4.3.6 Differences between HTLV-I and HTLV-II

As discussed in section 2.1, HTLV-I is associated with human leukaemia whereas HTLV-II is not. Section 1.1.7 summarized the differences in genomic structure between HTLV-I and HTLV-II.

It is unlikely that there is a functional homologue of HTLV-I present in HTLV-II, but deletions in the region between the HTLV-II env gene and the second tax exon, which would eliminate expression of any potential homologue of HTLV-I p12', p13' or p3011, have no effect on virus production, envelope function or transforming potential in vitro (Green et al., 1995). The effect of disrupting the G4 and R3 reading frames of BLV, located in a similar region of the BLV genome but of only limited similarity to HTLV-I p12', p13' or p30' (Alexandersen et al., 1993), is discussed in Sections 1.1.7 and 3.3. In conclusion, it is not clear whether any of the small accessory proteins found only in HTLV-I, e.g., p21, is responsible for the leukaemogenic properties of HTLV-I in humans, and the precise roles of HTLV-I p12', p13' and p30' during in-vivo leukaemogenesis remain to be established.

It is also conceivable that as yet unidentified minor differences in the in-vitro transforming potential between HTLV-I and HTLV-II might translate into a weak oncogenic effect in vivo (for example, a long latency period for leukaemia development) for HTLV-I but not for HTLV-II.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Human T-lymphotropic viruses (HTLV-I and HTLV-II), the only known human oncornavirinae, have distinct genetic and structural features. Both HTLV-I and HTLV-II are complex retroviruses. Their genomes encode structural core and envelope proteins, regulatory proteins (Tax and Rex) and several additional proteins which may play an important role in the pathogenesis of the HTLV-I-associated diseases. Several related viruses (known as simian T-lymphotropic viruses; STLVs) have been identified in African and Asian non-human primates, and such primates appear to have been the original sources of the human retroviruses.

Serological detection of specific reactivity to Gag and Env HTLV-I or HTLV-II antigens, confirmed if necessary by western blot, is indicative of current infection. HTLV-I and HTLV-II infection can also be confirmed by amplification of viral sequences by polymerase chain reaction (PCR) from peripheral blood mononuclear cells. Three major clades of HTLV-I with distinct geographical distribution have been distinguished by PCR and sequencing or by restriction fragment length polymorphism. A higher prevalence among women, particularly over the age of 50 years, has been observed in highly endemic areas.

Three modes of transmission have been described for HTLV-I and HTLV-II: mother-to-child transmission, mainly due to breast-feeding beyond six months, sexual trans-
mission predominantly from men to women and transmission by transfusion of cellular 
blood products and through intravenous drug use.

HTLV-I prevalence varies widely worldwide, with high levels in diverse geographic 
areas: i.e., southwest Japan, the Caribbean basin, parts of South America, Central and 
West Africa and parts of Melanesia. Clusters of especially high endemicity occur within 
these areas. HTLV-I remains endemic among emigrants from these areas.

It is estimated that worldwide between 15 and 20 million individuals are infected by 
HTLV-I.

Independent of the background of HTLV-I seroprevalence, geographical and ethnic 
differences in the prevalence of tropical spastic paraparesis/HTLV-I-associated myelo-
pathy (TSP/HAM; a major HTLV-I-associated disease) have been reported. This is a 
chronic spastic myelopathy that preferentially affects middle-aged women. TSP/HAM 
may develop shortly after transfusion-acquired HTLV-I infection. Other inflammatory 
conditions associated with HTLV-I are uveitis, infective dermatitis, polymyositis, alveo-
litis, arthritis, thyroiditis and Sjögren’s syndrome. Various combinations of these condi-
tions may co-exist in the same patient and are often found in patients with TSP/HAM. 
HTLV-I-infected individuals may have impairment of the immune system, and some 
have reduced ability to clear Strongyloides stercoralis.

HTLV-II is endemic in several African pygmy and Amerindian populations and is 
epidemic among intravenous drug users in the Americas and parts of Europe. HTLV-II 
has not been clearly associated with any non-neoplastic human disease.

Control and prevention of HTLV-I and HTLV-II infection depend on reduced trans-
mission by the three major routes: perinatal, sexual and parenteral. Perinatal transmission 
has been greatly reduced in Japan by avoidance of prolonged breast-feeding. Passive and 
active immunization is effective in animal models but no preventive vaccine is available 
for humans. A number of countries have introduced universal screening of blood donors 
to prevent transmission of HTLV-I and HTLV-II and in Japan a decline in the incidence 
of post-transfusion TSP/HAM has been demonstrated.

5.2 Human carcinogenicity data

Adult T-cell leukaemia/lymphoma (ATLL) occurs almost exclusively in areas where 
HTLV-I is endemic, such as Japan, the Caribbean and West Africa. Cases of ATLL 
described in Europe and the United States have mostly been in immigrants from HTLV-I 
endemic regions or their offspring. Evidence of HTLV-I infection was originally found 
in at least 90% of patients with ATLL in endemic regions. Subsequently, HTLV-I has 
become part of the diagnostic criteria for ATLL. In ATLL, the virus is clonally inte-
grated into the tumour cells. ATLL develops in 2–5% of HTLV-I-infected individuals. 
Infection early in life appears to be important for the development of ATLL. No environ-
mental cofactor promoting the progression to ATLL has so far been identified.

