Hot News

Update of the DHHS Antiretroviral Treatment Guidelines

The U.S. Department of Health and Human Services (DHHS) released on May 1st an update of its Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (www.aidsinfo.nih.gov). Among the major changes is the addition of a new section on cost considerations and a recommendation for less frequent CD4+ T-cell monitoring for people without advanced disease.

Past versions of the DHHS guidelines did not formally discuss expenses related to antiretroviral therapy (ART), but the new edition includes an overview of costs as they relate to adherence, cost-sharing, prior authorization, and use of generic drugs, with strategies for cost containment that do not compromise treatment effectiveness.

The new guidelines emphasize that viral load, rather than CD4 count, is the most important measure of response to ART. The CD4 count should be assessed when a person initiates care, but after starting ART this count is most helpful for people with advanced HIV disease to guide discontinuation of opportunistic infection prophylaxis or treatment (threshold 200 cells/mm^3). Frequent CD4 count monitoring is generally not required for people with high CD4 counts and long-term viral load suppression, and the panel now advises that CD4 testing be done annually for people with > 300-500 cells/mm^3. Monitoring of CD8+ T-cells is not clinically useful and not routinely recommended.

Other key changes in the latest edition of the guidelines focus on,

1. The classification of "Preferred" regimens has been changed to "Recommended", recognizing the expanded range of effective and well-tolerated options. Ten combinations are recorded as recommended regimens for people starting ART. As shown in the Table, for the first time they are divided into those recommended for any treatment-naive individual regardless of baseline viral load, and additional options for people with low viral load (< 100,000 HIV RNA copies/ml). Most combinations include tenofovir plus emtricitabine as nucleos(t)ide backbone. The third agent is a nonnucleoside analogue (efavirenz), two ritonavir-boosted protease inhibitors (darunavir or atazanavir), or any integrase inhibitor (raltegravir, elvitegravir/cobicistat or dolutegravir).
2. Given the large number of Recommended and Alternative options, several drugs are no longer recommended for first-line therapy, including zidovudine, nevirapine, unboosted atazanavir, boosted fosamprenavir or saquinavir, and maraviroc.
3. A new section has been added summarizing clinical trial data on first-line ART strategies for people who cannot use either tenofovir (e.g. due to kidney illness) or abacavir (e.g. positive HLA-B*5701).
4. More emphasis is made on switching antiretrovirals in people with prolonged viral suppression.

Table. Recommended combinations for first-line antiretroviral therapy

Any patient	Patients with low viral load (plasma HIV RNA < 100,000 copies/ml)
Tenofovir, emtricitabine & efavirenz	Abacavir, lamivudine & atazanavir/r*
Tenofovir, emtricitabine & darunavir/r	Tenofovir, emtricitabine & rilpivirine***
Tenofovir, emtricitabine & atazanavir/r	Abacavir, lamivudine & efavirenz*
Tenofovir, emtricitabine & raltegravir	
Tenofovir, emtricitabine & elvitegravir/cobi**	
Tenofovir, emtricitabine & dolutegravir	
Abacavir, lamivudine & dolutegravir*	

* Only for individuals negative for HLA-B*5701.
** Only for patients with creatinine clearance > 70 ml/min.
*** Only for patients with CD4 counts > 200 cells/mm^3.

The key principle is maintaining undetectable viral load without compromising future treatment options. Patient's prior treatment history, response to ART, resistance profile, and drug tolerance should be considered when contemplating a regimen switch. Nucleos(t)ide analogue-sparing regimens, such as ritonavir-boosted protease inhibitor monotherapy, should generally be avoided due to concerns on its poorer performance compared to classical triple therapy.

Vincent Soriano
Internal Medicine & Infectious Diseases
La Paz University Hospital
Madrid, Spain

Highlights from CROI 2014 on Experimental HIV Drugs

Despite the extensive therapeutic arsenal currently available to treat HIV infection, new agents allowing long-term safety and tolerability, with novel mechanism of action and more convenient administration, would be desirable to fight this chronic infection. In this regard, news on this topic has been highlighted at the last CROI held in Boston at the beginning of March, 2014.

BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, blocking the initial interaction between virus and host cell. The safety and efficacy of BMS-663068 was evaluated in a phase IIb trial in treatment-experienced patients in comparison with atazanavir/ritonavir, each with a background of tenofovir plus raltegravir (Lalezari, et al. CROI 2014. Abstract 86). Similar rates of subjects in the BMS-663068 had HIV-RNA < 50 cop/ml at week 24 (78-87%) compared with atazanavir/ritonavir (86%). All BMS-663068 doses were well tolerated and no adverse events leading to discontinuation were related to BMS-663068. The favorable safety and tolerability profiles showed in this study support further development of BMS-663068.

