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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.

Discontinuation of prophylaxis for opportunistic infections

Chemoprophylaxis to prevent initial episodes of certain opportunistic infections (primary prophylaxis) and subsequent episodes (secondary prophylaxis) were widely used before highly active antiretroviral therapies became available in 1996. The success of the new therapies in reducing the incidence of AIDS-related opportunistic diseases has led to a reassessment of the role of prophylaxis against these infections in patients who have durable antiviral responses. A recent review (Kovacs *et al.* N Engl J Med 2000; 342: 1416-29) has provided an updated perspective on the principles and recent developments that should form the basis for modifications in the approach to the prevention of both initial episodes and recurrences of these infections. Accordingly, primary prophylaxis for Pneumocystis and Toxoplasmosis can be safely removed in subjects experiencing on HAART CD4 count increases above 200 cells/μL for 3 to 6 months. A multicenter Italian trial (Mussini *et al.* J Infect Dis 2000; 181: 1635-42) has confirmed these assumptions, as no episodes of PCP nor Cerebral toxoplasmosis (419 patient-years) were seen after discontinuing primary prophylaxis for these agents in subjects on HAART whose CD4 counts had risen above 200 cells/μL for at least 3 months. In respect to Mycobacterium avium, primary chemoprophylaxis can be discontinued as soon as the CD4 count rises above 100 cells/μL.

Clinicians have been more reluctant to stop secondary prophylaxis against opportunistic infections, except for Cytomegalovirus retinitis, for which robust data support the discontinuation of either ganciclovir or foscarnet. Now, a recent report (Soriano *et al.* AIDS 2000; 14: 383-6) has pointed out that prophylactic agents for almost all illnesses can be safely discontinued as soon as 3 months after beginning HAART if the CD4 count rises above 100 cells/μL and plasma viremia falls below 500 HIV-RNA copies/mL. Briefly, these authors reported that after 76.5 patient-years of follow-up no opportunistic events were recorded in 59 subjects who had previous episodes of Pneumocystis pneumonia, Cerebral Toxoplasmosis, Mycobacterium avium disseminated infection, CMV retinitis, recurrent oroesophageal candidosis, or recurrent herpes zoster. Apparently, a rapid complete control of HIV replication with combination antiretroviral therapy might allow the discontinuation of chemoprophylaxis even before the CD4 cell count has reached the widely used threshold of 200 cells/μL. Conversely, it appears that stressing the immune system with even low levels of virus replication can negatively influence the function of CD4 T-cells, despite their numbers being increased in response to treatment. Therefore, both CD4 counts and plasma HIV-RNA need to be taken into account when decisions on stopping prophylaxis are made.

Juan González-Lahoz
Service of Infectious Diseases
Instituto de Salud Carlos III
Madrid, Spain

Controversy on the origins of HIV

Britain's Royal Society had scheduled a meeting in May about the origins of HIV. However, its decision to include a discussion on the Oral Polio Vaccine (OPV) theory raised serious doubts among the scientific community. Scientists' concerns were focused on the lack of sufficiently credible scientific data about the debate fostered by the publication of Hooper's book *The River*. Hooper claims that the HIV-1 epidemic in humans originated during the 1950s, as a consequence of the vaccination campaign for polio. He conjectures that the vaccine was made with chimpanzee tissues contaminated with a simian immunodeficiency virus which eventually gave raise to HIV. However, HIV researchers have challenged the theory as very unlikely. Phylogenetic and molecular clock analyses seem to exclude the OPV scenario, and Hooper himself has not been able to show any proof that chimpanzee

tissues were effectively used for the vaccine preparation. After the refusal of several scientists to participate in the meeting, the Royal Society decided to postpone it to September. Sir Aaron Klug, the President of the Society, explained that the decision was necessary in order to have "a well-balanced set of speakers". In addition, a blind analysis of the original OPV samples has been carried out in the last few months by three independent research groups and the results should be available by September. Hooper remains on the speaker list, and three phylogeneticists will have the opportunity to present their data. The meeting will take place in London on September 11-12, 2000.