HTLV-I has been associated with non-ATLL cutaneous T-cell malignancies by a few 
investigators, but most studies have not found an association. Difficulties in distin-
guishing cutaneous T-cell lymphomas from ATLL may have contributed to these incon-
persistent findings. Some investigators have detected HTLV-I genome sequences in HTLV-I and HTLV-II-seronegative patients with cutaneous T-cell lymphomas, but this has not been confirmed by others.

HTLV-II antibody has been reported in a few patients with large granular lymphocyte leukaemia, but prevalence surveys and a lack of clonal integration of the virus have not supported an association.

Several case–control studies have found an association between HTLV-I seroprevalence and tumours of the vagina, cervix and liver, but confounding effects and bias could not be excluded.

5.3 Animal carcinogenicity data

In the few studies on HTLV-I infection of animals, no neoplastic disease was demonstrated.

While neoplastic disease has not been induced experimentally in non-human primates by infection with STLV-I, there is strong evidence that ‘natural’ infection with STLV-I is associated with lymphoid neoplasia in non-human primates. The following evidence supports this hypothesis: lymphoma is the most common malignancy in Old World non-human primates; STLV-I is endemic in Old World non-human primates; the disease in monkeys is very similar to ATLL; STLV-I is very similar biologically, morphologically, physicochemically and molecularly to HTLV-I; and STLV-I has the ability to activate and immortalize lymphocytes in culture. Monoclonally integrated provirus has been identified in all neoplastic tissues from STLV-I-infected non-human primates that have been evaluated.

Bovine leukaemia virus, which belongs to the same family as HTLV-I, is a good model for the study of lymphomas induced by viruses with tax and rex genes. This virus induces lymphomas in approximately 5% of infected cattle and in all experimentally infected sheep. Unlike HTLV-I-associated lymphomas in humans, all tumours are of B-cell origin.

5.4 Molecular mechanisms of leukaemogenesis

HTLV-I, as well as HTLV-II, is capable of immortalizing human and rabbit T-cells in vitro. Transfection of HTLV-I tax alone immortalizes and transforms primary human T-cells and transforms cells of fibroblastoid lineage. In transgenic models, HTLV-I tax under the control of HTLV-I long terminal repeat induces tumours of mesenchymal origin, whereas lymphomas have so far only been obtained by using a granzyme B promoter to control tax expression, or by producing mice transgenic for both c-myc and tax. Tax activates the expression of several cellular genes which are themselves involved in the control of cell proliferation. Tax achieves this pleiotropic effect by interfering with at least three different classes of transcription factors, at either nuclear or cytoplasmic levels. However, HTLV-I transformed cell lines, although capable of inducing lymphomas in severe combined immunodeficient mice (SCID) under certain conditions, are different from ATLL cells, for the development of which subsequent cellular changes are
required. In keeping with this scenario, clonally expanded HTLV-I-infected T-cell populations can persist in vivo for long periods of time without progression to leukaemia. While tax is expressed in non-neoplastic T-cell populations, its expression is lost in ATLL cells.

Observations made in tax-transgenic mice suggest that cytokines secreted by tax-expressing cells are responsible for some aspects of the pathologies observed in these animals; whether this applies to the pathogenesis of ATLL in humans is uncertain. The expression of tax during the early stages of leukaemogenesis may interfere with mechanisms of DNA repair by reducing the expression of β-polymerase and p53, and increasing chromosomal instability.

HTLV-I and HTLV-II have similar transforming properties in vitro. HTLV-I is associated with leukaemia, whereas HTLV-II is not. HTLV-I and HTLV-II differ in some of their small accessory proteins. The role of some of these HTLV-I encoded viral proteins, in particular the small accessory protein p12, during the early stages of leukaemogenesis is still uncertain, but in-vitro experiments suggest a possible involvement. There is no indisputable evidence that these accessory proteins are expressed in ATLL cells.

Cellular alterations required during the transition from an HTLV-I-infected T-cell to a malignant ATLL cell are largely undefined, but constitutive activation of signal transduction pathways may play a role. Mutations in several tumour-suppressor genes occur in some ATLL samples and HTLV-I-transformed cell lines and may play a role during tumour progression.

Cytotoxic T-cell (CTL) immunity is directed mainly against the Tax protein and there is evidence that CTLs play a role in killing HTLV-I expressing T-cells, but not ATLL cells as these do not express tax. The role of natural killer cells in human HTLV-I infection remains to be established, although such cells limit the growth of HTLV-I transformed human cells in immunodeficient mice. Studies in Japan suggest an association of certain human leukocyte antigen (HLA) haplotypes with TSP/HAM and ATLL. Different genotypes of HTLV-I do not appear to be associated with different diseases.

5.5 Evaluation

There is sufficient evidence in humans for the carcinogenicity of HTLV-I.

There is inadequate evidence in humans for the carcinogenicity of HTLV-II.

Overall evaluation

HTLV-I is carcinogenic to humans (Group 1).

HTLV-II is not classifiable as to its carcinogenicity to humans (Group 3).

\footnote{For definition of the italicized terms, see Preamble, pp. 22–25.}