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HIV as the cause of AIDS and associated diseases

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Abstract

This brief article is in response to the previous article by Peter Duesberg and David Rasnick titled 'The AIDS Dilemma: Drug Diseases Blamed on a Passenger Virus.' We focus our response on thirteen specific issues raised by Duesberg and Rasnick.

HIV, AIDS, and associated diseases

The first point to address concerning 'The AIDS dilemma' is the re-definition of HIV infection and AIDS. HIV is the causative agent of AIDS and associated diseases (Chermann et al., 1992). The virus is transmissible by sex, blood and blood products, as well as by perinatal route. AIDS is the final manifestation of HIV infection after an estimated ten-year latency period and is characterized by the emergence of fatal opportunistic infections due to the absence of immunological defenses. AIDS is not contagious by itself, but HIV is transmissible. Due to the protracted HIV latency period, most individuals infected by HIV through their first sexual contacts will develop AIDS at an adult age.

AIDS is characterized by a significant decrease in immunological defense mechanisms and, more particularly, by a profound progressive depletion of the CD4 T lymphocytes. We first showed in 1992 and have subsequently confirmed that the decline of the CD4 T lymphocytes in HIV-infected patients is correlated with the isolation of a cytopathic virus from infected lymphocytes. In particular, we find that the virus is consistently isolated from peripheral blood lymphocytes (PBL) in AIDS patients and that a virus isolated once in an HIV-infected patient will always be found in subsequent virus isolation from that patient's PBL, except after antiviral combined therapy.

HIV can also be isolated in asymptomatic HIV-positive patients without depletion of CD4 T cells when the target cell is different from the CD4 T lymphocytes. Currently, PCR technology to measure plasmatic viral loads can ascertain the presence of a retrovirus in the plasma without knowing whether the cellular origin of the virus is CD4 lymphocytes or/and circulating monocyte-macrophages. This last point is important as the virus may be associated with a macrophage tropic strain and not a CD4 lymphotropic HIV, resulting in a situation in which the viral load is high without depletion of CD4 cells. Patients infected with such a virus do not progress to AIDS and constitute a 'non-progressor group' (Chermann, 1998; Chermann, 1991). For this reason, plasmatic viral load should be correlated with a CD4 decline (indicating a CD4-tropic virus) before antiviral treatment is initiated (Mellors et al., 1997).

AIDS and HIV epidemic

P. Duesberg writes that 'AIDS and HIV epidemics have moved in different directions in the United States and Europe' based on the fact that 'new HIV infections have declined from 1985 to 1993 in blood donations collected at this time ... and in contrast AIDS has increased during the same time.' A noticeable decline in HIV-positive donated blood began in 1985 due to the widespread institution of screening programs. While it is true that during the same period AIDS cases rose, this was due to the fact that people infected before 1985 were now suffering full development of the disease. Due to HIV's latency period, a decrease in new cases of HIV infection will not be correlated with a

decrease in AIDs until several years later. Thus, even if new HIV infections declined from 1985 to 1993 while AIDS cases increased, it does not follow that the two phenomena are causally disconnected.

It should also be noted that since the beginning of the HIV epidemic, the number of HIV-infected individuals has continued to increase. For example, in 1997 alone, 5.2 million adults and 590,000 children have been infected with HIV (UNAIDS report, December 1997).

HIV is transmissible without discrimination by sex or age and leads to a fatal, infectious disease

According to the UNAIDS report on the global HIV/AIDS epidemic (December 1997), 5.2 million newly HIV-infected individuals were registered in 1997. Among these, 2.1 million, or 40%, were women. Of those living with HIV/AIDS today, 41% are women. Among new cases of HIV, more than 50% are teenagers or young adults (between 15 and 24 years old).

HIV is transmissible by blood, blood derivates, sexual contact and from mother to child

It has been widely reported that HIV is transmitted mainly by blood, blood derivatives and sexual contact.

Blood and its derivates

Early in the AIDS epidemic, it was well documented that HIV had been transmitted by transfusions of blood (Feorino et al., 1984) and other anti-hemophiliac factors (Melbye et al., 1984; Vilmer et al., 1984). However, HIV inactivation was described in 1984 and used in derivative blood products (Spire et al., 1984; Spire et al., 1985). For example, IgG ethanolic precipitation was shown to inactivate HIV. As a result, those who underwent passive immunotherapy with inactivated purified immunoglobulins deriving from HIV-infected donors had not been infected with HIV and did not develop AIDS (Henin et al., 1988; Spire et al., 1984). Today, donated blood is screened for the presence of HIV, so no additional cases of AIDS or HIV infection have been reported in the transfused population. Indeed, HIV-negative hemophiliacs presenting with severe Hemophilia A show no significant change in the number of white cells after they receive purified blood (Smid, van der Meer & Halie, 1995); this datum was confirmed by J.A. Evans (1991) in a population of hemophiliacs who remained free of HIV, HBV, or HCV after receiving purified derivative blood products. This indicates that receiving derived-blood products does not by itself lead to a decline in CD4 T cells.

Only HIV-infected hemophiliacs present a CD4 decrease (Cooper et al., 1988) and T. O'Brien confirms the correlation between presence of plasma HIV-1 RNA and decrease of $CD4^+$ with the development of AIDS (O'Brian et al., 1996). Likewise, Gail et al. recently reported that factors such as initial AIDS-defining diagnosis also affect survival after diagnosis of AIDS in hemophiliac patients (Gail et al., 1997). In the hemophiliac population of the United Kingdom, 85% of the deaths in seropositive patients were due to HIV infection (Darby et al., 1995) and certified as due to AIDS. However, some non-progressors are also found in the hemophiliac population (Vicenzi et al., 1997), indicating that, as in other HIV-infected groups, some people remain free of AIDS despite HIV infection.

It is untrue that people who receive infected blood products do not transmit HIV to their partners. Studies based on hemophiliac groups report an estimated 6.8 to 22% rate of heterosexual HIV transmission from infected individuals to their stable spouses, with some spouses developing AIDS (Pichenik et al., 1984; Smiley et al., 1988; Andes et al., 1989). These data confirm that HIV is a transmissible agent that induces AIDS in non-drug abusers.

Sexual contact

Ducsberg writes: 'It takes an average of over 1000 sexual contacts with an HIV-positive [person]...to acquire HIV."

