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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.

Pig retroviruses and xenotransplantation- A key safety question answered?

The AIDS pandemic which is believed to have originated from simian retroviruses is often cited to illustrate the direct public health consequences of cross-species transmission of animal retroviruses to humans. The HIV pandemic has also heightened concerns regarding iatrogenic transmission of other animal retroviruses to humans by xenotransplantation, the grafting of living animal tissues or cells in humans.

Xenotransplantation offers the promise of unlimited transplants for humans. Despite greater immunological barrier, pigs are favored over primates as sources of xenografts for a variety of practical and ethical reasons. Among the many microbes harbored by pigs, the porcine endogenous retrovirus (PERV) represents a particular concern. PERV is endogenous by nature, which means that its proviral DNA is integrated in the pig genome, and thus, cannot be eliminated by pre-transplant screening. PERV is also able to infect human cells *in vitro*.

A study reported by Paradis *et al*. (Science 1999; 285: 1236-41) provides reassuring data on risks of infection with PERV. In this retrospective study, investigators from Novartis and the US Centers for Disease Control and Prevention have independently analyzed samples from 160 patients who have been exposed to pig tissues. These exposures include pig skin in patients with burns, pig islet cells in diabetic patients, and extracorporeal perfusion with either porcine kidneys, spleens, or with livers or hepatocytes (in patients with liver failure). Evidence of PERV infection was sought by serologic screening for antibodies and by PCR screening for PERV DNA in peripheral blood lymphocytes and PERV RNA in plasma. No evidence of PERV infection was seen. Interestingly, evidence of pig DNA was found in 23 patients by PCR analysis with pig-specific sequences, suggesting microchimerism (or presence of circulating pig cells). The observed lack for PERV infection *in vivo* may provide a basis to allow clinical trials to go forward. However, it is expected that these trials will likely be small-scale, closely monitored, and may involve porcine cells rather than organs.

Walid Heneine
Centers for Disease Control and Prevention
Atlanta, Georgia, USA

Non-nucleosides: Good news again

During the summer, the antiviral activity of non-nucleosides has been open to new indications in HIV-infected persons. First, during the workshop on Drug Resistance (San Diego, June 23-26), Casado *et al*. (Abstract 114) demonstrated that nearly one third of nevirapine-resistant clinical isolates remain susceptible to efavirenz. So, rescue therapy with other NNRTIs should be explored in more detail in patients failing nevirapine.

Secondly, a large trial conducted in Uganda has concluded that giving one pill of nevirapine to HIV-infected pregnant women just before delivery can reduce the rate of vertical HIV transmission more than twice (Lancet 1999; 354: 309). In Africa, where there is no antiretroviral treatment, about 30% of infants of HIV-infected mothers are expected to be born infected. In this trial, however, only 13.1% of the children in the nevirapine group became infected, compared with 25.1% of those in the AZT group which neans a reduction of 47%. For ethical reasons, there was no control group without antiviral treatment. In more detail, mothers took a single 200 mg pill of nevirapine at onset of labour and the infants were given a dose of 2 mg/Kg sometime during the first 3 days of life. In the AZT group, at onset of labour the mothers took 600 mg orally, and then 300 mg every 3 h until delivery; and the infants were given 4 mg/Kg of AZT twice daily for the first week of life.

Nevirapine has a long half-life and readily passes from the mother to the fetus in utero. The total cost of the two-dose treatment is only about $4, a price that makes much more likely that the regimen could be widely adopted in the developing world,

where the treatment could save more than 300,000 newborns from HIV infection each year.

Lastly, Witvrouw *et al*. in Belgium (AIDS 1999; 13: 1477-83) have shown that HIV-2 is sensitive to several second generation NNRTIs, and that the virus develops at least two mutations when exposed to delavirdine. One E219D is homologous to the codon 219 mutation, conferring AZT resistance in HIV-1. Another, S102L, is within the NNRTI binding pocket in HIV-1 RT, and hypothetically also in HIV-2, although structure modelling does not seem to show a NNRTI binding pocket in HIV-2 RT. Since mutations develop only when drugs compromise virus replication, these observations indirectly suggest that the anti-HIV-2 activity recognized for some NNRTI is directed towards the viral RT enzyme. Why the resistant HIV-2 develops a mutation linked to AZT in HIV-1 is still a mystery, but it might have something to do with processivity.

Vincent Soriano
Instituto de Salud Carlos III
Madrid, Spain

Emergence of AZT resistance taking d4T

The activity of antiretroviral drugs seems to be compromised in some extent when compounds of the same family are used in second-line therapies. For instance, the antiviral effect of d4T is reduced in persons previously exposed to AZT. Two main reasons have been associated with this observation. First, a reduction in the phosphorylation of d4T after AZT exposure, since both AZT and d4T are thymidine analogues, and share the same phosphorylation pathways. Secondly, mutations emerging within the HIV reverse transcriptase (RT) gene which confer resistance to AZT might influence the subsequent response to d4T. A broad spectrum of RT genetic changes has been implicated in this phenomenon, including the development of multinucleoside-resistant genotypes caused by codon T69S inserts (Larder *et al*. Antimicrob Agents Chemother 1999; 43: 1961-7), or the codon 151 mutation complex. Even the classically «specific» AZT mutations, such at codon 215, have been implicated in this phenomenon, although *in vitro* studies have shown that viruses carrying mutations associated to AZT resistance do not show significant cross-resistance to d4T.

