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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.

A new search engine for analyzing HIV-1 reverse transcriptase and protease mutations

Sequence variation in HIV-1 reverse transcriptase (RT) and protease, the targets of antiretroviral drugs, can represent either naturally occurring polymorphims associated with different subtypes or viral groups, or genetic changes selected under antiretroviral drug pressure. The variability in the origin of mutations in HIV RT and protease sequences, and the lack of annotation in public databases has complicated the tasks of researchers aiming at analyzing the role of different mutations in the acquisition of drug resistance to RT and protease inhibitors. Robert Shafer and colleagues from Stanford University, reported in the November 2000 issue of Nature Medicine a paper (6: 1290-2) on a new online search engine that should facilitate the analysis of HIV-1 RT and protease mutations. The program called HIV-SEQ (for "HIV mutation search engine for queries") compares an HIV-1 sequence submitted by a researcher to a consensus sequence. Differences between the sequences are used as query parameters for the HIV RT and Protease Sequence Database. Data on the frequency with which each mutation occurs in individuals according to HIV-1 subtype and type of drug therapy can be accessed. Background data on potential drug resistance mutations and links to the Medline references and GenBank entries associated with published sequences are made available. The program is available at hyperlink "http://hivdb.stanford.edu/hiv/programs.htm"

As sequence analysis is used increasingly in studying or monitoring HIV-1 drug resistance, a program like HIV-SEQ that identifies mutations and helps in their interpretation in real time is a big step in the right direction.

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

Can therapy interruption during chronic infection cause an acute retroviral syndrome?

Acute HIV infection is associated with a clinical syndrome characterized by fever, fatigue, pharyngitis, lymphadenopathy, rash and weight loss in two thirds of patients. In 1998, Daar *et al.* published an intriguing report of a patient who initiated anitretroviral therapy during acute HIV infection before antibody seroconversion (Ann Intern Med 1998; 128: 827-9). After 6 months of treatment, the patient elected to discontinue therapy. His viral load precipitously increased, CD4 cells declined and he developed a syndrome identical to the acute retroviral syndrome. Daar postulated that early therapy delayed the full immunologic response to infection and clinical manifestations of acute HIV infection were unmasked when uncontrolled viral replication resumed.

Two recent reports suggest that the retroviral syndrome may not be limited to the setting of acute HIV infection. Colven described 3 patients with chronic HIV infection receiving antiretroviral therapy who developed a retroviral clinical syndrome 6 weeks within discontinuing their therapy (Colven *et al.* Ann Intern Med 2000; 133: 435-8). The clinical syndrome coincided with abrupt HIV--RNA increases and CD4 decline. Similarly, Kilby reported an individual who developed clinical symptoms 11 days after therapy discontinuation (Kilby *et al.* Ann Intern Med 2000; 133: 439-41). This patient was not symptomatic during primary seroconversion and had an earlier therapy interruption without illness. In all subjects, symptoms resolved with resumption of antiretroviral therapy.

Although other illness could potentially explain the clinical observations in these patients, taken together the data argue that acute antiretroviral syndromes can occur after therapy interruption in patients with chronic HIV infection. Characterization of immune responses in these cases deserves further attention and may provide insights into HIV pathogenesis. These reports are important from a practical clinical standpoint in view of the recent enthusiasm for therapy interruptions.

The frequency of this syndrome is not known, and may have been unrecognized because symptoms are nonspecific and easily attributed to a "viral syndrome". Prospective studies of therapy interruption are likely to provide the best characterization of this syndrome. In the mean time, clinicians should consider this entity in the differential diagnosis of patients with a mononucleosis-like syndrome after HIV therapy interruption.

Diane Havlir
University of California
San Diego, California, USA

HIV did not originate as a result of the OPV trials in the late 1950s

The Royal Society organised a discussion meeting in London 12-14 September 2000, on the origin of HIV and the AIDS Epidemic. The meeting intended to investigate the scientific support for the hypothesis that HIV originated due to accidental transfer into humans of SIVcpz, as a result of oral polio vaccination trials in central Africa during the late 1950s. This hypothesis has caught much attention following the publication by Edward Hooper of "The River: a journey to the source of HIV and AIDS" (eds. Little, Brown & Co. New York 1999). Other hypotheses, such as the 'natural transfer' theory, suggesting that SIVcpz crossed the species barrier to humans as a result of blood-blood contact between chimpanzees and humans following e.g. fighting during hunting or butchering of chimpanzee meat, were also largely debated. Most of the speakers presented scientific data on the epidemiology of HIV including dating its early spread using phylogenetic methods, on the prevalence of SIVcpz and migration of chimpanzees, on the genetic analysis of original OPV batches, on possible other iatrogenic origins of HIV. Yet almost all speakers were either defending or rejecting the hypothesis that HIV originated as a result of the OPV trials. The meeting was rather 'passionate' at some moments. The basic scientific facts are the following.

