HUMAN IMMUNODEFICIENCY VIRUS-1

Human immunodeficiency virus-1 was considered by a previous IARC Working Group in 1996 (IARC, 1996). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Taxonomy, structure, and biology

1.1.1 Taxonomy

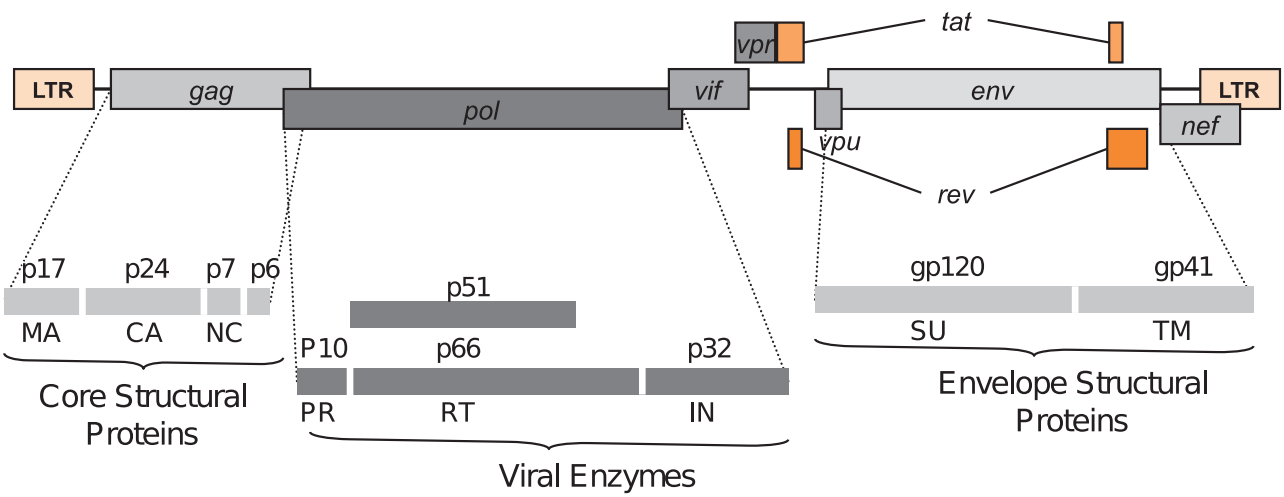
The human immunodeficiency virus type 1 (HIV-1) was first isolated in 1983 (Barré-Sinoussi *et al.*, 1983; Gallo *et al.*, 1983), and firmly associated with the acquired immunodeficiency syndrome (AIDS) in 1984 (Gallo *et al.*, 1984; Montagnier *et al.*, 1984). A second related virus, called HIV-2, was subsequently discovered in West Africa (Clavel *et al.*, 1986). HIV-1 and HIV-2 belong to the family of *Retroviridae* and subfamily *Orthoretrovirinae*. Retroviruses are enveloped RNA viruses that replicate via a DNA intermediate. They rely on the enzyme reverse transcriptase to transcribe their genome from RNA into DNA, which can then be integrated into the host's genome with an integrase enzyme, becoming part of the cellular DNA, and replicating with it. HIV-1 and HIV-2 are the two known human retroviruses that belong to the genus *Lentivirus* (lentus, Latin for "slow").

1.1.2 Structure of the virion

HIV-1 virions contain two copies of a single-stranded RNA genome within a conical capsid surrounded by a plasma membrane of host-cell origin containing viral envelope proteins. The RNA genome is 9750 nucleotides long (Ratner *et al.*, 1985; Wain-Hobson, 1989), and the virions measure approximately 120 nm in diameter. A detailed three-dimensional structure of HIV-1 envelope-glycoprotein spikes, which are required for the infection of host cells, has recently been elucidated by cryoelectron microscopy tomography (Zhu *et al.*, 2006).

The HIV-1 RNA is tightly bound to the nucleocapsid proteins, p6 and p7, which protect it from digestion by nucleases. This viral core further contains reverse transcriptase, integrase, and protease. The entire complex is surrounded by an icosahedral capsid (p24). A myristoylated matrix protein (p17) surrounds the capsid. Also enclosed within the virion particle are the proteins Vif, Vpr, and Nef (Fig. 1.1). The envelope is formed when the capsid buds from the host cell, taking some of the host-cell membrane with it. Embedded within the lipid bilayer are the viral envelope glycoproteins that form the HIV-1 spikes: the external surface glycoprotein (gp120), and the transmembrane glycoprotein (gp41) (Turner & Summers, 1999; Bukrinskaya, 2004; Freed & Martin, 2007).

Fig. 1.1 Genomic organization of HIV-1



Prepared by the Working Group

1.1.3 Structure of the viral genome

The HIV-1 genome, flanked by a long terminal repeat, contains the following genes (Fig. 1.1):

- *gag* (group-specific antigen): encodes p24 (viral capsid); p6 and p7 (nucleocapsid proteins); and p17 (matrix protein).
- b) *pol*: encodes the viral enzymes, which are reverse transcriptase (transcribes the viral RNA into double-stranded DNA), integrase (allows integration of the DNA produced by reverse transcriptase into the host genome), and protease (cleaves the proteins derived from gag and pol into functional proteins).
- c) *env* (envelope): encodes gp160, which is the precursor of the gp120 and gp41 proteins present in the viral envelope of mature virions. This protein forms spikes that allow the virus to attach to and fuse with target cells.
- d) *tat, rev, nef, vif, vpr, vpu*: each of these genes encodes for a single protein with the same name. Their function is described in Section 4.

The structural biology of HIV-1 has been reviewed (Turner & Summers, 1999; Bukrinskaya, 2004; Freed & Martin, 2007).

1.1.4 Host range

Humans are the natural hosts of both HIV-1 and HIV-2. Related viruses, e.g. simian immunodeficiency virus (SIV), naturally occur in African non-human primates. HIV-1 and HIV-2 have been shown to originate in West-Central Africa, and crossed species (zoonosis) from a non-human primate to humans. HIV-1 was found to be closely related to an SIV strain found in chimpanzees (*Pan troglodytes*) (SIVcpz) in Cameroon (Gao *et al.*, 1999). HIV-2 is more closely related to the SIV of sooty mangabeys (*Cercocebus atys*) (SIVsm) (Hirsch *et al.*, 1989), a primate species indigenous to West Africa.

1.1.5 Target cells

HIV-1 enters cells through interaction with the CD4 receptor and a chemokine co-receptor (CXCR4 or CCR5). The virus infects CD4-positive T cells and macrophages expressing these receptors (Broder & Collman, 1997). HIV-1 can also

infect dendritic cells (Knight *et al.*, 1990), which are thought to mediate transmission (de Witte *et al.*, 2008).

HIV-1 can be assigned to one of three classes based on its ability to use the two co-receptors. Class R5 comprises the viruses that use CCR5 but not CXCR4; they were previously called non-syncytia-inducing (NSI) or M-tropic viruses. The viruses that use CXCR4 are in class X4; they were previously called syncytia-inducing (SI) or T-tropic viruses. Viruses that can use either CCR5 or CXCR4 are referred to as R5X4 or dual viruses (Coakley *et al.*, 2005). Primary lymphocytes and macrophages express both co-receptors, so co-receptor use does not strictly define cell tropism (Goodenow & Collman, 2006). Thus, while X4 virus infects T-cell lines, and R5 virus infects macrophage cell lines, in primary cells, these definitions are not as clear. CD4-positive T cells in lymphoid tissues can express both CCR5 and CXCR4, and are the main target for replication *in vivo*. CCR5 is expressed predominantly on the $CD45R0^{+}$ memory subset of CD4-positive T lymphocytes, while CXCR4 is expressed on CD4-positive $CD45R0^{-}$ and on CD4-positive $CD45RA^{low}$ naïve cells (Bleul *et al.*, 1997).

Within single patients, mixed populations of the virus exist, with any combination of R5, X4 or R5X4. Phenotypic assays and genotyping can be used to determine tropism, as the primary determinants of co-receptor tropism are located in the V3 region of the gp120 envelope protein. Most individuals have the R5 virus at the time of diagnosis, whereas the presence of the X4 and dual virus is associated with progression to AIDS (Goodenow & Collman, 2006).

HIV-1 can be present in a variety of tissues, which is to be expected given the distribution of T cells, macrophages, and dendritic cells throughout the body. HIV-1 has been detected in tissues from infected patients by means of immunohistochemistry, in-situ hybridization, and transmission electron microscopy. HIV-1 has been shown to be associated with germinal centre follicular dendritic cells in lymph nodes, tonsils and adenoids, and mucosa-associated lymphoid tissue (MALT) as well as in T and B cells (Teruya-Feldstein *et al.*, 1995; Griffin *et al.*, 1996; Pantaleo *et al.*, 1998; Orenstein *et al.*, 1999). HIV-1 frequently infects the brain, and the microglial cells are the main location for viral replication in the central nervous system (Shaw *et al.*, 1985; Vazeux *et al.*, 1987). In reproductive organs of infected men, HIV-1 is present in cells of lymphocytic/monocytic morphology in the seminiferous tubules and interstitium of the testis, in the epididymal epithelium, and in connective tissue of the epididymis and prostate (Pudney & Anderson, 1991). In semen-cell subpopulations isolated by use of an immunoaffinity technique with magnetic beads, T cells were found to be most common cell type infected with HIV-1 (75% of samples), followed by macrophages (38%). Viral DNA was not detected in spermatozoa or in immature germ-cell populations (Quayle *et al.*, 1997).

1.1.6 Life cycle, replication, and regulation of gene expression

The HIV-1 virus first binds to target cells through semi-specific or nonspecific interactions between the viral envelope and cell-surface glycans or adhesion factors. The gp120 envelope glycoprotein then interacts with the CD4 molecule on the surface of the target cells. This induces a conformational change in gp120, which facilitates its binding to a co-receptor molecule (CCR5 or CXCR4), and the formation of a complex with the transmembrane glycoprotein gp41. Further conformational changes in the gp120–gp41 complex then lead to exposure of the fusion-peptide region of gp41, and its insertion into the host-cell membrane, which results in fusion of the virus with the host cell. Reverse transcription starts immediately after entry. A complex containing protein and viral cDNA (pre-integration complex) is transported

to the host-cell nucleus where the viral integrase enzyme catalyses the integration of viral cDNA into the hosts genomic DNA to form the provirus. The provirus may remain latent for years, producing few or no new copies of HIV-1, which has hampered the treatment of individuals infected with HIV-1, as antiretrovirals can only target replicating virus. When HIV-1 replicates, the provirus uses the cellular RNA polymerase II to create RNA copies of the HIV-1 genome, as well as viral mRNA that encodes the HIV-1 proteins. Transcription of the viral genome is driven by a promoter in the 5′ long terminal repeat of the integrated provirus. Tat increases the amount of viral RNA by increasing transcriptional initiation and/or elongation, and Rev regulates the splicing and transport of viral RNA from the nucleus to the cytoplasm. The core and envelope proteins are first synthesized as precursor polypeptides, which are then cleaved by proteases. Genomic RNA is subsequently packaged into virions. As the virion matures, Gag–Gag and Gag–Pol protein complexes are cleaved by the viral protease into subunit proteins, resulting in the mature virion, which is directed to the cell surface by *N*-terminal myristoylation of Gag. The virion is then released from the plasma membrane where it acquires its envelope. This completes the HIV life cycle (see review by Freed & Martin, 2007).

