HUMAN IMMUNODEFICIENCY VIRUSES

1. Exposure Data

1.1 Structure, taxonomy and biology

The human immunodeficiency virus type 1 (HIV-1) was discovered in 1983 (Barré-Sinoussi *et al.*, 1983) and firmly associated with the acquired immunodeficiency syndrome (AIDS) in 1984 (Gallo *et al.*, 1984). Later, a second virus was discovered in West Africa (HIV-2) that was sufficiently different from HIV-1 in its serological and molecular characteristics to be considered a separate, but related, virus (Clavel *et al.*, 1986). Initially the virus was referred to as lymphadenopathy-associated virus (LAV) or human T-cell lymphotropic virus type III (HTLV-III); the name human immunodeficiency virus was established in 1986. Between 1985 and 1989, several non-human primates were shown to harbour related retroviruses. All of these retroviruses belong to the lentivirus subfamily, have an RNA genome and replicate via a DNA intermediate (a 'provirus') by means of a viral RNA-directed DNA polymerase, more commonly called reverse transcriptase (RT). It is this 'backward' transfer of genetic information from RNA to DNA which classifies these viruses as retroviruses. HIV-1 and HIV-2 are the only known human lentiviruses.

1.1.1 *Structure*

All retroviruses share a similar overall morphology, but there is variation in detail (Table 1). Lentiviruses contain a diploid, single-stranded RNA genome within a protein core. Each HIV-1 virion measures approximately 120 nm in diameter and has a condensed cylindrical core surrounded by a lipid membrane. The inter-relationship of the genomic RNA, core proteins and surrounding viral envelope is schematically represented in Figure 1. The viral core is a complex made up of RT (p55/66), endonuclease or integrase (IN; p32), protease (PR; p10, p12 or p15[1]), and nucleocapsid proteins (NC; p6 and p7) and two copies of positive strand viral RNA, all of which is surrounded by an icosahedral capsid protein (CA; p24). The myristoylated matrix protein (MA; p17) lies just below the lipid bilayer which surrounds the virion. Embedded within the lipid bilayer are the viral envelope glycoproteins: the external surface glycoprotein (SU; gp120) and the transmembrane glycoprotein (TM; gp41), which are non-covalently associated on the virion surface (Gelderblom, 1991; Barker *et al.*, 1995).

[1]According to different researchers

Table 1. Morphological features of retroviruses

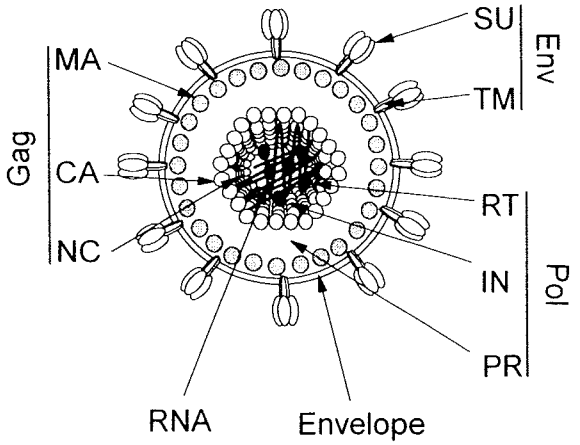
Classification	Morphological features	Examples
Oncoviruses		
A-type	Non-infectious, electron-dense, double shell, electron-lucent centre Intracytoplasmic particles: assembled core particles in B- or D-type infections Intracisternal particles: unknown function	Precursor of MMTV
B-type	Immature doughnut-shaped cores form prior to budding. Mature cores are located eccentrically within virus particles bearing prominent envelope spikes.	MMTV
C-type	No intracytoplasmic structures, immature cores; electron-lucent centres form simultaneously with budding. A centrally located electron-dense spherical core forms after maturation. Envelope spikes not always visible	MLV, ALV, FeLV, HTLVs, STLVs, BLV, GALV, SSAV, SNV
D-type	Ring-shaped immature cores; electron-lucent centres form prior to budding. Electron-dense, eccentrically located cores form on maturation. Less prominent spikes than MMTV	MPMV (SRV-2) Other SRVs
Lentiviruses	Immature cores form simultaneously with budding. Upon maturation, conical shaped cores are formed.	MVV, HIV-1, HIV-2, SIV, FIV
Spumaviruses	Electron-lucent cores form in the cytoplasm, which bud into extracellular medium or intracytoplasmic vacuoles. Very prominent envelope spikes	HFV, SFVs

MMTV, mouse mammary tumour virus; MLV, murine leukaemia virus; ALV, avian leukosis/sarcoma virus; FeLV, feline leukaemia virus; HTLV, human T-cell lymphotropic virus; STLV, simian T-cell lymphotropic virus; BLV, bovine leukaemia virus; GALV, gibbon ape leukaemia virus; SSAV, simian sarcoma-associated virus; SNV, spleen necrosis virus; MPMV, Mason–Pfizer monkey virus; SRV, simian retrovirus; MVV, maedi-visna virus; HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus; FIV, feline immunodeficiency virus; HFV, human foamy virus; SFV, simian foamy virus
Adapted from Weiss *et al.* (1985); Coffin (1996)

1.1.2 *Taxonomy*

Traditionally, retroviruses (family *Retroviridae*) have been classified according to a combination of criteria including disease association, morphology and cytopathic effects *in vitro* (Table 1; Weiss *et al.*, 1985). On this basis three subfamilies were defined. The oncoviruses (Greek, *onkos* = mass, swelling) consist of four morphological subtypes which are associated with tumours in naturally or experimentally infected animals, and non-oncogenic related viruses. The second group, the lentiviruses (Latin, *lentus* = slow), cause a variety of diseases including immunodeficiency and wasting syndromes, usually after a long period of clinical latency. The third subfamily, the spumaviruses (Latin, *spuma* = foam), so called because of the characteristic 'foamy' appearance induced in infected cells *in vitro*, have not been conclusively linked to any disease (Schweizer *et al.*, 1994; Ali *et al.*, 1996).

Figure 1. Schematic representation of a mature retrovirus particle



Genomic RNA is contained within a core consisting of NC and CA proteins, along with RT and IN enzymes which are required for the formation of an integrated provirus following infection of a new target cell. MA is thought to be associated with the inner face of the lipid envelope by virtue of N-terminal myristoylation and basic amino acids, although a proportion may be associated with the viral core in some cases (see text). The lipid envelope is traversed by TM oligomers to which are bound SU proteins containing receptor recognition motifs. TM may also contact MA on the inner face of the envelope. The particle is also assumed to contain PR, since Gag and Pol proteins are incorporated into particles as polyprotein precursors, and mature morphology is achieved only after proteolytic processing.

NC, nucleocapsid; CA, capsid; RT, reverse transcriptase; IN, integrase (endonuclease); MA, matrix; TM, transmembrane; PR, protease; SU, surface

More recently, the International Committee on the Taxonomy of Viruses has divided the *Retroviridae* family into seven genera on the basis of genetic structure. The lentiviruses and spumaviruses each constitute a genus; the oncoviruses have been subdivided into five genera.

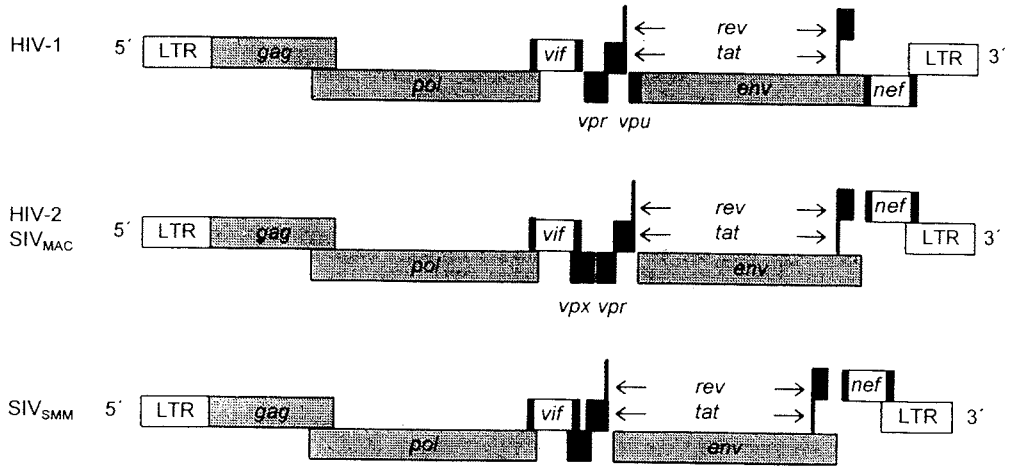
In addition to their morphological classification, retroviruses have been described as 'simple' or 'complex' according to their genome organization (Cullen, 1993; Figure 2). The defining feature of complex retroviruses is that in addition to *gag*, *pol* and *env* structural genes, they encode genes which regulate expression of structural genes (see Section 1.1.7). Most non-human and human primate lentivirus, oncovirus and spumavirus isolates so far analysed are complex retroviruses (Wilkenson *et al.*, 1994).

1.1.3 *Phylogeny*

(*a*) *Phylogenetic relationship of HIV-1 and HIV-2 to other retroviruses*

Several lentiviruses have been identified in various species of non-human primates as well as in other mammalian species. Genetically distinct simian immunodeficiency

Figure 2. Genomic organization of human and primate lentiviruses



Each genome is between 9 and 10 kb in length and has a similar overall organization of structural genes: *gag*, *pol*, *env* (grey), regulatory genes (*tat*, *rev*) and accessory genes (*nef*, *vif*, *vpr*, *vpx*, *vpu*) (black). The *vpu* gene is found exclusively in HIV-1, while HIV-2 and the closely related SIVs (SIV_{MAC}, SIV_{SMM}) have an additional gene, *vpx*. The genome is flanked by identical long terminal repeat (LTR) sequences (white).

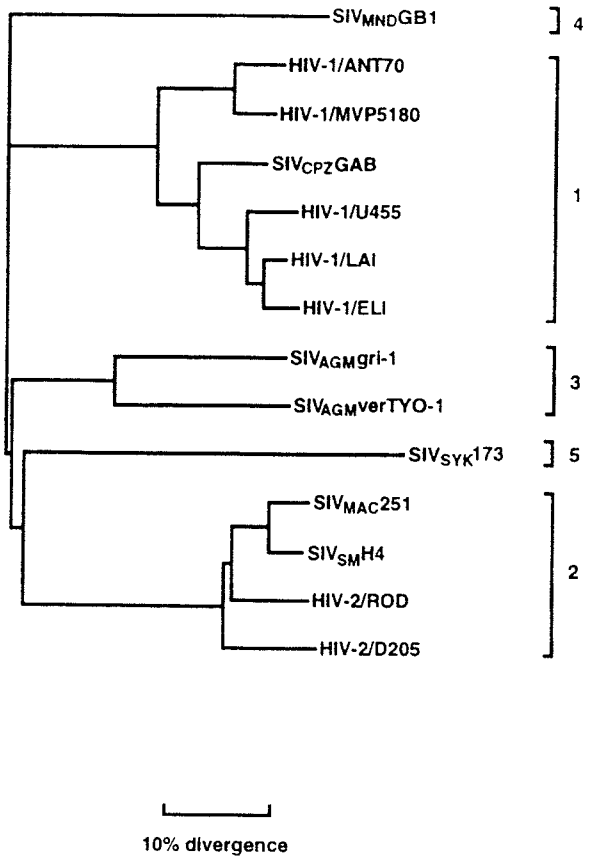
viruses (SIV) have been isolated from African green monkeys (*Cercopithecus aethiops*; SIV_{AGM}) (Kraus *et al.*, 1989), sooty mangabeys (*Cercocebus atys*; SIV_{SMM}) (Chen *et al.*, 1995; 1996), mandrills (*Mandrillus sphynx*; SIV_{MND}) (Tsujimoto *et al.*, 1988), Sykes' monkeys (*Cercopithecus mitis*; SIV_{SYK}) (Emau *et al.*, 1991) and chimpanzees (*Pan troglodytes*; SIV_{CPZ}) (Peeters *et al.*, 1989). The first primate lentivirus to be identified was SIV_{MAC} at the New England Regional Primate Research Center following an outbreak of lymphoma in rhesus (*Macaca mulatta*) and cynomolgus macaques (*Macaca fascicularis*) (Daniel *et al.*, 1985). SIV_{MAC} is not naturally found in Asian macaques (*Macaca mulatta*) (Lowenstine *et al.*, 1986; Wu *et al.*, 1991), but its close relationship to SIV_{SMM} can be explained by the introduction of SIV_{SMM}-infected mangabeys into primate centres in the United States during the late 1960s and subsequent transfer of SIV into macaques. Each SIV appears to be endemic to the respective monkey species and none has yet been associated with disease in the natural host (Gardner *et al.*, 1994).

Both the human and non-human primate immunodeficiency viruses exist as quasi-species (Wain-Hobson, 1993), i.e., as a population of closely related, yet genetically distinct, viruses which co-exist simultaneously in each infected host. This is a consequence of the sequence diversity generated from the high rates of nucleotide evolution (Coffin, 1986; Hahn *et al.*, 1986). The latter results from a combination of the high error rate associated with RT activity during viral RNA transcription (Ricchetti & Buc, 1990), the extremely high turnover and the ability of retroviruses to undergo recombination (Zhang & Temin, 1994).

Comparison of structural gene sequence data for human and simian lentiviruses has allowed analysis of the evolutionary relationships of these viruses. Basing a phylogenetic analysis on *pol* gene sequences, the primate lentiviruses form five distinct and approximately equidistant lineages: (1) HIV-1 and SIV_{CPZ}, (2) HIV-2, SIV_{SMM} and

SIV_{MAC}, (3) SIV_{AGM}, (4) SIV_{MND} and (5) SIV_{SYK} (Figure 3). Extensive genetic diversity exists within the lineages 1–3. For example, HIV-1 falls into two distinct groups and diverse isolates of HIV-2 constitute another independent group. Diversity within HIV-1 is discussed below. Interestingly, the two HIVs are more closely related to the nearest primate viruses than they are to one another: HIV-1 to SIV_{CPZ} and HIV-2 to SIV_{SMM} (Hirsch *et al.*, 1989; Huet *et al.*, 1990).

Figure 3. Phylogenetic relationships of representative primate lentiviruses, derived from *pol* protein sequences



Numbered brackets at the right indicate the five major lineages. Horizontal branch lengths are drawn to scale: the *bar* indicates 0.10 amino acid replacements per site. The approximate position of the root of the tree (at the left) was determined from analyses using nonprimate lentiviruses as outgroups. The precise order of branching of the five major lineages (near the root) is unclear, but bootstrap values for all other nodes (with the exception of the branching order of $HIV\text{-}2_{D205}$ and $HIV\text{-}2_{ROD}$) are in the range 99–100%.

From Robertson *et al.* (1995)

An SIV_{SMM} evolutionary provenance for HIV-2 is supported by their gene sequence relatedness (Gao *et al.*, 1992) and by ecological and social considerations: sooty mangabeys, of which 30% are SIV-infected, are indigenous to West Africa, where HIV-2 is

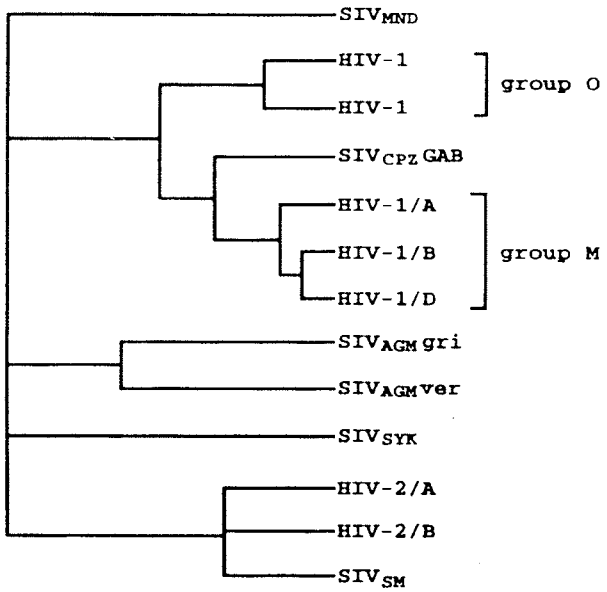
endemic. The human population is frequently exposed to SIV-infected monkey blood, since sooty mangabeys are hunted for food and kept as pets. Genetic characterization of diverse SIV_{SMM} isolates collected from a feral sooty mangabey troop suggests that each HIV-2 subtype found in West Africa originated from widely divergent strains of the simian virus, transmitted by multiple cross-species events in the same geographical region (Chen *et al.*, 1996). Since most chimpanzees in the wild appear to be seronegative for SIV_{CPZ}, there is less evidence for a similar transfer of HIV-1 from chimpanzees.

(*b*) *Relationship of HIV-1 and HIV-2 isolates to one another*

(i) *Genotypes*

Sequence analysis of the *env*, *gag* and *tat* genes from diverse geographical isolates of HIV-1 has revealed that the sequences cluster into two major groups: M, into which all the earliest known isolates fall, and a genetically distant and more diverse group containing more than 35% nucleotide differences, termed 'O' for outlier (Gürtler *et al.*, 1994; van den Haesevelde *et al.*,1994). Phylogenetic analyses of Group M sequences have revealed eight subgroups, designated A through H, also called clades (Greek, *klados* = branch) (Myers *et al.*, 1991) or sequence subtypes (Myers, 1993). The term 'genotype' has also been used (Ou *et al.*, 1993) to describe a distinct cluster of genetically related variants within a subtype (McCutchan *et al.*, 1991, 1992; Bobkov *et al.*, 1996) (see Figure 4).

Figure 4. Phylogeny of primate lentiviruses



Within the HIV-1 group M there are at least eight different sequence subtypes (A–H), of which just three are shown; within the HIV-2 group there are five known subtypes (A–E) and within the SIV_{AGM} group there are four lineages.
From Sharp *et al.* (1995)

Clade B is widespread and dominant (almost exclusively) in homosexual men and intravenous drug users throughout North America (Jain *et al.*, 1994) and Europe. With

the exception of F, clades A-H have been identified in sub-Saharan Africa (Jain *et al.*, 1994). Clade F has been identified only in Brazil and Romania (Dumitrescu *et al.*, 1994). Clade E is currently being transmitted heterosexually in Thailand (Jain *et al.*, 1994); a clade B variant (B') is circulating in Brazil (Potts *et al.*, 1993) and, besides southern Africa, clade C is found in India (Grez *et al.*, 1994). Moreover, more than one HIV-1 clade is found in some countries: in Uganda, clades A to D predominate over clade G (Kaleebu *et al.*, 1995); in Brazil, clades B, B', C and F have been identified, while in Thailand, clade A circulates among heterosexuals and clade B in intravenous drug users (Ou *et al.*, 1992).

Five clades (A–E) of HIV-2 have been identified (Gao *et al.*, 1994), but currently only clades A and B comprise more than one isolate.

(ii) *Antigenic diversity*

Although there is extensive literature on the genetic diversity of HIV-1 strains, less is known about antigenic diversity. It is clear that sequence data do not translate directly into antigenic information. A principal antigenic determinant of the virus envelope protein which elicits the greatest neutralizing antibody response is an epitope in the third variable domain of gp120, commonly called the V3 loop (Moore & Nara, 1991). A large number of HIV-1 V3 sequences have been reported, but it is still unclear how many distinct antigenic subtypes (also known as serotypes) exist.

HIV-1 neutralization assays were initially carried out using laboratory-adapted viral strains and immortalized T-cell lines (Weiss *et al.*, 1986). Primary isolates may have neutralizing phenotypes which are qualitatively and quantitatively different from T-cell line-adapted viruses. Viral diversity defined in terms of neutralization of field isolates propagated in peripheral blood mononuclear cells (PBMCs) remains to be determined, and may well be an important consideration in the development of a universally effective vaccine.

1.1.4 *Host range*

In addition to humans, HIV-1 and HIV-2 can infect some non-human primates (see Section 3.1).

1.1.5 *Cell tropism*

A distinguishing feature of HIV-1 and HIV-2 is their ability to infect $CD4^+$ T-lymphocytes and macrophages. Indeed, it was this early observation that led to the identification of the cell differentiation antigen CD4 as the receptor for HIV-1 entry into cells (Dalgleish *et al.*, 1984; Klatzmann *et al.*, 1984). All strains of HIV-1 and HIV-2 can infect peripheral blood $CD4^+$ lymphocytes (T-helper cells), but the extent to which immortalized or leukaemic T-cell lines are infected varies from strain to strain (Evans *et al.*, 1987).

Most primary HIV-1 strains (not adapted to propagate in T-cell lines) infect macrophages, although the limited extent of replication of some strains may necessitate co-cultivation of the macrophages with PBMCs to allow detection of the virus (Schrier

et al., 1990). Antigen presenting cells such as dendritic and Langerhans' cells may be important in mucosal and sexual transmission of HIV-1 (Pope *et al.*, 1994).

Since the identification of CD4 as the receptor for HIV-1 and HIV-2, it has become apparent that the virus is also capable of limited infection of certain $CD4^+$ cells, including fibroblasts, glial cells and rhabdomyosarcoma cells (Clapham *et al.*, 1991). The cellular tropism of HIV-1 appears to be determined primarily by its envelope, although other regions of the virus genome, e.g., *vpr*, may also have an influence. The identification of members of the seven-transmembrane G protein-coupled receptors which act as co-receptors helps to explain the cellular tropisms of HIV-1 (Alkhatib *et al.*, 1996; Deng *et al.*, 1996; Drajic *et al.*, 1996; Feng *et al.*, 1996).

1.1.6 *Target tissues*

(*a*) *Lymphoid tissue*

HIV-1 localizes in lymphoid tissue early in the course of infection (Biberfeld *et al.*, 1985; Tenner-Rácz *et al.*, 1985; Pantaleo *et al.*, 1993a). The presence of HIV-1 in lymphoid tissues throughout infection has been confirmed by in-situ methods (Embretson *et al.*, 1993). It remains uncertain whether HIV-1 infects other than lymphoid cells (Pantaleo *et al.*, 1993b).

(*b*) *Central nervous system*

HIV-1 frequently affects the brain. The microglial cells are the main location for viral replication in the central nervous system, although astroglial cells may be abortively infected (Shaw *et al.*, 1985; Epstein *et al.*, 1991; Donaldson *et al.*, 1994). However, there is controversy as to whether the productively infected cells of the brain are the resident microglia or are derived from invading macrophages.

(*c*) *Gastrointestinal tract*

HIV-1 isolated from the gastrointestinal tract of infected subjects has been reported to be biologically and molecularly different from viruses isolated from the peripheral blood of the same patient (Barnett *et al.*, 1991). In addition to lymphocytes and macrophages of the lamina propria (Smith, 1994), Nelson *et al.* (1988) reported HIV-1 to infect columnar epithelial cells and entero-chromaffin cells. Other investigators have failed to confirm these findings (DuPont & Marshall, 1995).

1.1.7 *The HIV-1 and HIV-2 genome and gene products*

The three major genes of HIV-1 and HIV-2 are the *gag*, *env* and *pol* genes, which initially give rise to polyproteins (respectively $Pr55^{gag}$, $Pr160^{gag\text{-}pol}$ and gp160) that are further processed to yield the structural proteins of the virus and enzymes (see Section 1.1.1 and Figure 1).

The *gag* gene products MA, CA and NC, the *pol* gene products PR, RT and IN and the *env* gene products SU and TM are always present in the same 5'–3' order. In addition, there are regulatory genes (*tat*, *rev*) and four accessory genes (*nef*, *vif*, *vpr*, *vpu*). In the proviral state, open reading frames are flanked by long terminal repeat (LTR) sequences

(Figure 2). These contain promoters of gene expression and specific enhancer elements which control viral gene expression and which are themselves influenced by cellular transcriptional proteins.

(i) *Structural proteins (Gag, Pol, Env)*

The primary product of the *gag* gene is a precursor polypeptide, p55, which undergoes systematic cleavage from its NH_2-terminus to yield the myristoylated MA, p17, and two antigens of the virus core: the CA, p24 and the PR, p15 or p14 (Levy, 1993). The latter is further processed into p7 and p6 (Barker *et al.*, 1995).

Enzymes which catalyse steps in the virus lifecycle are cleaved from the Gag-Pol polyprotein, $Pr160^{gag\text{-}pol}$ during virion morphogenesis. These are (i) the mature form of PR, composed of 99 amino acids with a molecular weight of 10 kDa (Katz & Skalka, 1994) and belonging to the category of aspartic proteinases, on the basis of the conserved Asp-Thr/Ser-Gly motif at the active site (Loeb *et al.*, 1989; Luciw, 1996); (ii) RT, which transcribes the viral RNA to DNA, and which has associated RNAse activity to degrade RNA/DNA hybrid molecules (Baltimore, 1970; Temin, 1976); (iii) IN, which results from the COOH-terminal of $Pr160^{gag\text{-}pol}$ to yield a 32 kDa protein with DNA cleavage and strand transfer activity, catalysing the covalent linkage of double-stranded DNA into the host genomic DNA (Luciw, 1996).

The initial envelope precursor protein gp160 is cleaved by a cellular protease to produce a mature glycosylated NH_2-terminal protein gp120 and the external spike glycoprotein gp41, which remain non-covalently linked (Figure 1) (reviewed by Moore *et al.*, 1993). The extracellular part of gp120 contains the binding site for the CD4 receptor, as well as the hypervariable region of about 36 amino acids referred to as the V3 loop (Freed *et al.*, 1991) (see Section 1.1.3). The gp 41 TM protein anchors gp120 in the viral lipid membrane and contains a hydrophobic peptide at its amino-terminus that is involved in membrane fusion.

(ii) *Regulatory proteins (Tat, Rev)*

The HIV-1 and HIV-2 genome encodes the major regulatory proteins Tat and Rev (reviewed by Peterlin, 1995; Luciw, 1996). Both are expressed from multiply spliced viral transcripts produced early after infection. Neither are packaged into virions and both are essential for virus replication.

The *tat* gene is bipartite, in that it has two coding exons, one located in the central region of the genome between *vpr* and *env* (Figure 2), the other overlapping the translation frames of *rev* and gp41. The 14 kDa Tat protein is localized in the nucleus by means of an arginine-rich nuclear localization signal within its basic domain. In the nucleus, Tat interacts with a stem-loop RNA structure in the LTR, designated the trans-activation response (TAR) element. Tat is essential for viral replication and acts to increase the steady-state levels of viral transcripts (for both structural and regulatory viral proteins) initiated in the LTR.

Viral structural protein expression is additionally regulated by the product of the *rev* gene. Rev is an essential 19 kDa protein which facilitates the appearance of partially spliced and unspliced transcripts in the cytoplasm. In the absence of Rev, only multiply

spliced transcripts are translated, so that no structural proteins, enzymes or genomic RNA can be packaged into the virus particle.

Rev, in keeping with its involvement with the splicing machinery, is located in the nucleolus. By binding to viral RNA at the Rev response element (RRE), Rev effectively shifts the balance from multiply spliced transcripts (encoding Tat, Rev, Nef and Vpr in the early stages of the virus replication cycle) to both unspliced and singly spliced transcripts which encode the viral structural proteins at a later stage in infection (Cullen, 1991).

(iii) *Accessory proteins (Nef, Vif, Vpr, Vpu)*

The role of the accessory proteins has been reviewed (Cullen, 1994; Hahn, 1994; Subbramanian & Cohen, 1994; Trono, 1995).

Nef, the first viral protein to be expressed, is a 25–30 kDa protein which is predominantly localized in the cytoplasm and inner surface of the membrane in infected cells (Yu & Felsted, 1992). Nef appears to be multi-functional: it down-regulates expression of the CD4 receptor in infected T-cells (Garcia & Miller, 1991; Aiken *et al.*, 1994), as indeed do Vpu and gp120, although the mechanism is unclear. Since the rate of CD4 endocytosis increases in the presence of Nef, it may be that Nef acts directly or indirectly via a cellular factor, to trigger removal of CD4 by endocytosis (Benichou *et al.*, 1994), thus preventing subsequent re-infection of cells already harbouring virus (Karn, 1991). The effects of Nef *in vivo* and *in vitro* are in sharp contrast. Deletion of *nef* appears to have little effect on infection by HIV-1 in T-cell lines (Cullen, 1994). However, macaques infected with SIV isolates expressing truncated Nef proteins maintain low-level viraemia and remain healthy, but if full-length Nef operates (due to a premature stop codon in SIV_{MAC239}), high-level viraemia and disease develop (Kestler *et al.*, 1991).

The *vpr* gene product is a 15 kDa oligomeric protein expressed from a singly spliced mRNA (Cohen *et al.*, 1990a,b; Zhao *et al.*, 1994). HIV-2 and most SIV strains carry an additional gene, *vpx*, which shares sequence homology with *vpr*, such that it has been suggested that *vpx* arose from *vpr* by gene duplication (Tristem *et al.*, 1992). Both Vpr and Vpx are packaged within the virions and by electron microscopy appear to be located outside the core structure (Wang *et al.*, 1994). Vpr induces differentiation and growth arrest in some tumour cell lines, even in the absence of other viral proteins (Rogel *et al.*, 1995). In terms of its effect on HIV replication, Vpr appears to enhance virus production in primary macrophages and, to a lesser extent in some T-cell lines (Hattori *et al.*, 1990; Connor *et al.*, 1995). Mutation in the nuclear localization signal of both the matrix protein p17 and Vpr of a macrophage tropic clone of HIV-1 led to a lower viral replication rate in macrophages and weakened the localization of uncoated viral complexes in the nucleus. Thus, p17 and Vpr appear to be able to mediate efficient nuclear importation of the pre-integration complex into non-dividing cells (Bukrinsky *et al.*, 1993; Heinzinger *et al.*, 1994). Vpr can also block the proliferation of human rhabdomyosarcoma cells and induce differentiation to muscle cells (Levy *et al.*, 1993a).

Vif, a 23 kDa cytoplasmic protein, is also essential for viral replication (Michaels *et al.*, 1993). In the absence of Vif, HIV-1 virions have abnormal morphology (Borman

et al., 1995) and have much reduced capacity to synthesize proviral DNA following infection of new target cells (Sova & Volsky, 1993).

HIV-1 and the related SIV_{CPZ} contain a *vpu* gene (Myers *et al.*, 1994), the 16 kDa phosphorylated product of which is localized in the perinuclear region of infected cells and is thus associated with the endoplasmic reticulum/Golgi system. Vpu-deficient HIV-1 mutants continue to replicate in $CD4^+$ T-cell lines, primary T-lymphocytes and macrophages, but at a reduced titre due to accumulation of virions in intracytoplasmic vesicles (Klimkait *et al.*, 1990). HIV-2 and other SIVs than SIV_{CPZ} lack a *vpu* gene, but its function is probably encoded elsewhere in the genome.

1.1.8 *Replication*

Infection by HIV is initiated when virus binds to the CD4 receptor on a target cell by means of the viral envelope glycoprotein, gp120 (Dalgleish *et al.*, 1984; Klatzmann *et al.*, 1984; Klasse *et al.*, 1993). This binding triggers a conformational change in the Env glycoprotein to expose the TM protein, gp41, resulting in fusion, possibly mediated by the co-receptor, between the virus and the host cell membrane (Weiss, 1993a). HIV-1 and HIV-2 enter the cell via a pH-independent mechanism (McClure *et al.*, 1990). After fusion, the viral core is released into the cell and single-stranded RNA, still associated with capsid protein, is converted to double-stranded proviral DNA through the polymerase and ribonuclease H activities of the viral reverse transcriptase.

The newly formed pre-integration complex enters the nucleus and the viral DNA integrates randomly in the host cellular DNA. This proviral DNA acts as a template for the production of viral RNA progeny. Transcription of the viral genome is driven by a promoter in the 5' LTR of the integrated provirus, resulting in the production of RNA molecules. These in turn serve both as messenger for synthesis of new viral proteins and as genomic RNA. Tat augments levels of viral RNA by increasing transcriptional initiation and/or elongation, and Rev regulates splicing and transport of viral RNA from the nucleus to the cytoplasm (reviewed by Cullen, 1993). Genomic RNA is subsequently packaged into virions which then bud at the surface from the cell membrane. As the virion matures, Gag and Gag–Pol polyproteins are cleaved by the viral protease into subunit proteins, resulting in the mature virion which is directed to the cell surface by the amino-terminal myristoylation of Gag (Smith *et al.*, 1993a). The virion is then released from the cell surface and this completes the life cycle (Figure 5).

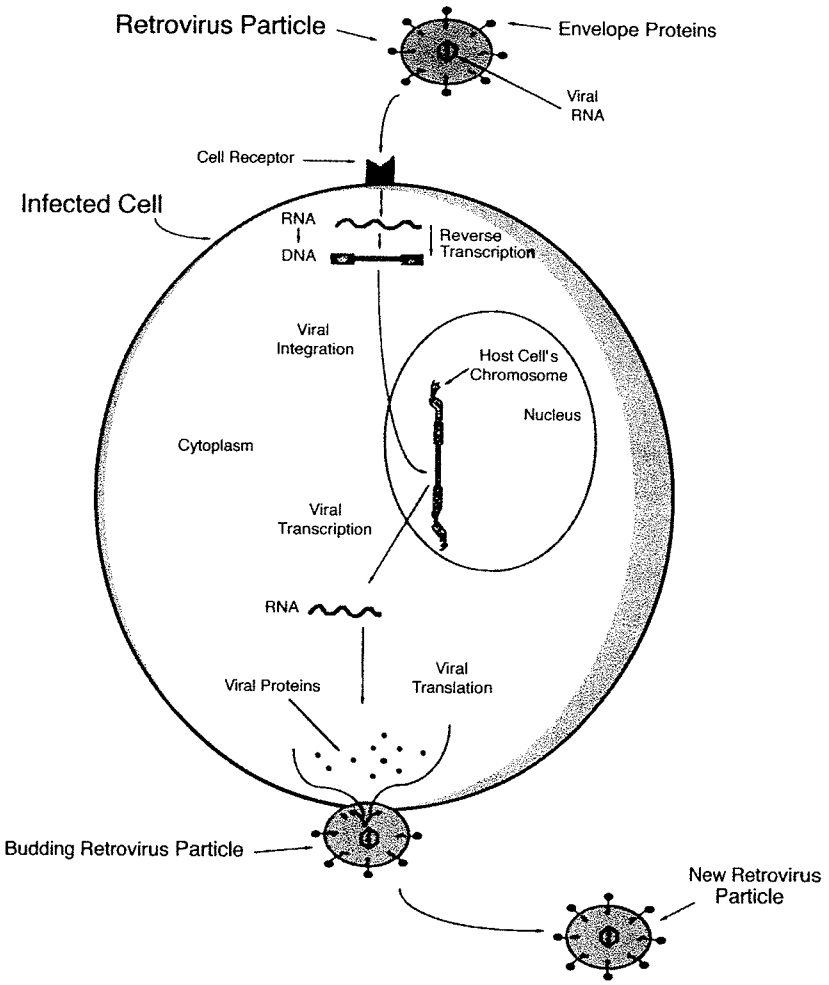
1.2 Methods of detection

In this section, HIV refers to both HIV-1 and HIV-2, unless otherwise specified.

1.2.1 *Antibody tests*

The confirmed presence of HIV antibodies is considered to represent current infection because as with other human retroviruses, once acquired, infection is lifelong. An antibody test for HIV-1 was first licensed in 1985, about two years after the virus was

Figure 5. Retrovirus life cycle



first isolated and identified as the causal agent for AIDS. The most widely used antibody tests for diagnosing HIV infection are enzyme-linked immunosorbent assays (ELISAs), with confirmation by western blot analysis.

(*a*) *ELISA*

Disrupted virions, purified from HIV-1-infected T-cells, were used as the antigen source in first-generation ELISAs. These partially purified antigens reacted with antibody to proteins from envelope (gp120 and gp41), core (p24) and reverse transcriptase (p55) regions of the virus. Early antigen preparations were often contaminated with non-viral antigens such as those originating from the major histocompatibility complex (MHC) expressed by the infected T-cells.

Sensitivity and specificity were substantially improved in second-generation ELISAs with the introduction of recombinant viral proteins or synthetic peptides. HIV-1 and HIV-2 are simultaneously detected in more sensitive third-generation ELISAs, also based on synthetic peptides of HIV or recombinant proteins (Simon *et al.*, 1992; Barbé *et al.*, 1994).

(*b*) *Western blot analysis*

In the western blot assay, enzyme-conjugated anti-human antibody is then used to detect membrane-bound HIV-specific antibody, observed as bands on the membrane corresponding to an antibody response to HIV proteins. The Centers for Disease Control (CDC; Atlanta, GA; United States of America) recommend that at least two bands corresponding to Gag and Env proteins must be reactive before a specimen can be classified as HIV-1 or HIV-2 antibody-positive (Centers for Disease Control, 1989a).

(*c*) *Indeterminate HIV antibody results*

Sera that do not meet the above criteria but exhibit reactivity to one or more bands are classified as 'indeterminate'. The proportion of serum samples that are repeatedly reactive on ELISA testing but interpreted as indeterminate by western blot analysis varies according to geographical region (Centers for Disease Control, 1989a).

HIV-1 indeterminate western blots can be seen in the early stages of HIV-1 infection (Gaines *et al.*, 1987; Ranki *et al.*, 1987; Sloand *et al.*, 1991) and throughout HIV-2 infection (Centers for Disease Control, 1989b). Indeterminate western blot patterns have rarely been found in healthy people with no identifiable risk for HIV infection (Dock *et al.*, 1991; Celum *et al.*, 1991), such as leprosy patients and pregnant women (Kashala *et al.*, 1994).

Further virological and immunological investigations such as HIV culture, quantification of p24 antigen and polymerase chain reaction (PCR) investigations can be used to diagnose HIV infection in individuals with indeterminate western blot results and a relevant exposure history (see Section 1.2.2).

(*d*) *Undetectable HIV antibody*

As with other infections, there is a delay between exposure and the development of antibodies (seroconversion), described as a 'window period'. Although antibodies to HIV-1 detectable by current ELISA may develop within weeks after infection, the usual public health practice is to retest 3–6 months after presumed exposure (Petersen *et al.*, 1994). The duration of the window period is variable and may be influenced by the mode of transmission, infectious dose and the host immune response. Improvement of ELISA has greatly reduced the window period.

(*e*) *Diagnosis of HIV infection in infants*

The serological diagnosis of HIV infection in children born to mothers with HIV infection is complicated by the passive transfer of maternal anti-HIV IgG antibodies to the baby. These antibodies decline steadily but can be detected for up to 15 months, so that standard serological assays cannot confirm or exclude HIV infection in the infant until then. The detection of IgA antibodies, which can only originate from the child (Livingston *et al.*, 1995), and serial testing to detect a rise in antibody titre after the initial fall during the first six months of life (Palasanthiran *et al.*, 1994), have been used to make an earlier diagnosis. However, where facilities exist, HIV infection is diagnosed in such infants by direct detection of HIV by culture and/or PCR on two occasions (McClure *et al.*, 1996; McMichael *et al.*, 1996).

Tests for HIV-specific antibodies remain useful for large-scale perinatal testing and in developing countries without facilities for viral culture or PCR analysis. To confirm that an infant is infected with HIV, antibody levels should be monitored to see if they persist beyond the first 15 months of life.

(*f*) *Detection of antibodies in saliva*

Testing for HIV antibody in saliva specimens has been shown to be a reliable technique for surveillance studies in populations with high prevalence of infection (Behets *et al.*, 1991; van den Akker *et al.*, 1992). The methods of collection of saliva specimens influence the detection of HIV antibody; therefore, these methods have not been recommended for individual diagnostic purposes (WHO, 1993).

1.2.2 *Direct detection of HIV*

Many of the problems encountered in antibody-based diagnosis of HIV infection, such as long seroconversion periods, the presence of cross-reactive antibody to non-viral proteins and diagnosis of HIV infection in neonates with maternal antibody to HIV, can be overcome by using techniques that detect virus or viral products directly.

HIV diagnosis is influenced by the amount of HIV present in the biological specimen tested. Table 2 shows how HIV load in various body fluids can vary dramatically.

Viral load varies greatly according to the stage of infection. In people recently infected with HIV and in those who have progressed to AIDS, viral load is high. Comparatively low levels of virus are found in asymptomatic individuals.

(*a*) *Viral culture*

Isolation of HIV by viral culture involves the co-culture of PBMCs with phytohaemagglutinin (PHA)-stimulated lymphocytes from an uninfected donor or a susceptible uninfected laboratory cell line (Feorino *et al.*, 1987). The presence of virus is then detected by measuring RT activity or p24 antigen.

Viral culture can take between two and four weeks to complete, requires experienced laboratory personnel to handle infectious material and is expensive.

(*b*) *p24 Antigen*

A quantitative p24 antigen capture assay has been developed, using a modified ELISA in which specific anti-p24 antibody is fixed to the wells of a microtitre plate so that free p24 antigen in serum is 'captured'. Enzyme-conjugated antibody specific to p24 is then added and the presence of immune complexes is visualized by a standard colour reaction.

The p24 antigen assay can detect HIV infection in some but not all recently exposed people before seroconversion. As antibodies to HIV develop, immune complexes form and p24 levels become low or undetectable. Late in the course of HIV disease, p24 antigen again becomes detectable.

Table 2. Representative data on isolation of HIV-1 from body fluids

Source	No. of specimens with virus isolated/ total specimens	Estimated quantity of HIV[a]
Free virus in fluid		
Plasma	33/33	1–5000[b]
Tears	2/5	< 1
Ear secretions	1/8	5–10
Saliva	3/55	< 1
Sweat	0/2	–[c]
Faeces	0/2	–[c]
Urine	1/5	< 1
Vaginal and cervical fluid	5/16	< 1
Semen	5/15	10–50
Milk	1/5	< 1
Cerebrospinal fluid	21/40	10–10 000
Infected cells in fluid		
Peripheral blood mononuclear cells	89/92	0.001–1%
Saliva	4/11	< 0.01%
Bronchial fluid	3/24	ND[d]
Vaginal and cervical fluid	7/16	ND[d]
Semen	11/28	0.01–5%

From Levy (1993)

[a] For cell-free fluid, quantities are given as infectious particles per millilitre; for infected cells, quantities are the percentage of total cells infected.

[b] High levels associated with symptoms and advanced disease

[c] –, no virus detected

[d] ND, not done

Acid dissociation of immune complexes in serum specimens increases the sensitivity of the p24 assay (Bollinger *et al.*, 1992).

(*c*) *Detection of viral genomes*

PCR and other nucleic acid amplification methods offer an alternative technique to cell culture for the detection and quantification of HIV in plasma or PBMCs. It is useful for diagnosing HIV infection in people at high risk for infection who remain antibody-negative, in people at low risk with an indeterminate western blot and in infants in whom maternal antibody is still present. Quantitative PCR is increasingly used to guide therapy; PCR is also used to detect mutations, including those which confer drug resistance.

(*d*) *HIV quantification*

The viral load can be quantified by viral culture and by nucleic acid detection methods (PCR, branched PCR, RT-PCR and nucleic acid sequence–base amplification).

The latter have the advantage of speed (2–3 h) and sensitivity (≤ 50 copies of HIV RNA can be detected per microlitre of plasma) (Holodniy *et al.*, 1991; Piatak *et al.*, 1993). In developed countries, viral load measurements are being introduced into routine patient management (see Section 1.4.2).

1.3 Epidemiology of HIV infection

In this section, HIV refers to HIV-1 unless otherwise specified.

1.3.1 *HIV transmission*

The three primary routes of HIV transmission — sexual intercourse, blood contact and from mother to infant — were proposed on the basis of AIDS case reports, even before the identification of this virus as the causative agent for AIDS. The appearance of AIDS first in homosexual men (Gottlieb *et al.*, 1981) suggested the possibility of sexual transmission, and its occurrence in recipients of blood and blood products (Anon., 1992a) and intravenous drug users (Small *et al.*, 1983) pointed strongly to transmissibility by blood contact. Once tests for detecting HIV antibodies became available in 1984, routes of transmission were established through identification of pairs of individuals with HIV antibody who were linked by a specific form of contact, such as blood donor–recipient, mother–child and members of the same sexual partnership.

(*a*) *Sexual contact*

There is extensive documentation of HIV transmission from man to woman and woman to man through vaginal and anal intercourse that is unprotected (i.e., without condom), and from man to man through unprotected anal intercourse. The risk of transmission associated with a single episode of unprotected intercourse appears to be highly variable and dependent on a number of factors (Mastro & de Vincenzi, 1996). Probably most important such factors are the disease stage of the infected partner (de Vincenzi, 1994; Nicolosi *et al.*, 1994a,b), which determines the amount of virus present in body fluids (Anderson *et al.*, 1992), and the presence of genital infection (Plummer *et al.*, 1991; Laga *et al*, 1993; Telzak *et al.*, 1993), particularly genital ulcerative disease (Cameron *et al.*, 1989). Other factors which have been less conclusively associated with an increased risk of transmission are lack of male circumcision (Cameron *et al.*, 1989; Hunter *et al.*, 1994), cervical ectopy (Moss *et al.*, 1991), intercourse during menstruation and older age for exposed women (European Study Group on Heterosexual Transmission of HIV, 1992). There may be an association between susceptibility to infection and specific HLA subtypes (Rowland-Jones *et al.*, 1995). The likelihood of HIV transmission per episode of sexual contact appears to be somewhat higher from man to woman than from woman to man, and anal intercourse presents a higher risk than vaginal intercourse for the receptive partner (de Vincenzi, 1994).

In the largest prospective study carried out to date (de Vincenzi, 1994), the cumulative risk of sexual transmission over the 20-month follow-up period of the study for couples practising unprotected intercourse was 13% from man to woman and 11% from woman to man. The transmission risks per episode were around 1/1000. A striking

feature of this study was that no transmission occurred among the 124 couples who consistently used condoms during sexual intercourse. Transmission risks per unprotected episode have been higher in studies of heterosexual partners from developing countries and in studies of homosexual men (Mastro & de Vincenzi, 1996). [The Working Group noted that some studies using a range of methodologies have found several-fold higher transmission risks than this study.]

A few cases of HIV transmission through penile-oral intercourse to the receptive partner have been reported (Mayer & DeGruttola, 1987; Rozenbaum *et al.*, 1988) but such transmission is thought to occur much less frequently than transmission by vaginal or anal intercourse.

HIV infection can occur through artificial insemination (Stewart *et al.*, 1985).

(*b*) *Blood contact*

The most efficient mode of HIV transmission is through direct blood-to-blood contact. In retrospective studies of people transfused with HIV-infected blood, transmission rates were essentially 100% (Donegan *et al.*, 1990). In a number of countries, the prevalence of HIV infection among haemophiliacs reached high levels due to the use of contaminated blood products before the introduction of systematic screening and heat treatment of donations. Transmission in the health care setting has also been documented following minor skin injury with needles and from splash exposure to mucous membranes. Overall, the risk of transmission following percutaneous or mucous membrane exposure to an HIV-infected source via occupational injury has been estimated to be around 0.3% per episode (Henderson *et al.*, 1990). However, the rate of transmission to health care workers who suffer a deep injury from a hollow-bore needle containing HIV-infected blood is much higher (Anon., 1995). HIV infection is also efficiently transmitted by organ transplantation.

Iatrogenic transmission of HIV infection has been minimized in developed countries and many developing countries through the use of procedures to defer (exclude) blood donors at risk of HIV infection and universal screening of blood and tissue donations for HIV antibody (Franceschi *et al.*, 1995a). However, a small number of cases of transmission still occur when a newly infected donor has not yet developed a detectable level of HIV antibody (Ward *et al.*, 1988). In a number of developing countries, the blood supply is not yet universally screened. In South Africa, 80% of HIV-positive donations came from first-time donors, and one approach has been to use only heat-treated blood products from first-time donors (Sitas *et al.*, 1994).

The other major pathway of blood-borne transmission is through the re-use of injecting equipment and related material by intravenous drug users (Friedman & Des Jarlais, 1991). The immediate re-use of a needle and syringe after they have been used by an HIV-infected person is an efficient means of transmitting the virus. Less clear is the extent to which the risk of transmission reduces with the time elapsed between use and re-use of the injecting equipment and by various methods of cleaning the equipment.

(*c*) *Mother-to-child transmission*

Between 15% and 35% of babies born to HIV-infected women acquire the infection, the risk depending on a range of factors which vary across population groups (Peckham & Gibb, 1995). As with sexual transmission, a key predictor is the HIV disease stage in the mother (European Collaborative Study, 1992), which is associated with viral load (Roques *et al.*, 1993). Breast-feeding is a strong independent risk factor, as shown by studies of women who became infected post-partum, either by blood transfusion (Ziegler *et al.*, 1985) or sexually (Van de Perre *et al.*, 1991) and of children of women already infected at the time of delivery. The majority of studies have found that delivery by Caesarian section reduces the risk of mother-to-child transmission (reviewed by the European Collaborative Study, 1994), suggesting that most transmission occurs during passage through the birth canal. This is supported by studies of twins in which the first-born twin has the higher risk of HIV infection (Goedert *et al.*, 1991).

(*d*) *Other modes of transmission*

There is no evidence that HIV transmission can occur through routes other than those described above (Friedland *et al.*, 1990; Gershon *et al.*, 1990; Anon., 1994). Although it is impossible to prove that a specific form of contact carries a zero likelihood of transmission, studies of the household and casual contacts of people with HIV infection have not revealed any risk of HIV transmission. Similarly, there is no evidence that mosquitoes, bed bugs or other arthropods act as vectors of HIV between humans.

Several well documented pairs or groups of cases of HIV infection are linked both epidemiologically and through molecular typing, but the specific mode of transmission has not been ascertained (Ciesiclski *et al.*, 1992; Chant *et al.*, 1993; Fitzgibbon *et al.*, 1993). It is believed that these cases represent unknowing or unacknowledged blood contact rather than evidence for new modes of transmission.

1.3.2 *Geographical distribution*

Assessment of the epidemiological pattern of HIV infection was initially based on AIDS case reporting (Buehler *et al.*, 1989). Since 1985, when HIV antibody testing became widely available, case reporting of HIV diagnoses (McDonald *et al.*, 1994) and serological surveys for HIV antibody in population subgroups (Dondero *et al.*, 1988) have complemented AIDS case reporting as mechanisms for monitoring the occurrence of HIV infection. Across geographical and administrative areas, there has been a wide variation in the specific approaches used for epidemiological surveillance of HIV infection, depending on a range of economic, political, cultural and ethical considerations. It is therefore difficult to compile an accurate and current picture of the HIV epidemic as it has spread around the world. Some countries, particularly those of the developed world, have produced national consensus reports on past and predicted patterns of HIV infection, while for other countries, there has been a reliance on estimates made by international bodies, such as WHO.

