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
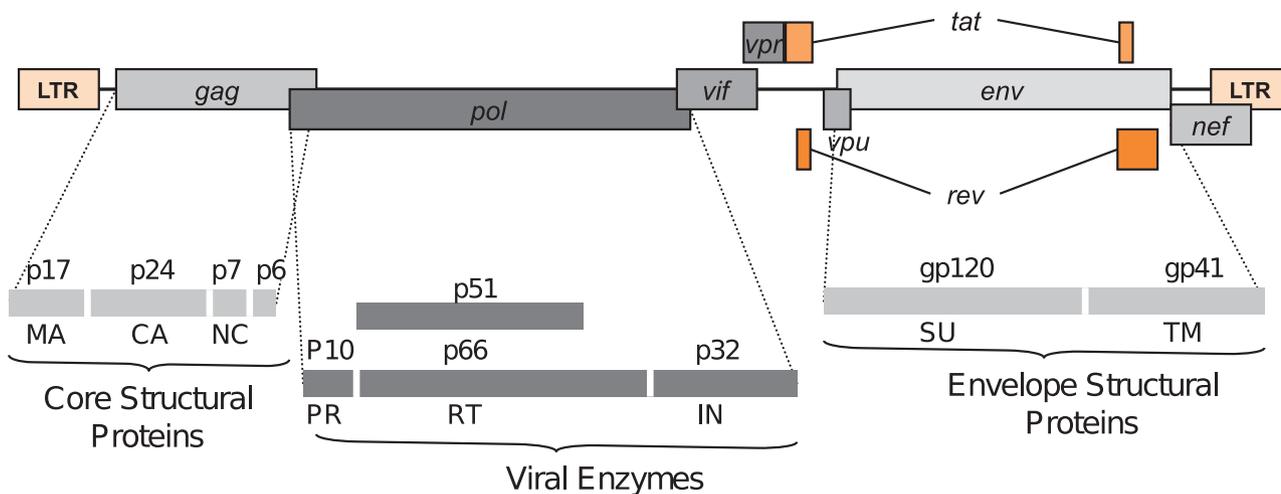
Prepared by the Working Group

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 re-viewed (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 onco-genic. 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 path-ways appear to account for this process: macro-pinocytosis, 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 regu-lator 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 trans-mission (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 mecha-nism 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 immuno-suppression, other aspects of the HIV-1 biology contribute to the increased cancer incidence in AIDS patients. Suggested mechanisms include HIV-1-mediated immune dysregula-tion, 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 trans-formation 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).*

References

Aboulafia DM, Ratner L, Miles SA, Harrington WJ JrAIDS Associated Malignancies Clinical Trials Consortium. (2006). Antiviral and immunomodulatory treatment for AIDS-related primary central nervous system lymphoma: AIDS Malignancies Consortium pilot study 019. *Clin Lymphoma Myeloma*, 6: 399–402. doi:10.3816/CLM.2006.n.017 PMID:16640817

Ahdieh L, Gange SJ, Greenblatt R *et al.* (2000). Selection by indication of potent antiretroviral therapy use in a large cohort of women infected with human immu-nodeficiency virus. *Am J Epidemiol*, 152: 923–933. doi:10.1093/aje/152.10.923 PMID:11092434

Albini A, Soldi R, Giunciuglio D *et al.* (1996). The angio-genesis induced by HIV-1 tat protein is mediated by the Flk-1/KDR receptor on vascular endothelial cells. *Nat Med*, 2: 1371–1375. doi:10.1038/nm1296-1371 PMID:8946838

Alimonti JB, Ball TB, Fowke KR (2003). Mechanisms of CD4+ T lymphocyte cell death in human immuno-deficiency virus infection and AIDS. *J Gen Virol*, 84: 1649–1661. doi:10.1099/vir.0.19110-0 PMID:12810858

Altavilla G, Caputo A, Trabanelli C *et al.* (2004). Prevalence of liver tumours in HIV-1 tat-transgenic mice treated with urethane. *Eur J Cancer*, 40: 275–283. doi:10.1016/j.ejca.2003.08.025 PMID:14728943

Amin HM, Medeiros LJ, Manning JT, Jones D (2003). Dissolution of the lymphoid follicle is a feature of the HHV8+ variant of plasma cell Castleman's disease. *Am J Surg Pathol*, 27: 91–100. doi:10.1097/00000478-200301000-00010 PMID:12502931

An FQ, Folarin HM, Compitello N *et al.* (2006). Long-term-infected telomerase-immortalized endothe-lial cells: a model for Kaposi's sarcoma-associated herpesvirus latency in vitro and in vivo. *J Virol*, 80: 4833–4846. doi:10.1128/JVI.80.10.4833-4846.2006 PMID:16641275

Andersen JL, Le Rouzic E, Planelles V (2008). HIV-1 Vpr: mechanisms of G2 arrest and apoptosis. *Exp Mol Pathol*, 85: 2–10. doi:10.1016/j.yexmp.2008.03.015 PMID:18514189

Antinori A, Larocca LM, Fassone L *et al.* (1999). HHV-8/KSHV is not associated with AIDS-related primary central nervous system lymphoma. *Brain Pathol*, 9: 199–208. doi:10.1111/j.1750-3639.1999.tb00218.x PMID:10219737

Aoki Y & Tosato G (2004). HIV-1 Tat enhances Kaposi sarcoma-associated herpesvirus (KSHV) infectivity. *Blood*, 104: 810–814. doi:10.1182/blood-2003-07-2533 PMID:15073028

Aoki Y & Tosato G (2007). Interactions between HIV-1 Tat and KSHV. *Curr Top Microbiol Immunol*, 312: 309–326. doi:10.1007/978-3-540-34344-8_12 PMID:17089803

Arzoo KK, Bu X, Espina BM *et al.* (2004). T-cell lymphoma in HIV-infected patients. *J Acquir Immune Defic Syndr*, 36: 1020–1027. doi:10.1097/00126334-200408150-00004 PMID:15247554

Ascoli V, Signoretti S, Onetti-Muda A *et al.* (2001). Primary effusion lymphoma in HIV-infected patients with multicentric Castleman's disease. *J Pathol*, 193: 200–209. doi:10.1002/1096-9896(200102)193:2<200::AID-PATH773>3.0.CO;2-L PMID:11180167

Astrin SM & Laurence J (1992). Human immunodefi-ciency virus activates c-myc and Epstein-Barr virus in

human B lymphocytes. *Ann N Y Acad Sci*, 651: 1 CDS B Cells i422–432. doi:10.1111/j.1749-6632.1992.tb24642.x PMID:1318011

Ateenyi-Agaba C (1995). Conjunctival squamous-cell carcinoma associated with HIV infection in Kampala, Uganda. *Lancet*, 345: 695–696. doi:10.1016/S0140-6736(95)90870-6 PMID:7885126

Babel N, Vergopoulos A, Trappe RU *et al.* (2007). Evidence for genetic susceptibility towards development of post-transplant lymphoproliferative disorder in solid organ recipients. *Transplantation*, 84: 387–391. doi:10.1097/01.tp.0000269617.60751.c4 PMID:17700165

Baggaley RF, White RG, Boily MC (2008). Systematic review of orogenital HIV-1 transmission probabilities. *Int J Epidemiol*, 37: 1255–1265. doi:10.1093/ije/dyn151 PMID:18664564

Baiocchi OC, Colleoni GW, Navajas EV *et al.* (2002). Impact of highly active antiretroviral therapy in the treatment of HIV-infected patients with systemic non-Hodgkin's lymphoma. *Acta Oncol*, 41: 192–196. doi:10.1080/028418602753669599 PMID:12102166

Barak O, Aronheim A, Shaul Y (2001). HBV X protein targets HIV Tat-binding protein 1. *Virology*, 283: 110–120. doi:10.1006/viro.2001.0883 PMID:11312667

Barclay LR, Buskin SE, Kahle EM, Aboulafia DM (2007). Clinical and immunologic profile of AIDS-related lymphoma in the era of highly active antiretroviral therapy. *Clin Lymphoma Myeloma*, 7: 272–279. doi:10.3816/CLM.2007.n.002 PMID:17324334

Barillari G, Sgadari C, Fiorelli V *et al.* (1999a). The Tat protein of human immunodeficiency virus type-1 promotes vascular cell growth and locomotion by engaging the alpha5beta1 and alphavbeta3 integrins and by mobilizing sequestered basic fibroblast growth factor. *Blood*, 94: 663–672. PMID:10397733

Barillari G, Sgadari C, Palladino C *et al.* (1999b). Inflammatory cytokines synergize with the HIV-1 Tat protein to promote angiogenesis and Kaposi's sarcoma via induction of basic fibroblast growth factor and the alpha v beta 3 integrin. *J Immunol*, 163: 1929–1935. PMID:10438928

Barré-Sinoussi F, Chermann JC, Rey F *et al.* (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*, 220: 868–871. doi:10.1126/science.6189183 PMID:6189183

Baskin GB, Cremer KJ, Levy LS (2001). Comparative pathobiology of HIV- and SIV-associated lymphoma. *AIDS Res Hum Retroviruses*, 17: 745–751. doi:10.1089/088922201750237013 PMID:11429114

Baur AS, Sawai ET, Dazin P *et al.* (1994). HIV-1 Nef leads to inhibition or activation of T cells depending on its intracellular localization. *Immunity*, 1: 373–384. doi:10.1016/1074-7613(94)90068-X PMID:7882168

Bedimo R, Chen RY, Accortt NA *et al.* (2004). Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002. *Clin Infect Dis*, 39: 1380–1384. doi:10.1086/424883 PMID:15494916

