# 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.**

## Reversion of lipodystrophy after switching from protease inhibitors to non-nucleosides

The great enthusiasm with which protease inhibitors (PI) were received was curbed in the first months of 1998 when body shape changes and lipid abnormalities were reported in subjects exposed for a while to these drugs. In some cases, these mid, or long-term side effects were even associated with cardiovascular disease, including coronary ischemia. The rate of this lipodystrophy syndrome, as the illness is known, seems to increase over time of exposure to PI, and is on average 50% of in patients having being on PI for one year.

Potent non-nucleosides, such as nevirapine and efavirenz, have shown an antiviral potency equivalent to PI in recent clinical trials, such as the ATLANTIC and the DMP-066. Moreover, they have several advantages over PI. Their long half-life allows them to be prescribe once daily, and the pill burden is thus only two or three pills daily (instead of 6 to 10 for PI). Considering these facts, some authors have questioned whether patients being on virological suppression under PI-containing regimens could switch to PI-sparing combinations, including a non-nucleoside. In a preliminary report, Martínez *et al*. (*AIDS* 1999; 13: 805-10) have shown that undetectable viremia persists in those individuals moving from PI to non-nucleosides, and that most metabolic abnormalities (hypertriglyceridemia, hypercholesterolemia, and insulin resistance) tend to regress. However, the body shape changes, such as fat wasting of the face, extremities and buttocks, together with fat accumulation in the abdomen and breasts, improve to a lesser extent. Since the number of adipocytes tend to be established early in life, before puberty, it is possible that their destruction by apoptotic mechanisms as an indirect consequence of the use of PI, might make the fat wasting in face and extremities irreversible.

In summary, switching from PI to non-nucleosides seems to provide a benefit for patients having shown a good response to treatment. The advantages of this strategy are many, such as reduction in costs, improvement in the patients' quality of life (2-3 pills once a day without food restrictions) and the disappearance of disturbing metabolic abnormalities which may increase the risk of long-term cardiovascular disease. However, cosmetic effects, which are not negligible when we are facing much more prolonged survival for HIV-positive individuals, will not revert. If this is the case, clinicians will prefer to start antiretroviral treatment with non-nucleosides and reserve PI for patients with advanced HIV disease, or as part of rescue therapies.

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## Intensification of antiretroviral therapy: Why not?

International guidelines recommend switching to a new drug regimen including at least two new anti-HIV compounds as soon as virological failure is recognized under any antiretroviral treatment. Following this advise, no more than three consecutive changes can be provided to patients failing on treatment, since the number of drugs currently available are limited and, of note, some of them show a high degree of cross resistance.

The availability of ultrasensitive assays for measuring viral load has provided the opportunity of recognizing very low levels of virus replication. Consequently, the proportion of patients considered as having achieved complete virus suppression under any treatment has been reduced significantly. The question now is whether the damaging consequences of residual levels of viremia can be avoided without switching all treatment agents, but just by adding a new drug to those in use. Evidences supporting intensification strategies have recently appeared. At least three situations can be recognized as targets for this kind of intervention.

In the first place, when complete virological suppression is not achieved at the expected nadir with an appropriate treatment (e.g. less than 500 HIV-RNA copies per mL at 3 months, or less than 50 HIV-RNA copies per mL at 6 months after beginning triple combinations). If the patient is compliant with its medications, adding a new drug with the inten-

tion of strengthening the ongoing treatment should allow to reach complete virus replication. It is very unlikely that in these early times, the emergence of drug resistance will have already occurred. So, there is no need to withdraw any of the drugs in use, even although alone they are not potent enough.

Secondly, intensification can be considered when early rebounds in viral load are seen in patients who had shown complete virus suppression for a while under an adequate drug combination. It is likely that mechanisms of cellular resistance, such as those mediated by P-glycoprotein or down-regulation in phosphokinases, will reduce the activity of antiviral compounds over time. For some drugs, such as lamivudine or nelfinavir, even the early appearance of drug resistance mutations specific for each drug (M184V and D30N, respectively), can not preclude the success of intensification, since these mutations compromise viral fitness to some extent.

The last group of candidates for intensification might be patients having shown complete virological response under an inadequate regimen. Those are subjects still on mono or bi-therapy. The rationale for intensifying in them is to prolong as much as possible the success until then achieved with those old regimens.

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## Can drugs force HIV into error catastrophe?

RNA viruses in general and HIV in particular have a high error rate, due to their high replication rate and the error prone RNA polymerase or reverse transcriptase. It was first suggested in the 1980s by Eigen, Schuster *et al.* at the Max-Planck-Institute for Biophysical Chemistry (Gottingen, Germany) that RNA viruses are replicating near the error catastrophe threshold, over which they would accumulate so many errors in their genome that they would loose their genetic integrity, resulting in a dead virus. Forcing these viruses over this threshold would result in eradication of the virus (either in vitro on in an infected individual). The first experimental evidence of the existence of such an error catastrophe threshold was provided by Holland, Domingo, De la Torre, and Steinhauer (*J Virol* 1990; 64: 3960-2), who could increase the error rate of these two RNA viruses only 2 to 3-fold before passing this error catastrophe threshold. The concept was also neatly summarized in their recent review (Domingo & Holland. *Ann Rev Microbiol* 1997; 51: 151-78).

