AIDS Rev 2001; 3: 178-180

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.

A promising new lead for therapeutic intervention

The inevitable emergence of drug-resistant HIV-1 seen in patients receiving antiretroviral therapy underscores the continuous need for developing new drugs. While all licensed drugs target HIV-1 proteins, cellular proteins implicated in HIV replication represent attractive new targets. Research led by Ganjam Kalpana at the Albert Einstein College of Medicine in New York (Yung, et al. Nature Med 2001;7:920-6) has identified a cellular protein that may provide a novel strategy to control HIV-1 replication. The authors studied the integrase interator 1 (INI1) protein which directly interacts with HIV-1 integrase during gag processing. The authors demonstrate that S6, a 111 amino acid mutant fragment of INI1, strongly inhibits HIV-1 particle production and replication. Inhibition was found to be mediated by a direct interaction of S6 with integrase within the context of *gag-pol*. S6 does not appear to be cytotoxic and as a host protein is unlikely to be immunogenic. The identification of a small fragment of a cellular protein that acts as a strong inhibitor of late events in the HIV-1 life cycle provides the first step for defining new possibilities for therapeutic intervention.

Walid Heneine
Centers for Disease Control and Prevention
Atlanta, Georgia, USA

Salvage therapy - hope or despair?

In the clinic, the most challenging and difficult treatment decisions surround the management of antiretroviral-experienced patients. Individualized treatment regimens are designed based on prior treatment, drug resistance and toxicity. Great uncertainty exists regarding the expected efficacy of salvage regimens in any individual patient due to our limitations in understanding of drug resistance and pharmacokinetics. Great uncertainty also surrounds the optimal timing of therapy switches. Salvage therapy regimens, which provide temporary benefit in the short-term may ultimately, reduce therapeutic options in the long-term.

Over the years, clinical studies have provided some guiding principles in salvage therapy. In patients failing an initial regimen, the use of at least two new agents (preferably new classes) is recommended in order to achieve viral suppression. A recently published study (ACTG 364) emphasizes this point (N Engl J Med 2001;345:398-407). Highly nucleoside treated patients were randomized to a salvage regimen which included efavirenz (EFZ), nelfinavir (NFV) or both drugs. The nucleoside backbone of the regimen was modified according to patient history. Overall, 74% of patients who received EFZ plus NFV exhibited viral suppression (HIV RNA < 500 copies/ml) at 48 weeks. Rates of suppression were significantly lower in patients randomized to the EFZ arm (60%) and the NFV arm (35%).

While the response rates in the EFZ plus NFV arm in the ACTG 364 study was encouraging, for most patients, two new classes of drugs are not available to for salvage therapy. For this reason, some published reports in cohort studies indicate dismal rates of response in salvage therapy regimens in the 30-40% range. Fortunately, drug development is actively ongoing to address the need, but new drugs typically become available one at a time, often perpetuating the use of a single new drug in a failing regimen.

There is hope, however in the salvage therapy arena. There are other approaches apart from adding new classes of drugs. Pharmacologically boosted protease inhibitor regimens can overcome low level reductions in protease inhibitor susceptibility and improve response rates without the addition of two new drug classes. For patients where viral rebound is detected early, regimen intensification may prove a viable strategy if resistance is limited in magnitude and scope. Therapy interruption strategies, which permit repopulating of wild type virus, may also improve outcome. Finally, therapeutic drug monitoring may prove very useful in the salvage therapy setting.

Even with these new strategies, novel drugs are desperately needed. Entry inhibitors will be the next new class of drugs expected to join the therapeutic armamentarium, but resistance to these drugs, like others will develop soon if they are utilized in non-suppressive regimens. Although many patients in the clinic receiving therapy with viral rebound have adequate immune function, it is only a matter of time before the majority of these patients will be in urgent need of salvage therapy regimens. A combination of therapeutic strategies and new agents will be needed to sustain the progress made in the treatment of HIV disease.

Diane Havlir
University of California
San Diego, California, USA

Anti-atherogenic effects of nevirapine

Several reports in the literature have highlighted the impact of lipid disorders on the outcome of subjects on antiretroviral therapy. In a recent study, investigators from Wisconsin (Stein, et al. Circulation 2001;104:257-62) demonstrated that the use of protease inhibitor (PI)-containing regimens is associated with atherogenic lipoprotein changes and endothelial dysfunction, both of which predispose to atherosclerosis and further cardiovascular risk. In a cross-sectional study the authors examined a total of 37 adults with HIV infection who were receiving antiretroviral therapy. In comparison to subjects not previously exposed to PIs (n = 15), those receiving PIs (n = 22) showed significantly higher total cholesterol and triglyceride levels as well as an impaired vasodilatation measured at the brachial artery, indicative of significant endothelial dysfunction. This difference was noticed after an average time of 30 months on treatment. Interestingly, among patients not exposed to PIs, no differences were seen between those receiving nucleoside analogues (NRTI) plus non-nucleoside analogues (NNRTI) and those receiving 3 NRTIs.

