# Hot News

## Hepatitis in the New IAS-USA Panel Antiretroviral Treatment Guidelines

The newly released International AIDS Society 2010 guidelines for antiretroviral treatment of adults with HIV infection (Thompson, et al. JAMA. 2010; 304:321-33) represents an important step for setting up the optimal management of HIV-infected persons at a time when new, more potent and safer antiretroviral agents have become available and when the deleterious impact of inflammatory processes associated to uncontrolled HIV replication regardless of CD4 counts have been fully appreciated. Moreover, given the accelerated course of liver disease in the subset of HIV-infected patients with chronic viral hepatitis, the panel agreed to recommend earlier initiation of antiretroviral therapy in most coinfected individuals. Three aspects, however, merit some consideration.

First, the IAS-USA panel suggested using entecavir when tenofovir is contraindicated in patients coinfected with HIV and HBV. However, nothing is mentioned about the risk for a potential inhibitory competition between lamivudine or emtricitabine when given along with entecavir, since all these agents interact with the catalytic sites of the respective reverse transcriptases or both HIV and HBV. Moreover, a potential pharmacodynamic interaction may result within cells when combining entecavir and abacavir, since both are guanosine analogs and may compete in the shared phosphorylation pathway (Soriano, et al. Antiviral Res. 2010;85:303-15). Therefore, until all these issues are solved, it seems too premature to recommend entecavir for treating HBV in HIV-infected individuals.

Second, the IAS-USA panel advises against using abacavir when treating chronic hepatitis C in HIV-infected individuals and wrongly records a reference (Laufer, et al. Antivir Ther. 2008;13:953-7), which in fact does not support their statement. A substudy of the RIBAVIC trial was the first to alert about a potential negative impact of abacavir on hepatitis C treatment response in HIV/HCV-coinfected patients (Bani-Sadr, et al. J Acquir Immune Defic Syndr. 2007;45:123-5). Soon thereafter and testing larger populations, we confirmed this observation (Vispo, et al. Antivir Ther. 2008;13:429-37; Mira, et al. Antivir Ther. 2010;15:91-9). However, we and others have pointed out that the deleterious impact of abacavir use on hepatitis C treatment outcomes seems to operate through a pharmacodynamic inhibitory competition between ribavirin and abacavir, both of which are guanosine analogs and compete in the phosphorylation pathway, but only compromising ribavirin effects when low doses (800 mg/day) are given. In fact, prescription of weight-based ribavirin (1,000-1,200 mg/day), as currently recommended (Soriano, et al. AIDS. 2007;21:1073-89), seems to overcome this effect.

Third, the IAS-USA panel considered that treatment of hepatitis C might be provided before beginning antiretroviral therapy when patients are infected with HCV genotypes 2 or 3 and have high CD4 cell counts. However, given the recent recognition of the huge impact of interleukin 28B (IL28B) polymorphisms on HCV treatment responses (Rallón, et al. AIDS. 2010;24:F23-9), we feel that HIV/HCV-coinfected individuals carrying HCV genotypes 1 or 4 with high CD4 counts and favorable IL28B genotypes might also benefit from earlier hepatitis C therapy, deferring antiretroviral treatment to later moments.

*Eugenia Vispo*
*Infectious Diseases Department*
*Hospital Carlos III*
*Madrid, Spain*

## New ARV Guidelines from the IAS-USA Panel

An updated version of the IAS-USA panel antiretroviral treatment guidelines was released in July 2010 (Thompson M, et al. JAMA. 2010;304:321-33). A new spirit with a wider openness to different treatment options emanates from this document in comparison with older versions. The consideration of two aspects largely explains this new view. First, the appreciation that uncontrolled HIV replication is associated with deleterious immune activation and inflammatory processes that ultimately accelerates damage of multiple organs, causing, among others, an increase in cardiovascular risk, neurological deterioration, etc. Second, the much more potent antiviral activity and safer profile of the newer antiretroviral drugs has permitted building unprecedented robust and convenient drug combinations.