No single approach to epidemiological monitoring of HIV infection is fully satisfactory. Compilation and analysis of AIDS case reports only provide an indication of

past HIV infection patterns, because of the long and variable interval between the acquisition of infection and development of AIDS. AIDS case counts are also prone to substantial under-enumeration, because of reliance on individual medical practitioners to diagnose and report cases centrally. On the other hand, the occurrence of AIDS is generally a severe and life-threatening condition which almost always results in contact with the health system, thereby providing unbiased data in relative, if not absolute, terms within a population and over time. Surveillance based on HIV diagnosis suffers from its dependence on the extent of HIV testing and may be biased by variation in the level of testing across population subgroups. It can nevertheless provide an indication of transmission patterns earlier than would be available from AIDS case reports. Both AIDS and HIV reporting are difficult to implement on a routine basis in countries with limited resources.

Serological surveys for HIV antibody have been carried out in some countries on a routine basis (Gill *et al.*, 1989; Dondero & Gill, 1991; Ministry of Public Health, 1994), while in other countries they are implemented occasionally. Provided sampling frames are carefully chosen, such surveys can provide good estimates of HIV prevalence (and, with more difficulty, incidence) in selected population subgroups. Groups included in serological surveys have generally been either people considered to be at elevated risk of HIV infection, such as homosexual men, sexually transmitted disease clinic attendees, sex workers (prostitutes), intravenous drug users or prisoners. More representative of the general population may be people who are easily accessible within the health system or some other institutional setting, such as pregnant women, hospital in-patients, blood donors (who are now universally tested for HIV antibody in many countries) and military recruits and serving personnel.

(*a*) *Global estimates and projections*

At the end of 1995, WHO released a comprehensive set of estimates of HIV prevalence in adults by country (WHO, 1995), along with the Organization's routinely published counts of reported AIDS cases. The prevalence estimates (see Table 3) were provided by national bodies or expert groups in each country or were calculated by WHO if current national estimates were not available. The picture that emerges is one dominated by sub-Saharan Africa, where the HIV epidemic is believed to have started. The proportion of adults estimated to have HIV infection is above 14% in Malawi and Uganda and 17% in Zambia and Zimbabwe. Among the developed countries, the United States and Spain have the highest prevalence rates of HIV infection among adults, above 0.5%, while rates in other developed countries range down to below 0.05%. Apart from Cambodia, Myanmar and Thailand, with prevalence rates of 1.5–2.0%, HIV prevalence remains low in Asia, but India is now estimated to be the single country with the greatest number of people living with HIV infection.

Mathematical models have been used to carry out projections of the future course of the HIV epidemic globally, on the basis of available data and assumptions about future trends in transmission rates. These models predict that in the years up to 2000, there will be a declining annual incidence of AIDS in North America and Europe, a stable or slightly declining incidence in Africa and a sharply rising incidence in Asia (Chin, 1995).

By 2000, it is predicted that Asia will have over 1.3 million new infections per year, compared with 800 000 in Africa and 100 000 in North America and western Europe.

Table 3. Estimated prevalence of HIV infection among adults, in selected countries, at the end of 1994

Country	Number	%	Country	Number	%
North America			Greece	5 000	0.098
Canada	30 000	0.19	Hungary	3 000	0.058
United States	700 000	0.52	Ireland	1 700	0.094
Caribbean			Italy	90 000	0.31
Cuba	1 300	0.021	Netherlands	3 000	0.036
Dominican Republic	40 000	1.0	Norway	1 250	0.057
Haiti	150 000	4.4	Poland	10 000	0.05
Jamaica	12 000	0.91	Portugal	8 000	0.16
Latin America			Romania	500	0.004
Argentina	60 000	0.36	Russian Federation	3 000	0.004
Brazil	550 000	0.65	Spain	120 000	0.58
Chile	10 000	0.13	Sweden	3 000	0.072
Colombia	40 000	0.21	Switzerland	12 000	0.32
Mexico	200 000	0.42	Turkey	500	0.002
Peru	30 000	0.25	United Kingdom	25 000	0.087
Venezuela	35 000	0.32	Ukraine	1 500	0.006
Africa			**Asia**		
Egypt	7 500	0.025	Bangladesh	15 000	0.026
Ethiopia	588 000	2.5	Cambodia	90 000	1.9
Ghana	172 000	2.2	China	10 000	0.002
Kenya	1 000 000	8.3	India	1 750 000	0.38
Malawi	650 000	14	Indonesia	50 000	0.049
Morocco	5 000	0.036	Japan	6 200	0.01
Mozambique	400 000	5.7	Korea, Democratic	100	0.001
Nigeria	1 050 000	2.2	People's Republic of		
Rwanda	250 000	7.1	Korea, Republic of	2 000	0.008
Senegal	50 000	1.3	Malaysia	30 000	0.3
South Africa	650 000	3.2	Myanmar	350 000	1.5
Tanzania, United	840 000	6.4	Pakistan	40 000	0.063
Republic of			Philippines	18 000	0.054
Uganda	1 300 000	14	Thailand	700 000	2.1
Zaire	680 000	3.7	Vietnam	25 000	0.069
Zambia	700 000	17	**Oceania**		
Zimbabwe	900 000	17	Australia	11 000	0.12
Europe			New Zealand	1 200	0.065
Denmark	4 000	0.15	Papua/New Guinea	4 000	0.19
Finland	500	0.019	**Middle East**		
France	90 000	0.31	Israel	2 000	0.073
Germany	43 000	0.11	Saudi Arabia	1 000	0.012

From WHO (1995)

More detailed analyses of HIV prevalence and transmission patterns are available for most developed countries and a number of developing countries through national reports or papers published in the scientific literature.

(*b*) *United States and Canada*

As the country where AIDS was first recognized (Gottlieb *et al.*, 1981) and the developed country with the highest number of cases of HIV infection in absolute terms (WHO, 1995), the United States has carried out a large number of investigations into HIV infection. It is now apparent that two distinct HIV epidemics have occurred, beginning in the late 1970s and early 1980s. One was focused on the major communities of homosexual men, particularly in San Francisco, Los Angeles and New York. Retrospective tests of stored serum samples from homosexual men taken in the course of longitudinal studies of hepatitis B vaccination revealed a sharp rise in the incidence of HIV infection from the late 1970s (Hessol *et al.*, 1989; van Griensven *et al.*, 1993). These studies, as well as subsequent cohort studies (Winkelstein *et al.*, 1987; Kingsley *et al.*, 1991), showed that the incidence of new infection peaked at around 10% of homosexual men per year in the early 1980s. This finding was confirmed by back-projection (Rosenberg *et al.*, 1992; Rosenberg, 1995), a mathematical method that estimates past incidence of HIV infection based on AIDS case reports combined with knowledge about the rate of progression from HIV infection to the development of AIDS.

The other major epidemic in the United States was among inner-city, largely 'African-American' or 'Hispanic' residents of the major eastern cities, such as New York, Chicago, Philadelphia, Miami, Baltimore and Newark (Centers for Disease Control and Prevention, 1994a). Transmission was associated mainly with the use of illicit drugs, either directly through injection (Schoenbaum *et al.*, 1989) or indirectly through sexual contacts by people seeking money to buy drugs or partners of intravenous drug users (Diaz *et al.*, 1994; Ellerbrock *et al.*, 1995). To the end of 1994, 53% of AIDS cases reported in the United States were men who became infected through homosexual contact, but the proportion of such cases for 1994 alone had fallen to 44%, with corresponding increases in the proportion of AIDS cases attributed to intravenous drug use and heterosexual contact (Centers for Disease Control and Prevention, 1994b; Rosenberg, 1995).

In Canada, the patterns of HIV infection have generally been similar to those in the United States, but the overall rates of infection have been lower, and a higher proportion of cases have been transmitted through homosexual contacts between men (Remis & Sutherland, 1993).

(*c*) *Caribbean*

Early case reports of AIDS in the United States documented an association with Haitian origin (Anon., 1992b), and subsequent serological surveys confirmed high rates of HIV infection in Haiti and some other Caribbean countries (WHO, 1995; Cáceres & Hearst, 1996). The predominant mode of transmission in the Caribbean is heterosexual contact (Cáceres & Hearst, 1996). An apparent exception to the pattern of high HIV

infection rates in the Caribbean is Cuba, where the adult prevalence has been estimated to be 0.02% (WHO, 1995).

(*d*) *Latin America*

In the early 1980s, the pattern of HIV transmission in Latin American countries closely resembled those in the United States and Europe, being largely through sexual contact between men and among intravenous drug users (Cáceres & Hearst, 1996). More recently, some Latin American countries have experienced substantial increases in the extent of heterosexual transmission. In Brazil, the most populous country of the region, 23% of AIDS cases reported in 1992 were attributed to heterosexual transmission of HIV infection, compared with 7% in 1987 (Ministério da Saúde, 1993). There remains considerable variation between countries in the extent to which HIV transmission has extended beyond the population subgroups initially affected (Cáceres & Hearst, 1996).

(*e*) *Sub-Saharan Africa*

From retrospective testing of stored sera and tissue, HIV infection is known to have existed in Africa since before 1963 (Quinn *et al.*, 1986). Numerous serological surveys have documented the rapid spread of HIV infection through sub-Saharan Africa over the past decade. The most affected countries have been in central and southern Africa, including Kenya, Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe (Nkowane, 1991; WHO, 1995). Within these countries, HIV prevalence has generally been substantially higher in cities than in rural communities (Berkley *et al.*, 1989) and epidemic spread has been associated with major transport routes (Grosskurth *et al.*, 1995), but is not strongly associated with social class, as measured by characteristics such as educational level attained (Malamba *et al.*, 1994). Transmission to adults has been mainly through heterosexual contact, with roughly equal numbers of men and women infected (Rwandan HIV Seroprevalence Study Group, 1989). Medical procedures such as injections and blood transfusion have also played a role.

Studies of women engaged in commercial sex work (prostitution) had already found HIV prevalence as high as 80% by the late 1980s in several African countries (Padian, 1988). The prevalence of infection in pregnant women has reached 30% in some urban surveys, resulting in high numbers of babies being born with HIV infection (Allen *et al.*, 1991).

In west Africa, HIV-2 was the predominant form in the mid-1980s, but in some urban areas, HIV-1 is now becoming more prevalent (Kanki *et al.*, 1994).

(*f*) *Europe*

In most European countries, HIV infection and AIDS were first reported among homosexual men in the early to mid-1980s (Downs *et al.*, 1987), but three distinct epidemiological patterns have emerged subsequently. In Germany, the Netherlands, the Nordic countries and the United Kingdom, sexual transmission between men has remained by far the most important route of transmission. In these countries, the cumulative proportions of AIDS cases attributed to male homosexual contact exceeded 60% in 1994 (European Centre for the Epidemiological Monitoring of AIDS, 1995a) and the

prevalence of HIV infection in pregnant women has generally been below 0.1% (European Centre for the Epidemiological Monitoring of AIDS, 1994). There are exceptions, such as parts of inner London, where large sections of the population are ethnic minority groups, in which the prevalence in pregnant women has been estimated at 0.4% (PHLS (Public Health Laboratory Service) Communicable Diseases Surveillance Centre, 1993).

In other European countries, the pattern of HIV infection became dominated by transmission related to intravenous drug use during the 1980s. Particularly affected were Italy, Spain and Switzerland, where HIV prevalence among people who inject drugs exceeded 50% in several cities (Friedman & Des Jarlais, 1991; European Centre for the Epidemiological Monitoring of AIDS, 1995a). As a consequence, these countries have experienced increasing rates of HIV infection and AIDS among women, acquired either through the sharing of injecting equipment or by sexual contact with male intravenous drug users, and of mother-to-child transmission of HIV infection (Franceschi *et al.*, 1994; European Centre for the Epidemiological Monitoring of AIDS, 1995b).

In a third group of European countries, primarily those of eastern Europe, HIV transmission appears to have been very limited so far (European Centre for the Epidemiological Monitoring of AIDS, 1995b). There are notable exceptions, such as a major outbreak of nosocomially-acquired HIV infection among children in Romania in the mid-1980s (Patrascu & Dumitrescu, 1993). In Poland, nearly half of the reported AIDS cases have been among intravenous drug users (European Centre for the Epidemiological Monitoring of AIDS, 1995a).

(*g*) *Asia*

There has been considerable variation between Asian countries in the extent to which rates of HIV infection have been monitored. However, there appears to be substantial heterogeneity, both within and across countries, in the patterns of HIV transmission (Kaldor *et al.*, 1994). As in Europe, the first Asian cases of HIV infection and AIDS were reported in homosexual men (Weniger *et al.*, 1991), but other routes of transmission later became predominant in a number of countries. In Myanmar (Htoon *et al.*, 1994) and Thailand (Brown *et al.*, 1994a), the prevalence of HIV infection among intravenous drug users increased rapidly during the mid- to late 1980s, reaching levels of 40–50% within a few years. High prevalences were reported among intravenous drug users in Yunnan Province, China (Xinhua *et al.*, 1994), the north-east Indian state of Manipur (Sarkar *et al.*, 1993) and, more recently (and to a lesser extent so far), in Malaysia (Singh *et al.*, 1994) and Vietnam (Kaldor *et al.*, 1994).

A separate HIV epidemic in Thailand initially arose through transmission between sex workers and their clients. Some surveys of prostitutes have found up to 70% having HIV infection, with a strong inverse association between prevalence of infection and the price charged per client, presumably through association with frequency of contact and prevalence in client groups (Brown *et al.*, 1994a).

A high prevalence of HIV infection has also been found among female prostitutes in a number of Indian cities (Jain *et al.*, 1994).

In several Asian countries, monitoring of population subgroups more representative of the general population, such as pregnant women and military recruits, has revealed a steady increase in HIV prevalence, presumably as a consequence of heterosexual transmission. By 1993, the prevalence of HIV infection in pregnant women had reached 2% in Thailand overall and 8% in the northern province of ChiangMai. The prevalence among military recruits in northern Thailand (men aged around 20) was of the order of 10% (Brown *et al.*, 1994a). In several other countries, including Cambodia and India, the reported HIV prevalence among volunteer blood donors has already exceeded 1% (Jain *et al.*, 1994; Kaldor *et al.*, 1994).

Nevertheless, a large part of the Asian population so far appears to be relatively untouched by the global spread of the HIV epidemic. The small numbers of cases reported from China (mostly from Yunnan province), Pakistan, Bangladesh and Indonesia (WHO, 1995) may to some extent be attributable to limited surveillance systems, but probably also reflect very low rates of HIV transmission in these countries.

(h) Oceania

In Australia and New Zealand, HIV transmission has overwhelmingly been through sexual contact between men (Crofts *et al.*, 1994). Transmission via this route occurred at high levels in the early 1980s but declined sharply in the second half of the decade.

In Papua New Guinea, heterosexual contact has emerged as the most important route of transmission (Malau *et al.*, 1994).

(i) Middle East

Few cases of HIV infection or AIDS have been reported from Middle Eastern countries (WHO, 1995), and distinct transmission patterns have not been discerned.

1.4 Clinical description of non-neoplastic disorders

1.4.1 *Seroconversion syndrome*

The 'seroconversion syndrome', also known as 'primary HIV infection' or 'acute retroviral syndrome', refers to a complex of symptoms that occur in the first one to six weeks after HIV-1 infection in many adult patients (Tindall *et al.*, 1988a,b) during the 'window period' before HIV antibody is detectable (see Section 1.2.1). Early observations on a few patients (Cooper *et al.*, 1985; Ho *et al.*, 1985a) indicated that these included truncal maculopapular rash, fever, arthralgia, myalgia, sore throat, lymphadenopathy, abdominal cramps, diarrhoea and headache (Ho *et al.*, 1985a). Subsequent studies of series of patients in the United States (Fox *et al.*, 1987), Australia (Tindall *et al.*, 1988a,b), Italy (Sinicco *et al.*, 1990) and Switzerland (Kinloch-de Loës *et al.*, 1993) have confirmed this constellation of signs and symptoms (see Table 4), although the frequency varies somewhat depending on the definitions used, the means of determination (e.g., self-reported versus observed) and the severity or persistence of symptoms. Additional signs and symptoms in persons with primary HIV infection include lethargy and malaise, anorexia and weight loss, retro-orbital pain and, more rarely, rhinorrhoea, dark urine and irritability (Cooper *et al.*, 1985; Tindall *et al.*, 1988a,b).

Table 4. Selected common symptoms in series of patients with seroconversion syndrome

Reference	No.[a]	Percentage with						
		Fever	Skin rash	Sore throat	Myalgia/ arthralgia	Headache	Diarrhoea	Enlarged[b] nodes
Kinloch-de Loës *et al.* (1993)	31	87	68	48	42	39	32	57
Sinicco *et al.* (1990)	12	100	58	75	75	NR	17	92
Tindall *et al.* (1988a)	39	77	23	56	56	49	28	43
Fox *et al.* (1987)	22	23	14	23	14	23	14	36

[a] Number of patients in series
[b] Enlarged nodes, polyadenomegaly; enlarged lymph nodes/lymphadenopathy
NR, not reported

In the first weeks of HIV-1 infection, there are very high levels of circulating virus (Clark *et al.*, 1991; Daar *et al.*, 1991) and 'antigen excess' as determined by p24 antigen assays (Kessler *et al.*, 1987; Henrard *et al.*, 1995). Numbers of peripheral $CD4^+$ T-lymphocytes decrease markedly and $CD8^+$ T-lymphocytes increase (Roos *et al.*, 1992; Weiss *et al.*, 1992; Zaunders *et al.*, 1995). Leukopenia and thrombocytopenia may be seen (Cooper *et al.*, 1985; Ho *et al.*, 1985a; Scully *et al.*, 1989; Kinloch-de Loës *et al.*, 1993) (Figure 6).

The occurrence of the seroconversion syndrome and its clinical severity may be prognostic of a rapid rate of progression to AIDS (Sinicco *et al.*, 1993; Henrard *et al.*, 1995).

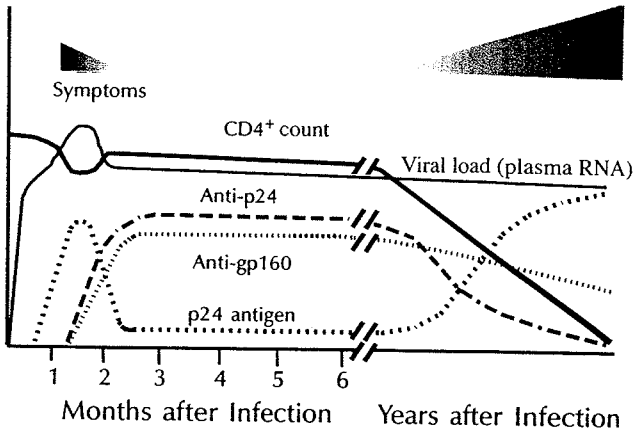
1.4.2 *Immunological decline*

Following infection, there is a variable period during which most patients are asymptomatic but undergo progressive immunological decline. This may be measured by various parameters such as $CD4^+$ T-cell counts and percentages of total lymphocytes, the ratio of $CD4^+$ to $CD8^+$ T-cells and serum levels of β_2-microglobulin and neopterin (Fahey *et al.*, 1990; Gruters *et al.*, 1991). Immunological decline is not smooth or consistent over the prolonged course of infection. As a general rule, some parameters, such as $CD4^+$ T-cell count, percentage and $CD4^+$ to $CD8^+$ ratio, decline with duration of HIV infection and appearance of symptomatic disease, whereas markers of lymphocyte activation, such as serum levels of β_2-microglobulin and neopterin, increase (see Figure 6).

Peripheral blood measurements, particularly the absolute $CD4^+$ T-cell count (or $CD4^+$ T-cell percentage), are used clinically to indicate the stage of HIV disease. $CD4^+$ T-cell decline and rate of decline have proven to be useful, if imperfect, markers of the development of the disease (Fahey *et al.*, 1990; Phillips *et al.*, 1991). During primary HIV infection, $CD4^+$ T-cells and their percentage typically fall rapidly, rise again with

the appearance of HIV antibody, then gradually decline during a long 'latent' (asymptomatic) period of several years (Margolick *et al.*, 1993, 1994; Holmberg *et al.*, 1995a). Subsequently, a more rapid drop in $CD4^+$ T-cell count or percentage presages the onset of AIDS-defining conditions and opportunistic infections (Krämer *et al.*, 1992; Galai *et al.*, 1993; Phillips *et al.*, 1994a). The prognostic value of rapidly declining or low $CD4^+$ T-cell counts as predictors of AIDS onset has been amply demonstrated in populations at risk for HIV infection, including homosexual and bisexual men (Schechter *et al.*, 1989; Veugelers *et al.*, 1993), intravenous drug users (Zangerle *et al.*, 1991; Margolick *et al.*, 1992; Muñoz *et al.*, 1992; Alcabes *et al.*, 1993a), heterosexual women (Flanigan *et al.*, 1992) and haemophilic men (Eyster *et al.*, 1987; Phillips *et al.*, 1989).

Figure 6. Schematic model of the natural history of HIV-1 infection



Markers of immunological decline other than $CD4^+$ T-cells have been investigated for prognostic purposes. In particular, serum levels of β_2-microglobulin and neopterin, non-specific markers of inflammation, correlate with declining immunity and the onset of AIDS-related conditions (Krämer *et al.*, 1992; Lifson *et al.*, 1992; Muñoz *et al.*, 1992; Galai *et al.*, 1993). Some investigators have found that addition of serum β_2-microglobulin or neopterin determinations to $CD4^+$ T-cell counts improves prognostic ability, but in general, the clinical role of these markers is diminishing (Melmed *et al.*, 1989; Fahey *et al.*, 1990; Krämer *et al.*, 1992; Muñoz *et al.*, 1992; Galai *et al.*, 1993).

The various immunological markers do not reflect accurately the total body burden of HIV (Pantaleo *et al.*, 1993a). HIV is actively replicating throughout the long asymptomatic period of infection. Although the decline in $CD4^+$ T-cells is gradual (Figure 6), up to 30% of the PBMCs may be infected by HIV and lost each day. The total viral load varies, but 10^{10} or more new virions may be generated per day and viral load measurements have been shown to have prognostic value beyond the $CD4^+$ count (Ho *et al.*, 1995; Wei *et al.*, 1995; Mellors *et al.*, 1996; O'Brien *et al.*, 1996).

During HIV-1 and HIV-2 infection, cellular immunity is compromised more than humoral immunity (Fauci *et al.*, 1991; Pantaleo & Fauci, 1995). Not only the number but also the function of $CD4^+$ and $CD8^+$ cytotoxic T-lymphocytes decrease, particularly in the

initial stages of HIV infection (Gruters *et al.*, 1991; Mackewicz *et al.*, 1991; Margolick *et al.*, 1993; Torpey *et al.*, 1993; Koup *et al.*, 1994). Anergy to delayed-type hypersensitivity skin tests is also more likely to occur as the disease progresses (Blatt *et al.*, 1993; Gordin *et al.*, 1994).

1.4.3 *Non-AIDS-defining manifestations of HIV infection*

(*a*) *Classification of HIV disease*

The use of the term 'AIDS' has been complicated by changes in its definition and the need to apply somewhat different definitions depending upon local situations. The initial definition of AIDS was developed in 1982 by the CDC and subsequently accepted by WHO in 1985. There were major revisions of the classification system in 1987 (WHO, 1988); cervical cancer, recurrent pneumonia, pulmonary tuberculosis and, for persons in the United States, a $CD4^+$ T-cell count of less than 200 cells/mm^3 (or percentage less than 14%) in HIV-positive individuals were added to the definition at the beginning of 1993 (Centers for Disease Control and Prevention, 1992a). Each of these revisions resulted in a large increase in reported numbers of AIDS cases in subsequent years, as AIDS was diagnosed earlier by including a broader range of conditions and, particularly in the United States, by including $CD4^+$ T-cell counts in patients who had not developed an AIDS-defining opportunistic infection or malignancy.

Because of the different spectrum of AIDS-related diseases in developing countries, and the shortage of sophisticated diagnostic equipment there, a WHO workshop in 1985 adopted a provisional clinical case definition of AIDS for use in such regions of the world (WHO, 1986).

Some non-malignant, non-AIDS-defining conditions have been described in the past as 'persistent generalized lymphadenopathy' and 'AIDS-related complex'. The former term was used to describe the lymphadenopathies often seen in HIV-infected persons before AIDS was recognized as an entity (Centers for Disease Control, 1982). In 1983, the Extramural AIDS Working Group of the US National Cancer Institute and National Institutes of Allergy and Infectious Diseases first defined the term 'AIDS-related complex' to cover the status of persons whose clinical condition did not meet the AIDS surveillance definition but who exhibited clinical and laboratory abnormalities that appeared to be related to AIDS (Abrams, 1988). This definition was never widely adopted. AIDS-related complex originally referred to persistent lymphadenopathy (Kaplan *et al.*, 1988), fever, weight loss, diarrhoea, fatigue and night sweats and, in standard laboratory tests, leukopenia, thrombocytopenia (Abrams, 1988; Sloand *et al.*, 1992) and anaemia. Later, other non-fatal conditions such as oral candidiasis, oral hairy leukoplakia and herpes zoster (Buchbinder *et al.*, 1992; Holmberg *et al.*, 1995b) were included, as well as some major manifestations that later became part of the most recent CDC definition of AIDS (Centers for Disease Control and Prevention, 1992a; see Table 5).

Table 5. Conditions included in the 1993 AIDS surveillance case definition[a]

Candidiasis of bronchi, trachea or lungs
Candidiasis, oesophageal
Cervical cancer, invasive[b]
Coccidiomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (> 1 month's duration)
Cytomegalovirus disease (other than liver, spleen or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex; chronic ulcer(s) (> 1 month's duration); or bronchitis, pneumonitis or oesophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (> 1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary[b] or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukencephalopathy
Salmonella septicaemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV
Immunodeficiency as measured by a $CD4^+$ T-cell count less than 200 cells/mm^3 or $CD4^+$ T-cell percentage less than 14%[b,c]

[a] From Centers for Disease Control and Prevention (1992a) [Appendix B]

[b] Added in the 1993 expansion of the AIDS surveillance case definition

[c] United States only

(*b*) *Non-AIDS illness*

To summarize a large body of research and clinical observations, it is clear that there are many pre-AIDS conditions, signs and symptoms of HIV infection. In persons with immunological impairment, many of these conditions reflect opportunistic or reactivated infection. Generally, these include 'constitutional' symptoms, namely persistent weight loss, diarrhoea, sweating and headaches (independent of intracranial causes) (Greenberg *et al.*, 1992; Hoover *et al.*, 1993; Holmberg *et al.*, 1995b); oral and sinus problems, including oral candidiasis, oral hairy leukoplakia and sinusitis (Farizo *et al.*, 1992;

Holmberg *et al.*, 1995b); skin manifestations, such as herpes zoster, seborrhoeic dermatitis and eczema; and anogenital problems, such as ulcers, fissures, warts and vaginal candidiasis (Renzullo *et al.*, 1991; Holmberg *et al.*, 1995b). Finally, several early neurological manifestations can be added to the spectrum of morbidity suffered by persons before they develop AIDS (Janssen *et al.*, 1989; Holmberg *et al.*, 1995b).

(*c*) *Time to AIDS*

The incubation time between HIV infection and the appearance of clinical AIDS conditions is of obvious importance to clinicians caring for HIV-infected patients, to epidemiologists and statisticians trying to model the size and direction of the HIV epidemic, to health care planners and administrators attempting to anticipate future health care needs of the HIV-infected population and last but not least to the patients themselves. This incubation period has been examined in populations in which dates of HIV-1 infection could be ascertained or interpolated, including homosexual and bisexual men (Lui *et al.*, 1988; Bacchetti & Moss, 1989; Biggar *et al.*, 1990; Giesecke *et al.*, 1990; Rutherford *et al.*, 1990; Kuo *et al.*, 1991) and transfusion recipients (Ward *et al.*, 1989). Almost all studies indicate that the median incubation period is 7–11 years (Alcabes *et al.*, 1993b). Many studies have attempted to discern host factors that may shorten or lengthen the incubation period of HIV infection, but only one 'cofactor', age, has been found consistently. In adults, the older the HIV-infected patient is, the shorter is the incubation period (Biggar & International Registry of Seroconverters, 1990; Mariotto *et al.*, 1992; Darby *et al.*, 1996). Antiretroviral therapies against HIV and prophylactic therapies against diseases associated with it, such as *Pneumocystis carinii* infection, have been shown to delay the onset of AIDS (Collier *et al.*, 1996).

1.4.4 *AIDS manifestations*

Table 5 lists the 26 AIDS-defining conditions recognized by CDC. Apart from the recognized HIV-associated malignancies, almost all are opportunistic infections. However, there is geographical variation, probably related to the varying prevalence of relevant pathogens. In Thailand, *Penicillium marneffei*, not included in CDC's definition of AIDS, is a very common fungal pathogen in AIDS patients (Sirisanthana & Sirisanthana, 1995).

The most frequently reported opportunistic infection of HIV-infected adults and children in the United States and most other developed countries is *Pneumocystis carinii* pneumonia (PCP) (Hughes, 1995). However, as treatment recommendations and guidelines have been published and promulgated (Centers for Disease Control and Prevention, 1992b), the incidence of cases of AIDS-defining PCP has declined (Muñoz *et al.*, 1993; Katz *et al.*, 1994; Centers for Disease Control and Prevention, 1995a; see Section 1.5.3).

Tuberculosis and non-tuberculous mycobacterial infections, particularly *Mycobacterium avium* complex (*M. avium* and *M. intracellulare*) (Horsburgh, 1991) are common. These have received much attention, because many multi-drug-resistant strains of *M. tuberculosis* have become epidemic in HIV-1-infected persons, especially in New York City in recent years (Frieden *et al.*, 1993). The continuing high rates of tuberculosis in

HIV-infected persons in developing countries present great problems for prevention, diagnosis and treatment (Pitchenik, 1990).

Candidiasis of the oesophagus, bronchi, trachea and lungs are all AIDS-defining conditions in HIV-infected persons.

Other fungal infections, such as cryptococcosis, coccidioidomycosis and histoplasmosis, are AIDS-defining opportunistic infections (Galgiani & Ampel, 1990; Currie & Casadevall, 1994; Stevens, 1995; Rinaldi, 1996) and have been included in several comprehensive clinical guidelines and preventive efforts for persons with HIV infection (Centers for Disease Control and Prevention, 1995b).

Parasitic infections of the central nervous system, notably with *Toxoplasma gondii,* are life-threatening complications in the HIV-immunocompromised host and require early diagnosis to optimize treatment (Wang *et al.*, 1995). The protozoans *Cryptosporidium* and *Isospora* have long been recognized as important causes of chronic diarrhoea in AIDS patients (DeHovitz *et al.*, 1986; Lopez & Gorbach, 1988).

Cytomegalovirus infections of the retina and intestines are often seen late in the course of HIV infection. Cytomegalovirus retinitis and colitis are much more difficult to prevent or treat than PCP and some other parasitic and bacterial infections. Therefore, as a proportion of AIDS diagnoses, their frequency has increased in developed countries, while that of PCP has decreased (Katz *et al.*, 1994).

Bacterial infections are frequent in HIV-infected persons, especially community-acquired pneumonia (Caiaffa *et al.*, 1993; Holmberg *et al.*, 1995b) and septicaemia (Whimbey *et al.*, 1986). Recurrent salmonellosis, an AIDS-defining condition, is an important, if less frequent, enteric infection (Lopez & Gorbach, 1988).

Progressive multifocal leukoencephalopathy is caused by the JC virus (Fong *et al.*, 1995). Focal neurological manifestations can be caused by opportunistic infections, such as toxoplasmosis, or by lymphoma. HIV can also directly cause peripheral nervous system abnormalities, such as sensory neuropathy, and AIDS-related dementia in late HIV infection (Simpson & Tagliati, 1994).

Wasting syndrome (DuPont & Marshall, 1995; Grunfeld, 1995), originally referred to as 'Slim disease' in Africa (Serwadda *et al.*, 1985), has long been recognized as a major cause of HIV-related morbidity and mortality. Reduced calorific intake is the prime determinant of this weight loss (Macallan *et al.*, 1995).

Paediatric AIDS has a somewhat different clinical profile, with an increased incidence of lymphocyte intestinal pneumonia in HIV-infected children (Horowitz & Pizzo, 1990; Chintu *et al.*, 1993).

1.4.5 *Long-term non-progressors*

'Long-term non-progressors', 'healthy long-term survivors' and other such terms describe persons known to be infected for several years but who have no or minor symptoms of HIV infection and who have $CD4^+$ T-cell counts that are normal or near normal (e.g., more than 500 $CD4^+$ T-cells/mm^3). About 5–10% of HIV-infected persons remain asymptomatic and maintain $CD4^+$ T-lymphocyte counts above 500 cells/mm^3 for 10 or more years (Buchbinder *et al.*, 1994). With time after infection, the percentage of

long-term non-progressors declines (Baltimore, 1995). While few in number, these persons have become the focus of much current research from two broad points of view: the host and the virus.

Most research into host factors has focused on factors associated with preserved immune function, and indicates that non-progressors, compared with other HIV-infected persons, have higher $CD8^+$ T-lymphocyte counts and lower antigenaemia and viral load (Lifson *et al.*, 1991; Buchbinder *et al.*, 1994; Cao *et al.*, 1995; Hogervorst *et al.*, 1995; Pantaleo *et al.*, 1995). $CD8^+$ T-cell function appears to be important in the control of viral replication (Lifson *et al.*, 1991; Landay *et al.*, 1993), while the role of neutralizing antibodies is unclear (Hogervorst *et al.*, 1995).

Viral variants may have different pathogenicity. Evidence of at least one less virulent strain of HIV-1 with a variant form of *nef* gene has come from a cluster of long-term healthy survivors infected from a single blood donor (Deacon *et al.*, 1995).

1.4.6 *Human immunodeficiency virus type 2 (HIV-2)*

HIV-2 has been recovered mainly from patients in west Africa. A seroconversion syndrome has also been described in relation to HIV-2 infection (Besnier *et al.*, 1990). Symptomatic patients usually have been described as having chronic diarrhoea, weight loss, lymphadenopathy and tuberculosis. However, HIV-2-infected persons can have the same immunological and clinical spectrum of disease as HIV-1 (Clavel *et al.*, 1987; Marlink *et al.*, 1988; Nauclér *et al.*, 1989; Odehouri *et al.*, 1989). Sexual and mother–child transmission seem to be less efficient (Matheron *et al.*, 1990; Markowitz, 1993; Kanki *et al.*, 1994). There is evidence that HIV-2 is less pathogenic than HIV-1. HIV-2-infected patients may have longer incubation periods between infection and AIDS-defining conditions than do HIV-1-infected patients (Burin Des Roziers *et al.*, 1987; Pepin *et al.*, 1991; Markowitz, 1993; Whittle *et al.*, 1994).

1.5 Control and prevention

1.5.1 *Behavioural prevention*

In the absence of a vaccine, behavioural change remains necessary to stem the worldwide HIV epidemic. To prevent sexual transmission, two general categories of preventive activity are usually urged: reducing the number of sexual partners and modifying the types of sexual contact; and the use of condoms.

Protection of sex partners from exposure to semen, blood and vaginal fluid during intercourse can be accomplished by the consistent and correct use of condoms, and this recommendation has been promulgated worldwide (Choi & Coates, 1994; Johnson, 1994; Stryker *et al.*, 1995). Other strategies to minimize risk of infection may be useful, such as penile withdrawal prior to ejaculation (de Vicenzi *et al.*, 1994) and the use of the vaginal pouch (or 'female condom') (Farr *et al.*, 1994).

Various programmes to change behaviour — such as increasing the use of condoms — have been effective to varying extents (Choi & Coates, 1994; Kelly *et al.*, 1994; Moore *et al.*, 1994; Stryker *et al.*, 1995). The greatest change has occurred among older

European and American homosexual men, who dramatically decreased their sexual exposures and HIV infection rates as early as the mid-1980s (Winkelstein *et al.*, 1987; Centers for Disease Control and Prevention, 1992c). The change in sexual behaviour and use of condoms among heterosexual men and women has been more modest (Catania *et al.*, 1992; Diaz *et al.*, 1994).

Empirical evidence indicates that behaviourally based HIV prevention programmes have had a favourable impact in specific populations, especially when delivered with sufficient resources, intensity and cultural sensitivity (Holtgrave *et al.*, 1995; Office of Technology Assessment, 1995). However, outcomes of prevention programmes, such as partner notification (Potterat *et al.*, 1989), have not been well evaluated. Some programmes or measures have been evaluated, and found to be ineffective, for example, programmes for counselling and testing (Higgins *et al.*, 1991a) and mandatory premarital testing for HIV (Turnock & Kelly, 1989).

Behavioural interventions are thought to have reduced the spread of HIV among intravenous drug users who share needles, syringes and other blood-tainted effects (Booth & Watters, 1994; Chitwood, 1994; Watters, 1994). Firstly, treatment for drug dependence can reduce the number of intravenous drug users in a community and so, presumably, decrease HIV transmission (Sisk *et al.*, 1990). Secondly, previously used needles may be disinfected, usually with bleach, but the contact times with bleach that are necessary to reduce or eliminate HIV in injection equipment are considerably longer than those generally applied by intravenous drug users (Centers for Disease Control and Prevention, 1994b; Garza *et al.*, 1994; Gleghorn *et al.*, 1994). Thus, it is not clear that bleach disinfection has reduced the risk of HIV infection among intravenous drug users (Booth & Watters, 1994; Titus *et al.*, 1994).

Recent attention has focused on the effectiveness of needle and syringe exchange and distribution programmes. There is accumulating evidence that providing sterile needles reduces the transmission of HIV among intravenous drug users (Donoghoe *et al.*, 1989; Hart *et al.*, 1989; Hartgers *et al.*, 1989; Stimson, 1989; van Ameijden *et al.*, 1994; Heimer *et al.*, 1994; Watters *et al.*, 1994; Centers for Disease Control and Prevention, 1995c; Hagan *et al.*, 1995). A recent international comparison of cities with and without needle exchange programmes supports the effectiveness of such measures (Feachem *et al.*, 1995). To provide sterile needles for injection, the deregulation of the sale and possession of needles and syringes has been advocated (Des Jarlais *et al.*, 1994; Vlahov, 1995). However, some countries in which disposable syringes are commercially available and cheap, such as Italy, have nevertheless experienced a high prevalence of HIV among intravenous drug users.

1.5.2 *Screening*

Antibody-test screening of all blood or plasma donors has been universal in developed countries since the mid-1980s and has resulted in a marked reduction in HIV transmission by blood transfusion or use of clotting factor concentrates. For example, it has been estimated that among 12 million blood donations collected in the United States, only 18–27 are now infectious (Lackritz *et al.*, 1995) because the donors were in the

'window period'. Blood transfusion has remained a major mode of HIV transmission in some developing countries, where screening of blood donors is not universal (N'tita *et al.*, 1991; Vos *et al.*, 1994).

Several countries recommend the counselling and voluntary screening of pregnant women for HIV infection (Centers for Disease Control and Prevention, 1995d) to allow them to take informed decisions about continuation of pregnancy, and enable suitable medical care and interventions to reduce the risk of vertical transmission to be applied. The rationale for screening mothers antenatally has received additional impetus from the finding that zidovudine (also called azidothymidine, AZT) taken by infected pregnant women and their newborns substantially reduces the probability of mother-to-child transmission (Connor *et al.*, 1994; Centers for Disease Control and Prevention, 1995e). Studies of simplified treatment protocols, particularly for use in developing countries, are being conducted (Dabis *et al.*, 1995).

1.5.3 *Treatment*

Zidovudine may reduce the levels of HIV in the semen of HIV-infected men (Anderson *et al.*, 1992) and hence its infectiousness; similarly, women taking zidovudine may be less likely to transmit HIV to their HIV-uninfected regular male partners (Nicolosi *et al.*, 1994b). However, the evidence that use of zidovudine prevents the sexual transmission of HIV should be considered as tentative and zidovudine-resistant strains of HIV are now being identified in newly acquired infections.

The literature on the efficacy of zidovudine and other reverse transcriptase inhibitors (e.g., didanosine (also called dideoxyinosine, ddI); dideoxycytidine (also called zalcitabine, ddC); stavudine) in prolonging survival of patients with HIV infection and AIDS is extensive. Briefly, improvements in survival time after AIDS diagnosis have been observed in America and Europe (Fischl *et al.*, 1987; Lafferty *et al.*, 1991; Jacobson *et al.*, 1993; Whitmore-Overton *et al.*, 1993; Blum *et al.*, 1994; Lundgren *et al.*, 1994). However, most recent reports indicate that zidovudine monotherapy is of modest benefit in the prolongation of this incubation time (Holmberg & Byers, 1993; Concorde Coordinating Committee, 1994; Volberding *et al.*, 1994, 1995). It has been suggested that improved incubation and survival times may be more attributable to improved prophylaxis and treatment of *Pneumocystis carinii* pneumonia than to use of zidovudine and other antiretroviral drugs (Lundgren *et al.*, 1994).

Antiretroviral therapy is in constant evolution. Chemotherapeutic agents have been evaluated on the basis of their ability to reduce viral load, as measured by the level of HIV-1 RNA in plasma (O'Brien *et al.*, 1996). A number of promising new agents may retard the development of HIV disease and prolong survival (Hirsch & D'Aquila, 1993; Saag *et al.*, 1993; Sande *et al.*, 1993). At present, interest has centred on the so-called 'protease inhibitors' (Danner *et al.*, 1995; Kitchen *et al.*, 1995), on combination therapy with two or more antiretroviral drugs used together or in rotation (Fauci, 1992; Kahn *et al.*, 1992; Abrams *et al.*, 1994; Yarchoan *et al.*, 1994; Collier *et al.*, 1996) and on the use of ILs (Schnittman *et al.*, 1994).

1.5.4 *Prospects for vaccines*

The development of a safe, effective and cheap preventive vaccine for HIV-1 or HIV-2 faces many obstacles: the considerable antigenic variability of the virus; the integration of proviral DNA in the host gene; the viability of the virus both inside and outside cells; the mucosal (sexual) and blood-borne modes of transmission; and the persistent nature of the infection even in the presence of host immunity (Girard, 1995; Graham & Wright, 1995; Hilleman, 1995). Nevertheless, more than 20 candidate vaccines have undergone preclinical evaluation for safety and immunogenicity in about 2000 volunteers. Several have entered phase I clinical testing in uninfected volunteers, and a few vaccines are now being evaluated in phase II studies in larger numbers of persons at risk for HIV infection. Candidate vaccines have been of various types, including whole killed virus and recombinant live vectors (e.g., canary pox) expressing antigens. Most of those still under consideration rely on immunization with recombinant or synthetic HIV peptides or envelope proteins such as gp120 or gp160 (see Section 1.1.7). These may induce neutralizing antibodies or lymphoproliferative responses (e.g., cytotoxic T-cell activity), but only variably and, even then, only to laboratory-adapted HIV-1 strains (not primary or wild-type isolates) (Johnston *et al.*, 1993; Dolin, 1995). Furthermore, several 'breakthrough' HIV infections have been documented in volunteers who received partial or complete series of vaccinations (Kahn *et al.*, 1995). In addition to immunization with antigenic peptides or proteins, another direction of research has been the use of live, attenuated mutant virus, which has provided immunological protection in some simian models. However, serious concerns about the use of live, attenuated virus vaccines in humans remain because viruses with deleted *nef* gene have been shown to cause disease in neonatal macaques (Baba *et al.*, 1995).

1.5.5 *Other approaches*

There is considerable interest in the safety and efficacy of agents such as Nonoxyl 9 (Elias & Meise, 1993) and dextrin sulfate (Stafford *et al.*, 1995) as vaginal virucides to protect against heterosexual transmission of HIV-1 and HIV-2. A perceived advantage of such agents over condoms is that they may be used unobtrusively by women in situations where condom usage is not acceptable to either or both partners.

Recent data from Tanzania show that HIV transmission can be reduced by effective, syndromic treatment of other sexually transmitted diseases (Grosskurth *et al.*, 1995; Hayes *et al.*, 1995; Dik *et al.*, 1995; Foulkes *et al.*, 1995; O'Reilly *et al.*, 1995; Rygnestad *et al.*, 1995; Whitaker & Renton, 1995).

2. Studies of Cancer in Humans

Most epidemiological studies of HIV have not differentiated between HIV-1 and the rarely seen HIV-2, which occurs almost exclusively in West Africa. In this section, unless specifically designated as HIV-2, the term HIV should be assumed to refer to HIV-1.

As described in Section 1.1.3, several different clades of both HIV-1 and HIV-2 have been defined. To date, there are no conclusive epidemiological data on the association between infection with specific clades and the occurrence of cancer in humans.

2.1 Kaposi's sarcoma

Kaposi's sarcoma is an AIDS-defining condition (see Section 1.4.4).

2.1.1 *Pathology and clinical disease*

In 1872, Dr Moriz Kaposi, a Hungarian dermatologist, first described an idiopathic, multiple, pigmented sarcoma, now called 'classic' Kaposi's sarcoma (Kaposi, 1872; Breimer, 1994). For many years, Kaposi's sarcoma was thought to be a lesion predominantly affecting elderly men of Mediterranean and eastern European origin (Dörffel, 1932; Landman *et al.*, 1984; Franceschi & Geddes, 1995). However, in the 1950s, as cancer registries became established in Africa, it was found that Kaposi's sarcoma comprised up to 8% of malignancies in some sub-Saharan regions, with an unusual endemic focus in parts of central Africa (Oettlé, 1962; Hutt & Burkitt, 1965). This 'endemic' Kaposi's sarcoma, like classic Kaposi's sarcoma, predominated in elderly men, but also occasionally affected children. In the 1960s and 1970s, Kaposi's sarcoma constituted up to 5% of cancers among immunosuppressed patients who had organ transplants (Penn, 1983, 1988a,b). In the early 1980s, a fourth variant of Kaposi's sarcoma, the so-called 'epidemic' Kaposi's sarcoma, heralded the onset of the AIDS epidemic in the United States (Hymes *et al.*, 1981).

The main pathological features of Kaposi's sarcoma are described in Section 4.2.1. The histopathology is identical in all variants (Templeton, 1981; Cockerell, 1991).

(*a*) *Clinical disease in HIV-seronegative individuals*

Classic or endemic Kaposi's sarcoma predominantly affects the skin of the lower limbs, and internal organs are rarely involved. The disease typically follows an indolent course, with patients surviving for an average of 10–15 years (Tappero *et al.*, 1993). Young children tend to have more severe disease than adults, often affecting the lymphatic system and internal organs rather than the skin, and shorter survival (Oettlé, 1962; Ziegler & Katongole-Mbidde, 1996). Adults develop plaques or nodules that may progress to sarcomatous or deeply infiltrative lesions (Taylor, 1971; Templeton, 1981). Kaposi's sarcoma in immunocompromised individuals (mainly transplant recipients and long-term users of steroids and cytotoxic drugs) often involves internal organs, lymph nodes and the face, mimicking the 'epidemic' type (Tappero *et al.*, 1993). In transplant recipients, Kaposi's sarcoma appears before most other tumours and may regress completely when immunosuppressive therapy is terminated (Penn, 1988a,b).

(*b*) *Clinical disease in HIV-seropositive individuals*

Kaposi's sarcoma may occur at milder levels of immunosuppression than other AIDS-defining illnesses. Lesions are usually multiple, progress rapidly, and may affect any area of the skin as well as internal organs. The tumours frequently begin as dusky-

red or violet macules, progressing over weeks or months to raised, painless, firm nodules and plaques. Although the tumour may affect the legs, as seen with classic Kaposi's sarcoma, lesions on the trunk, arms, genitalia and face are also common (Smith & Spittle, 1987). Lymph nodes and the oral cavity, most notably the palate, may be extensively involved. Oral Kaposi's sarcoma is often associated with involvement elsewhere in the gastrointestinal tract (Levine, 1993; Regezi *et al.*, 1993). Pulmonary Kaposi's sarcoma generally presents with shortness of breath and cough and is clinically difficult to distinguish from other pulmonary complications of AIDS (Levine, 1993).

Median survival following diagnosis of AIDS-related Kaposi's sarcoma is 14–18 months, a relatively long survival compared with other AIDS-defining illnesses (Casabona *et al.*, 1993; Jacobson *et al.*, 1993; Lundgren *et al.*, 1994; 1995; Luo *et al.*, 1995).

2.1.2 *Descriptive epidemiology of Kaposi's sarcoma*

(*a*) *Demographic variations: age and sex*

Formerly a tumour predominantly affecting the elderly (Oettlé, 1962; Templeton, 1981; Hutt, 1984; Geddes *et al.*, 1994; Hjalgrim *et al.*, 1996), Kaposi's sarcoma has shown a substantial alteration in age distribution in recent years, both in Africa and in Europe and the United States. In developed countries, the median age is now in the late thirties.

Age-specific incidence rates of Kaposi's sarcoma in Uganda and Zimbabwe in the early 1990s show a modest peak in children aged 0–4 years, a decline until age 15, and then the main peak at age 35–39 in men and age 25–29 in women (Wabinga *et al.*, 1993; Bassett *et al.*, 1995). In Europe and the United States, childhood Kaposi's sarcoma is very rare, only 32 cases having being recorded up to 1993 (Serraino & Franceschi, 1996a). Many of the European cases were in Romania, where intravenously acquired HIV infection had previously been documented (Hersh *et al.*, 1991; Orlow *et al.*, 1993).

Before the advent of AIDS, Kaposi's sarcoma was generally more frequent in men than in women, except among transplant recipients and children (Qunibi *et al.*, 1993; Serraino & Franceschi, 1996a,b), with a male : female ratio in developed countries as high as 15 : 1, although later studies found ratios of 2–3 : 1 in persons thought to be HIV-seronegative, possibly reflecting improved case ascertainment in women (Biggar *et al.*, 1984a; Franceschi & Geddes, 1995; Hjalgrim *et al.*, 1996). In Africa, male : female ratios above 10 from earlier surveys (Wahman *et al.*, 1991), have declined to about 3 : 1 more recently (Wabinga *et al.*, 1993; Bassett *et al.*, 1995; Newton *et al.*, 1996).

(*b*) *Geographical variations*

The incidence of Kaposi's sarcoma exhibits wide geographical variation.

In the 1960s, it represented up to 8% of all malignancies in some parts of sub-Saharan Africa (Table 6; Oettlé, 1962; Templeton, 1981; Hutt, 1984). Elsewhere, relatively high incidence rates were recorded in Israel (1970–79, 1.5/100 000 in both sexes combined; Landman *et al.*, 1984) and Italy (1976–84, 1.05/100 000 in men, 0.27/100 000 in women;

Geddes *et al.*, 1994), particularly in the south. The rates were lower in the United States (1973–79, 0.29/100 000 in men and 0.07/100 000 in women; Biggar *et al.*, 1984a) than in Europe (Grulich *et al.*, 1992; Hjalgrim *et al.*, 1996).

