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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.

The trick that HIV uses to productively infect non-dividing cells

Nuclear import of macromolecules is regulated by a pathway for which nuclear localization signals are necessary. However, even in the presence of such signals, the size limit of nuclear pores still excludes large complexes such as the HIV pre-integration complex (PIC). Recently, the team of Dr. Greene (De Noronha, et al. Science 2001; 294: 1105-8) unraveled the enigma of how HIV is able to productively infect non-dividing cells. HIV is one of the few viruses that can insert its (pro-) viral DNA genome into the chromosomes of non-dividing cells. That is precisely why its genome is such an attractive vector for gene therapy. The exact mechanism of nuclear entrance of the bulky HIV PIC was however not entirely clear. Previous results showed that Vpr was somehow involved in the process (Heinzinger, et al. Proc Natl Acad Sci USA 1994; 92: 7311-8). Now, De Noronha et al. reported that Vpr induces herniations in the nuclear envelope, which subsequently burst, causing free traffick between the cytoplasm and the nucleus. These disruptions in the nuclear membrane heal quickly, but the ruptures might provide an opportunity to the HIV PIC to enter the nucleus. Since Vpr is not concentrated at the herniations, its effect must be indirect, possibly catalyzing the rupture event. As often happens in science, new discoveries raise new questions: how exactly is Vpr catalyzing herniation and nuclear rupture? These questions pose new challenges to HIV researchers.

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Rate and mechanisms of hepatotoxicity due to nevirapine

A warning on the potential risk of liver toxicity due to nevirapine (NVP) was released by health authorities last year. It specifically recommended close monitoring of laboratory parameters during the first 12 weeks on NVP therapy. Although transaminase elevations are a common side effect using NVP, and grade 3-4 toxicity occurs in around 10% of patients taking the drug, clinical hepatitis has shown to develops in less than 2% of cases in two recent trials (Martínez, et al. AIDS 2001;15:1261-8; Núñez, et al. J AIDS 2001;27: 426-31).

Two mechanisms have been involved in NVP-associated liver toxicity. The first implies an immune-mediated mechanism, and account for cases of transaminase elevations seen in subjects experiencing at the same time skin reactions few days-weeks after beginning NVP-containing regimens. This hypersensitivity reaction seem to be more common in subjects having elevated CD4+ lymphocyte counts, which may explain the unexpected occurrence of fulminant hepatitis noticed among a few immunocompetent HIV-negative subjects who underwent post-exposure prophylaxis with NVP (Johnson, et al. JAMA 2000;284:2722-3).

A second mechanism of NVP-related liver toxicity, which does not involve other organs, has a delayed onset, often several months, and might represent an intrinsic toxic effect of the drug. Supporting this hypothesis, a recent trial in which 610 subjects who began NVP were examined (Martínez et al. AIDS 2001;15:1261-8) has highlighted that the incidence of grade 3-4 liver toxic-

Table 1. *Clinical presentation of liver toxicity associated with antiretroviral drugs*

	Early onset	Late onset
Interval	1-6 weeks	4-8 months
Mechanism	immune-mediated	direct toxic cumulative
Dose-related	no	yes
Role of HCV	no	yes
Role of CD4	yes	no
Common drugs	abacavir, nevirapine	d4T, ddI, PI, nevirapine

Table 2. *Mechanisms of liver damage using antiretroviral drugs*

- Direct toxic effect:
  - Cytopathic action (i.e., ritonavir).
  - Cholestasis (i.e., indinavir, nevirapine).
  - Mitochondrial toxicity and steatosis (i.e., stavudine, zidovudine, etc)
- Immune-mediated effect:
  - Hypersensitivity reaction (i.e., nevirapine, abacavir).
  - Immune reconstitution syndrome in subjects with chronic viral hepatitis.

ity increased over time in subjects treated with NVP, being of 4, 10 and 20% at 3, 6 and 12 months, respectively. If NVP liver toxicity increases steadily over time and is in the range of what is seen with protease inhibitors (Savès, et al. AIDS 1999;13:F115-21), there is no rationale to defend an intensive clinical and laboratory monitoring of subjects who began NVP during the first 12 weeks of therapy. However, since chronic hepatitis C enhances the risk of delayed liver toxicity taking NVP (Núñez, et al. J AIDS 2001;27:426-31), treatment of hepatitis C should be particularly assessed in those patients.