Now Loeb *et al.* (*PNAS* 1999; 96: 1492-7) have taken this concept even one step further and tested five mutagenic nucleoside analogues of which one worked as expected, acting not as chain-terminator but was mis-incorporated into the growing cDNA chain inducing a mutation. Addition of the drug in cell culture resulted in loss of viral replication most likely due to the accumulation of a disproportionate increase of G→A substitutions, resulting from the mis-incorporation of the nucleoside analogue during cDNA synthesis. Since the drug was not cytotoxic at the concentrations used, it might be considered for further evaluation and potentially that this, or a similar compound, could end up in the clinic as part of a drug combination therapy. To what extent this concept is subject to virus drug resistance, for example by reducing the affinity of the viral reverse transcriptase for the drug, should be investigated extensively.

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## Host gene polymorphisms influence the clinical course of HIV-1 infection

Chemokine receptors act as important co-receptors mediating HIV-1 entry into susceptible cells. The discovery that homozygotes for a 32-basepair deletion in the gene for chemokine receptor CCR5 (CCR5-A32) are almost completely protected against infection with HIV-1 has initiated a search for other 'protective' polymorphisms in genes encoding chemokine receptors and their ligands. While not rendering resistance to HIV-1 infection, CCR5-A32 heterozygosity and a point mutation in the CCR2 chemokine receptor gene (CCR2-64I) are associated with delayed progression to AIDS, whereas a promoter variant of CCR5 appears to accelerate the clinical course of the disease (Martin *et al. Science* 1998; 282: 1907-11).

In 1998, a polymorphism in the promoter region of the gene coding for stromal cell-derived factor 1 (SDF-1), the ligand of CXCR4), was shown to affect disease progression. Recently, a similar effect of a RANTES chemokine promoter polymorphism has been described (Liu *et al. PNAS* 1999; 96: 4581-5). In spite of some initial conflicting reports about the effect of CCR5 and CCR2 heterozygosity, the evidence for the influence of host genetic constitution in the clinical course of HIV-1 infection is building up (Fig. 1).

In the March 1999 issue of *Blood*, Magierowska *et al.* reported that combined genotypes of CCR5, CCR2, SDF-1 and HLA genes can predict the long-term non-progressor status in HIV-1-infected individuals. (*Blood* 1999; 93: 936-41). The mechanisms by which host genomics influence the clinical course of HIV-1 infection are not completely clarified. The CCR5-A32 deletion leads to formation of a truncated receptor, while promoter polymorphisms of the SDF-1 and RANTES genes can cause altered expression of chemokines, interfering with the function of chemokine receptors used for viral entry. The CCR2 receptor, however, does not appear to play a significant role in viral entry. Furthermore, the pres-

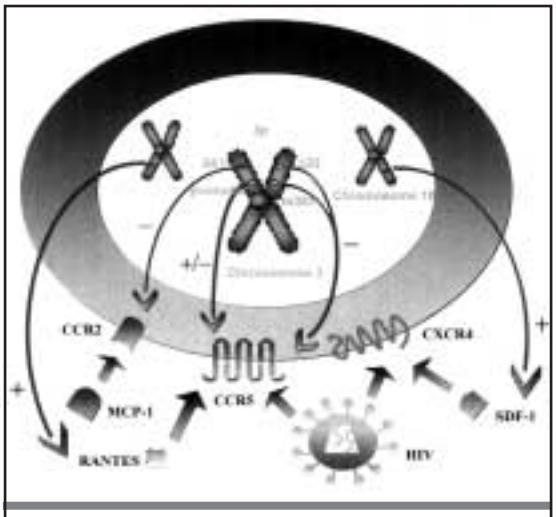


***Fig. 1.*** *HIV-1 co-receptors, Chemonines and genetics.*

ence of a CCR2-64I mutation, leading to a Val to Ile transition in a transmembrane segment of the receptor, is unlikely to strongly alter the structure or function of the CCR2 receptor. The finding that CCR2-64I is strongly linked to a mutation in the CCR5 promoter region (Kostrikis *et al. Nat Med* 1998; 4: 350-3) offers an attractive explanation for the observed protective effect of CCR2-64I on the clinical course of HIV-1 infection. However, the presence of the CCR2-64I polymorphism could not be associated with an altered expression or function of the CCR5 co-receptor (Mariani *et al. J Virol* 1999; 73: 2450-9). This leaves the mechanism of the delayed progression of HIV-1 infection in CCR2-64I bearing individuals as yet unexplained.