1.2 Epidemiology of infection

1.2.1 Prevalence, geographic distribution

Based on national surveillance systems, the joint United Nations programme on HIV/AIDS (UNAIDS) updates every year the geographic distribution of HIV-1 worldwide. In 2007, the HIV-1 prevalence ranged from less than 0.5% in most developed countries to up to 30% in Central and Southern Africa (UNAIDS, 2007).

1.2.2 Transmission, and risk factors for infection

HIV-1 infection is transmitted through three main routes: sexual intercourse, blood contact, and from mother to infant. HIV-1 infectivity, i.e., the average probability of transmission to another person after that person is exposed to an infected host, is determined by the interplay of three main groups of factors: host-related factors, environmental factors, and agent factors. The probability of HIV-1 transmission is highest for blood transfusion (> 0.95), followed by mother-to-child transmission (about 0.10), intermediate for needle-sharing (about 0.01), and lowest for woman-to-man sexual transmission (about 0.001) (Royce *et al.*, 1997).

(a) Sexual contact

It has been well documented, since the first years of the epidemic, that HIV-1 is transmitted through unprotected (i.e., without condom) vaginal or anal intercourse from man to woman and from woman to man, and through anal intercourse from man to man. Worldwide, the majority of new HIV-1 infections originate from sexual exposures to virus transmitted from semen, with the risk of transmission being related to several virological, biological, and behavioural factors (e.g., HIV-1 subtype, mode of sexual exposure, condom use, penile circumcision, mucosal inflammation, the co-existence of other sexually transmitted diseases, stage of HIV-1 infection, hormonal factors or host genetic background). Before the introduction of Highly Active Anti-Retroviral Therapy (HAART), the quantification of the risk of HIV-1 sexual transmission related to these factors was reviewed by Royce *et al.* (1997). Most of the accumulated evidence was already described in the previous *IARC Monograph* (IARC, 1996).

Higher viral load and genital ulceration are among the main determinants of sexual HIV-1 transmission, and this also applies during the

HAART era. In a Ugandan population, the probabilities of transmission per single coital act increased from 0.0001 at viral loads of less than 1700 copies/mL to 0.0023 at 38500 copies ($P = 0.002$), and were 0.0041 with genital ulceration versus 0.0011 without ($P = 0.02$) (Gray *et al.*, 2001). The impact of antiretroviral therapy on HIV-1 transmission has been extensively assessed. A 70% reduction in risky sexual behaviour (e.g., not using condoms with HIV-1-negative partners or of unknown HIV-1 status) and a 98% reduction in HIV-1 transmission rate (from 45.7 to 0.9/1000 person–years) was reported from a prospective study conducted among 926 infected adults enrolled in an antiretroviral therapy programme in Uganda (Bunnell *et al.*, 2006). A study on 393 monogamous heterosexual couples conducted in Spain noted a reduction of approximately 80% in the heterosexual transmission of HIV-1 when HAART became available (Castilla *et al.*, 2005). HIV-1 prevalence declined from 10.3% during the pre-HAART period (1991–95) to 1.9% in the late HAART period (1999–2003) (odds ratio[OR], 0.14, 95%CI: 0.03–0.66), a decrease that was not influenced by potential confounders like condom use, duration of partnership, CD4-positive lymphocyte count and AIDS-defining diseases (Castilla *et al.*, 2005).

HIV-1 sexual transmission from men to men occurs through anal intercourse, with seminal plasma viral load and blood plasma viral load associated with an increased risk of transmission (Butler *et al.*, 2008), though other uncommon routes of transmission have also been suggested – mainly via oral sex (Richters *et al.*, 2003). A systematic review of the literature, however, concluded that current data are insufficient to precisely estimate the risk of orogenital transmission of HIV-1 due to the small number of studies – the probability estimate was about 0.02–0.45% per single orogenital act (Baggaley *et al.*, 2008).

(b) Blood contact

HIV-1 transmission through blood-to-blood contact occurs through the transfusion of HIV-1-infected blood iatrogenically, occupationally, or through needle-sharing by intravenous drug users (IARC, 1996).

Iatrogenic transmission of HIV-1 is now extremely rare in developed countries due to the recruitment of safe donors, deferral of high-risk donors, and screening. The introduction of nucleic acid testing, and of a new method for computing the residual risk of transfusion-transmitted infections, has allowed precise estimates for the infectious window period (Soldan *et al.*, 2005; O'Brien *et al.*, 2007). Accordingly, the risk (per million transfusions) of an HIV-1-infected donation entering the blood supply was estimated at 1.91 in Italy (Gonzalez *et al.*, 2005), at 0.14 in the United Kingdom (Soldan *et al.*, 2005), and at 0.13 in Canada (O'Brien *et al.*, 2007). Conversely, in many parts of Africa and in other developing countries, blood screening and banking programmes have been difficult to implement and to sustain. In Kenya, the prevalence of HIV-1 among blood donors ranged from 2–20%, with an estimated 2% of transfusions that transmitted HIV-1 infection to HIV-1-negative blood recipients (Moore *et al.*, 2001). Reasons for such elevated transfusion-transmitted HIV-1 infections include inconsistent refrigeration, data entry errors, equipment failure, and a lack of quality assurance programmes.

Occupational transmission of HIV-1 in the health care setting has also been documented. The Health Protection Agency has registered, as of March 2005 (worldwide), 106 cases of HIV-1 infections certainly acquired through occupational exposures (of those, 57 occurred in the United States of America and 35 in Europe). Moreover, for another 238 cases, an occupational source of HIV-1 infection was considered highly probable (Health Protection Agency, 2005). The occupational transmission of HIV-1 occurs

through skin injury with needles or bistouries or from splash exposure to mucosal membranes. Estimates from studies conducted in health settings of the USA and Italy have indicated that HIV-1 transmission occurs in 0.3% of percutaneous exposures, and in 0.1% of muco-membraneous exposures (Jagger *et al.*, 2003).

The sharing of injection equipment by intravenous drug users represents a major mode of HIV-1 transmission worldwide. Since the early 1980s, a high prevalence of HIV-1 has been reported among this group from many parts of the world; and in many areas, HIV-1 prevalence among intravenous drug users was raised to 50% or more within the first years of the epidemic. Such outbreaks continue to occur, and rapid spread has been documented in the newly independent states of the former Soviet Union (Rhodes *et al.*, 2002). In England and Wales, HIV-1 prevalence declined from 5.9% in 1990 to 0.6% until 1999, and thereafter it increased to 1.4% in 2003 (Hope *et al.*, 2005). The timely introduction of comprehensive harm reduction measures, particularly needle exchange programmes, has prevented the rapid spread of HIV-1 in several northern European countries and Australia. Furthermore, trends in the prevalence of HIV-1 have reversed in several areas, like Northern Italy and New York City, and have been partially attributed to behavioural change, improved access to treatment, and needle exchange programmes (Hurley *et al.*, 1997; Des Jarlais *et al.*, 2000; Sabbatini *et al.*, 2001). In Asia, 30% of intravenous drug users were reported to be infected with HIV-1 in India and Thailand (Razak *et al.*, 2003; Panda *et al.*, 2005). In Yunnan province, China, HIV-1 infection was documented in 59.9% of 314 intravenous drug users, and it was positively associated with frequency of injection (Yao *et al.*, 2009).

(c) Mother-to-child transmission

Despite substantial reductions in mother-to-child transmission of HIV-1 infection achieved in North America and Europe (Fiscus *et al.*, 1999; Townsend *et al.*, 2008), paediatric HIV-1 infection remains a major worldwide pandemic. It is estimated that about 1800 new HIV-1 infections are transmitted daily from mother to infants (UNICEF, http://www.unicef.org/media/files/RegionalSummary.doc) during pregnancy, labour, delivery, and postpartum through breastfeeding. Several randomized clinical trials were conducted in developing countries (where the majority of pregnant women have no access to antiretroviral therapies to treat their own HIV-1 infection), to assess mother-to-child transmission rates through the use of antiretroviral regimens (reviewed by Kourtis *et al.*, 2006). Although not completely defined yet, the timing and mechanisms of mother-to-child transmission are important to quantify transmission rates, and to implement prevention strategies. In the absence of any intervention, it is estimated that in-utero and intra-partum transmission of HIV-1 occurs in approximately 25% of infants born to HIV-1-positive women (Connor *et al.*, 1994). The administration of zidovudine from 14 weeks of gestation through to delivery, and to the newborn for 6 weeks, decreased intra-partum and delivery HIV-1 transmission by 67%, from 25.5% to 8.3% ($P < 0.01$) in a randomized, double-blind, placebo-controlled efficacy trial (Connor *et al.*, 1994). Similarly, a study conducted in Thailand that used a shortened zidovudine regimen starting at 36 weeks of gestation prevented 50% of HIV-1 transmission (Shaffer *et al.*, 1999). Adding a single maternal/infant nevirapine dose to zidovudine further reduced the in-utero and intra-partum transmission risk (Lallemant *et al.*, 2004). Overall, the findings from in-utero and intra-partum transmission studies indicate that the risk of mother-to-child transmission increases steadily towards the late stages of pregnancy, with nearly 80% of new HIV-1 infection occurring from 36 weeks to delivery (Kourtis *et al.*, 2006). Thus, the HIV-1 transmission risk is reduced by up to 70% by elective Caesarean delivery, as compared to vaginal delivery

(European Mode of Delivery Collaboration, 1999). In developed countries, where the majority of pregnant HIV-1-infected women are treated with HAART, mother-to-child transmission rates are less than 10% (Cooper *et al.*, 2002). In resource-limited settings, postnatal transmission via breastfeeding may be as high as 18% (Miotti *et al.*, 1999; Fawzi *et al.*, 2002). Several intervention studies have demonstrated, in this context, the efficacy to extend antiretroviral prophylaxis to reduce HIV-1 transmission. Studies have indicated that 8.9 transmissions per 100 child–years of breastfeeding occur, with cumulative probabilities of transmission at 6 months being about 5% lower than that at 18 months (the standard duration of breastfeeding in African countries) (Coutsoudis *et al.*, 2004). The extension of antiretroviral prophylaxis of breastfed infants born to HIV-1-positive mothers with nevirapine or with nevirapine plus zidovudine for the first 14 weeks of life significantly reduces the rate of postnatal HIV-1 infection in 9-month-old infants from 10.6% in controls to 6.4% (nevirapine) or to 5.2% (nevirapine plus zidovudine) (Kumwenda *et al.*, 2008).