Table 6. Relative frequencies of Kaposi's sarcoma among all cancers in various areas of Africa

Reference	Location	Year(s) of study or report	Percentage of all cancers		
			Men	Women	Both
Oettlé (1962)	Belgian Congo	1956–57	–	–	9–13
	French Equatorial Africa	1953	–	–	5
	French West Africa	1954	–	–	1
	Gold Coast	1956	–	–	1
	Kenya	1948–61	–	–	2–4
	Mozambique	1958	–	–	2
	Natal	1957	–	–	1
	Nigeria	1934–44	–	–	2
	Rhodesia	1949	–	–	1
	South Africa	1960, 51	–	–	1–3
	Tanganyika	1960	–	–	3
	Tunisia	1960	–	–	< 1
Hutt & Burkitt (1965)	Uganda	1964	–	–	4
Bayley (1984)	Zaire	1983	–	–	9
Melbye *et al.* (1987)	Zaire	1984	16	–	–
Otu (1986)	Nigeria	1986	–	–	15–20
Ngendahayo *et al.* (1989)	Rwanda	1979–86	–	–	6
Wabinga *et al.* (1993)	Uganda	1989–91	49	18	–
Bassett *et al.* (1995)	Zimbabwe	1990–92	23	10	–
Newton *et al.* (1996)	Rwanda	1991–93	10	3	–
Patil *et al.* (1995)	Zaire	1980–89	–	–	7.0
Sitas *et al.* (1996)	South Africa				
	Black	1990–91	0.54	0.14	0.3
	White	1990–91	0.12	0.03	0.1

Since the advent of the AIDS epidemic, Kaposi's sarcoma has become even more common in parts of Africa (Table 6; Ziegler, 1993; Patil *et al.*, 1995). The prevalence of Kaposi's sarcoma in different areas of the world reflects both the proportion of homosexual and bisexual men and the proportion of people from high-risk countries such as Africa (see Section 2.1.5(*a*)).

Although widespread in parts of Africa before the AIDS epidemic, endemic Kaposi's sarcoma was not associated with HIV infection (Biggar *et al.*, 1984b). In some countries, modest increases in the incidence of Kaposi's sarcoma were already occurring before the onset of the AIDS epidemic (Dictor & Attewell, 1988; Hjalgrim *et al.*, 1996).

Volcanic dust has been proposed to contribute to the etiology of Kaposi's sarcoma. The evidence supporting this hypothesis came largely from the ecological observation that, for endemic Kaposi's sarcoma, the areas of highest incidence are located in seismically active regions around the Rift Valley of east Africa and (to a lesser extent) parts of Italy and Greece (Ziegler, 1993). One report described a two-fold increase (of borderline significance) in the risk for endemic Kaposi's sarcoma in a volcanic area of Italy (Montella *et al.*, 1996). However, many areas of endemic Kaposi's sarcoma are not volcanic regions. In a study of the distribution of endemic Kaposi's sarcoma in Italy, residence in flat lands and former malaria areas was a risk factor (Geddes *et al.*, 1995). [The Working Group noted that these hypotheses cannot explain the higher risk among homosexual men than other HIV-infected persons.]

(*c*) *Temporal changes*

The incidence of Kaposi's sarcoma increased dramatically with the arrival of the HIV epidemic. This increase is still being observed in some developing countries (Wabinga *et al.*, 1993; Bassett *et al.*, 1995) and some southern European countries, but the incidence appears to have reached a plateau in other developed countries, such as the United States (Dal Maso *et al.*, 1995).

2.1.3 *Descriptive epidemiological studies*

(*a*) *Studies in men in relation to marital status*

Studies of various types have attempted to quantify the incidence of Kaposi's sarcoma in groups affected by the HIV epidemic. Never-married young men were used as a surrogate representing homosexual men, who had the highest incidence of HIV infection in the populations studied (Table 7).

From 1973–80 to 1981–82, a significant increase in the odds ratio (OR) for Kaposi's sarcoma among never-married men compared to ever-married men was observed in San Francisco, CA, United States: 51.8 (95% confidence interval (CI)), 18.6–143.6), and in other areas covered by the Surveillance, Epidemiology and End Results (SEER) Program: 18.6 (95% CI, 2.2–154.5) (Biggar *et al.*, 1985). In San Francisco County, an OR of approximately 2000 was estimated in young single men when comparing data from 1973–79 and 1982. No similar increase was recorded among ever-married men. By 1984, Kaposi's sarcoma represented 56% of all malignancies among young never-married men in San Francisco city. In single men, the relative risk for Kaposi's sarcoma in 1984 compared with 1973–78 approached 2500 (Biggar *et al.*, 1987). In Los Angeles County, CA, United States, for never-married men, the proportionate OR for Kaposi's sarcoma in 1983–85 was nearly 100 times greater than that of 1972–79 (Bernstein *et al.*, 1989).

In 1985–87 in San Francisco County, compared with 1973–78, the incidence of Kaposi's sarcoma had increased over 5000-fold in single men under 50 years old and 200-fold in young married men. In the nine SEER areas combined (including low AIDS-incidence areas), the corresponding increase in young single men was 733-fold (Rabkin *et al.*, 1991).

Table 7. Increase in risk for Kaposi's sarcoma among never-married men since the beginning of the AIDS epidemic in the United States

Reference	Study area	Control group	Time period	Risk measure		95% CI[a] or χ^2_1 for trend
Biggar *et al.* (1985)	San Francisco County	Never-married men aged 20–49, 1973–79	1982	OR	2043	$p < 0.001$
	San Francisco area	Never-married men aged 20–49, 1973–80	1981–82	OR	52	19–144
	Other SEER areas	Never-married men aged 20–49, 1973–80	1981–82	OR	19	2–155
Biggar *et al.* (1987)	San Francisco City	Never-married men aged 20–49, 1973–78	1984	OR	2479	$p < 0.0001$
	San Francisco area	Never-married men aged 20–49, 1973–78	1984	OR	182	$p = 0.0001$
Rabkin *et al.* (1991)	San Francisco County	Never-married men aged 20–49, 1973–78	1985–87	RIR	5060	$p < 0.001$
	Total SEER areas	Never-married men aged 20–49, 1973–78	1985–87	RIR	733	$p < 0.002$
Bernstein *et al.* (1989)	Los Angeles County	Never-married men aged 18–54, 1972–79	1983–85	POR	96	$p < 0.0001$
Biggar *et al.* (1989)	Manhattan	Never-married men aged 20–49, 1973–76	1985	OR	1851	$p < 0.0001$
	Rest of New York City	Never-married men aged 20–49, 1973–76	1985	OR	484	$p < 0.0001$
	New York State	Never-married men aged 20–49, 1973–76	1985	OR	109	$p < 0.0001$

CI, confidence interval; OR, odds ratio; RIR, relative incidence ratio; SEER, Surveillance, Epidemiology and End Results; POR, proportionate OR

[a] In the absence of 95% CI, p value or χ^2_1 for trend is given

Rabkin and Yellin (1994) examined the incidence of Kaposi's sarcoma in a population-based study of never-married men, aged 25–54 years, in San Francisco, of whom an estimated 20 000 (24%) were HIV-seropositive in late 1984. In 1988–90, the estimated standardized incidence was 540/100 000, over 20 times higher than the concurrent rate in ever-married men (25/100 000; $p < 0.001$).

In 1985, the OR for Kaposi's sarcoma in single men in Manhattan, NY, United States, compared with the pre-AIDS period (1973–76), was 1851 (Biggar *et al.*, 1989). ORs were somewhat lower for the rest of New York City (484) and rest of New York State (109).

In New York City, small but consistent increases in the numbers of cases of Kaposi's sarcoma were seen also among married men and women of the same age group (Biggar *et al.*, 1989). Between 1976–78 (baseline period) and 1987–88, the annual incidence of Kaposi's sarcoma in women aged 20–49 years increased from 0 to 1.8/100 000 in black

women and 0 to 0.8/100 000 in white women in New York City, but did not change in the remainder of New York State (Rabkin *et al.*, 1993a).

(*b*) *Linkage studies between AIDS and cancer registries*

Record linkage between AIDS and cancer registration databases is an alternative methodology for examining associations between HIV infection and cancer in a population (Coté *et al.*, 1995). Such studies are facilitated by the relative completeness of AIDS and cancer registries with respect to Kaposi's sarcoma (Reynolds *et al.*, 1990; Barchielli *et al.*, 1995; Coté *et al.*, 1995). By matching 2528 AIDS registry cases with 62 500 cancer registry cases from the State of Illinois, United States, Coté *et al.* (1991) found a standardized incidence ratio (SIR) of Kaposi's sarcoma in AIDS patients of 972 compared with the general population of Illinois, an area of low risk for AIDS. This ratio was based on 137 linked cases of Kaposi's sarcoma.

Reynolds *et al.* (1993) linked 1454 cases of Kaposi's sarcoma in the California Tumor Registry (active since 1969) with all AIDS cases diagnosed in San Francisco since 1980. Before 1980, Kaposi's sarcoma was very rare. In 1980–87, the relative risk in AIDS patients was 716 compared with the general population.

Similar results have been reported from Italy and Switzerland (Franceschi *et al.*, 1992; Barchielli *et al.*, 1995; Serraino *et al.*, 1995a). Data for children are shown in Table 8 (Serraino & Franceschi, 1996a,b).

2.1.4 *Analytical studies*

(*a*) *Cohort studies*

Veugelers *et al.* (1994) from the Tricontinental Seroconverter Study studied 407 homosexual men with known date of HIV seroconversion, among whom 37 developed Kaposi's sarcoma.

Lundgren *et al.* (1995) studied 687 AIDS patients diagnosed in Denmark up to the end of 1990. Among these, 437 were homosexual or bisexual men who had died at the end of follow-up and 138 had developed Kaposi's sarcoma either at the time of AIDS diagnosis or during follow-up.

Dore *et al.* (1996) carried out a retrospective cohort study of 2580 people diagnosed with AIDS in Australia in 1983–94, among whom Kaposi's sarcoma was the AIDS-defining illness for 451, and among the remaining 2129 patients, Kaposi's sarcoma developed subsequently in 265.

[The Working Group noted that, although none of these studies reported the number of expected cases based on the incidence in the corresponding general population, the high proportions of persons in these cohorts who developed Kaposi's sarcoma must reflect a very high relative risk.]

Table 8. Odds ratio (OR) and 95% confidence interval (CI) for Kaposi's sarcoma (KS) according to selected characteristics and geographical area in children with AIDS, 1981–93

Characteristic	Europe			United States		
	KS/AIDS[a]	OR[b]	95% CI	KS/AIDS[a]	OR[c]	95% CI
Age (years)						
≤ 4[d]	5/3875	1		15/3796	1	
5–12	5/525	12.0	2.22–52.4	7/914	1.95	0.7–5.1
Gender						
Females[d]	3/1920	1		12/2224	1	
Males	7/2480	[1.5	0.3–7.2]	10/2486	0.8	0.3–1.9
Ethnic group						
White[d]		–		5/2136	1	
Black		–		17/2574	2.8	1.0–8.6
Transmission category						
Mother to child[d]	2/1802	1		20/4121	1	
Haemophiliacs and transfused	7/1671	3.13	0.4–162.1	2/523	0.9	0.1–4.2
Period of diagnosis						
≤ 1990[d]	[3/2440]	1		[20/3283]	1	
1991–93	[7/1788]	[2.3]	[0.5–12.5]	[2/1427]	[0.2]	[0.04–1.01]

Modified from Serraino & Franceschi (1996a,b)
[a] Some numbers do not add up to the same total because of missing values.
[b] Adjusted for age and European country
[c] Adjusted for age
[d] Reference category
[ ] calculated by the Working Group

(*b*) *Case–control studies*

Early studies measured the prevalence of antibodies to HIV in AIDS patients, including those with Kaposi's sarcoma, compared with various control groups. These studies established that antibodies to HIV were strongly associated with the development of Kaposi's sarcoma.

HIV infection was found in 11/18 Kaposi's sarcoma patients and in 8/200 control persons with other cancers in Rwanda (relative risk, 35.0; 95% CI, 8.2–206.7) (Newton *et al.*, 1995).

(*c*) *Analytical studies of the relationship between degree of immunosuppression and Kaposi's sarcoma among HIV-infected persons*

Muñoz *et al.* (1993) followed a cohort of HIV-infected homosexual and bisexual men during 1985–91. Among the 873 AIDS cases observed in the cohort, 194 had Kaposi's sarcoma as AIDS-defining illness. A diagnosis of Kaposi's sarcoma was strongly associated with $CD4^+$ T-cell count, with an incidence of 15/100 person-years for those with

$CD4^+$ count below 100 cells/mm^3 to 0.3/100 person-years for those with $CD4^+$ count above 500. Only 7.8% (12/153) of all initial AIDS-defining diagnoses of Kaposi's sarcoma were made in men with a $CD4^+$ count above 500 cells/mm^3. These data clearly show that the risk for Kaposi's sarcoma among AIDS patients is associated with the degree of immunosuppression.

In the early period of the AIDS epidemic, Kaposi's sarcoma was considered to be a relatively early manifestation of AIDS compared with, for example, lymphomas and many opportunistic infections. In recent years, Kaposi's sarcoma has been reported to occur later in the course of HIV disease than in the past. Lundgren *et al.* (1995) documented a significant decline in median $CD4^+$ count among AIDS patients from Denmark with Kaposi's sarcoma as initial AIDS diagnosis from 96 cells/mm^3 before 1987 to 28 cells/mm^3 in 1989–90.

Very similar results were obtained by Dore *et al.* (1996), who found a significant decline in median $CD4^+$ count for Kaposi's sarcoma patients as initial AIDS diagnosis from 92 cell/mm^3 in 1983–87 to 40 cells/mm^3 in 1991–94 ($p < 0.0005$).

Veugelers *et al.* (1995) studied the AIDS outcomes among 407 homosexual men. Their data showed that HIV-infected men who seroconverted before 1985 did not progress faster to Kaposi's sarcoma than men who seroconverted later.

2.1.5 *Factors influencing the occurrence of Kaposi's sarcoma in HIV-1-infected individuals*

(*a*) *Behavioural cofactors*

(i) *Descriptive studies*

The risk for Kaposi's sarcoma varies greatly with HIV transmission risk group, being particularly high in homosexual and bisexual men (see Tables 9–12, which were produced on the basis of AIDS surveillance data (Dal Maso *et al.*, 1995)). Figure 7 shows that even in young homosexual and bisexual men (aged 13–24 years), there is already an elevated proportion with Kaposi's sarcoma compared with other HIV-transmission groups. Since first homosexual intercourse must have been recent, this finding implies a rapid increase in risk following sexual transmission of the putative Kaposi's sarcoma agent (Franceschi & Serraino, 1995).

Beral *et al.* (1990) found that, among 88 739 AIDS patients in the United States, 13 616 (15%) developed Kaposi's sarcoma. The proportion varied from 21% in homosexual or bisexual men to 3% in heterosexuals, 2% in intravenous drug users, 3% in transfusion recipients, 1% in haemophiliacs and 1% in children infected by perinatal transmission.

In Spain, Casabona *et al.* (1990) found that, among 1074 AIDS patients, 124 presented with Kaposi's sarcoma: 36% in homosexual or bisexual men, 2% in intravenous drug users and none in 35 heterosexuals, 5 transfusion recipients, 23 haemophiliacs and 33 children infected by perinatal transmission.

Table 9. Numbers and proportions of male AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and HIV transmission group, in Europe and United States, 1981–94

Country[a]	Homo/bisexual men		Intravenous drug users		Heterosexuals				Haemophiliac and transfused		Other/ unknown		All	
	KS cases	(%)[d]	KS cases	(%)[d]	Pattern II countries[b]		Natives		KS cases	(%)[d]	KS cases	(%)[d]	KS cases	(%)[d]
					KS	(%)[d]	KS	(%)[d]						
Austria	106	(20)	2	(1)	0	(0)	3	(4)	0	(0)	9	(6)	120	(11)
Belgium	209	(28)	2	(2)	40	(14)	9	(5)	4	(7)	1	(2)	265	(19)
Denmark	217	(18)	0	(0)	1	(6)	2	(2)	1	(2)	1	(2)	222	(15)
France	5 396	(31)	122	(2)	94	(6)	157	(9)	34	(3)	188	(11)	5 991	(20)
Germany	2 151	(24)	35	(3)	10	(10)	22	(7)	5	(1)	88	(14)	2 311	(20)
Greece	107	(19)	2	(7)	2	(25)	8	(14)	2	(2)	18	(11)	139	(15)
Italy	934	(21)	300	(2)	10	(6)	96	(7)	21	(5)	100	(9)	1 461	(7)
Netherlands	493	(19)	0	(0)	1	(2)	8	(5)	0	(0)	4	(9)	506	(16)
Portugal	216	(28)	15	(2)	0	(0)	55	(12)	3	(3)	13	(14)	302	(15)
Spain	1 333	(26)	217	(1)	0	(0)	85	(5)	10	(1)	91	(5)	1 736	(7)
Sweden	134	(18)	0	(0)	4	(8)	5	(7)	1	(2)	0	(0)	144	(14)
Switzerland	480	(26)	28	(2)	6	(12)	38	(11)	2	(3)	9	(11)	563	(16)
UK	1 569	(20)	5	(1)	59	(12)	11	(5)	0	(0)	10	(6)	1 654	(17)
USA White	30 255	(21)	548	(4)	–[c]	–[c]	93	(5)	109	(2)	382	(8)	31 387	(19)
Black	4 198	(10)	711	(2)	–[c]	–[c]	101	(2)	30	(3)	331	(4)	5 371	(6)
Other	5 583	(19)	560	(3)	–[c]	–[c]	67	(4)	30	(4)	204	(6)	6 444	(12)

KS, Kaposi's sarcoma

[a] Only countries with > 100 cases of Kaposi's sarcoma over the period 1981–94 are included.

[b] Individuals originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which heterosexual transmission has predominated and continues to)

[c] Data not available

[d] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective risk group

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 10. Numbers and proportions of female AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and HIV transmission group, in Europe and United States, 1981–94

Country[a]	Intravenous drug users		Heterosexuals		Haemophiliacs and transfused		Other/ unknown		All	
	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]	KS cases	(%)[b]
Belgium	1	(3)	22	(7)	2	(4)			25	(5)
France	33	(1)	83	(3)	16	(2)	6	(1)	138	(2)
Italy	55	(2)	33	(2)	3	(2)	13	(4)	104	(2)
Spain	55	(1)	16	(7)	2	(1)			74	(1)
UK			42	(7)	1	(1)			43	(5)
US White	60	(1)	42	(1)	18	(1)	14	(2)	134	(1)
Black	136	(1)	48	(1)	9	(1)	46	(1)	250	(1)
Other	56	(1)	37	(1)	5	(1)	4	(1)	103	(1)

KS, Kaposi's sarcoma

[a] Only countries with > 25 cases over the period 1981–94 are included.

[b] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective risk group

[c] Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

In the United Kingdom, Beral *et al.* (1991a) found that, among 2830 AIDS patients, 566 developed Kaposi's sarcoma. The proportion varied from 23% in homosexual or bisexual men and 10% in heterosexuals to 0% in 83 intravenous drug users, 47 transfusion recipients, 163 haemophiliacs and 23 children infected by perinatal transmission.

European (Serraino *et al.*, 1992a; Franceschi *et al.*, 1995b; Serraino *et al.*, 1995b) and Australian (Elford *et al.*, 1993) surveillance data have confirmed that Kaposi's sarcoma is more common among homosexual and bisexual men and women who reported sexual rather than parenteral exposure to HIV. This finding is particularly notable since a high proportion of transfusion-associated AIDs cases have received blood from homosexual or bisexual men, so that even massive blood contact does not appear to increase the risk as much as sexual contact (Busch *et al.*, 1991).

Among people who acquired HIV by heterosexual contact, the risk for developing Kaposi's sarcoma varies according to country of origin: Kaposi's sarcoma occurred in 18% of AIDS cases in Rwanda (Van de Perre *et al.*, 1984), 16% in Zaire (Piot *et al.*, 1984), 13% of infected Africans resident in Belgium (Clumeck *et al.*, 1984), 8% of infected Africans resident in the United States, 6% of AIDS cases in Haitians resident in

the United States and 14% of infected Africans resident in the United Kingdom, as compared to 2–5% of AIDS patients in the United States or Europe (Beral *et al.*, 1990, 1991a) [Data calculated by Beral (1991a) from the original papers.]

Table 11. Numbers and proportions of AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and year of AIDS diagnosis, among homosexual and bisexual men in Europe and the United States, 1981–94

Country[a]	Year of diagnosis											
	Pre-1985		1985–86		1987–88		1989–90		1991–92		1993–94	
	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]
Austria	6	50	5	22	18	20	17	14	35	24	25	18
Belgium	4	29	15	35	30	29	41	23	64	29	55	28
Denmark	11	31	22	24	34	19	47	17	54	19	49	16[b]
France	107	45	485	41	968	33	1274	31	1353	30	1209	28[b]
Germany	53	39	227	36	420	26	538	25	547	24	366	17[b]
Greece			4	17	12	17	16	14	40	24	35	21
Italy	8	38	39	22	126	26	202	21	263	21	296	19[b]
Netherlands	17	35	44	24	97	21	115	18	135	19	85	15[b]
Portugal	3	100	13	36	29	30	46	24	77	32	48	24
Spain	12	60	54	33	181	29	313	25	429	27	344	22[b]
Sweden	4	25	22	30	25	21	31	17	33	21	19	10[b]
Switzerland	14	44	63	40	102	31	106	24	107	22	88	22[b]
UK	54	39	169	28	276	21	315	19	374	18	381	19[b]
USA												
White	2525	44	4603	29	6485	22	7260	21	7043	18	2339	15[b]
Black	249	20	460	13	741	10	1091	10	1112	8	545	8[b]
Other	292	32	678	26	1080	21	1370	19	1522	17	641	14[b]

KS, Kaposi's sarcoma

[a] Only countries with > 100 cases of Kaposi's sarcoma over the period 1981–94 are included.

[b] χ^2_1 for trend, > 3.84; $p < 0.05$

[c] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective calendar period

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 12. Numbers and proportions of AIDS cases with Kaposi's sarcoma as AIDS-defining condition, by country and year of AIDS diagnosis, among men (other than homosexual and bisexual) and women in Europe and the United States, 1981–94

Country[a]	Year of diagnosis											
	Pre 1985		1985–86		1987–88		1989–90		1991–92		1993–94	
	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]	KS cases	%[c]
Men												
Belgium	8	12	8	14	13	14	9	8	10	6	8	5[b]
France	12	12	34	9	94	6	119	4	171	5	165	4[b]
Germany	6	16	13	9	37	8	28	4	44	6	32	5[b]
Italy	2	10	20	6	69	4	113	3	149	3	174	3[b]
Portugal			2	8	7	8	17	9	14	4	46	7
Spain	4	9	8	2	44	2	81	2	130	2	136	2
UK			2	2	8	4	15	4	31	6	29	5
USA												
White	40	7	83	5	165	4	272	5	349	5	223	5
Black	76	6	104	4	174	3	274	3	327	2	218	2[b]
Other	29	6	65	4	143	3	200		283	4	141	3[b]
Women												
France	3	8	12	5	22	3	28	2	36	2	37	2[b]
Italy			6	5	12	2	22	2	19	1	45	2
Spain	1	14	4	4	10	2	15	1	17	1	27	1
UK	3	43	1	5			5	3	18	6	15	4
USA												
White	17	9	24	3	26	1	39	1	48	1	21	1[b]
Black	23	5	28	2	56	2	83	1	107	1	65	1[b]
Other	1	1	17	3	29	2	41	2	52	2	30	1

KS, Kaposi's sarcoma

[a] Only countries with > 40 cases of Kaposi's sarcoma in each group over the period 1981–94

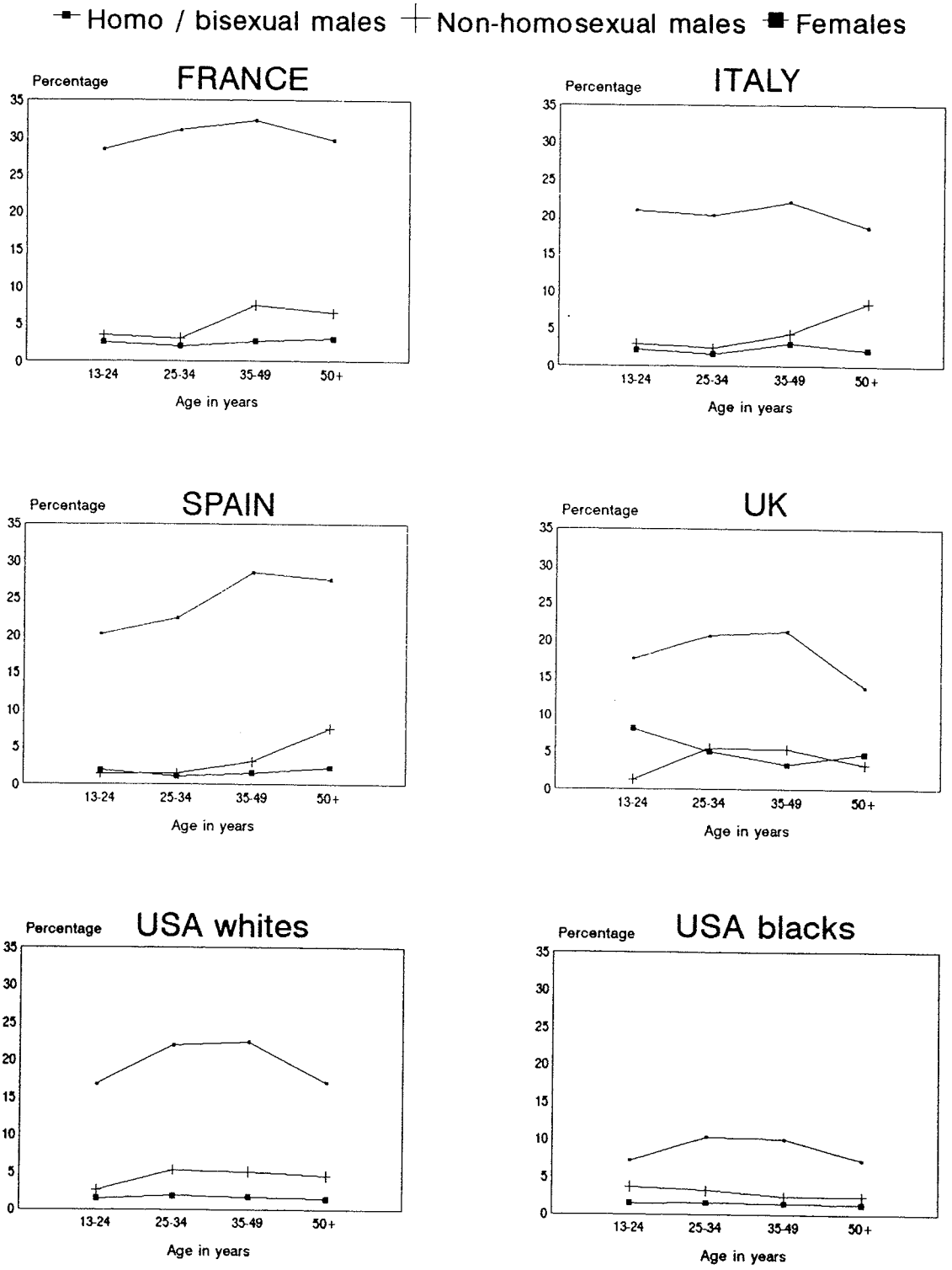
[b] χ^2_1, for trend, > 3.84; $p < 0.05$

[c] Number of Kaposi's sarcoma cases as percentage of total AIDS cases in the respective calendar period

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

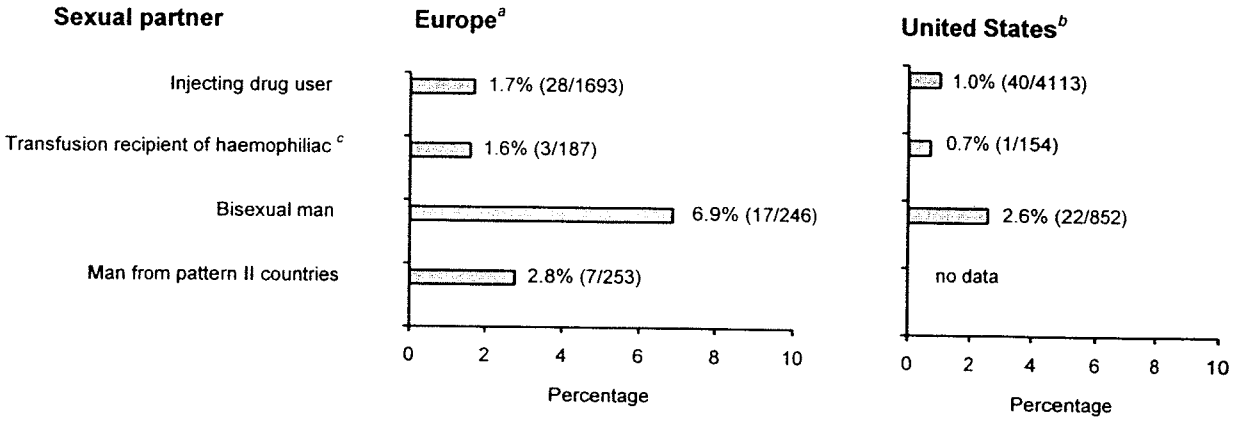
In addition, the proportion of sexually infected female AIDS patients presenting with Kaposi's sarcoma was highest in those whose reported sexual partners were bisexual men (2.6% in the United States, Peterman *et al.*, 1993; 6.9% in Europe, Serraino *et al.*, 1995b) (Figure 8).

Figure 7. Percentage of Kaposi's sarcoma as AIDS-defining illness by age in homosexual and non-homosexual males and females in selected European countries and the United States (whites and blacks), 1981–94



Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Figure 8. Percentage of Kaposi's sarcoma in women who acquired AIDS via heterosexual contact by their sexual partner's reported HIV-transmission group, Europe, 1981-93 and United States, [1981-91]



Pattern II countries: Extensive spread of HIV began in the mid-to-late 1970s or early 1980s. Heterosexual transmission has predominated and continues to.

[a] Modified from Serraino *et al.* (1995b)

[b] Modified from Peterman *et al.* (1993)

[c] In United States, transfusion recipient of haemophiliac. In Europe, blood recipient

(ii) *Analytical studies*

A number of studies have contrasted the sexual practices of homosexual men with Kaposi's sarcoma with those of men with opportunistic infections or other manifestations of AIDS (Tables 13 and 14).

Several studies have reported on the number of sexual partners among homosexual and bisexual men with Kaposi's sarcoma compared with homosexual and bisexual men with other AIDS manifestations (Table 13). Most of these studies (Haverkos *et al.*, 1985; Goedert *et al.*, 1987; Archibald *et al.*, 1990; Armenian *et al.*, 1993), but not all (Lifson *et al.*, 1990a,b), found that the Kaposi's sarcoma patients had a higher number of sexual partners. Goedert *et al.* (1987) also reported that Kaposi's sarcoma patients had more sexually transmitted diseases.

Similar studies have been undertaken of insertive oral–anal contact among Kaposi's sarcoma patients compared with men with other AIDS manifestations. Some studies (Archibald *et al.*, 1990; Beral *et al.*, 1992; Darrow *et al.*, 1992), but not all (Lifson *et al.*, 1990b; Elford *et al.*, 1992; Kaldor *et al.*, 1993; Page-Bodkin *et al.*, 1992; Armenian *et al.*, 1993) have found this sexual practice to be more common among Kaposi's sarcoma patients than among other AIDS patients (Table 14).

In conclusion, men who developed Kaposi's sarcoma have tended to be more sexually active, have had more sexually transmitted diseases and had more sexual partners from areas where Kaposi's sarcoma is common. In conjunction with the much higher risk for

Kaposi's sarcoma in homosexual men than in other HIV transmission groups, the data have led some authors to suggest that an infectious and sexually transmitted agent (independent of HIV) is associated with Kaposi's sarcoma. It should be noted that very few data on risk factors for Kaposi's sarcoma are available from Africa.

Table 13. Studies of the association between risk factors and Kaposi's sarcoma in homosexual men

Reference	Risk behaviour	AIDS manifestations	Proportion of cases	
			No.	%
Haverkos *et al.* (1985)	≥ 100 male sexual partners in year before illness	KS	29/47	61
		PCP	6/20	30
Goedert *et al.* (1987)	≥ 100 homosexual partners during the previous year	KS	3/8	38
		PCP	3/10	30
	≥ 3 STDs	KS	1/8	13
		PCP	0/10	
Archibald *et al.* (1990)[a]	> 20 male sexual partners in prior year	KS	19/25	76
		Other infections	25/48	52
	> 20 sexual partners from areas of high risk for KS[b]	KS	14/25	56
		Other infections	10/48	21
Lifson *et al.* (1990a,b)	Median no. of sexual partners: 300	KS	71 cases	
	Median no. of sexual partners: 278	Other	107 cases	
Armenian *et al.* (1993)[c]	≥ 49 male partners in the last 2 years	KS	159/314	51
		Non-cancerous AIDS controls	194/508	38
	Having partners from high risk areas[d]	KS	65/314	21
		Non-cancerous AIDS controls	61/508	12

KS, Kaposi's sarcoma; PCP, *Pneumocystis carinii* pneumonia; STD, sexually transmitted disease

[a] A reanalysis of the same cohort in 1992 found very similar results (Archibald *et al.*, 1992)

[b] San Francisco, Los Angeles, New York

[c] This cohort was first studied by Jacobson *et al.* (1990)

[d] From San Francisco for participants from other than Los Angeles

(*b*) *Infectious cofactors*

(i) *Human herpesvirus 8*

For a more detailed description of human herpesvirus 8 (HHV-8), see Section 4.2.4.

Chang *et al.* (1994) announced the discovery of a previously unknown human herpesvirus in Kaposi's sarcoma tissue of AIDS patients from the United States. The

Table 14. Studies of insertive oro-anal contact as a risk factor for Kaposi's sarcoma among AIDS patients

Reference	Location	Period of interview	Period of sexual behaviour assessed	KS post-AIDS included in cases	Index of IOAC	Proportion reporting IOAC[a] Numbers (%)	
						AIDS patients with KS	AIDS patients without KS
Armenian *et al.* (1993)	4 US cities	1984–85, 1987–91	2 years before enrolment	No	Being rimmed	240/314 (76%)	357/508 (70%)
Beral *et al.* (1992)	London, UK	1984-85	Previous five years	Yes	Insertive rimming, less than once a month and at least once a month but less than once a week	[14/30 (47%)]	[5/35 (14%)]
Darrow *et al.* (1992)	4 US cities	1981	Previous one year	No	> 10% of sexual contacts	22/49 (45%)	0/8
Archibald *et al.* (1990)	Vancouver, Canada	1982–84	At enrolment	Yes	Insertive fists	18/25 (72%)	23/48 (48%)
Lifson *et al.* (1990b)	San Francisco, USA	1983–86	1978–80 to 1983–84	Yes	Proportion of steady sexual partners with whom practised	4/71 (5%)	5/107 (5%)
Elford *et al.* (1992)	Sydney, Australia	1984, then 6-monthly[b]	1984 to diagnosis of AIDS	No	Any	29/55 (53%)	65/116 (56%)
Page-Bodkin *et al.* (1992)	San Francisco, USA	1984–91	2 years before interview	Yes	With some or most of sexual partners	43/87 (49%)	51/100 (51%)
Kaldor *et al.* (1993)	Sydney, Australia	1984–85	3 months before enrolment	No	[Insertive rimming]	[22/45 (49%)]	[34/88 (39%)][c]

KS, Kaposi's sarcoma; IOAC, insertive oro-anal contact

[a] Except where specified

[b] Self-administered questionnaire

[c] Numbers recalculated by the Working Group

virus, described as 'Kaposi's sarcoma-associated herpesvirus' (KSHV) or as human herpesvirus 8 (HHV-8), was identified by the use of representational difference analysis to discern DNA sequences in tumour tissue that were absent from normal DNA. The sequences, which showed similarity to a number of gammaherpesviruses (including Epstein–Barr virus (EBV)), were found in 21/27 (78%) people with AIDS-related Kaposi's sarcoma, 6/39 (15%) AIDS patients without Kaposi's sarcoma and 0/103 non-AIDS controls ($p < 10^{-7}$ using non-Kaposi's sarcoma controls).

A number of laboratories have since reported the detection of HHV-8 in biopsies of all epidemiological forms of Kaposi's sarcoma and/or in PBMCs from Kaposi's sarcoma patients (see Table 15). Overall, HHV-8 has been detected in more than 98% of Kaposi's sarcoma biopsies, but much less frequently and in lower amounts in skin of Kaposi's sarcoma patients. Using PCR, HHV-8 has been detected in PBMCs from about 50% of Kaposi's sarcoma patients (Ambroziak *et al.*, 1995 (in 100%); Howard *et al.*, 1995; Whitby *et al.*, 1995), but not at all (Ambroziak *et al.*, 1995; Whitby *et al.*, 1995) or in only 9% (Bigoni *et al.*, 1996) in those of healthy blood donors. In asymptomatic HIV-infected individuals, detection of HHV-8 in peripheral blood strongly predicts progression to Kaposi's sarcoma (Collandre *et al.*, 1995; Howard *et al.*, 1995; Whitby *et al.*, 1995). These findings suggest that HHV-8 has only a limited distribution in developed countries, but is an independent risk factor for classic (Mediterranean), African endemic and AIDS-associated Kaposi's sarcoma. However, the distribution of HHV-8 in the general population is not yet fully clear. Two groups have found HHV-8 in semen samples and prostate of healthy HIV-seronegative individuals (Lin *et al.*, 1995; Monini *et al.*, 1996), whereas others have not confirmed this observation (Ambroziak *et al.*, 1995; Li *et al.*, 1995).

Preliminary serological data also support the view that HHV-8 is infrequent in the general populations of developed countries. Antibodies to several proteins of HHV-8 can be detected in the majority of Kaposi's sarcoma patients, but only infrequently in HIV-infected individuals without Kaposi's sarcoma (Miller *et al.*, 1996; Moore *et al.*, 1996) and in the general population. These findings underline the strong association between detection of HHV-8 and the presence of Kaposi's sarcoma. However, in view of the conflicting PCR-based evidence, it needs to be established whether the presence of antibodies to HHV-8 reflects infection with, rather than reactivation of, HHV-8.

The advent of serological tests for HHV-8 should allow larger and more thorough epidemiological studies to be conducted, looking at the prevalence of the agent in populations at differing risk of developing Kaposi's sarcoma. If the virus is ubiquitous, it throws into question the issue of causality for Kaposi's sarcoma. Using an immunoblot assay for two latent nuclear antigens specific for HHV-8, Gao *et al.* (1996a) showed that the seroprevalence of HHV-8 did vary between groups with differing risk of Kaposi's sarcoma, being most prevalent in those at highest risk. Of 40 patients with Kaposi's sarcoma (recruited from the Multicentre AIDS cohort study (MACS)), 32 (80%) were positive for antibodies to HHV-8, compared to 7/40 (18%) homosexual men without the disease (just before the onset of AIDS). Of 122 HIV-seronegative blood donors and

Table 15. Proportion of patients with HHV-8 in relation to Kaposi's sarcoma and HIV/AIDS status

Reference	HHV-8-positive proportion of patients				
	AIDS/HIV+ KS+	AIDS/HIV– KS+	AIDS/HIV+ KS–	AIDS/HIV– KS–	Comments
Chang *et al.* (1994)	21/27		6/39[a]	0/103[b]	[a] Lymphomas, lymph nodes biopsies [b] Non-AIDS lymphomas, lymph nodes, cancers, other biopsies
Su *et al.* (1995)	4/4	2/3	0/5[a]	0/32[b]	[a] AIDS lymph nodes [b] Benign and malignant lymphoid tissue
Dupin *et al.* (1995)	4/4[a]	5/5[b]		0/6[c]	[a] Homosexual [b] Mediterranean KS [c] Other patients
Boshoff *et al.* (1995a)	14/14[a]	16/17[b] 8/8[d] 1/1[e]		0/11[c]	[a] 12 males, 2 females [b] Mediterranean patients [c] Various skin lesions (9 M, 2 F) [d] Organ transplant recipients [e] Homosexual
Ambroziak *et al.* (1995)	12/12[a] 7/7[b]	1/1[a] 3/3[b]	0/6[b]	0/14[b,c]	[a] Homosexual patients [b] HHV-8 detected in PBMCs [c] Healthy lab volunteers
Moore & Chang (1995)	10/11[a]	6/6[b] 4/4[a]		1/11 0/10[c]	[a] 10/11 Homosexual [b] Mediterranean 'classic' [c] PBMCs
Howard *et al.* (1995)	11/14[a,c] 0/6[b,c] 11/17[d]		1/19[c,e] 0/6[a]		All homosexual [a] Pulmonary and cutaneous KS [b] Cutaneous KS only [c] Bronchoalveolar lavage fluid [d] HHV-8 detected in PBMCs [e] The patient re-presented with [a] 3 months later

Table 15 (contd)

Reference	HHV-8-positive proportion of patients				Comments
	AIDS/HIV+ KS+	AIDS/HIV− KS+	AIDS/HIV+ KS−	AIDS/HIV− KS−	
Whitby *et al.* (1995)	24/46[a]		11/143[a]	0/160[a,b]	[a] HHV-8 detected in PBMCs [b] 134 blood donors, 26 cancer patients
Buonaguro *et al.* (1996)	19/19[a] 0/5[e]	42/42[b] 9/13[e]	0/15[c]	0/17[d]	[a] 5 Italian, 5 North American, 3 Ugandan, 3 Kenyan origin, KS tissues [b] 28 classic KS (5 Greek, 6 North American, 17 Italian), 2 iatrogenic (Greek), 12 African endemic KS (Ugandan) [c] PBMCs [d] Human biopsies from healthy individuals or affected by other pathologies [e] Autologous uninvolved skin of a and b
Chang *et al.* (1996)[a]	22/24	17/20	1/7	2/15	[a] Ugandan patients
Huang *et al.* (1995)	12/12[a]	14/18[b]			[a] US origin [b] Mediterranean (classic) and African origin
Lebbé *et al.* (1995)	2/2	14/14[a] 0/5[b]			[a] Immunosuppressed (1), classic (10), endemic (3) KS [b] PBMCs
Schalling *et al.* (1995)	17/17[a] 8/8[b]	18/18[a] 3/3[b]			[a] KS biopsies, Ugandan origin [b] KS biopsies, Swedish origin

Table 15 (contd)

Reference	HHV-8-positive proportion of patients				Comments
	AIDS/HIV+ KS+	AIDS/HIV– KS+	AIDS/HIV+ KS–	AIDS/HIV– KS–	
Bigoni *et al.* (1996)			0/10[b] – 4/58[d]	7/80[b] 1/11[c] 5/56[d]	[a] Italian patients [b] Non-Hodgkin's lymphoma patients [c] Reactive lymphadenopathy [d] HHV-8 detected in PBMCs
Prospective studies: Whitby *et al.* (1995)	No. developing KS[a] HIV+				[a] AIDS patients KS-free at recruitment; average 30 months follow-up [b] HHV-8 detected in PBMCs
	HHV-8+[b]	HHV-8–[b]			
	6/11 55% ($p < 0.00005$)	12/132 (9%)			

KS, Kaposi's sarcoma; PBMC, peripheral blood mononuclear cell; M, male; F, female

20 HIV-infected haemophiliacs, none were seropositive. The 40 patients with HIV-associated Kaposi's sarcoma had each been followed for a period of between 13 and 103 months before diagnosis of the disease (all were HIV-seropositive on entry). In that time, 11/40 (28%) were seropositive for HHV-8 throughout, 21 (52%) became positive between 6 and 75 months prior to diagnosis, 6/40 (15%) remained seronegative throughout and 2/40 (5%) changed from seropositive to seronegative during the course of the study. These data support the hypothesis that HHV-8 is causal for Kaposi's sarcoma and suggest that many of those who get the disease seroconvert to antibodies against the virus relatively soon before its onset. Further studies in these patients (using a different serological assay: an immunofluorescent assay) showed that they had an antigen profile suggestive of primary infection with HHV-8 rather that reactivation of a chronic existing infection (high titres of IgC and absence of IgA and IgM).

A second study by Gao *et al.* (1996b) compared the prevalence of HHV-8 in those with and without Kaposi's sarcoma from Uganda, Italy and the USA. There is a very strong association between seropositivity for HHV-8 and Kaposi's sarcoma, both in HIV-seropositive and in HIV-seronegative patients. However, the prevalence of HHV-8 in HIV-seronegative blood donors or patients with cancers other than Kaposi's sarcoma (for which there is no evidence of an association with HHV-8), varied dramatically between countries, being highest in Uganda (51%), followed by Italy (4%) and then the USA (0%). Kaposi's sarcoma remains virtually unknown outside of HIV-seropositive homosexual men in the USA (and some immigrant groups), but has existed at a low incidence in Italy and a considerably higher incidence in Uganda since well before the early 1980s (Templeton, 1973). Therefore, these results might be expected if HHV-8 were causal for Kaposi's sarcoma.

(ii) *Cytomegalovirus*

Even before the HIV epidemic, there were reports that cytomegalovirus antibody was more commonly present in persons with endemic forms of Kaposi's sarcoma (Giraldo *et al.*, 1975, 1978); cytomegalovirus genome was detected in Kaposi's sarcoma tissue from endemic cases (Giraldo *et al.*, 1980). Early in the AIDS epidemic, it was observed that the great majority of homosexual men had cytomegalovirus antibodies, compared with only half of the general population of the same age (Drew *et al.*, 1982; Melbye *et al.*, 1983; Rogers *et al.*, 1983), leading some investigators to suggest that it was a plausible candidate for the causal agent of AIDS itself (Urmacher *et al.*, 1982; Mintz *et al.*, 1983). However, other studies failed to confirm the consistent presence of the cytomegalovirus genome within Kaposi's sarcoma tissue (Ambinder *et al.*, 1987; Kempf *et al.*, 1995).

In retrospect, the reported associations between AIDS, immunosuppression or Kaposi's sarcoma and cytomegalovirus antibody prevalence or titre were probably due to failure to obtain controls adequately matched by sexual habits (Johnston *et al.*, 1990).

(iii) *Other infectious agents*

There is little evidence to support a relationship between human herpesvirus 6 (HHV-6) and Kaposi's sarcoma. One study failed to detect an elevated HHV-6 prevalence in

Kaposi's sarcoma tissue compared with normal skin; when detected, it was the more common B variant (Kempf *et al.*, 1995). However, another study reported that the less common A variant of HHV-6 was present in nearly a third of both endemic and HIV-related cases (Bovenzi *et al.*, 1993). Infection with HHV-6 occurs early in life and antibodies are common in adults (Krueger *et al.*, 1988; Dolcetti *et al.*, 1994).

Two studies have found human papillomaviruses (see IARC, 1995) in Kaposi's sarcoma tissue from AIDS cases, detected by PCR (Huang *et al.*, 1992) and by immunohistochemistry (Nickoloff *et al.*, 1992), but other investigations have failed to confirm these findings (Biggar *et al.*, 1992; Kaaya *et al.*, 1993a).

Rochalimaea henselae is a bacterium associated with angiomatoses that might be confused with Kaposi's sarcoma. It has been considered as a causal agent for Kaposi's sarcoma (Bignall, 1993) but is thought unlikely to be related to this disease (Taylor *et al.*, 1993).

Mycoplasma fermentans has been isolated from cells transformed with human DNA from Kaposi's sarcoma tissue (Lo *et al.*, 1989). However, there are no epidemiological data to support an association with Kaposi's sarcoma. Katseni *et al.* (1993) found HIV-positive and HIV-negative subjects to have comparable frequencies of *M. fermentans*. Another mycoplasma, *M. penetrans* (Lo *et al.*, 1991), seems to be more common in HIV-infected than in HIV-negative individuals, as shown by the prevalence of antibodies to this organism (Wang *et al.*, 1992). Serological evidence suggests that *M. penetrans* might be more common in HIV-infected homosexuals, but not in intravenous drug users or haemophiliacs, suggesting a link to those patient groups known to be at an increased risk for Kaposi's sarcoma (Wang *et al.*, 1993).

(*c*) *Genetic susceptibility*

In 1983, early in the AIDS epidemic, the HLA-DR5 haplotype was reported to be associated with the occurrence of Kaposi's sarcoma in homosexual men from New York City (Pollack *et al.*, 1983a; Prince *et al.*, 1984), an association also reported among cases of endemic Kaposi's sarcoma (Pollack *et al.*, 1983b; Contu *et al.*, 1984; Papasteriades *et al.*, 1984). Subsequent studies have failed to confirm such an association in either AIDS-related or endemic Kaposi's sarcoma (Melbye *et al.*, 1987; Brunson *et al.*, 1990; Mann *et al.*, 1990; Ioannidis *et al.*, 1995; Strichman-Almashanu *et al.*, 1995).

One suggestion to explain this discrepancy was that HIV-infected persons with elevated genetic susceptibility (in this case, DR5-positive) developed Kaposi's sarcoma sooner after infection and hence were not seen in later studies. However, large numbers of newly infected persons continue to enter the pool of persons at risk and exhaustion of the susceptible subgroups seems an unlikely explanation. Another explanation is that this marker is more common in some subgroups, particularly in Mediterranean and Jewish populations, and that control for this factor was inadequate. Reported associations with other HLA markers have not been confirmed (summarized by Ioannidis *et al.*, 1995), and the relationship between HLA and Kaposi's sarcoma is still controversial. [The Working Group noted that the multiple comparisons made in the analysis of the HLA data make it difficult to interpret the findings.]

(*d*) *Miscellaneous factors*

The use of amyl nitrite inhalants has been considered as a factor increasing risk for Kaposi's sarcoma in homosexual men. Use of these drugs was especially popular among very sexually active homosexual men at the time when the AIDS epidemic was emerging in the late 1970s and early 1980s (Jaffe *et al.*, 1983; Melbye *et al.*, 1983). They act as smooth muscle relaxants and potent vasodilators (Newell *et al.*, 1984) and are thought to be potentially carcinogenic (Jørgensen & Lawesson, 1982). Therefore, they seemed plausible candidate etiological agents for a tumour prominently involving blood vessels. Early studies found their use to be associated with both immunosuppression and with development of Kaposi's sarcoma (Goedert *et al.*, 1982; Marmor *et al.*, 1982; Haverkos *et al.*, 1985).