HIV is a sexually transmitted virus when it is present in the sperm or cervical fluid. Some HIV-infected individuals contract the virus through one sexual contact, but in other cases, infection occurs after many contacts, or even after several years of sexual contact. In our studies, we found no relationship between the plasmatic viral load and the presence of the virus in the sperm. We found (Brechard et al., 1997a, 1997b) that the virus was not always present in the ejaculate of the same HIV-infected male when collected at different times, as was also observed by Atkins et al. (1996). The virus was never detected in living and mobile

spermatozoa, although it could be found in seminal fluid or in the cellular population within the sperm (lymphocytes, macrophages). This deviated from what had been previously known of oncoviruses such as the mouse mammary tumor virus in which proviral DNA is integrated into the germinal cells.

Today, HIV transmission is increasing within the heterosexual population with an efficiency of male-to-female transmission greater than that of female-to-male transmission (Nicolosi et al., 1994; O'Brien et al., 1994). This is confirmed by a large majority of epidemiologic studies showing an increased incidence of HIV/AIDS infection among women.

Perinatally-acquired HIV

An exhaustive study done by the French pediatric HIV infection group and published in JAMA (Mayaux et al., 1996, 1997) clearly associates HIV and AIDS in children born to HIV-positive mothers, demonstrating that early virus detection in neonates is correlated with a severe disease in the first 12 months of life. They also conclude that particular HIV viral strains, large viral loads, or transmission early in fetal life are responsible for rapid progression to AIDS.

It is now well documented that transmission of HIV from mother to child is not a classic 'vertical' transmission through the germinal cell lines, but a cell to cell transmission in the trophoblast (Mano & Chermann, 1991a). Some, but not all, organs of the fetus are infected with HIV which is not the expected outcome with a true vertical transmission (Mano & Chermann, 1991b).

Before 1986, repeated exposure to HIV, either through multiple sexual partners or by sharing needles and syringes (among intravenous drug abusers) increased the risk of developing AIDS. Today, in Europe and America, discussion of AIDS and its prevention and the adoption of safe-sex practices have led to a decrease in the incidence of new HIV transmission within these groups. This decrease, combined with the positive effects of antiviral therapy, has resulted in what appears to be a non-progressive group of HIV-positive individuals.

HIV is the pathogen responsible for AIDS: experimental induction of AIDS in the chimpanzee

While it is true that chimpanzees have been experimentally infected with HIV-1 (Francis et al., 1984; Fultz et al., 1986, 1987, 1991; McClure et al., 1984), development of AIDS has not been documented in these animals after the initial inoculation with HIV1-LAV, -MN, or -SF2. However, when the highly cytopathic virus HIV1-NDK was used as the inoculate in 1987 — after HIV1-SF2 in 1985 and HIV1-LAV in 1986 — the animals began immediately to develop thrombopenia and lymphopenia (Novembre et al., 1997). Subsequently, the chimpanzees developed chronic, intermittent diarrhea for which no enteric pathogens were identified and which was not resolved with antibiotics. In previous *in vitro* studies, HIV-NDK was shown both to infect intestinal cells which then exhibited impaired secretions (Fantini et al., 1991a, 1991b, 1992) responsible for the 'clean diarrhea' and to inhibit hematopoiesis (Calenda, Sebahoun & Chermann, 1992a), as similarly observed in the infected chimpanzees. As observed in the humans, the chimpanzee model demonstrates the importance of the variability of the isolates for the development of full-blown AIDS.

HIV is responsible for the different clinical manifestations of AIDS

Duesberg suggests that HIV is misnamed, as 'immunodeficiency is not a known cause of cancer, dementia, and weight loss.'

Because all HIV strains are not immunodeficiency virus, we agree that HIV is misnamed (Figure 1) and would prefer LAV (lymphadenopathy virus), as we first called it.

For dementia, we know that HIV is a true lentivirus with a tropism for macrophage but not for CD4 cells or continuous cell lines (Chermann, 1990; Gout et al., 1988; Schmidtmayerova et al., 1993). For intestinal disorders, some HIV strains can infect intestinal cells and be responsible for malabsorption and clean diarrhea (Fantini et al., 1991a, 1991b, 1992) without immunodeficiency.

HIV-2 has a preferred tropism for bone marrow progenitors (Calenda, Tamalet & Chermann, 1992b) and is less cytopathic for CD4 cells (Rey et al., 1991). It is seldom transmitted outside Africa, and has virtually no mother to child transmission. By infecting bone marrow progenitors (Calenda & Chermann, 1992d), HIV-2 induces anemia, lymphopenia, and thrombocytopenia, which are often found in HIV-infected patients as well (Calenda & Cher-