Marco Salemi
AIDS Research Unit
Rega Institute and University Hospitals
University of Leuven
Leuven, Belgium

Interferon plus ribavirin for chronic hepatitis C in HIV-infected persons

Chronic hepatitis C is common in HIV-infected persons, mainly among those who acquired HIV through the parenteral way (hemophiliacs, intravenous drug users). As the life expectancy of HIV-infected persons has improved significantly, chronic liver disease is becoming a growing problem in this population. Both increased rates of hepatotoxicity using antiretroviral drugs and an accelerated progression to cirrhosis seem to worsen hepatitis C in HIV-positive subjects. In accordance, it is not surprising that in Southern European countries up to a quarter of hospital admissions in HIV wards are due to liver complications, in most instances complicating chronic hepatitis C.

Two recent European trials (Pérez-Olmeda *et al.* J AIDS 1999; 22: 308-9; Landau *et al.* AIDS 2000; 14: 839-44) have concluded that the combination of interferon (IFN) plus ribavirin seems to be safe and active against chronic hepatitis C in HIV-positive carriers. In the Spanish trial, treatment was administered to 18 HIV-HCV co-infected patients who did not respond to a previous course of IFN alone. The rate of sustained response (6 months after stopping therapy) was 45% among those who completed six months on therapy. However, treatment discontinuation (suicidal ideation, anaemia, voluntary withdrawal) occurred in 7 (39%) patients. On the other hand, the French study reported clearance of HCV-RNA in up to 10 (50%) of 20 patients after 6 months on therapy. No data on sustained responses were provided, and the study population was too heterogeneous: 45% of subjects were cirrhotic and 20% had received without success a previous course of IFN, being the remaining subjects IFN-naive. Treatment was very well tolerated since none of the patients stopped therapy.

These two trials emphasise the fact that treatment of chronic hepatitis C in HIV-infected subjects must be considered a priority for the appropriate candidates. So far, those are individuals with CD4 counts above 300 cells/μL, and undetectable plasma HIV-RNA if on HAART or below 10,000 HIV-RNA copies/mL if not (Soriano *et al.* J Hepatol 1999; 31 (Suppl. 1): 119-23). Of note, the use of zidovudine should be discouraged, since the risk of anaemia will be enhanced by taking ribavirin concomitantly. Moreover, there seems to be a competitive inhibition between thymidine analogues (zidovudine, stavudine) and ribavirin, which might hamper their respective clinical activity. The availability of the new pegylated forms of IFN (administered once weekly) will impact even more favourably on the tolerance and success of treatment in HIV-positive individuals suffering chronic hepatitis C.

Rafael Rodríguez-Rosado
Service of Infectious Diseases
Instituto de Salud Carlos III
Madrid, Spain

Lactic Acidemia: More Questions than Answers

Early in the development of nucleoside reverse transcriptase inhibitors (NRTIs), a syndrome of hepatic steatosis and lactic acidosis was recognized as a rare, but often fatal complication of therapy. Many of these cases were reported in obese patients, particularly women. The underlying mechanism of this complication is thought to result from inhibition of mitochondrial DNA polymerase-gamma activity by NRTIs. Mitochondrial ATP production is impaired, resulting in cellular dysfunction, evidence of which is readily demonstrated on electron microscopy evaluation of liver tissue from afflicted patients.

Recently, it has been reported that a substantial proportion of asymptomatic patients receiving NRTI regimens have elevated lactate levels (Harris et al., 3rd International Workshop for Salvage Therapy for HIV Infection, 2000, Abstract 34) In a cross sectional survey of 149 patients on stable antiretroviral therapy followed in Canada, 29% of patients had elevated lactate levels with no other attributable cause. Risk factors associated with elevated lactate levels included treatment with stavudine and hydroxyurea.

Lonergan and colleagues have suggested that some of the patients with elevated lactate levels develop a clinical syndrome that represents a milder, less severe version of the classic "lactic

acidosis" syndrome (Lonergan et al, 7th Conference on Retroviruses and Opportunistic Infections, 2000, Abstract 56). They reported 20 patients with hyperlactemia, abdominal symptoms and elevated alanine aminotransferase. The anion gap was elevated in only 4 of the patients, indicating that this parameter was an insensitive marker of the syndrome. All patients in their case series were receiving stavudine plus either a protease inhibitor or nonnucleoside for a mean of 1 year. Only one patient required hospitalization, symptoms resolved upon discontinuation of antiretroviral therapy and there were no deaths.

Hyperlactemia may also appear to be associated with lipodystrophy (Carr et al. AIDS 2000; 14: 213-338) . These authors identified a group of patients with clinical features of lipodystrophy among patients who had received NRTIs only and compared their profile to patients with lipodystrophy who were receiving a protease inhibitor regimen. Interestingly, the lactate levels were significantly higher in the NRTI group and abdominal symptoms and elevated liver function tests were also more common in this group compared to the protease inhibitor recipients.