However, since nitrite inhalants were often used to facilitate anal intercourse, their use was correlated with the frequency of receptive anal intercourse with multiple partners. In one study, adjusting for anal intercourse eliminated the relationship between Kaposi's sarcoma and nitrite inhalant use (Darrow *et al.*, 1992), although in another study (Archibald *et al.*, 1990), a residual 'independent' effect remained. [The Working Group noted that, among homosexual men in developed countries, nitrite inhalant users also became HIV-infected early in the epidemic and thus manifested AIDS symptoms (including Kaposi's sarcoma) earlier. Thus, the evidence of the association between nitrite inhalants and Kaposi's sarcoma is not convincing.]

Data about androgen levels is conflicting. Klauke *et al.* (1995) report higher testosterone levels in 17 HIV-infected men with Kaposi's sarcoma than other HIV-infected men who had no symptoms (11), mild symptoms (12) or non-Kaposi's sarcoma AIDS (29). In contrast, Christeff *et al.* (1995) found higher levels of testosterone and dehydroepiandrosterone in 28 men with Kaposi's sarcoma compared to 34 HIV-infected men without Kaposi's sarcoma, after stratifying for $CD4^+$ T-cell count. Further studies are needed to clarify this issue.

Lunardi-Iskandar *et al.* (1995a) reported that Kaposi's sarcoma Y1 cells could not be grown in pregnant mice and that human chorionic gonadotropin (HCG) appeared to induce apoptosis in Kaposi's sarcoma derived cells in culture (see Section 4.2.1). The incidence of Kaposi's sarcoma in HIV-infected pregnant women (who would have high HCG levels soon after conception) in Africa was similar to that in post-pregnant women or women not recently pregnant, arguing against a role for HCG at physiological doses. Similarly, there was no difference between pregnant and non-pregnant women in the frequency of disseminated Kaposi's sarcoma lesions (Rabkin *et al.*, 1995a).

2.1.6 *Human immunodeficiency virus type 2*

Because of a paucity of data, it is unclear whether the clinical spectrum of diseases in HIV-2-infected individuals differs from that of HIV-1, particularly with respect to Kaposi's sarcoma (De Cock & Brun-Vézinet, 1989).

Kaposi's sarcoma in people with HIV-2 infection was reported in two patients from Senegal (Le Guenno *et al.*, 1987), one from France (Brücker *et al.*, 1987), four of 17 HIV-2-associated AIDS cases from western Africa (Clavel *et al.*, 1987), but not in two

follow-up studies, namely a one-year follow-up of 62 HIV-2-seropositive individuals (Poulsen *et al.*, 1989) and a two-year follow-up of 133 similar subjects from Guinea Bissau, a few of whom had an AIDS diagnosis (Ricard *et al.*, 1994).

No Kaposi's sarcoma was observed in a few case reports and small case series of HIV-2-seropositive individuals (Clavel *et al.*, 1986; Mølbak *et al.*, 1986; Ancelle *et al.*, 1987; Brun-Vézinet *et al.*, 1987; Burin Des Roziers *et al.*, 1987; Kroegel *et al.*, 1987; Saimot *et al.*, 1987; Veronesi *et al.*, 1987; Vittecoq *et al.*, 1987; Agut *et al.*, 1988; Centers for Disease Control, 1988; Hugon *et al.*, 1988)

2.2 Non-Hodgkin's lymphoma

In this monograph, Hodgkin's disease is covered under other cancers (Section 2.3.3).

2.2.1 *Description of the clinical disease and pathology*

Lymphomas have been classified on the basis of pathological appearance in various classification schemes. The use of different schemes and changes in these over time have complicated comparisons of the occurrence of non-Hodgkin's lymphoma between places and between time periods.

Non-Hodgkin's lymphoma is a recognized complication of other immunosuppressed conditions. Both primary and iatrogenic immunosuppression are associated with increased risk for non-Hodgkin's lymphoma (see Section 4.3.1). In particular, Burkitt's lymphoma incidence is increased in X-linked lymphoproliferative disease and ataxia telangiectasia, but not in relation to iatrogenic immunosuppression (Filipovich *et al.*, 1994).

Non-Hodgkin's lymphoma accounts for approximately 4% of cancer cases and 4% of cancer deaths in the general population not infected with HIV (Parkin *et al.*, 1992). Incidence rates for non-Hodgkin's lymphoma rise exponentially with age, and there is a male predominance (ratio 3 : 2), which is more marked at younger than older ages. The incidence has been rising steadily for several decades, since long before the advent of HIV. Among United States men aged 0–64 years, the increase over the past 40 years has been estimated to be above 40%. Even after accounting for the effect of HIV, the incidence of non-Hodgkin's lymphoma has continued to increase more rapidly than that of most other tumours (Devesa *et al.* 1987; Coleman *et al.*, 1993). The incidence of high histological grades of disease has increased more than that of low-grade ones, and extranodal disease has increased more rapidly than nodal disease (Rabkin *et al.*, 1993b). The reasons for these increases are not understood. Even after accounting for the impact of changes in diagnosis and well established risk factors on the trends, there remains an unexplained increase in the incidence of non-Hodgkin's lymphoma in the United States (Hartge & Devesa, 1992).

(*a*) *Classification of AIDS-related lymphomas*

Most types of non-Hodgkin's lymphoma are AIDS-defining conditions.

Non-Hodgkin's lymphoma can arise either in the lymph nodes or in extranodal lymphoid tissue. In the absence of HIV infection, approximately three quarters of the cases have a nodal primary site and one quarter originate extranodally. The central nervous system is an unusual site of non-Hodgkin's lymphoma in the absence of HIV infection. In 2687 HIV-negative cases reported to a Danish Lymphoma Registry, the central nervous system was the primary site in 4.2% of extranodal non-Hodgkin's lymphomas and in 1.6% of all non-Hodgkin's lymphomas (Krogh-Jensen *et al.*, 1994).

HIV-associated lymphomas are distinctive in their site distribution. Nearly half of the cases of HIV-associated lymphoma have an extranodal primary site. The central nervous system is a particularly favoured primary site, accounting for about 20% of all AIDS-related non-Hodgkin's lymphoma in the United States (Beral *et al.*, 1991b).

As shown in Table 16, the spectrum of HIV-related lymphoproliferative disorders includes: (i) systemic non-Hodgkin's lymphomas; (ii) body cavity-based lymphoma; (iii) primary lymphoma of the brain; and (iv) multicentric Castleman's disease.

(i) *Systemic non-Hodgkin's lymphomas*

Systemic AIDS-related non-Hodgkin's lymphomas are a heterogeneous group of malignancies, usually of the B-cell phenotype. The overwhelming majority fall within three Working Formulation histological categories: large non-cleaved-cell lymphoma; large-cell immunoblastic lymphoma; and small non-cleaved-cell lymphoma, which includes Burkitt's tumour. It has been proposed that large non-cleaved-cell lymphoma and large-cell immunoblastic lymphoma be classified as a single category under the term 'diffuse large-cell lymphoma'. This latter definition has been further expanded to include also $CD30^+$ anaplastic large-cell lymphoma of B-cell origin (Harris *et al.*, 1994). $CD30^+$ anaplastic large-cell lymphomas constitute a heterogeneous group of high-grade lymphomas at the borderline between Hodgkin's disease and non-Hodgkin's lymphomas, and have been described in association with AIDS (Carbone *et al.*, 1991; Chadburn *et al.*, 1993; Tirelli *et al.*, 1995a).

An interesting feature of systemic lymphomas in HIV patients is the frequency of pleomorphic features, with overlap between established histological subtypes (Raphael *et al.*, 1991). An atypical variant made up mainly of blastic cells exhibiting features intermediate between small non-cleaved-cell lymphoma with plasma-cell differentiation and immunoblastic plasmacytoid cells has also been observed in HIV patients (Lennert & Feller, 1990; Carbone *et al.*, 1995a). These atypical morphological features may bias a correct discrimination of small non-cleaved-cell lymphoma from large-cell immunoblastic lymphoma. This intermediate variant also includes Burkitt-like tumours (Harris *et al.*, 1994).

Whether extramedullary plasmacytoma should be included among AIDS-related lymphomas is still debated (reviewed by Levine, 1993).

(ii) *Body cavity-based lymphoma*

Body cavity-based lymphoma, growing in the pleural, pericardial and peritoneal cavities as primary lymphomatous effusions, represents an additional rare AIDS-related non-Hodgkin's lymphoma variant (Knowles *et al.*, 1989; Cesarman *et al.*, 1995). This

lymphoma has morphological features between those of large-cell immunoblastic lymphoma and anaplastic large-cell lymphoma (Ansari *et al.*, 1996; Carbone *et al.*, 1996a; Cesarman *et al.*, 1996). Its identification is based on pathology, clinical features, phenotype, genotype and etiology (Jaffe, 1996).

Table 16. Pathological features of AIDS-related non-Hodgkin's lymphomas and other lymphoproliferative disorders

Non-Hodgkin's lymphomas
Systemic lymphomas
(*a*) *'Blastic'[a] cell lymphomas*
Large non-cleaved cell (G - WF)
Immunoblastic (H - WF) with or without plasma cell differentiation
Small non-cleaved cell (J - WF) with or without plasma cell differentiation
Extramedullary (plasmacytoma)[b]
Blastic cells with 'intermediate' features
(*b*) *'Anaplastic'[c] cell lymphomas*
Anaplastic large cell (CD30/Ki-1$^+$)
(*c*) *Others (rare types)*
Body cavity-based lymphoma
Primary brain lymphoma (immunoblastic)
Multicentric Castleman's disease

Updated and adapted from Gaidano & Carbone (1995)
WF, International Working Formulation for non-Hodgkin's lymphomas
[a] The term 'blastic' is used in analogy with the suffix 'blastic' used in the Kiel Classification (Stansfeld *et al.*, 1988).
[b] Whether extramedullary plasmacytomas should be included among HIV-related lymphomas is still debated.
[c] The term 'anaplastic' is used in analogy with the term used in the definition of CD30$^+$ anaplastic large-cell lymphomas; it indicates blastic large cells which display marked pleomorphism, with giant cells possessing bizarre and irregular nuclei and large nucleoli (Harris *et al.*, 1994).

(iii) *Primary lymphoma of the brain*

Unlike the heterogeneous systemic AIDS-related non-Hodgkin's lymphomas, non-Hodgkin's lymphomas arising in the central nervous system represent a more uniform group and, in the majority of cases, tend to display histological features consistent with immunoblastic–plasmacytoid lymphomas (Remick *et al.*, 1990; Camilleri-Broët *et al.*, 1995).

(iv) *Multicentric Castleman's disease*

Multicentric Castleman's disease, also called multicentric angiofollicular lymphoid hyperplasia, is an atypical, usually polyclonal lymphoproliferative disorder which involves multiple lymphoid organs. Multicentric Castleman's disease in HIV-infected individuals is a distinct clinicopathological entity (Oksenhendler *et al.*, 1996). It is characteristically associated with Kaposi's sarcoma, which occurs during the clinical course of most HIV-associated cases of multicentric Castleman's disease (Soulier *et al.*, 1995).

(*b*) *Phenotypic and genotypic features*

The vast majority of AIDS-related non-Hodgkin's lymphomas are B-cell neoplasms (reviewed by Levine, 1993). Most of them, especially systemic and primary brain lymphomas, express monotypic surface immunoglobulin or B-cell antigens (CD19, CD20, and CD22), but lack T-cell-associated antigens (reviewed by Knowles, 1993). The remaining AIDS-related B-cell non-Hodgkin's lymphomas, particularly $CD30^+$ anaplastic large-cell lymphomas (Carbone *et al.*, 1993a, 1996b) and those preferentially involving body cavities (Knowles, 1993; Cesarman *et al.*, 1995), usually exhibit an indeterminate immunophenotype. Both lymphoma types lack surface immunoglobulin and B-cell-associated antigens, but express the leukocyte common antigen and various antigens associated with activation (Cesarman *et al.*, 1995; Carbone *et al.*, 1996b).

Almost all AIDS-related non-Hodgkin's lymphomas, including those displaying B-cell phenotypes as well as those displaying indeterminate phenotypes, exhibit clonal immunoglobulin heavy-chain and light-chain gene rearrangements and lack clonal T-cell receptor β-chain gene rearrangements (reviewed by Knowles, 1993). A higher proportion of anomalously matured B-cell neoplasms has been observed in HIV-infected individuals than among non-Hodgkin's lymphomas in the general population (Boiocchi *et al.*, 1990).

Polyclonality has been reported in rare instances, based on absence of immunoglobulin heavy chain gene rearrangements in three B-cell tumours (McGrath *et al.*, 1991). However, Raphael *et al.* (1994) reported that two cases without rearrangement did have clonal EBV termini. Similarly, Boiocchi *et al.* (1993a) noted clonal light chain rearrangement in all of three cases of AIDS-associated non-Hodgkin's lymphoma without heavy chain rearrangement.

2.2.2 *Descriptive epidemiology of non-Hodgkin's lymphoma*

As a primary AIDS-defining illness, non-Hodgkin's lymphoma accounts for 2.9% of AIDS cases in United States (Beral *et al.*, 1991b; Biggar & Rabkin, 1992) and 3% in European (Serraino *et al.*, 1992b) surveillance data. However, at least as many non-Hodgkin's lymphomas occur as a clinically recognized secondary diagnosis after another AIDS-defining illness. In the United States death certification data for 1992, 5.7% of persons dying of HIV infection had non-Hodgkin's lymphoma recorded (Selik *et al.*, 1995).

(a) Cancer registry data

Population-based cancer registration data yield indirect estimates of HIV-associated risk for non-Hodgkin's lymphoma based on surrogate indicators of groups at risk for HIV infection, such as never-married marital status as a surrogate indicator of homosexuality among men (see Table 17).

Table 17. Increase in risk for non-Hodgkin's lymphoma among US never-married men since beginning of the AIDS epidemic

Reference	Study area	Age group	Time period		Relative risk	*p* value
			Before	After		
Kristal *et al.* (1988)	New York City, high AIDS mortality neighbourhood	25–54	1980	1984	[2.6	< 0.01]
Biggar *et al.* (1989)	Manhattan	20–49	1973–76	1985	6.2	< 0.01
Harnly *et al.* (1988)	San Francisco	25–44	1975	1985	5.3	< 0.01
Ross *et al.* (1985)	Los Angeles	18–54	1972–79	1983	1.6	< 0.05
Rabkin & Yellin (1994)	San Francisco	25–54	1973–79	1988–90	20	< 0.01

Ross *et al.* (1985) studied the incidence of non-Hodgkin's lymphoma in never-married men aged 18–54 years in Los Angeles, CA, United States, from 1972 to 1983. Starting in 1982, there was a 60% increase in incidence; increases were especially marked for Burkitt-like lymphoma and immunoblastic sarcoma (lymphoma). During 1980–83, these high-grade tumours accounted for 20% of all cases of non-Hodgkin's lymphoma.

Kristal *et al.* (1988) examined cancer surveillance data and mortality statistics for residents of New York City, NY, United States, aged 25–54 years for the period 1980–85. They detected a three-fold increase in the incidence of non-Hodgkin's lymphoma up to 1984 among never-married men living in neighbourhoods with high AIDS mortality.

Biggar *et al.* (1989) examined lymphoma incidence among never-married men aged 20–49 years in Manhattan, NY, United States, from 1973 through to 1985. They detected a six-fold increase from baseline rates by the end of their study period. Increases were greatest for Burkitt-like lymphoma and immunoblastic lymphoma.

Harnly *et al.* (1988) examined cancer incidence in never-married men aged 25–44 years in San Francisco, CA, United States, for the period 1975–85. In census tracts with a high incidence of AIDS, the incidence of non-Hodgkin's lymphoma was increased five-fold by 1985.

Rabkin and Yellin (1994) found that the incidence of non-Hodgkin's lymphoma in never-married men aged 25–54 years in San Francisco increased 20-fold between 1973–79 and 1988–90. However, the increases were not uniform for all sub-types of non-Hodgkin's lymphoma. Burkitt-like tumours peaked in incidence in 1985–87, then decreased in 1988–90, whereas incidence of immunoblastic lymphomas increased continuously through to 1990. The incidence of extranodal (especially central nervous system) lymphoma increased more rapidly than that of nodal disease, accounting for half of the incidence in the most recent period. [On the basis of the estimated 25% prevalence of HIV in this population, the incidence of non-Hodgkin's lymphoma in HIV-infected San Francisco men was 0.7% per year in 1988–90.]

Rabkin *et al.* (1993a) examined cancer registration data for New York women at high risk for HIV infection. Between 1976–78 and 1987–88, the incidence of non-Hodgkin's lymphoma doubled in black women, but not in white women, consistent with the distribution of AIDS, which was also primarily concentrated among black women.

Another set of studies has relied on linkage between cancer registry and AIDS registry data.

Coté *et al.* (1991) used linkage of AIDS and cancer registries in Illinois, United States, to detect cases of non-Hodgkin's lymphoma in patients diagnosed with AIDS between 1 January 1981 and 15 February 1989. Compared with general population rates, they found a 140-fold increase in incidence of non-Hodgkin's lymphoma among AIDS patients.

Reynolds *et al.* (1993) linked AIDS and cancer registry data in San Francisco for the period 1980–87. Risk for non-Hodgkin's lymphoma was increased 71-fold over concurrent general population incidence rates and 97-fold over the 1973–77 rates in the same geographical area. [The Working Group noted that the former risk estimate may be biased downwards by HIV-associated non-Hodgkin's lymphoma not being recognized as AIDS, whereas the latter may be biased upwards by the temporal trend in non-Hodgkin's lymphoma independent of HIV infection.]

(*b*) *Cohort data*

Lyter *et al.* (1995) examined the incidence of non-Hodgkin's lymphoma in 430 HIV-seropositive homosexual men in Pittsburgh, PA, United States, between 1984 and 1993. The annual incidence was [0.6%], which was 83 times that of contemporaneous population rates.

Ragni *et al.* (1993) followed a cohort of 1295 HIV-positive haemophiliacs in a collaborative study. The overall incidence of non-Hodgkin's lymphoma was 0.16 case/100 person-years, which constituted a 36.5-fold increase over expected rates.

Peters *et al.* (1991) reported a case-series of 347 AIDS patients treated at a hospital in London, United Kingdom, between October 1982 and December 1989. They found that the proportion of AIDS deaths due to lymphoma increased from 0 to 16% between 1984 and 1989. [The Working Group noted that these figures may be confounded by the introduction of *Pneumocystis carinii* pneumonia prophylaxis.]

2.2.3 *Role of immunosuppression*

Non-Hodgkin's lymphoma is considered to be a relatively late manifestation of AIDS, compared with Kaposi's sarcoma and some opportunistic infections.

Muñoz *et al.* (1993) analysed the incidence of non-Hodgkin's lymphoma in 2627 HIV-infected homosexual men in four United States cities between 1985 and 1991. They noted a nonsignificant increase with decreasing $CD4^+$ T-cell count: the relative risk for non-Hodgkin's lymphoma as an initial AIDS-defining illness was 0.38 (95% CI, 0.14–1.09) with 101–200 $CD4^+$ cells/mm^3 versus ≤ 100 cells/mm^3.

Rabkin *et al.* (1992) followed a cohort of 1701 haemophiliacs, of whom 1065 (63%) were HIV-seropositive. The incidence of non-Hodgkin's lymphoma after HIV seroconversion averaged 0.15 cases/100 person-years and rose exponentially with increasing duration of HIV infection. However, $CD4^+$ T-cell counts of cases of non-Hodgkin's lymphoma were similar to those in AIDS-free subjects after the same duration of HIV infection. Haemophiliac patients without HIV infection showed no increased risk for non-Hodgkin's lymphoma.

In clinical trials of zidovudine and dideoxyinosine in AIDS and AIDS-related complex patients, the three-year cumulative incidence of non-Hodgkin's lymphoma among 116 patients was 19%. There was no significant difference between subjects receiving the two antiretroviral treatments (Pluda *et al.*, 1990, 1993). Patients with less than 50 $CD4^+$ T-cells/mm^3 were at significantly higher risk for primary central nervous system lymphoma, but not for systemic lymphoma (Pluda *et al.*, 1993).

Moore *et al.* (1991) followed 1030 patients with AIDS or advanced AIDS-related complex receiving zidovudine at 12 sites in the United States between 1987 and 1990. The incidence of non-Hodgkin's lymphoma was 1.6 cases/100 person-years. Kaposi's sarcoma, oral hairy leukoplakia and cytomegalovirus disease, markers of immune dysfunction, were each independently associated with increased risk for non-Hodgkin's lymphoma.

The association between immune decline and non-Hodgkin's lymphoma appears to differ with the subtype of the disease. Roithmann *et al.* (1991) reported 131 HIV-associated non-Hodgkin's lymphomas recorded at a French registry during 1987–89. The median $CD4^+$ T-cell count was significantly higher in cases of small non-cleaved-cell lymphoma (266/mm^3) than in those of large-cell (125/mm^3, $p < 0.05$) or immunoblastic (80/mm^3, $p < 0.01$) lymphoma.

These studies have consistently found increasing risk of non-Hodgkin's lymphoma with increasing duration of HIV infection and with progression in immune dysregulation. It is not clear what aspect of immune dysfunction corresponds directly to this risk.

The potential role of HIV as a direct cause of non-Hodgkin's lymphoma is addressed in Section 4.3.

2.2.4 *Co-factors*

(*a*) *Demographic*

The proportion of AIDS patients presenting with non-Hodgkin's lymphoma is greater in adults than in children. In United States surveillance data, 0.5% of AIDS cases under one year and 1.9% of cases one to nine years of age had non-Hodgkin's lymphoma (Beral *et al.*, 1991b). Children were somewhat more likely to have Burkitt-like lymphoma, and older adults were more likely to have immunoblastic or large-cell lymphoma. In this series, women were one third to one half less likely than men to have non-Hodgkin's lymphoma as an AIDS-defining illness.

Biggar and Rabkin (1992) reviewed United States AIDS surveillance data for AIDS-defining lymphomas. The proportion of AIDS cases presenting with non-Hodgkin's lymphoma was higher in older persons, men and whites. As the authors noted, these same characteristics are associated with increased risk for non-Hodgkin's lymphoma in non-HIV-infected individuals, suggesting that an environmental cofactor(s) for AIDS lymphoma is unlikely to be important.

In European surveillance data, the proportion of AIDS patients presenting with non-Hodgkin's lymphoma is also greater in adults than in children (Serraino *et al.*, 1992c). In cases reported up to the end of June 1991, among intravenous drug users, females had a relative risk for non-Hodgkin's lymphomas of 0.7 (95% CI, 0.6–0.9) compared with males in the same risk group, whereas among AIDS patients with heterosexually acquired HIV infection, females had a relative risk of 1.2 (95% CI, 0.8–1.8).

(*b*) *Geographic*

Non-Hodgkin's lymphoma accounts for a similar proportion of AIDS cases in various locations. In surveillance data, non-Hodgkin's lymphoma accounted for 2.9% of United States AIDS cases recorded up to June 1989 and 3.0% of European cases up to June 1991 (Beral *et al.*, 1991b; Serraino *et al.*, 1992c). In European surveillance data, there was little difference between four regions (northern, central, southern and eastern) in the fraction of AIDS with non-Hodgkin's lymphoma as the initial diagnosis (Serraino *et al.*, 1992c).

Casabona *et al.* (1991) analysed national surveillance data from 15 European countries up to March 1989. They found similar proportions of AIDS-related non-Hodgkin's lymphoma in three regions (northern, central, southern) for homosexual men and for other risk groups, and there was no consistent variation in the geographic pattern with time for either transmission category.

Data from Africa are less complete and it is unclear whether the risk for non-Hodgkin's lymphoma is the same as that observed in developed countries. In South African AIDS surveillance data, seven (5.6%) of the first 126 cases reported between 1982 and 1988 had non-Hodgkin's lymphoma (Sitas *et al.*, 1993). However, most of these patients were of Caucasian origin.

Lucas *et al.* (1994) reported an autopsy study of HIV-positive adults and children admitted in 1991 and 1992 to the largest hospital in Abidjan, Côte d'Ivoire. In this series, 7/247 (2.8%) adult (> 14 years) decedents had non-Hodgkin's lymphoma at autopsy

versus 0/78 paediatric decedents. The proportion was similar in patients seropositive for HIV-1 and HIV-2.

Bassett *et al.* (1995) examined cancer incidence rates in the African population of Harare, Zimbabwe, for 1990–92 and compared them with rates in Bulawayo, Zimbabwe, 20–30 years earlier. With the advent of the AIDS epidemic, annual age-standardized (world standard) Kaposi's sarcoma incidence increased by [22 and 88/100 000] in men and women, respectively. In contrast, the respective increases in non-Hodgkin's lymphoma incidence were only [2 and 3/100 000], similar to increases over this period in populations without HIV infection.

Wabinga *et al.* (1993) examined cancer surveillance data for Kampala, Uganda, for the period between September 1989 and December 1991. They noted a marked increase in Kaposi's sarcoma compared with baseline data from 1954–1960. In contrast, there was no detectable increase in the incidence of non-Hodgkin's lymphoma. Annual age-standardized (world standard) rates of non-Hodgkin's lymphoma actually decreased slightly between these two periods, from 3.9 to 3.2/100 000 for men and from 2.9 to 2.6/100 000 for women.

Newton *et al.* (1995) reported 245 cancer cases registered in Butare, Rwanda, between October 1992 and April 1994. Seven (37%) of 19 patients with non-Hodgkin's lymphoma were HIV-seropositive compared with 4% of control cancer cases, corresponding to an odds ratio of 12.6 (95% CI, 2.2–54.4).

[The Working Group noted that the apparent deficit of AIDS-associated non-Hodgkin's lymphoma in Africa cannot be explained by underdiagnosis only. It is possible that patients with severe immunodeficiency in this part of the world tend to die from infectious diseases before manifesting non-Hodgkin's lymphoma.]

(*c*) *Behavioural*

In contrast to the variation in risk for Kaposi's sarcoma, there are relatively small differences in risk for non-Hodgkin's lymphoma between HIV exposure groups in developed countries.

As seen in Tables 18 and 19, the proportion of AIDS cases presenting with non-Hodgkin's lymphoma is consistently between 2 and 5% in western European countries and the United States, and varies little between HIV-exposure categories.

In United States surveillance data up to 30 June 1989, 5.2% of haemophilic AIDS cases, 3.4% of homosexual or bisexual male cases and 1.6% of intravenous drug user cases were reported with non-Hodgkin's lymphoma (Beral *et al.*, 1991b).

Reynolds *et al.* (1993) linked AIDS and cancer registries in San Francisco, CA, United States, for an analysis of cancers diagnosed during 1980–87. Intravenous drug users comprised 2% of 3826 AIDS cases without cancer versus 1% of 234 AIDS-associated non-Hodgkin's lymphoma, but this difference was not statistically significant.

Serraino *et al.* (1992c) analysed data on 53 042 AIDS cases reported from the World Health Organization European Region as of June 1991. Non-Hodgkin's lymphoma accounted for 1% of initial AIDS diagnoses among HIV-infected children and 4% among

Table 18. Numbers and proportions of male AIDS cases with non-Hodgkin's lymphoma as the AIDS-defining condition, by country and HIV transmission group in Europe and the United States, 1981–94

Country	Homo/ bisexual men		Intravenous drug users		Heterosexuals (Pattern II countries)[b]		Heterosexuals (other)		Haemophiliacs and transfused		Others/ unknown		Total NHL	
	NHL cases	%[c]	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%
Austria	14	3	8	3	0	0	5	7	2	3	7	5	36	3
Belgium	26	3	3	3	7	3	15	9	0	0	3	10	54	4
Denmark	45	4	2	3	1	6	6	5	4	4	2	5	60	4
France	642	4	204	3	25	2	84	5	61	5	50	5	1096	4
Germany	372	4	37	3	1	1	11	3	31	5	52	9	504	4
Greece	16	3	0	0	1	12	3	5	5	5	6	4	31	3
Italy	168	4	386	3	6	4	54	4	16	4	50	5	682	3
Netherlands	105	4	5	2	1	2	6	4	1	2	1	2	119	4
Portugal	19	2	6	1	0	0	8	2	1	1	2	3	36	2
Spain	160	3	265	2	0	0	36	2	25	4	49	3	535	2
Sweden	38	5	4	5	0	0	1	1	2	3	0	0	45	4
Switzerland	68	4	23	2	0	0	14	4	1	2	1	2	107	3
United Kingdom	246	3	15	4	14	3	12	5	28	5	5	3	320	3
United States White	3821	3	301	2	–[d]	–[d]	53	3	137	3	146	3	4518	3
Black	549	1	315	1	–[d]	–[d]	57	1	19	2	103	1	1043	1
Other	581	2	284	1	–[d]	–[d]	26	1	20	2	69	2	980	2

NHL, non-Hodgkin's lymphoma

[a] Only countries with > 30 cases of NHL over the period 1981–94 are included.

[b] Individuals not originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which heterosexual transmission has predominated and continues to) which include Africa and the Caribbean.

[c] Number of NHL cases as percentage of total AIDS cases in the respective risk group

[d] Data not available

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

Table 19. Numbers and proportions of female AIDS cases with non-Hodgkin's lymphoma as the AIDS-defining condition, by country and HIV transmission group in women in Europe and the United States, 1981–94

Country[a]		Intravenous drug users		Heterosexual (Pattern II countries)[b]		Heterosexual (other)		Haemophiliacs and transfused		Other/ unknown		Total NHL	
		NHL cases	%[c]	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%	NHL cases	%
France		55	3	17	2	50	3	18	2	21	4	161	3
Germany		14	2	1	1	8	2	3	2	6	5	32	2
Italy		79	2	2	3	32	2	5	4	9	2	127	2
Spain		36	1	0	0	24	2	2	1	9	3	71	1
Switzerland		13	2	0	0	8	3	0	0	0	0	21	2
United Kingdom		5	3	6	2	7	3	5	7	1	1	24	3
United States	White	43	1	–[d]	–[d]	80	2	32	2	24	2	179	2
	Black	60	0	–[d]	–[d]	80	1	10	1	38	1	188	1
	Other	38	1	–[d]	–[d]	42	1	8	2	13	1	101	1

[a] Countries with > 30 cases of NHL over the period 1981–94 are included.

[b] Individuals not originating from Pattern II countries (countries in which extensive spread of HIV began in the mid-to-late 1970s or early 1980s and in which transmission has predominated and continues to), which include Africa and the Caribbean.

[c] Number of NHL cases as percentage of total AIDS cases in the respective risk group

[d] Data not available

Data derived from the European Non-aggregate AIDS Data Set (ENAADS) updated to June 1995, prepared by the European Centre for the Epidemiological Monitoring of AIDS, Paris, and from the AIDS Public Information Data Set (PIDS) updated to December 1994, prepared by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, United States

haemophiliacs; homosexual men were significantly more likely to have non-Hodgkin's lymphoma than intravenous drug users.

Pedersen *et al.* (1995) investigated 6550 European patients with AIDS followed at 52 centres, diagnosed with AIDS from 1979 up to the end of 1989. In this study, non-Hodgkin's lymphoma constituted a higher fraction of AIDS-defining illnesses in intravenous drug users (4.1%) than in homosexual men (3.0%); however, lymphoma incidence after AIDS diagnosis was significantly lower among intravenous drug users than among homosexual men. The authors suggested that their results indicate that national surveillance data may underreport AIDS-related non-Hodgkin's lymphoma in drug users.

Similarly, the Italian Cooperative Group for AIDS-Related Tumours (GICAT) (1988) reported that intravenous drug users accounted for a slightly higher proportion of AIDS-associated non-Hodgkin's lymphoma than of total AIDS cases in Italy. They identified 93 AIDS-associated non-Hodgkin's lymphomas diagnosed between January 1980 and November 1987, of which 63 (68%) were in intravenous drug users as compared with 59% of all AIDS cases in the United States.

(*d*) *Infections*

AIDS-associated non-Hodgkin's lymphoma is a heterogeneous entity, and subsets of cases have been associated with various viruses, particularly two herpes viruses, EBV and HHV-8.

(i) *Epstein–Barr virus*

Monoclonal Epstein–Barr virus (EBV) infection is found in AIDS-related non-Hodgkin's lymphomas, especially those in the central nervous system, which are almost always EBV-positive (MacMahon *et al.*, 1991). Table 20 lists studies in which central nervous system lymphomas have been tested for EBV. MacMahon *et al.* (1991) found EBV in all of 21 cases of AIDS-related central nervous system lymphoma, and this high prevalence is consistent with results of most other studies (DeAngelis *et al.*, 1992; Cinque *et al.*, 1993; Arribas *et al.*, 1995). An exception is the study by Morgello (1992), which reported only 50% of cases to be EBV-positive, perhaps because of a less sensitive method of detection. Cinque *et al.* (1993) found EBV in cerebrospinal fluid to be highly predictive of central nervous system lymphoma at subsequent necropsy. These data suggest that EBV is necessary for lymphomagenesis in the central nervous system in patients with AIDS.

In AIDS-related systemic non-Hodgkin's lymphoma, EBV is less frequently detected (Table 21). It is found preferentially in tumours with immunoblastic histology. The prevalence of EBV-positivity reported has varied from 28% (Ernberg & Altiok, 1989) to 66% (Shibata *et al.*, 1993). No single histological type was uniformly positive for EBV, which suggests that the systemic AIDS-related lymphomas have a more complex etiology than primary central nervous system disease. However, where EBV clonality has been examined, EBV-positive tumours have been uniformly monoclonal (Ballerini *et al.*, 1993; Shibata *et al.*, 1993). Thus, EBV infection precedes clonal outgrowth of

Table 20. Prevalence of Epstein–Barr virus in central nervous system non-Hodglkin's lymphoma and control tissue in relation to HIV status

Reference	Study area	Lymphoma site	EBV detection method	EBV+ non-Hodgkin's lymphoma cases		EBV+ controls		Comments
				HIV+	HIV–	HIV+	HIV–	
MacMahon *et al.* (1991)	Baltimore, USA	CNS	EBER1 ISH	21/21	2/15	0/13	0/6	1/1 HIV–transplant patient EBV-positive
DeAngelis *et al.* (1992)	New York, USA	CNS	BamHI-W PCR	11/13	7/13			
Morgello (1992)	New York, USA	CNS	EBNA-1 PCR	6/12				
Cinque *et al.* (1993)	Stockholm and Milan	CNS	EBER ISH	16/16				
				0/2				
		CSF	EBNA-1 PCR	17/17	1/66		0/10	
				0/2				
Arribas *et al.* (1995)	St Louis, MO, USA	CNS	LMP PCR	6/6				
				1/1				Systemic lymphoma
		CSF	EBNA-1 PCR	4/7[a]		0/16		
				1/1				Systemic lymphoma
			BamHI-W PCR	6/7[b]		1/16		
				1/1				Systemic lymphoma

Abbreviations: CNS, central nervous system; EBER, Epstein–Barr encoded RNA; ISH, in-situ hybridization; EBNA, Epstein–Barr nuclear antigen; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; BamHI-W, first internal repeat sequence; LMP, latent membrane protein

[a] Including 3/6 patients with CNS lymphoma

[b] Including 5/6 patients with CNS lymphoma

Table 21. Prevalence of Epstein–Barr virus in systemic lymphoma tissue in relation to HIV status

Reference	Study area	Histology	EBV detection method	EBV+ non-Hodgkin's lymphoma cases		Comments
				HIV+	HIV–	
Ernberg & Althiok (1989)	Sweden		Southern blot	7/25		1/7 PGL nodes also positive
MacMahon *et al.* (1991)	Baltimore, USA		EBER1 ISH	3/7	0/2	
Shibata *et al.* (1993)	Los Angeles, USA	Diffuse large-cell Immunoblastic Small non-cleaved-cell	EBNA-1 PCR + (EBER-1 ISH or Southern blot)	6/11 17/20 16/28	0/12 1/13 1/12	EBV clonal in 12/12 cases
Carbone *et al.* (1993b)	Aviano, Italy	Diffuse large-cell Immunoblastic Small non-cleaved-cell Anaplastic large-cell	EBER1/2 ISH	1/6 1/1 2/4 3/4		
		Immunoblastic Small non-cleaved-cell Anaplastic large-cell	BamHI-W PCR	2/6 4/11 10/12		
		Diffuse large-cell Immunoblastic Small non-cleaved-cell Anaplastic large-cell	LMP PCR	0/6 3/7 0/15 9/12		
Ballerini *et al.* (1993)	New York, USA	Diffuse large cell Immunoblastic Small non-cleaved cell	Southern blot	1/4 4/4 5/16		EBV clonal in all positive cases
Finn (1995)	New York, USA		Immunohistochemistry	8/17	9/23	Head and neck lymphomas

Abbreviations: PGL, persistent generalized lymphadenopathy; EBER, Epstein–Barr encoded RNA; ISH, in-situ hybridization; EBNA, Epstein–Barr nuclear antigen; PCR, polymerase chain reaction; BamHI-W, first internal repeat sequence; LMP, latent membrane protein

these tumours, which is consistent with an etiological role of this virus. The specific role of EBV in lymphomagenesis is uncertain.

Detection of EBV in lymph nodes from patients with persistent generalized lymphadenopathy has been associated with subsequent non-Hodgkin's lymphoma. Shibata *et al.* (1991) studied 32 patients with persistent generalized lymphadenopathy who were non-Hodgkin's lymphoma-free. Two of 10 patients with EBV-positive lymph nodes versus one of 22 patients with EBV-negative lymph nodes developed non-Hodgkin's lymphoma over a median follow-up of 12 months ($p > 0.1$). [The Working Group noted that insufficient data were presented to allow analysis by survival methods accounting for duration of follow-up.]

(ii) *HHV-8*

HHV-8 is a recently identified human herpes virus that is a nearly universal infection in Kaposi's sarcoma tissues (see Section 2.1.5). In the first report of this virus, Chang *et al.* (1994) examined 27 AIDS lymphomas and 29 non-AIDS lymphomas by PCR. Three (11%) of the AIDS lymphomas and none of the non-AIDS lymphomas had HHV-8 sequences in the tumour tissue.

In a follow-up to this study, Cesarman *et al.* (1995) reported on an examination of 193 AIDS-associated lymphomas in 42 patients from New York, United States, which included the 27 from the report by Chang *et al.* (1994). HHV-8 was detected in all eight tumors associated with lymphomatous effusions (body-cavity based), but not in 185 others without effusions. Furthermore, there were on average 40–80 copies of the HHV-8 sequence per cell, whereas Kaposi's sarcoma tissue contained 1–2 copies per cell. Significantly, all eight tumors also contained EBV detected by PCR, which was clonal by Southern blot in 6/6 cases.

Pastore *et al.* (1995) tested 180 lymphoid malignancies in Italy and Spain. HHV-8 was present in all of three cavity-based lymphomas, but was not found in 177 other non-Hodgkin's lymphomas.

(iii) *HHV-6*

In a French study, the presence of HHV-6 DNA was determined by PCR in HIV-positive and HIV-negative patients with non-Hodgkin's lymphoma or lymph node follicular hyperplasia. Twelve (44%) of the 27 AIDS-associated lymphomas versus seven (35%) of the 20 lymphomas from HIV-seronegative patients contained HHV-6 DNA ($p = 0.51$) (Fillet *et al.*, 1995). HHV-6 prevalence was similar in the hyperplastic lymph nodes from both HIV-positive (2/4, 50%) and HIV-negative patients (5/9, 55%).

In an Italian study, HHV-6 DNA was detected by PCR in DNA extracted from paraffin-embedded tissue from 16 (89%) of 18 HIV-infected individuals. However, nine (64%) of 14 non-lymphoma tissue samples from the same patients also contained detectable HHV-6 (Trovato *et al.* 1995).

In summary, EBV and HHV-8 are almost always found in AIDS-related lymphoma of the brain and body cavity-based lymphomas, respectively, and may be found in other AIDS lymphomas (HHV-8 has been detected in all (14/14) cases of HIV-associated

lymphomas). Their role in the etiology of these malignancies will be examined in Section 4.3. HHV-6 has not been specifically related to non-Hodgkin's lymphoma.

(*e*) *Zidovudine and other therapy*

As non-Hodgkin's lymphoma occurs more frequently in advanced-stage HIV infection, concern has been raised regarding a potential role of antiretroviral therapy in lymphomagenesis. An exceptionally high risk of non-Hodgkin's lymphoma was found in Phase I trials of nucleoside analogues in patients with advanced HIV infection at the National Institutes of Health in the United States (Pluda *et al.*, 1990, 1993). Patients treated with either zidovudine or dideoxyinosine had a 19% risk of non-Hodgkin's lymphoma three years after starting therapy, with no significant difference between these two antiretroviral agents.

Levine *et al.* (1995) performed a case–control study of AIDS-related non-Hodgkin's lymphoma compared with other AIDS diagnoses. The matched odds ratio for prior use of zidovudine was 0.43 (95% CI, 0.17–1.12).

Muñoz *et al.* (1993) examined antiretroviral therapy as a risk factor for non-Hodgkin's lymphoma in a cohort study of homosexual men. They found a protective effect of treatment, with a relative risk of 0.47, which was not statistically significant.

Coté and Biggar (1995) linked AIDS and cancer registries to compare risk for non-Hodgkin's lymphoma before and after zidovudine therapy became available in 1987. The observed : expected ratios for non-Hodgkin's lymphoma incidence were 222 pre-zidovudine (1981–86) and 193 post-zidovudine (1988–90).

Rabkin *et al.* (1993c) examined the incidence of non-Hodgkin's lymphoma in relation to $CD4^+$ count in a cohort of HIV-infected homosexual men. They compared incidence in the periods before and after January 1988 to assess changes after zidovudine was introduced. The cumulative risk for non-Hodgkin's lymphoma at 50 $CD4^+$ cells/mm^3 was $25 \pm 12\%$ before January 1988 and $10 \pm 5\%$ after that date ($p = 0.4$).

In summary, there is no consistent evidence from these studies that antiretroviral therapies increase the risk for non-Hodgkin's lymphomas in AIDS patients.

2.2.5 *HIV-2 and non-Hodgkin's lymphoma*

When they occur, HIV-2-associated non-Hodgkin's lymphomas appear to have clinical features similar to those of HIV-1-associated non-Hodgkin's lymphomas. In a report of three cases of non-Hodgkin's lymphomas associated with HIV-2 infection, all were high-grade malignancies with B-cell immunophenotype (Forjaz Lacerda *et al.*, 1990).

In the study from the Côte d'Ivoire by Lucas *et al.* (1994) (see Section 2.2.4), 7/247 HIV-positive adult decedents had non-Hodgkin's lymphoma. The proportion was similar in patients who were seropositive for HIV-1 (5/154), HIV-2 (1/40) and both (1/53).

2.3 Cervical, anal and other cancers

Cancers other than Kaposi's sarcoma and non-Hodgkin's lymphoma have been studied considerably less often and reported in far fewer HIV-positive patients. Some

positive findings may have been inflated by publication bias, surveillance bias or misclassification with Kaposi's sarcoma and non-Hodgkin's lymphoma; confounding is also possible on account of the existence of several risk factors shared by HIV infection and some neoplasms. Data on cancer occurrence in HIV-infected individuals are particularly inadequate in developing countries, where the largest numbers of AIDS cases occur.

Research attempting to clarify the potential relationship between HIV and anogenital cancers has so far been based primarily on small cross-sectional and case–control studies of populations at particular risk for HIV infection and with the outcome variable being precancerous lesions rather than invasive cancer. The short existence of the HIV epidemic, the initial male predominance, and the young populations at risk have in particular limited the possibilities for studying large numbers of HIV-infected female cases — especially HIV-infected cases with cervical cancer.

Specific genital types of human papillomavirus (HPV) are involved in the etiology of invasive cervical cancer and in some of its precursor lesions. There is also preliminary evidence for an association with anal cancer and anal intraepithelial lesions (IARC, 1995). Both HIV and most known oncogenic types of HPV are sexually transmitted. Therefore, the ability to control for confounding is particularly essential in studying the influence of HIV on anogenital malignancies. The small sample size in many of the studies undertaken so far has limited their ability to control adequately for behavioural covariates and risk factors associated with HIV infection.

2.3.1 *Cervical intraepithelial neoplasia and invasive cancer*

The influence of HIV on invasive cervical cancer and its precursor lesions has been reviewed (Palefsky, 1991; Rabkin & Blattner, 1991; Sillman & Sedlis, 1991; Northfelt & Palefsky, 1992; Braun, 1994; Stratton & Ciacco, 1994).

(*a*) *Precancerous lesions*

(i) *Association with HIV*

In the late 1980s, the first case reports and case series were published which suggested an association between HIV infection and cervical intraepithelial neoplasia (CIN) (Bradbeer, 1987; Byrne *et al.*, 1989; Henry *et al.*, 1989). In a review by Mandelblatt *et al.* (1992), 21 of the earliest case reports and series were described in more detail. Table 22 summarizes relevant data.

In a blind cytological analysis of cervicovaginal smears, a significantly higher percentage of cytological squamous atypia was documented in HIV-positive (11/35; 31%) than HIV-negative women (1/23; 4%) (Schrager *et al.*, 1989). Furthermore, cytological or histopathological findings suggestive of HPV infection were observed in 26% of HIV-positive women compared with 4% of HIV-negative women. [The Working Group noted that the controls in this study were not comparable with HIV-positive cases in terms of sexual behaviour, history of sexually transmitted diseases or frequency of barrier methods used.]

Fruchter *et al.* (1994) estimated that approximately 13% of 482 women referred to a public colposcopy clinic in Brooklyn, NY, United States, with abnormal Papanicolaou

Table 22. Studies of precancerous lesions of the uterine cervix in HIV-infected persons

Reference, study area	No. and type of HIV+ cases	No. and type of HIV− controls	HPV prevalence			Cervical abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	Percentage		Odds ratio (95% CI)			
Schrager *et al.* (1989) USA	35	23	HIV+ HIV−	26% 4%		*Squamous atypia* HIV+ HIV−	31% 4%		Cytological or histopathological findings	Pap smear	HIV-infected: fewer barrier methods, more STD
Feingold *et al.* (1990) USA	35	32	HIV+ HIV−	49% 25%		*SIL* HIV+ HIV−	40% 9%		Southern blot (cervico-vaginal lavage)	Pap smear	48 IVDU 18 heterosexual partners of IVDU
Vermund *et al.* (1991a) USA	51 (18 asymptomatic 33 symptomatic)	45	HIV+ symptomatic asymptomatic HIV−	53% 70% 22% 22%		*SIL* HIV+ symptomatic asymptomatic HIV−	 42% 17% 13%	 12 (1.3–108) [2.0 (0.1–30)] 4.6 (0.8–28)	Southern blot (lavage)	Pap smear	IVDU, heterosexual contacts with IVDU
Byrne *et al.* (1989) UK	19 recruited from HIV+ STD clinic attenders					3 CIN III 1 CIN II 1 Atypia 1 SPI 1 HPV			Colposcopy	Pap smear and biopsy	
ter Meulen *et al.* (1992) Tanzania	46 gynaecological in-patients	313 gynaecological in-patients	*Any type* HIV+ HIV− *HPV 16/18* HIV+ HIV−	 78% 56% 30% 14%	*HPV (total)** 2.5 ($p = 0.02$) *HPV-16/18** 2.4 ($p = 0.02$)	HIV+ HIV−	2.4% 2.8%		PCR	Pap smear	*Adjusted for age
Kreiss *et al.* (1992) Nairobi, Kenya	147 prostitutes	51 prostitutes	HIV+ HIV−	37% 24%	1.7 (0.8–3.6)*	*CIN* HIV+ HIV− *HPV+* HIV+ HIV− *HPV−* HIV+ HIV−	 26% 24% 47% 57% 9% 7%	 0.9 (0.2–3.5) 9.4 (1.7–52.1) 17.3 (1.4–217)		Cytology	*Adjusted for age and years of prostitution

Table 22 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– controls	HPV prevalence			Cervical abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	Percentage		Odds ratio (95% CI)			
Laga *et al.* (1992) Kinshasa, Zaire	47 prostitutes	48 prostitutes	HIV+ HIV– HIV+/CIN+ HIV+/CIN–	38% 8% 73% 30%	6.8 (1.9–26.8) 6.2 ($p = 0.02$)	*CIN* HIV+ HIV–	 27% 3%	 14.7 (1.8–95.3)	ViraType™ Southern blot	Cytology	13 Pap smears inadequate for interpretation
Conti *et al.* (1993) Italy	273 former IVDU	161 former IVDU				HIV+ HIV–	42% 8%	4.2 (2.1-8.4) *HPV–/HIV+* 1.2 (0.2-0.6) *HPV+/HIV–* 10.8 (2.8–41.6) *HPV+/HIV+* 64.0 (19.2–214)	Cytological diagnosis	Cytology confirmed by biopsy	Cross-sectional study, potential selection bias (inflated), odds ratios *CIN II,III/HIV+* CD4⁺ ≥ 500 1.0 CD4⁺ < 500 5.4 (2.6–11)
Maggwa *et al.* (1993) Nairobi, Kenya	205 attenders, family planning clinic	3853 attenders, family planning clinic				HIV+ HIV–	4.9% 1.9%	2.8 (1.3-5.9) adj. sexual behaviour, demographic variables		Cytology	
Van Doornum *et al.* (1993) The Netherlands	25 IVDU and prostitutes	44 IVDU and prostitutes	HIV+ HIV–	32% 7%	6.4 (1.3–40.1)	HIV+ HIV–	0% 4.6%		PCR	Cytology	HIV–: More clients per month than HIV+ women
Smith *et al.* (1993b) UK	43 mostly IVDU	43 matched to HIV+ cases	*HPV-6/11* HIV+ HIV– *HPV-16* HIV+ HIV–	 11.6% 2.3% 11.6% 4.7%		HIV+ HIV–	14% 9%		Southern blot	Histology	Tendency to increased CIN prevalence in HIV+ women with increasing immunosuppression
Ho *et al.* (1994) New York, USA	97 IVDU, HIV-related disease, IVDU partner	110 same	*All HPV types* HIV+ HIV– CD4⁺ > 20% CD4⁺ ≤ 20% *Oncogenic types* HIV+ HIV–	 49.5% 22.7% 45.0% 60.7% 14.4% 6.4%	 3.3 (1.8–6.1) 2.8 (1.3–6.0) 5.3 (2.2–12.7) 3.5 (1.3–9.2)				Southern blot hybridization		*Strong HPV signal*, odds ratios: HIV– 1.0 HIV+ CD4⁺ > 20% 2.6 CD4⁺ ≤ 20% 5.9

Table 22 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– controls	HPV prevalence		Cervical abnormality		HPV test	Pathology reading	Comments
			Percentage	Odds ratio (95% CI)	Percentage	Odds ratio (95% CI)			
Klein *et al.* (1994) New York, USA	114 IVDU, HIV-related disease, sex partner IVDU	139 same			HIV+ 21.9% HIV– 10.1% CD4 > 20% 16.7% CD4 ≤ 20% 35% *Multivariate analysis* HPV infection high-risk HPV Strong HPV signal Low CD4⁺ count	2.5 (1.2-5.1) 1.8 (0.7–4.6) 4.8 (2.0–11.6) 6.8 (2.9–15.7) 11.8 (4.1–34.1) 10.8 (3.5–33.7) 3.1 (1.0–9.5)	Southern blot hybridization	Cytology	No demographic or behavioural variables associated with SIL
Williams *et al.* (1994) San Francisco, USA	55 IVDU	59 IVDU	*Dot blot* HIV+ 19% HIV– 5% *PCR* HIV+ 57% HIV– 13%		9 out of 11 abnormal smears in HIV+	6.1 (1.2–60.5)	ViraType™ and PCR	Cytology	Recruited from larger cohort, see also Table 23
Sun *et al.* (1995) New York, USA	344 cross-sectional	325	*All HPV types* HIV+ 60% HIV– 36% *HPV-16* HIV+ 27% HIV– 17% *HPV-18* HIV+ 24% HIV– 9%	< 0.001	*All HPV types* HIV+/CIN II/III 53% HIV–/CIN II/III 50% *HPV-16* HIV+/CIN II/III 35% HIV–/CIN II/III 0 *HPV-18* HIV+/CIN II/III 35% HIV–/CIN II/III 50%		PCR	Cervico-vaginal lavage, colposcopy and sometimes biopsy	HIV+ HPV+ women had more CIN irrespective of CD4⁺ level than HIV– HPV+ women
Langley *et al.* (1996) Senegal	HIV-1 68 HIV-2 58 both 14 commercial sex workers	619 commercial sex workers	HIV-1+ 57% HIV-2+ 50.0% both 75.0% HIV– 40.1%	2.3 (1.4–3.7) 1.7 (1.0–3.0) 3.9 (1.9–8.1) 1.0	HIV-1 7.5 HIV-2 11.1 both 16.7 HIV– 6.8	1.8 (0.7–4.7) 2.9 (1.2–7.2) 5.2 (1.4–19.6) 1.0 Adjusted for no. of sexual partners and study site	PCR	Cytology	No analysis of the independent effect of HIV and HPV on CIN development was presented

STD, sexually transmitted disease; SIL, squamous intraepithelial lesions; CIN, cervical intraepithelial neoplasia; SPI, subclinical papillomavirus infection; PCR, polymerase chain reaction; IVDU, intravenous drug user; [ ] calculated by the Working Group

smears were HIV-seropositive. A more detailed characterization of 208 of these women showed the 47 HIV-positive women had more advanced CIN, larger cervical lesions and more associated vulvo-vaginal lesions than the 161 HIV-seronegative women.

