THE BRIDGE

Treatment Session

Guidance for use of new drugs offered

"HIV is a shark," according to Italy's Stefano Vella, one of three senior researchers offering a treatment primer on Monday morning. "Shoot early, but not too early. Remember that you only have one shot – two if you're quick. And aim well."

With these words of warning, Vella outlined the current consensus on when to begin antiretroviral therapy, although he warned that "no controlled trials tell us exactly when to start."

A delegate and a discussant exchange views during a poster session. Discussants are with their posters three times each day to explain their research. Pascal Frautschi

He suggested beginning treatment early for patients at "risk for progression", including those with CD4 counts that drop below 500 or who have viral loads of more than 10,000 copies. He said achieving viral suppression of below 50 copies is essential to achieving long-term success. Doug Richman, who spoke later on resistance issues, concurred, saying "the lower one goes, and the faster one gets there, the more likely you are to remain there."

As many other sessions will outline at this Conference, the risks associated with beginning triple therapy as recommended include adherence difficulties, the limitation of future treatment options, and unknown long-term toxicities. In particular, the difficulty of adhering to complicated regimens remains a problem. Vella sent a message to other physicians that "we need to support and improve adherence rather than just making note of it."

He also offered data about the use of triple therapy in children, noting that trial data indicated "immune reconstitution in children was very, very quick." On this basis, he called for better access to drug treatment for children.

Patrick Yeni from Paris concluded the session with the latest data on maintenance and salvage therapies. Citing both a US and a French trial, Yeni explained that efforts to simplify treatment regimes have not been successful. Dubbed "induction-maintenance therapies," these trials tried hitting hard with triple therapy, then pulling back to one or two drugs.

The trials "were stopped due to [unacceptable] failure rates," Yeni said. While this "doesn't mean that the concept of treatment simplification is not valid," he suggested that maximum but simplified dosing regimens may be a better route of investigation.

Chemokines and Receptors

Natural immunity to HIV explored

Natural properties of the immune system play an important role in HIV infection and its course, including long-term non-progressors (LT-NPs), a topic explored in Session A12 on chemokines and their receptors.

Jay Levy, of the University of California, San Francisco, introduced the session on a non-chemokine note. His discovery several years ago that CD8 cells produce a factor (CAF) that blocks HIV infection was one stimulus to the discovery that chemokine receptors CCR5 and CXCR4 are co-receptors for HIV infection. Production of CAF is strong in healthy persons and lost during disease progression, but remains strong in LT-NPs. CAF has proved difficult to isolate because it is present in such low quantities. "Factors have a ten-year life," Levy said. "We have two more years." Some have suggested that chemokines might be used clinically to block HIV infection. But, Levy said, "I question whether they'll be of any use in therapy."

Co-receptors CCR5 and CXCR4 influence which host cells a strain of HIV favours. Heterosexual transmission, which accounts for an increasing proportion of new infections among women, most often involves CCR5 virus. Julie McElrath, of the University of Washington, asked whether this could be due to the type of co-receptors predominantly found in immune cells of the female genital tract. She reported that HIV infects lymphocytes, which express both co-receptors, but does not replicate in them, while the opposite situation occurs with dendritic cells, which express mostly CXCR4. Productive replication of HIV requires "stable conjugates" of lymphocytes and dendritic cells, she discovered. These cell couples occur naturally in the genital mucosa. "Co-receptor expression alone cannot account for preferential [heterosexual] transmission of CCR-5 strains," Dr. McElrath concluded.

After infection occurs, genetic factors help determine its natural course, according to Magdalena Magierowska, of the French ALT and IMMUNOCO Study Groups. She compared the frequency of deletions in the genes for three co-receptors between rapid progressors and LT-NPs, as well as the frequency of several HLA alleles. The deletion CCR532 occurred significantly more often in LT-NP, she found, as did characteristic HLA allele patterns, such as B27-positive and DR6-negative. "Host genetic background plays an important role in evolution of HIV disease," Magierowska concluded. Its predictive value for LT-NP was 66%, "still a long way from 100%,"she acknowledged.

In Session A13, Kuan-Teh Jaeng, of the US NIAID, investigated why heterozygotes – persons carrying one normal CCD5 gene and one 32 allele – are relatively resistant to HIV infection. There has been "a flurry of excitement" about biological resistance to HIV infection, he said, some of which is due to the 32 variant. But why are persons with one good copy of CCR% partially resistant? "How does the bad copy of the gene interfere with the good copy?" Jaeng wondered. He found that, in heterozygotes, CCR5 protein doesn't reach the cell membrane. It is trapped inside the cell, bound to copies of 32 protein. This shows that co-receptor proteins form multimers, or "shake hands with each other," as Jaeng explained. His finding suggests that reducing the amount of CCR5 should interfere strongly with its receptor activity.