These recently reported observations are intriguing and raise many questions about hyperlactemia. How commonly does it occur? Do patients with mildly elevated lactate levels progress to symptomatic disease? Can patients safely be continued on regimens associated with asymptomatic elevations in lactate levels? Can NRTIs be safely reintroduced in patients who have had life-threatening episodes of lactic acidosis? How is hyperlactemia related to syndromes of lipodystrophy? Ongoing studies should shed light on these issues, including how to monitor and manage patients who develop this complication.

Diane Havlir
University of California
San Diego, California, USA

HIV's hitchhiking through the immune system

Upon studying how dendritic cells and T-lymphocytes interact, the group of Van Kooyk (Geijtenbeek *et al.*, Cell 2000; 5: 575-86) has stumbled onto a dendritic cell protein that binds the ICAM-3 T-cell adhesion molecule very strongly, which they called DC-SIGN (dendritic cell-specific ICAM-3-grabbing nonintegrin). A database search subsequently revealed that an identical protein was previously described to strongly bind HIV's gp120 (Curtis *et al.*, Proc Natl Acad Sci USA 1992; 89: 8356-60). Geijtenbeek *et al.* (Cell 2000; 5: 587-97). They therefore further studied the meaning of this binding and they found how HIV is using DC-SIGN, not to enter dendritic cells, but to hitchhike from the mucosa, where the virus meets the dendritic cells, to the lymph nodes where HIV is delivered to infect CD4 cells. This is really a remarkable magic trick that HIV plays to pass the mucosal barrier and infect the immune system. It may also be a new target to combat HIV, by designing vaccines to induce antibodies that prevent this DC-SIGN gp120 interaction. HIV is still providing us whith major scientific surprises.

Anne-Mieke Vandamme
Rega Institute and University Hospitals
AIDS Reference Laboratory
University of Leuven
Leuven, Belgium

Cytokine disturbances cause HAART-associated lipodystrophy

The pathogenesis of HAART-associated lipodystrophy still remains largely unknown. The lack of a standard definition, with subsequent large differences in the incidence and prevalence of the syndrome in different studies, makes it difficult to obtain valid conclusions with regard to its etiology and pathogenesis. What is becoming increasingly clear is that the development of lipodystrophy is related to potent therapy rather than to HIV infection itself. However, it remains to be established whether lipodystrophy is the side effect of a particular drug (or group of drugs) or it is an unspecific effect of any medication, when it produces virological control and immune reconstitution.

Now, Ledru *et al.* (Blood 2000; 95: 3191-8) have suggested that the alterations in the distribution of body fat and the metabolic abnormalities included in the lipodystrophy syndrome are related to a disturbance in the production of some cytokines, mainly TNF-α. In a case-control study, the investigators evaluated whether successful HAART was responsible for a dysregulation in the homeostasis of TNF-α. Patients treated with combination regimens that included protease inhibitors (PIs) and suffering lipodystrophy had significantly more TNF-α CD8+ T cell producers than patients treated with PIs and without lipodystrophy. Insights into the mechanisms of this difference led the authors to conclude that the accumulation of CD8 T cells producing TNF-α during HAART is a consequence of the escape from physiological apoptosis of these cells, mediated by a decrease in the co-synthesis of IL-2 T-cell producers. The number of T-cell-producing TNF-α was strongly correlated with lipid parameters in PI-treated patients.

Ledru's study is the first to suggest the cellular mechanisms that may be involved in the lipodistrophy syndrome associated to PIs. It is unknown whether the same findings can be reproduced in patients with lipodystrophy related to exposure to

only nucleoside reverse transcriptase inhibitors (NRTIs) or non-nucleosides (NNRTIs). It should also be explored whether the disturbances found are unspecific and common to any highly active combination or wethed there are certain combinations or some drugs that exert a more potent dysregulation in the number of T cells producing TNF-α. Overall, the study offers more questions than answers, but it certainly identifies a risk factor for the development of lipodystrophy in HIV-positive patients, which could lead to a better control of this complication, including the possibility of treatment and prevention.

Santiago Moreno
Service of Infectious Diseases
Hospital Ramón y Cajal
Madrid, Spain