National Toxicology Program
U.S. Department of Health and Human Services

Report on Carcinogens

Monograph on Human Immunodeficiency Virus Type 1

RoC MONOGRAPH 08

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Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

The Report on Carcinogens Monograph series began in 2012. Report on Carcinogens Monographs present the cancer hazard evaluations of environmental agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") under review for the Report on Carcinogens. The Report on Carcinogens is a congressionally mandated, science-based, public health document that provides a cumulative list of substances that pose a cancer hazard for people in the United States. Substances are reviewed for the Report on Carcinogens to (1) be a new listing, (2) reclassify the current listing status, or (3) be removed.

NTP evaluates cancer hazards by following a multistep process and using established criteria to review and integrate the scientific evidence from published human, experimental animal, and mechanistic studies. General instructions for the systematic review and evidence integration methods used in these evaluations are provided in the *Handbook for the Preparation of Report on Carcinogens Monographs*. The handbook's instructions are applied to a specific evaluation via a written protocol. The evaluation's approach as outlined in the protocol is guided by the nature, extent, and complexity of the published scientific information and tailored to address the key scientific issues and questions for determining whether the substance is a potential cancer hazard and should be listed in the Report on Carcinogens. Draft monographs undergo external peer review before they are finalized and published.

The Report on Carcinogens Monographs are available free of charge on the NTP website and cataloged in PubMed, a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in the Health Assessment and Workspace Collaborative. Information about the Report on Carcinogens is also available on the NTP website.

For questions about the monographs, please email NTP or call 984-287-3211.

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Peer Review

Peer review of the Draft RoC Monograph on Human Immunodeficiency Virus Type 1 (HIV-1) was conducted by an ad hoc expert panel at a public meeting held December 17, 2015, in the Rodbell Auditorium at the National Institute of Environmental Health Sciences, David P. Rall Building, Research Triangle Park, NC (see http://ntp.niehs.nih.gov/go/38854) for materials, minutes, and panel recommendations from the peer-review meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and federal policies and regulations. The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

The charge to the Peer-Review Panel was as follows:

(1) Comment on the draft cancer evaluation component for HIV-1, specifically, whether it was technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the RoC listing criteria.

(2) Comment on the draft substance profile for HIV-1, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of the substance (available in the 14th edition of the Report on Carcinogens).

The panel was asked to vote on the following questions:

(1) Whether the scientific evidence supports the NTP's preliminary conclusion on the level of evidence for carcinogenicity for the specific types of cancer from cancer studies in humans.

(2) Whether the scientific evidence supports the NTP's preliminary listing decision for HIV-1 in the RoC.

This RoC monograph on HIV-1 has been revised based on NTP's review of the panel's peer-review comments. The Peer-Review Panel Report, which captures the panel recommendations for listing status of HIV-1 in the RoC and their scientific comments, and the NTP Response to the Peer-Review Report are available on the Peer-Review Meeting webpage for human immunodeficiency virus type 1 (http://ntp.niehs.nih.gov/go/38854).

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Abstract

Introduction: Approximately 1.2 million U.S. residents are infected with human immunodeficiency virus type-1 (HIV-1), an enveloped, single-stranded RNA retrovirus of the subfamily *Orthoretrovirinae*. In high-income countries, HIV-1 is transmitted from person to person primarily through sexual activity and contact with blood (e.g., sharing of needles by people who inject drugs). In lower-income countries, maternal-to-child transmission is also a concern. HIV-1 infection can cause the death of T-cells (CD-4) and severe immune suppression; if untreated, the infection progresses over time to AIDS, a range of immune-related opportunistic infections and related diseases, including cancer. These diseases, including three types of cancer—Kaposi sarcoma, non-Hodgkin lymphoma, and cervical carcinoma—are referred to as AIDS-defining conditions.

Methods: The National Toxicology Program (NTP) conducted a cancer hazard evaluation of HIV-1 infection and 12 types of cancer. The evaluation included the findings from studies reported in the IARC monograph in Volume 100B, as well as from human cancer studies and mechanistic reviews published after 2008. For each cancer site, the evidence from human and mechanistic studies was integrated considering the following guidelines: Hill's characteristics of causality, multicausality epidemiology considerations, and concepts of direct and indirect carcinogenesis proposed several virus experts. Finally, NTP applied the Report on Carcinogens (RoC) listing criteria to its assessment to reach an overall cancer hazard conclusion.