Johnstone *et al.* (1994) conducted a retrospective case–control study in Edinburgh, United Kingdom, which included IVDU women or women having a seropositive IVDU partner and computer-matched neighbourhood controls. Cytological smears were retrieved subsequently for both cases and controls. There were more abnormal smears from the HIV-seropositive group than from the drug-related seronegative ($p < 0.01$) group or the neighbourhood control group ($p < 0.001$). [The Working Group noted that no information on HPV was presented.]

(ii) *Association with HIV and HPV*

Vermund *et al.* (1991) extended a study by Feingold *et al.* (1990) on HPV-associated disease in women taking intravenous drugs in the United States. In this study of 96 women, non-white subjects were disproportionately represented among HIV-infected women but other behavioural and sociodemographic characteristics were similar. Symptomatic HIV-positive women had more HPV DNA (70%), measured by Southern blot hybridization, compared with asymptomatic (22%) and seronegative women (22%). Among symptomatic HIV-positive women, a strong association between HPV and squamous intraepithelial lesions was documented (odds ratio, 12; 95% CI, 1.3–108), whereas the association was nonsignificant for the other two groups. These and other studies conducted in the late 1980s and early 1990s suggest that more severe HIV disease might exacerbate HPV-mediated cervical cytological abnormalities (Maiman *et al.*, 1991; Schäfer *et al.*, 1991; Johnson *et al.*, 1992; Conti *et al.*, 1993).

In a cross-sectional study of 359 gynaecological in-patients without cancer in Tanzania (ter Meulen *et al.*, 1992), 1/42 (2.4%) HIV-positive women compared with 8/285 (2.8%) HIV-negative women had an abnormal Pap smear. However, none of the HIV-positive women was suspected to be severely immunosuppressed, in view of the lack of severe HIV-related symptoms. HIV-positive women were 3.3 times more likely to be positive for HPV types 16 or 18, as detected by PCR, after adjusting for differences in sexual behaviour, history of sexually transmitted diseases and other factors. [The Working Group noted that no analysis of the association between HPV and smear abnormality by HIV status was presented.]

Kreiss *et al.* (1992) performed a nested case–control study of 147 HIV-positive and 51 HIV-negative women within a large cohort of prostitutes in Nairobi, but did not observe a significant difference with respect to the prevalence of HPV DNA between the two groups (adjusted odds ratio, 1.7; 95% CI, 0.8–3.6). A strength of this study is that the populations studied were relatively homogeneous with respect to sexual behaviour and condom use. Papanicolaou smears were available only for the most recently enrolled 63 women in the study. Among women with cervical HPV DNA, HIV infection was not associated with an increased prevalence of CIN (47% in HIV-positive versus 57% in HIV-negative women).

In contrast, in a somewhat smaller but otherwise similarly designed study conducted in Kinshasa, Zaire, Laga *et al.* (1992) found a significantly higher prevalence of HPV

DNA in HIV-positive cases (18/47; 38%) than in HIV-negative controls (4/48; 8%; odds ratio, 6.8; 95% CI, 1.9–26.8). HPV was detected both by ViraType™ and Southern blot. Eight (73%) of 11 HIV-positive women who had CIN also had HPV DNA detected compared with nine (30%) of 30 with no CIN (Fisher's exact test $p = 0.02$). Cases and controls in this study did not differ in terms of important demographic or sexual behavioural characteristics, but clinical AIDS was more frequent (7% of HIV-positive cases) than in the population studied by Kreiss *et al.* (0.7%).

In a large study of 4058 women attending two semi-urban family planning clinics in Nairobi, Kenya, Maggwa *et al.* (1993) observed CIN on Pap smears of 10/205 (4.9%) HIV-positive women compared with 72/3853 (1.9%) HIV-seronegative women (odds ratio, 2.8; 95% CI, 1.3–5.9) controlled for sexual behaviour and other risk factors. [The Working Group noted that the association with HPV was not evaluated in this study.]

Langley *et al.* (1996) studied the effect of both HIV-1 and HIV-2 on the development of CIN lesions in a cross-sectional analysis of 759 female commercial sex workers in Senegal. After adjustment for number of sexual partners per week and study site, HIV-2 seropositivity was associated with a 2.9-fold increased risk for CIN (95% CI, 1.2–7.2) compared with a 1.8-fold (0.7–4.7) risk in HIV-1 infected women. Women infected with both HIV types had a 5.2-fold increased risk (1.4–19.6). [The Working Group noted that the authors did not report HPV status or $CD4^+$ T-cell counts in these analyses.]

(iii) *HIV, HPV and $CD4^+$ T-cell counts*

Whereas most studies reviewed above have used either HIV-positivity *per se* or degree of severity of HIV-associated disease as a surrogate marker for level of immune status, recent studies have often included an evaluation by $CD4^+$ T-cell count. Ho *et al.* (1994) found that among 207 primarily intravenous drug-using women, young age (less than 35 years) (odds ratio, 2.5; 95% CI, 1.3–4.8) and HIV-positivity (3.0; 1.5–5.7) were the only independent covariates associated with HPV DNA positivity. The association with HIV changed only marginally between the univariate and the multivariate analysis, indicating little influence of confounding. Prevalence of HPV increased with decreasing $CD4^+$ count, from 23% among immunocompetent HIV-negative subjects to 45% in mild or moderate immunosuppressive conditions (HIV-positive and $CD4^+$ percentage > 20%) and to 61% in severe immunosuppression ($CD4^+$ percentage < 20%). Oncogenic HPV types (16, 18, 31, 33 and 35) were not particularly strongly associated with HIV-positivity. A general increase in the quantity of viral copies of HPV detected was indirectly supported by the finding of a significant association between strong Southern blot hybridization signal strength and increasing HIV-induced immunosuppression (see Table 22). Among 29 study subjects who had no sexual exposure in the previous year, 1/16 (6.3%) HIV-seronegative women were HPV-positive compared to 8/13 HIV-positive women (61.5%). [The Working Group noted that this observation supports the conclusion that individuals with HIV-induced immunosuppression are prone to persistent HPV infection rather than self-limiting infection].

The influence of immunosuppression was also evaluated in a cross-sectional study by Williams *et al.* (1994) of 114 intravenous drug users in San Francisco. A close association between HIV, HPV and abnormal cervical cytology was observed (see Table 23).

In a multivariate model of risk factors for cervical epithelial abnormalities which excluded those showing only atypia with inflammation, both cervical HPV detected by dot blot (odds ratio, 32.1; 95% CI, 2.9–354) and HIV-seropositivity with $CD4^+$ T-cell count below 250 cells/mm^3 (odds ratio, 126.8; 95% CI, 7.5–2133) were independent predictors.

Table 23. Relation between human immunodeficiency virus serostatus, presence of cervical human papillomavirus, and cervical cytology (from Williams *et al.*, 1994)

HPV/HIV status	Cervical cytology		Odds ratio	95% CI	*p* value[a]
	Abnormal	Normal			
Dot blot					
HPV–/HIV–	0	47	1		
HPV–/HIV+	5	31	7.3	0.7–354	0.08
HPV+/HIV–	1	2	15.7	0.2–1254	0.2
HPV+/HIV+	4	4	37.6	2.7–1888	0.001
PCR					
HPV–/HIV–	0	41	1		
HPV–/HIV+	3	17	6.8	0.5–367	0.1
HPV+/HIV–	1	6	5.8	0.07–471	0.3
HPV+/HIV+	6	18	12.9	1.4–610	0.009

[a] *p* values compared with referent values (negative/negative)

In a population-based study of HIV-positive women exposed by intravenous drug use or from partners using intravenous drugs in Edinburgh, United Kingdom, Johnstone *et al.* (1994) found an association between prevalence of abnormal smears and reduced $CD4^+$ count ($p < 0.0005$), but there was no clear relation between $CD4^+$ count and the severity of the lesions.

Sun *et al.* (1995) conducted a large cross-sectional study in New York including 325 HIV-seronegative and 344 HIV-seropositive women. The two groups had similar age distribution, income and education. HPV of any type was detected in 60% of HIV-positive women and 36% of seronegative women. HPV-positive women who were also HIV-positive were significantly more likely to have CIN than were HPV-infected HIV-seronegative women. This difference was observed at all levels of immunosuppression. [The Working Group noted that these epidemiological data suggest that the association between HIV and CIN lesions cannot be explained exclusively by activation of a latent HPV infection mediated by HIV-induced immunosuppression. Thus, HIV could have an effect on the development of CIN which is independent of systemic immunosuppression. Such an effect could reflect a direct biological action but could also be a result of confounding by factors for which no adjustment was made, e.g., a behavioural variable linked with HIV seropositivity and often associated with CIN lesions.]

(iv) *Progression of disease and treatment of CIN lesions*

Adachi *et al.* (1993) conducted a prospective study among 48 women with abnormal Papanicolaou smear out of an original cohort of 232 women at high risk for HIV infection in the Bronx, New York. Subsequent colposcopic or histological findings in 36/38 were no more severe than those observed by cytology, indicating that abnormal cytological smears accurately reflect the severity of cervical and vaginal disease in HIV-positive women. Similar results were obtained by Korn *et al.* (1994) and Johnstone *et al.* (1994). A follow-up of between 3 and 37 months, based on small numbers, showed that all three HIV-negative and five out of ten HIV-positive women had normal examinations, whereas three HIV-positive women had persistent disease and two had progression to condyloma (Adachi *et al.*, 1993).

Sha *et al.* (1995) followed 82 HIV-positive women who were seen between 1986 and 1992 at a hospital in Chicago, IL, United States. Among 10 who presented with CIN confirmed by Papanicolaou smears, none developed invasive cervical cancer during a median follow-up time of 13 months (range, 3–61 months).

Maiman *et al.* (1993a) in Brooklyn, NY, found an equal distribution of CIN severity and lesion size among 44 HIV-positive and 125 HIV-negative women. However, more HIV-positive women (39%) developed biopsy-proven recurrent CIN after treatment than HIV-negative women (9%), and, among HIV-positive women, recurrent disease was clearly associated with degree of immunosuppression as measured by $CD4^+$ T-cell count.

Wright *et al.* (1994) performed a retrospective chart review of patients treated by electrosurgical excision for CIN at a hospital in Manhattan, NY, United States, during 1991–92. All patients had at least six months of follow-up or had documented recurrent and/or persistent disease during less than six months of follow-up. Age-distribution and grading of disease stage were similar in HIV-positive and -negative patients, but recurrent and/or persistent CIN occurred significantly more frequently in HIV-positive women (56%, 19/34) than in HIV-negative women (13%, 10/80; $p < 0.001$). In HIV-positive women, the occurrence of recurrent and/or persistent CIN was associated with degree of immunosuppression (> 500 $CD4^+$ cells/mm^3: 20%; ≤ 500 $CD4^+$ cells/mm^3: 61%).

These studies suggest that HIV infection and/or HIV-related immunosuppression accelerate the progression of CIN.

(*b*) *Invasive cervical cancer*

Since January 1993, CDC included invasive cervical cancer as an AIDS-defining illness in HIV-positive women (Centers for Disease Control and Prevention, 1992a) (see Table 5).

(i) *Case series*

Maiman *et al.* (1993b) studied 16 HIV-positive women (19%) out of 84 women below 50 years of age with invasive cervical cancer, at a hospital in Brooklyn. Three were known to be HIV-positive before enrolment whereas 81 were subsequently tested

for HIV. Almost 70% of the HIV-positive patients were at clinical stage III or IV disease, compared with 28% in the HIV-negative group ($p = 0.01$).

Zanetta *et al.* (1995) made a retrospective evaluation of all patients referred during 1991–94 to a hospital in Milan, Italy, with a diagnosis of invasive cervical carcinoma. Six (1.8%) out of 340 women with invasive cervical carcinoma were HIV-positive. The mean age at diagnosis was 30 years (range, 27–36) for the HIV-seropositive women, but 49 for the remaining population. Furthermore, HIV-seropositive women had more advanced disease ($p = 0.04$). [The Working Group noted that four out of the six seropositive women were intravenous drug addicts ($p < 0.0001$).]

(ii) *Prognosis*

Maiman *et al.* (1990, 1993b) reported a poorer response to therapy and a poorer prognosis among HIV-infected patients with invasive cervical cancer in Brooklyn, with higher recurrence and death rates compared with HIV-uninfected patients. The patient's immune status had a significant impact on subsequent disease. Thus, only seropositive patients with $CD4^+$ counts greater than 500 cells/mm^3 had prolonged or disease-free follow-up.

(iii) *Descriptive epidemiology*

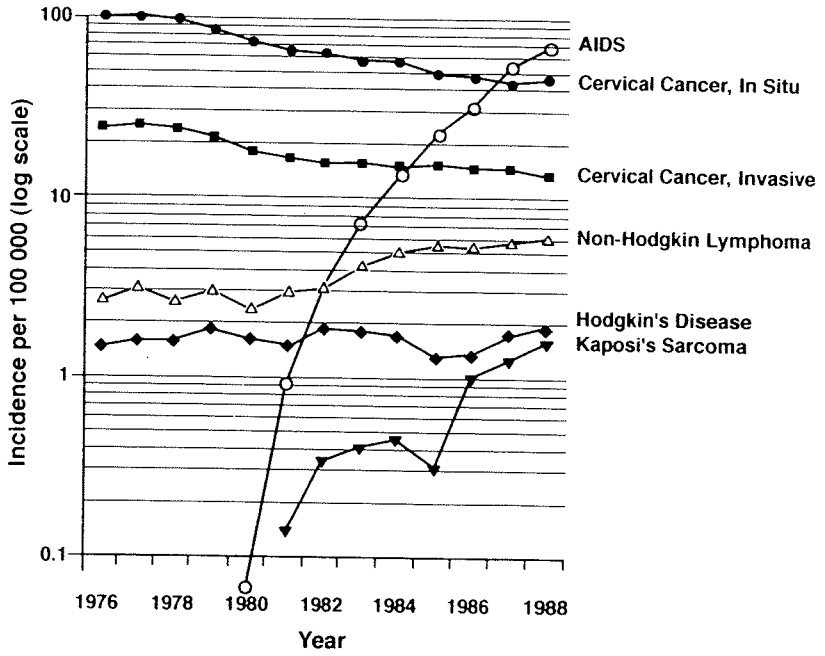
Rabkin *et al.* (1993a) used cancer registry incidence data from New York and northern New Jersey in the United States to study time trends in cervical cancer rates. The annual incidence of AIDS among women in upstate New York is low among white women and also significantly lower in black women compared to women from New York City and northern New Jersey. Nevertheless, cervical cancer in New York and northern New Jersey blacks declined during the study period (1976–88) by approximately 40% for invasive tumors and 50% for in-situ lesions (Figure 9). Because the incidence in whites remained rather stable, the ratio of incidence of invasive cervical carcinoma in blacks to incidence in whites decreased in all three regions.

Data from a pathological review of cervical cancer series from Lusaka, Zambia (Rabkin & Blattner, 1991; Patil *et al.*, 1995) indicated that both the total incidence and the age-distribution of cervical cancer remained stable during the period between 1980 and 1989 when HIV was rapidly spreading to large segments of the population. Nearly 10% of pregnant women and 18% of normal blood donors were already HIV-infected by 1985 (Melbye *et al.*, 1986).

Wabinga *et al.* (1993) compared cervical cancer incidence data for different time periods based on the cancer registry in Kyadondo County in Uganda. Invasive cervical cancer almost doubled from 22.2/100 000 in 1954–60 to 43.6 in 1989–91. The overall increase in cancer incidence during the same period was nearly 50%. [The Working Group noted that the quality of the data is uncertain and the incidence of cervical cancer appears to have been increasing in this population before the advent of HIV.]

In a large linkage study between AIDS and cancer registries in seven health departments in the United States, published as an abstract, Coté *et al.* (1993) found invasive cervical carcinoma in AIDS patients to be only marginally increased over background.

Figure 9. Incidence per 100 000 of AIDS and selected cancers in black New York City women aged 20–49, 1976–1988. Data smoothed by 3-point moving means



From Rabkin *et al.* (1993a)

(iv) *Case–control studies*

In Tanzania, ter Meulen *et al.* (1992) found that 8/270 (3%) cases of invasive cervical cancer were HIV-seropositive compared with 46/359 (13%) controls. [The Working Group noted that many of the controls were gynaecological patients and may have had conditions associated with other sexually transmitted diseases.]

In a study of cancer patients in Rwanda (Newton *et al.*, 1995), 0/23 cases of cervical cancer were HIV-seropositive compared to 8/200 (4%) in controls comprising other cancers.

In summary, the above studies are generally consistent in demonstrating an association between late-stage HIV infection and increased prevalence of CIN. However, there is at present no evidence of a significantly increasing incidence of invasive cervical carcinoma as a consequence of the HIV epidemic. This lack of increased risk of invasive disease may be partly explained by the late spread of HIV infection in the female population. In addition, active screening programmes among HIV-infected women may reduce the likelihood of progression to invasive cervical carcinoma. One result could be that HIV-infected women die from other causes before CIN progresses to invasive cervical carcinoma. HIV-infected women have in general higher rates of sexually transmitted diseases than women in the general population and are therefore more likely to be in close contact with the health care system both before and after their HIV infection.

2.3.2 *Anorectal intraepithelial neoplasia and invasive cancer*

A comprehensive and detailed review of anal cancer in HIV-infected individuals has been presented by Palefsky (1994).

The assessment of anorectal epithelial cytology poses special problems because of variable quality of sample collection and faecal contamination. Furthermore, biopsy materials have only rarely been obtained for confirmation of cytological results. A significant association between cytological and histopathological findings was observed in one study (Palefsky *et al.*, 1990), whereas Surawicz (1993) reported a three-fold greater prevalence of dysplasia for biopsy evaluation than by cytology in 90 homosexual men referred for internal lesions from a cross-sectional community-based study (see Table 24).

Table 24. Correlation of anal abnormalities with histological diagnosis

Anoscopic abnormalities	Negative	Low grade (AIN I)	High grade (AIN II-III)	Total
Discrete warts	3	26	8	37[a]
Circumferential ring of warts	2	14	7	23
Flat white epithelium	1	11	6	18
Normal or non-HPV-associated findings	7	0	1	8[a]
Total	13	51	22	86[a]

From Surawicz *et al.* (1993)

AIN, anal intraepithelial neoplasia

[a]Biopsies from two HIV-seronegative men in each of these categories were unsatisfactory.

(*a*) *Precancerous lesions*

(i) *Association with HIV*

Denis *et al.* (1992) studied 190 patients diagnosed with advanced HIV-associated disease (Group IV, CDC). Thirty-five patients had anal abnormalities, including one case of non-Hodgkin's lymphoma, but there was no case of anal carcinoma.

(ii) *Association with HIV and HPV*

The main features and results of published studies are summarized in Table 25.

Frazer *et al.* (1986) reported, from a prospective study of 61 homosexual men in Australia, cytological evidence of dysplasia with concomitant features of HPV infection in 24 men and of HPV without dysplasia in a further 26 men. HIV infection was associated with dysplasia in a univariate analysis, but the small sample size hindered more sophisticated analyses.

Table 25. Studies of precancerous lesions of the anorectal region in HIV-infected persons

Reference, study area	No. and type of HIV+ cases	No. and type of HIV− cases	HPV prevalence			Anal abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	% HIV+/HIV-		Odds ratio (95% CI)			
Frazer *et al.* (1986) Australia	20 homosexual men	41 homosexual men				HIV+ HIV−	[45%] [15%]		Cytological reading	Cytology	
Palefsky *et al.* (1990) San Francisco, USA	97 homosexual men with CDC group IV disease	None	HPV, all types HPV-6/11* HPV-16/18* HPV-31,33,35*	54% 23% 29% 20%		HIV+ condyloma atypia AIN I AIN II	39% 4 19 11 4		ViraType™	Cytology + histology	*Alone or in combination
Melbye *et al.* (1990) Denmark	33 homosexual men	87 homosexual men	HIV+	61.1%				*ASIL+HPV* CD4⁺/CD8⁺ ratio ≥ 1.0 < 1.0	ViraType™ 5.9 30.0	Cytology (ASIL)	
Caussy *et al.* (1990) USA	43 homosexual men	62 homosexual men	HIV+ HIV−	53% 29%	$p = 0.01$	HIV+ HIV−	24% 7%	$p = 0.03$	ViraType™ and PCR	Cytology (ASIL)	
Kiviat *et al.* (1990) USA	49 homosexual men	47 homosexual men	HIV+ HIV−	26% 6%					ViraType™		
Critchlow *et al.* (1992) USA	26 consecutive homosexual men for HIV testing	119 same	HIV+ HIV−	31% 8%	5.8 (1.1–30.1) adj. for STD history, age, anorectal symptoms				Dot filter hybridization		HIV positivity did not influence type of HPV. HPV prevalence up with severity of HIV-disease
Bernard *et al.* (1992) France	54 homosexual and IVDU men	54 partners of women with genital HPV or cervical dysplasia	*HIV+* Any type HPV-6/11 HPV-16/18 and/or 31/35/51 *HIV−* Any type HPV-6/11 HPV-16/18 and 1/35/51	 [66%] 17% 83% [54%] 62% 38%					In situ hybridization		Link between CMV and high-risk HPV observed irrespective of HIV status

Table 25 (contd)

Reference, study area	No. and type of HIV+ cases	No. and type of HIV– cases	HPV prevalence			Anal abnormality			HPV test	Pathology reading	Comments
			Percentage		Odds ratio (95% CI)	% HIV+/HIV-		Odds ratio (95% CI)			
Kiviat *et al.* (1993) USA	285 homosexual men seeking HIV testing	204 same	*Southern blot*		4.0 (2.7–6.2)	HIV+	26%	5.6 (3.0-10.5)	Southern transfer hybridization and PCR	Cytology Bethesda recommendation	*Southern transfer hybridization*
			HIV+	55%		HIV–	8%	*HIV+*			CD4⁺ ≤ 500 2.6 (1.2-5.7)
			HIV–	23%		*HIV+ only*					CD4⁺ > 500 1.0
			PCR			Atypia:		Atypia:			*PCR alone*
			HIV+	92%	3.1 (1.6–5.8)	CD4⁺ < 200	28%	4.2			CD4⁺ ≤ 500 6.3 (0.8-72.2)
			HIV–	78%		200–500	25%	3.3			CD4⁺ > 500 1.0
						501–800	25%	2.7			
						> 800	30%	2.6			
						ASIL:		ASIL:			
						CD4⁺ < 200	36%	9.9			
						200–500	35%	8.7			
						501–800	25%	5.1			
						> 800	8%	1.3			
Breese *et al.* (1995) Denver, USA	93 homosexual men	116 homosexual men	*HIV+*						ViraPap™/ ViraType™	None	HPV prevalence associated with increasing immunodeficiency
			HPV, any type	61%							
			HPV-6/11	8%							
			HPV-16/18	12%							
			HPV-31/35/35	18%							
			Mixed HPV-16/18+	19%							
			Mixed HPV-16/18–	4%							
			HIV–								
			HPV, any type	17%							
			HPV-6/11	4%							
			HPV-16/18	7%							
			HPV-31/33/35	0.8%							
			Mixed HPV-16/18+	4%							
			Mixed HPV-16/18–	0.8%							

ASIL, anal squamous intraepithelial lesions; PCR, polymerase chain reaction; IVDU, intravenous drug users; STD, sexually transmitted disease; CMV, cytomegalovirus

Kiviat *et al.* (1990) reported that 13/49 (26.5%) HIV-infected homosexual men compared with 3/47 (6.4%) HIV-negative homosexual men had detectable anal HPV by dot-blot hybridization ($p = 0.002$). No data on anal cytology or histology were available.

Critchlow *et al.* (1992) reported a significant association between HIV infection and HPV DNA as measured by dot filter hybridization, after adjustment for sexually transmissible disease history, age and current anorectal disease (odds ratio, 5.8; 95% CI, 1.1–30.1). HIV infection was not associated with the type of HPV detected but the severity of HIV-related disease was positively related to HPV prevalence.

In anal swabs or biopsies from homosexual men, Critchlow *et al.* (1995) reported a progressive increase in the detection of HPV-16 or HPV-18 DNA with declining $CD4^+$ T-cell count.

Bernard *et al.* (1992) studied 54 HIV-positive and 54 HIV-negative men, all presenting with anogenital lesions such as flat condyloma or condyloma acuminata. HIV-positive subjects were homosexual men (71%) or intravenous drug users (24%). HIV-negative subjects were partners of women with genital HPV infection or cervical dysplasia. High-risk types of HPV (16, 18, 31, 35, 51) were more prevalent (83.4%) in HIV-positive persons and the low-risk HPV types (6, 11) were more common in HIV-negative subjects (62.1%). Anal intraepithelial neoplasia (AIN) II/III was highly associated with high-risk HPV types (15/16, 94%) compared with low-risk HPV (1/24, 6%).

(iii) *HIV, HPV, and $CD4^+$ T-cell count*

Palefsky *et al.* (1990), in their study of 97 homosexual men with advanced HIV infection in San Francisco, CA, United States, found HPV DNA (detected by ViraPap™/ViraType™) in 54% and abnormal anal cytology in 39% (for details see Table 25). AIN was diagnosed in 15 specimens (15%). Abnormal cytology was significantly associated with anal HPV infection (odds ratio, 4.6; $p = 0.003$) and, among those infected with two or more HPV types, 10/12 had abnormal anal cytology (odds ratio, 39.0). $CD4^+$ counts obtained from medical records were inversely associated with cytological abnormality but did not contribute significantly in a multiple regression model which also included HPV.

Caussy *et al.* (1990) found that 41 (39%) of 105 homosexual men from Washington DC, and New York, United States, had infection with HPV-6/11, -16/18, or -31,33,35. The corresponding figures were 53% in 43 HIV-infected subjects and 29% in 64 HIV-negative subjects ($p = 0.01$). In HIV-infected subjects, low $CD4^+$ count was independently associated with anal HPV detection, whereas the number of partners and the frequency of receptive anal intercourse were unimportant. Abnormal cytology was seen in 9/37 (24%) HIV-infected men and in 4/55 (7%) HIV-negative men ($p = 0.03$) and was strongly associated with the detection of any HPV genotype. None of 15 subjects with HPV detected only by PCR had anal epithelial abnormality.

In a sample of 112 Australian homosexual men consecutively presented for routine screening for sexually transmitted diseases and HIV infection, 19% showed evidence of mild to moderate dysplastic changes (AIN I or AIN II). HPV DNA (types 6/11, 16/18) by dot blot hybridization was detected in 40% (6/11 in 18%; 16/18 in 11%; both groups in

12%). There was a significant association between presence of HPV-16/18 and anal dysplasia, but not between HPV infection or anal dysplasia and HIV-positivity, immune status, sexual practices or other sexually transmitted diseases (Law *et al.*, 1991).

In a larger study (Kiviat *et al.*, 1993), a random sample of 285 HIV-positive and 204 HIV-negative homosexual men was surveyed. HPV DNA was found by Southern blot hybridization in 55% and 23% (odds ratio, 4.0; 95% CI, 2.7–6.2) of HIV-positive and -negative men and by PCR in 92% and 78% (odds ratio, 3.1; 95% CI, 1.6–5.8), respectively. Each specific group of HPV DNA types surveyed was most common in HIV-infected men (Table 26). Detection of HPV by both Southern blot hybridization and PCR (high-level HPV infection) was significantly associated with anal intraepithelial lesions. However, after adjustment for level of HPV DNA, severely immunosuppressed HIV-positive men ($CD4^+$ count < 500 cells/mm^3) were at higher risk for anal intraepithelial lesions than men with a $CD4^+$ count of more than 500 cells/mm^3 (odds ratio, 2.9; 95% CI, 1.4–6.2). [The Working Group noted that this finding indicates a possible independent role of immunosuppression in addition to that of HPV].

Table 26. Prevalence of anal HPV DNA in HIV-positive and HIV-negative homosexual men as detected by dot-filter hybridization, low- and high-stringency Southern transfer hybridization, and PCR

	HIV+	HIV–	OR	95% CI
Dot blot	(*n* = 304)	(*n* = 211)		
Any HPV	52%	18%	5.1	3.3–7.9
Southern	(*n* = 285)	(*n* = 204)		
Any HPV	55%	23%	4.0	2.7–6.2
HPV-16,18[a]	21%	7%	5.0	2.6–9.6
HPV-31,33,35[a]	15%	3%	8.7	3.5–25.7
HPV-6,11[a]	21%	7%	5.0	2.6–9.6
Unclassified	16%	8%	3.7	1.7–6.3
Multiple	15%	3%	8.5	3.4–25.2
PCR	(*n* = 241)	(*n* = 152)		
Any HPV	92%	78%	3.1	1.6–5.8
HPV-16,18	53%	38%	3.6	1.8–7.2
HPV-31,33,35	43%	15%	7.4	3.4–16.2
HPV-6,11	47%	39%	3.1	1.6–6.2
Unclassified	19%	22%	2.2	1.0–4.9
Multiple	44%	23%	4.9	2.4–10.1

From Kiviat *et al.* (1993)
[a] Alone or in combination

Sixty-six (22%) HIV-positive and 24 (11%) HIV-negative men from the above-mentioned study were referred for biopsies of internal anorectal lesions (Surawicz *et al.*, 1993). Whereas only 31 (36%) had dysplasia diagnosed by cytology, 73/86 (85%) had dysplasia evident on biopsy (26% high-grade). The correlations of anal abnormalities

with histological diagnosis are presented in Table 24. HIV status did not influence the prevalence of high-grade lesions. Both high- and low-risk HPV types were common in many of the biopsy specimens.

In a study of 37 HIV-positive and 28 HIV-negative homosexual men, Palefsky *et al.* (1994) found both anal intraepithelial lesions and the presence of HPV to be closely associated with HIV-positivity in men with $CD4^+$ T-cell counts below 200 cells/mm^3. Furthermore, multivariate analysis indicated a possible influence of current smoking.

Several studies among women are in progress, but the results of only one have been published (Williams *et al.*, 1994). Among 114 intravenous drug users, anal infection with HPV was twice as frequent as cervical infection and was associated with HIV-positivity by both dot blot (odds ratio, 2.5; 95% CI, 0.9–7) and PCR (2.6; 1.03–6.8). Anal intraepithelial lesions were seen in 14% (15/109) of the women, of whom 11 were HIV-infected (odds ratio, 3.4; 95% CI, 0.9–15.5). The presence of anal squamous intraepithelial lesions (ASIL) was closely associated with a simultaneous high level (dot blot positive) of HPV DNA and HIV-positivity (odds ratio, 9.2; 95% CI, 1.6–63.6), whereas no association was found with $CD4^+$ count.

Breese *et al.* (1995) studied the expression of HPV in a cross-sectional, follow-up study of 116 HIV-seronegative and 93 HIV-seropositive homosexual men. HPV was significantly more common among HIV-positive persons and HPV types 16/18 accounted for more than 50% of the infections. HPV prevalence increased significantly with decreasing $CD4^+$ count; persistence of HPV during a six-month follow-up was also more common among men with clinical signs of severe immunosuppression (AIDS/ARC (AIDS-related complex)) (95%) compared with asymptomatic HIV-seropositive men (62%) and HIV-seronegative men (61%).

(iv) *Progression of disease*

Irrespective of HIV status, there are few data available relevant to the association between the different intraepithelial lesions and invasive anal cancer.

In San Francisco, Palefsky *et al.* (1992) followed 37 homosexual men with advanced HIV disease prospectively for an average of 17 months and found an increase in anal epithelial abnormality from 27% to 65%. The percentage of men with AIN increased from 8 to 32% and that of men with high-grade AIN from 0 to 16%. Presence of HPV DNA (detected by Virapap™/Viratype™) increased from 60 to 89%.

Morgan *et al.* (1994) identified all patients who had undergone excision biopsy of anal condylomata during 1984–88 at a hospital in London, United Kingdom. Overall, 27 had evidence of AIN and for these patients, results of HIV testing were traced. Five of six patients having carcinoma *in situ* (AIN III) were found to be HIV-seropositive and were followed for between four and six years without any evidence of progression of disease.

(*b*) *Invasive anal cancer*

(i) *Case reports and series*

Only a few case reports and series describe invasive anal cancer in HIV-infected persons (Rüdlinger & Buchmann, 1989; Lorenz *et al.*, 1991; Chadha *et al.*, 1994; Jebakumar *et al.*, 1994; Nasti *et al.*, 1994). Most cancers occurring in the anal region are of the (transitional) epidermoid type. Other anal cancers associated with HIV include small-cell carcinoma (Read *et al.*, 1985; Smitherman *et al.*, 1990; Nakahara *et al.*, 1993), non-Hodgkin's lymphoma and Kaposi's sarcoma.

(ii) *Prognosis*

Very little information is available on the possible influence of HIV infection on the prognosis of anal cancer. Some cases have shown an aggressive clinical course with low response to treatment (Lorenz *et al.*, 1991; Jebakumar *et al.*, 1994), whereas others have not (Chadha *et al.*, 1994; Nasti *et al.*, 1994).

(iii) *Descriptive epidemiology*

Reports from Sweden, Denmark and the United States have shown significant increases in the incidence of epidermoid anal cancer over the last 30 years, not only during the period of the AIDS epidemic (Goldman *et al.*, 1989; Frisch *et al.*, 1993; Melbye *et al.*, 1994a). The increase has been more pronounced in women than in men and more in urban than in rural areas. Furthermore, black people are at higher risk than whites and never-married men are at higher risk than ever-married men. The increased risk of anal cancer in never-married men has been documented as early as the 1940s and 1950s (Frisch *et al.*, 1993). These trends suggest that important behavioural and environmental changes were taking place before the beginning of the AIDS epidemic.

Melbye *et al.* (1994a) compared the proportion of men who were never-married (as a surrogate for homosexuality) among anal cancer patients with that in colon cancer patients (controls) in four metropolitan areas (San Francisco–Oakland, CA; Detroit, MI; Seattle, WA; Atlanta, GA) included in the SEER Programme in the United States. The relative risk for anal cancer patients rose from 5.8 (95% CI, 3.9–8.7) in 1973–78 to 6.7 (4.7–9.5) in 1979–84 and 10.3 (7.5–14.1) in 1985–89 ($p_{trend} = 0.02$). Among white men from the San Francisco Bay area, the incidence of anal cancer increased from 0.5/100 000 in 1973–75 to 1.2/100 000 in 1988–89 ($p_{trend} < 0.001$).

Biggar *et al.* (1987) and later Rabkin and Yellin (1994) used data from the SEER programme to study the evolution in anal cancer incidence in single, young (25–54 years) men within the city of San Francisco. The incidence of anal cancer in 1973–79 was 9.9 (95% CI, 4.5–18.7) times that expected from general population rate and in 1988–90 was 10.1 (95% CI, 5.0–18.0) times that expected.

Biggar *et al.* (1989) used a proportional incidence method to study cancers (period 1973–85) occurring among single young men and married young men in New York. A significant increase in anal/anorectal cancers was recorded for single but not for married men. However, the increase appeared to have already occurred by 1979–80, without a clear increasing trend thereafter.

Reynolds *et al.* (1993) linked AIDS registry files (San Francisco residents only) with the California Tumor Registry (period 1980–87) and compared the incidence of cancer in the AIDS population with that of the general population of the San Francisco Bay Area. Six cases of anal or rectal cancer were seen among the AIDS patients, which were more than expected (standardized incidence ratio [SIR], 3.5; 95% CI, 1.3–7.5). In-situ cancer of the anorectal area was also significantly elevated among persons with AIDS (7 cases; SIR, 65; 95% CI, 26.1–134). The SIR analysis included cancers that occurred before, concurrently with and subsequent to the diagnosis of AIDS.

Melbye *et al.* (1994b) used a linkage between AIDS (50 050 reports) and cancer (859 398 reports) registries in seven health departments in the United States to investigate the association between HIV infection and epidermoid anal cancer. Compared with general population rates, the relative risk for anal cancer at and after AIDS diagnosis was 84.1 (95% CI, 46.4–152) among homosexual men and 37.7 (9.4–151) among non-homosexual men. The relative risk was 13.9 (6.6–29.2) for occurrence of anal cancer in the period two to five years before AIDS diagnosis and 27.4 (15.9–47.2) during the two years before AIDS diagnosis (p for trend = 0.004) (Table 27).

Table 27. Relative risk (observed/expected ratio) of epidermoid anal and anorectal cancer among AIDS patients compared with population controls matched for age, sex, and race

Time from AIDS diagnosis	No. of cases		Relative risk (95% CI)
	Observed	Expected	
2–5 years before	7	0.502	13.9 (6.6–29.2)
0.25–2 years before	13	0.475	27.4 (15.9–47.2)
0.25 years before or after	9	0.113	79.6 (41.4–153)
0.25–0.75 years after	3	0.072	41.7 (13.4–129)
> 0.75–2.25 years after	4	0.082	48.7 (18.3–130)

From Melbye *et al.* (1994b)

In summary, the above studies are generally consistent in demonstrating an association between HIV infection (and the associated immunodeficiency) and anal dysplasias. However, even in the absence of HIV infection, anal cancer is more common in AIDS risk groups. Thus, a specific association of HIV infection with invasive cancer has not been convincingly demonstrated.

2.3.3 *Hodgkin's disease*

Misclassification of non-Hodgkin's lymphoma cases as cases of Hodgkin's disease occurs (Herndier & Friedman, 1992; Reynolds *et al.* 1993; Rabkin & Yellin, 1994; Knopf & Locker, 1995) and may at least partly explain the reported increased rates of Hodgkin's disease in HIV-positive persons. Non-Hodgkin's lymphoma incidence is

greatly increased in HIV-positive persons and only a small misclassification rate of these cases would cause a false impression of an elevation in rates of Hodgkin's disease (Glaser & Swartz, 1990). Assignment to a specific type is particularly difficult for those cases of Hodgkin's disease that have been reported in HIV-positive persons with an atypical lymphoid background. Sometimes even unusual atypical reactive processes make a firm diagnosis rather difficult (Herndier & Friedman, 1992).

(*a*) *Distribution of histological types*

(i) *Hodgkin's disease in HIV-uninfected persons*

Hodgkin's disease is a heterogeneous entity which is often described as two different diseases. In developed countries, it has a bimodal age–incidence curve with a first peak at 15–34 years and another among persons older than 55 years of age. Histologically, nodular sclerosis is primarily diagnosed in young Hodgkin's disease patients, whereas mixed cellularity predominates in the older age groups. Population-based data from the SEER programme show a significant increase in the incidence of nodular sclerosis, particularly in adolescents and young adults, whereas the mixed cellularity type has remained stable over time. A decrease in incidence in recent years among older age groups was explained by earlier misclassification of non-Hodgkin's lymphoma as Hodgkin's disease. Among 9418 microscopically confirmed cases of Hodgkin's disease reported to the SEER programme between 1973 and 1987, 51.0% were of the nodular sclerosis type, 23.8% of mixed cellularity, 6.7% with lymphocytic predominance, 5.7% with lymphocytic depletion and 12.8% were miscellaneous Hodgkin's disease (Medeiros & Greiner, 1995).

(ii) *Hodgkin's disease in HIV-infected persons*

Since the mid-1980s, a large number of case reports and small case series of Hodgkin's disease in HIV-infected persons have appeared (see Rubio, 1994) which, together with larger and more recent case series (Table 28), describe a particular natural history and histological distribution of Hodgkin's disease which are different from those of Hodgkin's disease in HIV-uninfected persons. Despite a young median age of the patients, mixed cellularity and lymphocyte depletion are the predominant histological features. The majority of cases have B symptoms and approximately 80% have advanced disease (stages III or IV). Extranodal dissemination and, in particular, bone marrow involvement are common, whereas mediastinal involvement is less frequent than is observed in HIV-uninfected persons (Rabkin & Blattner, 1991; Tirelli *et al.*, 1995b).

The Italian Cooperative Group on AIDS-related Tumors (GICAT) in 1988 and subsequently Monfardini *et al.* (1991), Tirelli *et al.* (1992), Serraino *et al.* (1993), Errante *et al.* (1994) and Tirelli *et al.* (1995b) have described cases of Hodgkin's disease in HIV-infected persons. Among 63 cases in intravenous drug users (median age, 27 years), reported to the organization during 1980–89, 74% were histologically characterized as showing mixed cellularity or lymphocyte depletion. Overall, 83% were in advanced stage, but atypical presentations (central nervous system, skin, endobronchial site or lung involvement with lack of mediastinal adenopathy) were uncommon (Monfardini *et al.*, 1991).

Table 28. Characteristics of Hodgkin's disease in HIV-infected persons (only studies with more than 20 cases)

Reference	Period	*N*	Age median (range)	Male no.	Female no.	Histopathology				Advanced stage (III, IV)	B symptoms	Extra nodal	Bone marrow involvement
						Mixed cellularity	Lymphocyte depletion	Nodular sclerosis	Lymphocytic predominance				
Rubio (1994) Spain	1984–91	46	27 (mean) (18–55)	43	3	41%	22%	22%	4%	89%	83%	50%	41% at diagnosis
Andrieu *et al.* (1993) France	1987–89	45[a]	30	39	6	49%	4%	40%	0	75%	80%	in all stage IV	[24%]
Monfardini *et al.* (1991) Italy	1980–89	63	27 (20–44)	59	4	48%[b]	23%	23%	0	83%	NR		
Tirelli *et al.* (1995b) Italy	1986–94	114[c]	29 (19–57)	103	11	45%	21%	30%	4%	81%	77%	63%	
Ree *et al.* (1991) USA	1983–90	24	34 (24–51)	23	1	100%	0	0	0	92%	100%		50% at presentation, confirmed in 25% by biopsy

[a] Three cases had undetermined histological subtype.
[b] 3% had lymphocyte depletion and mixed cellularity
[c] Seven cases not classified histopathologically

Tirelli *et al.* (1995b) compared 114 HIV-positive cases reported to GICAT during 1986–94 with 104 HIV-negative cases of Hodgkin's disease from a single institution. HIV-positive cases included a higher percentage of stage IV disease despite a lower median age.

Andrieu *et al.* (1993) compared all 45 cases of Hodgkin's disease collected by the French registry of HIV-associated tumours between 1987 and 1989 with a cohort of 407 HIV-negative Hodgkin's disease patients for whom similar diagnostic criteria had been used. The groups had a similar median age (30 and 31 years) but differed significantly with respect to advanced clinical stage (75% versus 33%), proportion of mixed cellularity (49% versus 20%) and absence of mediastinal disease (87% versus 29%).

In a series of 46 patients with Hodgkin's disease and HIV infection diagnosed in 1984–91 in nine hospitals in Madrid, Spain, 41% were classified as being of mixed cellularity, 22% with lymphocytic depletion, 22% with nodular sclerosis and 4% with lymphocytic predominance. Advanced disease (stages III or IV) was found in 89%; 83% had B symptoms and 41% had bone marrow involvement (Serrano *et al.*, 1990; Rubio, 1994).

(iii) *Prognosis*

Hodgkin's lymphoma in the immunocompromised host is particularly aggressive and difficult to treat (Carbone *et al.*, 1991).

Errante *et al.* (1994) studied treatment response and survival in 84 Italian HIV-negative and 92 HIV-positive patients. Remission was achieved in 51% of HIV-infected patients and in more than 90% of the HIV-negative patients. When HIV-infected patients were compared with only the older HIV-negative patients, who were primarily diagnosed with the mixed cellularity type of Hodgkin's disease, similar differences were observed. The estimated four-year survival was 33% in HIV-positive patients compared with 88–100% in HIV-negative patients, depending upon the age group.

In the French study, Roitmann *et al.* (1992), Andrieu *et al.* (1993) and Lévy *et al.* (1995) found a high rate (79%) of complete remission after standard therapy in 45 HIV-positive Hodgkin's disease patients, but haematological and infectious complications were very frequent. Overall, two-year survival was 41%.

Other authors have found full remission in HIV-positive persons to range between 47% and 58% (Serrano *et al.*, 1990; Monfardini *et al.*, 1991; Tirelli *et al.*, 1995b).

(*b*) *Descriptive epidemiology*

Already in the early 1980s, analyses of data from the SEER programme detected marked increases in the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among never-married young men, but no similar increase in Hodgkin's disease was observed (Biggar *et al.*, 1985; Bernstein *et al.*, 1989). Among never-married young men from San Francisco, CA, United States, Biggar *et al.* (1987) found a small but non-significant increase while Rabkin and Yellin (1994) observed an increase which predated the AIDS epidemic and which was not restricted to the mixed cellularity subtype most often associated with HIV-positive cases of Hodgkin's disease. Analyses of data from a cancer registry in New York State, not part of the SEER programme, revealed an abrupt

increase in Hodgkin's disease among never-married men in 1985 (Biggar *et al.*, 1989), whereas a study of women based on cancer registry data from New York and New Jersey did not detect an increase in the incidence of Hodgkin's disease during 1976–88 (Rabkin *et al.*, 1993a).

Medeiros and Greiner (1995) studied trends in Hodgkin's disease over three time periods (1973–77, 1978–82 and 1983–87), using data from the SEER programme. In San Francisco County, where young men are known to have a high prevalence of HIV infection, the age-specific incidence rates for Hodgkin's disease of mixed cellularity increased for men and was the most common subtype by the age of 50. This was in contrast to an unchanged age-adjusted rate among men based on the entire SEER database.

In another study based on SEER data, the risk was evaluated of developing another primary cancer after a diagnosis of Kaposi's sarcoma. Because of the more than 40 000-fold increase in risk for Kaposi's sarcoma among never-married men since the beginning of the HIV epidemic, this tumour was used as a surrogate for HIV-positivity. No indication of an increased risk for Hodgkin's disease was found among never-married men with Kaposi's sarcoma (Biggar *et al.*, 1994).

(*c*) *Cohort studies*

Reynolds *et al.* (1993) linked data from AIDS and cancer registries in San Francisco between 1980 and 1987. Compared with concurrent population rates for the same geographical area, the SIR for Hodgkin's disease in men with AIDS increased from 1.9 in 1980–81 to 18.3 in 1986–87. This observation was based on only 16 cases and the standardized intervals overlapped for each of the four periods studied. [The Working Group noted that the SIR analysis included 14 cases in which Hodgkin's disease was diagnosed before the AIDS diagnosis. This would tend to overestimate the risk in AIDS patients when comparing with population rates, because these cases entered the analysis only if they survived until AIDS diagnosis.]

Hessol *et al.* (1992) compared the risk for Hodgkin's disease in a cohort of 6704 homosexual men from the San Francisco City Clinic Cohort study with population-based rates from the SEER programme. Information on cancer events in the cohort was obtained by computer-matched identification of participants with the records of the Northern California Cancer Center registry. Among HIV-infected men, the age-adjusted standardized relative risk for Hodgkin's disease was 5.0 (95% CI, 2.0–10.3).

Ragni *et al.* (1993) found no increased incidence of Hodgkin's disease among 3041 haemophiliacs from the United States during 1978 and 1989. In fact, no case of Hodgkin's disease was reported among the 1295 HIV-positive patients.

In the NCI Multicenter Haemophilia Cohort Study, there were two cases of Hodgkin's disease among 1065 HIV-seropositive subjects and one case among 636 HIV-seronegative subjects (Rabkin *et al.*, 1992). These cases were 6.6 and 8.2 times the expected frequencies in HIV-seropositive and HIV-seronegative subjects, respectively, although neither excess was statistically significant.

Lyter *et al.* (1995) studied cancer events occurring during 1984–93 in a cohort of 769 HIV-seronegative and 430 HIV-seropositive homosexual men in Pittsburgh, PA, United States. Cancer information was collected through semiannual visits, medical records and death certificates. There was no difference in Hodgkin's disease rates between the seronegative homosexual men and the general male population of Pennsylvania, whereas two cases observed in the HIV-seropositive group were more than expected (SIR, 19.8; 95% CI, 2.4–71.5).