In favour of the OPV origin of AIDS: i) The earliest cases of AIDS were found in geographical areas in close proximity of OPV trial sites, in Congo and neighbouring countries, shortly after the OPV trials (Edward Hooper); ii) Monkey kidney cells, in which OPV was prepared, contain small amount of lymphocytes, the target cells of HIV. When experimentally preparing kidney cell cultures from SIV-infected monkeys, SIV-infected cells remained present after up to 6 passages in culture, although to such small amounts that they may not have been able to produce enough infectious virus (Philippe Lena, Pasteur Institute, Paris, France); iii) Eyewitnesses, not directly involved in vaccine production, told Hooper that chimpanzee kidneys were being used; iv) According to Hooper, no sufficiently clear written records exist of the manufacturing of particular batches used in these early OPV trials, and exactly where these batches were used; v) All HIV types and subtypes seem to have spread simultaneously during the sixties to eighties.

Against the OPV origin of AIDS: i) The OPV sites and early AIDS cases were both in proximity of major traffic roads and centres of medical care, these are confounding factors not necessarily indicating that OPV is the cause of the AIDS cases (Kevin De Cock, CDC); ii) Natural cross species transfer is a common way taken by animal viruses to infect humans or other animals (Albert Osterhaus, Erasmus University, Rotterdam, The Netherlands); iii) Several HIV-2 infections in humans have been documented to correlate very closely genetically and geographically with SIVsm in soothey mangabees most probably as a result of natural transfer. These are in general dead end infections, multiple human passages may be required to create an infectious HIV, possibly assisted by non-sterile vaccination campaigns (Preston Marx, Tulane Regional Primate Research Center, Covington, Louisiana, USA); iv) The chimpanzee species that were available to the vaccine manufacturers was Pan troglodytes schweinfurthii and Pan paniscus. These species are not the reservoir of HIV-1 group M. The earliest sample of HIV-1 was an HIV-1 group M virus (subtype B-D). This 1959 sample of Kinshasa is claimed by Hooper to originate from a recipient of OPV. SIVcpz at the origin of HIV-1 group M is however only found in Pan troglodytes troglodites (Beatrice Hahn, University of Alabama, Birmingham, USA); v) Using phylogenetic and molecular clock analyses, three groups independently and using different methods calculated the radiation of HIV-1 group M to be no later than the 1920s-1940s (Bette Korber, Los Alamos National Laboratory, New Mexico, USA; Paul Sharp, University of Nottingham, UK; Anne-Mieke Vandamme, Rega Institute, Katholieke Universiteit Leuven, Belgium). The simian to human transmission may have occurred any time between the end of the 17th century (date of the HIV-1 group M and SIVcpz most recent common ancestor) and the 1920s-1930s (most recent common ancestor of all HIV-1 group M strains) (Anne-Mieke Vandamme, Rega Institute, Katholieke Universiteit Leuven, Belgium); vi) There is statistical support for a single simian to human transmission of HIV-1 group M, based on the tree topology (Tom Burr, Los Alamos National Laboratory, New Mexico, USA). Independent of any dating, this observation is consistent with both the OPV theory and the natural transfer theory. In the context of dating the radiation of HIV-

1 group M earlier than 1920s-1940s (see point v above), only the natural transfer theory remains consistent with this observation; vii) Using epidemiological modelling, it was shown that small increases in the average number of sexual partners of infected individuals could theoretically have dramatic effects on the prevalence of HIV infection. Therefore, it is very well possible that AIDS could have stayed confined to small local populations, unnoticed by modern medicine, until it arrived in urban areas where the changes in sexual behaviour of the last decades sparked a real epidemic and pandemic (Sir Robert May, University of Oxford, UK); viii) All personnel alive today, that were directly involved in OPV production at the different production plants (in Belgium and the USA), provided Dr. Stanley Plotkin and Dr. Hilary Koprowsky (the OPV manufacturers) with written testimonies that chimpanzee kidney cells were never used for OPV production; ix) Dr Plotkin provided his original labnotes showing that the batch used in Congo was also used in Sweden and New Jersey, yet no AIDS epidemic was sparked from those regions; x) The remaining lots of the batch of OPV used in Congo were tested for the presence of HIV or SIV genomic material, and for the species of the cells used for vaccine production (mtDNA). The two labs who tested for the virus did not find any viral genomic RNA or DNA. The two labs who tested for the species found macaque mtDNA, no chimpanzee mtDNA (Claudio Basilico. New York University School of Medicine, USA); xi) Using the original vaccine production procedure with kidneys from SIV infected monkeys, the use of trypsin and the dilution of SIV resulted in no infectious virus remaining in a preparation corresponding to a field lot of OPV (John Garrett, NIBSC, UK).

From the list above, it is now clear that all available scientific evidence suggests that HIV did not originate from administration of OPV. We have been lucky that the few OPV batches that were produced in African Green Monkeys by other manufacturers did not result in the transmission of SIVagm to humans. Other iatrogenic help for the AIDS epidemic can however not be excluded. Preston Marx (Tulane Regional Primate Research Center, USA) explained how the virulence and spread of HIV could have been amplified, following the original natural transfer from simians to humans, because of the extensive re-use of unsterilized needles in Africa. This thorough investigation into the origin of HIV has led to a better understanding of the dangers associated with the use of animal cells for human medicine (vaccine production, xenotransplantation), and with the use of unsterilized medical equipment. We can only hope that the medical establishment has learned enough to avoid mistakes in the future. Especially in the light of the current threat of BSE and its transmission to humans as vCJD, we should keep stressing to the scientific community and to politicians that a lot is at stake when wrong decisions are made.