In contrast, two different studies reported at the last AIDS Conference, held in Buenos Aires during last July, have emphasized the cardiovascular benefits of nevirapine. A substudy from the Atlantic trial, namely FRAMS (Fat Redistribution And Metabolic Substudy), has concluded that subjects recruited at the trial arm containing nevirapine (n = 34) showed a striking 49% increase in HDL-cholesterol together with significant increases in HDL particle size, LpA1 and apoA1 (Van der Valk, et al. AIDS [in press]). Likewise, results from the COMBINE study highlighted significantly higher HDL-cholesterol levels in *naïve* patients randomly assigned to nevirapine-containing combinations (n = 23) after 12 weeks of follow-up [abstract 506]. The total cholesterol/HDL ratio, which is the best predictor of coronary artery disease, was particularly diminished in subjects on nevirapine in both studies, which would be expected to confer significant benefits if maintained over a prolonged period of time. In contrast, most patients treated with indinavir or lamivudine (ATLANTIC) or nelfinavir (COMBINE) arms, showed metabolic changes favoring a higher cardiovascular risk. Moreover, a remarkable proportion of patients on nelfinavir in the COMBINE study met intervention criteria to correct high LDL-cholesterol levels.

As lifelong continued treatment is needed in HIV+ patients, avoiding toxicity has become a primary goal. Cardiovascular disease has already been associated to certain drugs, particularly PIs. In this context, careful assessment and monitoring of other cardiovascular risk factors is strongly recommended as a routine in clinical practice. In addition, appropriate applying of recently published clinical guidelines for hyperlipidaemia in adults (NCE, Adult Treatment Panel III. JAMA 2001;285:2486-97), will be essential for controlling future cardiovascular morbidity among HIV+ persons. Nevirapine´s anti-atherogenic profile should be highlighted and especially considered when initiating HAART, particularly in subjects with baseline high cardiovascular risk.

Teresa García-Benayas
Instituto de Salud Carlos III
Madrid, Spain

Highlights from the AIDS Vaccine 2001 meeting

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 22 million people have already died from HIV-related diseases since the beginning of the AIDS epidemic. Even though highly active antiretroviral therapy has become available, 16,000 new HIV infections occur daily mostly in the countries of sub-Saharan Africa. The rapid spread of the HIV epidemic underlines the urgent need for an effective HIV vaccine.

According to Dr A. Fauci's keynote lecture during the opening session at the AIDS vaccine meeting, September 5, in Philadelphia: "The National Institute of Allergy and Infectious Diseases (NIAID) has played a major role in the development of vaccines for many other important diseases, such as hepatitis B, Haemophilus influenzae type B, pertussis and pneumococcal infections. We fully expect that the experience, expertise and commitment of NIAID-funded investigators and our partners in the United States and abroad will lead to the development of a useful HIV vaccine as well." To accelerate the HIV vaccine discovery, NIH has increased the HIV vaccine research funding by 6-fold since 1990.

The NIAID supported a wide range of vaccine strategies such as novel proteins, synthetic peptides, different kinds of vectors, DNA vaccines and synthetic HIV-like particles, increasing thus tremendously the number of new vaccine candidates.

Among many promising studies, several groups working with animals indicated that vaccinated monkeys maintained a durable control of viral replication following infection with pathogenic simian immunodeficiency viruses or chimeric simianhuman immunodeficiency viruses. More specifically, according to Dr. L. Letvin's talk: "Monkeys receiving vaccines that elicit cytotoxic T-lymphocyte responses that are then infected with human immunodeficiency viruses have low virus loads, and accordingly, slow disease progression." "Thus, vaccinated individuals who subsequently become infected with HIV may have lower viral burdens and a longer survival than those who are unvaccinated."

The first phase III trials of AIDS vaccine in the Northern America/Europe (AIDSVAX B/B, VaxGen, Inc.) and in Thailand (AIDSVAX B/E, VaxGen, Inc.) is being tested in more than 7,000 volunteers for its ability to prevent the infection with the HIV-1 virus. The vaccines have been well tolerated and no disease acceleration was encountered in those who were infected after vaccine receipt. The final results of these trials will be available in the next years.

At the HIV database in Los Alamos, the regions of the viral proteins, which contain experimentally defined CTL epitopes were characterized. Interestingly according to Dr. B. Korber: "The genomic epitope-rich regions were conserved and have sequences that are likely to be cleaved and processed, in contrast to the epitope-poor regions that are highly variable. More specifically, they are enriched for amino acids that do not serve as anchor residues, and are less likely to be cleaved and processed." These findings would possibly maximize the potential to use vaccine strains that elicit broadly cross-reactive immune responses to different HIV-1 strains.

Despite many exciting advances, a number of obstacles remain in the development of an effective HIV vaccine. "Perhaps the greatest obstacle to HIV vaccine development is an insufficient understanding of the correlates of immune protection, which are better understood for other viral diseases" says Dr. Fauci. Among many challenges, it is essential to further illuminate the roles of cytotoxic T lymphocytes and antibodies in HIV disease. Other important challenges to HIV vaccine development include the high rate of HIV mutation within populations and individuals, the limitations of all current animal models of HIV disease, and the fact that HIV integrates itself into the DNA of host cells, where it can escape immune surveillance."

In conclusion, the primary goal in the HIV vaccine research is the development of a vaccine that confers sterilizing immunity against HIV. This final goal is not in sight yet. Possible strategies include administration of antigens that elicities broadly neutralizing antibodies against primary R5 HIV-1 isolates, and a cross-reactive CD8+CTL response. In the mean time, a vaccine, which provides controlled viremia and only delayed disease progression may still have clinical benefit and a significant impact on the AIDS epidemic.

Dimitrios Paraskevis
National Retrovirus Reference Center
Athens University Medical School
Athens, Greece