Hot News

Welcome to "Hot News", a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

British HIV Guidelines for the Management of Hepatitis B and C in HIV-Coinfected Patients

Chronic infection with the hepatitis B virus (HBV), but especially with the hepatitis C virus (HCV), has acquired great importance over the last few years in the setting of HIV infection. Given the increased liver-related morbidity and mortality in this population, efforts are currently being made to treat, and more ambitiously, to cure these coinfections, in order to halt the progression to end-stage liver disease. However, the management of HBV and HCV coinfections in HIV-infected patients is often challenging. Numerous questions such as, "What is the assessment needed?", "Who needs to be treated?", "When?" and "How?" are still in the air, and there are no definitive answers. With the purpose of guiding HIV care providers in the management of coinfected patients, experts have gathered on several occasions and then released their recommendations.

The latest guidelines published on this subject are those developed by the British HIV Association (HIV Medicine 2005;6 [suppl 2]:84-106). These recommendations are well written and organized, and therefore easy to follow. They are supported by abundant information published on every issue, although the reviews are sometimes incomplete.

The HCV guidelines are thorough, but skip relevant matters. For instance, the question of treatment duration is not addressed at all. This is a very important issue given the high incidence of relapses after initial response in some of the trials conducted in HIV/HCV-coinfected subjects. Studies evaluating the potential benefit of prolonging anti-HCV therapy to prevent relapses are underway. In contrast, the points of how important it is to give high enough doses of ribavirin, or the need for an individualized approach to manage these patients are very well elaborated.

The comments pertaining to the need for a liver biopsy as part of the assessment prior to the treatment of HCV indicate that this is a highly controversial subject. However, vague statements as well as phrases strongly recommending its performance can be found throughout the text. There is no mention of the new noninvasive tools to assess liver fibrosis, such as elastography (FibroScan®) and/or serum biochemical tests (i.e., Fibrotest®). At the end, the expression "consider liver biopsy" in the algorithm leaves the door open to the readers to follow their own judgment in each case.

Regarding HBV recommendations, the first comment that can be made is that the lag between the preparation and the publication of the guidelines has been sufficiently long so as to explain some limitations. For instance, entecavir, a drug which is already approved as an anti-HBV agent, should be considered the first choice for patients requiring anti-HBV therapy but not antiretrovirals, given the potential risk of adefovir for selecting resistance mutations in HIV. On the other hand, the principles established for HBV-mono-infected patients may have been too rigorously applied to the HBV/HIV-coinfected population; e.g. the recommendation about the use and duration for nucleos(t)ide analogues (NRTI). The discontinuation of NRTI once anti-HBe seroconversion has been achieved may not necessarily apply in patients who are receiving highly active antiretroviral therapy (HAART). Several reports have highlighted that clearance of HBsAg can be attained over time by a growing proportion of patients receiving prolonged, anti-HBV, active HAART.

The guidelines are very cautious in advising not to use interferon in cirrhotic HBV/HIV-coinfected patients. However, while this is clear in cases of decompensated cirrhosis, early cirrhosis is not a contraindication and these patients may be treated with interferon if the chances of clearing HBV are high (i.e., elevated transaminase levels, positive HBeAg and/or low HBV-DNA).

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HIV Chemotherapy Revisited

Nearly 60 million people have been infected with HIV since the beginning of the pandemic, and of these one third have already died. For those infected more recently, however, the life expectancy has improved dramatically due to the favorable impact of highly active antiretroviral therapy (HAART). Unfortunately, antiretrovirals are moving only slowly into the developing world, where most persons are infected and where their benefit will have the largest impact.

The drawbacks of HAART are mainly associated to its side effects, particularly because the medication should be taken indefinitely in most cases as HIV can not be eradicated. Long-term toxicities of antiretrovirals, including metabolic abnormalities (hyperlipidemia, diabetes, etc) and the lipodystrophy syndrome, have halted its widespread use. It is somewhat paradoxical that, despite more than 20 antiretrovirals being currently approved for the treatment of HIV infection, the consideration of their strong efficacy along with their risk of adverse events has resulted in the restriction of their prescription only to patients with evidence of immunodeficiency (i.e. < 350 CD4+ T-cells per microliter). For the rest, periodic controls are usually enough.

The second drawback of antiretroviral therapy regards the selection of drug-resistant viruses. Moreover, given that cross-resistance between compounds within the same drug class is common, new inhibitors are needed for a growing number of patients who already have bourn the current medications.