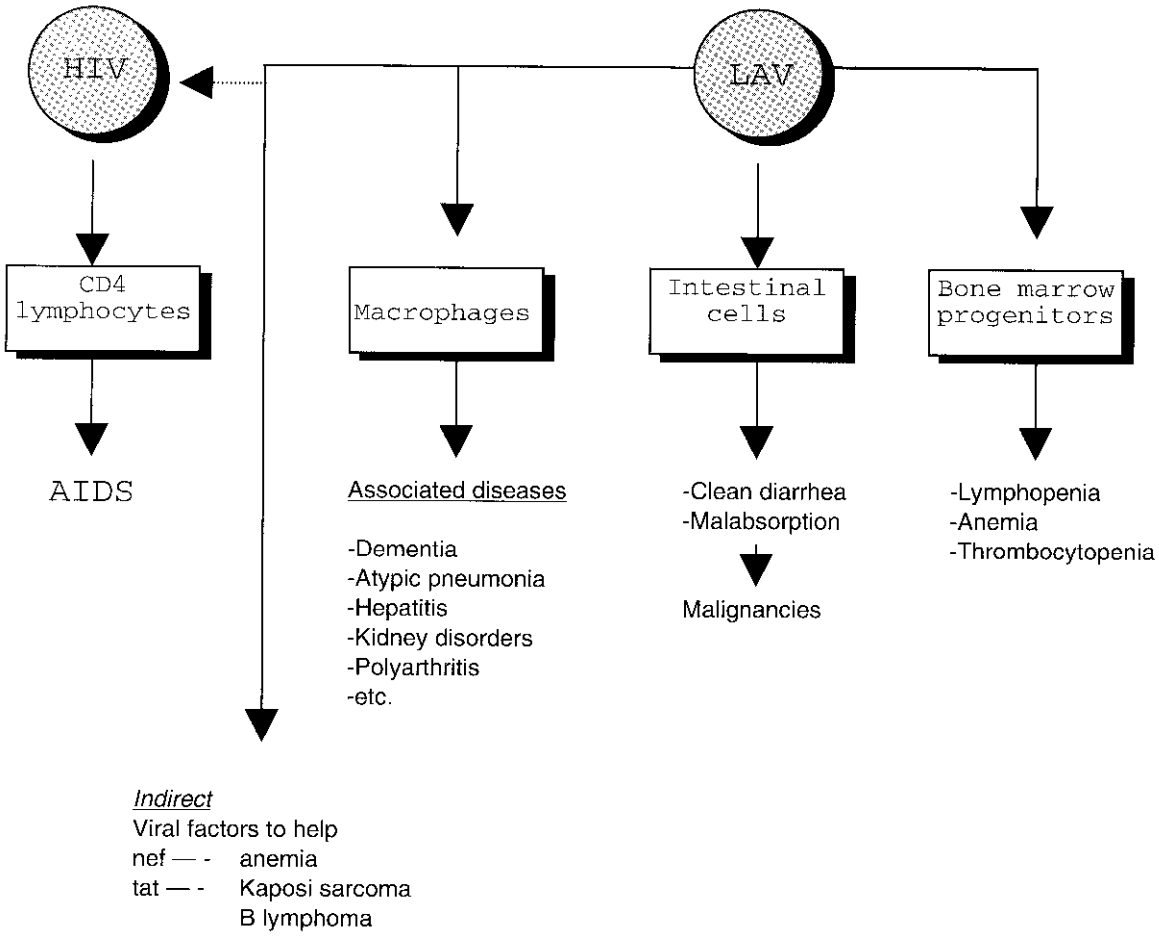

Figure 1. HIV is lymphotropic and cytopathic for the $CD4^+$ lymphocytes; it is responsible for the $CD4^+$ decline and AIDS.
LAV is a true lentivirus. By infection of macrophages, it is responsible for associated diseases: by moving to the brain, it induces dementia; to the lung, atypic pneumonia; to the liver, hepatitis; to the kidney, proteinuria; and to the synovial fluid, polyarthritis.
LAV is also enterotropic: by infection of intestinal cells, it provokes malabsorption with weight loss and hypersecretion leading to 'clean diarrhea.' Through regulatory genes, like tat, it can activate papillomavirus and then be responsible for ano-recto carcinomas.
Like LAV2, LAV1 can infect bone marrow progenitors, inducing lymphopenia, anemia and thrombocytopenia. By analogy to the Friend Leukemia Virus, LAV2-HIV-2 may subsequently induce erythroleukemia in HIV-2 infected patients.

mann, 1992c). Some secreted viral factors produced by infected cells such as bone marrow progenitors (Calenda et al., 1994; Calenda & Chermann, 1995) can be responsible for activating the virus-like papillomavirus or oncogen, which induce malignancies often associated with AIDS.

Duesberg statement: CD4 decline — '... only 1 per 1000 cells are infected'

In addition to the direct HIV cytopathic effect, many indirect events contribute to the CD4 cell decline and loss of the defenses. Among them:

- down regulation of CD4 expression by *nef* secreted from infected cells (Aiken et al., 1994; Anderson et al., 1993; Benson et al., 1993; Curtain et al., 1997; Mariani & Skowronski, 1993).

- induction of CD4 cell apoptosis (Ameisen & Capron, 1991) by gp120 during HIV infection (Banda et al., 1992; Corbeil & Richman 1995; Diamond et al., 1988; Samuelsson et al., 1997).

- induction of non-infected CD4 apoptosis by macrophage infected with a macrophage-tropic strain of HIV (Godard et al., 1997).

- killing of HIV-infected CD4 cells by activated CD8 cells (Borrow et al., 1994; Carmichael et al., 1993; Klein et al., 1995; Yang & Walker, 1997).
- induction of CD4 cell death following superantigen presentation by cellular antigens such as HLA present at the virion surface (Rossio et al., 1995).
- infection of CD4- and CD8- progenitor cells by HIV: only the differentiated $CD4^+$ cells are killed by HIV, contributing to the nonrenewal of CD4 cells (Lunardi-Iskandar et al., 1989).

HIV is a cytotoxic virus

We know that HIV is a cytopathic virus (Barré-Sinoussi et al., 1983), but one with a high degree of variability according to isolates, with some being less cytopathic and some being highly cytopathic.

We are able to correlate the cytopathic effect of HIV and the decline of the CD4 T lymphocytes with the progression to AIDS. When the clinical evolution of AIDS is rapid (less than two years), we always isolate highly cytopathic viruses from such patients. For highly cytopathic viruses, the transmission is easier (less virus is needed to kill CD4 cells and less virus is needed for blood or sexual transmission) (Ellrodt et al., 1984).

The cytopathic effect has been shown to be an intrinsic property of the proviral DNA. We have identified regions in the viral genome that explain the cell-to-cell or the virus-to-cell fusion mechanisms. By constructing a chimeric virus between the low cytopathic HIV-LAV and the highly cytopathic HIV-NDK, we showed that each of the two fusion events were under the control of different genomic regions that were also different from the region governing replication (De Mareuil et al., 1992, 1995; Ellrodt et al., 1984; Hirsch et al., 1990, 1992; Spire et al., 1989, 1990).

Numerous studies have clearly demonstrated the importance of the *env* glycoprotein for induction of HIV-1 cytotoxicity or host range tropism. In addition to the *env* gene, other HIV-1 genes have been reported to influence HIV-1 cytopathogenicity: *nef* defective viruses are less cytopathic than the wild type, and some non-progressor patients present such viruses (Kirchhoff et al., 1995; Sanchez et al., 1997); *vpu* is also responsible for the delayed cytopathicity of HIV, as reported by Iwatani et al. (1997). Highly cytopathic viruses may be *Vpu* deficient and, in this case, the envelope glycoprotein accumulates at the infected cell surface and causes the cell death.

Taken together, these data establish clearly that HIV is also a true cytopathic virus.

HIV is a rapidly replicating virus that causes disease only after decades

We agree that HIV is not a slow virus. The level of HIV cytopathogenicity for the CD4 lymphocytes, the mutation rate, and cofactors such as lifestyle, infection route, and sexual disease can explain the 'paradox' of relatively slow progression.

When the macrophage is the target cell, HIV may be considered as 'a harmless passenger' as observed in some non-progressor patients. However, change of cell target toward the CD4 lymphocyte will rapidly induce a CD4 cell loss with increased plasmatic viral load and an accompanying evolution to AIDS. The new, mutated virus will escape the immunological defense and be selected in large numbers to cause AIDS.

HIV and the immune system

It is not true that HIV cannot be detected in most AIDS patients as, by definition AIDS patients have a fully replicating virus. All patients infected with HIV (asymptomatic or AIDS patients) have antibodies to conserved HIV proteins. Additionally, antibodies directed to *env* protein fail to neutralize all HIV strains because of the genomic variability of HIV.