Beral V & Newton R (1998). Overview of the epidemiology of immunodeficiency-associated cancers. *J Natl Cancer Inst Monogr*, 23: 1–6. PMID:9709294

Besson C, Goubar A, Gabarre J *et al.* (2001). Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood*, 98: 2339–2344. doi:10.1182/blood.V98.8.2339 PMID:11588028

Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EAHIV/AIDS Cancer Match Study. (2007). AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst*, 99: 962–972. doi:10.1093/jnci/djm010 PMID:17565153

Biggar RJ, Engels EA, Frisch M, Goedert JJAIDS Cancer Match Registry Study Group. (2001). Risk of T-cell lymphomas in persons with AIDS. *J Acquir Immune Defic Syndr*, 26: 371–376. doi:10.1097/00042560-200104010-00015 PMID:11317081

Biggar RJ, Horm J, Goedert JJ, Melbye M (1987). Cancer in a group at risk of acquired immunodeficiency syndrome (AIDS) through 1984. *Am J Epidemiol*, 126: 578–586. PMID:3631049

Biggar RJ, Jaffe ES, Goedert JJ *et al.* (2006). Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood*, 108: 3786–3791. doi:10.1182/blood-2006-05-024109 PMID:16917006

Blagoveshchenskaya AD, Thomas L, Feliciangeli SF *et al.* (2002). HIV-1 Nef downregulates MHC-I by a PACS-1- and PI3K-regulated ARF6 endocytic pathway. *Cell*, 111: 853–866. doi:10.1016/S0092-8674(02)01162-5 PMID:12526811

Bleul CC, Wu L, Hoxie JA *et al.* (1997). The HIV coreceptors CXCR4 and CCR5 are differentially expressed and regulated on human T lymphocytes. *Proc Natl Acad Sci USA*, 94: 1925–1930. doi:10.1073/pnas.94.5.1925 PMID:9050881

Bonnet F, Balestre E, Thiébaut R *et al.*Groupe d'Epidemiologie Clinique du SIDA en Aquitaine. (2006a). Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. *Clin Infect Dis*, 42: 411–417. doi:10.1086/499054 PMID:16392091

Bonnet F, Jouvencel AC, Parrens M *et al.* (2006b). A longitudinal and prospective study of Epstein-Barr virus load in AIDS-related non-Hodgkin lymphoma. *J Clin Virol*, 36: 258–263. doi:10.1016/j.jcv.2006.04.005 PMID:16762591

Bossolasco S, Cinque P, Ponzoni M *et al.* (2002). Epstein-Barr virus DNA load in cerebrospinal fluid and plasma of patients with AIDS-related lymphoma. *J Neurovirol*, 8: 432–438. doi:10.1080/13550280260422730 PMID:12402169

Bower M, Gazzard B, Mandalia S *et al.* (2005). A prognostic index for systemic AIDS-related non-Hodgkin

lymphoma treated in the era of highly active antiretroviral therapy. *Ann Intern Med*, 143: 265–273. PMID:16103470

Bower M, Powles T, Nelson M *et al.* (2003). HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS*, 17: 371–375. doi:10.1097/00002030-200302140-00011 PMID:12556691

Bower M, Powles T, Nelson M *et al.* (2006). Highly active antiretroviral therapy and human immunodeficiency virus-associated primary cerebral lymphoma. *J Natl Cancer Inst*, 98: 1088–1091. doi:10.1093/jnci/djj302 PMID:16882946

Bower M, Powles T, Newsom-Davis T *et al.* (2004). HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? *J Acquir Immune Defic Syndr*, 37: 1563–1565. doi:10.1097/00126334-200412150-00004 PMID:15577408

Breen EC, Boscardin WJ, Detels R *et al.* (2003). Non-Hodgkin's B cell lymphoma in persons with acquired immunodeficiency syndrome is associated with increased serum levels of IL10, or the IL10 promoter -592 C/C genotype. *Clin Immunol*, 109: 119–129. doi:10.1016/S1521-6616(03)00214-6 PMID:14597210

Breen EC, Epeldegui M, Boscardin WJ *et al.* (2005). Elevated levels of soluble CD44 precede the development of AIDS-associated non-Hodgkin's B-cell lymphoma. *AIDS*, 19: 1711–1712. doi:10.1097/01.aids.0000184924.04983.7c PMID:16184051

Brink NS, Sharvell Y, Howard MR *et al.* (1998). Detection of Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus DNA in CSF from persons infected with HIV who had neurological disease. *J Neurol Neurosurg Psychiatry*, 65: 191–195. doi:10.1136/jnnp.65.2.191 PMID:9703169

Broder CC & Collman RG (1997). Chemokine receptors and HIV. *J Leukoc Biol*, 62: 20–29. PMID:9225988

Bukrinskaya AG (2004). HIV-1 assembly and maturation. *Arch Virol*, 149: 1067–1082. doi:10.1007/s00705-003-0281-8 PMID:15168195

Bunnell R, Ekwaru JP, Solberg P *et al.* (2006). Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*, 20: 85–92. doi:10.1097/01.aids.0000196566.40702.28 PMID:16327323

Burton GF, Keele BF, Estes JD *et al.* (2002). Follicular dendritic cell contributions to HIV pathogenesis. *Semin Immunol*, 14: 275–284. doi:10.1016/S1044-5323(02)00060-X PMID:12163303

Butler DM, Smith DM, Cachay ER *et al.* (2008). Herpes simplex virus 2 serostatus and viral loads of HIV-1 in blood and semen as risk factors for HIV transmission among men who have sex with men. *AIDS*, 22: 1667–1671. doi:10.1097/QAD.0b013e32830bfed8 PMID:18670228

Carbone A, Gloghini A, Larocca LM *et al.* (1999). Human immunodeficiency virus-associated Hodgkin's disease derives from post-germinal center B cells. *Blood*, 93: 2319–2326. PMID:10090942

Carrieri MP, Pradier C, Piselli P *et al.* (2003). Reduced incidence of Kaposi's sarcoma and of systemic non-hodgkin's lymphoma in HIV-infected individuals treated with highly active antiretroviral therapy. *Int J Cancer*, 103: 142–144. doi:10.1002/ijc.10790 PMID:12455069

Caselli E, Galvan M, Cassai E *et al.* (2005). Human herpesvirus 8 enhances human immunodeficiency virus replication in acutely infected cells and induces reactivation in latently infected cells. *Blood*, 106: 2790–2797. doi:10.1182/blood-2005-04-1390 PMID:15976177

Castilla J, Del Romero J, Hernando V *et al.* (2005). Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr*, 40: 96–101. doi:10.1097/01.qai.0000157389.78374.45 PMID:16123689

CDC1985). http://wonder.cdc.gov/wonder/help/aids/mmwr-06-28-1985.html

Cesarman E, Chadburn A (2007). *Lymphoproliferations and immunodeficiency*. In: *Molecular Pathology in Clinical Practice*. Leonard DGB, Bagg A, editors. New York: Springer-Verlag, pp. 373–382.

Chandra A, Demirhan I, Massambu C *et al.* (2003). Cross-talk between human herpesvirus 8 and the transactivator protein in the pathogenesis of Kaposi's sarcoma in HIV-infected patients. *Anticancer Res*, 23: 1B723–728. PMID:12680174

Chang HC, Samaniego F, Nair BC *et al.* (1997). HIV-1 Tat protein exits from cells via a leaderless secretory pathway and binds to extracellular matrix-associated heparan sulfate proteoglycans through its basic region. *AIDS*, 11: 1421–1431. doi:10.1097/00002030-199712000-00006 PMID:9342064

Chaturvedi AK, Pfeiffer RM, Chang L *et al.* (2007). Elevated risk of lung cancer among people with AIDS. *AIDS*, 21: 207–213. doi:10.1097/QAD.0b013e3280118fca PMID:17197812

Chiao EY, Giordano TP, Richardson P, El-Serag HB (2008). Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol*, 26: 474–479. doi:10.1200/JCO.2007.14.2810 PMID:18202423

Chiappini E, Galli L, Tovo PA *et al.*Italian Register for HIV Infection in Children. (2007). Cancer rates after year 2000 significantly decrease in children with perinatal HIV infection: a study by the Italian Register for HIV Infection in Children. *J Clin Oncol*, 25: 97–101. doi:10.1200/JCO.2006.06.6506 PMID:17194910

Clavel F, Guyader M, Guétard D *et al.* (1986). Molecular cloning and polymorphism of the human immune deficiency virus type 2. *Nature*, 324: 691–695. doi:10.1038/324691a0 PMID:3025743

Clayton A & Mughal T (2004). The changing face of HIV-associated lymphoma: what can we learn about optimal therapy inl the post highly active antiretroviral therapy era? *Hematol Oncol*, 22: 111–120. doi:10.1002/hon.735 PMID:15991221

Clifford GM, Gonçalves MAG, Franceschi SHPV and HIV Study Group. (2006). Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*, 20: 2337–2344. doi:10.1097/01.aids.0000253361.63578.14 PMID:17117020

Clifford GM, Polesel J, Rickenbach M *et al.*Swiss HIV Cohort. (2005). Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*, 97: 425–432. doi:10.1093/jnci/dji072 PMID:15770006

Clifford GM, Rickenbach M, Polesel J *et al.*Swiss HIV Cohort. (2008). Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS*, 22: 2135–2141. doi:10.1097/QAD.0b013e32831103ad PMID:18832877

Coakley E, Petropoulos CJ, Whitcomb JM (2005). Assessing chemokine co-receptor usage in HIV. *Curr Opin Infect Dis*, 18: 9–15. doi:10.1097/00001432-200502000-00003 PMID:15647694