GSK1265744 (744) is an integrase strand-transfer inhibitor under development that has been formulated as both oral tablet and long-acting injectable. The LATTE study evaluated the efficacy of the oral combination of GSK744 with the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) rilpivirine as suppressive maintenance therapy. The combination of these two drugs provided similar antiviral activity to efavirenz in combination with tenofovir/emtricitabine (TDF/FTC) through the 48 week primary analysis (Margolis, et al. CROI 2014. Abstract 91LB). GSK744 plus rilpivirine was safe and well tolerated across all GSK744 doses (10, 30, or 60 mg). These findings support further development of 744 and set the stage for studies evaluating these drugs in long-acting injectable formulations that would be given by intramuscular injection every 4 or 8 weeks.

In this regard, very promising results were reported by García-Lerma, et al. in a proof-of-concept study evaluating the ability of long-acting GSK744 to prevent vaginal HIV transmission (García-Lerma, et al. CROI 2014. Abstract 40LB).They demonstrated that single, monthly infections of GSK744 long-acting that reproduce the human dose fully protected macaques against repeated vaginal SHIV exposures. These data support advancement of GSK744 long-acting formulation as a pre-exposure prophylaxis (PrEP) candidate to prevent HIV infection in women. The use of long-acting antiretroviral drugs could potentially decrease adherence problems associated with daily PrEP.

Doravirine (MK-1439) is an investigational NNRTI active *in vitro* against both wild-type and most common NNRTI-resistant HIV variants at concentrations achieved with once-daily dosing. The safety and antiviral efficacy of MK-1439 (25, 50, 100, and 200 mg qd) in combination with TDF/FTC were evaluated in a dose-finding study presented by Morales-Ramirez J, et al. (CROI 2014. Abstract 92LB). The results obtained were able to demonstrate the potent antiviral activity across all doses of MK-1439 in combination with TDF/FTC as compared with efavirenz in ART-naive HIV-1-infected patients at 24 weeks. The incidence of drug-related adverse events was comparable among the doravirine-treated groups and overall was lower than in the efavirenz-treated group. Based on these findings, the 100 mg once-daily dose was selected for a dose-confirmation study.

Considering the data presented at the last CROI edition, it seems that not all has been said in the field of antiretroviral drug development, and significant improvements related with efficacy and more convenient dosing are waiting on the horizon.

Eva Poveda and José D. Pedreira
Division of Clinical Virology
INIBIC-Complejo Hospitalario Universitario de A Coruña
A Coruña, Spain

More Pre-Exposure Prophylaxis for Rising HIV Infection?

In May 2014, the US Centers for Disease Control and Prevention (CDC) issued new recommendations for the prescription of Truvada® as pre-exposure prophylaxis (PrEP) for persons engaged in high-risk

HIV behaviors, be they homosexuals, heterosexuals, or injecting drug users (www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf).

Every year around 50,000 people become infected with HIV in the USA. Incident cases are stable among heterosexuals and injecting drug users, but are rising in homosexuals (12% increase yearly), particularly in the group under 24 years old (22% increase yearly). Nearly two-thirds of new HIV diagnoses occur in homosexual men.

Despite long and intense efforts to promote condoms, their use has been going down in recent years. According to the CDC, up to 20% of individuals with high-risk encounters acknowledge having unprotected sex. Recent syphilis, urethritis, and hepatitis C outbreaks reflect this public health breakdown. The pressure of these data has prompted US authorities to launch a new PrEP strategy, despite available studies showing an only 44-84% efficacy in preventing HIV in high-risk populations. Of note, the variation in this rate is mostly dependent on the strength of adherence to a once-a-day pill regimen.

In the new CDC document, PrEP is recommended for homosexual men with recent diagnosis of sexually transmitted infections, and in heterosexual men or women that infrequently use condoms with distinct partners. Sexual relationships with HIV-positive partners are now considered as a universal indication for PrEP, and this may include stable serodiscordant couples wishing to conceive. The CDC recommends HIV testing before PrEP and every three months thereafter.

Besides economic issues, as a large number of people may become candidates for a 10,000 US$ yearly therapy, concerns on selection of drug resistance and toxicities may complicate this strategy. Furthermore, a compensatory effect may be the encouraging of unprotected sexual risk behaviors that ultimately translate in increases of other sexually transmitted diseases which are not prevented by Truvada®. The HIV numbers may also increase as result of progressively declining rates of good PrEP adherence. Overall it seems worrisome that an uncontrolled HIV epidemic in certain scenarios may need to assume these additional uncertain risks. Further efforts in education are needed and would be less expensive.

Pablo Barreiro
Internal Medicine & Infectious Diseases
La Paz University Hospital
Madrid, Spain