5. Summary of Data Reported and Evaluation

5.1 Exposure data

The human immunodeficiency viruses (HIV-1 and HIV-2), the etiological agents of the acquired immune deficiency syndrome (AIDS), belong to the lentivirus subfamily of the *Retroviridae* family. Sequence analysis of viral DNA indicates a separate ancestral lineage for HIV-1 and HIV-2. Phylogenetic analysis of diverse geographical isolates has shown HIV-1 to cluster into two distinct major groups and HIV-2 into another. Multiple viral clades (subtypes) exist on the basis of sequence diversity within these groups, but these are not the same as virus serotypes which are based on antigenic diversity.

HIV-1 interaction with the cellular receptor (CD4) and its co-receptor helps to explain why the virus is tropic for $CD4^+$ lymphocytes and macrophages.

HIV-1 and HIV-2 have similar, but not identical, complex genomes consisting of three genes encoding structural proteins, two genes which are essential for virus replication and four accessory genes which contribute to the efficiency of replication. Once the virus has bound to its receptor on the cell membrane, it internalizes by fusion and releases its core in which the RNA undergoes reverse transcription. The resultant proviral DNA, once integrated into the host cell DNA, exploits the biochemical machinery of the cell to synthesize new viral proteins which assemble intracytoplasmically, mature and are released at the cell membrane.

Diagnosis of infection with HIV-1 and HIV-2 relies on the identification of specific antibodies to, or the direct detection of, the viruses. The direct detection of virus or viral protein provides the definitive diagnosis for HIV-1 and HIV-2.

The main routes of HIV-1 transmission are sexual intercourse, blood–blood contact and from mother to infant, including breast-feeding. The risk of transmission through all routes is associated with viral load in the infected person. Other factors which increase the rate of sexual transmission are the presence of other sexually transmitted diseases, especially genital ulcerative disease, and the type of sexual intercourse. Transmission from mother to child is associated with vaginal delivery and with breast-feeding.

Patterns of HIV-1 transmission vary substantially with time and geographical area. Most developed countries experienced early waves of HIV-1 infection among homosexual men, and in some of these countries intravenous drug use is an important mode of transmission. In Africa, heterosexual contact has remained the predominant mode of transmission, with transmission from mother to child also occurring extensively. There have been substantial increases in HIV-1 transmission in certain Asian countries in the past decade, initially through homosexual contact between men and through injecting drug use, but increasingly through heterosexual contact.

Infection with HIV-1 and HIV-2 has protean clinical manifestations. As early as one to six weeks after HIV-1 infection, many adult patients have a seroconversion syndrome. The timing of HIV-1-related symptoms and diseases reflects virological and immunological changes that occur. In the first few weeks after HIV-1 infection, the level of $CD4^+$

lymphocytes and the $CD4^+$ cell : $CD8^+$ cell ratio decrease and viral load increases. Generally the immunological parameters stabilize, although not to normal levels, after the initial phase of infection. This is followed by a long period of clinical latency, marked by gradually declining $CD4^+$ counts, and then the appearance of a range of symptoms (constitutional, oral, pulmonary or skin conditions). The development of AIDS is defined by the occurrence of one or more specific opportunistic infections, malignancies and related diseases occurring in patients with HIV-1 and HIV-2 infection. The median incubation period (from infection to AIDS) for HIV-1 in developed countries is 10 years, and may be longer for persons infected with HIV-2.

In the absence of an effective treatment or vaccine, control and prevention of HIV-1 and HIV-2 infection continue to rely mainly on behavioural interventions. In preventing sexual transmission, reducing the number and modifying the types of sexual contact, and the consistent and correct use of condoms are essential. Drug-dependence treatment programmes and improving the availability of sterile needles are putatively effective ways of stemming the HIV epidemic among intravenous drug users.

Screening the blood of donors for HIV-1 and HIV-2 antibody has virtually eliminated transmission of these viruses in blood products in many countries. A significant reduction in perinatal transmission of HIV-1 can be achieved by maternal use of zidovudine during pregnancy and delivery, and by treatment of newborns immediately after delivery. This has become clinical practice in many countries. Delivery by Caesarian section has been associated with a reduction in mother-to-child transmission in most studies.