The idea that 'acute anti-HIV immunity completely neutralizes HIV, but does not protect against AIDS' is not true. On the virus coat, we have identified the presence of a determinant common to all HIV strains that induces neutralizing antibodies (Le Contel et al., 1996). These neutralizing antibodies have been identified in non-progressor, but not in progressor, patients. The common antigen, called R7V, originates from the cellular proteins, is acquired by the virus when it buds from the cell surface (Arthur et al., 1992), and is presented differently than on the cells.

By using R7V, we have developed an ELISA assay which detects these specific antibodies in non-progressor patients. These antibodies have been purified on a R7V-affinity column, they immunoprecipitate and neutralize the different clades of HIV. These neutralizing antibodies protect non-progressor

patients, who, as shown by preliminary results of sequential study (Galéa et al., 1996), present with a high titer of antibodies against AIDS and maintain this high level with time (Galéa et al., 1997b; 1997c). It is still unclear why some patients are developing such antibodies and are protected while others do not and progress to AIDS.

Duesberg statement 'Antiviral drugs are responsible for the decrease of AIDS in industrial countries'

Today, through the use of combined therapies and by adding anti-protease to reverse transcriptase inhibitors, we observe a decrease in mortality associated with a decrease in AIDS. The tri-therapy acts on the virus and also blocks the disease, as reported by the Centers for Disease Control and Prevention (1997) and by the European Centre for Epidemiological Monitoring of AIDS (1997).

How can an old virus cause a new epidemic?

HIV, a longe-stablished virus, is claimed to cause the new AIDS epidemic. HIV is not a new virus, as indicated by P. Duesberg, but AIDS is a new epidemic. Can a long-established, nonfatal virus like a lentivirus mutate and become pathogenic for CD4 lymphocytes?

One can postulate that the old virus was present as a nonpathogenic lentivirus in the host macrophage and was responsible for reversible encephalopathy, atypic pneumonia, and polyarthritis, as found in the animal lentiviruses such as VISNA, CAEV, and EIAV. With increased air travel, the mild form of the old virus could have been brought to Africa and from the macrophage could have acquired the CD4 lymphotropism. The constantly activated immune system of the African population and the mutation rate of the virus would have allowed infection of $CD4^+$ cells and development of AIDS. Indeed, AIDS was not described in Africa before the worldwide epidemic, which began at the same time everywhere. Given the high mutation rate since the development of the AIDS epidemic, the above hypothesis can possibly explain how an old virus may cause a new epidemic. The same phenomenon has already been seen in the mild form of smallpox in European countries, which, imported, became fatal for Native Americans.

Conclusion

Taken together, clinical and academic studies clearly demonstrate that HIV is the causative agent of AIDS. Infection takes different clinical aspects according to the variability of the HIV strains as well as the variability of the target cells. Cofactors such as sexually transmitted diseases or drug abuse may contribute to or accelerate the development of AIDS, but without HIV, AIDS will not follow.

References

Aiken, C., J. Konner, N.R. Landau, M.E. Lenburg & D. Trono, 1994. Nef induces CD4 endocytosis: requirement for a critical dileucine motif in the membrane-proximal CD4 cytoplasmic domain. Cell 76: 853–864.

Ameisen, J.C. & A. Capron, 1991. T cell dysfunction and depletion in AIDS: the programmed cell death hypothesis. Immunol. Today 4: 102.

Anderson, S., D.C. Shugars, R. Swanstrom & J.V. Garcia, 1993. Nef from primary isolates of human immunodeficiency virus type 1 suppresses surface CD4 expression in human and mouse T-cells. J. Virol. 67: 4923–4931.

Andes, W.A., S.R. Rangan & K.M. Wulff, 1989. Exposure of heterosexuals to human immunodeficiency virus and viremia: evidence for continuing risks in spouses of hemophiliac. Sex. Transm. Dis. 16: 68–073.

Arthur, L.O., J.W Bess, J.W. Sowder, R.C. Sowder, R.E. Benveniste, D.L. Mann, J.C. Chermann & L.E. Henderson, 1992. Cellular proteins bound to immunodeficiency viruses: implications for pathogenesis and vaccines. Science 258: 1935–1938.

Atkins, M.C., E.M. Carlin, V.C. Emery, P.D. Griffiths & F. Boag, 1996. Fluctuations of HIV load in semen of HIV-positive patients with newly acquired sexually transmitted disease. BMJ 313: 341–342.

Banda, N.K., J. Bernier, D.K. Kurahara, R. Kurrle, N. Haigwood, R.P. Sekaly & T.H. Finkel, 1992. Crosslinking CD4 by human immunodeficiency virus gp120 primes T cells for activation-induced apoptosis. J. Exp. Med. 176: 1099–1106.

Barré-Sinoussi, F., J.C. Chermann, F. Rey, M.T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Brun-Vezinet, C. Rouzioux, W. Rozenbaum & L. Montagnier, 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220: 868–870.

Benson, R.E., A. Sanfridson, J.S. Ottinger, C. Doyle & B.R. Cullen, 1993. Downregulation of cell surface CD4 expression by simian immunodeficiency virus nef prevents viral super infection. J. Exp. Med. 77: 1561–1566.

Borrow, P., H. Lewicki, B.H. Hahn, M.G. Shaw & M.B.A. Oldstone, 1994. Virus-specific $CD8^+$ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. J. Virol. 68: 6103–6110.

Bréchard, N., P. Galéa, F. Silvy, M. Amram & J.C Chermann, 1997a. HIV detection in seropositive male ejaculation at different times. Contracept. Fertil. Sex. 25: 725–729.

Bréchard, N., P. Galéa, F. Silvy, M. Amram & J.C Chermann, 1997b. Study of HIV localization in sperm. Contracept. Fertil. Sex. 25: 389–391.

Calenda, V., G. Sebahoun & J.C. Chermann, 1992a. Modulation of normal human erythropoietic progenitor cells in long term liquid cultures after HIV infection. AIDS Res. Hum. Retroviruses 8: 61–67.

Calenda, V., C. Tamalet & J.C. Chermann, 1992b. Transient stimulation of granulopoiesis and drastic inhibition of erythropoiesis in HIV-2 infected long term liquid bone marrow cultures. J. Acquir. Immune Defic Syndr. 5: 1148–1157.

Calenda, V. & J.C. Chermann, 1992c. The effects of HIV on hematopoiesis. Eur. J. Haematol. 48: 181–186.

Calenda, V. & J.C. Chermann, 1992d. *In vitro* severe inhibition of erythropoiesis and transient stimulation of granulopoiesis after bone marrow infection with eight different isolates of HIV2. AIDS 6: 943–948.

Calenda, V., P. Graber, J.F. Delamarter & J.C. Chermann, 1994. Involvement of HIV nef protein in abnormal hematopoiesis in AIDS: in vitro study on bone marrow progenitor cells. Eur. J. Haematol. 52: 103–107.

