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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.

HIV escape at late stage may be due to the lack of V3 loop carbohydrates

Most of the neutralising antibodies present in the sera of HIV-1 infected patients are directed against the V3 loop of gp120 or to the epitopes overlapping the CD4-binding sites of gp120 (Chamat S *et al*. J Immunol 1992; 149: 649-54; Burton D. Proc Natl Acad Sci USA 1997; 94: 10018-23). A point mutation within the epitope, or a point mutation elsewhere in the env gene that alters the conformation of the epitope, can result in resistance towards the neutralisation activity of antibodies (Park E *et al*. J Virol 1998; 72: 7099-107).

N-linked glycans present in the envelope play an important role in the immunological neutralisation of HIV-1. During infection and under the selective pressure of antibodies directed to the envelope, this manifests itself in the selection of virions carrying fully glycosylated gp120. Data presented at the 7th European Conference on Clinical Aspects and Treatment of HIV Infection (Mueller *et al*. Abstract 1206; Lisbon, October 23-27 1999) demonstrated that in HIV-1 infected patients, viruses are selected which are presenting nonglycosylated V3 loops. This was especially observed in CXCR4 viruses and to a significantly lesser extent in CCR5 viruses. Using in-vitro mutagenesis experiments, mutants were created that were lacking one or more of the five N-linked glycans in the V3 loop. It was shown that mutants lacking at least two of these glycosylation sites have high replication rates and are able to infect cells expressing low CXCR4 levels. Manifestation of these in vitro observations can be observed in the late stage of infection when the immune system is impaired. At that point of the infection, partially nonglycosylated variants can escape from immunological neutralisation resulting in variants that, in turn, show a more efficient binding to the CXCR4 coreceptor and give rise to an increased viral load, despite the number of CD4+ T-cells declining.

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Hepatitis B is more severe in HIV infection

Up to recently it was believed that liver disease caused by the hepatitis B virus (HBV) was less severe in HIV co-infected persons, since hepatic damage in HBV carriers is mainly immunomediated, and inflammatory lesions are reduced in situations of immunodeficiency, as occurs in HIV infection. In accordance, chronic hepatitis B in HIV-infected persons typically presents lower transaminase levels, despite serum HBV DNA titers being much higher. The latter is due to the lack of control over hepatitis virus replication in immunosuppressed conditions. In summary, HBV could be more transmissible but less damaging in HBV/HIV co-infected individuals.

A recent French study (Colin *et al*. Hepatology 1999; 29: 1306-10) has broken the peace for HBV/HIV carriers. They examined 132 homosexual men with chronic hepatitis B (HBsAg+), of whom 65 were co-infected with HIV. As expected, HIV-positive subjects had lower ALT and higher serum HBV DNA levels than HIV-negatives However, the rate of cirrhosis in specimens collected through liver biopsy was higher in HIV-positives. The authors concluded that chronic hepatitis B in HIV infection is associated with an enhancement in HBV replication and a higher risk for cirrhosis without increased liver necrotic-inflammatory process.

The new findings are in agreement with what is occasionally seen in liver transplant recipients, in whom HBV relapses can evolve rapidly to liver failure, as a consequence of dramatic HBV replication and direct hepatocyte destruction.

Until recently, alpha-interferon was the only treatment available for chronic hepatitis B. Administered either at doses of 10 million units 3-times a week, or 5 million units daily for 16 weeks, a response was not seen in more than one third of patients. Response is defined as a normalisation of liver enzymes, loss of serum HBeAg and development of anti-HBe (seroconversion), and disappearance of circulating HBV DNA. Although a recent European trial (Janssen *et al*. Hepatology 1999; 30: 238-43) has demonstrated that response is slightly higher

when interferon is administered for longer periods of time (32 weeks), the best expectations for the treatment of chronic hepatitis B are focused on the use of new drugs, such as adefovir, lamivudine (3TC), emtricitabine (FTC), or PMPA. All these nucleoside analogues are taken once daily, and have anti-HIV activity, which can be of further benefit in HBV/HIV co-infected persons. As with the treatment of HIV infection, combination drug therapy for HBV infection is likely to produce the most significant reduction in viral load, minimise the emergence of drug resistance (already noticed for 3TC), and ultimately increase the rate of cure.

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Did HIV originate as a result of oral poliovaccine administration in Africa during the late 50s?

The origin of HIV-1 has always been very debated. The fact that in phylogenetic analyses the HIVs are not a monophyletic group, but rather cluster with simian strains from different species already showed that these 'human' viruses were in fact simian viruses that crossed species barriers causing the current AIDS pandemic (Sharp PM et al. AIDS 1994; 8: 27). The closest simian relative to HIV-1 is the chimpanzee virus (SIVcpz) (Peeters M et al. AIDS 1992; 6: 447), and to HIV-2 the sooty mangabey virus (SIVsm). Extensive research showed indeed that most likely HIV-1 comes from chimpanzees (Gao F et al. Nature1999; 397: 436) and HIV-2 from sooty mangabeys (Hirsch VM et al. Nature 1989; 339: 389; Sharp PM et al. Biol Bull 1999; 196: 338), but how? Several hypotheses exist, the most plausible of which is infection transmitted through slaughtering of monkeys and apes for bushmeat, called the 'natural' way.