Results and Discussion: Epidemiological studies demonstrated consistent evidence of a causal association between HIV-1 infection and nine types of cancer and limited evidence of an association with three types of cancer. Most cancers are related to coinfection with both HIV-1 and another cancer-causing virus. In coinfected individuals, HIV-1 impairs their immune system's ability to suppress or destroy cancer-causing viruses, resulting in an increased risk of cancer from those viruses.

Nine infection-related cancers: NTP concluded there was sufficient evidence of the carcinogenicity of HIV-1 from studies in humans for seven cancers—Kaposi sarcoma, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, cervical cancer, invasive anal cancer, vaginal/vulvar cancer, and penile cancer—based on consistent findings of statistically significant increased risk in numerous epidemiological studies in different populations. Limited evidence was found for liver and oral cancers because confounding and other biases could not be reasonably excluded. Kaposi sarcoma-associated herpesvirus was a covirus for Kaposi sarcoma and NHL; Epstein-Barr virus for NHL and Hodgkin lymphoma; hepatitis B virus and hepatitis C virus for liver cancer; and human papilloma viruses for the three reproductive cancers, anal cancer, and oral cancer. Mechanistic studies, especially those evaluating CD-4 cell counts, support the evidence from epidemiological studies.

Three noninfection-related cancers: NTP concluded there was sufficient evidence of the carcinogenicity of HIV-1 from studies in humans for two cancers—conjunctival eye cancer and nonmelanoma skin cancer—based on consistent findings of statistically significant increased risks in numerous epidemiological studies in different populations. Although most studies have reported a positive association between HIV-1 infection and lung cancer, it is not clear whether tobacco smoking can explain the excess risk, and the evidence was considered limited. Mechanistic studies provide some evidence for a direct carcinogenic effect of HIV-1 and its proteins.

NTP Hazard Conclusion and Significance: The conclusion of the cancer hazard evaluation was that HIV-1 should be listed as k*nown to be a human carcinogen* in the RoC. The Secretary of Health and Human Services approved the listing of HIV-1 in the 14th RoC. The rationale for the listing was sufficient evidence from studies in humans (human cancer and mechanistic) for nine types of cancer. In the United States, HIV-1 was estimated to be responsible for approximately 3,900 cancers in 2010.

Introduction and Methods

This is one of a collection of five monographs that provide cancer hazard evaluations for the following human viruses for potential listing in the Report on Carcinogens (RoC): Epstein-Barr virus, Kaposi sarcoma-associated herpesvirus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, and Merkel cell polyomavirus. Viruses currently listed in the RoC include human papillomaviruses: some genital mucosal types (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Each virus was selected for review for the RoC based on a large database of scientific information (including authoritative reviews), public health concerns for adverse health outcomes, and evidence that a significant number of people are infected with each virus both in the United States and worldwide.

This section provides background information on the preparation of the monographs as well as a discussion of overarching issues related to evaluating the evidence for cancer from human epidemiological studies and evaluating the causation by viruses.

Monograph Contents

The RoC monograph for each virus reviews the relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status. Information reviewed in the monographs, with the exception of information on properties and exposure, comes from publicly available and peer-reviewed sources. All sections of the monographs underwent scientific and quality assurance review by independent reviewers.

The monograph provides the following information relevant to a RoC listing recommendation: Properties and Detection (Section 1), Human Exposure (Section 2), Human Cancer Studies (Section 3), Mechanistic and Other Relevant Data (Section 4), and Overall Cancer Hazard Evaluation and Listing Recommendation (Section 5). Because these viruses are primarily species-specific for humans, we are not conducting an evaluation of the level of evidence for carcinogenicity from studies in experimental animals and are including studies in animals that inform the mechanisms of carcinogenicity in the Mechanistic and Other Relevant Data section of the monographs, which is similar to the approach used by the International Agency for Research on Cancer (IARC). Also, specific details about the strains of the viruses are given only if needed to provide context, such as in the viral Properties and Detection section. The monographs relied on the information and data provided in previous IARC monographs on these five viruses in addition to newer key studies or reviews published since the IARC monographs; it is a peer review assessment of available data through August 17, 2015. Literature search strategies to obtain information relevant to the cancer evaluation are in Appendix A of each virus monograph; search terms were developed in collaboration with a reference librarian.