In contrast with AZT, d4T has been always considered a robust drug against resistance (Holguin *et al*. Antiviral Therapy 1998; 3:183-6). This fact and the lack of evidence for a reduced susceptibility to AZT in persons previously exposed to d4T have been argued in favor of using d4T instead of AZT as part of first-line therapies. Moreover, d4T tends to be better tolerated than AZT.

The release of the preliminary data from the CHORUS study in the past spring have questioned the previous assumptions, since in this trial persons exposed to d4T-containing regimens responded in a lesser extent to AZT. Up to now, there is no clear explanation for how d4T could reduce the subsequent response to AZT. However, at least four presentations at the San Diego's Workshop on Drug Resistance (June 1999) have enlightened this topic. A reduction in AZT sensitivity in patients failing on d4T-containing regimens might be related to at least four genotypic changes within the HIV RT gene. A few patients can develop classically AZT-linked mutations at codons 215 and 41 after long periods of exposure to d4T. Secondly, when d4T is taken with 3TC, the emergence of the codon 184 + 211 + 214 multidrug-resistant complex might compromise AZT efficacy thereafter (Loveday *et al*. AIDS 1999; 13: 627-8). Since R211K and L214F mutations can be considered as polymorphisms, the emergence of the codon M184V mutation in response to 3TC could act as trigger for driving to the acquisition of this resistant genotype. Lastly, the activity of AZT might be compromised in subjects exposed to d4T by the emergence of multinucleoside-resistant genotypes (T69S inserts, and codon 151 mutant complexes). The role played by d4T in the emergence of cross-resistance to AZT should be explored in more detail.

Pablo Barreiro
Instituto de Salud Carlos III
Madrid, Spain

Attenuated HIV vaccines

After 14 to 18 years of infection, half of the surviving patients in an Australian cohort infected with HIV-1 carrying natural deletions in Nef are showing CD4 cell decline and viral load rise (Learmont *et al*. NEJM 1999; 340: 1715-22). Thus, although highly attenuated, Nef-deleted or-mutated viruses are unsuitable as vaccine strains. Johnson *et al*. (J Virol 1999; 73: 4952) showed that the degree of protection by even further attenuated SIV strains, carrying deletions in Nef, Vpr, Vpx and/or the U3 (LTR) region, against challenge with intact SIV was inversely related to the extend of attenuation. Animals infected with virus carrying deletions in Nef, U3 and Vpr were all protected against superinfection. One of the 4 animals infected with SIV deleted in Nef, vpx and U3 could be superinfected with intact SIV by vaginal challenge, while half of the monkeys infected with Nef, Vpr, Vpx and U3 deleted SIV were not protected against superinfection. Challenge route and dose had also influence: Protection against vaginal challenge and lower doses was easier to achieve than protection against intravenous challenge and higher dose. It seems that mucosal protection can be achieved in monkeys using attenuated SIV strains, but further research will be needed to find the correct balance between attenuation of the vaccine strain (minimizing the risk of disease progression caused by the vaccin strain itself) and protection against superinfection (maximizing immune response).

Anne-Mieke Vandamme
Rega Institute
Leuven, Belgium

Promising new inhibitors of HIV coreceptors

Ever since their discovery in 1996, chemokine receptors which act as HIV coreceptors have been an interesting new target for drug development. The first class of CXCR4 targeted drugs, the non-peptidic bicyclams, were discovered in 1992 (De Clercq *et al*. PNAS 89: 5286-90), long before its precise mechanism of action was unraveled (Schols *et al*. J Exp Med 1997; 186: 1383-8). Another drug, ALX40-4C was also found to block HIV entry through the CXCR4 coreceptor (Doranz *et al.* J Exp Med 1997; 186: 1395-400). One of the bicyclam drugs, AMD3100, is currently starting Phase II clinical trials to investigate its potency in HIV-infected individuals. Since the majority of clinical HIV strains use either the CXCR4 or the CCR5 coreceptor, inhibitors of strains entering through the CCR5 coreceptor will be wellcome. Modified chemokines have already been identified that block HIV entry through CCR5 (Cocchi *et al*. Science 1995; 270: 1811-5; Simmons *et al*. Science 1997, 276: 276-9). However, small chemical molecules acting against CCR5, much more attractive as clinical drugs, had not been found yet. Now, Baba *et al*. (PNAS 1999; 96: 5698-703) found a chemical compound, TAK 779, which blocks HIV-1 entry through the CCR5 coreceptor. Together, CXCR4 and CCR5 blocking drugs might add the necessary new breath to fight HIV with new drug combinations, especially for strains that had acquired resistance to all currently used clinical drugs.

Anne-Mieke Vandamme
Rega Institute
Leuven, Belgium