(*d*) *Cofactors*

Little is known about potential cofactors for Hodgkin's disease occurring in HIV-positive persons. HIV-positive persons express a higher proportion of EBV-positive B-lymphocytes that are capable of spontaneous outgrowth *in vitro* than HIV-uninfected persons (Birx *et al.*, 1986).

Moran *et al.* (1992) used PCR to detect the presence of EBV DNA sequences in 10 HIV-positive patients with Hodgkin's disease. Eight (80%) were positive for EBV, compared with 23 (40%) of 57 specimens from HIV-negative patients with Hodgkin's disease.

Tirelli *et al.* (1995b) observed the expression of the EBV-encoded latent membrane protein-1 (LMP-1) in the diagnostic Reed–Sternberg cells (Mueller, 1996) in 14/18 (78%) HIV-positive and 27/104 (25%) HIV-negative Hodgkin's disease patients ($p < 0.001$). Monoclonal expression of EBV genomes was found in 8/10 (80%) tumours from HIV-infected persons compared with 12/44 (38%) tumours from HIV-negative individuals. Using PCR-based amplification of EBNA-2-specific sequences, the authors showed 6/11 EBV-positive tumours in HIV-positive persons to contain type 2 EBV compared with 1/26 such tumours from HIV-negative persons. The great majority of tumour biopsies from HIV-1-positive patients with Hodgkin's disease have been consistently found to be positive for the EBV genome or viral proteins (Mueller, 1996).

In summary, the above studies indicate that Hodgkin's disease in the presence of HIV infection is more likely to have mixed cellularity or lymphocyte-depleted histology and is clinically more aggressive. Absolute Hodgkin's disease incidence may also be elevated in HIV-infected persons, particularly injecting drug users, but an association is not proven because of the modest magnitude of the observed increases and the diagnostic overlap with non-Hodgkin's lymphoma.

2.3.4 *Testicular cancer*

The incidence of both testicular germ-cell tumours and infection with HIV is highest in young men aged 20–40 years. It is to be expected that a proportion of testicular cancer patients will be HIV-positive by chance.

(*a*) *Case reports and series*

A number of case reports and small case series of testicular cancer in HIV-infected men have been published. Some of these have been summarized by Csiszar and Zimmern (1993) and Buzelin *et al.* (1994) and together with other series (Moyle *et al.*, 1991;

Bernardi *et al.*, 1995; Timmerman *et al.*, 1995) constitute a total of at least 120 cases. Of these, five were reported as being lymphomas, often with accompanying extensive systemic disease. The remaining cases were testicular germ-cell tumours. Seminomas were the most frequently observed histological type of germ-cell tumour (49–67%). Non-seminomatous tumours comprised a proportion similar to that reported in uninfected individuals with testicular germ-cell tumours (Einhorn *et al.*, 1993).

Moyle *et al.* (1991) reported three testicular seminomas among 2205 known HIV-seropositive patients attending a hospital clinic in London, United Kingdom. They calculated the risk among HIV-infected persons to be increased 68-fold compared with expected rates.

Timmerman *et al.* (1995) reviewed 294 cases of testicular germ-cell tumours diagnosed between 1980 and 1993 at four hospitals in San Francisco, CA, United States, using cancer registry files and pathology reports. Overall, 11 HIV-seropositive cases (4%) were identified. These were further evaluated together with four additional seropositive cases diagnosed at private medical centres in San Francisco and compared with the remaining 279 cases without evidence of HIV infection. There was no difference in tumour stage at presentation (low-stage (I and IIA) tumours in HIV-positive persons, 67%; those in HIV-negative persons, 63%). Standard therapy including orchiectomy, retroperitoneal lymph node dissection, radiation therapy and chemotherapy was well tolerated. In these HIV-positive patients, there was no indication of a more aggressive course of disease compared with that seen in HIV-negative patients.

Bernardi *et al.* (1995) performed a retrospective analysis of 26 cases of testicular germ-cell tumours diagnosed between 1986 and 1994 in HIV-positive men in Italy. Of these patients, 61% had low-stage tumours (stages I to IIb) and only 35% had advanced disease, a proportion similar to that observed among HIV-seronegative patients. The complete response rate of 95% and overall three-year survival of 65% in this series did not differ substantially from those in HIV-uninfected persons (Kaplan, 1995). The median $CD4^+$ T-cell count at presentation was 261 cells/mm^3 (range, 2–1229) and only six had a $CD4^+$ count below 200 cells/mm^3, which suggests that the clinical behaviour of testicular cancer in HIV-positive persons is not directly related to level of immunosuppression.

(*b*) *Descriptive and cohort studies*

Descriptive studies based on cancer incidence data from various parts of the United States have unanimously failed to show a link between cancer of the testis and the HIV epidemic. Biggar *et al.* (1987) used never-married men as a surrogate for homosexuality in their study of cancer incidence trends in San Francisco from 1973 to 1984. Neither this study nor that of Rabkin and Yellin (1994), with the same data series updated to 1990, showed any indication of an increasing trend in the 1980s for cancer of the testis. In an analysis of cancer incidence data from New York City based on the period 1973–85, Biggar *et al.* (1989) similarly found no increasing trend for cancer of the testis.

Reynolds *et al.* (1993), using data from population-based registries for AIDS and cancer for San Francisco residents for the period 1980–87, found no indication of an

increased risk for testis cancer in AIDS patients (1973–77: SIR, 1.0; 95% CI, 0.2–2.8); 1980–87: SIR, 0.7; 95% CI, 0.2–2.2).

Lyter *et al.* (1995) found two cases of testicular seminoma in a prospective cohort study of 430 HIV-infected men (SIR, 8.2 (95% CI, 1.0–30)). When a third case of extragonadal seminoma was included and the age-adjusted population rates for all seminomas were compared, a 21-fold increase ($p < 0.001$) in the HIV-infected cohort was observed.

In summary, there is some suggestion of an association of testicular cancers with HIV infection, but the studies are not yet conclusive.

2.3.5 *Non-melanoma cancers of the skin*

Skin cancers and, in particular, squamous-cell carcinomas have been associated with a wide variety of immunodeficiency conditions (Hintner & Fritsch, 1989). Transplant patients who are immunocompromised have a disproportionately high incidence of squamous-cell carcinomas as compared to basal-cell carcinomas, in a ratio of 15 : 1 according to one study (Barr *et al.*, 1989) (see Section 4.1).

(*a*) *Case reports and series*

A number of case reports on skin cancers other than Kaposi's sarcoma in HIV-infected persons have been published (for references see Smith *et al.*, 1993c). However, only one large series has been described.

Lobo *et al.* (1992) identified all HIV-infected male patients with a non-melanoma skin cancer diagnosed in the dermatology clinic at the University of California, San Francisco, United States, and performed a retrospective case–control study with age-matched controls. Overall, 116 non-melanoma skin cancers were identified in 48 patients, 101 occurring in 47 patients were basal-cell carcinomas and 15 in 10 patients were squamous-cell carcinomas. The basal-cell : squamous-cell carcinoma ratio (6.7 : 1) was similar to that observed in HIV-uninfected persons in the same area but different from that observed among transplant patients, as discussed above. The major risk factors associated with non-melanoma skin cancer in this group of men were the same as those in the normal population: fair skin, a family history of skin cancer and sun exposure.

(*b*) *Descriptive and cohort studies*

Reynolds *et al.* (1993) found, in their linkage study of AIDS and cancer cases among San Francisco residents, three non-melanoma skin cancers (one dermatofibroma, one haemangiosarcoma, one sarcoma unspecified), a significantly higher number than expected (SIR, 10.0). Because the study was purely registry-based, it was impossible to confirm that these cases were not misclassified Kaposi's sarcoma cases.

Non-melanoma skin cancers are not registered in the SEER programme. The incidence of melanoma of the skin has been found to be marginally increased among never-married men from New York City and from San Francisco (Biggar *et al.*, 1989; Rabkin & Yellin, 1994), but these findings are possibly related to the specific behaviour of single men in terms of recreational sun exposure, rather than to the HIV epidemic. No increase incidence with time was observed in any of the studies.

Smith *et al.* (1993c) followed 724 HIV-infected military employees in the United States for a period of 36 months and diagnosed 13 cases of basal-cell carcinoma (1.8%), two cases of squamous-cell carcinoma (0.3%) of the face, 2 cases of squamous-cell carcinoma (0.3%) in the anus and three malignant melanomas (0.6%). The basal-cell : squamous-cell carcinoma ratio was more similar to that of the general population than to that observed among transplant recipients. Most of the patients studied were at an early stage of their HIV disease and not severely immunosuppressed, and had lightly pigmented skin.

In their cohort study of 1701 haemophiliacs (see Section 2.2.3), Rabkin *et al.* (1992) observed five cases of basal-cell carcinoma (2 in HIV+, 3 in HIV– persons), corresponding to rates of [0.2 and 0.8 per 1000 person-years] in HIV-infected and HIV-uninfected subjects, respectively. No comparison was made with rates in the general population.

Ragni *et al.* (1993) performed a retrospective cohort study of 3041 haemophiliacs (56.6% HIV-infected) from 18 haemophilia centres in the United States during the period 1978–89. The incidence of basal-cell carcinoma in HIV-infected patients was 18.3 times greater than that in HIV-uninfected patients ($p < 0.0001$) but 11.4 times greater than that in the general population, a finding which remains unexplained. Among HIV-infected patients, the observed-to-expected ratio was 2.0 ($p < 0.001$).

In a large cohort study of 1199 homosexual men (period 1984–1993) (Lyter *et al.*, 1995) found three cases of basal-cell carcinoma in HIV-infected persons and seven cases of basal-cell carcinoma and two of squamous-cell carcinoma in seronegative men. No more cases were found in either HIV-infected or -uninfected men than expected from general population rates.

In a study of 1073 homosexual and bisexual men (434 HIV+) in three United States cities, followed for over 10 000 person-years, the relative risk for incidence of skin cancers —25/35 basal-cell carcinomas — was 2.2 in HIV-infected compared with uninfected men (Holmberg *et al.*, 1995b).

In summary, there is conflicting evidence regarding an association between non-melanoma skin cancers and HIV infection. [The Working Group noted that the diagnosis and reporting of these tumours are highly variable and this possible association may be particularly difficult to investigate.]

2.3.6 *Conjunctival tumours*

Although rare in Europe and North America, squamous-cell carcinoma of the conjunctiva was already more common in Africa before the advent of AIDS (Templeton, 1973; Newton *et al.*, 1996). Strong associations have been reported between dysplasia and invasive carcinoma of the conjunctiva and HPV (IARC, 1995).

(*a*) *Case reports*

Two case reports of squamous-cell carcinoma of the conjunctiva in HIV-seropositive men in the United States (Winward & Curtin, 1989; Kim *et al.*, 1990), coupled with a dramatic increase in the number of tumours being seen by ophthalmologists in at least two African centres, led to the suggestion of an association with HIV infection (Kestelyn

et al., 1990; Ateenyi-Agaba, 1995). Several studies from Africa and one from the United States have investigated this association.

(*b*) *Descriptive study*

In an analysis based on the Multistate AIDS-Cancer Match Registry in the United States, Goedert and Coté (1995) found four AIDS patients with a diagnosis of conjunctival squamous-cell carcinoma, a significantly higher number than expected (observed : expected, 13 [95% CI, 4–34]).

(*c*) *Case–control studies*

In Rwanda, Kestelyn *et al.* (1990) found that 9/11 cases of conjunctival squamous-cell carcinoma were HIV-seropositive, compared with 6/22 controls (odds ratio, 13.0; 95% CI, 2.2–76.9).

In Uganda, Ateenyi-Agaba (1995) found that 36/48 cases of conjunctival squamous-cell carcinoma were HIV-seropositive, compared with 9/48 controls (odds ratio, 13.0; 95% CI, 4.5–39.4).

In Rwanda, Newton *et al.* (1995) examined the association of HIV infection with all ocular tumours, excluding retinoblastoma and melanoma. The proportion of HIV-positive cases was 2/8 versus 8/200 controls (odds ratio, 8.4; 95% CI, 0.8–96.9).

In summary, HIV infection has been consistently associated with conjunctival carcinoma in case–control studies in several African locations. The association has been inconsistent in western countries and the discrepancy between these regions may be due to the lower background rates of this tumour in developed countries.

2.3.7 *Leiomyosarcoma*

Leiomyosarcoma is an extremely rare tumour in childhood, with an annual incidence of less than two cases per 10 million children (Lack, 1986). It has been reported in immunocompromised children following liver and renal transplantation (Ha *et al.*, 1993).

(*a*) *Case reports and series*

Spindle-cell tumours (leiomyoma and leiomyosarcoma) in HIV-infected children have been described relatively frequently, at sites such as the gastrointestinal tract (Chadwick *et al.*, 1990; McLoughlin *et al.*, 1991; Mueller *et al.*, 1992), liver (Mueller *et al.*, 1992; Ross *et al.*, 1992; Levin *et al.*, 1994), tracheobronchial tree (Martinez *et al.*, 1990; Balsam & Segal, 1992), lung (Chadwick *et al.*, 1990) and subcutaneous tissue (Orlow *et al.*, 1992). Several of the cases were discovered only at autopsy as solitary small spherical tumour masses.

DiCarlo *et al.* (1990) described eight cancers in 102 HIV-infected children followed at the Children's Hospital AIDS programme of New Jersey, NY, during 1984–88, of which one was an unusually aggressive case of leiomyosarcoma.

The above reports and a further one by McClain *et al.* (1995, 6 cases in 5 children) document at least 14 spindle-cell tumours in HIV-infected children, a much higher

number than expected considering that less than 10 000 children are infected with HIV in developed countries.

A few cases of spindle-cell tumours of the liver, colon, adrenal glands and spinal cord in HIV-infected adults have also been reported (Radin & Kiyabu, 1992; Steel *et al.*, 1993; Prévot *et al.*, 1994; McClain *et al.*, 1995).

(*b*) *Descriptive studies*

Rabkin and Yellin (1994) found, using cancer incidence data from the SEER programme, an increasing although nonsignificant trend in the observed-to-expected ratio of leiomyosarcomas among never-married men resident in San Francisco, CA, United States.

(*c*) *Cofactors*

McClain *et al.* (1995) suggested that EBV may contribute to the pathogenesis of leiomyomas and leiomyosarcomas in HIV-infected patients but not in HIV-uninfected persons. Using in-situ hybridization, they detected EBV genomes in all muscle cells of five leiomyosarcomas and two leiomyomas from six HIV-infected persons but not in three leiomyosarcomas or four leiomyomas from HIV-uninfected persons. Quantitative PCR showed high levels of EBV in the tumour tissues. Furthermore, separate tumours in the same patients contained different episomal EBV clones, signifying the presence of distinct monoclonal EBV-related tumours.

Lee *et al.* (1995) studied three children who developed smooth muscle tumours following organ transplantation. In each case, clonal EBV genome was detected in tumour tissue. In the two cases studied, the tumours were positive for EBNA-2 and the tumours from each of the patients were positive for EBERs. Both viral protein products expressed in latent infection.

In summary, leiomyomas and leiomyosarcomas appear to be associated with HIV infection in children. EBV appears to be an important etiological co-factor. The association is not apparent in HIV-infected adults.

2.3.8 *Other cancers*

There have been a large number of case reports and small case series of tumours other than those described above in HIV-infected persons.

Apart from effects on specific tumours, HIV infection and associated immunosuppression have been suspected of causing a global increase in the incidence of cancers of all types. This hypothesis has been examined in cohort studies (Rabkin & Yellin, 1994; Lyter *et al.*, 1995) and in analyses of registry data (Coté *et al.*, 1991; Reynolds *et al.*, 1993; Biggar *et al.*, 1994). Excluding cases of Kaposi's sarcoma and non-Hodgkin's lymphoma, total incidence of other cancers was either not increased or minimally increased. Since HIV-infected persons may have increased exposure to other cancer risk factors (e.g., cigarette smoking), the significance of the elevations seen in some of these studies is uncertain.

A small increase in the number of registered hepatomas at the SEER cancer registry in San Francisco, CA, United States, was observed among single white men between 1973–78 (baseline) and 1984 (Biggar *et al.*, 1987). However, there was no obvious further increase in incidence when the data were followed through to 1990 (Rabkin & Yellin, 1994). No case of liver cancer was recorded in a cohort of San Francisco AIDS patients followed from 1980 to 1987 (Reynolds *et al.*, 1993). Similarly, no case of liver cancer was found among 1065 HIV-infected haemophiliacs in the United States followed over 12 years (Rabkin *et al.*, 1992). In another study of United States haemophiliacs (Ragni *et al.*, 1993), no significant difference in liver cancer was seen in HIV+ and HIV– patients. In a study of 1227 HIV-infected haemophiliacs in the United Kingdom between 1985 and 1992, the risk of death from liver cancer (compared with the United Kingdom population) was similar in the HIV-infected (observed : expected, 15.1) and HIV-uninfected cohorts (observed : expected, 18.7) (Darby *et al.*, 1995). No association between HIV infection and liver cancer was found in Rwanda (Newton *et al.*, 1995); 1 person out of 35 (3%) with liver cancer was HIV-positive versus 7/165 (4%) controls.

In a large linkage analysis based on AIDS and cancer records from different regions within the United States, no association between EBV-associated nasopharyngeal carcinoma and AIDS was found (Melbye *et al.*, 1996).

Oral squamous-cell carcinomas have been hypothetically linked to infection with HPV. A small number of case reports have described these tumours, primarily located on the tongue, in HIV-infected persons (Salas-Buzon & Saez-Eligido, 1992). However, there are no data to support an association with HIV-infection (Ficarra & Eversole, 1994). *Nasal cavity tumours* were in excess ($n = 2$) in a linkage study of AIDS and cancer registry data from San Francisco (Reynolds *et al.*, 1993) but the authors ascribed this finding to possibly misclassified Kaposi's sarcoma cases.

Plasma-cell tumours that have been hypothetically linked with EBV infection have been described at unusual sites with widespread dissemination and a clinically aggressive course in HIV-infected persons (Israel *et al.*, 1983; Vandermolen *et al.*, 1985; Kaplan *et al.*, 1987; Monfardini *et al.*, 1989; Voelkerding *et al.*, 1989; Kumar *et al.*, 1994). *Lymphomatoid granulomatosis* (Mittal *et al.*, 1990) and a number of typical and more atypical cases of *acute myeloblastic leukaemia* have been reported (Al-Bahar *et al.*, 1994; Rabaud *et al.*, 1995). However, there has been no indication from either registry studies or cohort studies of an increased risk for leukaemia associated with the HIV epidemic (Biggar *et al.*, 1989; Rabkin & Yellin, 1994; Ragni *et al.*, 1993; Reynolds *et al.*, 1993; Lyter *et al.*, 1995).

Reports on *lung cancer* in HIV-infected persons have reflected differences in the clinical course in comparison with HIV-uninfected persons. Survival is short and appears to be worse than that seen in HIV-uninfected lung cancer patients (Flores *et al.*, 1995). However, these data probably reflect the dismal course of infection with HIV. Rabkin and Yellin (1994) reported a small relative increase in lung cancer among never-married men in San Francisco, but unrelated behavioural risk factors such as cigarette smoking may be responsible.

Other tumours that have been reported in HIV-positive persons but for which an association with the infection is not convincing include *mesothelioma* (Behling *et al.*, 1993), *cerebral glial tumours* (Chamberlain, 1994; Moulignier *et al.*, 1994) and *cancer of the colon* (Kaplan *et al.*, 1987; Cappell *et al.*, 1988), *pancreas* (Kaplan *et al.*, 1987; Monfardini *et al.*, 1989) and *kidney* (Monfardini *et al.*, 1989).

In summary, the available data do not support an association of these other tumours with HIV infection.

3. Studies of Cancer in Animals

3.1 HIV-1 and HIV-2

There have been many unsuccessful attempts to infect a variety of laboratory animal species (rats, hamsters, guinea-pigs) with HIV-1 and HIV-2 (Morrow *et al.*, 1987). In some studies, rabbits have been infected successfully (Filice *et al.*, 1988; Kulaga *et al.*, 1989), but the most reliable models involve HIV infection of nonhuman primates.

Chimpanzees (*Pan troglodytes*) (Morrow *et al.*, 1989), gibbons (*Hylobates lar*) (Lusso *et al.*, 1988) and pigtailed macaques (*Macaca nemestrina*) (Frumkin *et al.*, 1993; Gartner *et al.*, 1994) can be infected with HIV-1, whereas HIV-2 infection has been reported in rhesus monkeys (*M. mulatta*), cynomolgus monkeys (*M. fascicularis*) and baboons (*Papio papio sp.*) (Stahl-Hennig *et al.*, 1990; Castro *et al.*, 1991; Barnett *et al.*, 1994).

Despite persistent infection and immunological disorders such as lymphopenia and a decrease in $CD4^+$ T-cell counts, clinical signs are rare in HIV-1- and HIV-2- infected non-human primates. Chimpanzees show definite serological and haematological features of HIV infection (Morrow *et al.*, 1989). No clinical disease was seen in HIV-1-infected pigtailed macaques with persistent HIV-1 infection more than one year after first incubation (Gartner *et al.*, 1994).

Transient lymphadenopathy and/or splenomegaly have been observed in HIV-2-infected rhesus and cynomolgus monkeys (Stahl-Hennig *et al.*, 1990; Livartowski *et al.*, 1992), but in most cases they remained clinically healthy (Putkonen *et al.*, 1989). Diarrhoea and weight loss were reported in one of eight infected rhesus macaques (Castro *et al.*, 1991). A case of central nervous system and lung lesions due to actinomycetes was reported by Livartowski *et al.* (1992).

One rapidly growing mammary adenocarcinoma has been observed in an HTLV-I/-HIV-1-infected rabbit (Kulaga *et al.*, 1989). [The Working Group considered that the occurrence of this tumour was probably unrelated to the retroviral infection.]

Among six HIV-2 infected baboons (*Papio cynocephalus*), five animals became persistently infected. After 28 months, one baboon developed an AIDS-like condition with fibromatosis involving lymph nodes, skin, thyroid and pancreas. Another animal was reported to follow a similar clinical course (Barnett *et al.*, 1994).

3.2 Lymphomas in nonhuman primates

Prior to the first documented lymphoma outbreak in colonies of rhesus monkeys, malignant lymphomas in nonhuman primates had been reported only rarely (Stowell *et al.*, 1971). However, lymphomas have been reported to develop in various species of monkeys treated with immunosuppressive agents (Reitz *et al.*, 1980) and in newborn tamarins experimentally infected with Epstein-Barr virus (EBV) (Young *et al.*, 1989). Lymphomas have also been found in various nonhuman primates naturally or experimentally infected with herpesvirus saimiri (HVS) (Adamson *et al.*, 1975), or with STLV-I (see Section 3.2.1 of the monograph on HTLV in this volume, p. 308).

3.2.1 *Occurrence of lymphomas in nonhuman primates infected with simian immunodeficiency virus*

Lymphomas in simian immunodeficiency virus (SIV)-infected nonhuman primates have been documented in rhesus, cynomolgus and pigtailed macaques, but the incidence of these lymphomas is not well defined. In a study of cynomolgus macaques, an incidence of 38% (9/24) was reported (Feichtinger *et al.*, 1990). In a retrospective necropsy study in the USA, King *et al.* (1983) observed nodular lymphoproliferative infiltrates of well differentiated lymphocytes in liver, kidney and bone marrow tissues in 3/16 macaques (*M. mulatta* and *M. fascicularis*) and, in addition, a clear malignant lymphoma was found in one macaque (*M. mulatta*). All four animals were immunodeficient. Letvin *et al.* (1983) also reported three lymphoma cases in the same colony. [The Working Group noted that it was unclear whether these were the same animals as previously reported.] It was subsequently recognized that this colony was infected with SIV (Letvin & King, 1990).

The likely transfer of nonpathogenic SIV from its natural host (the sooty mangabey monkey: *Cercocebus atys*) to the highly sensitive macaques, as manifested by the development of lymphoma, was demonstrated by Baskin *et al.* (1986). These studies involved the inoculation of a rhesus macaque (*M. mulatta*) with a homogenate of a cutaneous leprosy lesion from a sooty mangabey monkey. Subsequently, the rhesus monkey developed a lymphoma, and cells from this lymphoma induced a further lymphoma when injected into another rhesus macaque. Lymphoblastoid cell lines from the second rhesus macaque were established *in vitro* from tumour cell suspensions and shown to produce a herpesvirus related to EBV and a retrovirus morphologically similar to SIV (Baskin *et al.*, 1986). Baskin *et al.* (1988) also observed one case of lymphoma in a study of 24 rhesus monkeys experimentally infected with this virus designated SIV_{SMM}. SIV_{MNE} was also isolated from a pigtailed macaque (*M. nemestina)* with lymphoma (Benveniste *et al.*, 1986; Henderson *et al.*, 1988). SIV_{MNE} was shown to be related to HIV-2.

Five lymphoma cases out of 49 necropsied stump-tailed macaques (*M. arctoides*) were observed by Lowenstine *et al.* (1992). Among these 49 animals, 75% had pathological lesions compatible with a diagnosis of SIV infection and the SIV-related mortality was 68%. SIV_{STM} was pathogenic for rhesus macaques.

In the UK, Ramsay *et al.* (1991) observed B-cell lymphomas in 2/26 rhesus monkeys infected with SIV_{MAC} over a two-year period. These lymphomas occurred 11.5 and 20

months after infection. In a study of 7 rhesus and 3 cynomolgus monkeys infected with SIV_{MAC} or SIV_{SMM}, one animal developed a lymphoma involving the lumbar spinal cord 11.5 months after the onset of SIV infection (Baskerville *et al.*, 1990).

In a Swedish study, malignant lymphoma was observed in 10/33 wild-caught cynomolgus monkeys 5 to 15 months after intravenous inoculation with SIV_{SMM} (Feichtinger *et al.*, 1990, 1992a,b).

3.2.2 *Pathological and molecular features of lymphoma*

The SIV_{SMM}-associated lymphomas in cynomolgus monkeys were clinically malignant, with visceral metastasis, and were in some cases also observed to develop in testis, brain and spinal cord (Feichtinger *et al.*, 1990; Ramsay *et al.*, 1991; Feichtinger *et al.*, 1992a,b). By histology, the lymphomas were mostly high grade and all those tested were phenotypically B-cell derived. Most showed clonal heavy- and light-chain immunoglobulin restrictions and immunoglobulin gene rearrangements (Feichtinger *et al.*, 1990; Ramsay *et al.*, 1991; Feichtinger *et al.*, 1992a,b; Rezikyan *et al.*, 1995).

No integrated viral genomes were found in lymphoma cells (Feichtinger *et al.*, 1990, 1992a,b). In another study, an SIV-like virus was identified in a lymphoblastoid cell line established from a transmissible lymphoma associated with SIV infection (Baskin *et al.*, 1986).

In a monkey cohort in Sweden, the time to lymphoma development varied from five to 46 months after SIV infection. The lymphomas were all of B-cell origin. DNA analysis of VDJ immunoglobulin genes showed both monoclonal and oligoclonal rearrangements. In some instances, the lymphoma clone was already detectable in lymph nodes soon after SIV infection and before manifestation of clinically apparent lymphoma (Rezikyan *et al.*, 1995). All the lymphomas were associated with an EBV-like B-lymphotropic herpesvirus (HVMF-1) (Feichtinger *et al.*, 1990, 1992a,b; Rezikyan *et al.*, 1995; Li *et al.*, 1993a, 1994), which had 65% DNA homology in exonic regions with EBV (Li *et al.*, 1994).

The SIV_{SMM}-related lymphomas have features very similar to those of the AIDS-related lymphomas in man which are associated with EBV, supporting the hypothesis of an important role of EBV-type viruses in the pathogenesis of such lymphomas.

3.2.3 *Other neoplastic conditions*

Neoplastic conditions other than lymphomas have not been documented as being related to SIV infection, with the possible exception of occasional cases of retroperitoneal fibromatosis. However, retroperitoneal fibromatosis has been seen mostly in macaques infected with the simian immunosuppressive type D retrovirus (SRV-2) (Giddens *et al.*, 1985; Tsai *et al.*, 1995) and in one case of SIV-induced AIDS (Baskerville *et al.*, 1990) (see also Section 4.2.3).

3.2.4 *Cofactors in SIV oncogenesis*

As discussed for AIDS-related malignant lymphoma in humans (Section 2.2.4), the interaction of several oncogenic cofactors at various stages of the lymphomagenic

process has to be considered. These factors can be classified into those inducing: (*a*) activation, (*b*) deregulated proliferation and (*c*) genomic abnormalities in B-cells.

Marked B-cell follicular hyperplasia, seen in early stages of SIV as well as HIV infection (Biberfeld *et al.*, 1985; Chalifoux *et al.*, 1986; Kaaya *et al.*, 1993b), could predispose to B-cell lymphomagenesis. In both SIV and HIV infections, viral antigens appear after infection in hyperplastic follicles on the follicular dendritic cells (FDC). These cells have the foremost antigen-presenting effect on follicular B-cells and are therefore related to the development of the characteristic follicular hyperplasia (Biberfeld *et al.*, 1985; Tenner-Rácz *et al.*, 1986; Kaaya *et al.*, 1993b). With progression of infection, the FDC-antigen-presenting cell-reticulum is destroyed, probably by immunopathological mechanisms and/or viral cytopathic effects (Biberfeld *et al.*, 1985; Stahmer *et al.*, 1996). This leads to the breakdown 'lysis' of follicles, which probably is reflected functionally by the development of impaired immune responses to neoantigens. This follicle 'lysis' may promote the selection of FDC-independent, deregulated autocrine B-cells which during migration through extranodal tissues settle and develop into malignant lymphomas. This extranodal homing is probably promoted by the capacity of AIDS-related malignant lymphomas in humans to produce growth factors (IL-6, IL-10) with possible autocrine functions (Emilie *et al.*, 1992).

A highly deregulated cytokine growth factor homeostasis and the disruption of the antigen-presenting FDC network are thus likely also to play an important role in B-cell activation and proliferation with an increased risk for genomic changes and lymphomagenesis in SIV-infected monkeys (Kaaya *et al.*, 1993b).

Despite the clear association of SIV infection with lymphomagenesis, no evidence yet indicates a direct oncogenic effect of the SIV or HIV genome. However, in-vitro experiments have suggested a transforming effect on 3T3 cells transfected with the SIV PBj_{14} *nef* gene (Du *et al.*, 1995).

The well recognized oncogenic effects of EBV in certain human lymphomas appear to be mirrored in SIV-infected nonhuman primates. Thus studies have shown a direct transforming/immortalizing effect of the EBV-like HVMF-1 in cynomolgus monkeys associated with SIV-related lymphomas (Li *et al.*, 1994).

3.3 Feline immunodeficiency virus infection in cats

Lentiviral infections of animals other than non-human primates include infections with feline immunodeficiency virus (FIV), bovine immunodeficiency virus, maedi-visna virus, caprine arthritis-encephalitis virus and equine infectious anaemia virus (Coffin, 1992). An association between viral infection and the development of neoplasia, in particular B-cell lymphomas, has been documented only for FIV infections.

FIV was first isolated in 1986 and has become recognized as a common infection in pet cats worldwide (Pedersen *et al.*, 1987). Initial epidemiological studies of a representative sample of the pet cat population in the United Kingdom reported a 19% prevalence of FIV in sick cats, a 6% prevalence in healthy cats and a 21% prevalence among cats in households with more than one cat (Hosie *et al.*, 1989). In studies in the United States, 10–14% of sick cats and 1–4% of healthy cats were FIV-positive (Grindem *et al.*, 1989;

Shelton *et al.*, 1989; Yamamoto *et al.*, 1989; O'Connor *et al.*, 1991). In Japan, infection rates as high as 44% in sick cats and 12% in healthy cats have been recorded (Ishida *et al.*, 1989).

High-grade B-cell neoplasms in association with both naturally acquired and experimentally induced infections have been described. The term 'lymphosarcoma' is used throughout the text to designate tumours of lymphoid lineage. Five cases of lymphosarcoma and one case of a poorly differentiated myeloproliferative disorder are the only tumours that have been documented in association with experimental FIV infections (Yamamoto *et al.*, 1988; English *et al.*, 1994; Poli *et al.*, 1994; Callanan *et al.*, 1996). A broader range of tumours in cats with naturally acquired infections has been described and case reports include lymphosarcomas (Shelton *et al.*, 1990; Hutson *et al.*, 1991; Barr *et al.*, 1993; Callanan *et al.*, 1996), fibrosarcomas (Ishida *et al.*, 1989), myeloproliferative diseases (Ishida *et al.*, 1989; Shelton *et al.*, 1990; Hutson *et al.*, 1991), mast-cell tumours (Shelton *et al.*, 1990; Barr *et al.*, 1993; Terry *et al.*, 1995), cutaneous squamous-cell carcinomas (Hutson *et al.*, 1991; Pedersen & Barlough, 1991), miscellaneous adenomas and carcinomas (Gruffydd-Jones *et al.*, 1988; Hopper *et al.*, 1989) and oligodendrogliomas (Hurtrel *et al.*, 1992).

3.3.1 *Occurrence of lymphosarcomas in FIV infection*

In natural FIV infection, the majority of clinical and epidemiological studies demonstrate that lymphosarcomas occur in less than 10% of FIV-infected cats (Hopper *et al.*, 1989; Hosie *et al.*, 1989; Ishida *et al.*, 1989; Yamamoto *et al.*, 1989; Shelton *et al.*, 1990). Evaluation of the association between FIV infection and lymphoid malignancies is confounded by concurrent infection with the C-type feline leukaemia virus (FeLV), the most common cause of lymphosarcoma in cats (Hardy, 1981). In a study of 161 cats with leukaemia and/or lymphoma, Shelton *et al.* (1990) performed a stratified analysis controlling for FeLV infection using the Mantel–Haenszel test, which revealed a significant association between FIV infection and leukaemia/lymphoma. The estimated relative risk for developing leukaemia/lymphoma was 5.0 for cats infected with FIV only, compared with uninfected cats. In the same study, a relative risk of 62.1 was found for FeLV-infected animals and, when animals were co-infected with both viruses, the risk was 77.3.

Two reports have described lymphosarcomas in two of seven experimentally infected cats at 9 and 21 months after infection (English *et al.*, 1994) and in two of 20 experimentally infected cats at 30 and 42 months after infection (Callanan *et al.*, 1996); the specific pathogen-free cats were infected intravenously or intraperitoneally with the North Carolina State University (NCSU1) or Glasgow (Gla-8) strains of FIV, respectively. Lymphosarcoma associated with experimental infection has also been documented in a cat intravenously infected with FIV (Pisa M2 strain), 18 months after infection (Poli *et al.*, 1994) and a myeloproliferative disorder was reported 8.5 weeks after inoculation with FIV (Petaluma strain) (Yamamoto *et al.*, 1988).

3.3.2 *Pathological and molecular features of lymphosarcoma*

In FIV-associated lymphosarcomas, as with HIV and SIV, sites of tumour distribution are predominantly extranodal, with involvement of the heart, eyes, brain, spinal cord, pancreas and urinary bladder (Hutson *et al.*, 1991; Callanan *et al.*, 1996).

Limited information is available on the immune function of FIV-infected cats with lymphosarcomas. Callanan *et al.* (1992) found normal responses of lymphocytes to mitogens in one case, and Poli *et al.* (1994) detected a marked reduction in circulating $CD4^+$ T-lymphocytes in another case.

In a series of eight FIV-infected cats (two experimental and six natural) with lymphosarcoma, seven of the tumours were high-grade B-cell lymphomas of the centroblastic or immunoblastic subtypes. The remaining case was a T-cell tumour associated with concurrent FeLV infection (Callanan *et al.*, 1996). Lymphosarcomas in experimental infection described by English *et al.* (1994) and Poli *et al.* (1994) were also of B-cell origin, based on immunoglobulin expression. However, the single neoplasm described by Poli *et al.* (1994) was low-grade.

Four of the tumours reported by Callanan *et al.* (1996) were examined with molecular probes to establish tumour cell lineage and to screen for integrated viral sequences (Terry *et al.*, 1995). Confirmation of a B-cell origin was supported by the identification of monoclonal or oligoclonal immunoglobulin heavy-chain gene rearrangements and the lack of rearrangements of T-cell receptor β-chain genes in all four cases. Rearrangement of the *c-myc* locus, which occurs in many FeLV lymphosarcomas, was not found in any of the FIV-associated tumours and none of the tumours showed evidence of integrated FIV sequences by Southern blot hybridization. Poli *et al.* (1994) identified DNA of the FIV *gag* gene in many tissues including tumour tissue of an experimentally FIV-infected cat. However, in this tumour tissue, it could not be determined whether the infection was of neoplastic cells.

Thus lymphosarcomas in FIV-infected cats share similar morphological, immunophenotypic and molecular qualities to those associated with HIV and SIV infections. The evidence available supports an indirect role for FIV in tumour development. FIV induces activation of lymphoid tissue, polyclonal B-cell activation and increased serum cytokine levels, all of which may facilitate malignant transformation of B cells (Lawrence *et al.*, 1992; Rideout *et al.*, 1992; Callanan *et al.*, 1993; Flynn *et al.*, 1994).

4. Other Data Relevant to an Evaluation of Carcinogenesis and its Mechanisms

4.1 Immunity and cancer

In mice and humans with inherited or acquired immunodeficiency, only certain types of malignancy are significantly increased in incidence (Weiss, 1993b). Many of these tumours are associated with viruses that have established persistent infections, and others are tumours arising within the immune system. Consideration of malignancies deve-

loping in cases of immunodeficiency caused by factors other than HIV is restricted in this monograph to humans. The highest relative risks in human non-AIDS immunodeficiency are for non-Hodgkin's lymphoma, Kaposi's sarcoma and non-melanoma skin cancer (Beral, 1991b).

4.1.1 *Types of cancer seen in non-HIV-associated human immunodeficiency*

The vast majority of data concerning the incidence of malignancies occurring in persons with an acquired immunodeficiency other than those with HIV infection comes from patient populations undergoing organ transplantation. In addition to immunosuppressive therapy and the foreign graft, such patients are exposed to incidental infections of donor origin. Birkeland *et al.* (1995) reported on the subsequent risk of malignancy in all 5692 renal transplant patients during 1964–86 within the Nordic countries, using the national population-based cancer registries for long-term follow-up. The data were analysed by standardized incidence ratios (SIR), using the population rates as the reference. Overall, there was a significant increase in overall cancer rates of 4.5 for women and 4.6 for men. Very highly increased risks (SIR, ≥ 10-fold) were seen for cancers of the lip, kidney, cervix and vulva–vagina and non-melanoma cancer of the skin and for non-Hodgkin's lymphoma. In addition, there were significantly increased SIRs (2–5-fold) for a range of common malignancies including cancers of the colon, larynx, lung, bladder, prostate and testis. However, only two cases of Kaposi's sarcoma were reported.

Penn (1993) analysed data on a series of 7192 organ transplant patients followed by the Cincinnati Transplant Tumor Registry in the United States up to 1993. [The institutional sources of these patients were not specified.] Only the numbers of subsequent cancer cases were reported; these were compared with the proportional distribution of site-specific malignancy in the 'general population' without statistical analysis. [It is not clear whether the referent distribution was corrected for age and sex.] The most common tumours in the transplant patients were cancers of the skin (predominantly squamous-cell carcinoma) and lip and non-Hodgkin's lymphoma. There were 307 cases (2.4%) of Kaposi's sarcoma. Other common sites included vulva/peritoneum and kidney. The proportion of cervix cancer cases [3.5%] was reported to be the same as that in the general population. Subsequently, Penn and Porat (1995) reported on cases of central nervous system non-Hodgkin's lymphoma in this registry. Of a total of 1332 non-Hodgkin's lymphoma cases recorded, 289 (22%) involved the central nervous system. Penn (1994) similarly reported on the 326 paediatric patients recorded in the Cincinnati Registry. [These patients appear to be also included in the report above.] Compared with the distribution of cancer sites in adult transplant patients, paediatric patients had a higher frequency of lymphoma (50% versus 15%) and a lower proportion of cancers of the skin and lip (20% versus 38%).

Kinlen *et al.* (1979) reported on the follow-up of 3823 renal transplant patients in Australia, New Zealand and the United Kingdom. Compared with age- and sex-specific national mortality rates, the relative risk for any malignancy was 3.5 and that for non-Hodgkin's lymphoma was almost 60, with an excess evident for squamous skin cancer and mesenchymal tumours including one Kaposi's sarcoma.

In a hospital-based series from London, United Kingdom, Gaya *et al.* (1995) reported on 274 renal transplant patients whose graft survived three years or more, using survival analysis and comparison with national rates. Skin cancers were most common, particularly among men, followed by lymphomas and renal, urinary bladder and bronchial cancer. The actuarial risk of development of any tumour was 18.4% at 10 years and 49.6% at 20 years. There was a higher risk among males than among females, which was attributable to a higher incidence of skin cancer.

Schmidt *et al.* (1995) reported on the occurrence of genito-urinary malignancies among 868 renal transplant patients in a hospital-based series in Germany. Twelve cases were noted, of which one was transplanted in the graft. The 11 de-novo cases included four kidney, three cervical and one each of testicular, vulvar, urinary bladder and renal duct carcinomas.

Levy *et al.* (1993b) reported on 556 liver transplant patients followed between 1985 and 1991 at Baylor University in Dallas, TX, United States. Of these, 25 developed new malignancies, including 10 with lymphoma and 9 with at least one skin cancer. Other malignancies seen included lung, breast, prostate, pancreas, hepatocellular and colon cancers and Kaposi's sarcoma.

Dresdale *et al.* (1993) reported on 112 cardiac transplant patients seen at a hospital in Detroit, MI, United States, between 1985 and 1991. Of these, nine developed a new malignancy, including four cancers of the skin, two of the colon, and one each of the bone and bladder and one Kaposi's sarcoma. Guettier *et al.* (1992) reported on 174 cardiac transplant patients from a hospital in Paris between 1984 and 1990. The only malignancies reported were four gastrointestinal non-Hodgkin's lymphomas. Zahger *et al.* (1993) reported two cases of Kaposi's sarcoma occurring among 18 cardiac transplant patients in Jerusalem; both patients were Mediterranean Jews.

Table 29 summarizes the data from more than 15 000 organ (mostly kidney) transplant patients. The most common findings are the substantial excesses of squamous-cell carcinoma of the skin and non-Hodgkin's lymphoma. In addition, risks for cancers of the kidney and urinary bladder, cervix and vulva, and head and neck were commonly increased. Less frequently seen are unusual tumours including Kaposi's sarcoma and testicular cancer.

Table 30 summarizes the experience of more than 11 000 patients receiving bone marrow transplants, primarily for haematopoietic malignancies and disorders. The findings in this patient population were similar to those in the organ transplant patients, with the additional common finding of leukaemia. Kolb *et al.* (1992) reported only the number of new malignancies occurring among the 9732 bone marrow transplant patients reported to the International Bone Marrow Registry and among the 226 patients reported to the European Bone Marrow–European Late Effects Project. Of the former, 116 had a subsequent cancer: 58 were lymphoma, 15 leukaemias including myelodysplasia, 14 cancers of the skin including 5 melanomas, 4 cervical including dysplasia, 3 vulvar/-vaginal, 2 oropharyngeal, 2 breast and 2 thyroid cancers, among others. Among the latter group of patients, there were 11 new cancers including 6 skin cancers.

Table 29. Cancer risks following organ transplants: cohort studies

Reference	Population, number	Time period	Case identification	Comparison group	Sites	Results			Notes
						SIR			
						M	(Σ)	F	
Birkeland *et al.* (1995)	Nordic countries: kidney transplant only 5692 (32 392 person-years) Follow-up for life	1964–86	Population registries	Population rate	Lip	14.0		117.0	SIR increase seen within first 5 years, peaking in the next decade with some decrease after 15 years. Risk higher in younger patients (< 45) and if the donor was a family member. Cyclosporin and OKT3 not used. (All SIRs listed are statistically significant.)
					Colon	3.2		3.9	
					Rectum	4.5		–	
					Larynx	3.8		15.0	
					Lung	1.8		4.9	
					Cervix	–		8.6	
					Vulva/vagina	–		31.0	
					Prostate	2.1		–	
					Testis	3.9		–	
					Ureter/kidney	4.6		19.0	
					Urinary bladder	3.1		17.0	
					Non-melanoma skin	29.0		18.0	
					Brain, etc.	3.0			
					Thyroid	16.0		5.1	
					Connective tissue	7.3			
					NHL	10.0		11.0	
					Hodgkin's lymphoma	–		11.0	
Gaya *et al.* (1995)	Hammersmith Hospital, London — Graft survived 3 years: kidney transplant only 274 (2622 person-years) 29-year follow-up	1961–90	Hospital follow-up	Population rates	Skin	23.3		12.0	4-fold RR increase for non-skin cancers seen within first 5 years and stabilized 2–3 thereafter. RR for skin cancer increased with time. Greater risk in younger patients (< 40 years). No effect seen for cyclosporin. Median time to diagnosis, 7.7 years.
					NHL		(45.0)		
					Kidney	34.0	25.0		
					Urinary bladder	9.5	(7.6)		

Table 29 (contd)

Reference	Population, number	Time period	Case identification	Comparison group	Sites	Results	Notes
Schmidt *et al.* (1995)	University of Cologne: kidney transplant only 868 (1209 person-years) Follow-up 42 ± 45 months	1968–94	Hospital follow-up	Population rates	Genito-urinary cancer only: sites 6 Kidney, renal duct 3 Cervical 1 Testis 1 Bladder 1 Vulva		RR for males, 7.3; females, 11.2 All but one cancer developed in the 324 patients aged 20-40 years [$p = 0.001$]
Penn (1993)	Cincinnati Transplant Tumor Registry 6798	[1968]–93	Special registry	General population		Proportional incidence	
					Skin	52% *vs* 32%[a]	Mean time to diagnosis: KS, 22 months (2–226); lymphomas, 32 months (1–254); epithelial excl. vulva and perineum, 69 months (1–299); vulva, perineum, 113 months (3–286); 94% lymphomas were NHL. In heart or heart–lung transplant cases, 42% were cardiac lymphomas. Large increase in SCC.
					Lymphoma	23% *vs* 5%	
					Lip	7% *vs* 0.3%	
					KS	6% *vs* < 0.1%	
					Kidney	5% *vs* 2%	
					Vulva/perineum	4% *vs* 0.5%	
					Cervix	3% *vs* 3%	
					Hepatobiliary	2.6% *vs* 1.4%	
					Other sarcomas	1.7% *vs* 0.5%	
Penn (1994)	Cincinnati Transplant Tumor Registry: paediatric patients 326	1968–93	Special registry	Adult transplant patients	Lymphoma	50% *vs* 15%	Mean time to diagnosis: KS, 46 months (4–197); lymphoma, 20 months (1–177); skin and lip, 118 months (10–282); vulva/perineum, 140 months (43–262). 98% lymphomas were NHL — these were much more frequent in non-renal transplants. There were six cases of cervix cancer (including in situ) among the 158 females: mean age at diagnosis, 25 years.
					Skin and lip	20% *vs* 38%	
					Malignant melanoma	15% *vs* 5%[b]	
					Vulva/perineum	4% *vs* 3%	
					KS[c]	2% *vs* 4%	
					Other sarcoma	3% *vs* 1%	
					Liver	3% *vs* 2%	
					Thyroid	3% *vs* 1%	
					Cervix	2% *vs* 4%	

Table 29 (contd)

Reference	Population, number	Time period	Case identification	Comparison group	Sites	Results		Notes
						RR	No.	
Kinlen *et al.* (1979)	United Kingdom Australasian Transplant Study 3823	1970–77/8	Special registry	Population rates	NHL Skin[d] Other	58.6 4.5 1.7	34 5 30	(Other: Kidney/bladder, 6; colon, 4; lung, 3; genital, 3; leukaemia, 3; other, 11)
						CI		
Levy *et al.* (1993b)	Baylor University Medical Center: liver transplant only 556	1985–91	Hospital follow-up	NG	Lymphomas Skin	1.7% 1.6%		Mean time to diagnosis: lymphomas, 7 months; skin, 18 months. For skin, ratio of BCC to SCC, 1:4.
Dresdale *et al.* (1993)	Henry Ford Hospital, Detroit: cardiac transplant treated with antilymphocyte globulin 112	1985–91	Hospital follow-up	None	SCC Colon Other	[3%] [2%] [4%]		
Guettier *et al.* (1992)	Hôpital Broussais, Paris: cardiac transplant 174	1984–90	Hospital follow-up	None	NHL	3%		All were gastrointestinal

SIR, standardized incidence rate; OKT3, orthotopic kidney transplantation therapy; NHL, non-Hodgkin's lymphoma; KS, Kaposi's sarcoma; RR, relative risk; NG, not given; CI, cumulative incidence; BCC, basal cell carcinoma of the skin; SCC, squamous cell carcinoma of skin

[a] Proportion of all malignancies

[b] Proportion of all skin cancers

[c] Two of these KS patients were HIV-positive

[d] United Kingdom only

Table 30. Cancer risks following bone marrow transplants: cohort studies

Reference	Population number	Time period	Case identification	Comparison group	Results	Notes
Lowsky *et al.* (1994)	Princess Margaret Hospital, Toronto 557 (1608 person-years)	1970–93	Hospital follow-up	Population rates	Any cancer, relative risk = 4.2 (10 malignancies in 9 patients) 2 oral cavity, 1 malignant melanoma, 2 skin, 1 endometrium, 1 breast, 1 NHL, 1 AML (donor cells), 1 lung. 7 patients developed in situ cancer: 5 cervical, 1 vulvar, 1 rectal Addendum: 1 endometrium, 1 NHL	Risk associated with total body irradiation and development of acute GVHD
Socié *et al.* (1993)	European Bone Marrow Transplantation–Severe Anaplastic Anemia Working Group 748	1971–92	Hospital follow-up	Population rates	Any cancer, relative risk = 28.6 (9 malignancies) 2 acute leukaemia, 5 head and neck, 1 stomach, 1 liver	Rish higher among males, increased with age, and with use of radiation-based conditioning regimen
Socié *et al.* (1991)	Hôpital Saint-Louis, Paris; Fanconi anaemia patients 40	1976–90	Hospital follow-up	Population rates	1 tongue cancer	

Table 30 (contd)

Reference	Population number	Time period	Case identification	Comparison group	Results	Notes
Kolb *et al.* (1992)	International Bone Marrow Transplant Registry: cancer patients 9732				(116 malignancies) 58 lymphoma, 15 leukaemia including myelodysplasia, 14 skin including 5 melanoma, 4 cervical including dysplasia, 3 vulva/vaginal, 12 other solid, 10 unspecified	
	Late Effect Study Group 226				(11 malignancies) 4 within 6 years: 2 squamous cell of skin, 1 breast, 1 chloroma; 7 > 10 years: 4 basal cell of skin, 1 'spinalioma', 1 parotid, 1 uterus	

GVHD, graft versus hot disease; AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma

Lowsky *et al.* (1994) reported on 557 consecutive bone marrow transplant patients from a hospital in Toronto, Canada between 1970 and 1993. The actuarial probability of having a new malignancy was 12% at 11 years after the transplant for the first nine cancers reported. Of the total of 11 patients who developed cancer, three had developed cancer of the skin, two of the oral cavity, two of the endometrium (of whom one also had breast cancer), two had myelogenous leukaemias (one of donor origin), and one each had non-Hodgkin's lymphoma and cancer of the lung.

