

## **Infectious Diseases**

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### *HIV/HCV Co-Infection in Hemophilia*

Jorge Daruich, Argentina

It is not surprising that human immunodeficiency virus (HIV) and hepatitis C (HCV) co-infection poses serious complications in the lives and treatment of people with hemophilia. It also is not surprising that co-infection is so prevalent, since both were transmitted via blood products before the advent of heat-treating and other viral inactivation techniques for clotting factor, Dr. Jorge Daruich said. Studies suggest that the rate of HIV/HCV co-infection ranged between 40% and 80% at its height.

The use of highly active anti-retroviral therapy (HAART) in the treatment of HIV/AIDS has significantly improved outcomes for those who have been infected with the virus, to the extent that it can now be considered a lifelong chronic infection, he said. The improvement in HIV treatment has also significantly reduced mortality for those with HIV/HCV co-infection.

However, HIV co-infection is one of the main factors associated with liver disease progression in HCV, Dr. Daruich observed. Patients solely infected with HCV have a spontaneous recovery rate between 25% and 50%. For those co-infected with HIV, this rate drops to between 0% and 25%. Co-infected patients receiving HAART are living longer, healthier lives. Unfortunately, the morbidity and death caused by HCV have shown a corresponding rise, since co-infected patients are living long enough to progress to serious liver disease.

Although successful treatment with HAART can slow liver disease progression, co-infected patients are significantly more likely than mono-infected patients to develop more serious liver inflammation and to develop cirrhosis sooner, especially if CD4 co-receptor (CD4+) counts are under 200. They are also at greater risk of developing hepatic cancer. HAART-related liver toxicity is also more likely in those being treated for HIV.

Once HIV is controlled with HAART, patients should be assessed to determine the appropriateness of HCV treatment with drugs such as interferon and ribavirin. Decisions about whether and how to treat for HCV should be made by weighing the potential benefits against the risks of treatment and should include an assessment of whether the patient's clotting factor disorder is likely to interfere with a particular treatment modality.

Patients with HIV or HCV should always be tested for co-infection, as well as hepatitis A and B, Dr. Daruich concluded. "To know who should be treated and how, it's important to know all the clinical conditions present, including personal history, co-morbidities, and pharmacological interactions that might weaken treatment response. Interdisciplinary team approaches get the best possible results."

### *The Natural and Unnatural History of Hepatitis C Virus Infection*

Harvey Alter, National Institutes of Health, Bethesda, MD, United States

The progression from a normal liver to advanced liver disease is neither linear nor inevitable with HCV, Dr. Harvey Alter said. In fact, earlier, more dire estimates have not been borne out, and it appears that most patients do not progress to cirrhosis, even in the absence of treatment.

Hepatitis C accounts for only 15% of all forms of hepatitis. However, it is the major cause of chronic liver disease, because the virus replicates rapidly, doubling every 13 to 17 hours. By the time immune response kicks in, the viral load has grown to enormous proportions. In addition, HCV (like HIV) comprises a large family of viral variants. So even when antibodies to the bulk of the viral load are developed, there are still many variants to be fought.

Dr. Alter presented case studies to demonstrate that as time progresses, so does viral diversity. This factor suggests that antibody production actually drives HCV variation, making it much more difficult for the immune system to keep up with the load. At the same time, the disease appears to mute T-cell response, resulting in severe impairment that seems to be related to inhibitions from the viral protein itself.

Progressive analysis of the rate of severe disease shows that, in the absence of alcohol abuse or immunodeficiency, the likelihood of progression to severe liver disease is only around 28%. More than 20% of patients will spontaneously recover. Of those who progress, nearly half can be successfully treated with combination interferon and ribavirin therapy.

However, Dr. Alter cautioned against excessive optimism, because the rate of HCV infection is so high internationally that even with these relatively positive outcomes, the disease will have a staggering impact on global health.

#### *25 Years of HIV Research:*

##### *What We Have Learned and What We Still Need to Know*

Lucy Dorrell, Weatherall Institute of Molecular Medicine, MRC Human Immunology Unit, University of Oxford, United Kingdom

Over the past three decades, great insights have been gained in the study of AIDS and HIV, Dr. Lucy Dorrell said, but much remains to be learned and much is still to be done in effectively treating and preventing the disease.

In 2007, more than 33 million people were living with HIV worldwide. Advances in prevention approaches include voluntary testing, condom distribution, safer blood products, drug prevention of mother-to-child transmission, circumcision (which can reduce transmission by 60%), post-exposure prophylaxis, and treatment of sexually transmitted infections (STIs). However, these measures have not been universally adopted, and more than 7,000 new infections occur daily.

The advent of HAART has led to significant improvement in health outcomes for those living with HIV. While programs to extend this life-saving therapy to developing countries are under way, millions of people still lack access to treatment.

The early promise of vaccine development and vaginal microbicides has also not been borne out, Dr. Dorrell said, because of the enormous genetic diversity of the virus, immune evasion, and the latent infection of critical immune cells. One research avenue that shows promise is the study of a relatively rare group of individuals who maintain normal CD4 counts, even without retroviral therapy.

A substantial number of people, many of whom received infected blood products before viral inactivation, were repeatedly exposed to HIV but did not become infected. Dr. Dorrell said that studying this population could yield important clues about host genetic resistance to the disease. To more systematically examine this possibility, the Center for HIV-AIDS Vaccine Immunology (CHAVI) has initiated a study to identify the gene variants that influence susceptibility to HIV 1 in people with hemophilia A. Dr. Dorrell invited patients who had received blood products between 1979 and 1984 to enrol in the study.

*Variant Creutzfeldt-Jakob Disease:  
Transmission by Clotting Factor*  
James Ironside, United Kingdom

Variant Creutzfeldt-Jakob Disease (vCJD) is a prion disease that appears to be associated with consuming meat products containing transmissible spongiform encephalopathies (TSEs), Dr. James Ironside said. It is different from other viral diseases because it has a long incubation period during which there is no antibody response, which has thus far made testing for it impossible. The transmissible agent is very small and has proven to be extremely resistant to deactivation.

The disease has been reported in the U.K. and 10 other countries in Europe, North America, and Asia. Because the infectious agent spreads outside the central nervous system, its possible presence in blood has been a concern, Dr. Ironside said. Since some of the people who died from vCJD had donated blood, and since there is no known way to deactivate the virus, a further serious concern has been that the disease may be transmissible in blood products, even those that are virally inactivated.

Dr. Ironside said the good news is that no evidence of vCJD transmission through blood or blood products has been found to date, and the number of people dying from the disease appears to be declining. However, because of the disease's long incubation period, it is too soon to say that clotting factor and other blood products are safe from vCJD, or that the bulk of the disease crisis has passed.

Dr. Ironside emphasized the necessity of developing a screening and confirmatory test for vCJD that will yield an accurate estimate of the extent of infection, improving treatment and prophylaxis, and instituting better standards for decontamination of surgical instruments to prevent inadvertent disease transmission.