Collins KL, Chen BK, Kalams SA *et al.* (1998). HIV-1 Nef protein protects infected primary cells against killing by cytotoxic T lymphocytes. *Nature*, 391: 397–401. doi:10.1038/34929 PMID:9450757

Colombrino E, Rossi E, Ballon G *et al.* (2004). Human immunodeficiency virus type 1 Tat protein modulates cell cycle and apoptosis in Epstein-Barr virus-immortalized B cells. *Exp Cell Res*, 295: 539–548. doi:10.1016/j.yexcr.2004.01.018 PMID:15093750

Connor EM, Sperling RS, Gelber R *et al.* (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*, 331: 1173–1180. doi:10.1056/NEJM199411033311801 PMID:7935654

Cooper ER, Charurat M, Mofenson L *et al.*Women and Infants' Transmission Study Group. (2002). Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*, 29: 484–494. PMID:11981365

Corallini A, Altavilla G, Pozzi L *et al.* (1993). Systemic expression of HIV-1 tat gene in transgenic mice induces endothelial proliferation and tumors of different histotypes. *Cancer Res*, 53: 5569–5575. PMID:8221699

Coté TR, Manns A, Hardy CR *et al.*AIDS/Cancer Study Group. (1996). Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. *J Natl Cancer Inst*, 88: 675–679. doi:10.1093/jnci/88.10.675 PMID:8627644

Coutsoudis A, Dabis F, Fawzi W *et al.*Breastfeeding and HIV International Transmission Study Group. (2004). Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis*, 189: 2154–2166. doi:10.1086/420834 PMID:15181561

D'Souza G, Wiley DJ, Li X *et al.* (2008). Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr*, 48: 491–499. doi:10.1097/QAI.0b013e31817aebfe PMID:18614927

Dal Maso L, Franceschi S, Polesel J *et al.*Cancer and AIDS Registy Linkage Study. (2003a). Risk of cancer in persons with AIDS in Italy, 1985–1998. *Br J Cancer*, 89: 94–100. doi:10.1038/sj.bjc.6601017 PMID:12838307

Dal Maso L, Polesel J, Serraino D *et al.*Cancer and AIDS Registries Linkage (CARL) Study. (2009). Pattern of cancer risk in persons with AIDS in Italy in the HAART era. *Br J Cancer*, 100: 840–847. doi:10.1038/sj.bjc.6604923 PMID:19223894

Dal Maso L, Polesel J, Serraino D, Franceschi SCancer and AIDS Registry Linkage Study. (2003b). Lung cancer in persons with AIDS in Italy, 1985–1998. *AIDS*, 17: 2117–2119. doi:10.1097/00002030-200309260-00013 PMID:14502015

Daling JR, Weiss NS, Hislop TG *et al.* (1987). Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med*, 317: 973–977. doi:10.1056/NEJM198710153171601 PMID:2821396

de Koning MN, Waddell K, Magyezi J *et al.* (2008). Genital and cutaneous human papillomavirus (HPV) types in relation to conjunctival squamous cell neoplasia: a case-control study in Uganda. *Infect Agent Cancer*, 3: 12 doi:10.1186/1750-9378-3-12 PMID:18783604

De Luca A, Antinori A, Cingolani A *et al.* (1995). Evaluation of cerebrospinal fluid EBV-DNA and IL-10 as markers for in vivo diagnosis of AIDS-related primary central nervous system lymphoma. *Br J Haematol*, 90: 844–849. doi:10.1111/j.1365-2141.1995.tb05205.x PMID:7669663

De Milito A (2004). B lymphocyte dysfunctions in HIV infection. *Curr HIV Res*, 2: 11–21. doi:10.2174/1570162043485068 PMID:15053337

de Witte L, Nabatov A, Geijtenbeek TB (2008). Distinct roles for DC-SIGN+-dendritic cells and Langerhans cells in HIV-1 transmission. *Trends Mol Med*, 14: 12–19. doi:10.1016/j.molmed.2007.11.001 PMID:18055263

Deacon NJ, Tsykin A, Solomon A *et al.* (1995). Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients. *Science*, 270: 988–991. doi:10.1126/science.270.5238.988 PMID:7481804

Des Jarlais DC, Marmor M, Friedmann P *et al.* (2000). HIV incidence among injection drug users in New York City, 1992–1997: evidence for a declining epidemic. *Am J Public Health*, 90: 352–359. doi:10.2105/AJPH.90.3.352 PMID:10705851

Desrosiers RC, Sasseville VG, Czajak SC *et al.* (1997). A herpesvirus of rhesus monkeys related to the human Kaposi's sarcoma-associated herpesvirus. *J Virol*, 71: 9764–9769. PMID:9371642

Di Martino V, Rufat P, Boyer N *et al.* (2001). The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology*, 34: 1193–1199. doi:10.1053/jhep.2001.29201 PMID:11732009

Diamond C, Taylor TH, Aboumrad T *et al.* (2005). Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis*, 32: 314–320. doi:10.1097/01.olq.0000162366.60245.02 PMID:15849533

Dittmer D, Stoddart C, Renne R *et al.* (1999). Experimental transmission of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) to SCID-hu Thy/Liv mice. *J Exp Med*, 190: 1857–1868. doi:10.1084/jem.190.12.1857 PMID:10601360

Dolei A, Curreli S, Marongiu P *et al.* (1999). Human immunodeficiency virus infection in vitro activates naturally integrated human papillomavirus type 18 and induces synthesis of the L1 capsid protein. *J Gen Virol*, 80: 2937–2944. PMID:10580055

Dosch HM, Cochrane DM, Cook VA *et al.* (1991). Exogenous but not endogenous EBV induces lymphomas in beige/nude/xid mice carrying human lymphoid xenografts. *Int Immunol*, 3: 731–735. doi:10.1093/intimm/3.7.731 PMID:1655005

Drobacheff C, Dupont P, Mougin C *et al.* (2003). Anal human papillomavirus DNA screening by Hybrid Capture II in human immunodeficiency virus-positive patients with or without anal intercourse. *Eur J Dermatol*, 13: 367–371. PMID:12948917

Duchardt F, Fotin-Mleczek M, Schwarz H *et al.* (2007). A comprehensive model for the cellular uptake of cationic cell-penetrating peptides. *Traffic*, 8: 848–866. doi:10.1111/j.1600-0854.2007.00572.x PMID:17587406

Dupin N, Fisher C, Kellam P *et al.* (1999). Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. *Proc Natl Acad Sci USA*, 96: 4546–4551. doi:10.1073/pnas.96.8.4546 PMID:10200299

Engels EA (2007). Infectious agents as causes of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*, 16: 401–404. doi:10.1158/1055-9965.EPI-06-1056 PMID:17337646

Engels EA, Biggar RJ, Hall HI *et al.* (2008). Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer*, 123: 187–194. doi:10.1002/ijc.23487 PMID:18435450

Engels EA, Frisch M, Goedert JJ *et al.* (2002). Merkel cell carcinoma and HIV infection. *Lancet*, 359: 497–498. doi:10.1016/S0140-6736(02)07668-7 PMID:11853800

Engels EA & Goedert JJ (2005). Human immunodeficiency virus/acquired immunodeficiency syndrome and cancer: past, present, and future. *J Natl Cancer Inst*, 97: 407–409. doi:10.1093/jnci/dji085 PMID:15769998

Engels EA, Pfeiffer RM, Goedert JJ *et al.*for the HIV/AIDS Cancer Match Study. (2006). Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS*, 20: 1645–1654. doi:10.1097/01.aids.0000238411.75324.59 PMID:16868446

Ensoli B, Barillari G, Salahuddin SZ *et al.* (1990). Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature*, 345: 84–86. doi:10.1038/345084a0 PMID:2184372

European Mode of Delivery Collaboration. (1999). Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet*, 353: 1035–1039. doi:10.1016/S0140-6736(98)08084-2 PMID:10199349

Evison J, Jost J, Ledergerber B *et al.* (1999). HIV-associated non-Hodgkin's lymphoma: highly active antiretroviral therapy improves remission rate of chemotherapy. *AIDS*, 13: 732–734. doi:10.1097/00002030-199904160-00018 PMID:10397572

Fan H, Kim SC, Chima CO *et al.* (2005). Epstein-Barr viral load as a marker of lymphoma in AIDS patients. *J Med Virol*, 75: 59–69. doi:10.1002/jmv.20238 PMID:15543571

Fawzi W, Msamanga G, Spiegelman D *et al.* (2002). Transmission of HIV-1 through breastfeeding among women in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr*, 31: 331–338. doi:10.1097/00126334-200211010-00010 PMID:12439210

Fiscus SA, Adimora AA, Schoenbach VJ *et al.* (1999). Trends in human immunodeficiency virus (HIV) counseling, testing, and antiretroviral treatment of HIV-infected women and perinatal transmission in North Carolina. *J Infect Dis*, 180: 99–105. doi:10.1086/314840 PMID:10353867

Fong IW, Ho J, Toy C *et al.* (2000). Value of long-term administration of acyclovir and similar agents for protecting against AIDS-related lymphoma: case-control and historical cohort studies. *Clin Infect Dis*, 30: 757–761. doi:10.1086/313761 PMID:10816144

Foreman KE, Friborg J, Chandran B *et al.* (2001). Injection of human herpesvirus-8 in human skin engrafted on SCID mice induces Kaposi's sarcoma-like lesions. *J Dermatol Sci*, 26: 182–193. doi:10.1016/S0923-1811(01)00087-1 PMID:11390203