2. Cancer in Humans

The studies included in this section were published since the previous *IARC Monograph* (IARC, 1996), a calendar period that coincided with the introduction of HAART in developed countries, and later in developing countries. The introduction of HAART has dramatically improved the survival of HIV-1-infected patients and has reduced the incidence of several diseases associated with HIV-1 infection, including some types of cancer. In the years following the introduction of HAART (the post-HAART era), the spectrum of cancers associated with HIV-1 infection has substantially changed. This section focuses on those cancers for which the data are most strongly suggestive of a true increase in risk. It should be noted that HIV-1 infection causes cancer indirectly through immune deficiency, and the increased expression of the effects of oncogenic infections. In this way, the patterns of cancer are generally similar to those in other immunodeficient populations, such as solid organ transplant recipients. In addition, it is possible that immune deficiency results in impaired immune surveillance and the emergence of cancers that are usually controlled by the immune system, as originally hypothesized by Thomas and Macfarlane Burnet in the early 1950s (Beral & Newton, 1998; Kinlen, 2004).

2.1 Kaposi sarcoma

Kaposi sarcoma herpesvirus (KSHV) is now recognized as a necessary condition for the development of Kaposi sarcoma, with HIV-1-related immunosuppression increasing the risk of developing Kaposi sarcoma by several orders of magnitude (in the thousands). In addition to the studies referenced in the previous *IARC Monograph* (IARC, 1996), there have been a large number of cohort studies (in developed countries) and a few case–control studies (all from Africa) that confirmed the strong association between HIV-1 infection and Kaposi sarcoma. Kaposi sarcoma has become the most frequently reported cancer in many subSaharan African countries. However, the relative risks (RRs) reported from Africa, though still elevated, are substantially lower than those reported in developed countries. The reasons for this are unclear but may reflect differences in background risk and competing mortality.

Effective antiretroviral therapy in individuals with HIV-1-related immunosuppression usually results in a substantial and rapid reduction in the risk of Kaposi sarcoma. Nevertheless, Kaposi sarcoma incidence rates remain very substantially raised above population rates (and are no longer declining), and Kaposi sarcoma remains

a considerable cause of morbidity and mortality in people infected with HIV-1. According to a calendar-period meta-analysis on 47936 HIV-1-positive people in North America, Europe and Australia, the relative risk for Kaposi sarcoma in the early post-HAART era (1997–99) was 0.32 (95%CI: 0.26–0.40) when compared to the pre-HAART era (International Collaboration on HIV-1 and Cancer, 2000). Similar declines by calendar period were reported in Italy from 1986 through to 1998 (Franceschi *et al.*, 2003), and in the USA (RR, 0.19; 95%CI: 0.12–0.30, 1997–2002 versus 1989–96) (Bedimo *et al.*, 2004). When the follow-up of HIV-1-positive patients was continued through to the late post-HAART period (2002), time trends incidence rates for Kaposi sarcoma were observed to level off in the last study years (Patel *et al.*, 2008). In the USA, the risk for Kaposi sarcoma declined 83.5% during 1990–95 and 1996–2002 (standardized incidence ratio [SIR], 22100 and 3640, respectively; $P < 0.0001$). The pattern presented a steady decline that began in the 1980s and continued through 1990–95, with a further fall in risk offsetting the 1996–2002 period from the 1990–95 period (RR, 0.41; 95%CI: 0.28–0.60). Subsequently, during the HAART era itself, the risk for Kaposi sarcoma remained constant (Engels *et al.*, 2006).

A similar temporal pattern was observed for Kaposi sarcoma in Australia (Grulich *et al.*, 2001), and in Europe (Franceschi *et al.*, 2003; Clifford *et al.*, 2005). In Switzerland, the incidence of Kaposi sarcoma in the Swiss HIV-1 cohort study following the advent of HAART fell abruptly in 1996–98 to reach a plateau. Individual data on HAART use showed that the risk for Kaposi sarcoma declined steeply in the first months after HAART initiation, and continued to be low for another 7–10 years (hazard ratio [HR], 0.06; 95%CI: 0.02–0.17) (Franceschi *et al.*, 2008).

In addition to making Kaposi sarcoma a relatively rare event, HAART use has also diminished the variation in Kaposi sarcoma risk by host characteristics, including gender, age group, HIV-1-transmission category, and CD4-positive cell count. Increases in SIR with declining number of CD4-positive count were seen in most of the studies with relative risks estimates according to strata of CD4-positive cell counts. In the Swiss HIV-1 cohort study, the SIR for Kaposi sarcoma was 571 (95%CI: 449–716) among persons with CD4-positive counts of less than 100 cells/mm^3, but 76.5 (95%CI: 52.3–108) among persons with CD4-positive counts of ≥ 500 cells/mm^3 (Clifford *et al.*, 2005). In the USA, the risk for Kaposi sarcoma increased by 36% for each fall of 100 CD4-positive cells/mm^3 (95%CI: 29–43%) (Mbulaiteye *et al.*, 2003). A longitudinal study of 2002 HIV-1-infected persons in Italy with known date of seroconversion followed up to 2004 found a relative risk of 0.11 (95%CI: 0.06–0.19) for Kaposi sarcoma associated with a CD4-positive count ≥ 350 cells/mm^3 at enrolment (vs < 200) (Serraino *et al.*, 2005). Homosexual men were at higher risk than injecting drug users (RR, 6.67; 95%CI: 3.58–12.42), and women were at lower risk of Kaposi sarcoma than men (RR, 0.23; 95%CI: 0.06–0.83) (Serraino *et al.*, 2005).

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.3.pdf.

2.2 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma has been part of the AIDS case definition since 1985 (CDC, 1985). A recently published meta-analysis that included population-based prospective studies comparing rates of non-Hodgkin lymphoma in people with HIV-1 or AIDS to the general population reported an SIR of 77 in HIV-1 patients, and of 8 in solid organ transplant recipients (Grulich *et al.*, 2007a). In Africa, the relative increase in people

with HIV-1 appears much less, and was about 6-fold in case–control studies in Uganda, and in a South African case–control study (Newton *et al.*, 2001; Stein *et al.*, 2008). Non-Hodgkin lymphoma also occurs at increased rates in people with primary immune deficiency (Beral & Newton, 1998; Mellemkjaer *et al.*, 2002).

There is no evidence that HIV-1 causes non-Hodgkin lymphoma through a direct effect. Rather, the profound depletion of CD4-positive T lymphocytes that is caused by HIV-1 allows the dysregulation of control of B cells, and the expression of the effects of lymphotrophic viruses (Engels, 2007). As in the general population, more than 90% of cases of non-Hodgkin lymphoma due to AIDS are of the B-cell phenotype. There are three B-cell lymphoma subtypes that occur most commonly. First, primary brain lymphoma occurs at profound levels of immune deficiency, and occurs several thousand times more commonly in people with AIDS than in the general population (Coté *et al.*, 1996). Second, large-cell immunoblastic lymphoma occurs in the severely immunodeficient, and occurs several hundred times more commonly than in the general population (Engels & Goedert, 2005). Third, Burkitt lymphoma can occur at any stage of immune deficiency and, again, occurs nearly a hundred times more frequently than in the general population (Engels *et al.*, 2008; Stein *et al.*, 2008a). A rare lymphoma subtype that occurs in people with HIV-1 is primary effusion lymphoma, which presents as either a pleural or peritoneal effusion. It is associated with infection with KSHV, is more likely to present in a person with Kaposi sarcoma (Mbulaiteye *et al.*, 2002), and has also been described in association with the KSHV-related disease, multicentric Castleman disease (Ascoli *et al.*, 2001). In addition to these B-cell subtypes, a record linkage study in the USA demonstrated a 15-fold increase in the incidence of T-cell non-Hodgkin lymphoma (Biggar *et al.*, 2001). The pathological spectrum of T-cell non-Hodgkin lymphoma in HIV-1 is diverse, and tends to occur at very low CD4-positive counts (Arzoo *et al.*, 2004).

Of the non-Hodgkin lymphoma subtypes that are associated with HIV-1, the incidence of two primary brain lymphoma and diffuse large B-cell lymphoma is correlated closely with the severity of immune deficiency. These two types of lymphoma are uncommon when CD4-positive counts are maintained at relatively normal levels. Similarly, in organ transplant recipients, the risk of non-Hodgkin lymphoma is proportional to the intensity of immune suppression (Grulich *et al.*, 2007b). On the other hand, the third non-Hodgkin lymphoma subtype associated with HIV-1, Burkitt lymphoma, can occur at any level of immune deficiency. All three B-cell lymphoma subtypes are associated with markers of immune activation, such as serum immunoglobulin (Martínez-Maza & Breen, 2002), soluble CD44 (Breen *et al.*, 2005), and IL10 (Breen *et al.*, 2003).

There was initially considerable debate about whether or not non-Hodgkin lymphoma rates decreased after the introduction of HAART (Grulich, 1999, 2000; Matthews *et al.*, 2000; Powles *et al.*, 2000; Tirelli *et al.*, 2000; Ives *et al.*, 2001; Vilchez *et al.*, 2002), but by around the turn of the millennium, it became clear that rates of non-Hodgkin lymphoma due to AIDS were declining (International Collaboration on HIV and Cancer, 2000; Besson *et al.*, 2001; Grulich *et al.*, 2001; Franceschi *et al.*, 2003; Clayton & Mughal, 2004; Kinlen, 2004; Stebbing *et al.*, 2004; Engels *et al.*, 2006; Gingues & Gill, 2006; Chiappini *et al.*, 2007; Long *et al.*, 2008; Polesel *et al.*, 2008). Further case–control (Bonnet *et al.*, 2006a) and cohort studies (Carrieri *et al.*, 2003; Stebbing *et al.*, 2004; Clifford *et al.*, 2005; Kirk *et al.*, 2007; Serraino *et al.*, 2007; Polesel *et al.*, 2008) have shown that individual receipt of HAART is associated with a reduced risk of non-Hodgkin lymphoma. It is remarkable that the risk of non-Hodgkin lymphoma appears to decrease markedly within months of starting HAART (Kirk *et al.*, 2007; Polesel *et al.*, 2008).

Of the subtypes of AIDS-related non-Hodgkin lymphoma, rates have declined most dramatically for primary brain non-Hodgkin lymphoma (International Collaboration on HIV and Cancer, 2000; Besson *et al.*, 2001; Kirk *et al.*, 2001; Inungu *et al.*, 2002; Bower *et al.*, 2006; Diamond *et al.*, 2006; Haldorsen *et al.*, 2008). Rates of large-cell immunoblastic lymphoma have also declined substantially, though not as markedly. Rates of Burkitt lymphoma appear to have changed little in most studies (International Collaboration on HIV and Cancer, 2000; Engels *et al.*, 2006; Babel *et al.*, 2007; Barclay *et al.*, 2007), although a decline in risk was reported in a large European cohort (Kirk *et al.*, 2001). Despite these recent very large declines in non-Hodgkin lymphoma risk, in the most recent studies, rates of non-Hodgkin lymphoma remain 10-fold or more greater than population rates (Engels *et al.*, 2008; Patel *et al.*, 2008). Before 1996, AIDS-related non-Hodgkin lymphoma was almost universally fatal (Tirelli *et al.*, 2000). Since the advent of HAART, the mean CD4-positive count at non-Hodgkin lymphoma presentation has increased substantially, and the prognosis has improved remarkably (Evison *et al.*, 1999; Besson *et al.*, 2001; Little *et al.*, 2001; Baiocchi *et al.*, 2002; Gérard *et al.*, 2002; Vaccher *et al.*, 2003; Robotin *et al.*, 2004; Bower *et al.*, 2005; Lascaux *et al.*, 2005; Lim *et al.*, 2005; Mounier *et al.*, 2006; Miralles *et al.*, 2007). Treatment schedules and responsiveness are now similar to that in the HIV-1-negative population (Clayton & Mughal, 2004; Lim *et al.*, 2005).