Calenda, V. & J.C. Chermann, 1995. HIV tat protein potentiates in vitro granulomonocytic progenitor cell growth. Eur. J. Haematol. 54: 180–185.

Carmichael, A., X. Jin, P. Sissons & L. Borysiewicz, 1993. Quantitative analysis of the human immunodeficiency virus type 1 (HIV-1)-specific cytotoxic T lymphocyte (CTL) response at different stages of HIV-1 infection: differential CTL responses to HIV-1 and Epstein-Barr virus in late disease. J. Exp. Med. 177: 249–256.

Center for Disease Control and Prevention. Update: trends in AIDS incidence-United States, 1996. Morbidity and Mortality Weekly Report 46: 861–867.

Chermann, J.C., 1988. HIV: the ethiologic agent of AIDS and associated diseases. Biomed. & Pharmacother. 42: 3–4

Chermann, J.C., 1990. HIV-associated diseases: acute and regressive encephalopathy of a seropositive man. Res. Virol. 141: 137–141.

Chermann, J.C., 1991. Promising Directions in HIV Research. PAAC Notes 3: 41–43

Chermann, J.C., J. Fantini, V. Calenda, F. Silvy & I. Hirsch, 1992. Immunopathogenesis of AIDS and associated diseases involves HIV variants and target cells interactions. AIDS Res. Hum. Retroviruses 8: 711–718.

Corbeil, J. & D.D. Richman, 1995. Productive infection and subsequent interaction of CD4-gp120 at the cellular membrane is required for HIV-induced apoptosis of $CD4^+$ T cells. J. Gen. Virol. 76: 681–690.

Cooper, D.A., B. Tindall, E.J. Wilson, A.A. Imrie & R. Penny, 1988. Characterization of T lymphocyte responses during primary infection with human immunodeficiency virus. J. Inf. Dis. 157: 889–896.

Curtain, C.C., M.G. Lowe, C.K. Arunagiri, P.W. Mobley, I.G. Macreadie & A.A. Azad, 1997. Cytotoxic activity of the amino-terminal region of HIV type 1 *nef* protein. AIDS Res. Hum. Retroviruses 13: 1213–1220.

Darby, S.C., D.W. Ewart, P.L.F. Giangrande, P.J. Dolin, R.J.D. Spooner & C.R. Rizza, 1995. Mortality before and after HIV infection in the complete UK population of haemophiliacs. Nature 377: 79–82.

De Mareuil, J., B. Brichacek, D. Salaun, J.C. Chermann & I. Hirsch, 1992. The human immunodeficiency virus (HIV) gag gene product p18 is responsible for enhanced fusogenicity and host range tropism of the highly cytopathic HIV-1-NDK strain. J. Virol. 66: 6797–6801.

De Mareuil, J., D. Salaun, J.C. Chermann & I. Hirsch, 1995. Fusogenic determinants of highly cytopathic subtype D Zairian isolate HIV-1-NDK. Virology 209: 649–653.

Diamond, D.C., B.P. Sleckman, T. Gregory, L.A. Lasky, J.L. Greenstein & S.J. Burakoff, 1988. Inhibition of $CD4^+$ T cell function by the HIV envelope protein, gp120. J. Immunol. 141: 3715–3717.

Ellrodt, A., F. Barré-Sinoussi, P. Le Bras, M.T. Nugeyre, L. Palazzo, F. Rey, F. Brun-Vézinet, C. Rouzioux, P. Segond, R. Caquet, L. Montagnier & J.C. Chermann, 1984. Isolation of a new human T-lymphotropic retrovirus (LAV) from a married couple of Zairians, one with AIDS, the other with prodromes. Lancet I: 1383–1385.

European Centre for the Epidemiological Monitoring of AIDS. HIV/AIDS surveillance in Europe. AIDS cases reported by 30 June 1997, 1997. Quarterly report 54.

Evans, J.A., K.J. Pasi, M.D. Williams & F.G.H. Hill, 1991. Consistently normal $CD4^+$, $CD8^+$ levels in haemophilic boys only treated wih a virally safe factor VIII concentrate (BPL 8Y). British J. Haematol. 79: 457–461.

Fantini, J., N. Yahi & J.C. Chermann, 1991a. Human immunodeficiency virus can infect the apical and basolateral surfaces of human colonic epithelial cells. Proc. Natl. Acad. Sci. USA 88: 9297–9301.

Fantini, J., S. Baghdiguian, N. Yahi & J.C. Chermann, 1991b. Selected human immunodeficiency virus replicates preferentially through the basolateral surface on human colon epithelial cells. Virology 185: 904–907.

Fantini, J., N. Yahi, S. Baghdiguian & J.C. Chermann, 1992. Human colon epithelial cells productively infected with human immunodeficiency virus (HIV) show an impaired differentiation and an altered secretion. J. Virol. 66: 580–585.

Feorino, M.P., V.S. Kalyanaraman, H.W. Haverkos, C.D. Cadradilla, D.T. Warfield, H.W. Jaffe, A.K. Harrison, D. Goldringer, M.S. Gottlieb, J.C. Chermann, F. Barré-Sinoussi, T.J. Spira, J.S. McDougal, J.W. Curran, L. Montagnier, F.S Murphy & D.P. Francis, 1984. Lymphadenopathy Associated Virus (LAV) infection of a blood donor-recipient pair with acquired immunodeficiency syndrome. Science 225: 69–72.

Francis, D., P. Feorino, R. Broderson, H. McClure, J. Getchell, C. McGrath, B. Swenson, S. McDougal, E. Palmer, A. Harrison, F. Barré-Sinoussi, J.C. Chermann, L. Montagnier, J. Curran, C. Cabradilla & S. Kalyanaraman, 1984. Infection of chimpanzees with Lymphadenopathy-Associated Virus. Lancet II: 1276–1277.

Fultz, P.N., H.M. McClure, R.B. Swenson, C.R. McGrath, A. Brodie, J.P. Getchell, F.C. Jensen, D.C. Anderson, J.R Broderson & D.P. Francis, 1986. Persistent infection of chimpanzees with human T-lymphotropic virus type III/lymphadenopathy-associated virus: a potential model for acquired immunodeficiency syndrome. J. Virol. 58: 116–124.

Fultz, P.N., A. Srinivasan, C.R. Greene, D. Butler, R.B. Swenson & H.M. McClure, 1987. Superinfection of a chimpanzee with a second strain of human immunodeficiency virus. J. Virol. 61: 4026–4029.