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## HIV-1 Resistance testing comes on age in 1999

Only a year ago HIV-1 resistance testing was regarded as promising but its role in clinical practice was still undetermined (Hirsch M *et al. JAMA* 1998; 279: 1984-91). A substantial body of evidence has accumulated since then indicating that resistance testing is ready to enter clinical practice in 1999. As a result, the British Columbia Centre for Excellence on HIV/AIDS in Vancouver, Canada, has now implemented resistance testing for patients initiating or changing antiretroviral therapy. This decision was based on the evidence summarized below. Although relatively infrequent, primary resistance has been widely recognized among antiretroviral naive patients, both within seroincident and chronically infected cohorts (Wegner *et al. Abstract* LB9, 6th CROI, 1999). This is hardly surprising considering the abundance of early reports on the transmission of drug-resistant HIV-1 variants from source patients that received partially suppressive therapy (Conlon *et al. J Infect Dis* 1994; 169: 411-5. Angarano G *et al. AIDS* 1994; 8: 1013-4. Ippolito G *et al. JAMA* 1994; 272: 433-4. Veenstra J *et al. Clin Infect Dis* 1995; 21: 556-60). More recently transmission of multi-drug resistant HIV-1 variants has been documented. Furthermore, resistant strains have been transmitted through sexual contact (Hecht F *et al. N Engl J Med* 1998; 339: 307-11 ), sharing needles among drug users (De Ronde A *et al. Abstract* B.2122, 11th International AIDS Conference, 1996) and through vertical transmission (Johnson V *et al. Abstract* 266, 6th CROI, 1999). Havlir *et al.* have demonstrated that early rebound in viral load among patients receiving triple drug regimens is not always associated with resistance to each of the drugs present in the regimen *(Abstract* LB12, 6th CROI, 1999). In this study early rebound in viral load among patients receiving ZDV/3TC/indinavir was associated with 3TC resistance only. This would confirm that the development of resistance to a regimen is a gradual process and that it tends to start trough the most virologically vulnerable agent. From a clinical stand point this could open the door to a number of important options including the possibility of recycling drugs. Several observational studies have linked viral resistance with virologic outcomes. Harrigan *et al. (Abstract* I-78, ICAAC 1998) examined a group of 84 antiretroviral-experienced patients who received ritonavir/saquinavir-based regimens in two different dosing schedules. Multivariate analyses showed that having a "resistant" virus at baseline according to genotypic or phenotypic assays severely diminished a patient's likelihood of achieving a virologic response. Similarly, Miller *et al. (Abstract* 130, 6th CROI, 1999) showed that the majority of 24 heavily pretreated patients who achieved a sustained viral load below 500 copies/mL while on therapy with 6 or more antiretrovirals had received at least 4 drugs to which their viral isolates were sensitive at baseline. Similarly, we recently reported on a cohort of patients who started multiple drug rescue therapy (MDRT) with up to 9 drugs after failing several regimens (Montaner J *et al. Abstract* B-221, 8th CAHR 1999). In this analysis sensitivity to one, two and three antiretrovirals included in the MDRT regimen was associated with an increasingly favourable virologic response. The role of resistance testing in the management of patients presenting with detectable plasma viral load while on therapy was recently examined in two randomized, prospective clinical trials. In both studies patients who had their next regimen designed taking into account the results of the resistance test had an increased likelihood of achieving a good virological response (Baxter JD *et al. Abstract* LB8, 6th CROI, 1999. Durant J *et al. AIDS* 1998; 12: S16). A note of caution is required when considering the role of resistance testing in clinical practice. Clinicians must understand that the results of such tests may be difficult to interpret or to implement. In particular, the test will best reflect the resistance status of the patient in the context of the current therapy. Of importance, the test

may not accurately reflect the presence of resistance to regimens which the patient was exposed in the distant past. A major concern at this time relates to the need for standarization of the test, as well as the need for implementation of appropriate quality assurance programs. Also, it should be recognized that the resistance testing may not be particularly useful when there are no remaining treatment options. Finally, it should be stressed that the absence of resistance is only one of the many factors that will contribute to enhance the likelihood of treatment success. Despite these limitations, given the above evidence it is abundantly clear that resistance testing has come of age in 1999.

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## Origin of HIV-1 linked to a subspecies of chimpanzee

The origin of HIV-1 has been a puzzle ever since the virus was identified in 1983. In contrast, sooty mangabeys have been implicated as the origin of HIV-2. In the February 4 issue of Nature (vol 397, pages 436-41), Gao *et al*. provided evidence that HIV-1 was transmitted to humans from the chimpanzees, *Pan troglodytes*, which harbor related simian immunodeficiency viruses, SIVcpz. Gao *et al*. demonstrated further by genetic typing of the mitochondrial DNA that the three known SIVcpz most closely related to HIV-1 all come from the same subspecies, *Pan troglodytes troglodytes*, which lives in the same part of Central Africa where AIDS is thought to have originated. HIV-1 is classified into three major groups: The main (M) which comprises the majority of HIV-1 strains that have spread around the world; the O (outlier) group is found less frequently in Cameroon, Gabon and Equatorial Guinea; and the group N (nonM/nonO) which was identified last year in two persons in Cameroon. The phylogenetic analyses by Gao *et al*. indicated that SIVcpz from *Pan troglodytes troglodytes* and the M, N, and O HIV-1 all grouped together suggesting that these distinct HIV-1 lineages represent three separate transmissions to humans from *Pan troglodytes troglodytes*.

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