New approaches to the treatment of HIV-1-infected people include combination therapy and use of new classes of drugs such as protease inhibitors. The development of a safe, effective and economical preventive vaccine for HIV-1 and HIV-2 faces many obstacles.

5.2 Human carcinogenicity data

Epidemiological evidence indicates that the incidence of Kaposi's sarcoma is greatly increased in persons infected with HIV-1. Some studies in developed countries point to a relative risk of more than 1000-fold. The incidence increases markedly as HIV-1-related immunosuppression progresses. Within developed countries, the risk varies between HIV-1-transmission categories, with homosexual and bisexual men having a 5–10-fold greater risk than other HIV-1-infected groups. In parts of Africa, Kaposi's sarcoma incidence is rapidly increasing, probably as a result of HIV-1 infection. These variations suggest the existence of cofactor(s), for which human herpesvirus type 8 (HHV-8) is the leading candidate.

Non-Hodgkin's lymphoma incidence is greatly increased in persons with HIV-1-infection. Case–control and cohort studies of HIV-1-infected individuals have consistently demonstrated large increases in risk for non-Hodgkin's lymphoma in developed countries. In AIDS patients, the rate may be at least 100-fold increased. This increased risk has been found to be similar in all HIV-1-transmission groups. It appears that the association is mediated by HIV-1-related immune dysregulation. Co-infections with

specific viruses are associated with primary lymphoma of the brain (Epstein–Barr virus; EBV) and body-cavity lymphomas and multicentric Castleman's disease (HHV-8). Viruses may be involved in some other cases of HIV-1-associated lymphomagenesis.

In HIV-1-infected persons, total cancer incidence does not appear to be increased, after exclusion of Kaposi's sarcoma and non-Hodgkin's lymphoma. However, increases have been observed for several specific cancers. Studies of women with HIV show increases in cervical carcinoma *in situ* among HIV-1-infected women. The risk increases with increasing immunodeficiency. However, there may be confounding due to common exposure factors between HIV-1 and human papillomavirus (HPV). This confounding has made assessment of the relationship between HIV-1 and carcinoma *in situ* difficult. To date, there is no association between invasive cervical cancer and HIV-1 infection.

Anal cancer incidence has been increasing for several decades and the trend has not increased in the AIDS era. However, homosexual men have a high risk for anal HPV infection and anal cancer, which appears to be associated with their lifestyle.

There are several reports suggesting an association with HIV-1-infection with leiomyosarcoma in children, conjunctival squamous-cell tumours in Africa and, to a lesser extent, Hodgkin's disease. Studies reported to date have not documented a relationship between HIV-1 and any other form of cancer.

Kaposi's sarcoma has also been seen in some HIV-2-infected persons, but the strength of any association has not been determined.

There are a few case reports and one case–control study suggesting that HIV-2 infection may be associated with non-Hodgkin's lymphoma.

There are no reports of an association of HIV-2 with cancers other than Kaposi's sarcoma and non-Hodgkin's lymphoma.

5.3 Animal carcinogenicity data

In nonhuman primates infected with HIV-1 or HIV-2, a single case of fibromatosis has been observed in a baboon infected with HIV-2.

Lymphomas occur more frequently in simian immunodeficiency virus (SIV)-infected macaques than in uninfected macaques. Most malignant lymphomas are of B-cell origin and are associated with an EBV-like simian herpesvirus and with immunodeficiency.

Lymphosarcoma in the cat is associated with experimental and naturally acquired feline immunodeficiency virus (FIV) infection. Lymphosarcoma is a B-cell lymphoma which has similar morphological, immunophenotypic and molecular characteristics to HIV- and SIV-associated lymphomas. There is no evidence of FIV sequence integration into tumour cells, indicating that the role of the virus in tumour development is possibly indirect.

