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.

Involvement of Efavirenz in Lipodystrophy

Characteristic body-shape changes and serious metabolic complications such as insulin resistance and dyslipidemia have been largely associated to the use of protease inhibitors. On the other hand, peripheral lipoatrophy has been mainly linked to some nucleoside analogues, particularly stavudine. So far, no data have definitively associated the development of lipodystrophy syndrome with the use of non-nucleoside reverse transcriptase inhibitors (NNRTI). However, two recent reports presented during the 13th International Symposium on HIV & Emerging Infectious Diseases, held in Toulon (France) in June 2004, have postulated for the first time an involvement of efavirenz in the lipodystrophy syndrome.

In the first study, a group from Paris demonstrated, *in vitro,* that adipocyte differentiation may be inhibited in the presence of efavirenz (El Hadri, et al. [abstract OP 5.3]). Pre-adipocytes failed to accumulate cytoplasmic triacylglycerol droplets, and this effect reverted after removing efavirenz. The authors found that efavirenz induced a dose- and time-dependent reduction in gene and protein expression of the lipogenic transcription factor SREBP-1c (sterol regulatory element-binding protein 1c). The result was a sharp reduction in the adipocyte lipogenic activity in efavirenz-treated cells. These observations may be on the basis of the adipose tissue atrophy seen in patients exposed to efavirenz for long periods of time.

In the second study (Manfredi, et al. [abstract PP 4.35]), a large cross-sectional survey was conducted in Bologna (Italy). The lipid profile was assessed in patients treated for at least 12 months with either nevirapine (n = 236) or efavirenz (n = 256). The groups were matched for concomitant antiretroviral medications, age, gender, hepatitis coinfection, CD4 counts and plasma HIV-RNA. In subjects who replaced with a NNRTI a prior PI-based regimen due to dyslipidemia, a drop in triglycerides and/or cholesterol greater than 30% was seen in 67% of patients on nevirapine, but only in 29% of those who switched to efavirenz ($p < 0.01$). Furthermore, in 141 drug-naive individuals, dyslipidemia appeared in 19% of subjects receiving efavirenz, but only in 2% of patients on nevirapine ($p < 0.001$).

These new data should alert physicians to the potential risk of efavirenz for causing lipid abnormalities and lipodystrophy in HIV-infected individuals, and may favor the use of nevirapine, particularly in patients with other cardiovascular risk factors.

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Could Enfuvirtide Ameliorate the Pathogenesis of HIV Infection?

Enfuvirtide (ENF; T-20) is the first approved entry inhibitor for the treatment of HIV infection. Many aspects regarding HIV response to this new drug remain unknown. One of them concerns the selection of ENF-resistance mutations, their impact on susceptibility to ENF, and their influence on viral fitness. Although information derived from HIV-1 *pol* resistance mutations has proven this relationship (Deeks, et al. N Engl J Med 2001;344:472-80), this has not been proven yet for ENF. If this is the case, it may have important clinical implications, since ENF tends to be used in heavily pre-treated individuals in whom impairment of viral fitness may be one goal of HIV therapeutics. In the *pol* gene, specific resistance mutations such as D30N (PR) or K65R and M184I/V (RT) have been particularly associated with significant reductions in the replication capacity of the virus, which may account for viro-immunologic discordant responses to HAART (Nicastri, et al. J Clin Microbiol 2003;41:3007-12).

Recent evidences have suggested that long-term ENF-treated patients might experience an immunological benefit, in spite of the rapid selection of ENF-resistance mutations within the HR1 region of gp41 and subsequent virological failure (Poveda, et al. AIDS 2002;16:1959-61). More recently, it has been reported that these patients may show a reduced T-cell activation. Two recent articles may offer an explanation for this fact, revealing how an additional benefit of ENF on HIV pathogenesis could be obtained in some instances. In the first (Lu, et al. J Virol 2004;78:4628-36), the presence

of ENF-resistance mutations within the HR1 region of gp41 was clearly associated with a reduction in viral fitness. Thus, ENF-resistant viruses are less fit than wild-type viruses and, consequently, could be less pathogenic. In a second study (Schaeffer, et al. J Virol 2004;78:1375-83), an inhibition of the HIV fusion pathway to enter the cells was associated with a compensatory increase in the endocytosis pathway. While virion endocytosis by macrophages may result in a productive infection, HIV entry into CD4+ T-cells by endocytosis does not seem to lead to productive infection. If these observations are further confirmed, they might explain, at least in part, the recognition of CD4-viral load disconnects in some individuals failing ENF-based therapies. Thus, the benefit of ENF may go beyond its intrinsic antiviral activity.