The book "HIV Chemotherapy", recently released and edited by Salvatore Buttera, represents a comprehensive and updated description of the state of the art of antiretroviral therapy. Some of the best experts in the field have summa-

rized their views about how to use anti-HIV drugs, how to prevent and manage drug resistance, and how to deal with the need to implement HAART in the developing world. The reading of Buttera's book provides a new sentiment in which the knowledge of HIV therapeutics by health care providers is mandatory if they are to be useful for the many HIV-infected persons who will need them.

The opening chapters deal with the management of HIV infections and include a fascinating review of current molecular strategies to protect and strengthen the host immune system at the cellular level. The following chapter summarizes the strategies required for the implementation of effective anti-HIV therapies in developing countries (90% of worldwide AIDS cases). Thereafter, two excellent chapters comprehensively review the genetics of drug resistance and technologies. The remaining chapters provide cutting-edge reviews of the latest viral and cellular targets for anti-HIV chemotherapy, including the development of iRNA and other molecular-based strategies that target latent virus reservoirs in infected individuals.

This is essential reading for scientists and clinicians working on AIDS, HIV, and other retroviruses as well as for all health care professionals interested in expanding their current understanding of the subject.

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Discontinuation of Aplaviroc Trials due to Hepatotoxicity

CCR5 is the major chemokine coreceptor that HIV uses to enter CD4+ T-cells. Its blocking is being explored as a new anti-HIV strategy. Three competitive inhibitors have entered clinical trials: Maraviroc (UK-427,857; Pfizer), Vicriviroc (SCH-D; Schering-Plough) and Aplaviroc (GSK-873140; GlaxoSmithKline).

Aplaviroc is an orally bioavailable spirodiketopiperazine derivative that specifically blocks the binding of macrophage inflammatory protein 1-alpha (MIP-1α) to CCR5, potently inhibiting HIV-1 gp120 binding to CCR5, and preserves natural ligands RANTES and MIP-1β binding to CCR5. Although other CCR5 inhibitor binding sites are often found in the transmembrane domain, Aplaviroc CCR5 binding sites appear clustered around the ECL2 interface. Limited variability in anti-HIV activity has been observed against different R5-tropic isolates in peripheral blood mononuclear cells (PBMC) from multiple donors.

Aplaviroc shows substantial occupancy of CCR5 binding sites at *in vivo* attainable concentrations and a longer binding duration than the other CCR5 inhibitors currently under investigation. *In vitro* studies suggest that the drug has prolonged CCR5 coreceptor occupancy, with a half-life > 100 hours. It exhibits > 97% CCR5 coreceptor occupancy in blood during repeat oral administration and sustains viral suppression for 24 to 48 hours after therapy discontinuation. In a dose-ranging study, after therapy was stopped and plasma drug levels became undetectable, CCR5 coreceptor occupancy remained > 50% for approximately five days.

In a phase I/II, randomized, double-blind, placebo-controlled, dose-ranging study, Aplaviroc was given as monotherapy for 10 days to HIV-infected antiretroviral-naive and -experienced patients at doses of 200 or 600 mg twice daily and 200 or 400 mg once daily (eight receiving drug, two receiving placebo per arm). All doses were given with a moderate-fat meal. Antiretroviral-experienced patients abstained from treatment for 12 weeks prior to entry. All patients had a viral load of ≥ 5,000 copies/ml and a CD4 count nadir > 200 cells/mm^3. All patients were infected with R5-tropic HIV. A > 1 log, dose-dependent, viral load decrease was observed in patients taking 400 mg once daily and 200 or 600 mg twice daily. The greatest viral load reduction was observed between 24 and 36 hours after Aplaviroc discontinuation, suggesting a long CCR5 coreceptor occupancy. Evidence of viral tropism conversion to dual-tropic virus was seen in one patient on day 10, but virus reverted back to R5-tropic virus on day 24.

Aplaviroc appears safe and well tolerated when taken orally. The most common adverse effects noted in the 10-day, monotherapy, dose-ranging study were loose stools, diarrhea, abdominal pain, nausea, and flatulence. Headache, dizziness, and fatigue also occurred. Most adverse effects resolved within the first three days. No serious Grade 3 or 4 adverse effects were reported. No changes in laboratory or ECG abnormalities were observed.

The drug displays additive or synergistic activity when combined with other antiretroviral agents. In PBMC exposed to R5-tropic HIV, Aplaviroc had synergistic effects when combined with zidovudine, nevirapine, indinavir, and enfuvirtide, and additive effects when combined with another investigational CCR5 antagonist, SCH-C. Potent synergism was observed in PBMC exposed to dual-tropic HIV and treated with Aplaviroc when combined with investigational CXCR4 inhibitors AMD3100 or TE14011. No antagonistic effects or synergistic cellular toxicities were observed *in vitro*.