A more controversial theory has recently caught much attention through the book of Edward Hooper "The River: a journey to the source of HIV and AIDS" (Little, Brown & Co. eds, New York, 1999). According to Hooper, both HIV-1 and HIV-2 originated at the end of the 1950s when live oral poliovaccines (OPV), grown on primate kidney cells, were administered to African children. Thus, medicine is to blame. Much can be said about the book, but certainly this work of Hooper was very carefully researched, lots of data and interviews with the original protagonists give the reader a profound feeling of what happened during the early days of the AIDS epidemic. I talked to some of the Belgian protagonists of these early days of OPV. They pointed to me that some scientific extrapolations in the book are not entirely correct. First of all, minced kidney cell cultures only contain a small amount of lymphocytes, in which SIV might have been replicating. Secondly, poliovirus grows much more rapidly to a high titre in cultured kidney cells than SIV/HIV in PBMCs. Thirdly, the cell-free polio vaccine was an oral vaccine, a route that is generally not taken by HIV and that would require high virus titres and/or SIV/HIV producing cells for infection to occur. Fourthly, the species does not fit, chimpanzee kidney cultures of the subspecies *Pan troglodytes troglodytes,* which carry the SIVs closest resembling HIV-1 were not used for preparing these vaccines. The chimpanzees from Lindi referred to by the author were *Pan troglodytes Schweinfurthi,* which carry a much more divergent SIV. In fact there are no documentations that chimpanzee kidneys were used at all (although one can never be sure indeed). Fifthly, the time frame does not fit entirely, the oldest confirmed HIV-1 infection dates back from 1959, in an African adult. The virus was later sequenced and found to be close to the common ancestor of HIV-1 subtypes B and D, which diverged later than most other subtypes in group M (Nahmias A et al. Lancet 1986; 11:1279; Zhu T et al. Nature 1998; 391: 594). These observations place the origin of HIV-1 at least some years before 1959. Yet OPV was administered to African children around that time, in 1959-1960, not several years earlier. Sixthly, other simian retroviruses such as the simian foamy viruses have been transmitted to humans occupationnaly exposed to monkeys (Heneine et al. Nature Medicine 4; 403), essentially via the 'natural' way. There is also evidence that the human T-cell leukemia viruses (HTLV) which are cousins of HIV, probably infected humans many thousands of years ago for some HTLV subtypes, and a few hundred years ago for others (Vandamme A-M et al. Trends Microbiol 1998; 6: 477), but in any case long before administration of OPV or any other vaccine. So these cross species infections have occurred with similar viruses before, not only from monkeys to humans, but also between monkey and ape species, both for STLV-I and SIV; all through the "natural" way. Seventhly, the geography does not fit entirely. HIV-2 and HIV-1 group O and N arose in West Africa, where no OPV was tested, whereas the geographic location of the simian species, from which HIV-1 and HIV-2 originated, fits with the geographic distribution of the early HIV-1 and HIV-2 epidemic. In addition, the OPV was also tested in Eastern Europe, and no HIV epidemic started from that region.

Yet, how unlikely the OPV hypothesis, the opposite has not been proven. One way to test the hypothesis is of course check old stocks of the OPV and verify or exclude the presence of HIV. Although this seems rather simple, the freezers that harboured these stocks have been moved from lab to lab and probably succumbed long ago. The stocks themselves seem to be lost, except for a few vials at Wistar, which is now considered for testing. If this vial turns out negative, the hypothesis becomes weaker, but is still not disproven. A second, more indirect way would be to extrapolate back the date of origin of HIV from its current genetic diversity, assuming that the radiation of this diversity started after the interspecies transmission. All one would

need is a reliable estimate of the evolutionary rate. Rough estimates of that origin using this approach have raised much controversy, because of the lack of a molecular clock for HIV (Goudsmit J et al. Nature 1999; 400: 325; Korber B et al. Science 1998; 280: 1868; Korber B et al. Nature 1999; 400: 326). Still it is worth trying to stretch current mathematical techniques a little further, possibly to arrive at some useful way to calibrate a clock for HIV. Preliminary molecular clock calculations reported at the 7th European Conference on Clinical Aspects and Treatment of HIV infection (Lisbon, October 23-27 1999) suggest that HIV-1 group M strains were already present in Africa during the 1930s-1940s, dating the interspecies transmission from chimpanzees to humans at least several decades earlier (Sharp PM et al. Biochem Soc Trans, in press). Yet exposure of humans to animal retroviruses continues. Xenotransplantation poses risks of transmission of both known or unknown viruses, although no evidence of transmission of baboon viruses (for the single baboon transplant) or pig endogenous retroviruses has thus far been seen (Heneine et al. Lancet 1998 352: 695; Paradis et al. Science 1999, 285: 1236). Reverse transcriptase activity has recently been detected in many chicken cell-derived measles and mumps vaccines used today likely associated with endogenous avian retroviral particles (Tsang S et al. J Virol 1999; 73: 5843). Again, no transmission to recipients has been documented.

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