Evaluating the Evidence from Human Epidemiological Studies

The available studies of specific types of cancer for these human viruses present several challenges with respect to the evaluation of methodological strengths and limitations of the body of evidence. Large prospective cohort studies, particularly those that follow individuals for whom infection status is documented prior to follow-up or cancer diagnosis, have several potential methodological strengths, including evidence that infection precedes cancer diagnosis,

adequate statistical power, and, in some studies, have the ability to analyze dose-response relationships. However, there is the potential for misclassification of exposure in studies with a long follow-up period that measure the virus once and have a long follow-up period as new infections might not be identified. For most types of cancer, only cross-sectional or retrospective cohort studies or hospital- or clinic-based case-control studies are available, all of which lack direct evidence of temporality and may lack power or adequate exposure data, e.g., on viral load. However, molecular evidence from human studies and mechanistic data can be used in the evaluation of temporality, distinguishing latent infections caused by the tumor virus and causality. For some (typically rare) outcomes (e.g., cutaneous T-cell lymphoma and human T-cell lymphotropic virus type 1, or lymphoepithelial carcinoma of the salivary gland and Epstein-Barr virus), only case-comparison studies, in which selection of comparison groups may be biased, unmatched, or inadequately described, or case series are available.

For several rare types of cancer, e.g., adult T-cell leukemia/lymphoma and human T-cell lymphotropic virus type 1, or primary effusion lymphoma and Kaposi sarcoma-associated herpesvirus, the presence of the virus in the tumor cells is used as a diagnostic criterion to define the cancer, and thus, evidence of causality relies on cases defined by this criterion and molecular evidence from human studies rather than on epidemiological population-based studies of the association of the virus with a level of cancer risk.

In addition, methodologically adequate studies should include measurement of cofactors and consider potentially confounding factors; however, relatively few studies have measured a panel of other viruses or taken into account other cofactors. Further, while studies comparing cancer risk in treated vs. untreated populations may provide indirect evidence of the role of human immunodeficiency virus-1, these studies, in particular calendar-period analyses, may not adequately account for changes in risk attributable to improved survival rates or changes in other risk factors.

Evaluating Causality of Viruses

Approximately 12% of all human cancers have been attributed to viral infections. Although the known oncogenic viruses belong to different virus families, they often share several common traits, such as, viral cancers appear in the context of persistent infections, occur many years to decades after acute infection, and the immune system can play a deleterious or a protective role (Mesri et al. 2014). Many viruses generally increase cancer risk in the context of immunosuppression or chronic inflammation (Mesri et al. 2014). Similar to other carcinogenic agents, only a small percentage of infected or exposed individuals develop cancer, often decades after the initial infection, reflecting the complex nature of oncogenesis. Some cofactors produced by other organisms or agents in conjunction with risk modifiers such as virus-host cell interactions, host genetic factors, immune dysfunction or chronic inflammation often can contribute to malignant transformation. In addition, severe immunosuppression, as seen with congenital immunodeficiency syndromes, chronic human immunodeficiency virus type 1 infection, or as a result of tissue anti-rejection medication, can severely compromise the immune surveillance capabilities of the patient. There are also other challenges that are somewhat unique to the evaluation of the epidemiological studies of viruses and cancer (discussed below) and thus molecular evidence from human tissues is often considered in the evaluation of causality.

In light of these issues, IARC monographs and several other publications have recommended paths to evaluate causality, which are discussed below and incorporated into the NTP approach for evaluating causality of the viruses. What is important for public health in determination of causation of a health effect, such as risk for cancer, is whether the health effect is eliminated or mitigated by removal of the substance (Rothman and Greenland 2005).

A number of attempts have been made to develop criteria or considerations that address causal associations. However, all of them have limitations, especially when applied to infectious agents (Moore and Chang 2010). The following sections identify factors to consider for evaluating causality, some limitations arising from a strict application of the criteria in the context of virally induced cancers, some alternative approaches, and finally, the NTP's approach for evaluating the role of select viral agents in human cancer.

Hill's Characteristics of Causality

Hill proposed nine characteristics to consider when evaluating causality, primarily for epidemiological studies, although they have been expanded for evaluating mechanistic and other types of data (Table 1). Several considerations—strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure (Hill 1965)—are used to help guide the RoC evaluations of the human epidemiological data (see RoC Handbook, NTP (2015)). However, it should be noted that these are not criteria; and, with the exception of temporality, each and every element is not required in order to demonstrate causality (Rothman and Greenland 2005). Hill (1965) avoided discussing the meaning of "causation," noting that the "cause" of an illness could be immediate and direct or remote and indirect. The primary question addressed by Hill was "whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A."

