load is not below 1,000 copies at weeks 4 and 12, or if HCV viral load remains detectable at week 24. Additionally, if HCV viral load increases by 1 log or more at any time point, Incivek should be discontinued.

Victrelis

- If Victrelis is prescribed, therapy should begin with four weeks of pegylated interferon and ribavirin alone. From there, Victrelis is added to the regimen and continued for an additional 44 weeks.
- At present, the authors recommend Victrelis in combination with only one HIV treatment regimen: Norvir -boosted Reyataz plus Truvada. Standard doses of these medications should be used, along with Victrelis 800 mg every seven to nine hours. “Until research demonstrates safety,” they add, “[Victrelis] should NOT be used with efavirenz, [Intelence] etravirine or [Viramune] nevirapine.”
- Victrelis, pegylated interferon and ribavirin treatment should be stopped if the HCV viral load is above 100 copies after 12 weeks of treatment. Additionally, individuals who meet the week 12 milestone but have a detectable HCV viral load at week 24 should discontinue therapy. Thomas and his colleagues also point out that, to ensure that the benefits of treatment are sustained and outweigh the risks, “persons should be judged to have a limited risk of reinfection.”

Finally, the authors reiterate that pegylated interferon, ribavirin and the use of an HCV PI is expected to be less effective in coinfected individuals who did not clear HCV with prior pegylated interferon and ribavirin treatment—so-called partial responders and nonresponders—and/or those with cirrhosis, unfavorable IL28B genotype or African ancestry. “Data regarding the use of these agents in HCV treatment-experienced patients are lacking,” they write. “However, triple-therapy response is higher in re-treated patients than in patients treated with peginterferon and ribavirin

alone, and guidelines for use similar to that in treatment-naïve patients should be applied pending availability of additional data."

"Approvals of boceprevir and telaprevir for treatment of HCV infection are major advances for the care of persons with chronic genotype 1 HCV infection," Thomas and his colleagues conclude. "Although the medications are not approved by the US Food and Drug Administration for treatment of HIV/HCV-coinfected persons, the benefits of including these medications will outweigh the risks for some individuals. In the future, HIV/HCV-coinfected persons should be included at earlier stages in drug development so that practice guidelines can be based more on data and less on expert opinion."

Editor's note (2/16/12): The provisional guidelines reviewed in this report have been "temporarily withdrawn due to new information about the treatment recommendations contained therein," according to Clinical Infectious Diseases. The new information pertains to a February 6 warning to health care providers regarding significant drug-drug interactions between Merck's Victrelis and various HIV protease inhibitors. "The authors are updating the article and a revised version will be posted as soon as possible," the CID placeholder text reads.