Socié *et al.* (1993) reported on the experience of 748 patients followed by the European Bone Marrow Transplantation–Severe Aplastic Anemia Working group from 1971 to 1991. [The Working Group noted that these patients may overlap with those of Kolb *et al.* (1992) noted above.] Of these, 748 were treated by bone marrow transplantation. Of the latter, all but 20 (3%) received short-term immunosuppression (primary cyclophosphamide) as a conditioning regimen before transplantation. Nine patients developed a new malignancy, including five cancers of the head and neck, two acute leukaemias, one stomach and one liver cancer. In the group receiving only immunosuppression, 28 myelodysplasias and 15 acute leukaemias were diagnosed, plus 3 liver, 2 breast, and 1 each of stomach and head/neck cancer and non-Hodgkin's lymphoma. The cumulative incidence at 10 years for any secondary malignancy was much higher in the immunosuppressed group (18.8%) than in the bone marrow transplant group (3.1%). In another report, Socié *et al.* (1991) reported on 40 patients who received a bone marrow transplant to treat Fanconi anaemia. [The Working Group noted that these patients may also overlap with those reported by Kolb *et al.* (1992) noted above.] Of these, one boy developed a cancer of the tongue 74 months after the transplantation.

Mueller and Pizzo (1995) reviewed reports on cancers in children with primary immunodeficiencies (Table 31). In these conditions, the occurrence of malignancy is substantial (5–25%) over a variable number of years and is mostly lymphoma, followed by leukaemia. An earlier review by Kinlen (1992) noted that about half of these malignancies were non-Hodgkin's lymphoma, 13% leukaemia and 9% Hodgkin's disease.

4.1.2 *Time of onset of cancers in non-HIV-associated immunodeficiency*

Among the 5692 renal transplant recipients followed on average for 5.7 years reported by Birkeland *et al.* (1995) (see Section 4.1.1), the risk for cancer at all sites was increased nearly four-fold in the first five years, over five-fold in the next decade and four-fold in the subsequent period. The risk for skin cancers increased continuously with time since receiving the transplant. In the registry-based series of 7668 tumours in 7192 patients reported by Penn (1993), the 307 Kaposi's sarcomas appeared on average at 22 (range, 1–226) months after organ transplantation; the 1252 lymphomas at 32 (1–254) months and other tumours at 67 (1–299) months. The average time of onset of non-Hodgkin's lymphoma involving the central nervous system was the same as that seen for all non-Hodgkin's lymphoma: 33 (0.1–249) months (Penn & Porat, 1995). In the paediatric patients from this cohort, the range of time intervals for any malignancy was the same as that for adults. However, the average time of onset of the 8 Kaposi's

Table 31. Cancers arising in children with primary immunodeficiency

Syndrome	Malignancy	Cumulative incidence (%)	Estimated latency in years
X-linked gamma globulinaemia	Leukaemia, NHL	6	10
Wiskott–Aldrich	NHL, leukaemia, Hodgkin's disease	>10	6
Bloom's syndrome	Leukaemia, NHL, Hodgkin's disease, adenocarcinoma	25	During first 40 years
Ataxia telangiectasia	Leukaemia, NHL, Hodgkin's disease, other	>12	9
Common variable immunodeficiency	NHL, stomach	8–10	16
Severe combined immunodeficiency	NHL	5	< 1
X-linked lympho-proliferative	NHL	4	(following EBV infection)
Selective IgA deficiency	NHL, gastric, thymoma	NG	NG

Modified from Mueller & Pizzo (1995)
NHL, non-Hodgkin lymphoma; EBV, Epstein-Barr virus; NG, not given

sarcomas was only 13 months (0–34) and that for the 167 lymphomas was 22 (0.2–217) months (Penn, 1994). In the United Kingdom–Australasian study of 3823 renal transplant patients, the authors noted that the risk for any malignancy was elevated within the first two years, and remained so through ≥ 4 years of follow-up. In the series of 274 renal transplant patients followed on average for 9.6 years reported by Gaya *et al.* (1995), the relative risk was also about four-fold within the first five years, and remained within the same range thereafter. Among non-skin tumours, there did not appear to be a time trend. However, the appearance of skin cancer increased significantly with time. Among the 868 renal transplant patients followed on average for 41.8 months for genito-urinary system malignancies, the 11 cancers (excluding the transplanted kidney adenocarcinoma) occurred on average at 66 (24–131) months (Schmidt *et al.*, 1995).

Fewer follow-up data are available for other organ transplants. In patients who generally receive more immunosuppression, malignancies occur earlier. Among the 556 liver transplant patients followed on average for 35 months by Levy *et al.* (1993b), the 10 lymphomas occurred on average at 8 (1–29) months after transplantation, 1 Kaposi's sarcoma at 16 months, 6 other solid tumours at 34 (12–66) months and 9 skin cancers at 17 (2–66) months. Among the 112 cardiac transplant recipients followed on average for 41.5 months by Dresdale *et al.* (1993), there were one patient with Kaposi's sarcoma at 47 months, four with skin cancer at an average of 43 (8–70) months and four others at 23 (6–60) months. Guettier *et al.* (1992) reported that the four gastrointestinal tract non-

Hodgkin's lymphomas occurring in a cohort of 174 cardiac transplant patients had an average time of onset of 22 (15–29) months. The two cases of Kaposi's sarcoma in cardiac transplant patients in Israel occurred two months after transplantation (Zahger *et al.*, 1993). Among 9732 bone marrow recipients, who generally receive both radiation and chemotherapy, Kolb *et al.* (1992) reported that most of the new malignancies found occurred 'in the first few months', although 9% of 79 patients developed malignancies after more than 10 years of follow-up.

In 1608 patients treated with either immunosuppression or bone marrow transplantation for aplastic anaemia reported by Socié *et al.* (1993) after mean follow-up times of 30 and 47 months, respectively, the median time to development of myelodysplasia syndrome was 52 (2–122) months, that for acute leukaemia was 47 (7–115) months, that for non-Hodgkin's lymphoma was 33 months (one case) and that for other tumours was 52 (1–94) months.

Of 557 bone marrow transplant patients followed by Lowsky *et al.* (1994), a non-Hodgkin's lymphoma developed at 7 months, a leukaemia at 46 months, three skin cancers at an average of 47 (30–64) months and five other cancers at 84 (31–127) months.

Among the cases of congenital immunodeficiency reviewed by Mueller and Pizzo (1995), the length of time to cancer diagnosis ranged from an average of less than one year in severe combined immunodeficiency syndrome to over 40 years in Bloom's syndrome.

4.1.3 *Similarities and differences between AIDS- and transplantation-associated tumours*

(*a*) *In immunity*

HIV-associated immunodeficiency shares with the other acquired or inherited immunodeficiencies reviewed above a diminution of host cellular immunity, the primary control mechanism of latent viral infections. The effect of cyclosporin A, which has been causally associated with an increased incidence of both non-Hodgkin's lymphoma and Kaposi's sarcoma in organ transplant patients, is quite similar to that seen in HIV-infection, with the selective inhibition of T-helper function (IARC, 1990). The populations reviewed above were immunosuppressed by a variety of means, either by inborn genetic defect, by cytotoxic chemotherapy or, in the vast majority of cases, by exposure to a range of therapeutic agents designed to create tolerance to a foreign organ or tissue. In the latter case, the level of immunosuppression can be modulated or withdrawn in response to clinical status, and there is regression of a lymphoma and of Kaposi's sarcoma with reduction or cessation of the treatment (IARC, 1990; Penn, 1993). Further, the impact on the immune system is generally immediate, unlike the apparently cumulative effect that is seen in the natural history of HIV infection. A general characteristic of malignancy occurring in non-HIV/AIDS-related immunosuppression is that the risk and rapidity of onset are directly related to the severity of the immunosuppression (Brusamolino *et al.* 1989; IARC, 1990; Kinlen, 1992; Gaya *et al.*, 1995).

(*b*) *In cancer types*

The types of malignancy which develop excessively in non-HIV-infected patients are generally similar to those seen in AIDS, with a predominance of non-Hodgkin's lymphomas, of which a high proportion involves the central nervous system, and Kaposi's sarcoma. A much higher proportion of non-Hodgkin's lymphomas (> 90%) in transplant recipients are EBV-positive than in AIDS-related non-Hodgkin's lymphoma (~ 50%). Among non-Hodgkin's lymphomas, Burkitt's lymphoma is relatively frequent in AIDS patients and in inherited ataxia telangiectasia and X-linked lymphoproliferative disease (Duncan's syndrome), but rare in adult transplant recipients. Further, in both AIDS and transplant patients, the malignancies tend to be more aggressive and include sites other than those usually seen in the general population (Bayley *et al.*, 1985; Kinlen, 1992; Barrett *et al.*, 1993). In regions where Kaposi's sarcoma in non-immunocompromised patients is relatively frequent, it occurs in transplant recipients at a higher frequency than non-Hodgkin's lymphoma (Qunibi *et al.*, 1988).

Transplant patients also differ from those with AIDS in their excessive development of cancers of the skin, primarily squamous-cell but also basal-cell — particularly with long-term follow-up. In renal transplant patients, there is commonly an excess of cancers of the urinary tract; however, an excess of these cancers has been seen in patients with chronic renal failure without transplantation. In patients treated for haematopoietic diseases, there is an excess of leukaemias; however, this is part of the spectrum of disease seen in many of these conditions. It used to be supposed that the excess cancer risk in transplant patients did not include those fatal malignancies which are common in older non-immunocompromised populations in the developed countries (Kinlen, 1992), and Prehn (1994) postulated that immune reactions may exert a stimulatory effect on such tumours. However, a report from the Nordic countries (Birkeland *et al.*, 1995), consolidating population-based registry data for 5692 renal transplant patients linked to the generally mutually standardized population cancer registries, found, in contrast to other studies, significantly increased risks for the incidence of cancers of the colon, lung, testis, thyroid and prostate.

(*c*) *In onset*

New malignancies in non-HIV-infected immunosuppressed individuals can occur within a very short period. A substantially increased relative risk is consistently seen in the first five years. This is in contrast to the extended latent period preceding the diagnosis of the malignancies seen in HIV-1 infection. The time from start of immunosuppressive therapy to tumour development is shorter in patient groups with more severe immunosuppression. In general, the relative risk for the associated tumours remains fairly constant over time since initiation of treatment, although Kaposi's sarcoma tends to occur earlier than non-Hodgkin's lymphoma; however, the relative risk for skin cancer shows a marked increase with time. In those studies in which both Kaposi's sarcoma and non-Hodgkin's lymphoma were seen, the former generally occurred earlier than the latter, as is seen in AIDS.

4.1.4 *Occurrence of other viruses in malignancies associated with non-HIV immunosuppression*

HHV-8 has been detected in 11/11 biopsies of Kaposi's sarcoma in transplant patients (Boshoff *et al.*, 1995a; Lebbé *et al.*, 1995; Buonaguro *et al.*, 1996). EBV was detected in 28/29 non-Hodgkin's lymphomas from transplant patients (Ho *et al.*, 1985b; Shapiro *et al.*, 1988; Nakhlen *et al.*, 1991). Transplantation of PBMCs from EBV-positive healthy humans into severe combined immunodeficient (SCID) mice frequently results in the development of immunoblastic lymphoma in the immunodeficient mouse.

IARC (1995) reviewed the data on the role of HPV in malignancies among transplant patients. In the case–control studies, the prevalence of cervical infections with HPV detected in women with organ transplants ranged from 22 to 45%, which was significantly higher than that in controls (3–6%). [The Working Group noted that these studies preceded the introduction of more sensitive primers for PCR detection of the high-risk HPV types and probably underestimated HPV prevalence.]

IARC (1995) also reviewed the prevalence of detectable HPV in skin cancers occurring in transplant patients. For 539 squamous-cell carcinoma specimens tested using the more sensitive methods, the positivity rate ranged between studies from zero to 100%, with half of the 16 studies having case positivity rates of at least 50%. Similarly, in eight published studies, among a total of 40 basal-cell carcinomas in transplant patients, nine cases (23%) were scored HPV-positive. A study using new PCR primers detected a high frequency of HPV-5, HPV-8 and other strains related to those occurring in epidermodysplasia verruciformis in skin cancer of renal transplant recipients (Berkhout *et al.*, 1995).

4.1.5 *Mechanisms by which immune dysfunction may contribute to the genesis of cancer*

(*a*) *Activation of oncogenic viruses with immunosuppression*

In immunocompetent persons, cell-mediated immunity may act to limit viral oncogenesis at two levels: first by controlling the overall viral burden by eliminating cells productively infected by the virus; second by recognizing viral antigen expressed on latently preneoplastic and neoplastic cells.

(*b*) *Stimulation and hyperreactivity of remaining cells in immunosuppressed persons*

The presence of the graft itself may modulate the immune system as a source of chronic antigenic stimulation. Lowsky *et al.* (1994) reported that the risk for new malignancies in bone marrow transplant patients was significantly associated with the presence of acute graft versus host disease, but not with the treatment modality itself. Bouwes Bavinck *et al.* (1991) observed that HLA-B mismatching (as well as homozygosity for HLA-DR) was significantly associated with the risk for squamous-cell carcinoma of the skin in renal transplant patients. This association appeared to be independent of the amount and type of treatment. However, B-cell hyperplasia is not a feature of

iatrogenic immunosuppression as it is in HIV infection, which may explain why a larger proportion of non-Hodgkin's lymphomas in AIDS are EBV-negative (see Section 4.3.2).

4.2 Kaposi's sarcoma

Epidemiological and clinical studies (summarized in Section 2.1) have yielded the following conclusions regarding the etiology of Kaposi's sarcoma in HIV-infected individuals:

(i) the immunosuppressive effect of HIV is a major factor;

(ii) HIV component(s) may directly promote the development of Kaposi's sarcoma lesions, as the disease is often more aggressive in HIV-infected patients;

(iii) an infectious agent distinct from HIV and mainly transmitted sexually may have an important role.

This section reviews the virological and cell biological evidence which is relevant to these observations.

4.2.1 *Cell biology of Kaposi's sarcoma lesions*

(*a*) *Origins of Kaposi's sarcoma spindle cells*

The hallmark of the advanced Kaposi's sarcoma lesion is the spindle cell surrounding slit-like spaces. Endothelial cells (either vascular or lymphatic endothelium), cells from venous lymphatic junctions, fibroblasts, smooth muscle cells and dermal dendrocytes have all been proposed as possible progenitors of Kaposi's sarcoma spindle cells (reviewed by Roth *et al.*, 1992; Stürzl *et al.*, 1992a; Kaaya *et al.*, 1995). Rappersberger *et al.* (1991) reported that spindle cells stain with the monoclonal antibody EN-4 (which detects both vascular and lymphatic endothelium) but lack reactivity with the monoclonal antibody Pal-E (which reacts with blood-vessel but not lymphatic endothelial cells). This observation is compatible with spindle cells originating from lymphatic endothelium. However, other markers for blood vessel endothelium (but not lymphatic endothelium; OKM-5 and anti-factor VIII-related antigen; von Willebrand factor; vWF) stain Kaposi's sarcoma endothelial or spindle cells, although slightly varying results have been reported by different laboratories (Nadji *et al.*, 1981; Modlin *et al.*, 1983a; Little *et al.*, 1986; Rappersberger *et al.*, 1991; further references in Roth *et al.*, 1992).

Ultrastructural examination has failed to show the presence of Weibel–Palade bodies, the storage vesicles for vWF and therefore a characteristic feature of vascular endothelium, in spindle cells from Kaposi's sarcoma lesions (Rappersberger *et al.*, 1991). Staining with monoclonal antibody BMA 120, that detects an antigen specific to endothelial cells, lends support to an endothelial origin of Kaposi's sarcoma cells (Roth *et al.*, 1988). Kaposi's sarcoma spindle cells and endothelia lining vascular spaces in lesions express leukocyte adhesion molecule-1 (LAM-1) and thrombomodulin, which are markers of lymphokine-activated endothelial cells (Zhang *et al.*, 1994). This observation supports the notion that Kaposi's sarcoma spindle cells are of endothelial origin and are activated by growth factors (see below).

The staining (observed by some laboratories but not by others) of spindle cells with antibodies to CD14, CD68 and factor XIIIa has been interpreted to reflect a possible link between Kaposi's sarcoma spindle cells and cells of the monocyte/macrophage lineage, possibly dermal dendrocytes (Nickoloff *et al.*, 1989; Rappersberger *et al.*, 1991; Kaaya *et al.*, 1995). These cells are distinct from Langerhans' cells (Nickoloff *et al.*, 1989). The staining of cultured Kaposi's sarcoma spindle cells with an antibody to smooth muscle α-actin (Weich *et al.*, 1991) and other similar histochemical data have been interpreted to suggest a relationship with smooth muscle cells or myofibroblasts (reviewed by Roth *et al.*, 1992). These discrepant results suggest either that cells of different lineages can adopt a spindle-like morphology or that these markers are common to different cells of mesenchymal origin. [The Working Group considered that the weight of evidence pointed to the spindle cells being most closely related to vascular endothelial cells.]

A number of laboratories have cultured cells from Kaposi's sarcoma that express markers characteristic for vascular or lymphatic endothelium (Delli-Bovi *et al.*, 1986; Nakamura *et al.*, 1988; Roth *et al.*, 1988; Siegal *et al.*, 1990; Corbeil *et al.*, 1991; Herndier *et al.*, 1994a), but cultures expressing smooth muscle α-actin (Albini *et al.*, 1988; Wittek *et al.*, 1991) as well as mixed populations (Siegal *et al.*, 1990; further references in Roth *et al.*, 1992) have also been reported. The lineage identity of cultured cells has been defined by staining for the same markers as in the in-situ studies, notably vimentin and cytokeratin (for discrimination of mesenchymal and epithelial cells respectively), the endothelial markers vWF, Pal-E, OKM-5, BMA 120 (specific for blood-vessel endothelium), and EN-4 and UEA-I lectin (reactive with blood-vessel and lymphatic endothelium), CD14, CD68 and factor XIIIa (for the monocyte/macrophage lineage), SMC α-actin (smooth muscle and myofibroblast) and others (reviewed by Roth *et al.*, 1992; Stürzl *et al.*, 1992a; Kaaya *et al.*, 1995). Spindle-shaped cells showing a moderate expression of endothelial antigens have been cultured from peripheral blood of Kaposi's sarcoma patients (Browning *et al.*, 1994).

(*b*) *Vascular lesions induced by Kaposi's sarcoma cell cultures in nude mice*

The various cell cultures established from Kaposi's sarcoma lesions differ in their ability to induce the growth of Kaposi's sarcoma-like vascular lesions in nude mice. A cell line expressing endothelial markers induced Kaposi's sarcoma-like tumours of human origin in nude mice (Siegal *et al.*, 1990; Herndier *et al.*, 1994a). This cell line had a normal diploid karyotype and expressed the endothelial markers factor VIII, EN-4 and UEA-I lectin. In addition, it produced high levels of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1; Herndier *et al.*, 1994a). Plasminogen activator has been shown to be involved in the development of endothelial tumours in mice transgenic for the polyoma middle T protein (Montesano *et al.*, 1990). More recently, a second cell line capable of causing tumours of human origin in nude mice has been described and these lesions could be inhibited by β-human chorionic gonadotropin (β-HCG) (Lunardi-Iskander *et al.*, 1995a). These cell lines meet the criteria for a tumorigenic cell line.

In contrast, a few other Kaposi's sarcoma cell cultures, also of an endothelial phenotype, are angiogenic *in vivo*, and induce transient Kaposi's sarcoma-like vascular lesions

of *murine* origin, when inoculated into nude mice (Nakamura *et al.*, 1988; Salahuddin *et al.*, 1988). Spindle-shaped cells grown from the peripheral blood of Kaposi's sarcoma patients have also been reported to induce murine angiogenesis in nude mice (Browning *et al.*, 1994). This angiogenic property, together with other in-vitro findings (see below), suggests that growth factors produced by the cultured cells could induce murine cells to produce lesions resembling early Kaposi's sarcoma.

However, most other cell cultures established from Kaposi's sarcoma lesions, including some which are capable of acidic low-density lipoprotein uptake and expressing the endothelial marker BMA 120 (Roth *et al.*, 1988), did not induce tumour formation in nude mice, were not capable of growing in soft agar and showed only a slightly reduced serum dependence. Similarly, cultures expressing the endothelial marker OKM-5 were not tumorigenic in nude mice (Delli-Bovi *et al.*, 1986).

Cell cultures of smooth muscle origin do not induce Kaposi's sarcoma-like lesions *in vivo* but are capable of local invasion in muscle organ cultures and through artificial basal membranes (Albini *et al.*, 1988; Wittek *et al.*, 1991). The reason for these differences is not clear but may be linked to differences in the cytokine profile secreted by these different cultures (see below).

(c) *Growth factors involved in the proliferation of spindle cells*

Extensive work by several laboratories has examined the role that lymphokines might play during the development of Kaposi's sarcoma. However, probably because of the different cell types grown by different laboratories, the findings reported are inconsistent. Fibroblast growth factors (FGFs) and platelet-derived growth factors (PDGFs) have been found to be expressed in Kaposi's sarcomas, or to be present in short-term cultures from Kaposi's sarcoma biopsies.

(i) *Fibroblast growth factors*

Basic fibroblast growth factor (bFGF) has been reported to be secreted by Kaposi's sarcoma cultures expressing endothelial cell markers and may promote the growth of these cells *in vitro* (Ensoli *et al.*, 1989). Other groups, working with Kaposi's sarcoma cultures of either an endothelial phenotype (Corbeil *et al.*, 1991) or mixed fibroblastoid/-endothelial appearance (Werner *et al.*, 1989) also found an FGF-like activity in supernatants of their Kaposi's sarcoma cultures which stimulated the growth of normal fibroblasts and endothelial cells.

Members of the FGF family, including bFGF and endothelial cell growth factor (ECFG), are known to stimulate the growth of normal endothelial cells, and cultured Kaposi's sarcoma cells with endothelial characteristics have been shown to induce transient neoangiogenesis in nude mice (Nakamura *et al.*, 1988). The FGF family of cytokines may thus play a crucial role during the development of Kaposi's sarcoma. In Kaposi's sarcoma, the expression of bFGF and FGF5 in spindle cells has been shown by in situ hybridization (Xerri *et al.*, 1991). Acidic FGF and FGF6 are also expressed in Kaposi's sarcoma (Li *et al.*, 1993b), but the technique employed in this study (RT-PCR) does not permit the identification of the cell type(s) secreting these two members of the FGF family. The importance of bFGF in the development of experimental Kaposi's

sarcoma-like lesions is further supported by the report that a bFGF-specific antisense oligonucleotide can inhibit the angiogenic effect of cultured Kaposi's sarcoma cells in nude mice (Ensoli *et al.*, 1994a).

(ii) *Platelet-derived growth factor*

Normal endothelial cells (Ensoli *et al.*, 1989; Roth *et al.*, 1989) as well as short-term cultures of endothelial cells with endothelial characteristics (Ensoli *et al.*, 1989) produce PDGF. Kaposi's sarcoma cell cultures that produce PDGF thus do not require exogenous PDGF to promote proliferation (Ensoli *et al.*, 1989; Corbeil *et al.*, 1991). However, PDGF has been found to be essential for the propagation *in vitro* of Kaposi's sarcoma cells expressing the endothelial cell marker BMA 120 and capable of acidic low-density lipoprotein uptake but exhibiting fibroblast-like growth properties. These cultures were also shown to express mRNA for the receptors for PDGF-A and PDGF-B (Roth *et al.*, 1989; Werner *et al.*, 1990). Kaposi's sarcoma spindle cells express *in vivo* mRNA for PDGF-B receptor, whereas mRNAs for PDGF-A and PDGF-B were expressed on some tumour cells located in the vicinity of slit-like spaces (Stürzl *et al.*, 1992b). Taken together, these findings suggest that Kaposi's sarcoma cells related to endothelial cells produce PDGF which is required for the growth of spindle cells exhibiting at least some fibroblastoid characteristics, thus highlighting the interdependence of the different cell lineages found in Kaposi's sarcomas.

(*d*) *Clonality of Kaposi's sarcoma and chromosomal abnormalities*

Individual nodules of HIV-associated Kaposi's sarcoma may contain predominant clonal populations (Rabkin *et al.*, 1995b). It is unknown whether different Kaposi's sarcomas from the same patient contain the same or different clonal populations. Therefore, whether individual lesions are derived from the same (as in a metastatic lesion) or different clones is also unknown. A tumorigenic cell line established from a Kaposi's sarcoma was reported to contain a marker chromosome (Lunardi-Iskandar *et al.*, 1995b). [The Working Group noted that evidence for chromosomal anomalies in primary Kaposi's sarcoma tissue is lacking.] Some short-term cultures of Kaposi's sarcoma biopsies have been noted to contain chromosomal rearrangements, but no consistent pattern has been confirmed either in primary sporadic tumours (Ottolenghi *et al.*, 1974; Scappaticci *et al.*, 1986) or in AIDS-associated tumours (Delli-Bovi *et al.*, 1986; Alonso *et al.*, 1987; Saikevych *et al.*, 1988).

Thus, clonal populations may develop in Kaposi's sarcoma and give rise to monoclonal tumorigenic cell lines.

4.2.2 *The role of HIV-1 Tat in the development of Kaposi's sarcoma lesions*

Experimental evidence suggests that the Tat protein of HIV-1 can enhance the growth of cultured 'endothelial' Kaposi's sarcoma cells (Ensoli *et al.*, 1990; Barillari *et al.*, 1993). In this in-vitro model, Tat is thought to cooperate with bFGF to enhance Kaposi's sarcoma cell proliferation. The effect of Tat seems to be mediated by its binding to a5 a1 and aV a3 integrins via an RGD (i.e. arginine-glycine-aspartic acid) sequence element in

a manner similar to, and replaceable by, their physiological ligands fibronectin and vitronectin (Barillari *et al.*, 1993; Ensoli *et al.*, 1994b).

Several cytokines, including tumour necrosis factor (TNF), interleukin (IL)-1 and γ-interferon, can render normal endothelial and smooth muscle cells susceptible to the growth-promoting effect of Tat (Barillari *et al.*, 1992), possibly by increasing the expression of integrin receptors which interact with Tat (Barillari *et al.*, 1993; Ensoli *et al.*, 1994b). Injection of Tat into nude mice (Ensoli *et al.*, 1994b) or immunocompetent C57/Bl mice (after incorporation into Matrigel; Albini *et al.*, 1994) induces angiogenesis and this effect is potentiated by bFGF (Ensoli *et al.*, 1994b) or heparin (Albini *et al.*, 1994). The formation of Kaposi's sarcoma-like lesions induced by Tat and heparin can be inhibited by the matrix metalloproteinase inhibitor TIMP-2 (Albini *et al.*, 1994) and Tat and bFGF act synergistically to increase the expression of collagenase IV in nude mice (Ensoli *et al.*, 1994b). These studies suggest the involvement of tissue proteinases in the development of Kaposi's sarcoma.

Several groups have investigated the role of HIV-1 *tat* in Kaposi's sarcoma pathogenesis using transgenic mice. Vogel *et al.* (1988) reported the emergence of Kaposi's sarcoma-like lesions in mice transgenic for HIV-1 *tat*. Transgenic mice carrying the early region of BK virus, included in an LTR-*tat* construct, also develop Kaposi's sarcoma-like lesions in addition to other malignancies (Corallini *et al.*, 1993) and extracellular Tat protein released by tumour cell lines derived from these animals protects them from apoptosis under conditions of serum starvation (Campioni *et al.*, 1995). The growth-promoting effect of extracellular Tat on cultured Kaposi's sarcoma cells and endothelial cells (Ensoli *et al.*, 1990; Barillari *et al.*, 1992) suggests that infection by HIV-1 of cells not directly involved in the Kaposi's sarcoma lesion may be sufficient for triggering the sequence of events leading to the development of Kaposi's sarcoma. In keeping with this interpretation, in *tat*-transgenic mice which did develop Kaposi's sarcoma-like lesions, the expression of *tat* was found not in spindle cells but in neighbouring keratinocytes (Vogel *et al.*, 1988). However, other lines of transgenic mice, carrying the complete HIV-1 genome, failed to develop similar lesions (Leonard *et al.*, 1988).

With regard to the question of whether sufficient levels of HIV-1 Tat are present in AIDS-related Kaposi's sarcoma lesions to achieve an angiogenic effect, Ensoli *et al.* (1994b) claimed that HIV-1 Tat could be detected on spindle cells by histochemical techniques. They suggested that Tat originated from a few HIV-1-infected mononuclear cells infiltrating these lesions.

Thus, the ability of Tat, in concert with other growth factors, to induce vascular lesions resembling Kaposi's sarcoma has been documented in a variety of experimental systems. However, this property may not be unique to HIV-1 infection, as supernatants from T-cell lines infected with HTLV-II have been shown to induce the propagation of Kaposi's sarcoma-derived cells *in vitro*. The lymphokine responsible for this growth-enhancing effect has been identified as oncostatin M (Nakamura *et al.*, 1988; Miles *et al.*, 1992; Nair *et al.*, 1992). This suggests that infection by other human retroviruses can lead to the production of lymphokines which promote the growth of cells found in Kaposi's sarcomas. Since some non-human retroviruses have been shown to induce

Kaposi's sarcoma-like lesions in several animal models (see Section 4.2.3), and since mice transgenic for the middle T gene of polyomavirus develop endothelial cell tumours (Bautch *et al.*, 1987), it is conceivable that various microorganisms could initiate such a cascade of events.

4.2.3 *An infectious agent as a cause of Kaposi's sarcoma*

Extensive epidemiological studies, reviewed in Section 2.1, suggest the involvement in the pathogenesis of Kaposi's sarcoma of an agent which can be transmitted sexually, although not exclusively so.

There is no convincing evidence to associate cytomegalovirus, HHV-6, papillomaviruses, hepatitis B virus (IARC, 1994), *Mycoplasma fermentans* or *M. penetrans* with Kaposi's sarcoma.

In the last two decades, several laboratories have either observed or tried to isolate viruses from Kaposi's sarcomas. Giraldo *et al.* (1972) reported the presence of herpes-like viruses in short-term cultures from Kaposi's sarcoma biopsies. The identity of these particles has never been satisfactorily established. Occasional herpes viral particles have also been seen in Kaposi's sarcoma tissue sections (Walter *et al.*, 1984).

C-Type retroviruses were detected in Kaposi's sarcoma biopsies from a group of HIV-negative Kaposi's sarcoma patients from a distinct region of the southern Peloponnese in Greece (Rappersberger *et al.*, 1991). Some of the clinical features of the disease in this group of patients (involvement of oral and genital mucosa and gastrointestinal tract; extensive involvement of facial skin) were reminiscent of African or AIDS-associated Kaposi's sarcoma rather than 'classical' Kaposi's sarcoma. Retroviral particles have also been found in Kaposi's sarcoma biopsies from patients with AIDS (Gyorkey *et al.*, 1984; Schenk, 1986). It is possible that these particles represented HIV-1.

As discussed in Section 3.2.3, there is no really good animal model for Kaposi's sarcoma. However, several animal models have provided indirect evidence supporting a possible role of retroviruses in the pathogenesis of Kaposi's sarcoma. Macaque monkeys infected with the D-type simian retrovirus type 2 (SRV-2) develop retroperitoneal and subcutaneous fibrosis with progressive fibrovascular proliferation, reminiscent of Kaposi's sarcoma lesions (Tsai *et al.*, 1995). Cell cultures established from these lesions induced self-limited, transient spindle cell proliferation, accompanied by pronounced vascularization, when inoculated into nude mice. In fowl, some strains of avian leukosis virus can induce, in addition to lymphoma, disseminated haemangiomatosis characterized by a progression from early patch-like lesions with predominant endothelial cell proliferation to haemangiosarcoma (Victor & Jarplid, 1988). In BALB/c mice, a strain of Moloney murine sarcoma virus (MMSV 349), containing the *mos* oncogene, induces lesions that resemble human Kaposi's sarcoma on the basis of both histopathology and electron microscopy. The *mos* oncogene does not seem to be sufficient to induce these lesions, as another strain of MMSV, also containing the *mos* oncogene, does not induce similar lesions (Stoica *et al.*, 1990).

In addition to some HIV-1 *tat* transgenic mice which develop Kaposi's sarcoma-like lesions (see Section 4.2.2), mice transgenic for the middle T antigen of polyomavirus develop endothelial tumours (Bautch *et al.*, 1987). These reports indicate that a variety of infectious agents or their proteins can induce vascular proliferation which bears some resemblance to Kaposi's sarcoma lesions. Yet it is difficult to extrapolate from these animal models to a candidate for an infectious agent involved in the pathogenesis of human Kaposi's sarcoma.

4.2.4 *The role of human herpesvirus 8*

A new human γ-herpesvirus (HHV-8), also termed Kaposi's sarcoma herpesvirus (KSHV), has been discovered in AIDS-associated Kaposi's sarcoma biopsies (Chang *et al.*, 1994) and is a strong candidate for the 'Kaposi's sarcoma agent' (see Section 2.1.5).

(*a*) *Genomic organization and relationship to other primate herpesviruses*

HHV-8 belongs to the γ_2 subgroup of herpesviruses and is most closely related to herpesvirus saimiri, a T-lymphotropic herpesvirus with transforming potential, found in squirrel monkeys (*Saimiri sciureus*) (Moore *et al.*, 1996). Several of the HHV-8 structural genes show significant levels of sequence homology to the corresponding genes of herpesvirus saimiri, but also to those of the slightly more distantly related EBV, and the organization of a 20 kb central segment of the HHV-8 genome is highly similar to that of these other two γ-herpesviruses (Moore *et al.*, 1996). In addition, HHV-8 contains a homologue of the human *cyclin D* gene and a member of the family of six-protein coupled receptors (Cesarman *et al.*, 1995). The HHV-8 cyclin homologue has been shown to be active in abrogating the function of the retinoblastoma tumour-suppressor protein and could thus be involved in dysregulating cellular proliferation or differentiation.

(*b*) *In-vivo tropism and association with Kaposi's sarcoma*

As described in Section 2.1.5, HHV-8 is consistently found in the vast majority (> 95%) of biopsies from all epidemiological forms of Kaposi's sarcoma, i.e. AIDS-associated Kaposi's sarcoma, classical Mediterranean Kaposi's sarcoma, post-transplant Kaposi's sarcoma and African endemic Kaposi's sarcoma (see Table 15).

HHV-8 has been found by PCR in-situ hybridization in the flat endothelial cells lining ectatic vascular spaces, as well as in spindle cells of Kaposi's sarcoma lesions (Boshoff *et al.*, 1995b). These two cell types represent the bulk of the lesion and this observation is therefore compatible with an important etiopathological role of HHV-8 in the development of Kaposi's sarcoma.

However, primary cultures established from fresh Kaposi's sarcoma biopsies lose HHV-8 after a few passages, and established Kaposi's sarcoma cell cultures, including permanent cell lines (see above) are negative for this virus (Ambroziak *et al.*, 1995; Lebbé *et al.*, 1995). The implications of this observation are unclear.

Therefore, it is possible that the murine angioproliferative lesions induced by Kaposi's sarcoma cell cultures in nude mice are not an adequate model for Kaposi's sarcoma. However, it is also possible that HHV-8 is not required for the development of Kaposi's sarcoma *in vivo* and may only infect and/or replicate preferentially in already established Kaposi's sarcoma endothelial or spindle cells.

In peripheral blood of HIV-infected individuals, HHV-8 is present in B-cells (Ambroziak *et al.*, 1995) and its detection correlates inversely with the number of $CD4^+$ T-cells, suggesting that its replication is under immunological control (Whitby *et al.*, 1995).

Thus, the available evidence suggests that HHV-8 is a strong candidate for the long-sought 'Kaposi's sarcoma agent', but its precise role and epidemiology remain to be established.

4.3 Non-Hodgkin's lymphomas and other lymphoproliferative disorders

As discussed in Sections 2.2 and 2.3.3 and listed in Table 16, the incidence of several types of lymphoproliferative disease is increased in HIV-infected patients.

4.3.1 *Pathological models of lymphomagenesis*

The biological basis and molecular genetics underlying the pathogenesis of AIDS-related non-Hodgkin's lymphomas and other lymphoproliferative disorders (Hodgkin's disease and multicentric Castleman's disease) are not well understood. Several pathological conditions seem to contribute to AIDS-related lymphomagenesis: immunosuppression, dysregulation of cytokine loops, accumulation of genetic lesions within the proliferating clones and infection by viruses (reviewed by Knowles, 1993; Gaidano & Carbone, 1995). These contributory factors may act at different stages of a proposed multistage model of lymphomagenesis (Pelicci *et al.*, 1986; Feichtinger *et al.*, 1992a; Gaidano & Dalla-Favera, 1992; Knowles, 1993; Gaidano *et al.*, 1994a; Herndier *et al.*, 1994b).

The development of AIDS-related non-Hodgkin's lymphoma is often preceded by polyclonal hypergammaglobulinaemia and persistent generalized lymphadenopathy (PGL) (Carbone *et al.*, 1991; Raphael *et al.*, 1991); furthermore, chromosomal abnormalities (Alonso *et al.*, 1987) and oligoclonal immunoglobulin gene rearrangements are detectable in a fraction of these HIV-associated lymphadenopathies (Pelicci *et al.*, 1986; Carbone *et al.*, 1989). Unlike PGL, AIDS-related non-Hodgkin's lymphoma is usually monoclonal and is characterized by a number of molecular alterations of dominantly-acting oncogenes and of tumour-suppressor genes (Ballerini *et al.*, 1993; Gaidano *et al.*, 1993). According to this model of lymphomagenesis, the emergence of oligoclonal B-cell expansions representing a pre-malignant condition is at first driven by several factors including immune dysregulation and viral infections. This phase clinically and pathologically corresponds to PGL. In subsequent phases, the neoplastic transformation of a B-cell clone is due to the accumulation of genetic lesions which eventually transform the clone developing the non-Hodgkin's lymphoma (Figures 10–12). The

Figure 10. Schematic representation of follicle disruption during the course of HIV infection, showing the progression from follicular hyperplasia to follicular involution

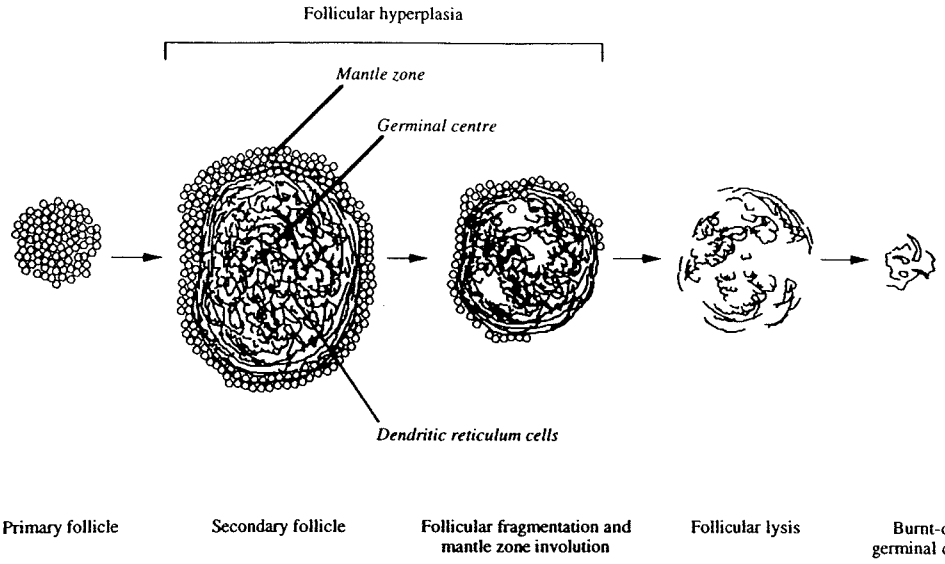
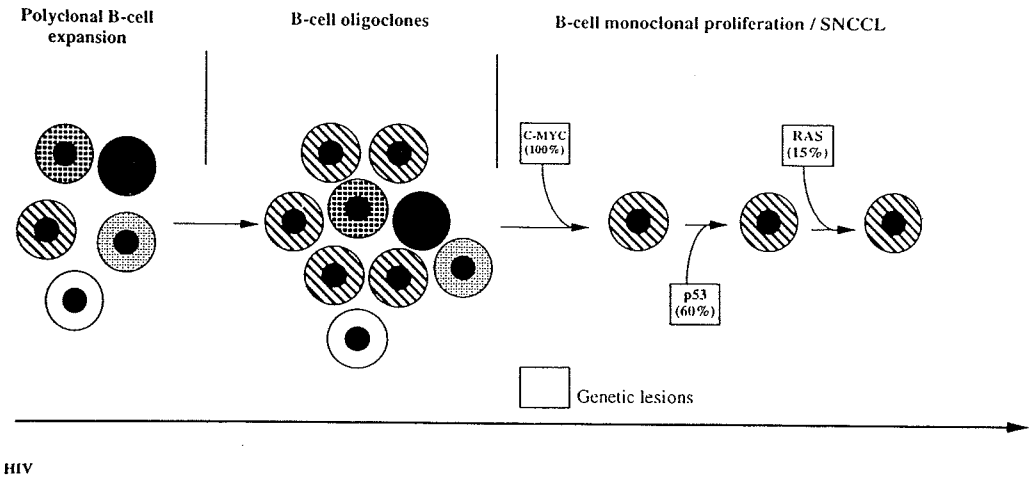


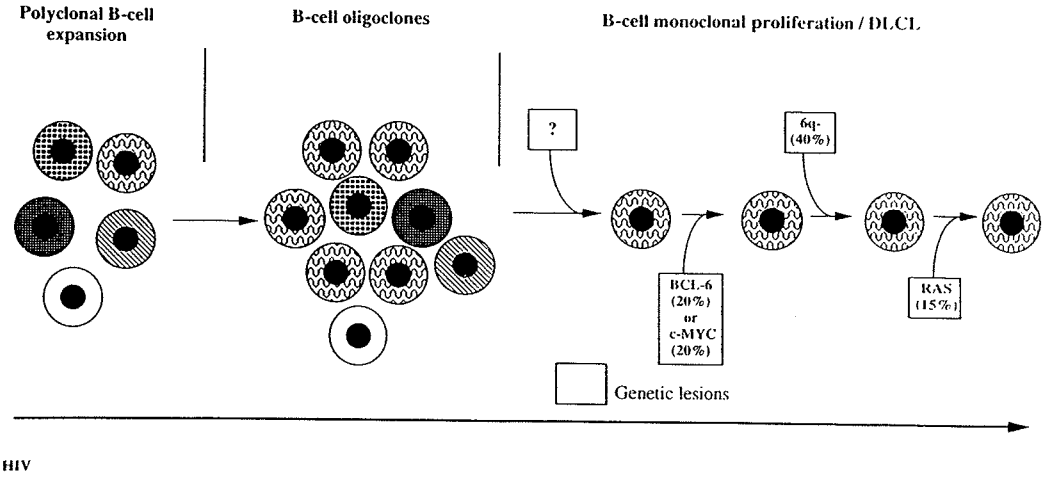
Figure 11. Genetic lesions contributing to pathogenesis of AIDS-related small non-cleaved-cell lymphoma



Adapted from Gaidano *et al.* (1994a)
SNCCL, small non-cleaved cell lymphoma

complex pathophysiological milieu of HIV infection is obviously of importance in the pathogenesis of AIDS-related lymphomas. Morphological, immunopathological, molecular and cytogenetic analyses of the pathological changes in lymphoid tissues during HIV infection have improved the understanding of the mechanisms leading to lymphoma onset and progression.

Figure 12. Genetic lesions contributing to the pathogenesis of AIDS-related diffuse large-cell lymphoma



Adapted from Gaidano *et al.* (1994a)
DLCL, diffuse large-cell lymphoma

As depicted in Figures 11 and 12, three biological stages in the development of B-cell lymphoma can be distinguished: (*a*) polyclonal B-cell hyperplasia; (*b*) oligoclonal expansion and (*c*) genetic changes. Combination of these factors leads to the eventual emergence of monoclonal lymphoma.

(*a*) *HIV infection of lymphoid tissue and polyclonal B-cell hyperplasia*

A critical event in initiating and establishing HIV infection is the localization of HIV in lymphoid organs which become the major reservoirs of HIV and sites of viral replication (Fox *et al.*, 1991). Viral particles and antigen become trapped on the surface of the web-like processes of the follicular dendritic cells which permeate the germinal centres. These cells then expand to form the core of the lymphoid tissue (Biberfeld *et al.*, 1985; Tenner-Rácz *et al.*, 1985; Pantaleo *et al.*, 1993a,b). Persistence of virus in lymphoid organs causes chronic stimulation of the immune system which ultimately leads to degeneration of the follicles (reviewed by Pantaleo & Fauci, 1995). Morphological analyses at different stages of HIV infection have demonstrated that lymphoid tissues undergo progressive destruction and depletion of B-cell areas as the disease advances (Biberfeld *et al.*, 1985, 1987; Ioachim *et al.*, 1990; Fox *et al.*, 1991). The severe immunosuppression at advanced stages of disease is one of the functional consequences of this process (reviewed by Pantaleo & Fauci, 1995). In contrast, lymph-node architecture and immune function appear to be intact in some HIV-infected individuals who remain free of disease for many years (Pantaleo *et al.*, 1995).

(i) *Pathological changes in HIV-infected lymphoid follicles*

The lymph nodes in HIV-infected patients with PGL have been extensively studied both histologically and immunophenotypically (Ioachim *et al.*, 1983; Baroni *et al.*, 1985; Janossy *et al.*, 1985; Wood *et al.*, 1985; Carbone *et al.*, 1986; Wood *et al.*, 1986). The first lymphadenopathic change is follicular hyperplasia (Biberfeld *et al.*, 1985), which is the expansion of the germinal centre by recruitment, proliferation and differentiation of antigen-reactive B-cells (follicular hyperplasia). Morphologically, follicles appear to be increased in size and number and show a marked variation in shape and irregular marginal zones. By immunohistochemical methods, a colocalization of HIV p24 antigen with follicular dendritic cells is clearly visible in the secondary germinal centres (Biberfeld *et al.*, 1985; Baroni *et al.*, 1986). Follicular fragmentation, which may represent an early degenerative change, can be perceived as a disruption of the dendritic reticulum of the germinal centre (Biberfeld *et al.*, 1985). Also, the follicular mantle zones become progressively reduced (Wood *et al.*, 1985). Such follicular changes in lymph nodes have also been detected in mucosal, 'hypertrophic' nasopharyngeal lymphoid tissue (Barzan *et al.*, 1989; Shahab *et al.*, 1994). Nasopharyngeal lymphoid tissue 'hypertrophy', often associated with PGL (Barzan *et al.*, 1990), is apparently linked to the early phase of HIV infection in the same way as follicular hyperplasia is in PGL (Carbone *et al.*, 1995b).

As HIV disease progresses, germinal centres show a reduction in the number of $CD4^+$ T-lymphocytes and an increase in the percentage of $CD8^+$ T-cells (Modlin *et al.*, 1983b; Said *et al.*, 1984; Carbone *et al.*, 1985; Biberfeld *et al.*, 1986), reflecting the decrease in $CD4^+ : CD8^+$ lymphocyte ratio of peripheral blood. The destruction of the follicular dendritic cell network and the collapse of the germinal centres become increasingly evident (the so-called burning-out phenomenon) (Biberfeld *et al.*, 1985). Follicular involution is characterized by hypervascularity, with small follicles resembling those seen in multicentric Castleman's disease. Germinal centres are small and show hyalinization and fibrosis (Figure 10).

These pathological changes, ranging from follicular hyperplasia to follicular involution, usually involve most lymphoid tissue, including tonsils, abdominal lymph nodes and spleen (Burke *et al.*, 1993).

(ii) *Destruction of follicular centres and B-cell hyperplasia*

It has been suggested that abnormal B-cell proliferation takes place when follicular architecture is disrupted by HIV (Armstrong & Horne, 1984; Tenner-Rácz *et al.*, 1985; Feichtinger *et al.*, 1992a). According to one version of this hypothesis, the destruction of follicular dendritic cells interferes with apoptosis and allows the proliferation of B-cell clones expressing low-avidity cell surface immunoglobulin (Herndier *et al.*, 1994b). Another aspect is the dissemination of follicular dendritic cells outside of lymphoid tissue, which could permit the formation of germinal centres in non-lymphoid tissue from which a polyclonal B-cell proliferation and B-cell lymphoma would emerge (Feichtinger *et al.*, 1992a; Herndier *et al.*, 1994b).

(iii) *Chronic antigen stimulation*

Chronic antigen stimulation, pathologically observed as florid B-cell hyperplasia, has been postulated to be a key factor in Burkitt's lymphoma pathogenesis in patients with AIDS (reviewed by Karp & Broder, 1992). Evidence for this is the finding that AIDS-related Burkitt's lymphomas frequently produce antibodies directed against self antigens; furthermore, the hypervariable regions of the immunoglobulin genes utilized by AIDS-related Burkitt's lymphoma carry somatic mutations, which may have been selected by antigen stimulation (Ng *et al.*, 1994; Riboldi *et al.*, 1994). Together, these data suggest that a process of B-cell clonal selection is involved in AIDS lymphomagenesis.

(iv) *Presence of HIV in tumour cells*

Tumours from AIDS-related non-Hodgkin's lymphoma are almost all of B-cell origin. In these tumours, HIV has not been detected in the B-lymphocytes. For example, Morgello (1992) reported a series of 12 primary central nervous system lymphomas from New York, United States. None was positive for HIV *gag* sequences by the sensitive technique of PCR. Similarly, Cornford *et al.* (1991) studied the immunohistochemical localization of HIV in seven cases of central nervous system lymphoma in Los Angeles, CA, United States. While they detected HIV near the mass lesions in five (70%) of the cases, in no instance was HIV detected within the neoplastic lymphoid cells themselves.

