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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.

Entry inhibitors come of age

Entry inhibitors can be grouped into three classes, including attachment inhibitors, chemokine receptor blockers, and fusion inhibitors. **T-20 and T-1249** (Trimeris & Roche) are peptide-based fusion inhibitors. T-20 (enfuvirtide) was one of the stars at the International AIDS Conference held in Barcelona last July. It is the first entry inhibitor entering the late steps of clinical development, and expanded access programs are expected to begin soon. The table records the results of the **TORO studies**, the first large trials in which the drug has been examined in pre-treated HIV-infected patients failing therapy (Henry, et al. Abstract LbOr19B & Clotet, et al. Abstract LbOr19A).

	TORO-1 (America)	TORO-2 (Europe & Australia)
No. of patients	491	504
Baseline CD4 count (mean)	80	98
Baseline viral load (mean)	5.2	5.1 logs
Mean reduction in viral load (logs) at 24 weeks	1.69 (T-20 + ART) vs –0.76 (ART)	1.43 (T-20 + ART) vs –0.65 (ART)

Resistance to T-20 involves the selection of mutations at codons 36-45 in the HR-1 region of the gp41 ectodomain. Whereas single mutations confer an average 33-fold increase in IC50 of wild-type viruses, double mutations increase the IC50 an average of 220-fold. All T-20 resistant viruses remain fully susceptible to T-1249. These mutations confer a significant reduction in viral fitness, comparable to that associated with the M184V RT mutation selected by 3TC. The extent by which this phenomenon will contribute to sustained virological and immunologic benefit remains to be determined.

PRO-140 (Progenics) is an anti-R5 monoclonal antibody. It blocks HIV entry by interfering with the interaction between viral gp120 and the cell CCR5 co-receptor. It is moving into phase I clinical trials (Olson, et al. Abstract MoOrA140).

Other CCR5 inhibitors are **SCH-C** and **SCH-D** (Schering-Plough®). The clinical development of the first molecule has been stopped after the recognition of arrhythmias in phase I clinical trials. **SCH-D** is a close molecule, with longer half-life, greater antiviral potency, and no apparent cardiac side effects (Baroudy, et al. Abstract MoOrA138).

AMD-3100 is a CXCR4 co-receptor inhibitor, on which clinical development was discontinued last year after the recognition of ventricular arrhythmias and minimal antiviral activity in experimental models. A new, related compound, **AMD 070**, may be given orally and has started clinical development (Bridger, et al. Abstract MoOrA141B).

BMS-806 (Bristol-Myers) is an attachment inhibitor. It is a small molecule that blocks the interaction between gp120 and CD4. For the first time, two key mutations were reported at the Drug Resistance Workshop in Seville last July, which confer resistance to this compound. Mutations at codons 434 and 475 of gp120 result in high-level resistance to BMS-806 (Lin, et al. Antiviral Ther 2002;7:S6).

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Evidence for HIV-1 Superinfection

Striking virological evidence that HIV-infected individuals can become re-infected with a second strain of HIV-1 was reported by a Swiss group at the XIV International AIDS Conference (Jost, et al. Abstract ThOrA1381), held in Barcelona last July. The report has been published later on (Jost, et al. NEJM 2002;347:731-6). This phenomenon, known as superinfection, has been commonly demonstrated *in vitro*, as well as with SIV in non-human primates. Although there have been previous reports of possible HIV-1 superinfection in humans (Angel, et al. 7th CROI. San Francisco 2000. Abstract LB2). Likewise, Bruce Walker also presented in Barcelona a patient who had been on regular follow-up for 3 years with low viremia (<5,000 copies/ml) without therapy and who rebounded to >50,000 copies/ml after a risky sexual intercourse. Sequence genetic analyses of the last virus

showed that it differed 12% from the original one (Seattle 2002. Abstract 96), there has not been conclusive evidence of this phenomenon.

In the recent case, a 38-year-old man developed an acute retroviral syndrome following multiple unprotected sexual contacts with male partners. He was enrolled in a treatment trial, and monitored for two years. The study also included six months of concomitant vaccination with ALVAC, followed by treatment interruption. The patient's viral load declined from more than 1 million copies/ml to undetectable levels while receiving HAART. However, one month after discontinuation of HAART and the therapeutic vaccine, his viremia rebounded to 80,000 copies/ml, then declined to 20,000 copies/ml, and finally rebounded again two weeks later to 200,000 copies/ml. Viremia then fluctuated between 200,000 and 400,000 copies/ml for five months before HAART was resumed.

Curious about the patient's second and persistent viremic rebound, the investigators undertook intensive gene sequencing of the viral isolates, analyzing the protease, RT, *gag*, and C2V3 *env* genes. This analysis demonstrated that the patient was initially infected with a subtype AE, whereas a subtype B was found at the time of the second rebound of viremia.