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Frequent "Natural" Zoonotic Transmission of Simian foamy Virus to Humans

Two recent studies documented the "natural" transmission of simian retroviruses to humans. The simian foamy virus (SFV) was implicated in both reports. SFV is the third "human" retrovirus, and like the others has been acquired from simians. The first human retrovirus to be discovered was the human T-cell lymphotropic virus (HTLV), closely related to the simian T-cell lymphotropic virus (STLV). The second was the human immunodeficiency virus (HIV), closely related to SIV, the simian virus. SFV has been previously reported in humans occupationally exposed to primates in research centers (Heneine, et al. Nat Med 1998;4:403-7), but it was not clear how widespread these infections were. Now, two studies led by Heneine's team at the Centers for Disease Control and Prevention extensively document the transmission of SFV to humans. In the first study, Wolfe, et al. (Lancet 2004;363:932-7) examined bush-meat hunters in Africa, while in the second study Switzer, et al. (J Virol 2004;78:2780-9) analyzed primate handlers and zoo keepers in the USA.

Since no human-to-human spread of the foamy viruses within the human population has yet been shown, SFV is still classified as a simian virus. The most striking observation is, however, the limited rate of transmission, restricted to exposure to simian blood or body fluids. In the first study, out of 1099 African forest people who reported direct contact with simian blood or body fluids, only 10 (1%) were infected with SFV. In the second study, SFV infection was found in 9 (5%) of 187 zoo keepers that had been in direct contact with simians.

The viruses were phylogenetically identified as having been acquired from De Brazza's guenon, mandrills, gorillas, baboons and chimpanzees. Most of these species are also infected either with STLV, SIV, or both. The second study reported the lack of SIV or STLV in the zoo keepers, suggesting that SFV may be more readily transmissible than SIV or STLV. So far no disease has been documented in SFV-infected persons, and the virus has not been transmitted through direct (including sexual and blood product) human-to-human contacts. These findings demonstrate that simian retroviruses are actively entering the human population by the so-called "natural" way, and highlight the importance of defining the consequent public health implications.

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Glucose Insulin Profile is Better Using Nevirapine than Using Efavirenz

Insulin resistance (IR) and hyperglycemia are frequent metabolic alterations in patients on HAART, and may be due to both direct and indirect pathogenic mechanisms induced by antiretrovirals. Although an increase in glycemia has been described associated with many different antiretroviral regimens, protease inhibitors (PI) have been mostly linked to it. Up to now, little information has been available regarding combinations not including PI, such as non-nucleoside containing regimens.

Two reports exploring the relationship between glucose metabolism and different antiretroviral drugs were presented at the last CROI, held in San Francisco in February 2004. In one of them, from the Multicenter AIDS Cohort Study (Brown, et al. [abstract 73]), the prevalence of hyperglycemia in 1,107 men recruited in the cohort from April 1999 through to September 2002 was examined. A total of 544 individuals were infected by HIV, with 423 being on HAART. After adjustment for age and body mass index (BMI), the hazard ratio (HR) of prediabetes and diabetes was 1.8 times (95% CI: 1.1-3) and 3.1 times (95% CI: 1.3-7.1) higher among HIV+ with respect to HIV–. Exposures to PI, d4T or efavirenz (EFV), were each significantly associated with a higher rate of incident prediabetes or diabetes. Interestingly, HAART regimens including EFV showed the highest HR (3.9; 95% CI: 1.6-9.5) when compared with those containing d4T (HR = 2.1; 95% CI: 1.1-3.9) or PI (HR = 1.9; 95% CI: 1.1-3.3).

In another survey (Shahmanesh, et al. [abstract 704]), insulin resistance in HIV– controls (n = 12)

and HIV+ subjects (n = 55) was analyzed. Among HIV+ individuals, 15 were treatment naive, and the rest were receiving HAART, including PI (n = 14), EFV (n = 14) and nevirapine (NVP) (n = 12). Groups had comparable BMI but controls were significantly younger than PI-treated and drug-naive patients. IR was calculated by the homeostatic model (HOMA). Patients on NVP had significantly lower glucose than those on PI or EFV, and also had lower HOMA compared to PI-treated but not EFV-treated subjects. This should be highlighted since the individuals on EFV had been under antiretroviral therapy for a significantly shorter time than the other treatment groups.

Group (n)	Age	Months on treatment (mean)	Glucose (mmol/l)	HOMA
Control (12)	31*	0	4.9	1.1
Naive (15)	38.1	0	4.9	1.4
PI (14)	43.4	47.1	5.2	2.3
EFV (14)	36.9	24.1**	5.3	1.7
NVP (12)	39.7	40.8	4.7***	0.9****

*p < 0.05 vs. naive and vs. PI, **p < 0.05 vs. PI and vs. NVP
***p < 0.05 vs. PI and vs. EFV, ****p < 0.05 vs. PI.

In conclusion, these are the first data which show an association between EFV and glucose metabolism disturbances, namely insulin resistance and hyperglycemia. Of note, HAART including EFV entails a greater risk of developing hyperglycemia and diabetes than regimens containing PI. Conversely, NVP appears to be less toxic than EFV regarding the development of hyperglycemia. This fact, together with its better atherogenic lipid profile, makes NVP a good alternative in order to prevent future cardiovascular risk, in comparison with other antiretroviral agents.

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