Fultz, P.N., R.I. Siegel, A. Brodie, A.C. Mawle, R.B. Stricker, R.B. Swenson, D.C. Anderson & H.M. McClure, 1991. Prolonged $CD4^+$ lymphocytopenia and thrombocytopenia in a chimpanzee persistently infected with human immunodeficiency virus type 1. J. Infect. Dis. 163: 441–447.

Gail, M.H., W.Y. Tan, D. Pee & J.J. Goedert, 2997. Survival after AIDS diagnosis in a cohort of hemophilia patients. J. Acquir. Immune Defic Syndr. Hum. Retrovirol. 15: 363–369.

Galéa, P., C. Le Contel & J.C. Chermann, 1996. Identification of a biological marker of resistance to AIDS progression. Cell. Pharmacol. Aids Science 3: 311–316.

Galéa, P., C. Le Contel, C. Coutton & J.C. Chermann, 1997b. Rationale for an HIV vaccine using cellular antigens. International Meeting on HIV and Immunoregulation. Porthmadog, North Wales. Oral Presentation, September 1997.

Galéa, P., C. Le Contel & J.C. Chermann, 1997c. Rationale for an HIV vaccine using cellular antigens. Second Annual Meeting of the Institute of Human Virology. Baltimore, USA. Oral Presentation, September 1997.

Gendelman, H.E., J.M. Orenstein, L.M. Baca, B. Weiser, H. Burger, D.C. Kalter & M.S. Meltzer, 1989. The macrophage in the persistence and pathogenesis of HIV infection. AIDS 3: 475–495.

Godard, C., H. Serriès, C. Fulachier & J.C. Chermann J.C, 1997. Apoptosis of $CD4^+$ T cells induced after contact with HIV-1 infected or non infected macrophages. Res. Virol. 148: 383–396.

Goldsmith, M.A., M.T. Warmerdam, R. E. Atchinson, M.D. Miller & W.C. Greene, 1995. Dissociation of the CD4 downregulation and viral infectivity enhancement functions of human immunodeficiency virus type 1 nef. J. Virol. 69: 4112–4121.

Goudsmit, J., 1995. The role of viral diversity in HIV pathogenesis. J. Acquir. Immune Defic Syndr. Hum. Retrovirol. 10: S15–S19.

Gout, O., B. Rouquette, E. Tournier-Lasserve, F. Barré-Sinoussi, O. Lyon-Caen & J.C. Chermann, 1988. Acute and regressive encephalopathy coincident with transient isolation of human immunodeficiency virus from cerebrospinal fluid of a seropositive man. Biomed. Pharmacother. 42: 15–20.

Haimovici, F., K.H. Mayer & D.J. Anderson, 1997. Quantitation of HIV-1-specific IgG, IgA, and IgM antibodies in human genital tract secretions. J. Acquir. Immune Defic Syndr. Hum. Retrovirol. 15: 185–191.

Henin, Y., V. Marechal, F. Barré-Sinoussi, J.C. Chermann & J.J. Morgenthaler, 1988. Inactivation and partition of human immunodeficiency virus during Kistler and Nitschmann fractionation of human blood plasma. Vox Sang. 54: 78–83.

Hirsch, I., B. Spire, Y. Tsunetsugu-Yokota, C. Neuvet, J. Sire & J.C. Chermann, 1990. Differences in cytopathogenicity of human immunodeficiency viruses type 1 (HIV-1) are not determined by long terminal repeats (LTR). Virology 177: 759–763.

Hirsch, I., D. Salaun, B. Brichacek & J.C. Chermann, 1992. HIV1 cytopathogenicity – genetic difference between direct cytotoxic and fusogenic effect. Virology 186: 647–654.

Iwatani, Y., S.K. Song, L. Wang, J. Planas, H. Sakai, A. Ishimoto & M.W. Cloyd, 1997. Human immunodeficiency virus type 1 Vpu modifies viral cytopathic effect through augmented virus release. J. Gen. Virol. 78: 841–846.

Johnson, B.K., G.A. Stone, M.S. Dodee, D.M. Asher, D.C. Cajdusek & C.J. Gibbs Jr, 1993. Long term observations of human immunodeficiency virus-infected chimpanzees. AIDS Res. Hum. Retroviruses 9: 375–378.

Kalter, D.C., M. Nakamura., J.A. Turpin, L.M Baca, C. Diefenbach, P. Ralph, H.E. Gendelman & M.S. Meltzer, 1991. Enhanced HIV replication in MCSF-treated monocytes. J. Immunol. 146: 298.

Kirchhoff, F., T.C. Greenough, D. B. Brettler, J.L. Sullivan & R.C. Desrosiers, 1995. Absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection. N. Engl. J. Med. 332: 228–232.

Klein, M.R., C.A. van Baalen, A.M. Holwerda et al., 1995. Kinetics of gag-specific cytotoxic T lymphocyte responses during the clinical course of HIV-1 infection: a longitudinal analysis of rapid progressors and long-term asymptomatics. J. Exp. Med. 181: 1365–1372.

Koenig, S., H.E. Gendelman, J.M. Orenstein, M.C. Dal Canto, G.M. Pezeshkpour, M. Yngbluth, F. Janotta, A. Aksamit, M.A. Martin & A.S. Fauci, 1986. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. Science 233: 1089.

Krieger, J.N., R.W. Coombs, A.C. Collier et al., 1995. Intermittent shedding of human immunodeficiency virus in semen: implications for sexual transmission. J. Urol. 154: 1035–1040.

Le Contel, C., P. Galéa, F. Silvy, I. Hirsch & J.C. Chermann, 1996. Identification of the β2m-derived epitope responsible for neutralization of HIV isolates. Cell. Pharmacol. Aids Science 3: 68–73.

Lu, Y.Y., Y. Koga, K. Tanaka, M. Sasaki, G. Kimura & K. Nomoto, 1994. Apoptosis induced in $CD4^+$ cells expressing gp160 of human immunodeficiency virus type 1. J. Virol. 68: 390–399.

Lunardi-Iskandar, Y., M.T. Nugeyre, V. Georgoulias, F. Barré-Sinoussi, C. Jasmin & J.C. Chermann, 1989. Replication of the human immunodeficiency virus 1 and impaired differentiation of T cells after in vitro infection of bone marrow immature T cells. J. Clin. Invest. 83: 610–615.

Mano, H. & J.C. Chermann, 1991a. Replication of human immunodeficiency virus type 1 in primary cultured placental cells. Res. Virol. 142: 95–104.

Mano, H. & J.C. Chermann, 1991b. Fetal human immunodeficiency virus type 1 infection of different organs in the second trimester. AIDS Res. Hum. Retroviruses 7: 83–88.

Mariani, R. & J. Skowronski., 1993. CD4 down-regulation by nef alleles isolated from human immunodeficiency virus type 1-infected individuals. Proc. Natl. Acad. Sci. USA 90: 5549–5553.