5.4 Other relevant data and mechanistic considerations on HIV-1-associated neoplasms

Patients with non-HIV-associated forms of acquired immunodeficiency — primarily as a result of organ transplantation — have a substantially increased risk for neoplastic lesions. These include consistent excesses of non-Hodgkin's lymphoma, Kaposi's sarcoma and skin cancers, particularly of squamous-cell origin. The increased relative risk for most of these malignancies is seen within the first few years after initiation of treatment and remains relatively constant over time. The exception to this is that the relative risk for skin cancer increases with time. Removal of the immunosuppressive therapy can lead to regression of both non-Hodgkin's lymphoma and Kaposi's sarcoma. Among patients with a variety of inborn immune dysfunctions, a substantial excess of haematopoietic malignancies is also documented. It may therefore be concluded that, in these patients, immunosuppression causes this excess of neoplastic lesions. Inherited immunodeficiencies of various kinds are also limited to increased cancer incidence.

It is likely that the immunosuppressive effect of HIV-1 is a major factor in the development of Kaposi's sarcoma. Kaposi's sarcoma lesions are composed of various cellular lineages, probably mainly endothelial cells and fibroblastoid cells, which proliferate in response to several growth factors. The HIV-1 Tat protein has been shown to have angiogenic properties in animal models and to stimulate the growth of Kaposi's sarcoma spindle cells *in vitro*, and may therefore be a factor for the development of Kaposi's sarcoma lesions. In addition to extracellular Tat, increased cytokine levels found in AIDS patients may be responsible for this effect. The production of these growth factors and the proliferation of spindle and endothelial cells may be associated with an additional infectious agent. HHV-8 seems the best candidate reported so far, but its role in the pathogenesis of Kaposi's sarcoma remains to be clarified.

Regarding non-Hodgkin's lymphoma, consistent failure to unequivocally detect HIV-1 sequences within the tumour clone suggests that HIV-1 does not directly cause transformation of B-cell lymphocytes. Its role in lymphomagenesis seems to be indirect and related to an effect of HIV-1 on immunoregulation. Several host factors (disrupted immunosurveillance, chronic antigen stimulation and cytokine dysregulation) play a role in lymphoma pathogenesis in HIV-1-infected persons. This results in oligoclonal expansion, which commonly occurs in the early phases of HIV-1 infection, corresponding to B-cell proliferation.

The potential role of cofactors in AIDS-related lymphomagenesis differs depending on the histopathological type and site of disease. Pathological and molecular data show that somatic genetic changes are frequently involved in the development of AIDS-related non-Hodgkin's lymphomas. These genetic changes cluster in distinct molecular pathways which correlate with different pathological types.

The frequent association of c-*myc* deregulation and *p53* inactivation in small non-cleaved-cell lymphoma may imply a synergistic involvement of these two events in the pathogenesis of this tumour. The striking association between EBV infection and specific types of lymphomas in HIV-1-infected persons (those arising primarily in the brain and body cavities as well as $CD30^+$ anaplastic large-cell lymphoma and Hodgkin's disease)

suggests that EBV may be important in their pathogenesis. The putative transforming role of EBV is further strengthened by data showing that the transforming genes of EBV, encoding EBV nuclear antigen-2 and EBV latent membrane protein-1, are expressed in EBV-positive tumour cells.

Preliminary evidence suggests that HHV-8 has a role in inducing some AIDS-related lymphoproliferative disorders in HIV-1-infected persons such as body cavity-based lymphoma and multicentric Castleman's disease.

The immunosuppressive effect of HIV-1 infection may promote the developmentof HPV-related precancerous and anogenital lesions. HIV-1 *tat* may also enhance their development.

5.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of infection with HIV-1.

There is *inadequate evidence* in humans for the carcinogenicity of infection with HIV-2.

Overall evaluation

Infection with HIV-1 is *carcinogenic to humans (Group 1).*

Infection with HIV-2 is *possibly carcinogenic to humans (Group 2B).*

In making this evaluation, the Working Group took into account data indicating that HIV-2 infection can show the same clinical manifestations, including severe immune deficiency, as HIV-1 infection.

[1]For definition of the italicized terms, see Preamble, pp. 22–25.