Foster JL & Garcia JV (2008). HIV-1 Nef: at the crossroads. *Retrovirology*, 5: 84 doi:10.1186/1742-4690-5-84 PMID:18808677

Franceschi S, Dal Maso L, Arniani S *et al.* (1998). Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. Cancer and AIDS Registry Linkage Study. *Br J Cancer*, 78: 966–970. doi:10.1038/bjc.1998.610 PMID:9764592

Franceschi S, Dal Maso L, Pezzotti P *et al.*Cancer and AIDS Registry Linkage Study. (2003). Incidence of AIDS-defining cancers after AIDS diagnosis among people with AIDS in Italy, 1986–1998. *J Acquir Immune Defic Syndr*, 34: 84–90. doi:10.1097/00126334-200309010-00013 PMID:14501799

Franceschi S, Herrero R, Clifford GM *et al.* (2006). Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. *Int J Cancer,* 119: 2677–2684. doi:10.1002/ijc.22241 PMID:16991121

Franceschi S & Jaffe H (2007). Cervical cancer screening of women living with HIV infection: a must in the era of antiretroviral therapy. *Clin Infect Dis*, 45: 510–513. doi:10.1086/520022 PMID:17638204

Franceschi S, Maso LD, Rickenbach M *et al.* (2008). Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *Br J Cancer*, 99: 800–804. doi:10.1038/sj.bjc.6604520 PMID:18665172

Freed EO, Martin MA (2007). *HIVs and Their Replication*. In: *Fields Virology*, 5th ed. Philadelphia: Wolters Kluwer Health / Lippincott Williams & Wilkins, pp. 2107–2186.

Friedman-Kien AE (1981). Disseminated Kaposi's sarcoma syndrome in young homosexual men. *J Am Acad Dermatol*, 5: 468–471. doi:10.1016/S0190-9622(81)80010-2 PMID:7287964

Frisch M, Biggar RJ, Engels EA, Goedert JJAIDS-Cancer Match Registry Study Group. (2001). Association of cancer with AIDS-related immunosuppression in adults. *JAMA*, 285: 1736–1745. doi:10.1001/jama.285.13.1736 PMID:11277828

Frisch M, Biggar RJ, Goedert JJ (2000). Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*, 92: 1500–1510. doi:10.1093/jnci/92.18.1500 PMID:10995805

Fujii Y, Otake K, Tashiro M, Adachi A (1996). Soluble Nef antigen of HIV-1 is cytotoxic for human CD4+ T cells. *FEBS Lett*, 393: 93–96. doi:10.1016/0014-5793(96)00859-9 PMID:8804432

Galceran J, Marcos-Gragera R, Soler M *et al.* (2007). Cancer incidence in AIDS patients in Catalonia, Spain. *Eur J Cancer*, 43: 1085–1091. doi:10.1016/j.ejca.2007.01.028 PMID:17349785

Gallo RC, Salahuddin SZ, Popovic M *et al.* (1984). Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*, 224: 500–503. doi:10.1126/science.6200936 PMID:6200936

Gallo RC, Sarin PS, Gelmann EP *et al.* (1983). Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science*, 220: 865–867. doi:10.1126/science.6601823 PMID:6601823

Gao F, Bailes E, Robertson DL *et al.* (1999). Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature*, 397: 436–441. doi:10.1038/17130 PMID:9989410

Garcia JV & Miller AD (1991). Serine phosphorylation-independent downregulation of cell-surface CD4 by nef. *Nature*, 350: 508–511. doi:10.1038/350508a0 PMID:2014052

Gatignol A (2007). Transcription of HIV: Tat and cellular chromatin. *Adv Pharmacol*, 55: 137–159. doi:10.1016/S1054-3589(07)55004-0 PMID:17586314

Gérard L, Galicier L, Maillard A *et al.* (2002). Systemic non-Hodgkin lymphoma in HIV-infected patients with effective suppression of HIV replication: persistent occurrence but improved survival. *J Acquir Immune Defic Syndr*, 30: 478–484. doi:10.1097/00126334-200208150-00003 PMID:12154338

Gessain A & Duprez R (2005). Spindle cells and their role in Kaposi's sarcoma. *Int J Biochem Cell Biol*, 37: 2457–2465. doi:10.1016/j.biocel.2005.01.018 PMID:16188485

Gingues S & Gill MJ (2006). The impact of highly active antiretroviral therapy on the incidence and outcomes of AIDS-defining cancers in Southern Alberta. *HIV Med*, 7: 369–377. doi:10.1111/j.1468-1293.2006.00395.x PMID:16903981

Giordano TP & Kramer JR (2005). Does HIV infection independently increase the incidence of lung cancer? *Clin Infect Dis*, 40: 490–491. doi:10.1086/427028 PMID:15668878

Gómez-Gonzalo M, Carretero M, Rullas J *et al.* (2001). The hepatitis B virus X protein induces HIV-1 replication and transcription in synergy with T-cell activation signals: functional roles of NF-kappaB/NF-AT and SP1-binding sites in the HIV-1 long terminal repeat promoter. *J Biol Chem*, 276: 35435–35443. doi:10.1074/jbc.M103020200 PMID:11457829

Gonzalez M, Règine V, Piccinini V *et al.* (2005). Residual risk of transfusion-transmitted human immunodeficiency virus, hepatitis C virus, and hepatitis B virus infections in Italy. *Transfusion*, 45: 1670–1675. doi:10.1111/j.1537-2995.2005.00576.x PMID:16181219

Goodenow MM & Collman RG (2006). HIV-1 coreceptor preference is distinct from target cell tropism: a dual-parameter nomenclature to define viral phenotypes. *J Leukoc Biol*, 80: 965–972. doi:10.1189/jlb.0306148 PMID:16923919

Gottlieb MS, Schroff R, Schanker HM *et al.* (1981). Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med*, 305: 1425–1431. doi:10.1056/NEJM198112103052401 PMID:6272109

Graham CS, Baden LR, Yu E *et al.* (2001). Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*, 33: 562–569. doi:10.1086/321909 PMID:11462196

Gray RH, Wawer MJ, Brookmeyer R *et al.*Rakai Project Team. (2001). Probability of HIV-1 transmission per coital act in monogamous, heterosexual,

HIV-1-discordant couples in Rakai, Uganda. *Lancet*, 357: 1149–1153. doi:10.1016/S0140-6736(00)04331-2 PMID:11323041

Griffin GE, Castello-Branco LR, Ortigão-de-Sampaio MB, Shattock R (1996). Mucosal immunology and models of mucosal HIV infection. *Mem Inst Oswaldo Cruz*, 91: 367–369. doi:10.1590/S0074-02761996000300022 PMID:9040858

Grulich AE (1999). AIDS-associated non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*, 21: Suppl 1S27–S30. PMID:10430215

Grulich AE (2000). Update: cancer risk in persons with HIV/AIDS in the era of combination antiretroviral therapy. *AIDS Read*, 10: 341–346. PMID:10881365

Grulich AE, Li Y, McDonald A *et al.* (2002). Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. *AIDS*, 16: 1155–1161. doi:10.1097/00002030-200205240-00009 PMID:12004274

Grulich AE, Li Y, McDonald AM *et al.* (2001). Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination anti-retroviral therapy. *AIDS*, 15: 629–633. doi:10.1097/00002030-200103300-00013 PMID:11317001

Grulich AE, Vajdic CM, Cozen W (2007b). Altered immunity as a risk factor for non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*, 16: 405–408. doi:10.1158/1055-9965.EPI-06-1070 PMID:17337643

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM (2007a). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*, 370: 59–67. doi:10.1016/S0140-6736(07)61050-2 PMID:17617273

Grulich AE, Wan X, Law MG *et al.* (2000). B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS. *AIDS*, 14: 133–140. doi:10.1097/00002030-200001280-00008 PMID:10708283

Guech-Ongey M, Engels EA, Goedert JJ *et al.* (2008). Elevated risk for squamous cell carcinoma of the conjunctiva among adults with AIDS in the United States. *Int J Cancer*, 122: 2590–2593. doi:10.1002/ijc.23384 PMID:18224690

Gupta S & Mitra D (2007). Human immunodeficiency virus-1 Tat protein: immunological facets of a transcriptional activator. *Indian J Biochem Biophys*, 44: 269–275. PMID:18341200

Habis A, Baskin GB, Murphey-Corb M, Levy LS (1999). Simian AIDS-associated lymphoma in rhesus and cynomolgus monkeys recapitulates the primary pathobiological features of AIDS-associated non-Hodgkin's lymphoma. *AIDS Res Hum Retroviruses*, 15: 1389–1398. doi:10.1089/088922299310098 PMID:10515154

Haigentz M Jr (2005). Aerodigestive cancers in HIV infection. *Curr Opin Oncol*, 17: 474–478. doi:10.1097/01.cco.0000174036.46785.8f PMID:16093799

Haldorsen IS, Kråkenes J, Goplen AK *et al.* (2008). AIDS-related primary central nervous system lymphoma: a Norwegian national survey 1989–2003. *BMC Cancer*, 8: 225 doi:10.1186/1471-2407-8-225 PMID:18684320

Hansen PB, Penkowa M, Kirk O *et al.* (2000). Human immunodeficiency virus-associated malignant lymphoma in eastern Denmark diagnosed from 1990–1996: clinical features, histopathology, and association with Epstein-Barr virus and human herpesvirus-8. *Eur J Haematol*, 64: 368–375. doi:10.1034/j.1600-0609.2000.90126.x PMID:10901590

Health Protection Agency (2005). *Occupational transmission of HIV. Summary of Published Reports*.