2.2.1 The Epstein-Barr virus in AIDS-related non-Hodgkin lymphoma

The Epstein-Barr virus (EBV) can be detected in AIDS-related non-Hodgkin lymphoma in virtually all cases of primary brain lymphoma (Hansen *et al.*, 2000; Tirelli *et al.*, 2000), around 40% of the cases are large cell lymphoma, and around 30% of the cases are Burkitt lymphoma (Tirelli *et al.*, 2000). In solid organ transplant recipients, the risk of non-Hodgkin lymphoma is much higher in EBV-seronegative organ transplant recipients who contract primary EBV infection from the donated organ (Shapiro *et al.*, 1999; Swinnen, 2000). In this population, high EBV plasma viral load predicts the development of non-Hodgkin lymphoma, and regression of lymphoma is associated with declining EBV in plasma. In addition, cytokine polymorphisms favouring a pro-inflammatory state increase the risk of lymphoma after transplantation (Babel *et al.*, 2007). In people with HIV-1, EBV viral loads are increased from the early stages of HIV-1 infection (Piriou *et al.*, 2004). In one study, high plasma EBV viral load was found in people with EBV-positive but not EBV-negative AIDS lymphoma, and viral loads fell with successful therapy (Fan *et al.*, 2005). In a French study, plasma EBV declined with chemotherapy for non-Hodgkin lymphoma (Bonnet *et al.*, 2006b). EBV DNA is found in the cerebral spinal fluid in 80–100% of cases of primary brain lymphoma in people with AIDS (De Luca *et al.*, 1995; Brink *et al.*, 1998; Antinori *et al.*, 1999; Bossolasco *et al.*, 2002; Fan *et al.*, 2005). There is interest in using anti-EBV therapies in the treatment of primary brain lymphoma in HIV-1 (Aboulafia *et al.*, 2006). In one small study, latent antigen EBNA-1-specific CD4 T cells were lost before the diagnosis of AIDS lymphoma, but not in those who progressed to other AIDS illnesses, suggesting an important role of immunity to EBNA-1 (Piriou *et al.*, 2005). A Japanese study documented a decline in the proportion of non-Hodgkin lymphoma positive for EBV, from 88% in the pre-HAART era down to 58% in the HAART era (Hishima *et al.*, 2006). This is consistent with the declining occurrence of opportunistic EBV-related non-Hodgkin lymphoma. Studies which have examined anti-herpesvirus agents as potential preventive agents for non-Hodgkin lymphoma have produced conflicting results (Fong *et al.*, 2000; Grulich *et al.*, 2000, 2001), and high-dose aciclovir was not protective against death from non-Hodgkin

lymphoma in a meta-analysis of trials of high-dose aciclovir in people with HIV-1 (Ioannidis *et al.*, 1998). [The Working Group noted that the power was limited to show this effect, and it was difficult to disentangle the subtypes of lymphoma from the individual trials.]

Despite an association of hepatitis C virus (HCV) infection with non-Hodgkin lymphoma in the general population, a cohort study did not find an association of non-Hodgkin lymphoma with HCV infection in those with HIV-1 (Waters *et al.*, 2005).

See Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.4.pdf, Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.5.pdf, and Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.6.pdf.

2.3 Hodgkin lymphoma

In the general population of developed countries, Hodgkin lymphoma is one of the most common malignancies diagnosed in people under the age of 45 years with upward trends recorded since the late 1990s (Hjalgrim *et al.*, 2001). Four subtypes have been distinguished within classical Hodgkin lymphoma: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. These subtypes cannot be distinguished by the immunophenotype of the tumour cells, but are different in terms of characteristics such as the sites of involvement, clinical features, growth pattern, and frequency of EBV infections (Stein *et al.*, 2008b).

The epidemiology of Hodgkin lymphoma is characterized by a bimodal incidence curve – with a first peak around the age of 30 years and the second peak around the age of 50 – that has been taken as suggestive of an infectious etiology (World Cancer Report, 2008). A particularly important etiological role has been attributed to EBV, whose genome is found in higher percentages among Hodgkin lymphoma cases that are HIV-1-positive compared to those that are HIV-1-negative (Carbone *et al.*, 1999; Frisch *et al.*, 2001; Rezk & Weiss, 2007). Epidemiological studies conducted during the first years of the HIV-1 epidemic lacked statistical power to assess a significantly increased risk of Hodgkin lymphoma among the HIV-1-infected population (Biggar *et al.*, 1987). However, with the spread of the epidemic and longer survival of HIV-1-infected persons, the scientific evidence has accumulated showing that HIV-1-positive persons have, overall, a 10-fold higher risk of developing Hodgkin lymphoma than HIV-1-negative persons of the same sex and age. Such evidence comes from the different types of epidemiological studies conducted worldwide.

In the pre-HAART period, a cohort study of 6704 homosexual men conducted in the USA was the first to demonstrate a statistically significant excess risk for Hodgkin lymphoma in HIV-1-positive persons (RR, 5.0; 95%CI: 2.0–10.3) (Hessol *et al.*, 1992). A nearly 10-fold higher risk (95%CI: 8–111) was documented thereafter, in Italy, in a cohort study on 1255 HIV-1-positive persons with a known date of seroconversion (Serraino *et al.*, 1997), by a record linkage of national AIDS registry and population-based cancer registries (SIR, 8.9; 95%CI: 4.4–16.0) (Franceschi *et al.*, 1998), and, in Australia, through a similar record linkage study (RR, 7.8; 95%CI: 4.4–13.0) (Grulich *et al.*, 2002). A meta-analysis of seven reports of HIV-1-associated cancer risk, involving 444172 people with HIV-1/AIDS in the USA, Australia, Scotland, Italy, Switzerland, and England (Grulich *et al.*, 2007a) reported an overall relative risk of 11.0 (95%CI: 8.4–14.4). Although to a lesser extent than in developed countries, significant excess risk for Hodgkin lymphoma in people with HIV-1 infection or AIDS were also noted in Uganda (RR, 5.7; 95%CI: 1.2–17) (Mbulaiteye *et al.*, 2006), and in South Africa (RR, 1.6; 95%CI: 1.0–2.7) (Stein *et al.*, 2008a).

The excess risk for Hodgkin lymphoma in HIV-1-infected persons was not consistently observed across Hodgkin lymphoma histological types. A comparative study based on a clinical series of 92 cases of Hodgkin lymphoma in HIV-1-positive persons, showed a 4-fold increased frequency of the mixed cellularity type, and a 12-fold increased frequency of the lymphocyte depletion type in HIV-1-positive cases compared with the general population (Serraino *et al.*, 1993). Similarly, a meta-analysis of 17 studies on Hodgkin lymphoma in HIV-1-positive individuals showed statistically significant differences in the proportion of distribution of all types, with odds ratios of 0.4 (95%CI: 0.3–0.6) for lymphocyte predominance, 0.3 (95%CI: 0.2–0.4) for nodular sclerosis, 3.2 (95%CI: 2.6–3.8) for mixed cellularity, and 6.3 (95%CI: 4.5–8.8) for the lymphocyte depletion type (Rapezzi *et al.*, 2001). In the USA, very elevated SIRs according to histological type were reported by a large record linkage study of AIDS and cancer registries investigating the association between cancer and immunosuppression. With regard to Hodgkin lymphoma, only the mixed cellularity type (RR, 18.3; 95%CI: 15.9–20.9) and the lymphocytic depletion type (RR, 35.3; 95%CI: 24.7–48.8) were associated with a significantly increased risk (Frisch *et al.*, 2001).

In contrast with non-Hodgkin lymphoma, whose incidence has declined with immune restoration due to the use of HAART (International Collaboration on HIV and Cancer, 2000), time trends in relative risks for Hodgkin lymphoma have generally shown upward trends in recent years. [Although the Working Group notesd that SIRs have methodological limitations when used to compare changes among HIV-1-positive persons.] Whereas a cohort study of 8074 HIV-1-positive persons in Italy and France showed no significant variations in the risk of Hodgkin lymphoma between those treated (RR, 9.4; 95%CI: 2.0–27.6) or not treated (RR, 11.1; 95%CI: 6.2–18.3) with HAART (Serraino *et al.*, 2007), the elevation in risk following HAART were noted in most investigations. Hodgkin lymphoma risk was higher in the post-HAART period (RR, 31.7) than in the pre-HAART period (RR, 22.8) according to a cohort study of 77025 HIV-1-positive persons in France (Herida *et al.*, 2003). As seen in France, the findings of a record linkage between the Swiss HIV-1 cohort and cancer registries pointed to a higher risk for Hodgkin lymphoma in HIV-1-positive persons treated with HAART (RR, 36.2), when compared to those who were never treated (RR, 11.4) (Clifford *et al.*, 2005). Another record linkage study of 57350 HIV-1-infected persons recruited from 1991–2002 with cancer registries in the USA indicated that the incidence of Hodgkin lymphoma increased 3-fold in the study period (RR, 2.7; 95%CI: 1.0–7.1; 1996–2002 versus 1991–95) (Engels *et al.*, 2008). These results, and those from another investigation from the USA showing increasing incidence rates of Hodgkin lymphoma with a higher count of CD4-positive cells in HIV-1-positive persons treated with HAART (Biggar *et al.*, 2006), might suggest that the excess risk for Hodgkin lymphoma is more pronounced in HIV-1-infected individuals with moderate immunosuppression, where the mixed cellularity type is more frequent. It has been hypothesized that this finding could be the result of the strong association of Hodgkin lymphoma with EBV infection (Frisch *et al.*, 2001).

See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.7.pdf, Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.8.pdf, and Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.9.pdf.

2.4 Cervical and anogenital cancers

2.4.1 Cancer of the cervix

HIV-1-positive women constitute a growing part of the population groups affected by the epidemic in developed countries, but they are particularly numerous in low- and middle-resource countries, where the infection with HIV-1 and the human papillomavirus (HPV) is common (Franceschi *et al.*, 2006). Because both HIV-1 infection and HPV infection are sexually transmitted, the two infections often co-exist (Strickler *et al.*, 2005; Clifford *et al.*, 2006). HPV is a necessary condition for cervical cancer to occur, and as a result of HIV-1-induced immune impairment in HIV-1-infected women, there is an increased probability that HPV infection will become persistent (Strickler *et al.*, 2005), and evolve into cancerous lesions of the cervix uteri (Frisch *et al.*, 2000; Dal Maso *et al.*, 2003a). Invasive cervical cancer was the last type of cancer included among the AIDS-defining diseases in 1993, but an association with HIV-1 infection started to emerge in Europe and in the USA several years later (Franceschi *et al.*, 1998; Serraino, 1999; Ahdieh *et al.*, 2000; Frisch *et al.*, 2000). The magnitude of the excess was weaker than that found for the other AIDS-defining cancers (i.e., Kaposi sarcoma and non-Hodgkin lymphoma), with increases 5–10-fold in developed countries, depending on the study site and characteristics of the populations under study. The relative risk for invasive cervical cancer among women living with HIV-1 infection varies from country to country, depending on factors like premature death due to other causes or early detection of cancer that prevents the progression of pre-invasive lesions to the invasive stage (Franceschi & Jaffe, 2007).