Table 1. Hill's Epidemiological Characteristics for Evaluating Causality

Criterion	Description
1. Strength of association	A strong association between a virus and a cancer increases the confidence for causality unless confounded by some other exposure. However, a weak association does not give evidence against causality.
2. Consistency	Consistent findings observed among different groups of people, in different places, circumstances, and times.
3. Specificity	A viral exposure is limited only to specific types of cancer; this is considered a weak factor because there are well-established examples in which a virus might cause several types of cancer.
4. Temporality	Exposure to the virus must occur prior to the onset of the cancer, in contrast to a "passenger infection."
5. Biological gradient	The virus is more likely to be found at the tumor site than at non-tumor sites.
6. Plausibility	Should be applied with caution because it is limited by current medical knowledge (e.g., an implausible mechanism may gain acceptance with increased understanding of the underlying biology).
7. Coherence	A virus-cancer association should not seriously conflict with known facts on the cancer's natural history and biology.

Criterion	Description
8. Experiment	Changing either exposure or continued infection in a randomized clinical trial should change the measure of clinical outcome (e.g., vaccination programs for HPV and HBV).
9. Analogy	Are related viruses clearly established to cause cancers in animals or humans?

Source: Moore and Chang (2014).

Evaluating Mechanistic Data from Human Studies

In their evaluation of the evidence for Epstein-Barr virus, the IARC working group noted that the large majority of people are latently infected with Epstein-Barr virus, thus, epidemiological studies may be limited in determining whether the presence of Epstein-Barr virus in tumor tissue is a cause of the cancer or an effect of the tumor. Therefore, in addition to the Hill characteristics, IARC (1997) considered the following factors in their evaluation of Epstein-Barr virus, which are also applicable to other viruses:

- The proportion of Epstein-Barr virus-positive cases in a given tumor entity.
- The proportion of tumor cells that carry the virus.
- The monoclonality of Epstein-Barr virus in the tumor.
- The expression of Epstein-Barr virus proteins.

zur Hausen (1994; 2001) proposed consideration of the following types of mechanistic or epidemiological evidence for evaluating causality of viruses and cancer:

- The presence and persistence of viral DNA in tumor biopsies and cell lines derived from the same tumor type.
- The growth-promoting activity of specific viral genes or of virus-modified host cell genes in tissue culture systems or in suitable animal systems.
- The continuous expression of viral oncogenes or on the modification of host cell genes containing viral sequences which maintains the malignant phenotype.
- The epidemiological evidence that the virus infection is a major risk factor.

It is difficult to prove that a virus causes cancer, and such determinations almost always generate considerable controversy and debate (Moore and Chang 2010). Viral cancers employ various mechanisms that involve both direct and indirect modes of interaction (Table 2) (zur Hausen and de Villiers 2014). Understanding and managing viral-induced cancers in humans has been hampered by a lack of suitable animal models, the disparate nature of tumor types, a long latency period between primary infection and cancer development, the different types of oncogenic viruses, and the complex nature of the virus-host cell interactions leading to cancer (Mesri et al. 2014; zur Hausen and de Villiers 2014)

Table 2. Direct and Indirect Modes of Interaction of Viral Infections and Cancers

Type	Description
Direct carcinogenesis	• Continued presence and expression of viral oncogenes usually after viral genome integration into host cell DNA. • Insertional gene activation or suppression. • Continued episomal presence of viral nucleic acid and suppression or activation of cellular genes (e.g., by viral microRNA).
Indirect carcinogenesis	• Induction of immunomodulation, activation of latent tumor virus genomes. • Induction of oxygen and nitrogen radicals. • Amplification of latent tumor virus DNA. • Induction of mutations and/or translocations. • Prevention of apoptosis.

Source: zur Hausen and de Villiers (2014).

Multicausality Issues

Although thousands of viruses are known to cause infection, only a few have been shown to cause cancer in humans (Moore and Chang 2010). An important consideration regarding causality (not limited to viruses) is "multicausality," that is, the concept that many determinants act together to cause a disease. Rothman and colleagues (Rothman and Greenland 2005) defined a sufficient cause as "complete causal mechanism" – not a single factor but a set of minimal factors (i.e., component causes) – that if present in an individual will cause disease. Most causes are neither necessary nor sufficient in the absence of other factors to produce the disease; however, a cause does not have to be either necessary or sufficient for its removal to result in disease prevention (Rothman and Greenland 2005; zur Hausen and de Villiers 2014).