Herida M, Mary-Krause M, Kaphan R *et al.* (2003). Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol*, 21: 3447–3453. doi:10.1200/JCO.2003.01.096 PMID:12972519

Hessol NA, Katz MH, Liu JY *et al.* (1992). Increased incidence of Hodgkin disease in homosexual men with HIV infection. *Ann Intern Med*, 117: 309–311. PMID:1637026

Hessol NA, Pipkin S, Schwarcz S *et al.* (2007). The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol*, 165: 1143–1153. doi:10.1093/aje/kwm017 PMID:17344204

Hirsch VM, Olmsted RA, Murphey-Corb M *et al.* (1989). An African primate lentivirus (SIVsm) closely related to HIV-2. *Nature*, 339: 389–392. doi:10.1038/339389a0 PMID:2786147

Hisada M, Chatterjee N, Kalaylioglu Z *et al.* (2005). Hepatitis C virus load and survival among injection drug users in the United States. *Hepatology*, 42: 1446–1452. doi:10.1002/hep.20938 PMID:16317675

Hishima T, Oyaizu N, Fujii T *et al.* (2006). Decrease in Epstein-Barr virus-positive AIDS-related lymphoma in the era of highly active antiretroviral therapy. *Microbes Infect*, 8: 1301–1307. doi:10.1016/j.micinf.2005.12.012 PMID:16697236

Hjalgrim H, Askling J, Pukkala E *et al.* (2001). Incidence of Hodgkin's disease in Nordic countries. *Lancet*, 358: 297–298. doi:10.1016/S0140-6736(01)05498-8 PMID:11498219

Holkar S, Mudhar HS, Jain A *et al.* (2005). Regression of invasive conjunctival squamous carcinoma in an HIV-positive patient on antiretroviral therapy. *Int J STD AIDS*, 16: 782–783. doi:10.1258/0956462057749888028 PMID:16336757

Hope VD, Judd A, Hickman M *et al.* (2005). HIV prevalence among injecting drug users in England and Wales 1990 to 2003: evidence for increased transmission

in recent years. *AIDS*, 19: 1207–1214. doi:10.1097/01. aids.0000176222.71355.a1 PMID:15990575

Hurley SF, Jolley DJ, Kaldor JM (1997). Effectiveness of needle-exchange programmes for prevention of HIV infection. *Lancet*, 349: 1797–1800. doi:10.1016/S0140-6736(96)11380-5 PMID:9269214

Hutchinson P, Chadban SJ, Atkins RC, Holdsworth SR (2003). Laboratory assessment of immune function in renal transplant patients. *Nephrol Dial Transplant*, 18: 983–989. doi:10.1093/ndt/gfg190 PMID:12686675

IARC (1996). Human immunodeficiency viruses and human T-cell lymphotropic viruses. *IARC Monogr Eval Carcinog Risks Hum*, 67: 1–424. PMID:9190379

IARC (2007). *Cancer incidence in five continents,* 9th ed. Curado MP, editor. Lyon.

International Collaboration on HIV and Cancer. (2000). Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst*, 92: 1823–1830. doi:10.1093/jnci/92.22.1823 PMID:11078759

Inungu J, Melendez MF, Montgomery JP (2002). AIDS-related primary brain lymphoma in Michigan, January 1990 to December 2000. *AIDS Patient Care STDS*, 16: 107–112. doi:10.1089/108729102317330445 PMID:11945206

Ioannidis JP, Collier AC, Cooper DA *et al.* (1998). Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis*, 178: 349–359. PMID:9697714

Ives NJ, Gazzard BG, Easterbrook PJ (2001). The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. *J Infect*, 42: 134–139. doi:10.1053/jinf.2001.0810 PMID:11531320

Jagger J, De Carli G, Perry J *et al.* (2003). *Occupational exposure to blood-borne pathogens: epidemiology and prevention*. In: *Prevention and Control of Nosocomial Infections*. Wenzel RP, editor. New York, NY: Lippincot Williams & Wilkins, pp. 430–466.

Kasiske BL, Snyder JJ, Gilbertson DT, Wang C (2004). Cancer after kidney transplantation in the United States. *Am J Transplant*, 4: 905–913. doi:10.1111/j.1600-6143.2004.00450.x PMID:15147424

Keller SA, Hernandez-Hopkins D, Vider J *et al.* (2006). NF-kappaB is essential for the progression of KSHV- and EBV-infected lymphomas in vivo. *Blood*, 107: 3295–3302. doi:10.1182/blood-2005-07-2730 PMID:16380446

Kenney S, Kamine J, Markovitz D *et al.* (1988). An Epstein-Barr virus immediate-early gene product trans-activates gene expression from the human immunodeficiency virus long terminal repeat. *Proc Natl Acad Sci USA*, 85: 1652–1656. doi:10.1073/pnas.85.5.1652 PMID:2830625

Kersten MJ, Klein MR, Holwerda AM *et al.* (1997). Epstein-Barr virus-specific cytotoxic T cell responses in HIV-1 infection: different kinetics in patients progressing to opportunistic infection or non-Hodgkin's lymphoma. *J Clin Invest*, 99: 1525–1533. doi:10.1172/JCI119315 PMID:9119996

Kestelyn P, Stevens AM, Ndayambaje A *et al.* (1990). HIV and conjunctival malignancies. *Lancet*, 336: 51–52. doi:10.1016/0140-6736(90)91562-O PMID:1973230

Kestler HW 3rd, Ringler DJ, Mori K *et al.* (1991). Importance of the nef gene for maintenance of high virus loads and for development of AIDS. *Cell*, 65: 651–662. doi:10.1016/0092-8674(91)90097-I PMID:2032289

Kim RH, Yochim JM, Kang MK *et al.* (2008). HIV-1 Tat enhances replicative potential of human oral keratinocytes harboring HPV-16 genome. *Int J Oncol*, 33: 777–782. PMID:18813791

Kinlen L (2004). Infections and immune factors in cancer: the role of epidemiology. *Oncogene*, 23: 6341–6348. doi:10.1038/sj.onc.1207898 PMID:15322509

Kirk GD, Merlo C, O' Driscoll P *et al.* (2007). HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis*, 45: 103–110. doi:10.1086/518606 PMID:17554710

Kirk O, Pedersen C, Cozzi-Lepri A *et al.* EuroSIDA Study Group. (2001). Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. *Blood*, 98: 3406–3412. doi:10.1182/blood.V98.12.3406 PMID:11719381

Knight SC, Macatonia SE, Patterson S (1990). HIV I infection of dendritic cells. *Int Rev Immunol*, 6: 163–175. doi:10.3109/08830189009056627 PMID:2152500

Kourtis AP, Lee FK, Abrams EJ *et al.* (2006). Mother-to-child transmission of HIV-1: timing and implications for prevention. *Lancet Infect Dis*, 6: 726–732. doi:10.1016/S1473-3099(06)70629-6 PMID:17067921

Kramer JR, Giordano TP, Souchek J *et al.* (2005). The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. *Am J Gastroenterol*, 100: 56–63. doi:10.1111/j.1572-0241.2005.40670.x PMID:15654781

Kumwenda NI, Hoover DR, Mofenson LM *et al.* (2008). Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*, 359: 119–129. doi:10.1056/NEJMoa0801941 PMID:18525035

Kwon HS, Brent MM, Getachew R *et al.* (2008). Human immunodeficiency virus type 1 Tat protein inhibits the SIRT1 deacetylase and induces T cell hyperactivation. *Cell Host Microbe*, 3: 158–167. doi:10.1016/j.chom.2008.02.002 PMID:18329615

Kyaw-Tanner MT, Esmore D, Burrows SR *et al.* (1994). Epstein-Barr virus-specific cytotoxic T cell response in cardiac transplant recipients. *Transplantation*, 57: 1611–1617. PMID:8009596

Lallemant M, Jourdain G, Le Coeur S *et al.* Perinatal HIV Prevention Trial (Thailand) Investigators. (2004). Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1

in Thailand. *N Engl J Med*, 351: 217–228. doi:10.1056/NEJMoa033500 PMID:15247338

Lascaux AS, Hemery F, Goujard C *et al.* (2005). Beneficial effect of highly active antiretroviral therapy on the prognosis of AIDS-related systemic non-Hodgkin lymphomas. *AIDS Res Hum Retroviruses*, 21: 214–220. doi:10.1089/aid.2005.21.214 PMID:15795527

Li CJ, Friedman DJ, Wang C *et al.* (1995). Induction of apoptosis in uninfected lymphocytes by HIV-1 Tat protein. *Science*, 268: 429–431. doi:10.1126/science.7716549 PMID:7716549

Li SL, Biberfeld P, Ernberg I (1994). DNA of lymphoma-associated herpesvirus (HVMF1) in SIV-infected monkeys (Macaca fascicularis) shows homologies to EBNA-1, -2 and -5 genes. *Int J Cancer*, 59: 287–295. doi:10.1002/ijc.2910590223 PMID:7927931

Lim ST, Karim R, Tulpule A *et al.* (2005). Prognostic factors in HIV-related diffuse large-cell lymphoma: before versus after highly active antiretroviral therapy. *J Clin Oncol*, 23: 8477–8482. doi:10.1200/JCO.2005.02.9355 PMID:16230675

Little RF, Gutierrez M, Jaffe ES *et al.* (2001). HIV-associated non-Hodgkin lymphoma: incidence, presentation, and prognosis. *JAMA*, 285: 1880–1885. doi:10.1001/jama.285.14.1880 PMID:11308402