A meta-analysis of seven reports of HIV-1-associated cancer risk, involving 444172 people with HIV-1/AIDS in the USA, Australia, Scotland, Italy, Switzerland, and England (Grulich *et al.*, 2007a) reported an overall relative risk of 5.8 (95%CI: 3.0–11.3), with risk estimates in individual studies ranging from 1.0 (95%CI: 0.2–2.9) in the United Kingdom (Newnham *et al.*, 2005) to 21.9 (95%CI: 13.0–34.7) in Italy (Dal Maso *et al.*, 2003a). An even higher risk for cervical cancer was reported among HIV-1-infected women in Spain (SIR, 41.8; 95%CI: 19.9–77.1) (Galceran *et al.*, 2007). In Italy and Spain, the particularly elevated cervical cancer risk could be attributed to the concomitant high prevalence of intravenous drug users among HIV-1 women (who are at a particularly elevated risk of cervical cancer), and to poorly organized screening strategies in this population. Conversely, elevated rates of cervical cancer in the general population and competing risks of deaths are likely to explain the observation that risks from studies conducted in Africa tended to be of lower magnitude than those from developed countries (Serraino, 1999). For instance, a comparison of cancer rates between 1988–2002 in Uganda showed that the relative risk of invasive cervical cancer among women with HIV-1, when compared to women in the general population, was 2.4 (95%CI: 1.1–4.4) (Mbulaiteye *et al.*, 2006).

Trends in SIRs of cervical cancer indicate that the introduction of HAART has not influenced the occurrence of this cancer among HIV-1-infected women. This observation was documented in the first years after HAART became available by a pooled analysis of cancer incidence data from 23 prospective studies that included 47936 HIV-1-seropositive individuals from North America, Europe, and Australia (International Collaboration on HIV and Cancer, 2000), as well as by several other single investigations. Among 2331 HIV-1-infected women in Italy and France, the risk of cervical cancer was 15.7 (95%CI: 9.1–25) in those treated with HAART, and 11.8 (95%CI: 3.8–27.5) in those who were not (Serraino *et al.*, 2007). Also, in Italy, no change was noted by a record linkage study of AIDS and cancer registries with risks varying from 51.0 (95%CI:

23.1–97.3) in the pre-HAART period from 1985–96 to 41.5 (95%CI: 28.0–59.3) in the post-HAART era from 1997–2002 (Dal Maso *et al.*, 2009). Similar findings were documented in the USA (Bedimo *et al.*, 2004; Biggar *et al.*, 2007; Patel *et al.*, 2008). Cervical cancer incidence rates were higher in 1996–2002 (86.5/100000 person–years) than in 1990–95 (64.2/100000 person–years) (RR, 1.41; 95%CI: 0.81–2.46), but this was not statistically significant (Biggar *et al.*, 2007). Data from two large prospective cohort studies in the USA, the Adult and Adolescent Spectrum of HIV Disease (ASD) Project and the HIV Outpatient Study (HOPS) had statistically significant SIRs of 11.8 in 1992–95, 13.3 in 1996–99, and 10.1 in 2000–03) (Patel *et al.*, 2008).

(a) Cancer of the cervix in immunosuppressed individuals

The incidence of cervical cancer also increased in transplant recipients [SIR, 2.50; 95%CI: 1.33–4.27] (Vajdic *et al.*, 2006). Pre-invasive cervical cancer lesions altered in HIV-positive women led to the decision that the cohort study estimates were not just due to confounding.

See Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.10.pdf, Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.11.pdf, and Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.12.pdf.

2.4.2 Cancer of the anus

A recent meta-analysis of population-based cohort studies estimated that rates of anal cancer are raised almost 30 times in people with HIV-1/AIDS, and are raised about 5 times in transplant recipients (Grulich *et al.*, 2007a). Anal cancer is closely related to anal infection with high-risk subtypes of HPV (IARC, 2007). Determining whether anal cancer is associated with HIV-1 infection is complicated by the fact that HIV-1-negative homosexual men are much more likely than others to develop anal HPV infection and anal cancer (Daling *et al.*, 1987). Nevertheless, cohort data do suggest that the rate of anal cancer is higher in HIV-1-positive than in HIV-1-negative homosexual men (D'Souza *et al.*, 2008). Anal cancer occurs at younger ages in HIV-1-positive cases than in the HIV-1-negative cases (Chiao *et al.*, 2008; D'Souza *et al.*, 2008). Among HIV-1-positive persons, lower CD4-positive counts are associated with a higher probability of infection with multiple HPV types (Orlando *et al.*, 2008). HPV infection of the anal canal is extraordinarily prevalent in both people with HIV-1, and in transplant recipients (Drobacheff *et al.*, 2003; Patel *et al.*, 2007; Orlando *et al.*, 2008). Rates of HPV infection of over 50% have been described even in HIV-1-positive women (Palefsky *et al.*, 2001), in whom anal cancer is relatively uncommon.

Many studies have noted increases in the incidence of anal cancer during the HAART era (Bower *et al.*, 2004; Diamond *et al.*, 2005; Hessol *et al.*, 2007; D'Souza *et al.*, 2008; Patel *et al.*, 2008; Piketty *et al.*, 2008); this may be related to increased screening for anal cancer and its precursors, to an increase in risky behaviour of patients feeling safer by taking HAART, and/or to increased longevity allowing enough time for the cancer to develop (Hessol *et al.*, 2007; Piketty *et al.*, 2008). [The Working Group noted that although initially the introduction of a screening programme (as is beginning to occur in some specialized centres) may lead to an increase in the reported prevalence of a cancer, in the longer term, the detection and treatment of pre-invasive disease should lead to a decline in the incidence of invasive malignancy in the screened population.] In the USA, record linkage of HIV/AIDS and cancer registries showed that the AIDS- and HIV-1-cancer matched rates of anal cancer were approximately the same in the pre- and post-HAART eras (Engels *et al.*, 2006; Engels *et al.*, 2008). Several studies conluded that the use of

HAART does not appear to reduce anal cancer risk (Clifford *et al.*, 2005; Hessol *et al.*, 2007; D'Souza *et al.*, 2008;).

See Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.13.pdf, Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.14.pdf, and Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.15.pdf.

2.4.3 Cancers of the vulva, vagina, and penis

A recent meta-analysis reported that rates of cancers of the vulva and vagina (SIR, 6.45; 95%CI: 4.07–10.2) and penis (SIR, 4.42; 95%CI: 2.77–7.07) are increased in persons with HIV-1 (Grulich *et al.*, 2007a). [The Working Group noted that the increase in transplant recipients is of a similar magnitude, suggesting that confounding by sexual behaviour does not completely explain the increased risk in people with HIV-1.] However, fewer than 50 cases of these cancers have been described in cohort studies of people with HIV-1 (See Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.16.pdf).

2.5 Cancer of the skin

There has been limited research on non-melanoma skin cancer in people with HIV-1, and a recent meta-analysis estimated that the rate was increased 4-fold (Grulich *et al.*, 2007a). In contrast, in solid organ transplant recipients, rates of non-melanoma skin cancer are raised around 30-fold (Grulich *et al.*, 2007a). While the majority of cases of non-melanoma skin cancer in transplant recipients is squamous cell carcinoma, this does not appear to be the case in people with HIV-1, in whom basal cell carcinoma predominates (Bedimo *et al.*, 2004). However, it is not clear whether data on basal cell carcinoma and squamous cell carcinoma are comparable in terms of completeness and allowance for differences in age distribution. In the US AIDS cancer match (record linked AIDS and cancer registries), increased rates of the rare Merkel cell carcinoma have been described (based on six cases), and this is also a cancer which has been described as occurring at increased rates in transplant recipients (Engels *et al.*, 2002).

See Table 2.17 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.17.pdf, and Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.18.pdf.

2.6 Cancer of the conjunctiva

An association of HIV-1 with conjunctival cancer was first suggested by clinical observations of an increased number of diagnoses of this cancer in Africa at the time of the onset of the HIV-1 epidemic (Kestelyn *et al.*, 1990; Waddell *et al.*, 1996). Moreover, data from the Ugandan cancer registry demonstrated a 6-fold increase in incidence in the late 1980s compared to the incidence rates in 1970–88 (Ateenyi-Agaba, 1995). Data in Table 2.19 (available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.19.pdf) and Table 2.20 (available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.20.pdf) demonstrate a consistent marked increase in risk of conjunctival cancer among HIV-1-infected people, with a relative risk of around 10. One study described a case of conjunctival cancer that completely regressed after HAART was instituted with the occurrence of immune reconstitution (Holkar *et al.*, 2005). Several studies suggest that mucosal HPV types are not involved in the etiology of this tumour, but a role for cutaneous types remains uncertain (de Koning *et al.*, 2008).

Previous observations that conjunctival carcinoma was more common in tropical regions led to a hypothesis that exposure to solar ultraviolet (UV) radiation would be important

(Guech-Ongey *et al.*, 2008). The risk is increased in those with a past history of skin cancer, and in an ecological analysis, rates were strongly correlated with ambient UV exposure (Newton, 1996). In the USA, rates of AIDS-associated conjunctival cancer are higher in regions with higher ambient UV radiation (Guech-Ongey *et al.*, 2008). Squamous cell carcinoma lesions contain classic UV-radiation-induced p53 mutations (Waddell & Newton, 2007). A direct role of HIV-1-associated immune deficiency is supported by the fact that the incidence is also increased in kidney transplant recipients (based on five cases) (Vajdic *et al.*, 2007). In addition, a case report of spontaneous regression of biopsy-proven cancer in an African woman commencing HAART, co-incident with an improvement in CD4 count, has been described (Holkar *et al.*, 2005). In the largest African series of 476 cases diagnosed in Uganda in 1995–2001, 64% of cases were HIV-1-positive, and the median CD4 count in these was 111 cells/mL (Waddell *et al.*, 2006). [The Working Group noted that the median CD4 count was based on a subset of 159 cases.]

