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Hot News

HIV Protease Inhibitors Associated with Increased HCV Viral Load in Coinfected Patients

Increases in serum HCV-RNA of 1 log on average after initiation of antiretroviral therapy have been reported in HIV/HCV-coinfected patients (Chung, et al. AIDS. 2002;16:1915-23). Accordingly, coinfected individuals on antiretroviral therapy depict greater HCV viremia than HCV-monoinfected individuals (Barreiro, et al. J Clin Virol. 2015;71:63-6). This observation could contribute to explaining lower treatment response rates in the coinfected population, even using the new oral direct-acting antivirals.

AIDS Clinical Trials Group (ACTG) investigators have recently unveiled a mechanism that could explain why HCV replication could increase following the initiation of antiretroviral therapy. They found that antiretrovirals increased most lipoproteins and apolipoproteins, which in turn led to increases in circulating HCV particles (Naggie, et al. Open Forum Infect Dis. 2015;2:ofv066).

Given that HCV circulates in the serum as very low-density lipo-viro-particles, that largely include triglycerides and apolipoproteins B and E, antiretrovirals that induce greater dyslipidemia, such as ritonavir-boosted protease inhibitors (i.e. lopinavir, atazanavir, and darunavir) (Aberg, et al. AIDS Res Hum Retroviruses. 2012;28:1184-95) may particularly push HCV biogenesis and increase HCV replication.

These findings add a further note of caution for using protease inhibitors in HIV/HCV-coinfected patients, since metabolic abnormalities and fatty liver disease may independently contribute to liver fibrosis progression (Blanco, et al. J Viral Hepat. 2011; 18:11-6) and may impair HCV treatment response. The ACTG authors concluded that with an increasing range of options for antiretroviral therapy now available, lipogenic changes associated to protease inhibitors should be avoided in HIV/HCV-coinfected individuals.

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Hepatitis B Reactivation During Successful HCV Therapy

Viral interference phenomena explain why individuals coinfected with several hepatitis viruses tend to display predominance of replication of one over others. Overall, HCV tends to suppress HBV, although both viruses may replicate overtly in severely immunosuppressed patients, as in those with advanced HIV disease (Soriano, et al. Curr Opin HIV/AIDS Rep. 2015, in press).

The advent of very potent inhibitors of HCV replication has unveiled a unique chance for HBV rebound in patients with prior low or undetectable serum HBV-DNA being either $HBsAg^+$ or more rarely only anti-HBc^+ (Collins, et al. CID. 2015, in press). The authors reported two patients successfully treated for chronic hepatitis C with sofosbuvir plus simeprevir that experienced HBV-DNA rebound along with liver enzyme flares after one month of direct-acting antiretroviral (DAA) therapy. The addition of tenofovir (± emtricitabine) permitted to regain HBV-DNA suppression and normalization of liver function tests. Upon DAA discontinuation, both patients were cured for HCV but continued on tenofovir therapy for HBV.

Current HCV treatment guidelines do not offer specific guidance on monitoring and management of patients coinfected with HBV (www.hcvguidelines.org). The two patients reported above support baseline testing of serum HBV-DNA before initiating DAA therapy for chronic hepatitis C in all patients with $HBsAg^+$ or occult hepatitis B infection (anti-HBc with HBV-DNA^+). Early initiation of anti-HBV therapy in patients experiencing HBV-DNA rebound while on DAA therapy may prevent significant hepatitis.

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Antiviral Therapy must be Offered to all Hepatitis C Patients, as Antiretrovirals to all HIV-Positive Individuals

Updated guidelines on hepatitis C from the AASLD/IDSA were released on July 2015 (www.hcvguidelines.org). The panel now strongly recommends oral antiviral treatment for all persons with chronic hepatitis C. It reflects the appreciation of both hepatic and extrahepatic benefits in individuals cured from HCV infection, even in those with minimal or null hepatic fibrosis (Metavir F0F1). The statement is a critical decision, with strong implications for medical services and budgets.

The new HCV guidelines specifically say that "treatment is recommended for all patients with chronic HCV infection". Antiviral therapy could be disregarded or deferred only in those with short life expectancies owing to comorbid conditions (i.e., terminal cancer, etc.). The new guidelines acknowledge that the most immediate and high-impact benefits of HCV cure will be seen in populations that are at the highest risk for liver-related complications, such as those with Metavir F3-F4, transplant recipients, HIV-coinfected persons, or those with clinically severe extrahepatic manifestations.

The shift in the treatment paradigm for HCV infection follows the steps of antiretroviral therapy in HIV infection, which currently is recommended for all infected persons regardless of CD4 counts (www.aidsinfo.nih.gov).

A further benefit of universal antiviral therapy expands to halt transmission to others. The principle of "treatment as prevention" is now well accepted in HIV infection, but has not been encouraged yet for HCV infection. There is no doubt that the good safety profile and convenient dosing of new oral antivirals will further facilitate its wider prescription.

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The START Trial: Definitive Evidence to Treat All HIV-Positive Persons Regardless of CD4 Counts

The Strategic Timing of Anti-Retroviral Treatment (START) study is the first large-scale randomized clinical trial to establish that earlier antiretroviral treatment (ART) benefits all HIV-infected individuals. The START trial was conducted by the International Network for Strategic Initiatives in Global Trials (INSIGHT) at 215 sites in 35 countries and enrolled 4,685 HIV-positive patients. All participants enrolled were ART naive with $CD4^+$ counts > 500 cells/mm^3. Approximately half of them were randomized to start ART immediately and the other half deferred therapy until their $CD4^+$ counts declined to < 350 cells/mm^3. All patients were followed for three years.

The rates of serious AIDS-related events and serious non-AIDS-related events were both lower in the early ART group than in the deferred treatment group. Results were consistent in low-, middle- and high-income countries. Although the study is expected to be finished at the end of 2016, in view of findings in an interim data review in March 2015, ART is being offered to all participants.

The last updated guidelines for HIV treatment developed by the DHHS panel (April 8, 2015; http://aidsinfo.nih.gov/guidelines) still recommends ART for all HIV-positive individuals to reduce the risk of disease progression and also to prevent HIV transmission. However, the strength of and evidence for this recommendation still vary by pretreatment CD4 counts, the strongest recommendation for treatment being initiation for patients with CD4 counts < 350 cell/mm^3. The recent data reported from the START study is a definitive proof of the clinical benefit of ART even in HIV-positive individuals with CD4 counts > 500 cells/mm^3. HIV treatment guidelines should be updated accordingly, acknowledging that all HIV-positive persons should be treated irrespective of CD4 counts.

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