Long JL, Engels EA, Moore RD, Gebo KA (2008). Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS*, 22: 489–496. doi:10.1097/QAD.0b013e3282f47082 PMID:18301061

Louie JK, Hsu LC, Osmond DH *et al.* (2002). Trends in causes of death among persons with acquired immuno-deficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. *J Infect Dis*, 186: 1023–1027. doi:10.1086/343862 PMID:12232845

Malim MH & Emerman M (2008). HIV-1 accessory proteins–ensuring viral survival in a hostile environment. *Cell Host Microbe*, 3: 388–398. doi:10.1016/j.chom.2008.04.008 PMID:18541215

Marone G, Florio G, Triggiani M *et al.* (2000). Mechanisms of IgE elevation in HIV-1 infection. *Crit Rev Immunol*, 20: 477–496. PMID:11396683

Martínez-Maza O & Breen EC (2002). B-cell activation and lymphoma in patients with HIV. *Curr Opin Oncol*, 14: 528–532. doi:10.1097/00001622-200209000-00009 PMID:12192272

Masood R, Cai J, Zheng T *et al.* (1997). Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma. *Proc Natl Acad Sci USA*, 94: 979–984. doi:10.1073/pnas.94.3.979 PMID:9023368

Matthews GV, Bower M, Mandalia S *et al.* (2000). Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. *Blood*, 96: 2730–2734. PMID:11023505

Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA (2002). Pleural and peritoneal lymphoma among people with AIDS in the United States. *J Acquir Immune Defic Syndr*, 29: 418–421. PMID:11917248

Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA (2003). Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr*, 32: 527–533. doi:10.1097/00126334-200304150-00010 PMID:12679705

Mbulaiteye SM, Katabira ET, Wabinga H *et al.* (2006). Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int J Cancer*, 118: 985–990. doi:10.1002/ijc.21443 PMID:16106415

McGinnis KA, Fultz SL, Skanderson M *et al.* (2006). Hepatocellular carcinoma and non-Hodgkin's lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. *J Clin Oncol*, 24: 5005–5009. doi:10.1200/JCO.2006.05.7984 PMID:17075119

Melkus MW, Estes JD, Padgett-Thomas A *et al.* (2006). Humanized mice mount specific adaptive and innate immune responses to EBV and TSST-1. *Nat Med*, 12: 1316–1322. doi:10.1038/nm1431 PMID:17057712

Mellemkjaer L, Hammarstrom L, Andersen V *et al.* (2002). Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clin Exp Immunol*, 130: 495–500. doi:10.1046/j.1365-2249.2002.02004.x PMID:12452841

Mercader M, Nickoloff BJ, Foreman KE (2001). Induction of human immunodeficiency virus 1 replication by human herpesvirus 8. *Arch Pathol Lab Med*, 125: 785–789. PMID:11371231

Miotti PG, Taha TE, Kumwenda NI *et al.* (1999). HIV transmission through breastfeeding: a study in Malawi. *JAMA*, 282: 744–749. doi:10.1001/jama.282.8.744 PMID:10463709

Miralles P, Berenguer J, Ribera JM *et al.*Grupo de Estudio del SIDA Register of Systemic AIDS-Related Lymphomas. (2007). Prognosis of AIDS-related systemic non-Hodgkin lymphoma treated with chemotherapy and highly active antiretroviral therapy depends exclusively on tumor-related factors. *J Acquir Immune Defic Syndr*, 44: 167–173. doi:10.1097/QAI.0b013e31802bb5d0 PMID:17117144

Montagnier L, Chermann JC, Barré-Sinoussi F *et al.* (1984). Lymphadenopathy associated virus and its etiological role in AIDS. *Princess Takamatsu Symp*, 15: 319–331. PMID:6100650

Moore A, Herrera G, Nyamongo J *et al.* (2001). Estimated risk of HIV transmission by blood transfusion in Kenya. *Lancet*, 358: 657–660. doi:10.1016/S0140-6736(01)05783-X PMID:11530174

Morini M, Benelli R, Giunciuglio D *et al.* (2000). Kaposi's sarcoma cells of different etiologic origins respond to HIV-Tat through the Flk-1/KDR (VEGFR-2):

relevance in AIDS-KS pathology. *Biochem Biophys Res Commun*, 273: 267–271. doi:10.1006/bbrc.2000.2941 PMID:10873597

Mosier DE (1991). Adoptive transfer of human lymphoid cells to severely immunodeficient mice: models for normal human immune function, autoimmunity, lymphomagenesis, and AIDS. *Adv Immunol*, 50: 303–325. doi:10.1016/S0065-2776(08)60828-7 PMID:1950798

Mosier DE, Baird SM, Kirven MB *et al.* (1990). EBV-associated B-cell lymphomas following transfer of human peripheral blood lymphocytes to mice with severe combined immune deficiency. *Curr Top Microbiol Immunol*, 166: 317–323. PMID:1963581

Mounier N, Spina M, Gabarre J *et al.* (2006). AIDS-related non-Hodgkin lymphoma: final analysis of 485 patients treated with risk-adapted intensive chemotherapy. *Blood*, 107: 3832–3840. doi:10.1182/blood-2005-09-3600 PMID:16410446

Mutlu AD, Cavallin LE, Vincent L *et al.* (2007). In vivo-restricted and reversible malignancy induced by human herpesvirus-8 KSHV: a cell and animal model of virally induced Kaposi's sarcoma. *Cancer Cell*, 11: 245–258. doi:10.1016/j.ccr.2007.01.015 PMID:17349582

Newnham A, Harris J, Evans HS *et al.* (2005). The risk of cancer in HIV-infected people in southeast England: a cohort study. *Br J Cancer*, 92: 194–200. doi:10.1038/sj.bjc.6602273 PMID:15583689

Newton R (1996). A review of the aetiology of squamous cell carcinoma of the conjunctiva. *Br J Cancer*, 74: 1511–1513. doi:10.1038/bjc.1996.581 PMID:8932327

Newton R, Ziegler J, Beral V *et al.*Uganda Kaposi's Sarcoma Study Group. (2001). A case-control study of human immunodeficiency virus infection and cancer in adults and children residing in Kampala, Uganda. *Int J Cancer*, 92: 622–627. doi:10.1002/1097-0215(20010601)92:5<622::AID-IJC1256>3.0.CO;2-K PMID:11340563

Nilsson K, Giovanella BC, Stehlin JS, Klein G (1977). Tumorigenicity of human hematopoietic cell lines in athymic nude mice. *Int J Cancer*, 19: 337–344. doi:10.1002/ijc.2910190309 PMID:14896

O'Brien SF, Yi QL, Fan W *et al.* (2007). Current incidence and estimated residual risk of transfusion-transmitted infections in donations made to Canadian Blood Services. *Transfusion*, 47: 316–325. doi:10.1111/j.1537-2995.2007.01108.x PMID:17302779

Orenstein JM, Feinberg M, Yoder C *et al.* (1999). Lymph node architecture preceding and following 6 months of potent antiviral therapy: follicular hyperplasia persists in parallel with p24 antigen restoration after involution and CD4 cell depletion in an AIDS patient. *AIDS*, 13: 2219–2229. doi:10.1097/00002030-199911120-00004 PMID:10563707

Orlando G, Tanzi E, Beretta R *et al.* (2008). Human papillomavirus genotypes and anal-related lesions among HIV-1-infected men in Milan, Italy. *J Acquir Immune Defic Syndr*, 47: 129–131. doi:10.1097/QAI.0b013e318156ec7b PMID:18156995

Orzechowska BU, Powers MF, Sprague J *et al.* (2008). Rhesus macaque rhadinovirus-associated non-Hodgkin lymphoma: animal model for KSHV-associated malignancies. *Blood*, 112: 4227–4234. doi:10.1182/blood-2008-04-151498 PMID:18757778

Palefsky JM, Holly EA, Ralston ML, Greenblatt RMDa Costa M. (2001). Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis*, 183: 383–391. doi:10.1086/318071 PMID:11133369

Panda S, Kumar MS, Lokabiraman S *et al.* (2005). Risk factors for HIV infection in injection drug users and evidence for onward transmission of HIV to their sexual partners in Chennai, India. *J Acquir Immune Defic Syndr*, 39: 9–15. doi:10.1097/01.qai.0000160713.94203.9b PMID:15851908

Pantaleo G, Cohen OJ, Schacker T *et al.* (1998). Evolutionary pattern of human immunodeficiency virus (HIV) replication and distribution in lymph nodes following primary infection: implications for antiviral therapy. *Nat Med*, 4: 341–345. doi:10.1038/nm0398-341 PMID:9500610

Parker MS, Leveno DM, Campbell TJ *et al.* (1998). AIDS-related bronchogenic carcinoma: fact or fiction? *Chest*, 113: 154–161. doi:10.1378/chest.113.1.154 PMID:9440583

Patel HS, Silver ARJ, Northover JMA (2007). Anal cancer in renal transplant patients. *Int J Colorectal Dis*, 22: 1–5. doi:10.1007/s00384-005-0023-3 PMID:16133005

Patel P, Hanson DL, Sullivan PS *et al.*Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. (2008). Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med*, 148: 728–736. PMID:18490686

Phelps RM, Smith DK, Heilig CM *et al.*HER Study Group. (2001). Cancer incidence in women with or at risk for HIV. *Int J Cancer*, 94: 753–757. doi:10.1002/ijc.1528 PMID:11745473

Picchio GR, Sabbe RE, Gulizia RJ *et al.* (1997). The KSHV/HHV8-infected BCBL-1 lymphoma line causes tumors in SCID mice but fails to transmit virus to a human peripheral blood mononuclear cell graft. *Virology*, 238: 22–29. doi:10.1006/viro.1997.8822 PMID:9375005