2.7 Cancer of the lung

Cancer of the lung is one of the most common cancers that occurs in men and women of the general population in developed countries (World Cancer Report, 2008). Most (> 90%) of the lung cancer cases are registered in cigarette smokers, and the risk of developing the disease is strongly associated with duration and intensity of the habit. Higher prevalence of smokers among HIV-1-infected people, as compared to their referent general population, has been hypothesized, but not well documented (Parker *et al.*, 1998; Bower *et al.*, 2003). In the USA, among a national representative sample of persons receiving care for HIV-1 infection in the late 1990s, 73% had ever smoked and 51% were current smokers, which is a much higher proportion than the 20–30% of the general US population who currently smoke (Giordano & Kramer, 2005). However, there was no evidence of an excess risk for lung cancer in HIV-1-infected people until prolonged survival due to the use of HAART had enhanced the likelihood of these persons developing cancer types (including lung cancer) rarely noted in the pre-HAART era. The epidemiological evidence of a statistically significant excess risk for lung cancer was consolidated in the post-HAART era, with relative risks in the range of 2–4 (Bower *et al.*, 2003; Dal Maso *et al.*, 2003a; Chaturvedi *et al.*, 2007; Patel *et al.*, 2008). The magnitude of the excess risk was, in Italy, 2.4 (95%CI: 1.5–3.7) during 1985–98 (Dal Maso *et al.*, 2003a); in the USA, 4.5 (95%CI: 4.2–4.8) during 1992–95, and 2.8 (95%CI: 2.4–3.1) during 2002–05 (Frisch *et al.*, 2001); and in Switzerland, 3.2 (95%CI: 1.7–5.4) during 1985–2003 (Clifford *et al.*, 2005). A meta-analysis of seven reports of HIV-1-associated cancer risk, involving 444172 people with HIV-1/AIDS in the USA, Australia, Scotland, Italy, Switzerland, and England reported an overall relative risk of 2.7 (95%CI: 1.9–3.9) (Grulich *et al.*, 2007a).

Studies that assessed the risk of lung cancer in HIV-1-infected people according to individual antiretroviral treatment failed to demonstrate an effect of HAART on lung cancer risk, thus indicating that lung cancer is not strongly associated with severe immunosuppression (Clifford *et al.*, 2005; Serraino *et al.*, 2007). In the United Kingdom, incidence rates of lung cancer increased from 0.8 (95%CI: 0.2–3.2)/10^5 patient–years follow-up in the pre-HAART era to 6.7 (95%CI: 3.1–13.9)/10^5 patient–years follow-up in the post-HAART era (Bower *et al.*, 2003), while in Italy, incidence rates were 10.7 (95%CI: 6.2–17.2)/10^4 person–years and 14.1 (95%CI: 3.7–36.4)/10^4 person–years, respectively (Dal Maso *et al.*, 2003b). An update of these data indicated that the SIR for lung cancer among Italian people with AIDS has nearly doubled from the pre- to the post-HAART period, from 2.1 (95%CI: 1.2–3.3) during 1985–96 to 4.1 (95%CI: 2.9–5.5) during

1997–2004 (Dal Maso *et al.*, 2009). [The Working Group noted that several aspects regarding the role of HIV-1-induced immunosuppression in the etiology of lung cancer still need to be clarified, because factors like duration and intensity of smoking have not been controlled for, and could deeply confound the association between HIV-1 infection and lung cancer.]

Several studies have attempted to control for confounding by smoking but residual confounding is possible in these studies (Engels *et al.*, 2006; Kirk *et al.*, 2007). In a population where smoking rates did not differ by HIV-1 status, lung cancer was not related to HIV-1 status (Stein *et al.*, 2008a). In the USA, it has been estimated that nearly twice as many cases of lung cancer would be observed in HIV-1-infected persons than the general population, simply because of the higher prevalence of smoking in that population (Giordano & Kramer, 2005). Only one study regarding the risk of lung cancer among HIV-1-infected persons (Phelps *et al.*, 2001) has included a control group with a history of smoking similar to that of the study group. Nearly 90% of the persons included in the study had ever smoked, and no statistically significant increase in the risk of lung cancer was reported. Interestingly, one study found a higher SIR for lung cancer among injecting drug users not infected with HIV-1 than among HIV-1-infected persons, which is further evidence that the relationship of HIV-1 infection to lung cancer is confounded by an exposure, most likely smoking (Serraino *et al.*, 2000). [The Working Group noted that, clearly, persons with HIV-1 infection are at increased risk for lung cancer, compared with persons without HIV-1 infection. Much of that risk is due to the high prevalence of smoking in the HIV-1-infected population. Studies of large cohorts that can adequately adjust for smoking are needed to determine if HIV-1 infection itself increases the risk of lung cancer; in addition, Kaposi sarcoma can appear in the lungs and be potentially misdiagnosed as lung cancer.]

See Table 2.21 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.21.pdf, and Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.22.pdf.

2.8 Cancer of the liver

HIV-1-positive persons, in particular injecting drug users, have a greatly increased prevalence of HBV and HCV infections compared to the general population, and hence are at a higher risk for liver cancer (i.e., hepatocellular carcinoma [HCC]) (Thio *et al.*, 2002; Hisada *et al.*, 2005; Kramer *et al.*, 2005; McGinnis *et al.*, 2006). Studies on HBV/HCV natural history have shown that HIV-1-related immune suppression worsens the risk of cirrhosis and of liver-related death (Di Martino *et al.*, 2001; Graham *et al.*, 2001; Thio *et al.*, 2002; Kramer *et al.*, 2005), but a direct effect of HIV-1-related immunodeficiency on HCC risk has not yet been demonstrated (Frisch *et al.*, 2001; Kramer *et al.*, 2005; McGinnis *et al.*, 2006). Following the widespread use of HAART, liver disease has become a progressively more important cause of morbidity and mortality among HIV-1-infected persons (Louie *et al.*, 2002; Weber *et al.*, 2006). Findings from cohort investigations, record linkage of HIV-1/AIDS registries with population-based cancer registries and case–control studies conducted across Europe, the USA and Australia have documented 2–20-fold excess risks for HCC. A 5.2-fold elevated risk (95%CI: 3.3–8.2) was reported in a meta-analysis of seven population-based studies of people with HIV-1 (Grulich *et al.*, 2007a). Excess risks were more pronounced among HIV-1-infected injecting drug users (SIR, 50.5; 95%CI: 15.9–11; Clifford *et al.*, 2005) (SIR, 24.3; 95%CI: 2.3–89.3; Serraino *et al.*, 2000); than among other HIV-1-transmission categories, and among HIV-1-infected persons with low CD4-positive cell counts (Clifford *et al.*, 2008). There is evidence indicating that the advanced

immunosuppression associated with HIV-1 disease progression does not influence the occurrence of HCC (Frisch *et al.*, 2001), but the role of HAART still needs to be better defined. Relative risks for HCC were higher in the HAART era than in preceding years (Hessol *et al.*, 2007), though studies based on individual data on HAART use either reported lack of association (Serraino *et al.*, 2007) or a significantly reduced risk of HCC in people treated with HAART (RR, 0.3; 95%CI: 0.1–0.9) (Hessol *et al.*, 2007). Data from African studies do not report an increase in risk in association with HIV-1 for that cancer (Newton *et al.*, 2001; Mbulaiteye *et al.*, 2006; Stein *et al.*, 2008a).

See Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.23.pdf, and Table 2.24 available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.24.pdf.

2.9 Other cancers

2.9.1 Cancer of the lip

A meta-analysis that included only studies that linked HIV-1/AIDS and cancer registries found an SIR for cancer of the lip of 2.80 (95%CI: 1.91–4.11), and in solid organ transplant recipients, the SIR was 30.0 (95%CI: 16.3–55.3) (Grulich *et al.*, 2007a). In the US AIDS cancer match, there was an increased risk of lip cancer, and a trend towards increasing risk across the pre- and post-AIDS periods, suggesting a link with advancing immune deficiency (Frisch *et al.*, 2001).

2.9.2 Cancer of the head and neck

A meta-analysis that included only studies that linked HIV-1/AIDS and cancer registries found an SIR for oral cavity and pharyngeal cancer of 2.32 (95%CI: 1.65–3.25), and in solid organ transplant recipients, the SIR was 3.23 (95%CI: 2.40–4.35) (Grulich *et al.*, 2007a). In people with HIV-1, HPV is particularly frequent, and it is also possible that the increase in rates is due to confounding factors, in particular, increased rates of smoking (Frisch *et al.*, 2001; Haigentz, 2005; Silverberg & Abrams, 2007).

2.9.3 Cancer in transplant patients

Data on cohort studies of transplant recipients are presented in Table 2.25 (available at http://monographs.iarc.fr/ENG/Monographs/Vol100B/100B-05-Table2.25.pdf). Transplant recipients share immune suppression with people with HIV-1, but are not at an increased risk of oncogenic sexually transmitted viruses. [The Working Group concluded that if cancer patterns are similar between these two populations, it is likely that immune deficiency is the main factor involved.]

3. Cancer in Experimental Animals

In this volume, the Working Group decided not to include a separate section on "Cancer in Experimental Animals" in the *Monographs* on viruses but rather to include description of such studies under Section 4 (below). The reasoning for this decision is explained in the General Remarks.

4. Other Relevant Data

The first indication of the AIDS pandemic came in October of 1981 from the observation that a specific type of cancer, namely Kaposi sarcoma, was occurring with increased frequency in young homosexual men (Friedman-Kien, 1981). This report was quickly followed by the recognition that the same risk group was affected by increased opportunistic infections and immunodeficiency (Gottlieb *et al.*, 1981; Siegal *et al.*, 1981), and the discovery of an AIDS-associated

virus, HIV (see Section 1). While HIV-1-infection has never been shown to transform any cell type, it is now clear that infected individuals are at a greatly increased risk for cancer development. The prevailing opinion is that HIV-1 acts indirectly, mainly through immunosuppression.

4.1 Biochemical and biological properties of relevant HIV-1 proteins

The proteins encoded by HIV-1 are illustrated in Fig. 1.1 (see Section 1.1). Several HIV-1 proteins are conserved as is the case for all other retroviruses. These include the structural proteins and viral enzymes described in Section 1.1. Although none of the proteins encoded by HIV-1 has been unequivocally shown to be directly oncogenic, some are unique to lentiviruses, and are associated with immunodeficiency, thereby indirectly promoting cancer development. In addition, there is evidence that some of the HIV-1-encoded proteins may promote cancer by other indirect mechanisms that are not dependent on immunodeficiency. Some of the proteins that are unique to HIV-1 and related immunodeficiency lentiviruses are discussed below.

4.1.1 Tat

This multifunctional protein is an important regulator of viral transcription. Tat recruits cellular transcription factors to the HIV-1 promoter. Tat interacts with the protein–kinase complexes Cdk9/cyclin T1 and Cdk2/cyclin E, with p300/CBP, p300/CBP-associated factor and hGCN5, and with protein phosphatases, and multiple other cellular proteins. Tat vastly increases the level of transcription of the HIV-1 DNA by inducing a positive feedback loop (Gatignol, 2007). It can also affect the course of HIV-1-associated disease indirectly, as it is secreted by infected cells, and can enter uninfected cells (Gupta & Mitra, 2007). Extracellular Tat has many functions, which are thought to play a major role in enabling HIV-1 to escape immune surveillance, and to act as a viral toxin contributing to the pathology of AIDS. Extracellular Tat is able to regulate cytokine–gene expression (Marone *et al.*, 2000), and immune cell hyperactivation (Kwon *et al.*, 2008). Arguments in favour of Tat being involved in oncogenesis include:

- Tat can induce apoptosis in neighbouring uninfected cells when secreted from infected cells (Li *et al.*, 1995; Westendorp *et al.*, 1995; Alimonti *et al.*, 2003). This is thought to be due to the ability of Tat to upregulate the expression of Fas ligand mRNA in macrophages and increase the susceptibility of bystander CD4-positive T cells to crosslinking-induced death. This may contribute to the massive depletion of CD4-positive T cells by apoptosis, leading to the severe immunodeficiency seen in AIDS.
- Tat has been shown to stimulate the growth of Kaposi sarcoma cells (Vogel *et al.*, 1988; Aoki & Tosato, 2007; see Section 4.3).

