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.

Discontinuation of the clinical development of fusion inhibitor T-1249

In a surprise move that signals a significant setback in second-generation fusion inhibitor drug development, Roche and Trimeris announced on January 2004 that they have halted, and put on indefinite hold, further clinical development of the experimental HIV fusion inhibitor T-1249.

Until now, T-1249 had been widely regarded as the leading next generation fusion inhibitor candidate, the successor to enfuvirtide (T-20), the first marketed HIV fusion inhibitor. The two pharmaceutical companies said the decision not to go forward with T-1249 was due to challenges with achieving the technical profile required of the current investigational formulation of T-1249. They emphasized that the current formulation of T-1249 would not be suitable for use in large-scale clinical trials. Apparently, T-1249's safety, efficacy and tolerability profile, as determined so far in phase 1 trials, were not the reasons for this decision.

Study results have shown that patients carrying T-20 drug-resistant viruses may still respond to treatment with T-1249. The decision to halt clinical development of T-1249 creates a difficult situation for such patients, most of whom have developed resistance to all other available HIV therapies. T-20 and T-1249 were developed, in part, specifically to provide 'salvage therapy' for this patient population, which comprises a significant number of people worldwide.

A new research program agreement has been signed by Roche and Trimeris. They are committed to design next-generation peptides with enhanced efficacy, more favorable resistance profiles, and technical properties that will enable much less frequent administration of fusion inhibitors coupled with the use of new injection device technologies. Interestingly, use of pegylation technology (as utilized in the pegylated alfa interferons) has specifically been ruled out by Roche as a potential method for achieving weekly or monthly dosing of fusion inhibitors.

T-20 is currently administered by twice-daily subcutaneous injection. In some patients using the drug, the injections have led to painful injection-site reactions. A new delivery system might improve these situations and thus improve overall quality of life for users of T-20 or other peptides. Officials from Roche have announced that they have created a once-daily formulation of T-20 that would allow for one injection a day dosing and to develop a unique injection device for administration of the drug. Moreover, sometime in 2004 they may announce the availability of a new formulation of T-20, which could be administered on a once-weekly or even once-monthly basis. However, this compound is expected to be in clinical development not earlier than 12 months after the announcement.

Luz Martín-Carbonero
Hospital Carlos III
Madrid, Spain

Regulation of HIV-1 gene expression by histone acetylation and factor recruitment at the LTR promoter

The packaging of eukaryotic DNA into chromatin plays an active role in transcriptional regulation by interfering with the accessibility of the transcription factors to DNA. Nucleosome structure is modulated by posttranslational covalent modifications of the histone tails (including acetylation), and by the action of ATP-dependent chromatin remodeling complexes. High histone acetylation level at the promoter of genes is generally associated with transcriptional activation. This acetylation level results from a competition between two antagonist classes of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs), which can be specifically recruited to DNA through interactions with transcription factors. Numerous reports have underlined the existence of multiple links between protein acetylation and HIV-1 transcriptional regulation (reviewed in Quivy and Van Lint. Biochem Pharmacol 2002;64: 925-34). De-acetylation events seem to be an important mechanism of HIV-1 transcriptional repression during latency, whereas acetylation events play critical functional roles in HIV-1 reactivation from latency.

The group of Mauro Giacca has exploited a quantitative chromatin immunoprecipitation (ChIP) approach to map, *in vivo*, the kinetics of histone acetylation and of HAT recruitment at the LTR during

transcriptional activation by Tat and phorbol esters (Lusic, et al. EMBO J 2003;22:6550-61). Their work demonstrates that, upon activation by either recombinant Tat or a phorbol ester, acetylation of both histones H3 and H4 occurs at discrete nucleosomal regions of the LTR before the onset of viral mRNA transcription. Concomitantly, Giacca's lab observed the recruitment of known cellular acetyltransferases to the promoter, including CBP, P/CAF and hGCN5. Strikingly, P/CAF was found associated with the HIV-1 promoter only in response to Tat. Previously, the group of Margolis has shown that activation of LTR expression by Tat resulted in the displacement of HDAC1 and in the increased acetylation of histone H4 (He and Margolis. Mol Cell Biol 2002;22:2965-73). Giacca, et al. confirmed that treatment with Tat increased the histone acetylation level and extended these observations to phorbol esters.

In the future, systematic and timing studies of the histone acetylation level associated to the HIV-1 promoter as well as the HAT and HDAC displacement and recruitment from and to the viral LTR, respectively, during the transcriptional activation process, could allow a fine understanding of the switch from a latent infection to a productive infection. Such studies could lead to the design of new therapeutic strategies aimed at purging the HIV-1 latent reservoirs.

Carine Van Lint
University of Brussels
Institute for Molecular Biology and Medicine
Gosselies, Belgium

Nevirapine clearly offers benefits regarding lipid status

New HIV therapies have significantly increased survival, but are often associated with multiple metabolic abnormalities, most of them related to the protease inhibitors (PIs). In a recent article, Fisac, et al. (J Clin Endocrinol Metabolism 2003;88:5186-92) goes deeper in this matter. In order to elucidate and compare morphological and metabolic alterations in HIV-infected drug-naive patients receiving two nucleosides plus nelfinavir or nevirapine, they examined a subset of patients enrolled in the COMBINE trial (Podzamczer, et al. Antiviral Ther 2002;7:81-90).

Forty-three patients (20 on NFV and 23 on NVP) who received 6-12 months of treatment were analyzed. Morphological changes were evaluated by bioelectrical impedance analysis, standard anthropometrics, and clinical examination. Serum total cholesterol (TC), low-density and high- density (HDL-c) lipoprotein cholesterol, triglycerides, glucose, and insulin were determined, among other metabolic parameters.