Mayaux, M.J., M. Burgard M., J.P. Teglas, J. Cottalorda, A. Krivine, F. Simon, J. Puel, C. Tamalet, D. Dormont, B. Masquelier, A. Doussin, C. Rouzioux & S. Blanche, 1996. Neonatal characteristics in rapidly progressive perinatally acquired HIV-1 disease. JAMA 275: 606–610.

Mayaux, M.J., E. Dussaix, J. Isopet, C. Rekacewicz, L. Mandelbrot, N. Ciraru-Vigneron, M.C. Allemon, V. Chambrin, C. Katlama, J.F. Delfraissy & J. Puel, 1997. Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: the french perinatal cohort studies. J. Infect. Dis. 175: 172–175.

McClure, H., B. Swenson, F. King, J.C. Chermann, F. Barré-Sinoussi, L. Montagnier, J. Eichberg, C. Saxinger, R. Gallo., H. Alter, H. Masur, A. Macher, C. Lane & A. Fauci, 1984. Experimental infection of chimpanzees with Lymphadenopathy-Associated Virus. J. Am. Med. Ass. 252: 995.

Mediema, F., C. Meyaard, M.Koot, M.R. Klein, M.T. Roos, M. Groenink, R.A. Fouchier & Van't Wout, 1994. Changing virus-host interactions in the course of HIV-1 infection. Immunol. Rev. 140: 35–72.

Melbye, E., R. J. Biggar, J.C. Chermann, L. Montagnier, S. Stenbjerg & P. Ebbesen, 1984. High prevalence of lymphadenopathy virus (LAV) in European haemophiliacs. Lancet II: 40–41.

Mellors, J.W., A. Munoz, J.V. Giorgi, J.B. Margolick, C.J. Tassoni, P. Gupta, L.A. Kingsley, J.A. Todd, A.J. Saah., R. Detels, J.P. Phair & C.R. Rinaldo Jr., 1997. Plasma viral load and $CD4^+$ lymphocytes as prognostic markers of HIV-1 infection. Ann. Intern. Med. 126: 946–954.

Meltzer, M.S., D.R. Skillman, D.L. Hoover, B.D. Hanson, J.A. Turpin, D.C. Kalter & H.E. Gendelman, 1990. HIV and the immune system. Immunol. Today 11: 217–223.

Montagnier, L., J.C. Chermann, F. Barré-Sinoussi, S. Chamaret, J. Gruest, M.T. Nugeyre, F. Rey, C. Dauguet, C. Axler-Blin, F. Vezinet-Brun, C. Rouzioux, G.A. Saimot, W. Rozenbaum, J.C. Gluckman, D. Klatzmann, E. Vilmer, C. Griscelli,

C. Foyer-Gazengel. & J.B. Brunet, 1984. A new human T-lymphotropic retrovirus: characterization and possible role in lymphadenopathy and acquired immune deficiency syndromes. Cold Spring Harbor Publication — Meeting on 'Human T-cell leukemia/lymphoma viruses' pp. 363–379.

Musey, L., J. Hughes, T. Schacker, T. Shea & L. Corey, 1997. Cytotoxic-T-cell responses, viral load, and disease progression in early human immunodeficiency virus type 1 infection. N. Engl. J. Med. 337: 1267–1274.

Nardelli, B., C.J. Gonzalez, M. Schechter & F.T. Valentine, 1995. $CD4^+$ blood lymphocytes are rapidly killed in vitro by contact with autologous human immunodeficiency virus-infected cells. Proc. Natl. Acad. Sci. USA 92: 7312–7316.

Nicolosi, A., M.L. Correa Leite, M. Musicco, G. Gavazzeni & A. Lazzarin, 1994. The efficiency of male-to-female sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Italian Study Group on HIV heterosexual transmission. Epidemiology 5: 570–575

Noraz, N., J. Gozlan, J. Corbeil, T. Brunner & S.A. Spector, 1997. HIV-induced apoptosis of activated primary $CD4^+$ T lymphocytes is not mediated by Fas-Fas ligand. AIDS 11: 1671–1680.

Novembre, F.J., m Saucier, D.C. Anderson, S.A. Klumpp, S.P. O'Neil, C.R. Brown II, C.E. Hart, P.C. Guenthner, R.B. Swenson & H.M. McClure, 1997. Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. J. Virol. 71: 4086–4091.

O'Brien, T.R., M.P. Bush, E. Donegan, J.W. Ward, L. Wong, S.M. Samson, H.A. Perkins, R. Altman, R.L. Stoneburner & S.D. Holmberg, 1994. Heterosexual transmission of human immun odeficiency virus type 1 from transfusion recipients to their sex partner. J. Acquir. Immune Defic. Syndr. 7: 705–710

O'Brien, T.R., W.A. Blattner, D.Waters, M.E. Eyster, M.W. Hilgartner, A.R. Cohen, N. Luban, A. Hatzakis, L.M. P.S. Aledort Rosenberg, W.J. Miley, B.L. Kroner & J.J. Goedert, 1996. Serum HIV-1 RNA levels and time to development of AIDS in the multicenter hemophilia cohort study. JAMA 276: 105–110.

Pitchenik, A.E., R.D. Shafron, R.M. Glasser & T.J. Spira, 1984. The acquired immunodeficiency syndrome in the wife of a hemophiliac. Ann. Intern. Med. 100: 62–65

Rey, F., G. Donker, I. Hirsch & J.C. Chermann, 1991. Productive infection of $CD4^+$ cells by selected HIV strains is not inhibited by an anti-CD4 monoclonal antibodies. Virology 181: 165–171.

Rinaldo, C.R., X.L. Huang, Z.F. Fan et al., 1995. High levels of anti-human immunodeficiency virus type 1 (HIV-1) memory cytotoxic T-lymphocyte activity and low viral load are associated with lack of disease in HIV-1-infected long-term nonprogressors. J. Virol. 69: 5838–5842.

Rossio, J.L., J. Bess Jr, L.E. Henderson, P. Cresswell & L.O. Arthur, 1995. HLA class II on HIV particles is functional in superantigen presentation to human T cells: implications for HIV pathogenesis. AIDS Res Hum. Retroviruses 11: 1433–1439.

Roy, S. & M.A. Wainberg, 1988. Role of the mononuclear phagocyte system in the development of acquired immunodeficiency syndrome (AIDS). J. Leukocyte Biol. 43: 91–97.

Samuelsson, A., C. Broström., N. van Dijk, A. Sönnerborg & F. Chiodi, 1997. Apoptosis of $CD4^+$ and $CD19^+$ cells during human immunodeficiency virus type 1 infection – Correlation with clinical progression, viral load, and loss of humoral immunity. Virology 238: 180–188.