The 2010 guidelines favors prescription of antiretroviral therapy to almost all HIV-infected individuals unless they are elite controllers or long-term nonprogressors, or for some reason prefer to defer therapy. Table 1 records the situations that support earlier initiation of antiretroviral therapy in subjects with CD4 counts > 500 cells/mm$^3$. As is evident, only a small subset of patients may not experience any of these conditions, and therefore almost everyone fulfils the criteria to be treated.

The IAS-USA panel revisited all comparative randomized clinical trials (RCT) released since the

**Table 1. Conditions favoring earlier initiation of ARV therapy**

- Symptomatic primary HIV infection
- Opportunistic infections
- Symptomatic HIV disease (wasting, fever, etc.) or complications (thrombopenia, etc.)
- Pregnant women
- Older than 60 years of age
- High viremia (plasma HIV RNA > 100,000 copies/ml)
- Rapid CD4 decline (> 100 cells/mm$^3$ per year)
- Chronic hepatitis B and/or C
- Elevated cardiovascular risk
- HIV-associated nephropathy
- Serodiscordant sexual couple

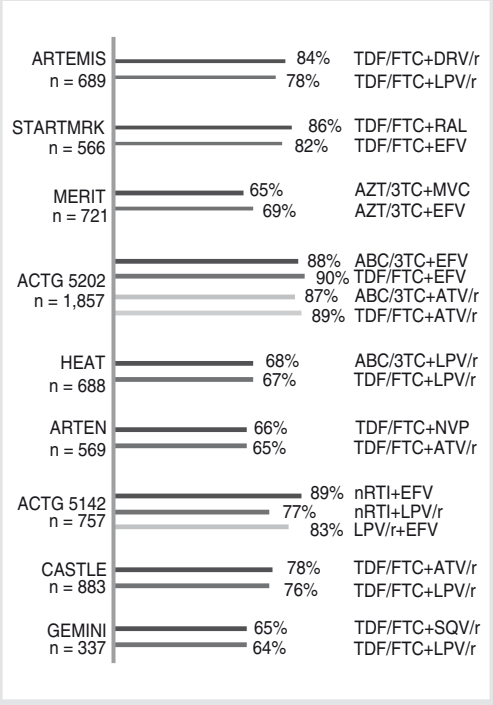


**Figure 1.** *Major randomized controlled trialsin HIV+ naive patients reported since the summer 2008.*

**Table 2. Recommended antiretroviral drugs for first-line therapy**

| | |
|---|---|
| **Preferred** | |
| NRTIs | Tenofovir/emtricitabine |
| **Plus a 3rd agent** | |
| NNRTI | Efavirenz |
| PI/r | Atazanavir/r |
| | Darunavir/r |
| INI | Raltegravir |
| **Alternative** | |
| NRTIs | Abacavir/lamivudine |
| **Plus a 3rd agent** | |
| NNRTI | Nevirapine |
| PI/r | Lopinavir/r |
| | Fosamprenavir/r |
| CCR5 antagonist | Maraviroc |

publication of the 2008 guidelines. Figure 1 summarizes the main results of these studies as the proportion of patients with undetectable viremia at week 48 using distinct drug regimens.

Based on the information recorded in these trials as well as from prior studies and accumulated clinical experience, the IAS-USA panel guidelines recommends specific antiretroviral regimens as first option in naive patients, and acknowledge that alternative regimens could be prescribed when justified (Table 2).

All this information is very welcome and should guide the current management of HIV-infected individuals. The recognition of the enormous improvement achieved in antiretroviral therapy in the Western world should now push to expand it to developing countries, where the majority of HIV-infected persons are living.

*Pablo Barreiro and Pablo Labarga*
*Infectious Diseases Department*
*Hospital Carlos III*
*Madrid, Spain*