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.

An old virus using chemokine receptors to enter cells might have selected for resistance to HIV infection

Chemokine receptors are known to act as co-receptors for HIV. Now Lalani *et al*. (Science 1999; 286: 1966-71) have reported that chemokine receptors (CCR1, CXCR4, or CCR5) are also the receptors for myxoma poxvirus. Non-permissive mouse cells transfected with chemokine receptor expression vectors became permissive to myxoma poxvirus infection. This infection could be blocked by high concentrations of RANTES, the natural ligand of CCR5. It is possible that the related smallpox virus might have entered cells in a similar way. The enigmatic CCR5 allele that has a 32 nucleotide deletion, responsible for an aberrant and non-functional CCR5 receptor molecule, might have had its origin in the selective forces of smallpox virus epidemics in Europe hundreds of years ago. It is this same CCR5 mutation that was shown to convey resistance to HIV infection to people at high risk that were homozygous for this allele (Dean *et al*. Science 1996; 273: 1856-62; for a review see Libert *et al*. AIDS Reviews 1999; 1: 221-9). It was suspected since a while that a major epidemic in Europe, several hundreds of years ago, might have been responsible for the selection of this allele in larger proportions in Caucasians than in respect to other populations, for example African blacks (Martinson *et al*. Nature Gen 1997; 16: 100-3). The report by Lalani *et al*. (Science 1999; 286: 1966-71) is the first to provide substantial support for one of the candidates, smallpox. Even though smallpox is now eradicated, these findings might argue in favour of the continuation of some basic research using smallpox virus, under very stringent conditions. There is still much to be learnt from these 'fossil' viruses, and new techniques will only improve our knowledge on them. Fears of the use of the last smallpox stocks are warranted, but some restricted research should still be made possible, for instance to resolve this enigma involving HIV protection.

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Putting the brakes on drug approval: Adefovir

Patient access to HIV drugs in the Unites States has been facilitated by an expedited 'fast track' process of drug approval by the Food and Drug Administration (FDA). Although this process can never be 'fast' enough for the individual afflicted with HIV, regulatory agencies bear the responsibility to weigh the relative risks and benefits of approving a drug for which both activity and safety information may be limited. It cannot be argued that the rapid approval of the protease inhibitors saved the lives of thousands of HIV-infected individuals. And certainly, in retrospect, delaying the release of these drugs would have been foolish even knowing now that the metabolic side effects of this class of drugs were underappreciated. The catalyst for the rapid approval of drugs in the 90s was the overriding sentiment shared by patient advocates, industry, academics and government that there was a dire urgency to provide access to effective treatments.

What is the urgency to approve drugs for HIV now that there are 14 drugs on the market? The answer to that question depends on who you ask. Some would argue that cautious approval of drugs is warranted unless a drug is distinguished by activity, safety or mechanism of action. Others, myself included, would argue that with the large number of patients in need of salvage therapy, the limitations of therapy produced by drug cross-resistance, and the consequences of the sequential introduction of therapies, drug approval must continue to be expedited.

Consider the case of adefovir. A randomized study evaluated the efficacy of 120 mg daily of adefovir in patients on stable antiretroviral therapy and viral rebound (Kahn *et al*. JAMA 1999; 282: 2305-12). Patients in the adefovir group showed a modest reduction in HIV RNA levels (0,4 log copies/mL) compared to the placebo group. Toxicity, however was quite appreciable, with an estimated 35% of patients developing significant (but reversible) nephrotoxicity by 48 weeks of therapy. Development of adefovir continued at a 60 mg daily dose which appeared to be associated with less toxicity. In late 1999, an FDA advisory committee convened

and voted 13 to 1 against the approval of adefovir. The reasons the majority of the members of FDA advisory committee voted against adefovir approval appeared to be a combination of 3 factors: Limited data on efficacy of 60 mg dose, similar concerns for safety, and the unknown long-term consequences of the nephrotoxicity.

Adefovir was the first drug to have the 'brakes' applied by the FDA. The reasons cited by the advisory panel, strictly by the book, appear legitimate. On the other hand, this drug certainly can provide benefit to a select group of patients at the 60 mg dose, particularly when one considers the risk-benefit ratio in the salvage setting and how a modest reduction in viral load can confer significant clinical benefit. For some patients, even a temporary reduction in viral load can be a life-saving measure.

Hopefully, the entire development of adefovir will not be; this drug also has promising activity against hepatitis B and herpes viruses. And hopefully drug developers and development will not be discouraged by this somewhat chilling episode. Developing and approving drugs for use in salvage therapy is necessary, urgent and will require courage and vision by those participating in every aspect of the process.