Insertional mutagenesis with a direct role of HIV has been proposed to explain some cases of AIDS-related non-Hodgkin's lymphoma. Shiramizu *et al.* (1994) reported four cases that had HIV clonally integrated in the tumour. In one case of T-cell immunophenotype, HIV was detectable in T-cells by anti-p24 immunostaining. The other three cases having a B-, T- or null phenotype contained a large histiocytic reactive component; HIV was localized to these reactive cells. All four cases were reported to have a common integration site of HIV upstream from the c-*fes/fps* proto-oncogene, which suggested an insertional mutagenesis role for HIV in a subset of AIDS-related lymphomas.

In another study, it was also suggested that HIV could play a direct role in B-cell transformation. This was based on the increased proliferation *in vitro* of B-lymphocytes dually infected with HIV and EBV (Laurence & Astrin, 1991). In addition, Astrin *et al.* (1992) reported detection by PCR of, on average, one HIV proviral DNA copy per cell in B-lymphoma tissue, but did not observe monoclonal integration of HIV DNA in B-lymphoma cells. These results therefore fall short of confirming a direct oncogenic effect of HIV in B-cells.

Indeed, consistent failure to detect HIV sequences unequivocally within the tumour clone has suggested that HIV is not directly involved in the development of malignancy (reviewed by Knowles, 1993).

(*b*) *Oligoclonal B-cell proliferation*

Three main groups of cofactors, cytokines, lymphotropic viruses and genetic changes, are thought to be involved during the transition from polyclonal B-cell proliferation to the expansion of oligoclonal B-cell populations.

(i) *Immunosuppression*

As for some other cancers in AIDS, immunosuppression also predisposes to the frequent development of B-cell lymphoma (reviewed by Gaidano & Dalla Favera, 1992; Karp & Broder, 1992).

The relation between immunosuppression and the development of lymphoma is recognized in several clinical conditions other than AIDS, including congenital and iatrogenic immunodeficiences (Frizzera, 1994) (see Sections 2.2.1 and 4.1.3). The relative risk for AIDS-related non-Hodgkin's lymphoma increases with progressive immune dysfunction (Section 2.2.1) (Pluda *et al.*, 1993). Immunosurveillance is known to play an important role in controlling the replication of EBV-infected B-lymphocytes in humans (Rickinson *et al.*, 1992). The specific importance of cytotoxic T-lymphocytes (CTLs) in the control of virus-associated lymphoproliferative disease in immunosuppression has been demonstrated in animal studies by Boyle *et al.* (1993). They showed that EBV-specific CTLs adaptively transferred into SCID mice engrafted with EBV-transformed and immortalized B-lymphoblastoid cell lines delayed or prevented the development of B-cell lymphomas. In another study, five patients who developed EBV-associated lymphoproliferative disease following bone marrow transplantation were given infusions of leukocytes from the original donors. The proliferating cells were of donor cell origin and contained EBV DNA which was clonally integrated in two out of the three cases adequate for study. Since the lymphoproliferation derived from donor cells, the leukocytes included EBV-sensitized CTLs. Complete responses, pathological or clinical, were sustained in the three surviving patients (Papadopoulos *et al.*, 1994). EBV-specific CTLs are now generated in some clinical centres for the prevention and treatment of EBV-associated lymphoproliferative disease or treatment of organ transplant recipients (Smith *et al.*, 1995). The impaired immunosurveillance in AIDS patients may give rise to the oligoclonal B-cell expansion seen in PGL (Birx *et al.*, 1986). Consistently, one third of hyperplastic lymph nodes from HIV-infected individuals with PGL contain EBV-positive clones (Shibata *et al.*, 1991). The presence of EBV-containing B-cell clones in PGL correlates with the simultaneous occurrence or subsequent development of EBV-containing non-Hodgkin's lymphoma (Shibata *et al.*, 1991). However, Dolcetti *et al.* (1995) only rarely observed monoclonal EBV episomes in PGL samples with a high content of EBV-infected cells.

(ii) *Cytokines*

Dysregulation of the normal 'steady-state' cytokine network is a key feature of HIV infection (Fauci *et al.*, 1991). However, data regarding the role of cytokines in AIDS-related lymphomagenesis are restricted to IL-6 and IL-10.

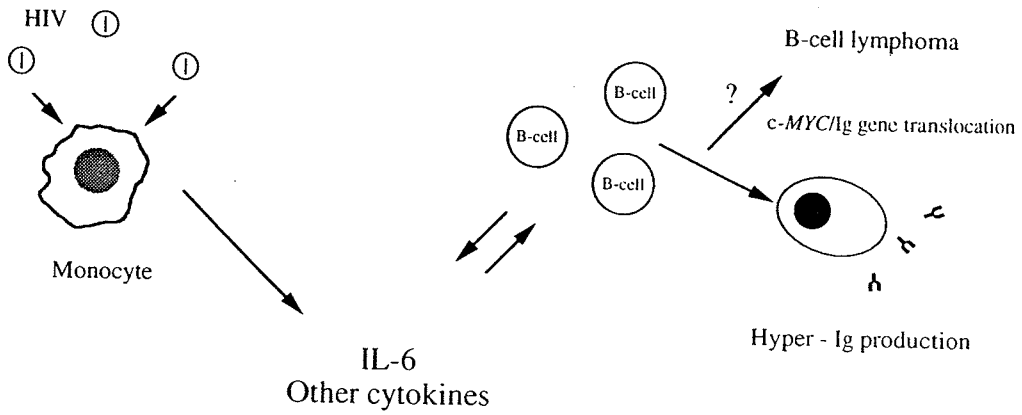
IL-6

The role of IL-6 is schematically depicted in Figure 13. IL-6 may be particularly important to both pre-malignant polyclonal B-cell expansion and malignant transformation.

Monocytes appear to be responsible for the major portion of IL-6 produced by PBMCs isolated from HIV-infected individuals (Birx *et al.*, 1990). The production of

IL-6 by HIV-infected monocytes promotes the proliferation of B-cells activated by, for example, EBV, thereby driving immunoglobulin synthesis and causing the non-specific hyperimmunoglobulinaemia commonly seen in early HIV infection (Birx *et al.*, 1986, 1990). Therefore, IL-6 excess in HIV infection seems to contribute to B-cell hyperstimulation and to hypergammaglobulinaemia (reviewed by Martínez-Maza, 1992) (Figure 13). Moreover, AIDS-related large-cell lymphomas containing a high proportion of immunoblasts express high levels of IL-6 (Emilie *et al.*, 1992). This finding is consistent with the role of IL-6 in the terminal differentiation of B cells. Further evidence linking IL-6 to AIDS-related lymphomagenesis is that HIV-infected patients with elevated serum levels of IL-6 are at high risk for later developing large-cell lymphomas (Pluda *et al.*, 1993). It has also been suggested that, once the lymphoma is well established, continuous tumour growth may be sustained by IL-6 through paracrine loops (Emilie *et al.*, 1992). Thus, IL-6 could contribute to lymphomagenesis either by acting as a chronic stimulus to B cells in HIV-infected people and/or, more directly, as an autocrine or paracrine growth factor for lymphoma cells (Martínez-Maza, 1992).

Figure 13. Potential role of IL-6 in AIDS-related lymphomagenesis



Contact between monocytes and HIV can cause IL-6 production. This increased IL-6 production could then induce B-cell hyperstimulation (hypergammaglobulinaemia) and, possibly, B-cell lymphoma.
Adapted from Martínez-Maza (1992)

An environment of dysregulated cytokines may also play a role in the pathogenesis of AIDS-related body cavity-based lymphomas that usually contain HHV-8 gene sequences. A recent study has demonstrated that IL-6 and IL-10 levels in lymphomatous effusions are much higher than those in normal plasma (Ng *et al.*, 1995). IL-6 protein has also been found in multicentric Castleman's disease (Yoshizaki *et al.*, 1989), another HHV-8-associated lymphoproliferative disorder (Soulier *et al.*, 1995). However, the functional relationship between IL-6 and HHV-8 needs to be clarified further (Levy, 1995).

In conclusion, it is clear that IL-6 is involved in B-cell lymphocyte expansion and could be involved at any stage during the development of B-cell lymphomas (Figure 13).

IL-10

IL-10, a potent B-cell stimulator, is a pleotropic cytokine sharing significant homology with the EBV protein BCRF1. Although the precise role of IL-10 in the development of AIDS-related lymphomagenesis is still unclear, a possible involvement is suggested by the finding that high levels of IL-10 are constitutively expressed by EBV-positive B-cell lines derived from patients with AIDS-related small non-cleaved-cell lymphoma (Benjamin *et al.*, 1992). Furthermore, an autocrine growth mechanism involving IL-10 can occur in AIDS-related lymphoma cells (Masood *et al.*, 1995).

(*c*) *Genetic abnormalities*

Various genetic abnormalities have been found in AIDS-related non-Hodgkin's lymphoma (Ballerini *et al.*, 1993; Gaidano *et al.*, 1993) (see Table 32 and Figures 11 and 12).

Table 32. Frequency of genetic lesions in AIDS-related non-Hodgkin's lymphomas

Histology	c-*myc*	*p53*	*BCL*-6	6q deletions	*ras*	EBV	HHV-8
Small non-cleaved-cell lymphomas (Ballerini *et al.*, 1993; Hamilton-Dutoit *et al.*, 1993a; Gaidano *et al.*, 1994b; Cesarman *et al.*, 1995; Carbone *et al.*, 1996b; Pastore *et al.*, 1996)[a]	100%	60%	Neg.	Neg.	15%	30%	Neg.
Diffuse large B-cell lymphomas (Ballerini *et al.*, 1993; Hamilton-Dutoit *et al.*, 1993a; Gaidano *et al.*, 1994b; Cesarman *et al.*, 1995; Pastore *et al.*, 1996)	20%	Neg.	20%	40%	15%	80%	Neg.
Anaplastic large-cell (CD30/Ki-1$^+$) lymphomas (Carbone *et al.*, 1993b; Chadburn *et al.*, 1993; Cesarman *et al.*, 1995; Carbone *et al.*, 1996b; Pastore *et al.*, 1996)	Neg.	Neg.	ND	Neg.	ND	90%	Neg.
Body cavity-based lymphomas (Cesarman *et al.*, 1995; Carbone *et al.*, 1996a)	Neg.	Neg.	ND	ND	Neg.	> 50%	> 70%

ND, not done

[a] Chromosome 1q abnormalities have been detected in AIDS-related small non-cleaved-cell lymphomas (Bernheim & Berger, 1988; Polito *et al.*, 1995)

(i) *c*-myc

Several reports have pointed to an association of AIDS-related non-Hodgkin's lymphoma with chromosomal translocations involving the c-*myc* oncogene. Activation

of c-*myc* has been detected in 100% of AIDS-related small non-cleaved-cell lymphomas, including Burkitt's lymphoma (Figures 11 and 14). In diffuse large-cell lymphomas including large non-cleaved-cell lymphomas and large-cell immunoblastic plasmacytoid lymphomas, activation is restricted to a minority (approximately 20%) of tumours (Ballerini *et al.*, 1993; Delecluse *et al.*, 1993; Bhathia *et al.*, 1994). Tumours with an intermediate morphology between small non-cleaved-cell and large-cell immunoblastic lymphomas have been shown to harbour a c-*myc* rearrangement. This finding is consistent with the notion that such a tumour may represent a small non-cleaved-cell lymphoma that has adopted an immunoblastic morphotype in the context of AIDS (Delecluse *et al.*, 1993). In contrast, no AIDS-related anaplastic large-cell lymphoma or body cavity-based lymphoma has shown c-*myc* alterations (Chadburn *et al.*, 1993; Cesarman *et al.*, 1995).

As in sporadic Burkitt's lymphoma, c-*myc* activation in AIDS-related non-Hodgkin's lymphoma occurs through gene rearrangements following chromosomal translocations between 8q24, the site of the c-*myc* proto-oncogene, and an immunoglobulin chromosomal locus, most commonly the immunoglobulin heavy-chain genes at 14q32 (Chaganti *et al.*, 1983). B-lymphocyte clones harbouring similar translocations can persist and be detected in peripheral blood of lymphoma-free HIV-positive homosexual men but are rare in HIV-negative controls (Müller *et al.*, 1995).

(ii) BCL-6

Chromosomal translocations in AIDS-related non-Hodgkin's lymphoma also involve *BCL*-6, a proto-oncogene affecting B-cell maturation, that maps to 3q27 (Ye *et al.*, 1993). Gross rearrangements of *BCL*-6 are mostly associated with AIDS-related diffuse large-cell lymphomas (20%) (Figures 12 and 15), and are consistently absent in AIDS-related small non-cleaved-cell lymphomas. This is similar to the chromosomal aberrations seen in the same histological subtypes of non-HIV-related non-Hodgkin's lymphoma. In diffuse large-cell lymphoma, gross rearrangements of *BCL*-6 and of c-*myc* appear to be mutually exclusive genetic lesions (Gaidano *et al.*, 1994b).

(iii) ras

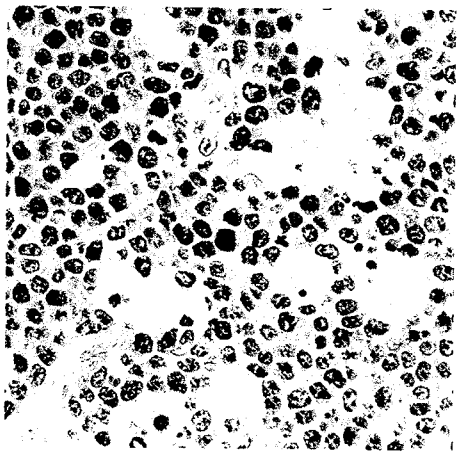
Other dominantly acting oncogenes commonly involved in the pathogenesis of lymphomas in immunocompetent hosts (e.g., *BCL*-1, *BCL*-2) do not seem to play a role in AIDS-related lymphomagenesis (reviewed by Gaidano & Dalla-Favera, 1992). On the other hand, mutations of K-*ras* or N-*ras* genes, which have not been detected in B-cell non-Hodgkin's lymphoma of immunocompetent hosts, were present in 4/27 (15%) of AIDS-related non-Hodgkin's lymphoma (Ballerini *et al.*, 1993).

(iv) p53

A role of tumour-suppressor gene inactivation in AIDS-related lymphomagenesis is supported by a number of observations. Mutations and/or losses of *p53* have been found in 60% of AIDS-related small non-cleaved-cell lymphomas (Ballerini *et al.*, 1993; Gaidano *et al.*, 1993), but not in the other types of AIDS-related non-Hodgkin's lymphoma (Gaidano *et al.*, 1991; Ballerini *et al.*, 1993; De Re *et al.*, 1994). In the small non-cleaved-cell lymphomas series examined (Ballerini *et al.*, 1993), *p53* mutations were

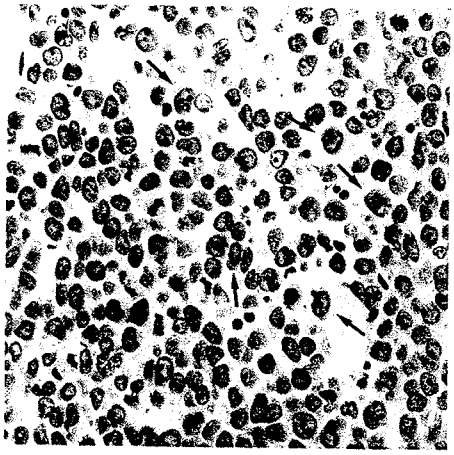
Figure 14

Small non-cleaved-cell lymphoma



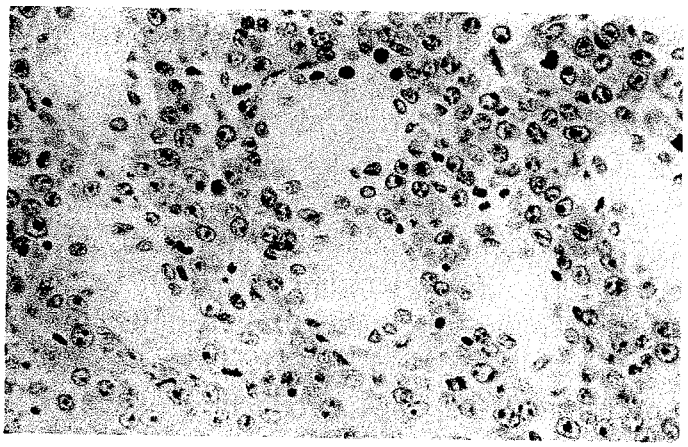
The tumour is composed of small to medium-sized monomorphic cohesive cells interspersed with large phagocytosine histiocytes (starry sky pattern). Haematoxylin–eosin, × 400

Small non-cleaved-cell lymphoma with plasma cell differentiation



Tumour cells have round or irregular, frequently eccentric, nuclei containing randomly located nucleoli. Larger basophilic cells with large nucleoli are recognizable (arrows). Haematoxylin–eosin, × 400

Figure 15. Diffuse large-cell lymphoma of the immunoblastic type with plasmacytic features



Gastric involvement by diffuse large-cell lymphoma of the immunoblastic type with plasmacytic features. Most tumour cells have large, solitary nucleoli. In this field mucosal glandular epithelium is surrounded, but not destroyed, by tumour growth. Haematoxylin–eosin, × 400.

seen only in tumours carrying a rearranged c-*myc* gene. p53 protein overexpression was observed in 3/3 lymphomas with a morphology intermediate between small non-cleaved-cell and large-cell immunoblastic lymphomas. It is unknown whether this overexpression was due to *p53* mutations (Carbone *et al.*, 1995b).

Little is known about the frequency of *p53* aberrations in anaplastic large-cell lymphomas. In contrast to small non-cleaved cell lymphoma, AIDS-related anaplastic large-cell lymphoma has been reported not to contain *p53* mutations, but accumulation of wild-type p53 protein has been observed by immunohistochemistry (Inghirami *et al.*, 1994; Carbone *et al.*, 1996b), as reported previously for this type of lymphoma in immunocompetent hosts (Cesarman *et al.*, 1993).

(v) *6q deletions*

Deletions of the long arm of chromosome 6 at band q27 occur in non-Hodgkin's lymphoma (both AIDS-related and -unrelated) and represent the putative site of a distinct tumour-suppressor gene. 6q deletions among AIDS-related non-Hodgkin's lymphoma were restricted to diffuse large-cell lymphomas (5/13 cases) (Pastore *et al.*, 1996), whereas, among non-Hodgkin's lymphoma in immunocompetent hosts, 6q deletions occur throughout the entire histological spectrum, including both diffuse large-cell and small non-cleaved-cell lymphomas (Gaidano *et al.*, 1992).

(vi) *Chromosome 1q abnormalities*

In AIDS-related small non-cleaved-cell lymphomas, structural changes of chromosome 1 have been found (Bernheim & Berger, 1988). Cell lines derived from such tumours have also been found to contain chromosome 1q abnormalities (Polito *et al.*, 1995). These chromosomal changes are very similar to those previously detected in AIDS-unrelated small non-cleaved-cell lymphomas or cell lines (Gurtsevitch *et al.*, 1988; Kornblau *et al.*, 1991). Owing to its very frequent involvement, chromosome 1q 21-25 is a site that should be examined in greater detail for genetic alterations that may play a pathogenetic role in small non-cleaved-cell lymphomas (Polito *et al.*, 1995).

4.3.2 *Lymphotropic viruses*

(*a*) *EBV*

EBV appears to play an important role in the development of some AIDS-related non-Hodgkin's lymphoma (Knowles, 1993; Herndier *et al.*, 1994b; Rabkin, 1994). The best evidence so far for its pathogenetic role is the ability of EBV-infected B cells to cause EBV-positive B-cell lymphomas in SCID mice (Mosier *et al.*, 1989; Rowe *et al.*, 1991). Other studies have demonstrated that the introduction of activated c-*myc* genes into EBV-transformed lymphoblasts confers tumorigenicity in nude mice (Lombardi *et al.*, 1987).

HIV-infected individuals possess abnormally high numbers of circulating EBV-infected B cells (Birx *et al.*, 1986). Moreover, EBV infection precedes the expansion of the tumour clone (Neri *et al.*, 1991), and a large fraction (see below) of AIDS-related non-Hodgkin's lymphoma cells contain EBV sequences and express at least some EBV

latent proteins known to have transforming properties (Hamilton-Dutoit *et al.*, 1989; Ballerini *et al.*, 1993; Hamilton-Dutoit *et al.*, 1993b).

It is likely that HIV-related immunosuppression permits the development of EBV-infected and immortalized B-cell clones. Such clones are susceptible to further genetic alterations resulting in the development of an EBV-containing monoclonal lymphoproliferation (Pelicci *et al.*, 1986).

The frequency of EBV infection in AIDS-related non-Hodgkin's lymphoma has been a matter of controversy (reviewed by Gaidano *et al.*, 1994a; Shibata, 1994). Discrepancies may depend on the different methods used for viral detection (Southern blot, PCR or in-situ hybridization) and on the different histological types or sites of disease investigated.

In contrast to systemic non-Hodgkin's lymphoma, AIDS-associated primary lymphomas of the central nervous system were positive for EBV in most studies (MacMahon *et al.*, 1991; Hamilton-Dutoit *et al.*, 1993a; Camilleri-Broët *et al.*, 1995; Cinque *et al.*, 1993) (see Table 20). However, Gunthel *et al.* (1994) reported a few primary lymphomas of the central nervous system that were negative for EBV by a sensitive PCR assay. Almost all lymphomas primarily involving body cavities contain clonal EBV genome (Knowles *et al.*, 1989; Cesarman *et al.*, 1995).

Most molecular studies have indicated that the presence of EBV within systemic AIDS-related non-Hodgkin's lymphoma varies according to the histopathological type (Table 21). EBV infection is found in the majority of diffuse large-cell lymphomas, particularly in the large-cell immunoblastic lymphoma subtype (80%), but in a much smaller fraction (30–50%) of small non-cleaved-cell lymphomas (Hamilton-Dutoit *et al.*, 1991; Ballerini *et al.*, 1993). A high frequency of EBV association has been shown in anaplastic large-cell lymphoma (80–90%) and Hodgkin's disease (90–100%) tissues from AIDS patients (Carbone *et al.*, 1993a; Hamilton-Dutoit *et al.*, 1993a; Tirelli *et al.*, 1995b). The EBV genomes in such cases have been reported to be episomal and clonal (Boiocchi *et al.*, 1993a), even when detected in multiple, independent lesions (Boiocchi *et al.*, 1993b).

There are two EBV subtypes which differ in the genomic region encoding the EBV nuclear antigen-2 (EBNA-2) (Adldinger *et al.*, 1985). Type 1 EBV is a more potent lymphocyte transformer than type 2 (Rickinson *et al.*, 1987). While type 2 virus rarely occurs in immunocompetent hosts in developed countries, it is found in a much higher proportion of subjects with HIV-related immunosuppression. The elevated frequency of type 2 virus in AIDS-related lymphoproliferative diseases appears to mirror the excess seen in HIV-infected subjects without such disease (Boyle *et al.*, 1991, 1993; De Re *et al.*, 1993).

A role of EBV in the pathogenesis of AIDS-related non-Hodgkin's lymphoma is further supported by data showing that the EBV-transforming proteins, EBV-encoded latent membrane protein-1 (LMP-1) and/or EBNA-2 may be expressed in EBV-positive cases.

Expression of LMP-1 has been detected in AIDS-related lymphomas of various localizations and histological types. In primary AIDS-related immunoblastic lymphomas of

the central nervous system, 10/11 (90%) of tumours expressed LMP-1 and 21/57 (54%) expressed EBNA-2, as assessed by immunohistochemistry. Expression of both *BCL-2* and LMP-1 in EBV-positive AIDS-related primary brain lymphomas *in vivo* has been described (Camilleri-Broët *et al.*, 1995). This is in agreement with in-vitro findings showing that *BCL-2* can be transactivated by LMP-1 in small non-cleaved-cell lymphoma cell lines. Also, *BCL-2* expression induced by LMP-1 may protect tumour B cells from apoptosis and lead to a higher proliferative rate (Henderson *et al.*, 1991; Finke *et al.*, 1992). Body cavity-based lymphoma cells exhibiting pleomorphic and anaplastic morphology are also associated with LMP-1 expression (Carbone *et al.*, 1996a,c).

Regarding AIDS-related systemic lymphomas, some investigators have reported that LMP-1 expression is restricted to anaplastic large-cell lymphomas (Carbone *et al.*, 1993a, 1994) and Hodgkin's disease (Audouin *et al.*, 1992; Carbone *et al.*, 1993a; Siebert *et al.*, 1995), while AIDS-related large-cell immunoblastic lymphomas show heterogeneity in both EBV presence and latency patterns (Carbone *et al.*, 1993a; Hamilton-Dutoit *et al.*, 1993b). In Hodgkin's disease, EBV adopts a latency type 2 pattern (LMP-1$^+$, EBNA-2$^-$) (Boiocchi *et al.*, 1993a), while AIDS-associated anaplastic large-cell lymphomas appear to be heterogeneous and both the type 2 patterns and, less frequently, a type 3 pattern (LMP-1$^+$, EBNA-2$^+$ phenotype) have been described (Carbone *et al.*, 1996b).

In contrast, EBV-positive AIDS-related small non-cleaved-cell lymphomas usually show the restricted latency pattern of EBV gene expression (latency type 1 pattern; EBNA-1$^+$, EBNA-2$^-$, LMP-1$^-$) also found in endemic Burkitt's lymphoma (Carbone *et al.*, 1993a; Hamilton-Dutoit *et al.*, 1993a). However, in some EBV-positive cases of small non-cleaved-cell lymphoma, a limited number of tumour cells express LMP-1 but not EBNA-2 (Hamilton-Dutoit *et al.*, 1993b; Carbone *et al.*, 1996b). Furthermore, both EBV latency type 2 pattern and a new latency pattern (EBNA-2$^+$, LMP-1$^-$) have been found in endemic, sporadic and AIDS-related small non-cleaved-cell lymphomas (Niedobitek *et al.*, 1995; Carbone *et al.*, 1996c). Altogether, these data document heterogeneous expression of EBV latent proteins throughout the entire spectrum of small non-cleaved-cell lymphomas.

LMP-1 expression has not been found in cases of EBV-associated plasmacytomas (Voelkerding *et al.*, 1989; Carbone *et al.*, 1993a).

In summary, EBV is more frequently present in large-cell AIDS-related lymphomas, including body cavity-based lymphomas, large-cell immunoblastic lymphomas, either systemic or arising in the brain, and anaplastic large-cell lymphomas. The two subtypes of EBV (types 1 and 2) are almost equally represented, and three types of EBV latency pattern (latency 1 — EBNA-1$^+$, EBNA-2$^-$, LMP-1$^-$; latency 2 — EBNA-1$^+$, EBNA-2$^-$, LMP-1$^+$; latency 3 — EBNA-1$^+$, EBNA-2$^+$, LMP-1$^+$) have been detected. Therefore, a large fraction of AIDS-related diffuse large-cell lymphomas can be considered as EBV-driven lymphoproliferations arising in the absence of effective cell-mediated immunity against EBV. Since EBV-transforming antigens are expressed by EBV-positive AIDS-related diffuse large-cell lymphomas, it is plausible that EBV is indeed a driving force for tumour growth and expansion. Moreover, while Hodgkin's disease may not be more

common in HIV-infected persons, it is more frequently associated with EBV infection in such individuals.

The grouping of the different pathological subtypes of AIDS-related lymphomas based on EBV association and EBV latent gene expression is shown in Table 33 (see also Figure 16).

Table 33. Grouping of pathological types of AIDS-related lymphomas based on EBV latent gene expression and genetic abnormalities

'Blastic'[a] cell lymphomas not associated with expression of Epstein–Barr virus-encoded latent membrane protein-1

- Large non-cleaved cell
- Small non-cleaved cell (always associated with c-*myc* rearrangements and frequently with *p53* inactivation)
- Extramedullary (plasmacytoma)[b]
- Blastic cells with 'intermediate' features

'Blastic'[a] cell lymphomas that may be associated with expression of Epstein–Barr virus-encoded latent membrane protein-1 expression

- Immunoblastic (either systemic or arising in the brain as a primary site)
- Occasional cases of small non-cleaved cell

'Anaplastic'[b] cell lymphomas associated with monoclonal Epstein–Barr virus infection and latent membrane protein-1 expression

- Anaplastic large-cell (CD30/Ki-1$^+$) lymphomas
- Body cavity-based lymphomas (associated with HHV-8 infection)[d]
- Hodgkin's lymphoma (mixed cellularity and lymphocyte depletion)[b]

Updated and adapted from Carbone *et al.* (1993b)

[a]The term 'blastic' is used in analogy with the suffix 'blastic' used in the Kiel classification (Stansfeld *et al.*, 1988).

[b]Whether extramedullary plasmacytomas and Hodgkin's lymphomas should be included among HIV-related lymphomas is still debated.

[c]The term 'anaplastic' is used in analogy with the term used in the definition of CD30-positive anaplastic large-cell lymphomas; it indicates blastic large cells which display marked pleomorphism, with giant cells possessing bizarre and irregular nuclei and large nucleoli (Harris *et al.*, 1994).

[d]The morphology of body cavity-based lymphoma cells includes both immunoblastic and anaplastic features (Ansari *et al.*, 1996)

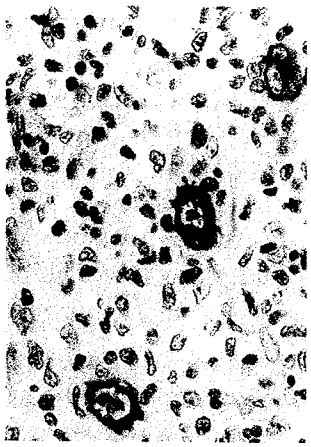
The frequent association between EBV infection and some lymphomas in HIV-positive persons, including those arising primarily in the brain and body cavities, as well as anaplastic large-cell lymphoma and Hodgkin's disease types, suggests that EBV is an important cofactor in their pathogenesis. Thus, the presence of EBV in these lymphoma cells appears important for their neoplastic transformation as well as for the expression of certain morphological and immunophenotypic features in the context of HIV infection (Cesarman *et al.*, 1995; Gaidano & Carbone, 1995). This conclusion is consistent with the observation discussed in Section 3.2.2, indicating that B-cell lymphoma in SIV-infected macaques is frequently associated with an EBV-related virus.

Figure 16

EBV-encoded latent membrane protein-1 (LMP-1) expression in AIDS-related CD30$^+$ anaplastic large cell lymphoma

Several large tumour cells show a strong cytoplasmic staining. Bouin-fixed paraffin-embedded tissue section, APAAP method, haematoxylin counterstain, × 400

EBV-encoded latent membrane protein-1 (LMP-1) expression in Hodgkin's disease



Reed–Sternberg cells of Hodgkin's disease, mixed cellularity subtype, show strong cytoplasmic staining for EBV-encoded LMP-1. Bouin-fixed paraffin-embedded tissue section, APAAP method, haematoxylin counterstain, × 400

(*b*) *HHV-6*

Human herpesvirus-6 (HHV-6) is a member of the herpesviridae family, and was originally isolated from peripheral blood mononuclear cells of patients with lymphoproliferative disorders or AIDS (Salahuddin *et al.*, 1986). HHV-6, like the human retroviruses HIV, HTLV-I and HTLV-II, predominantly infects T lymphocytes but can also infect other cell types including fibroblasts, epithelial cells, natural killer cells, megakaryocytes, neural cells and, occasionally, B lymphocytes.

Like other herpesviruses, HHV-6 is responsible for a latent, lifelong infection of the host and can reactivate during immunosuppression (Carrigan *et al.*, 1991; Knox & Carrigan, 1994).

The role of this virus in the pathogenesis of AIDS-related non-Hodgkin's lymphoma is still obscure. It has been hypothesized that HHV-6 may contribute to the development of lymphoproliferative disorders by stimulating polyclonal B-cell activation as a consequence of persistent active viral infection (Krueger *et al.*, 1989). A combined molecular and immunohistochemical study has shown that HHV-6 DNA sequences are significantly more prevalent in persistent generalized lymphadenopathy biopsies than in HIV-unrelated reactive lymphadenopathies. The presence of HHV-6 sequences closely correlates with follicular hyperplasia, while follicular involution is HHV-6-negative. Therefore, persistent generalized lymphadenopathy lymph nodes with B-cell hyperplasia

constitute one of the sites where biologically relevant interactions between HHV-6 and HIV may occur (Dolcetti *et al.*, 1996).

However, the prevalence of HHV-6 DNA in Hodgkin's disease and B-cell non-Hodgkin's lymphoma from HIV-infected patients is remarkably low (Carbone *et al.*, 1996b) and similar to that observed in lymphoproliferative disorders from HIV-seronegative patients (Di Luca *et al.*, 1994; Dolcetti *et al.*, 1996). These results suggest that HHV-6 may have no direct role in the pathogenesis of AIDS-related non-Hodgkin's lymphoma and Hodgkin's disease.

(*c*) *HHV-8*

HHV-8 (see Section 4.2.4) has been associated with several lymphoproliferative disorders. It has been found in the majority of body cavity-based lymphomas arising in patients with or without HIV infection (Cesarman *et al.*, 1995; Karcher & Alkan, 1995; Nador *et al.*, 1995; Pastore *et al.*, 1995) as well as in all (14/14) HIV-associated and a proportion (21/75) of HIV-unrelated multicentric Castleman's disease tissues (Soulier *et al.*, 1995). Both in fresh body cavity-based lymphoma samples and in cell lines derived from such tumours, HHV-8 is present in multiple episomal copies. Body cavity-based lymphomas are frequently co-infected with EBV (Cesarman *et al.*, 1995), but a few cases which contain only HHV-8 have been reported (Renne *et al.*, 1996) and a few others do not contain HHV-8 (Carbone *et al.*, 1996b; Hermine *et al.*, 1996).

Cell lines latently infected with HHV-8 and several cases also with EBV have been established from body cavity-based lymphoma effusions (Cesarman *et al.*, 1995; Gaidano *et al.*, 1996). HHV-8 is also present in peripheral blood B cells in some HIV-infected individuals with neither lymphoma nor Kaposi's sarcoma (Whitby *et al.*, 1995). In addition, HHV-8 has been detected in PMBCs and lymphoid tissue of less than 10% of HIV-uninfected individuals (Bigoni *et al.*, 1996). The issue of how common HHV-8 is in the general population is discussed in Section 2.1.5.

Whether HHV-8 , like its close relative EBV, is oncogenic in its own right is not yet clear. Mechanisms of pathogenesis that might operate in HHV-8-positive lymphomas include cooperation with EBV, and participation of an HHV-8-encoded cyclin homologue or HHV-8-induced lymphokines (Levy, 1995; Hermine *et al.*, 1996).

4.3.3 *Conclusion*

The putative role of cofactors differs substantially according to the pathological type and site of disease; moreover, several independent pathways in AIDS-related lymphomagenesis can be identified.

The first pathway of pathogenesis is associated with small non-cleaved-cell lymphomas (Figure 11). More than in other AIDS-related non-Hodgkin's lymphomas, antigen stimulation appears to play an important role in this form of non-Hodgkin's lymphoma (Riboldi *et al.*, 1994). At the molecular level, genetic changes appear to be fairly homogeneous (Table 32). They are characterized by rearrangement of c-*myc* (100%), mutation of *p53* (60%) and the presence of EBV infection (30%) (Ballerini

et al., 1993; Gaidano *et al.*, 1993); however, expression of EBV transforming protein is usually absent (Carbone *et al.*, 1993a; Hamilton-Dutoit *et al.*, 1993b).

A second pathway of pathogenesis is associated with diffuse large-cell lymphomas (Figure 12 and Table 32). Because of the very high frequency of EBV infection (60–100%) (Hamilton-Dutoit *et al.*, 1991; MacMahon *et al.*, 1991; Ballerini *et al.*, 1993), AIDS-related diffuse large-cell lymphomas, including those arising primarily in the brain, can be considered as EBV-driven lymphoproliferations developing in the context of a disrupted immunosurveillance against EBV (Birx *et al.*, 1986). Viral transforming proteins EBNA-2 and LMP-1 may be expressed by EBV-positive diffuse large-cell lymphomas (Carbone *et al.*, 1993a; Hamilton-Dutoit *et al.*, 1993b). The vast majority (80–90%) of AIDS-related anaplastic large-cell lymphomas are also associated with EBV infection (Carbone *et al.*, 1993b) (Table 33) and EBV-infected tumour cells consistently express LMP-1 (Carbone *et al.*, 1994) (Figure 16).

A third pathway may apply in the pathogenesis of body cavity-based lymphomas. This pathway includes EBV infection and consistent presence of HHV-8, at least in most cases, but not other known genetic lesions (Cesarman *et al.*, 1995) (Table 32).

Finally, Hodgkin's disease in HIV-infected persons appears to be an EBV-related lymphoma expressing LMP-1 (Audouin *et al.*, 1992; Carbone *et al.*, 1994; Siebert *et al.*, 1995), whereas multicentric Castleman's disease seems to be an HHV-8-related disorder in the HIV setting (Soulier *et al.*, 1995).

In summary, understanding of the mechanisms of lymphomagenesis is hampered by the heterogeneity of non-Hodgkin's lymphoma and the substantial number of cofactors examined. These have been studied independently, generally on relatively small numbers of tumours. Seldom have different mechanisms of lymphomagenesis been examined in the same study.

4.4 Cofactors in anal and cervical carcinomas and other cancers

As discussed in Section 2.3, preneoplastic anogenital lesions and HPV-related changes (koilocytosis) are associated with HIV infection, whereas no such association has been convincingly demonstrated for invasive cancer. Dysregulation of the expression of early proteins E6 and E7 of high-risk HPV types is strongly suggested by in-vitro studies to be an important factor in malignant progression, as well as by data from human tumours (see IARC, 1995).

Little is known about the pathogenetic mechanisms involved in anogenital oncogenesis associated with other viral and chemical agents; indirect and/or direct modulation of HPV expression, however, seems to be the most relevant pathway. There are two possible, not mutually exclusive, ways in which HIV may contribute to HPV-related carcinogenesis: the major indirect mechanism is immunosuppression; possible direct mechanisms include transactivation of HPV oncogenic early-gene expression and abnormal expression of cellular genes.

4.4.1 *The role of HPV in the molecular pathogenesis of anogenital cancers in immunocompetent patients*

HPVs have been recognized as sexually transmitted etiological agents for human lower genital tract malignancies (zur Hausen, 1989; IARC, 1995). Over 70 types of HPV have been identified, of which only a small subset (HPV-16, -18, -31, -33, -35, -45 and, more recently, -51 and -52) have been associated with anogenital cancers. Many more subtypes are associated with benign, epithelial neoplasms. During the life cycle of HPV, most of the viral DNA is maintained episomally in the nucleus of the infected cells. Integration of viral DNA sequences is frequently associated with malignant progression (Schwarz *et al.*, 1985; Jeon *et al.*, 1995), being detected more frequently in carcinomas than in cervical intraepithelial neoplasia (CIN) (Cullen *et al.*, 1991). In CIN, the mainly episomal HPV actively replicates (productive infection), whereas in cervical epithelial cancers the HPV DNA is prevalently integrated (latent infection). This transition results in changes at the level of viral DNA as well as of RNA and protein.

(*a*) *Status and level of HPV DNA in the natural history of infection*

In CIN lesions, the level of predominantly episomal, infecting viral genome detected varies according to the techniques used. PCR, with a detection limit of 10 copies per sample, detects HPV genomes in 72–91% of 'low-grade lesions' and in 90–100% of 'high-grade lesions' (van den Brule *et al.*, 1991; Bergeron *et al.*, 1992; Lungu *et al.*, 1992); procedures with a lower sensitivity (3×10^5 viral genomes per sample or 0.1 viral copy per cell when testing 1.5×10^5 cells = 1 μg genomic DNA), such as Southern blot, dot blot and ViraPap™, detect HPV genomes in only 36–55% of 'low-grade lesions' and in 43–81% of 'high-grade lesions' (Fuchs *et al.*, 1988; Lim-Tan *et al.*, 1988; McNicol *et al.*, 1989).

In invasive cancer, HPV DNA is present at > 1 viral copy per cell, because of the predominantly integrated high-risk HPVs in genomic DNA and the homogeneity of the clonal neoplastic population. At this level, both high- and low-sensitivity analytical techniques detect HPV in > 90% of samples. Furthermore, the HPV-type specificity of PCR equals that of Southern blot hybridization, with HPV-16 identified in over 60% of cervical cancers (Riou *et al.*, 1990; van den Brule *et al.*, 1991; Higgins *et al.*, 1991b; Lörincz *et al.*, 1992). In penile cancers, 'high-risk' genital HPVs were detected in more than 48% of the biopsies by both techniques, with no major geographical differences in the detection frequency (McCance *et al.*, 1986; Tornesello *et al.*, 1992; Wiener *et al.*, 1992).

(*b*) *Expression of HPV proteins in the natural history of infection*

In benign lesions, late HPV proteins are expressed, with viral transcription patterns that vary by epithelial layer: weak expression of early genes occurs in the basal layers of low-grade cervical dysplasias induced by HPV-16 or HPV-33 and in some HPV-6- or HPV-11-induced condylomas; late genes are expressed in terminally differentiated keratinocytes of the superficial strata (Dürst *et al.*, 1992; Stoler *et al.*, 1992). Studies in HPV-16- and HPV-18-infected female renal transplant recipients demonstrate that,

following immunosuppression, antibodies to the late proteins decrease, whereas antibodies against early proteins E2, E4 and E7 significantly increase. This pattern suggests reactivation of latent virus (Lewensohn-Fuchs *et al.*, 1993). The regulation of gene expression is complex and is controlled by various cellular and viral transcription factors, different promoter usage, differential splicing, differential transcription termination and stability of mRNA.

In malignant lesions, integration of HPV DNA, generally concomitant with the disruption of *E2/E1* gene sequences, determines the major transcriptional changes. *E6* and *E7* are always transcribed actively in tumour cells (Schwarz *et al.*, 1985). The *E2* and/or *E1* disruption could lead to derepression of the P97 promoter. This, in turn, would modulate the expression of transforming genes and increase the transforming potential of HPVs (Lambert & Howley, 1988; Schiller *et al.*, 1989; Romanczuk & Howley, 1992; Jeon *et al.*, 1995).

(c) *Molecular mechanisms of transforming activity of HPV*

The transforming activity of HPV seems to be associated mainly with E6 and E7 open reading frames, which are consistently expressed in cervical cancers and cell lines derived from them (Smotkin & Wettstein, 1986; Hsu *et al.*, 1993). HPV-16 and HPV-18 *E6* and *E7* early genes, when expressed by a LTR promoter and transduced into cells by retroviral infection, immortalize human primary keratinocytes *in vitro* (Pirisi *et al.*, 1987; Schlegel *et al.*, 1988; Halbert *et al.*, 1991).

(i) *Intrinsic properties of high-risk HPV E6 and E7*

The HPV strains associated with malignant tumours (mainly HPV-16, -18, -31, -33, -35) are designated 'high-risk' HPV (IARC, 1995).

The E6 zinc finger protein of HPV-16 and HPV-18, like SV40 T antigen and adenovirus 5E1B, interacts specifically with the p53 tumour-suppressor protein. The p53–E6 complexes are then targeted to destruction through the ubiquitin-mediated proteolysis pathway (Scheffner *et al.*, 1990; Crook *et al.*, 1991). Thus it has been shown that expression of E6 in transfected cells abrogates a p53-controlled G1/S cell-cycle checkpoint (Kessis *et al.*, 1993; Foster *et al.*, 1994; Gu *et al.*, 1994; Canman *et al.*, 1995).

The E7 protein of high-risk HPV shares sequence homology with conserved regions 1 and 2 of the adenovirus E1a 243- and 289-amino-acid proteins. Like E1a, it binds to the product of the retinoblastoma gene, pRB (Dyson *et al.*, 1989; Münger *et al.*, 1989; Gage *et al.*, 1990). The RB protein is a phosphoprotein which, in its underphosphorylated form, appears to negatively regulate entry into the S-phase of the cell cycle; the initiation of S-phase is accompanied by pRB phosphorylation, via cyclin-dependent kinases. Binding of HPV E7 to pRB indirectly enhances transcription of several genes involved in cycle control, such as c-*myc*, c-*myb*, *cdc2*, DNA polymerase alpha, ribonucleotide reductase and thymidylate synthetase (Mudryi *et al.*, 1990; Nevins, 1992).

(ii) *Regulation of E6 and E7 expression*

Early gene expression is controlled by the long control region (LCR), extending over 400–900 bp, which may be considered to consist of three functional units. The 5' region,

adjacent to the L1 gene, contains the first E2 binding site as well as negative regulatory elements acting at the level of late mRNA stability (Kennedy *et al.*, 1991). The 3' segment contains a single E1 binding site (which identifies the origin of replication), an Sp1 transcription binding site, two E2 binding sites and the E6/E7 transcription promoter (Phelps & Howley, 1987; Swift *et al.*, 1987; Guis *et al.*, 1988). Between these two regions lies the HPV enhancer, the activity of which depends on cellular nuclear factors (Nakshatri *et al.*, 1990). In particular, the HPV-16 and HPV-18 enhancers contain recognition sites for cellular transcription factors such as *jun/fos* (Cripe *et al.*, 1990; Thierry *et al.*, 1992), nuclear factor I (NFI), transcription factor Sp1, activator protein AP1, glucocorticoid receptor and other papillomavirus enhancer-associated, but not yet characterized, factors (Chong *et al.*, 1990; Hoppe-Seyler & Butz, 1992). The activities of individual *cis*-acting elements contribute to the full enhancer activity. Published data suggest that HPV enhancer function depends on the cooperative interaction of multiple factors. Short segments of the enhancer have only a weak transactivating function. Frequently, recognition sites bind multiple proteins, and individual factors can interact with different recognition sequences (Chong *et al.*, 1990; Cripe *et al.*, 1990; Hoppe-Seyler & Butz, 1992; Thierry *et al.*, 1992).

Thus the expression of E6 and E7 could be enhanced by several mechanisms: mutational inactivation of *E2* or *E1* genes during HPV integration events; extracellular stimuli (growth factors, promoting agents, cytokines, etc.) via membrane receptors; or intracellular factors that bind the regulatory LCR, either directly or through activation of nuclear factors. For example, expression of HPV E6 and E7 can be modulated by the tumour promoter 12-*O*-tetradecanoylphorbol 13-acetate, which activates protein kinase C in the plasma membrane, eventually activating the nuclear transcription factor AP1 (Chan *et al.*, 1990).

4.4.2 *Interactions between HIV and HPV*

HIV is transmitted sexually (see Section 1.3.1). Although infection of squamous and colorectal epithelial cell lines or primary cultures has been reported (Adachi *et al.*, 1987; Tan *et al.*, 1993; Phillips *et al.*, 1994b), there is no convincing evidence of infection of epithelial cells by HIV *in vivo*.

Epithelial Langerhans' cells and related antigen-presenting cells in the layers beneath the mucosal epithelium are thought to be a major route of genital infection by HIV or SIV (Spira *et al.*, 1996). It is thus unlikely that the same cells *in vivo* will be co-infected by HIV and HPV. Even where HIV has been detected in CIN II biopsies, immunohistochemical evidence indicates that the HIV is localized to cells resembling lymphocytes or macrophages in the subepithelial stromal layer (Vernon *et al.*, 1994).

Infection and malfunction of Langerhans' cells could affect the local immune control of other HIV-infected cells. Furthermore, Spinillo *et al.* (1993) reported that counts of Langerhans' cells in CIN biopsies from HIV-infected women with CDC stage IV disease were significantly lower than those in CIN biopsies from HIV-negative matched controls.

(*a*) *Effects of HIV-related immunosuppression on HPV replication and HPV-associated anogenital lesions*

There are no experimental data addressing the effects of HIV-induced immunosuppression on HPV replication and transformation.

The epidemiological data reviewed in Section 2.3 suggest an increase in HPV genome copy numbers with immunosuppression. Higher HPV load may increase the probability of chromosomal integration of viral DNA and subsequent neoplastic events, as described above. Besides the increase in the number of HPV copies, HIV-infected immunosuppressed homosexual men as well as female transplant recipients often have multiple types of HPV (Palefsky *et al.*, 1992; Brown *et al.*, 1994b). However, the role of multiple HPV infection in the pathogenesis of anogenital neoplasia is unknown.

(*b*) *HIV Tat stimulation of cytokines and their role in genital lesions*

Cytokines have been shown to stimulate HPV-transformed epithelial cells. In particular, the pro-inflammatory cytokines IL-1α and TNFα, the expression of which is induced by Tat (Philippon *et al.*, 1994; Biswas *et al.*, 1995), inhibit proliferation of normal epithelial cells cultured from human cervix. However, they also significantly stimulate proliferation of cervical cell lines immortalized by transfection with HPV-16 or HPV-18 DNAs and of HPV-positive cell lines derived from cervical carcinoma. Growth stimulation by IL-1α or TNFα is accompanied by a 6–10-fold increase in RNA encoding amphiregulin, an epidermal growth factor receptor ligand (Woodworth *et al.*, 1995). However, whether this chain of events occurs *in vivo* is not known.

(*c*) *Possible effect of HIV-1 Tat on HPV E6/E7 expression*

Tornesello *et al.* (1991) reported that transfection of HIV-1 *tat* increased the expression of HPV-18 E7 in HeLa cells constitutively harbouring 10–20 copies of HPV-18. Expression of the HPV-16 LCR is also enhanced by HIV-1 Tat (Tornesello *et al.*, 1993; Vernon *et al.*, 1993). In addition, Tat increased the efficiency of E6/E7-mediated transformation of NIH 3T3 cells (Buonaguro *et al.*, 1994). Vogel *et al.* (1995) reported that transgenic mice carrying the HIV-1 *tat* gene express Tat protein in their keratinocytes. This is not sufficient to cause epidermal tumours, but is able to promote tumours after a single subthreshold dose of a carcinogenic initiator. Such tumour promotion has an effect additive to that of phorbol esters.

Although, as discussed above, HIV-1 and HPV are unlikely to co-infect the same cell, HIV-1 Tat has been shown to be released from infected cells (Frankel & Pabo, 1988). Extracellular Tat can be taken up by cervical epithelial cell lines (Frankel & Pabo, 1988; Frankel *et al.*, 1989; Ensoli *et al.*, 1993) and could thus allow the direct transactivation of HPV promoters.

In conclusion, both the immunosuppressive effect of HIV-1 infection and the secretion of HIV-1 Tat could promote the development of HIV-related precancerous anogenital lesions. Similar mechanisms might account for the increased incidence of other HPV-related and unrelated neoplasms in HIV infection.

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.

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

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