No baseline differences were observed between the groups. TC increased in both arms (NVP, 11%; NFV, 17%). HDL-c also increased in both groups, although more markedly in those receiving NVP (44 *vs* 20%). As a consequence of these changes, the TC/HDL-c ratio dropped by 22% in the NVP arm and remained stable in the NFV group.

With the use of NFV, the TC/HDL-c ratio and attendant cardiovascular risk did not change. In contrast, NVP offered benefits regarding lipid status, as manifested by enhanced HDL-c concentrations and decreased TC/HDL-c ratios. The authors concluded by recommending consideration of NVP when deciding upon antiretroviral regimens for patients at high coronary risk.

At the recent 11th Conference on Retroviruses and Opportunistic Infections, the same authors presented the lipid metabolism results of a subset of patients from the NEFA trial (Martínez, et al. N Engl J Med 2003;349:1036-46) after two years of follow-up. In this study, known as LipNEFA, metabolic and morphologic data were prospectively evaluated in a group of patients with virological suppression, and who were randomly assigned to receive abacavir (ABC), efavirenz (EFV) or NVP instead of the PI-part of their previous regimen. Overall, switching to a PI-sparing regimen improved most lipid parameters after 12 months of follow-up. At 24-48 months, lipid improvements were maintained, except for TG whose levels partially returned to initial values. Despite lipid metabolism benefits having occurred in all three treatment arms, the HDL-c increases were significantly higher in both non-nucleosides groups than in the ABC group, and the TC median decrease became significantly stronger in those who had switched to ABC in comparison with those randomized to NVP. After two years of follow-up, the TC/HDL-c ratio significantly decreased only in patients in the NNRTI arms. Finally, the proportion of patients with a good lipid profile increased as a whole (from 30 to 46%) and by treatment analysis (from 24-35 to 43-50%) after two years. Finally, Fisac, et al. reported that the group of patients who initiated the study with either moderate or severe lipodystrophy seems to show a lesser sensitivity to lipid improvements, especially in relation to HDL-c increases. In the light of these results, many who replace the PI component of their regimen may expect to reduce the risk of cardiovascular events; however, further data are needed to determine precisely the extent of this benefit.

Daniel Podzamczer
Infectious Disease Service
Hospital Universitari de Bellvitge
Barcelona, Spain

Treatment of hepatitis C in HIV-coinfected patients at the CROI

Hepatitis C has been one of the stars at the latest CROI, which was held in San Francisco on February. Final results from three large prospective trials comparing pegylated interferon (peg-IFN) plus ribavirin (RBV) versus standard IFN plus RBV in HCV/HIV-coinfected patients were reported. The main features of these studies as well as their main results are summarised below.

	ACTG 5071	APRICOT	RIBAVIC
No. of patients on peg-IFN + RBV	67	289	205
IDUs	80%	62%	81%
Cirrhotics	11%	15%	18%
HCV genotypes 1-4	77%	67%	69%
Mean CD4 count	492	520	525
On HAART	85%	84%	82%
Treatment discontinuation	?	25%	42%
End-of-treatment response (ITT)	41%	49%	36%
Genos 1-4	29%	38%	?
Genos 2-3	80%	64%	?
Sustained virological response (ITT)	27%	40%	27%
Genos 1-4	14%	29%	16%
Genos 2-3	73%	62%	43%

Several important messages derive from these studies. Firstly, peg-IFN plus RBV is superior to standard IFN plus RBV, and should be considered the current standard of care for the treatment of hepatitis C in HIV-coinfected patients. This is true for any HCV genotype, although the benefit of using peg-IFN over standard IFN is more apparent for HCV genotypes 1 and 4 than for HCV genotypes 2 and 3.

Secondly, treatment needs to be provided for one year, with independence of the HCV genotype, in HCV/HIV-coinfected patients. In HCV-monoinfected patients with genotypes 2 or 3, therapy only needs to be provided for 6 months. In contrast, in HIV-coinfected patients this shorten course of therapy is associated with a higher relapse rate, and therefore treatment needs to be extended to 12 months in all cases.

Thirdly, the early virological response, which means >2 log HCV-RNA drop at week 12 predicts the chances of sustained virological response in HIV/HCV-coinfected patients as it does in HCV-monoinfected individuals. Therefore, treatment may be discontinued in patients who do not reach 2 log HCV-RNA reductions at week 12, in the light of side effects and cost.

Given the different features of the study populations and the distinct trial designs, at this time no conclusions can be drawn about the efficacy of distinct pegylated interferons. The best results were recorded in the APRICOT trial (40% sustained virological response), which used peg-IFN alpha 2a (Pegasys®, Roche) and the worst in the RIBAVIC trial (27% sustained virological response), which used peg-IFN alpha-2b (PegIntron®, Schering-Plough). However, the discontinuation rate was very high in the latest study (42%), perhaps reflecting a much poor management of side effects by the doctors in charge.

Overall, these data are good news and provides support to treat hepatitis C in HIV-coinfected patients. However, the reasons for the lower efficacy of anti-HCV therapy in coinfected patients in comparison with HCV-monoinfected individuals should be investigated. In the meantime, the administration of treatment for one year in HCV genotypes 2 or 3, and the use of adequate doses of RBV (1,000-1,200 mg/day) seem to be warranted.

Pablo Barreiro
Hospital Carlos III
Madrid, Spain