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Cardiovascular Risk of Antiretroviral Therapy

Both hypercholesterolemia and hypertriglyceridemia constitute known independent risk factors for cardiovascular (CV) complications. HIV-infected persons undergoing potent antiretroviral therapy often show high lipid levels and, consequently, CV complications may become more common in treated HIV-positive patients. Preliminary data support this assumption. Moreover, in this context CV disease may be not only more common but also may develop earlier. In a recent retrospective cohort study carried out in 4282 HIV-positive men on antiretroviral treatment and 459,855 uninfected controls, higher rates of coronary heart disease were found among HIV-infected persons having an ages between 25 and 44 years-old (39th Annual Meeting of the IDSA, San Francisco 2001, abstract 18).

The risk of CV complications should now be taken into account when prescribing any antiretroviral regimen. Particular concern arises in subjects who already belong to groups at higher risk for accelerated CV disease due to family history, smoking, hyperlipidemia, hypertension, or diabetes.

It has been widely demonstrated that protease inhibitors (PI) induce a rise in triglycerides and cholesterol levels, which may account for an increased risk of coronary artery disease and other CV disorders in HIV-positive patients. In a survey conducted since 1993 in the HIV Outpatient Study (HOPS), the incidence of and risk factors for myocardial infarction were examined in HIV-infected patients on PI and those under PI-sparing regimens (39th Annual Meeting of the IDSA, San Francisco 2001, abstract 941). Out of 3013 PI-experienced subjects, a total of 13 developed a myocardial infarction, angina, or cerebrovascular event (1.2 per 1000 person-years), compared with only 2 of 2665 individuals not being on PI (0.5 per 1000 person-years). Although most CV complications occurred among persons with known risk factors, the association with PI remained strongly significant, even when other CV risk factors were included in the analysis. Likewise, other studies have demonstrated a higher than expected prevalence of premature carotid lesions in PI-treated patients compared to naive (Maggi, et al. AIDS 2000; 14: 123-8) or subjects under non-nucleoside reverse transcriptase inhibitors (NNRTI) (8th European HIV Conference, Athens 2001, abstract P125).

New results from the metabolic sub-study of the Atlantic trial, in which 98 previously naive subjects were analyzed after a 96 week-follow up on treatment, were reported at the 8th European HIV Conference in Athens past October (abstract P126). They showed a 40% increase in HDL-cholesterol and a 6% decrease in the ratio total/HDL-cholesterol among patients randomly assigned to the nevirapine (NVP) arm. This lipid profile is linked to a reduced incidence of coronary artery disease in other settings. In contrast, an increase in total-cholesterol, LDL-cholesterol and triglycerides, along with a 25% increment in the ratio total/HDL-cholesterol, was noticed among patients on indinavir (IDV). This lipid profile is related to an elevated incidence of coronary artery disease.

Information on clinical and metabolic outcomes in switch strategies (PI ± NNRTI) was presented at the 8th European HIV Conference (Clotet B, Boehringer-Ingelheim Symposium). In a prospective, open-label study, patients taking a PI-containing regimen were randomly assigned to either continue on PI (n = 26), or switch to NVP (n = 26) or efavirenz (n = 25). After a 12-month follow-up, mean total and LDL-cholesterol, as well as triglyceride levels, fell significantly in patients receiving NVP, but remained unchanged in the other two groups. All three regimens provided a similar degree of viral suppression and mean CD4+ cell gain.

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