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Primary resistance to non-nucleosides

Evidence of moderate leves of phenotypic resistance to NNRTIs was recognized in two previous surveys conducted in the United States (Boden *et al*. JAMA 1999; 282: 1135-41; Little *et al*. JAMA 1999; 282: 1142-9). Since infection acquired through transmission of NNRTI-mutant viruses was unlikely in most of these subjects, Leigh Brown and colleagues investigated whether the presence of polymorphisms at the *pol* gene could explain this finding. The results were presented at the 7th Conference on Retroviruses and Opportunistic Infections (Abstract LB8). After examining 109 isolates from naive subjects, 13 showed reduced susceptibility to nevirapine, defined as a range above 2.5-fold reduction compared with wild type isolates. Three amino acid substitutions were associated with this altered sensitivity: 83R, 135T, and 283I. If all 3 of these mutations were present, there was a 3-fold loss of sensitivity to nevirapine. Reduced susceptibility to delavirdine was associated with another three mutations: 135T, 162S, and 214F. The presence of all three mutations conferred a 5-fold reduction in sensitivity. The clinical significance of these observations is unknown. However, since NNRTIs achieve high concentrations in plasma, by far exceeding the IC50, it should be expected that minor changes in phenotypic sensitivity will not be clinically significant. In other words, the response to treatment with NNRTIs should not be impaired in subjects carrying these polymorphisms, which seem to represent the predominant virus quasispecies in around 10% of naive HIV-infected persons.

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Lymphocyte chemotaxis and activation by HIV-1 Nef

HIV-1 nef is a regulatory protein that is only 27 kDa in size, yet despite it is relatively small it has been shown to have several distinct biological activities. HIV-1 nef down regulates cell surface expression of the CD4 receptor. This effect has been shown to enhance the spread of HIV-1 by preventing the budding HIV-1 virions to bind to previously infected cells. Nef can also down regulate the cell surface expression of MHC class I molecules which could interfere with antigen presentation by HIV-1 infected cells. This down regulation has been proposed to confer partial protection against lysis by cytotoxic T lymphocytes. In a recent report, Swingler *et al*. (Nature Med 1999; 5: 997-1003) provide new insights into the role of Nef in promoting the replication of HIV-1. These authors have shown that infection of macrophages by HIV-1 has a functional Nef results in secretions of the chemokines MIP-1 α and MIP-1 β. These chemokines promote the chemotaxis of resting T-lymphocytes, thus increasing the chances for CD4+ lymphocytes to encounter HIV-1 particles. Moreover, they provide additional evidence that Nef-expressing macrophages can activate the attracted lymphocytes and make them able to support infection by HIV-1. Therefore, these two Nef induced activities will enhance the rate of HIV-1 spread *in vivo*. These data may explain the previous observations that macrophage-tropic R5 isolates of HIV-1 are much more easily transmitted than are X4 isolates which cannot infect macrophages. The findings of Swingler *et al*. provide important evidence for a new biological activity of Nef that can explain two questions in HIV-1 pathogenesis -macrophage infections and the requirement for the Nef protein for disease–.

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Are non-nucleosides equally potent?

Up to now doubts remain as to whether nevirapine and efavirenz are equally potent. No studies comparing both drugs exist yet. The combination of AZT, 3TC and efavirenz was shown to be superior to AZT, 3TC and indinavir in the Du Pont 006 trial

(Staszewski *et al*. NEJM 1999; 341: 1865-73). However, since in this trial 200-mg capsules of indinavir instead of the normally prescribed 400 mg capsules were used for unknown reasons, and patients randomized to receive indinavir took the medication three times daily while those assigned to efavirenz had a more comfortable bid schedule, the results have been criticized (Clumeck. NEJM 1999; 341: 1925-6). In fact, patients included in the indinavir arm had to take a total of 16 pills divided three times per day while those assigned to efavirenz received only 2 pills in the morning and 5 at night. Therefore, the superior results of efavirenz in that trial could largely be due to better compliance and better acceptance of the regimen by the patients. There have been concerns that nevirapine-containing regimens may not be as potent, especially in patients with high viral loads (i.e., > 100,000 copies per mL). This question could not be answered by the Atlantic trial, in which nevirapine was compared with indinavir in the setting of a triple combination (Murphy *et al*. 39th ICAAC. Abstract 456), because of the low viral loads among study participants. Overall, no significant differences in the rate of virologic response were found comparing nevirapine and indinavir arms. However, preliminary data from the COMBINE study were presented in San Francisco during the 7th CROI suggesting that nevirapine may be as potent as triple drug regimens containing a PI (Podzamczer *et al*. Abstract 510). A total of 142 naive individuals with a median viral load of 4.9 logs were randomized to take either AZT/3TC/NVP or AZT/3TC/nelfinavir. At 24 weeks, viral load was below 20 cop/mL in 58% of the nevirapine group and 33% of the nelfinavir group by intent-to-treat analysis, and 80 and 45% buy on-treatment analysis. Although a longer follow-up is warranted, including a subset analysis by baseline viral load, these data provided support for the use of nevirapine in initial therapy.

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