Piketty C, Selinger-Leneman H, Grabar S *et al.*FHDH-ANRS CO 4. (2008). Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *AIDS*, 22: 1203–1211. doi:10.1097/QAD.0b013e3283023f78 PMID:18525266

Piriou ER, van Dort K, Nanlohy NM *et al.* (2004). Altered EBV viral load setpoint after HIV seroconversion is

in accordance with lack of predictive value of EBV load for the occurrence of AIDS-related non-Hodgkin lymphoma. *J Immunol*, 172: 6931–6937. PMID:15153512

Piriou ER, van Dort K, Nanlohy NM *et al.* (2005). Novel method for detection of virus-specific CD41+ T cells indicates a decreased EBV-specific CD4+ T cell response in untreated HIV-infected subjects. *Eur J Immunol*, 35: 796–805. doi:10.1002/eji.200425792 PMID:15724243

Polesel J, Clifford GM, Rickenbach M *et al.*Swiss HIV Cohort Study. (2008). Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS*, 22: 301–306. doi:10.1097/QAD.0b013e3282f2705d PMID:18097233

Pope M, Betjes MG, Romani N *et al.* (1994). Conjugates of dendritic cells and memory T lymphocytes from skin facilitate productive infection with HIV-1. *Cell*, 78: 389–398. doi:10.1016/0092-8674(94)90418-9 PMID:7914836

Powles T, Matthews G, Bower M (2000). AIDS related systemic non-Hodgkin's lymphoma. *Sex Transm Infect*, 76: 335–341. doi:10.1136/sti.76.5.335 PMID:11141847

Pudney J & Anderson D (1991). Orchitis and human immunodeficiency virus type 1 infected cells in reproductive tissues from men with the acquired immune deficiency syndrome. *Am J Pathol*, 139: 149–160. PMID:1853930

Qiao X, He B, Chiu A *et al.* (2006). Human immunodeficiency virus 1 Nef suppresses CD40-dependent immunoglobulin class switching in bystander B cells. *Nat Immunol*, 7: 302–310. doi:10.1038/ni1302 PMID:16429138

Quayle AJ, Xu C, Mayer KH, Anderson DJ (1997). T lymphocytes and macrophages, but not motile spermatozoa, are a significant source of human immunodeficiency virus in semen. *J Infect Dis*, 176: 960–968. doi:10.1086/516541 PMID:9333154

Rapezzi D, Ugolini D, Ferraris AM *et al.* (2001). Histological subtypes of Hodgkin's disease in the setting of HIV infection. *Ann Hematol*, 80: 340–344. doi:10.1007/s002770100294 PMID:11475147

Raphael BG & Knowles DM (1990). Acquired immunodeficiency syndrome-associated non-Hodgkin's lymphoma. *Semin Oncol*, 17: 361–366. PMID:2191439

Ratner L, Haseltine W, Patarca R *et al.* (1985). Complete nucleotide sequence of the AIDS virus, HTLV-III. *Nature*, 313: 277–284. doi:10.1038/313277a0 PMID:2578615

Rezk SA & Weiss LM (2007). Epstein-Barr virus-associated lymphoproliferative disorders. *Hum Pathol*, 38: 1293–1304. doi:10.1016/j.humpath.2007.05.020 PMID:17707260

Rhodes T, Lowndes C, Judd A *et al.* (2002). Explosive spread and high prevalence of HIV infection among injecting drug users in Togliatti City, Russia. *AIDS*, 16: F25–F31. doi:10.1097/00002030-200209060-00002 PMID:12218407

Richters J, Grulich A, Ellard J *et al.* (2003). HIV transmission among gay men through oral sex and other uncommon routes: case series of HIV seroconverters, Sydney. *AIDS*, 17: 2269–2271. doi:10.1097/00002030-200310170-00020 PMID:14523289

Robotin MC, Law MG, Milliken S *et al.* (2004). Clinical features and predictors of survival of AIDS-related non-Hodgkin's lymphoma in a population-based case series in Sydney, Australia. *HIV Med*, 5: 377–384. doi:10.1111/j.1468-1293.2004.00238.x PMID:15369514

Royce RA, Seña A, Cates W Jr, Cohen MS (1997). Sexual transmission of HIV. *N Engl J Med*, 336: 1072–1078. doi:10.1056/NEJM199704103361507 PMID:9091805

Sabbatini A, Carulli B, Villa M *et al.*Northern Italian Seronegative Drug Addicts (NISDA) study. (2001). Recent trends in the HIV epidemic among injecting drug users in Northern Italy, 1993–1999. *AIDS*, 15: 2181–2185. doi:10.1097/00002030-200111090-00014 PMID:11684938

Scala G, Quinto I, Ruocco MR *et al.* (1993). Epstein-Barr virus nuclear antigen 2 transactivates the long terminal repeat of human immunodeficiency virus type 1. *J Virol*, 67: 2853–2861. PMID:8386279

Secchiero P, Zella D, Capitani S *et al.* (1999). Extracellular HIV-1 tat protein up-regulates the expression of surface CXC-chemokine receptor 4 in resting CD4+ T cells. *J Immunol*, 162: 2427–2431. PMID:9973525

Serraino D (1999). The spectrum of Aids-associated cancers in Africa. *AIDS*, 13: 2589–2590. doi:10.1097/00002030-199912240-00013 PMID:10630529

Serraino D, Angeletti C, Carrieri MP *et al.*for the Immunesuppression and Cancer Study Group. (2005). Kaposi's sarcoma in transplant and HIV-infected patients: an epidemiologic study in Italy and France. *Transplantation*, 80: 1699–1704. doi:10.1097/01.tp.0000187864.65522.10 PMID:16378064

Serraino D, Boschini A, Carrieri P *et al.* (2000). Cancer risk among men with, or at risk of, HIV infection in southern Europe. *AIDS*, 14: 553–559. doi:10.1097/00002030-200003310-00011 PMID:10780718

Serraino D, Carbone A, Franceschi S, Tirelli UItalian Cooperative Group on AIDS and Tumours. (1993). Increased frequency of lymphocyte depletion and mixed cellularity subtypes of Hodgkin's disease in HIV-infected patients. *Eur J Cancer*, 29A: 1948–1950. doi:10.1016/0959-8049(93)90450-T PMID:8280487

Serraino D, Pezzotti P, Dorrucci M *et al.*HIV Italian Seroconversion Study Group. (1997). Cancer incidence in a cohort of human immunodeficiency virus seroconverters. *Cancer*, 79: 1004–1008. doi:10.1002/(SICI)1097-0142(19970301)79:5<1004::AID-CNCR17>3.0.CO;2-5 PMID:9041163

Serraino D, Piselli P, Busnach G *et al.*Immunosuppression and Cancer Study Group. (2007). Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern

Europe. *Eur J Cancer*, 43: 2117–2123. doi:10.1016/j.ejca.2007.07.015 PMID:17764927

Shaffer N, Chuachoowong R, Mock PA *et al.*Bangkok Collaborative Perinatal HIV Transmission Study Group. (1999). Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet*, 353: 773–780. doi:10.1016/S0140-6736(98)10411-7 PMID:10459957

Shapiro R, Nalesnik M, McCauley J *et al.* (1999). Posttransplant lymphoproliferative disorders in adult and pediatric renal transplant patients receiving tacrolimus-based immunosuppression. *Transplantation*, 68: 1851–1854. doi:10.1097/00007890-199912270-00006 PMID:10628763

Shaw GM, Harper ME, Hahn BH *et al.* (1985). HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science*, 227: 177–182. doi:10.1126/science.2981429 PMID:2981429

Siegal FP, Lopez C, Hammer GS *et al.* (1981). Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med*, 305: 1439–1444. doi:10.1056/NEJM198112103052403 PMID:6272110

Silverberg MJ & Abrams DI (2007). AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Curr Opin Oncol*, 19: 446–451. PMID:17762569

Soldan K, Davison K, Dow B (2005). Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003. *Euro Surveill*, 10: 17–19. PMID:15735312

Staudt MR, Kanan Y, Jeong JH *et al.* (2004). The tumor microenvironment controls primary effusion lymphoma growth in vivo. *Cancer Res*, 64: 4790–4799. doi:10.1158/0008-5472.CAN-03-3835 PMID:15256448

Stebbing J, Gazzard B, Mandalia S *et al.* (2004). Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol*, 22: 2177–2183. doi:10.1200/JCO.2004.11.097 PMID:15169806

Stein H, Delson G, Pileri SA *et al.* (2008b). *Classical Hodgkin lymphoma, introduction.* In: *World Health Organization Classification of Tumours – Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* Swerdlow SH, Campo E, Harris NL *et al.*, editors. Lyon: IARC Press, pp. 326–329.

Stein L, Urban MI, O'Connell D *et al.* (2008a). The spectrum of human immunodeficiency virus-associated cancers in a South African black population: results from a case-control study, 1995–2004. *Int J Cancer*, 122: 2260–2265. doi:10.1002/ijc.23391 PMID:18241034

Strickler HD, Burk RD, Fazzari M *et al.* (2005). Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*, 97: 577–586. doi:10.1093/jnci/dji073 PMID:15840880

Suhasini M & Reddy TR (2009). Cellular proteins and HIV-1 Rev function. *Curr HIV Res*, 7: 91–100. doi:10.2174/157016209787048474 PMID:19149558

Sunil-Chandra NP, Arno J, Fazakerley J, Nash AA (1994). Lymphoproliferative disease in mice infected with murine gammaherpesvirus 68. *Am J Pathol*, 145: 818–826. PMID:7943173

Swerdlow SH, Campo E, Harris NL *et al.* (2008). *Posttransplant lymphoproliferative disorders.* In: *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, France: IARC Press.