Sanchez, G., X. Xu, J.C. Chermann & I. Hirsch, 1997. Accumulation of defective viral genomes in peripheral blood mononuclear cells of human immunodeficiency virus type 1-infected individuals. J. Virol. 71: 2233–2240.

Schmidtmayerova, H., C. Bolmont, S. Baghdiguian, I. Hirsch & J.C. Chermann, 1992. Distinctive pattern of infection and replication of HIV1 strains in blood derived macrophages. Virology 190: 124–133.

Schmidtmayerova, H., O. Gayet, N. Guettari, C. Bolmont, I. Hirsch & J.C. Chermann, 1993. Characterization of HIV-1 PAR, a macrophage tropic strain: cell tropism virus/cell entry and nucleotide sequence of the envelope glycoprotein. Res. Virol. 144: 21–26.

Smiley, M.L, G.C. White II, P. Becherer, G. Macik, T.J. Matthews, K.J. Weinhold, C. McMillan & D. Bolognesi, 1988. Transmission of human immunodeficiency virus to sexual partners of hemophiliacs. Am. J. Hematol. 28: 27–32

Schwartz, O., Y. Rivière, J.M. Yeard & O. Danos, 1993. Reduced cell surface expression of processed human immunodeficiency virus type 1 envelope glycoprotein in the presence of *nef*. J. Virol. 67: 3274–3280.

Smid, W.M., J. van der Meer & M.R. Halie, 1995. Changes in T4/T8 ratio over a ten years period related to the factor VIII concentrates used in a group of HIV negative haemophiliacs. Thrombosis & Haemostasis 73: 552–553.

Spire, B., F. Barré-Sinoussi, L. Montagnier & J.C. Chermann, 1984. Inactivation of lymphadenopathy associated virus by chemical disinfectants. Lancet 2: 899–901.

Spire, B., D. Dormont, F. Barré-Sinoussi, L. Montagnier & J.C. Chermann, 1985. Inactivation of lymphadenopathy associated virus by heat, gamma rays and ultraviolet light. Lancet 1: 188–189.

Spire, B., J. Sire, V. Zachar, F. Rey, F. Barré-Sinoussi, F. Galibert, A. Hampe & J.C. Chermann, 1989. Nucleotide sequence of the HIV-1-NDK: a highly cytopathic strain. Gene 81: 275–284.

Spire, B., I. Hirsch, C. Neuveut, J. Sire & J.C. Chermann, 1990. The env gene variability is not directly related to the high cytopathogenicity of an HIV1 variant. Virology 177: 756–758.

Vernazza, P.L., J.J. Eron, M.S. Cohen, C.M. van der Horst, L. Troiani & S.A. Fiscus, 1994. Detection and biologic characterization of infectious HIV-1 in semen of seropositive men. AIDS 8: 1325–1329.

Vilmer, E., F. Barré-Sinoussi, C. Rouzioux, C. Gazengel, F. Vezinet-Brun, C. Dauguet, A. Fischer, P. Magnine, J.C. Chermann, C. Griscelli & L. Montagnier, 1984. Isolation of a new lymphotropic retrovirus in two hemophilia B siblings, one presenting with acquired immunodeficiency syndrome. Lancet I: 753–757.

Vicenzi, E., P. Bagnarelli, E. Santagostino, S. Ghezzi, M. Alfano, M.S. Sinnone, G. Fabio, L. Turchetto, G. Moretti, A. Lazzarin, A. Mantovani, P.M. Mannucci, M. Clementi, A. Gringeri & G. Poli, 1997. Hemophilia and nonprogressing human immunodeficiency virus type 1 infection. Blood 89: 191–200.

Von Briesen, H., W.B. Becker, K. Henco, E.B. Helm, H.R. Gelderblom, H.D. Brede & H. Rübsamen-Waigmann, 1987. Multiple simultaneous variants in a patient demonstrated by molecular cloning. J. Med. Virol. 23: 51–56.

Wu, M.X., J.F. Daley, R.A. Rasmussen & S.F. Schlossman, 1995. Monocytes are required to prime peripheral blood T cells to undergo apoptosis. Proc. Natl. Acad. Sci. USA 92: 1525–1529.

Yahi, N., S. Baghdiguian, H. Moreau & J. Fantini, 1992a. Galactosyl ceramide (or a closely related molecule) is the receptor for human immunodeficiency virus type 1 on human colon epithelial HT29 cells. J. Virol. 66: 4848–4854.

Yahi, N., S. Baghdiguian, C. Bolmont & J. Fantini, 1992b. Replication and apical budding of HIV-1 in mucous-secreting colonic epithelial cells. J. Acquir Immune Def. 5: 993–1000.

Yahi, N., J. Fantini & J.C. Chermann, 1992c. Infection of HIV-1 and HIV-2 through the luminal and serosal sides of polarized human intestinal epithelial cells. AIDS 6: 335–336.

Yahi, N., J. Fantini & J.C. Chermann, 1992d. Characterization of the env gene products of a highly cytopathic strain of HIV shows a specific pattern of glycosylation and a deletion in the proteic moiety of the extracellular envelope glycoprotein. Arch. Virol. 125: 287–298.

Yang, O.O. & B.D. Walker, 1997. $CD8^+$ cells in human immunodeficiency virus type 1 pathogenesis: cytolytic and noncytolytic inhibition of viral replication. Adv. Immunol. 66: 273–311.

Zachar, V., B. Spire, I. Hirsch, J.C. Chermann & P. Ebbesen, 1991. Human transformed trophoblast-derived cell lines lacking CD4 receptor exhibit restricted permissiveness to human immunodeficiency virus type 1. J. Virol. 65: 2102–2107.

Zachar, V., B. Spire, N. Norskov-Lauritsen, J.C. Chermann & P. Ebbesen, 1991a. Cultured trophoblastic choriocarninoma cells differentially express HIV-1 and cloned provirus. AIDS 5: 457–458.

Zachar, V., N. Norskov-Lauritsen, C. Juhl., B. Spire, J.C. Chermann & P. Ebbesen, 1991b. Susceptibility of culture human trophoblast to infection with human immunodeficiency virus type 1. J. Gen. Virol., 72: 1253–1260.

Ziza, J.M., F. Brun-Vezinet, A. Venet, C.H. Rouzioux, J. Traversat, B. Israel-Biet, F. Barré-Sinoussi, J.C. Chermann & P. Godeau, 1985. Lymphodenopathy-associated virus isolated from bronchoalveolar lavage fluid in AIDS-related complex with lymphoid interstitial pneumonitis. N. Engl. J. Med. 313: 183.