Nevertheless, it appears that although Tat may contribute to carcinogenesis, it is probably involved only as a cofactor. While early studies found an increased incidence of lymphomas in *Tat*-transgenic mice (Corallini *et al.*, 1993), these do not faithfully replicate the pathology of AIDS-related malignancies (Altavilla *et al.*, 2004).

Other effects of extracellular Tat include repression of major histocompatibility complex class I transcription (Weissman *et al.*, 1998), and upregulation of the expression of CXC-chemokine receptor 4 (CXCR4) on resting CD4-positive T cells (Secchiero *et al.*, 1999).

4.1.2 Rev

The HIV-1 Rev protein regulates post-transcriptional processing of viral mRNAs. Rev primarily functions to export unspliced and partially spliced viral RNAs from the nucleus into the cytoplasm (Suhasini & Reddy, 2009). Currently there is no evidence to support a direct role of this protein in the development of cancer.

A specific feature of primate immunodeficiency viruses is the presence of accessory proteins (e.g., Nef, Vif, Vpr, Vpu), which play a role in helping the virus to evade the various forms of cell-mediated antiviral resistance, thereby ensuring viral persistence and transmission (Malim & Emerman, 2008).

4.1.3 Nef

Nef is a multifunctional regulatory protein that affects HIV-1 virulence (Kestler *et al.*, 1991; Deacon *et al.*, 1995). Carriers of HIV-1 strains with Nef deletions have been identified, and they are characterized as slow progressors or long-term non-progressors. The mechanisms whereby Nef favours the development of AIDS remain unclear, but there are some interesting insights (Foster & Garcia, 2008). Nef downregulates CD4 (Garcia & Miller, 1991), thus preventing the interaction of budding virions on infected cells with CD4, which would interfere with the production of fully infectious virions. Nef also downregulates the expression of surface major histocompatibility complex class I by altering the endocytotic machinery (Blagoveshchenskaya *et al.*, 2002), thereby protecting infected cells from destruction by cytotoxic T lymphocytes (Collins *et al.*, 1998). Nef protects infected cells from apoptosis (Baur *et al.*, 1994). In addition, Nef manipulates signalling via multiple intracellular kinases, thereby enabling infected dendritic cells and macrophages to attract, and subsequently infect, permissive CD4-positive T cells (Pope *et al.*, 1994; Swingler *et al.*, 1999, 2003). Similarly to the HIV-1 Tat protein, infected cells release the Nef protein into the extracellular environment and affect neighbouring cells (Fujii *et al.*, 1996). Through this mechanism, Nef has been shown to be responsible for some B-cell defects seen in HIV-1-infected individuals by suppressing CD40-dependent immunoglobulin class-switching in bystander B cells (Qiao *et al.*, 2006). Therefore, Nef affects B-cell differentiation and antigen selection, and contributes to immune dysregulation. These findings suggest that Nef may play a role in lymphomagenesis, but this has not been demonstrated experimentally.

4.1.4 Vif

The accessory protein Vif is involved in the inhibition of cytoplasmic defenses. It is critical for *in vivo* replication of HIV-1, and for the production of infectious virions in a cell-type specific manner (Malim & Emerman, 2008). There is no evidence that Vif plays a role in AIDS-related malignancies.

4.1.5 Vpr

Truncation of the open reading frame that encodes the Vpr protein results in a slower-replicating virus (Wong-Staal *et al.*, 1987). *In vitro* analysis has demonstrated various Vpr functions that may contribute to HIV-1 pathogenesis. Vpr has been found to induce cell-cycle arrest in G2, followed by apoptosis, thereby leading to viral cytopathic effects in T cells (Andersen *et al.*, 2008). There is no evidence that Vpr plays a role in AIDS-related malignancies.

4.1.6 Vpu

The Vpu protein reduces the surface expression of CD4 of the host cell, and modulates the subcellular compartmentalization of the host membrane protein tetherin to help promote viral dissemination and replication (Malim &

Emerman, 2008). There is no evidence that Vpu plays a role in AIDS-related malignancies.

4.2 HIV-1, host immune system, and carcinogenesis

4.2.1 Comparison of AIDS-related and transplantation-associated tumours

(a) Immunosuppression

Although individuals with AIDS and those with iatrogenic immunosuppression following organ transplantation have immunodeficiency in common, the immunological abnormalities appear to differ significantly between these two conditions. A direct comparison is difficult because the immune dysregulation in both groups can be qualitatively and quantitatively heterogeneous. Among transplant recipients, immunodeficiency depends on multiple factors. The immunosuppressive regimen can be a major determinant of the immunological dysfunction, and these regimens vary according to the organ transplanted (for example, there is more tolerance for rejection in kidney than in heart/lung transplants), age, and time (as therapeutic approaches have evolved). Cytotoxic CD8-positive T-cell responses, in particular to EBV, have been recognized as a common immunological defect in organ transplant recipients with lymphoproliferative diseases (Kyaw-Tanner *et al.*, 1994). One study that focused on immune function in renal transplant patients found that the most common abnormality was B-cell lymphopenia (seen in 85% of the patients), followed by reduced production of reactive oxygen species in neutrophils (in 63%), NK-cell lymphopenia (in 50%), and abnormal lymphocyte mitogen response (in 49%). A low CD4 count was only found in about a quarter of the patients (Hutchinson *et al.*, 2003). A characteristic feature of AIDS is CD4 deficiency, which is well documented to be central to disease progression, but in addition, there is B-lymphocyte hyperactivation with hypergammaglobulinaemia, and increased release of soluble markers from activated cells (De Milito, 2004). However, AIDS patients, in particular those with advanced disease, suffer from a severe loss of memory B cells, and an impaired long-term serological memory (Titanji *et al.*, 2006). In HIV-1-infected individuals, EBV-specific cytotoxic T cells have been found in normal numbers, but their functional capacity decreases as AIDS progresses until, finally, immunological collapse occurs (Kersten *et al.*, 1997; van Baarle *et al.*, 2001). Thus, the immune dysfunction in AIDS patients and transplant recipients is heterogeneous, and although it is different between these two categories, there is also overlap in immunological defects in selected groups of individuals.

(b) Cancer types

An obvious similarity between post-transplant and AIDS patients is the increased incidence in B-cell lymphomas, which often have plasmacytoid differentiation, and are associated with EBV. However, there are significant differences in lymphoma subtypes (Raphael & Knowles, 1990; Swerdlow *et al.*, 2008). Specific differences include more frequent high-grade lymphomas in the setting of HIV-1 infection, and a more frequent EBV association and polymorphic lesions in transplant recipients (see Table 4.1).

The second important malignancy that is greatly increased in incidence in HIV-1-infected individuals and transplant recipients is Kaposi sarcoma. This is the most common cancer in patients with HIV-1, and an AIDS-defining condition. A recent study of renal transplant recipients reported a more than 20-fold increased incidence of Kaposi sarcoma compared with the general population (Kasiske *et al.*, 2004). While Kaposi sarcoma tends to be more aggressive in patients with AIDS than in those with other immunodeficiencies, there are no differences in histological, immunophenotypic, virological or

Table 4.1 Major categories of lymphoproliferations associated with acquired immunodeficiency

	Lymphoma subtype and frequency	Approximate relative frequency of lymphoma subtype	Approximate EBV frequency (LMP-1 positivity)	Other common oncogenic alterations
AIDS-related lymphomas	Burkitt and Burkitt-like lymphoma	30%	30–50% (Rare)	c-Myc, p53, BCL-6
	DLBCL-Centroblastic	25%	30% (Rare)	BCL-6
	DLBCL-Immunoblastic[a]	22%	> 80% (Common)	
	Primary effusion lymphoma[a]	2–4%	70–90% (None)	KSHV infection
	KSHV-positive extracavitary lymphoma[a]	2–4%	> 80% (Unknown)	KSHV infection
	Polymorphic B-cell lymphoma (PTLD-like) [a]	Rare	40% (Unknown)	Unknown
	Plasmablastic lymphoma of oral cavity[a]	Rare	80% (Rare)	Unknown
	Primary CNS lymphomas[a]	10–15%	> 95% (Common)	BCL-6
Post-transplant lymphoproliferative disorders	Plasmacytic hyperplasia	30%	> 90% (Common)	None
	Polymorphic PTLD	50%	> 90% (Common)	BCL-6
	Monomorphic PTLD (non-Hodgkin lymphoma/ multiple myeloma)	20%	60% (Variable)	BCL-6, c-Myc, N-Ras, p53

[a] These lymphoma subtypes occur much more frequently or almost exclusively in HIV-1-infected individuals, and share frequent EBV-positivity and plasmacytoid differentiation.
DLBCL, diffuse large B-cell lymphoma; PTLD, post-transplant lymphoproliferative disorder; CNS, central nervous system
Adapted from Cesarman & Chadburn (2007)

molecular features of AIDS-associated and post-transplant-related Kaposi sarcoma. Both types may regress (but they not always do) after reconstitution of the immune response.

4.2.2 Immune dysfunction and carcinogenesis

The importance of immunodeficiency is easy to understand in the context of virus-associated malignancies. The three most common cancers in HIV-1-infected individuals are Kaposi sarcoma (caused by KSHV), lymphomas (many EBV-positive), and cervical and anogenital carcinomas associated with HPV infection. These infectious etiologies explain the reasons as to why the associated cancers are greatly increased in individuals with immunodeficiencies. Infection by "oncogenic" viruses is much more common than the diseases caused by those viruses, and the incidence and severity of these cancers is greatly increased by immunodeficiency. Viruses have evolved to survive through three essential properties: they can go from host to host (transmission), get in and out of the host cells (lytic replication), and remain in the host in live cells without being recognized by its immune system (latency).

Immune dysregulation *per se* may facilitate cancer development. A clear example of this phenomenon is the B-cell hyperactivation manifested by lymphadenopathies seen in HIV-1-infected patients. Lymph nodes from these patients are characterized by a florid follicular hyperplasia, where the germinal centres are greatly enlarged. The germinal centre reaction is where B cells undergo somatic hypermutation of immunoglobulin genes and class-switch recombination. These are dangerous processes in that if uncorrected mistakes are made, oncogenic genetic alterations can occur. These mistakes can lead to translocations involving the *cMyc* oncogene and

mutations in the p53 tumour-suppressor gene, giving rise to Burkitt lymphomas.

4.3 HIV-1 and other infectious agents associated with human cancers

The HIV-1 genome is not present in cancer cells, which is in contrast to what is observed with infectious agents that are directly oncogenic. Therefore, any interaction between virus and host is indirect. The interaction between HIV-1 and some of the other infectious agents reviewed in this volume is discussed below.