Anne-Mieke Vandamme
Rega Institute and University Hospitals
Katholieke Universiteit Leuven,
Leuven, Belgium

Nevirapine and liver toxicity

Last April, the European Medicine's Evaluation Agency (EMEA) released a warning about the potential for severe and life-threatening skin reactions and serious liver toxicity in patients taking nevirapine (NVP). To use the drug safely, the agency advised close monitoring (every 2 weeks) of aminotransferases during the first 2-3 months on therapy.

Several reports presented at the 5th International Congress on Drug Therapy in Glasgow past October put Viramune's toxicity into context with that of other antiretrovirals. In one study (Martínez *et al.* Abstract PL8.5), data collected from 610 patients who began NVP in two sites in Barcelona and one in London were examined. Overall 15% of individuals experienced a ≥ 3-fold increase of ALT or AST, and one third a ≥ 3-fold increase in GGT. These abnormalities were asymptomatic in most instances. In fact, clinical hepatitis in this cohort was very rare and no case led to death. Hepatitis C co-infection was a significant risk factor for hepatotoxicity. Liver toxicity caused only 2% of the patients to stop treatment, although 9% quitted NVP due to rash. Taking into account this information, Martínez considered that an intensive liver function test monitoring during the first months of NVP therapy does not really appear to be justified.

In another study, Dr Pedro Cahn (Abstract PL8.6), from Buenos Aires, reported on the hepatic safety of NVP at the BI-1090 trial. The study was conducted a few years ago, when it was acceptable to compare triple therapy with dual nucleoside combinations. That study provided a unique opportunity to see what NVP added to the toxicity of nucleosides. The study included 2,249 patients from 4 continents. Overall, transaminase elevations greater than 5 times the upper limit of normal were noticed in 8.2% of the patients. While there were twice as many cases of clinical hepatitis in the NVP arm, overall the rate was rather low (2.8% vs. 1.4%). Moreover, there were 4 deaths due to hepatitis, only one of which was in the NVP arm.

In summary, these large series of patients being on NVP permit to be confident on the safety of the drug. Anecdotal cases of severe hepatic failure in subjects exposed to NVP are very rare,

and should not preclude its broad use as part of the current antiretroviral armamentarium.

Rafael Rodríguez-Rosado
Instituto de Salud Carlos III
Madrid, Spain

Lymphomas in the HAART era

Although HAART has greatly reduced the appearance of many AIDS-related complications, it does not appear to have reduced the incidence of non-Hodgkin's lymphomas (NHL). In fact, in the recently published US Remune trial (Kahn *et al.* JAMA 2000; 284: 2193-202), the follow-up of 2527 HIV+ subjects over 2.5 years since 1996 has shown an unexpected high incidence of NHL. Lymphomas were the second most common clinical progression event in the study after oral candidosis.

A recent British study (Matthews *et al.* Blood 2000; 96: 2730-4) involving 7840 HIV+ subjects (8% female, 92% male) has looked for changes in NHL before and after HAART became available. Overall, 150 subjects developed NHL. The researchers found little change when they looked at the symptoms associated with NHL or survival after a diagnosis of this cancer. Importantly, they did not find any significant increase in NHL over the course of their study. However, in the time before HAART, NHL was rarely the first AIDS-related illness, whereas since HAART became available, NHL is 6-fold more likely the first AIDS-defining condition. This increase occurred because currently patients are not developing the classical AIDS-related illnesses such as PCP, CMV or MAC.

In the British study, a past history of injection drug use, female gender, or ethnicity did not affect the risk for developing NHL. However, patients older than 37 years of age were 3 times more likely to develop NHL than subjects younger than 25 years old. Moreover, the lower the CD4+ count, the greater the risk of developing NHL. Subjects with fewer than 350 CD4+ cells were 14 times more likely to develop NHL than those whose counts remained above 350 cells.

Interestingly, subjects who used HAART were significantly less likely to develop NHL than those subjects who used nukes alone. Survival 2 years after the diagnosis and treatment of NHL tended to be higher after HAART was introduced (41% versus 29%), but without reaching statistical significance. A similar trend supporting the benefit of HAART over NHL survival has been noticed in a recent review of 369 AIDS-related lymphomas in California (Levine *et al.* Blood 2000; 96: 4084-90). Moreover, the median CD4+ count at the time of diagnosis has decreased significantly, and fewer cases of small non-cleaved lymphoma and conversely more cases of diffuse large cell lymphoma are currently seen.

In summary, the incidence of lymphomas in HIV+ individuals might be in increase, since patients are older and a large proportion survive long periods of time with low CD4 counts. However, survival of subjects with the diagnosis of lymphoma being on HAART has improved significantly.

Marina Núñez
Instituto de Salud Carlos III
Madrid, Spain