To rule out the possibility that the patient was infected with the two HIV-1 subtypes from the beginning, as opposed to acquiring the subtype B strain subsequently, the investigators set up a PCR assay using subtype-specific primers for AE and B viral isolates, designed according to the patient's viral sequences. The subtype-specific PCR confirmed the absence of subtype B virus both in plasma and in the form of proviral DNA before the second viremia. Moreover, it demonstrated the appearance of subtype B during the second rebound and thereafter as the predominant virus in both DNA and plasma. In addition, the C2V3 envelope sequence of the subtype B virus was found to be closely related to subtypes found in Brazil. Of note, the patient had had several unprotected sexual contacts during a vacation in Brazil three weeks before the second viral rebound. Viral cultures of the subtype B primary isolate demonstrated that it had a much higher replicative capacity than the AE subtype.

More recently, investigators from the CDC reported two similar cases of HIV-1 inter-subtype AE and B superinfections in two intravenous drug users from Thailand (Ramos, et al. J Virol 2002;76:7444-52).

Altogether, these data demonstrate conclusively the occurrence of HIV-1 superinfection. Whereas previous reports strongly hinted at this phenomenon, definitive proof from molecular virology was lacking. The fact that the two HIV-1 subtypes acquired by these three patients were different (AE and then B in two) increases the certainty that superinfection occurred in these individuals. Although these reports hold significant virological and epidemiological interest, its most compelling message is that HIV-1 - infected persons must avoid risk behaviors if they wish to avoid reinfection with potentially more virulent or possibly multidrug-resistant viruses.

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The first integrase inhibitors are coming

At the XI International HIV Drug Resistance Workshop held in Seville last July, investigators from Merck reported the first steps towards the clinical use of HIV integrase inhibitors (Hazuda, et al. & Young, et al. Antiviral Ther 2002;7:3 and 17). Integrase is a virally encoded enzyme that inserts (integrates) the double-stranded DNA product of reverse transcription into the DNA of the host cell chromosome. Two years ago, the same authors reported development of a novel screening assay for integrase inhibitors, and identified several compounds known as diketobutanoic acids which inhibited the HIV integrase (Hazuda, et al. Science 2000;287:646-50). These molecules, however, showed only modest anti-HIV activity *in vitro* and unfavorable chemical properties for further development as drugs.

Modification of these compounds led to the discovery of a new series of integrase inhibitors known as naphthyridine-7-carboxamides. Two such compounds, L-870812 and L-870810, show potent anti-HIV activity *in vitro*; the IC_{95} for L-870812 is approximately 350 nM in 50% monkey serum, and the IC_{95} for L-870810 is approximately 100 nM in 50% human serum. L-870812 was tested in macaques infected with an SIV/HIV recombinant virus that carried the HIV integrase gene. Plasma SHIV RNA became undetectable in 4 of 6 infected monkeys treated with L-870812, and virus load was reduced 1-2 logs in the other two animals. The analysis of integrase sequences from the two animals with incomplete SHIV suppression allowed the recognition of N155H as the mutation responsible for resistance to the drug. Moreover, viruses carrying such mutation are poorly fit and fail to grow *in vitro*. In these experimental studies, cessation of L-870812 led to rebound in virus load and re-emergence of wild-type virus, confirming the fitness advantage of wild-type over the N155H mutants. Phase 1 studies of L-870810 in humans are in progress.

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The essential role of the accessory protein Vif

One by one, the roles of HIV's accessory proteins get unraveled. Now it has become clear that Vif should no longer be considered an accessory protein, but deserves the full attention of drug designers. The Virion Infectivity Factor or Vif was originally designated an accessory protein, because Vif-deleted viruses were still able to replicate in 'permissive' cell lines. Now Sheehy, et al (Nature 2002;418:646-650) show that these cell lines, in contrast to 'non-permissive' cell lines, lack a protein, which they call CEM15 after the cell line in which the protein was identified. These cells produce CEM15 that can prevent the replication of Vif-deleted mutants when transfected into 'permissive' cell lines. How the CEM15 protein is able to block HIV replication of Vif-deleted mutants is not yet clear. However, it is clear that the Vif protein evolved into a mechanism to escape this blocking effect by CEM15.

Normal human cells produce the protein and, thus, Vif is essential for the survival of the virus. The CEM15 protein has a zinc-coordinating motive that resembles the one from a human RNA editing enzyme. It is tempting to speculate a similar activity of the here discovered cellular virus silencing tool CEM15, since Vif is known to bind to the viral RNA". In any case, this discovery opens new research areas in virus silencing, in understanding the molecular mechanism of HIV infection, and it adds a new antiviral target to the armamentarium of drug designers.

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