4.3.1 KSHV

(a) In vivo

KSHV and HIV-1 are not present in the same cells. In germinal centres of patients with HIV-1 infection, HIV-1 is frequently in dendritic cells and T cells (Burton *et al.*, 2002), whereas KSHV is present in mantle zone B cells (Dupin *et al.*, 1999; Amin *et al.*, 2003). In Kaposi sarcoma lesions, HIV-1 is localized to tumour-associated macrophages, whereas KSHV is in the Kaposi sarcoma spindle cells (Gessain & Duprez, 2005).

(b) At the molecular level

The only HIV-1 protein for which there is experimental evidence for a potential role in Kaposi sarcoma is Tat. Biologically active Tat is released by HIV-1-infected cells (Chang *et al.*, 1997), and it can enter readily into neighbouring infected and uninfected cells (Gupta & Mitra, 2007), a property that has also been found for other cationic peptides. Three endocytic pathways appear to account for this process: macropinocytosis, clathrin-mediated endocytosis, and caveolae/lipid-raft-mediated endocytosis (Duchardt *et al.*, 2007). This indicates that although HIV-1 does not directly infect tumour cells, it has the potential to produce Tat, which may then enter the tumour cells, although this phenomenon has not been demonstrated to occur *in vivo*. Nevertheless, the potential effects of Tat have prompted investigators to test a role for HIV-1, and specifically the Tat protein, in Kaposi sarcoma development (Aoki & Tosato, 2007). Tat binds and activates the Flk-1/kinase insert domain receptor (Flk-1/KDR) (Albini *et al.*, 1996; Morini *et al.*, 2000). Transgenic mice expressing HIV-1 Tat were found to develop vascular lesions that resembled Kaposi sarcoma (Vogel *et al.*, 1988). Several studies found that Tat has an effect on Kaposi sarcoma cell lines, increasing proliferation *in vitro*, and growth in mice (Ensoli *et al.*, 1990; Barillari *et al.*, 1999a, b; Morini *et al.*, 2000). However, when cells are removed from Kaposi sarcoma lesions and expanded *in vitro*, they lose the KSHV genome, therefore the question remains whether the "Kaposi sarcoma" cells lacking KSHV used in most of these studies represent a valid model for Kaposi sarcoma.

More recently, investigators have addressed the role of HIV-1 directly on KSHV infection. Individuals with Kaposi sarcoma and HIV-1 infection had a 4-fold higher KSHV viral load in serum than those with Kaposi sarcoma without HIV-1 (Chandra *et al.*, 2003). HIV-1 can induce lytic replication of KSHV by upregulating the expression of the replication and transcription activator (Rta) protein, which is the main regulator of the lytic switch in this virus (Varthakavi *et al.*, 2002). The HIV-1 Tat protein was shown to enhance the entry of KSHV into endothelial cells, thereby promoting KSHV cellular transmission (Aoki & Tosato, 2004). Conversely, KSHV can increase HIV-1 replication in T cells, monocytic cells, and endothelial cells (Mercader *et al.*, 2001; Caselli *et al.*, 2005). Thus, there is evidence that HIV-1 and KSHV may enhance each other's replication, which could be a mechanism whereby HIV-1 can act as a cofactor in the complex process of Kaposi sarcomagenesis.

4.3.2 EBV

There is some experimental evidence for a direct role for HIV-1 in EBV-related lymphomagenesis apart from the epidemiological associations, but most of the increase in incidence is probably due to immune dysfunction. As mentioned above, HIV-1 is not found to be present in lymphoma cells, but the virus can infect primary human B cells, and activate the expression of endogenous EBV (Astrin & Laurence, 1992). It is also possible that HIV-1-encoded proteins like Tat affect the growth of EBV-immortalized B cells (Colombrino *et al.*, 2004). Several studies where interactions between HIV-1 and EBV have been tested involve the forced expression of viral proteins or infection with both viruses of cells that are not naturally co-infected (Kenney *et al.*, 1988; Scala *et al.*, 1993; Zhang *et al.*, 1997).

4.3.3 HPV

The third most common malignancy in HIV-1-positive individuals, and an AIDS-defining condition, is cervical carcinoma associated with HPV infection. Anogenital intraepithelial neoplasms and carcinomas are also increased in frequency, and so are skin cancers associated with HPV infection. Infection of HPV-infected cells with HIV-1, or addition of Tat, induces transcriptional activation of the integrated HPV (Vernon *et al.*, 1993; Dolei *et al.*, 1999), and proliferation of infected cells (Kim *et al.*, 2008). However, a direct interaction between HIV-1 and HPV has not been demonstrated to occur *in vivo*.

4.3.4 HBV and HCV

HIV-1-infected individuals have a greatly increased incidence of infection with HBV and HCV, and are therefore at risk for HCC (Grulich *et al.*, 2007a). Although interactions between HBV and HIV-1 in co-infection experiments *in vitro* have been demonstrated (Barak *et al.*, 2001; Gómez-Gonzalo *et al.*, 2001), these have not been shown to occur *in vivo*.

4.4 Animal models for HIV-1-associated cancers

Because HIV-1, like the oncogenic herpesviruses EBV and KSHV, is species-specific, there are no ideal animal models for HIV-1-associated cancers. Four main approaches have been explored: a) the analysis of malignancies occurring in animals infected with the corresponding animal virus (i.e., SIV, simian EBV, etc); b) xenograft studies; c) the use of transgenic mice expressing selected viral oncogenes; and d) the use of chimeric mice infected with human viruses.

4.4.1 Lymphomas in animals infected with species-specific viruses

Lymphomas occurring in HIV-1-infected individuals have been compared with those in SIV-infected macaques (Baskin *et al.*, 2001). Like in humans, most simian AIDS-associated lymphomas are of the B-cell type, and may be classified as either immunoblastic/large-cell lymphoma or Burkitt-like lymphoma. Furthermore, these simian lymphomas tend to be morphologically indistinguishable from the same lymphomas occurring in humans. The systemic simian AIDS-associated lymphomas in rhesus monkeys frequently contain rhesus lymphocryptovirus (LCV), while simian AIDS-associated lymphomas in cynomolgus monkeys contain herpesvirus Macaca fascicularis 1 (HVMF-1), both of which are homologues of EBV (Li *et al.*, 1994; Habis *et al.*, 1999), thereby replicating virological AIDS-related lymphomas in humans. A rhesus monkey rhadinovirus that is closely related to KSHV has also been described (Desrosiers *et al.*, 1997). Although lymphoid hyperplasias and sometimes extranodal lymphomas are seen in some of these

monkeys (Wong *et al.*, 1999; Orzechowska *et al.*, 2008), neither primary effusion lymphoma or Kaposi sarcoma have been observed.

The similarities between simian and human AIDS-related lymphomas make these animal models very attractive for mechanistic studies, but they are limited by the fact that the incidence of lymphoma is relatively low. While this low incidence is not dissimilar to that seen in humans, it makes experiments with the monkeys challenging and expensive. For this reason, mouse models have been developed. The murine gammaherpesvirus 68 (gamma-HV68) is a member of the gammaherpesvirus family related to EBV and KSHV, and has been very useful in studies aimed at understanding the mechanisms of viral persistence and replication *in vivo*, and the role of several viral proteins. Lymphoproliferative disease, including lymphoma, has been reported in association with gamma-HV68 infection in wild-type mice, but at a low incidence (9%), and after a prolonged incubation period (up to 3 years) (Sunil-Chandra *et al.*, 1994). More recently, infection with gamma-HV68 of beta2-microglobulin-deficient mice was found to induce an atypical lymphoid hyperplasia that is similar to post-transplantation lymphoproliferative disease, and this model has been used to evaluate the function of some viral genes in pathogenesis (Tarakanova *et al.*, 2005, 2008).

4.4.2 Xenograft studies

Transplanting human cancers into immunodeficient mice is a common approach to evaluate the biology and possible treatment strategies for malignancies. Such models of HIV-1-related cancers include those for EBV-associated lymphomas (Nilsson *et al.*, 1977; Mosier *et al.*, 1990; Mosier, 1991), primary effusion lymphoma (Picchio *et al.*, 1997; Staudt *et al.*, 2004; Keller *et al.*, 2006), and Kaposi sarcoma (Masood *et al.*, 1997; Barillari *et al.*, 1999b; Mutlu *et al.*, 2007). Most Kaposi sarcoma models are imperfect, however, because the cells from Kaposi sarcoma lesions lose the KSHV genome. In an attempt to resolve this, murine and human haematopoietic precursors were infected with a bacterial artificial chromosome containing the entire KSHV genome (KSHV Bac36), and spindle cell sarcomas were obtained, which had some interesting features in common with Kaposi sarcoma (An *et al.*, 2006; Mutlu *et al.*, 2007).

4.4.3 Viral malignancies in chimeric mice

Several attempts have been made to develop a mouse model of herpesviral malignancy by infecting chimeric mice. One of the first such studies used BNX immunodeficient mice to graft human B cells, followed by injection of EBV particles, which led to the development of rapidly fatal, polyclonal lymphomas (Dosch *et al.*, 1991). More recently, immunodeficient mice reconstituted with human haematopoietic stem cells followed by EBV infection have been used to evaluate immune responses to EBV (Melkus *et al.*, 2006); some of these mice also developed B-cell lymphoproliferative disorders (Yajima *et al.*, 2008). Immunodeficient mice transplanted with human fetal thymus and liver grafts have been shown to be susceptible to KSHV infection. There was no effect of HIV-1 on KSHV viral replication, or vice versa (Dittmer *et al.*, 1999). In addition, human haematopoietic stem cells have been infected with KSHV before transfer into immunodeficient mice (Wu *et al.*, 2006), but these KSHV-infected mice did not develop angioproliferative or lymphoproliferative diseases. This may be due to the fact that these systems do not fully replicate the complexity of Kaposi sarcoma and lymphoma development in humans, or that these diseases would develop in only very rare occasions in mice, as is the case with KSHV-infected people. In contrast, injection of KSHV in human skin engrafted on SCID mice was found to induce Kaposi-sarcoma-like lesions (Foreman *et al.*, 2001).

4.5 Synthesis

HIV-1 increases the cancer risk in humans indirectly, primarily by immunosuppression.

Many of the AIDS-defining malignancies have a different primary cause, e.g. EBV, HPV, and KSHV.

In addition to HIV-1-mediated immunosuppression, other aspects of the HIV-1 biology contribute to the increased cancer incidence in AIDS patients. Suggested mechanisms include HIV-1-mediated immune dysregulation, in particular B-cell hyperactivation, and perhaps effects of the secreted HIV-1 Tat protein. However, unlike what is known about other cancer-associated viruses, there is no evidence that HIV-1-infection by itself leads to cell transformation or immortalization.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of infection with HIV-1. Infection with HIV-1 causes cancer of the cervix, anus, and conjunctiva, and Kaposi sarcoma, non-Hodgkin lymphoma, and Hodgkin lymphoma. Also, a positive association has been observed between infection with HIV-1 and cancer of the vulva and vagina, penis, and hepatocellular carcinoma, and non-melanoma skin cancer

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

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