Swingler S, Brichacek B, Jacque JM *et al.* (2003). HIV-1 Nef intersects the macrophage CD40L signalling pathway to promote resting-cell infection. *Nature*, 424: 213–219. doi:10.1038/nature01749 PMID:12853962

Swingler S, Mann A, Jacqué J *et al.* (1999). HIV-1 Nef mediates lymphocyte chemotaxis and activation by infected macrophages. *Nat Med*, 5: 997–103. doi:10.1038/12433 PMID:10470075

Swinnen LJ (2000). Diagnosis and treatment of transplant-related lymphoma. *Ann Oncol*, 11: Suppl 145–48. doi:10.1023/A:1008396821609 PMID:10707778

Tarakanova VL, Kreisel F, White DW, Virgin HW 4th (2008). Murine gammaherpesvirus 68 genes both induce and suppress lymphoproliferative disease. *J Virol*, 82: 1034–1039. doi:10.1128/JVI.01426-07 PMID:17977975

Tarakanova VL, Suarez F, Tibbetts SA *et al.* (2005). Murine gammaherpesvirus 68 infection is associated with lymphoproliferative disease and lymphoma in BALB beta2 microglobulin-deficient mice. *J Virol*, 79: 14668–14679. doi:10.1128/JVI.79.23.14668-14679.2005 PMID:16282467

Teruya-Feldstein J, Temeck BK, Sloas MM *et al.* (1995). Pulmonary malignant lymphoma of mucosa-associated lymphoid tissue (MALT) arising in a pediatric HIV-positive patient. *Am J Surg Pathol*, 19: 357–363. doi:10.1097/00000478-199503000-00014 PMID:7872434

Thio CL, Seaberg EC, Skolasky R Jr *et al.*Multicenter AIDS Cohort Study. (2002). HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*, 360: 1921–1926. doi:10.1016/S0140-6736(02)11913-1 PMID:12493258

Tirelli U, Spina M, Gaidano G *et al.* (2000). Epidemiological, biological and clinical features of HIV-related lymphomas in the era of highly active antiretroviral therapy. *AIDS*, 14: 1675–1688. doi:10.1097/00002030-200008180-00001 PMID:10985303

Titanji K, De Milito A, Cagigi A *et al.* (2006). Loss of memory B cells impairs maintenance of long-term serologic memory during HIV-1 infection. *Blood*, 108: 1580–1587. doi:10.1182/blood-2005-11-013383 PMID:16645169

Townsend CL, Cortina-Borja M, Peckham CS *et al.* (2008). Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS*, 22: 973–981. doi:10.1097/QAD.0b013e3282f9b67a PMID:18453857

Turner BG & Summers MF (1999). Structural biology of HIV. *J Mol Biol*, 285: 1–32. doi:10.1006/jmbi.1998.2354 PMID:9878383

UNAIDS (2007): http://data.unaids.org/pub/epislides/2007/2007_epiupdate_en.pdf

Vaccher E, Spina M, Talamini R *et al.* (2003). Improvement of systemic human immunodeficiency virus-related non-Hodgkin lymphoma outcome in the era of highly active antiretroviral therapy. *Clin Infect Dis*, 37: 1556–1564. doi:10.1086/379517 PMID:14614680

Vajdic CM, McDonald SP, McCredie MR *et al.* (2006). Cancer incidence before and after kidney transplantation. *JAMA*, 296: 2823–2831. doi:10.1001/jama.296.23.2823 PMID:17179459

Vajdic CM, van Leeuwen MT, McDonald SP *et al.* (2007). Increased incidence of squamous cell carcinoma of eye after kidney transplantation. *J Natl Cancer Inst*, 99: 1340–1342. doi:10.1093/jnci/djm085 PMID:17698951

van Baarle D, Hovenkamp E, Callan MF *et al.* (2001). Dysfunctional Epstein-Barr virus (EBV)-specific CD8(+) T lymphocytes and increased EBV load in HIV-1 infected individuals progressing to AIDS-related non-Hodgkin lymphoma. *Blood*, 98: 146–155. doi:10.1182/blood.V98.1.146 PMID:11418474

Varthakavi V, Smith RM, Deng H *et al.* (2002). Human immunodeficiency virus type-1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus through induction of KSHV Rta. *Virology*, 297: 270–280. doi:10.1006/viro.2002.1434 PMID:12083825

Vazeux R, Brousse N, Jarry A *et al.* (1987). AIDS subacute encephalitis. Identification of HIV-infected cells. *Am J Pathol*, 126: 403–410. PMID:3548405

Vernon SD, Hart CE, Reeves WC, Icenogle JP (1993). The HIV-1 tat protein enhances E2-dependent human papillomavirus 16 transcription. *Virus Res*, 27: 133–145. doi:10.1016/0168-1702(93)90077-Z PMID:8384765

Vilchez RA, Kozinetz CA, Jorgensen JL *et al.* (2002). AIDS-related systemic non-Hodgkin's lymphoma at a large community program. *AIDS Res Hum Retroviruses*, 18: 237–242. doi:10.1089/088922202753472793 PMID:11860669

Vogel J, Hinrichs SH, Reynolds RK *et al.* (1988). The HIV tat gene induces dermal lesions resembling Kaposi's sarcoma in transgenic mice. *Nature*, 335: 606–611. doi:10.1038/335606a0 PMID:2845275

Waddell KM, Downing RG, Lucas SB, Newton R (2006). Corneo-conjunctival carcinoma in Uganda. *Eye (Lond)*, 20: 893–899. doi:10.1038/sj.eye.6702043 PMID:16456599

Waddell KM, Lewallen S, Lucas SB *et al.* (1996). Carcinoma of the conjunctiva and HIV infection in Uganda and Malawi. *Br J Ophthalmol*, 80: 503–508. doi:10.1136/bjo.80.6.503 PMID:8759259

Waddell KM & Newton R (2007). The aetiology and associations of conjunctival intraepithelial neoplasia: further evidence. *Br J Ophthalmol*, 91: 120–121. doi:10.1136/bjo.2006.100297 PMID:17179130

Wain-Hobson S (1989). HIV genome variability in vivo. *AIDS*, 3: Suppl 1S13–S18. doi:10.1097/00002030-198901001-00003 PMID:2558685

Waters L, Stebbing J, Mandalia S *et al.* (2005). Hepatitis C infection is not associated with systemic HIV-associated non-Hodgkin's lymphoma: a cohort study. *Int J Cancer*, 116: 161–163. doi:10.1002/ijc.20988 PMID:15756687

Weber R, Sabin CA, Friis-Møller N *et al.* (2006). Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*, 166: 1632–1641. doi:10.1001/archinte.166.15.1632 PMID:16908797

Weissman JD, Brown JA, Howcroft TK *et al.* (1998). HIV-1 tat binds TAFII250 and represses TAFII250-dependent transcription of major histocompatibility class I genes. *Proc Natl Acad Sci USA*, 95: 11601–11606. doi:10.1073/pnas.95.20.11601 PMID:9751712

Westendorp MO, Frank R, Ochsenbauer C *et al.* (1995). Sensitization of T cells to CD95-mediated apoptosis by HIV-1 Tat and gp120. *Nature*, 375: 497–500. doi:10.1038/375497a0 PMID:7539892

Wong SW, Bergquam EP, Swanson RM *et al.* (1999). Induction of B cell hyperplasia in simian immunodeficiency virus-infected rhesus macaques with the simian homologue of Kaposi's sarcoma-associated herpesvirus. *J Exp Med*, 190: 827–840. doi:10.1084/jem.190.6.827 PMID:10499921

Wong-Staal F, Chanda PK, Ghrayeb J (1987). Human immunodeficiency virus: the eighth gene. *AIDS Res Hum Retroviruses*, 3: 33–39. doi:10.1089/aid.1987.3.33 PMID:3476127

World Cancer Report (2008). Available at http://www.iarc.fr/en/publications/pdfs-online/wcr/

Wu W, Vieira J, Fiore N *et al.* (2006). KSHV/HHV-8 infection of human hematopoietic progenitor (CD34+) cells: persistence of infection during hematopoiesis in vitro and in vivo. *Blood*, 108: 141–151. doi:10.1182/blood-2005-04-1697 PMID:16543476

Yajima M, Imadome K, Nakagawa A *et al.* (2008). A new humanized mouse model of Epstein-Barr virus infection that reproduces persistent infection, lymphoproliferative disorder, and cell-mediated and humoral immune responses. *J Infect Dis*, 198: 673–682. doi:10.1086/590502 PMID:18627269

Yao Y, Wang N, Chu J *et al.* (2009). Sexual behavior and risks for HIV infection and transmission among male injecting drug users in Yunnan, China. *Int J*

Infect Dis, 13: 154–161. doi:10.1016/j.ijid.2008.05.1228 PMID:18778963

Zhang RD, Guan M, Park Y *et al.* (1997). Synergy between human immunodeficiency virus type 1 and Epstein-Barr virus in T lymphoblastoid cell lines. *AIDS Res Hum Retroviruses*, 13: 161–171. doi:10.1089/aid.1997.13.161 PMID:9007201

Zhu P, Liu J, Bess J Jr *et al.* (2006). Distribution and three-dimensional structure of AIDS virus envelope spikes. *Nature*, 441: 847–852. doi:10.1038/nature04817 PMID:16728975