Aplaviroc is a cytochrome P450-3A substrate *in vitro,* and therefore ritonavir boosts plasma levels of the drug. In a trial conducted in eight HIV-uninfected adults, coadministration of Aplaviroc with lopinavir/ritonavir 400/100 mg twice daily resulted in significant increases of seven-fold in Cmin plasma concentrations of Aplaviroc. No changes in lopinavir levels, but small increases in ritonavir levels, were noticed.

GlaxoSmithKline announced in mid-September 2005 that it had halted safety and efficacy trials of Aplaviroc after two of the 250 treatment-naive trial participants developed severe liver toxicity. However, studies of Aplaviroc are continuing among treatment-experienced patients with drug-resistant viruses to currently approved treatments. Up this time no further information is available about the mechanisms involved in these cases of liver toxicity. The results are eagerly awaited.

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Safety-related Changes to the Nevirapine (Viramune®) Label

The nevirapine label has been revised several times over the last two years to include more information on liver toxicity associated with long-term nevirapine use. Based on a higher observed risk of serious liver toxicity in patients with elevated CD4+ cell counts prior to initiation of therapy, the "Indications and Usage" section of the Viramune® label now recommends against starting nevirapine treatment in women with CD4 counts > 250 cells/mm^3 and men with CD4 counts > 400 cells/mm^3, unless the benefits clearly outweigh the risks.

Regarding symptomatic nevirapine liver toxicity, it is important to note the following. Symptomatic nevirapine liver toxicity consists of elevated liver enzymes plus at least one symptom, which is typically rash but may include flu-like symptoms or fever, and typically occurs after only a few weeks of dosing and may progress to liver failure, despite monitoring of laboratory tests, which is not characteristic of other antiretrovirals. Females have a three-fold higher risk of symptomatic nevirapine liver toxicity than males, and females with CD4 counts > 250 cells/mm^3 have a 12-fold higher risk of symptomatic liver toxicity than females with CD4 counts < 250 (11% *vs*. 0.9%). Males with CD4 counts > 400 cells/mm^3 have a five-fold higher risk of symptomatic liver toxicity than males with CD4 counts < 400 (6.3% *vs*. 1.2%). Finally, nevirapine-related deaths due to symptomatic liver toxicity, including some in HIV-infected pregnant women, have been reported to FDA's Medwatch program. Serious and fatal liver toxicity has not been reported after single doses of nevirapine.

In spite of the potential for serious and life-threatening liver toxicity and skin rashes with nevirapine, there are multiple reasons why nevirapine remains an important part of an HIV treatment regimen for many HIV-infected individuals worldwide. These reasons include: 1) Triple antiretroviral drug regimens containing a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as nevirapine, are standard of care for HIV treatment and are needed to adequately and durably suppress virus replication; 2) Many options are needed for HIV-infected patients, since resistance to antiretroviral drugs or to an entire antiretroviral class can develop; 3) Symptomatic liver toxicity has not been reported with the use of single doses of nevirapine to the mother and to the child for prevention of perinatal HIV infection; 4) Alternatives to nevirapine are limited by other toxicities, potential drug interactions, and by the risk of drug-related birth defects (i.e. efavirenz) if given to a female in the first trimester of pregnancy; 5) Nevirapine liver toxicity is less frequent (< 2% for females with CD4 counts < 250 cells/mm^3 and for males with CD4 counts < 400 cells/mm^3) when started in patients with lower CD4 counts. Therefore, symptomatic liver toxicity in resource-poor countries is likely to be much lower if WHO standards are used for starting treatment. The WHO recommends the initiation of ART treatment in patients with advanced disease or with CD4 counts < 200 cells/mm^3; 6) Nevirapine is chemically stable in environmental conditions where other antiretrovirals are not; and 7) Symptomatic liver toxicity has not been reported in HIV-infected children, and nevirapine is available in a liquid formulation while many other antiretrovirals are not.

Finally, it is important to underline that this safety-related change to the Viramune® label is not an absolute contraindication. The warning is only related with starting antiretroviral therapy, but not for those patients actively receiving nevirapine, regardless of the CD4+ cell count, and the information has been almost exclusively collected from drug-naive patients who started nevirapine as a first-line therapy.

Health care providers should weigh the benefits and risks associated with nevirapine use before prescribing it for the treatment of their HIV-infected patients.

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