Application of Causality Criteria and Alternative Approaches

Moore and Chang (2010) investigated the difficulties associated with strict application of the Hill characteristics for two of the most recently discovered oncogenic viruses: Kaposi sarcoma-associated herpesvirus and Merkel cell polyomavirus. Kaposi sarcoma-associated herpesvirus was shown to fulfill Hill's characteristics for causality of Kaposi sarcoma; however, the application of the characteristics was problematic in the case of Merkel cell polyomavirus and Merkel cell carcinoma (see the monographs for Kaposi sarcoma-associated herpesvirus and Merkel cell polyomavirus). These two examples illustrate the diversity in the patterns of tumor virus epidemiology. Some of the reasons Hill's characteristics worked for Kaposi sarcoma-associated herpesvirus but not Merkel cell polyomavirus is that all clinical forms of Kaposi sarcoma require infection by Kaposi sarcoma-associated herpesvirus while most studies indicate that not all forms of Merkel cell carcinoma require the presence of Merkel cell polyomavirus. In the case of Merkel cell polyomavirus, additional considerations, as suggested by IARC (1997) and zur Hausen (1994; 2001) provide molecular evidence of the association between Merkel cell polyomavirus and Merkel cell carcinoma, such as mutation and monoclonal integration of the tumor-causing form of the virus into the cellular genome and requirement of tumor cells for the presence of viral oncoproteins for cell survival and proliferation.

While causal criteria can be helpful, there are flaws and practical limitations that restrict their use in cancer biology (Moore and Chang 2010). Therefore, a more probabilistic approach may be more useful for determining whether or not certain viruses cause human cancers. For example,

instead of trying to determine if virus A causes cancer B, the probabilistic approach examines if cancer B is more probable in the presence of virus A. Although a correlation does not imply causation, it can be argued that correlations that are strong, reproducible, and predictive have a similar value as a causative conclusion. In a similar fashion, zur Hausen and de Villiers (2014) also expressed concern over all attempts to summarize criteria for "causality" of infectious agents in cancer development and proposed replacing "causal factor" with "risk factor" and grading them according to their contribution to an individual's cancer risk. This will require a greater understanding of the complexity of factors involved and their mechanistic contribution to individual cancers.

RoC Listing Criteria

Known to Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans,* which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated to Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

NTP's Approach

For each virus, the NTP applied the RoC listing criteria (see text box) to the body of literature to reach the listing recommendation. The level of evidence conclusion from studies in humans considers the evidence from epidemiological studies as well as clinical and molecular studies of tissues from exposed (i.e., infected) individuals. In evaluating the mechanistic data and determining the recommendations for its level of evidence conclusion and overall listing recommendation, the NTP considered the principles outlined by Hill (1965), IARC (1997), zur Hausen (1994; 2001; 2014), and Rothman and Greenland (2005) in its assessment of causality

for the five viruses reviewed. However, these factors were not used as a strict checklist to either prove or disprove a causal association but rather as guidance to assess the level of epidemiological or molecular evidence that a virus contributes to a carcinogenic effect.

1. Properties and Detection

This section reviews the biological properties (Section 1.1) and detection methods (Section 1.2) for human immunodeficiency virus type 1 (HIV-1).

1.1. Biological Properties

The following section reviews the types of HIV, its structure, life cycle, and course of infection.

1.1.1. Family and Type

HIV-1 was first isolated in 1983 and was associated with acquired immunodeficiency syndrome (AIDS) the following year (IARC 2012a). A second type, HIV-2, is geographically limited to West Africa and is less pathogenic than HIV-1 which is distributed worldwide (De Cock et al. 1991; IARC 2012a). HIV-1 and HIV-2 are enveloped RNA viruses of the family *Retroviridae*, under the *Orthoretrovirinae* subfamily, in the genus *Lentivirus*, characterized by a long period between infection and symptomatic disease. HIV-2 is less transmissible than HIV-1 and is characterized by a slower progression of disease (IARC 2012a).

1.1.2. Viral Structure and Genome

The HIV-1 virion (120 nm diameter) is composed of a lipid membrane envelope with two surface proteins (gp120 and gp41), which surrounds a protein matrix, inside which is a protein capsid containing two copies of the viral single-stranded RNA (ssRNA) genome (9.8 kb) and the enzymes reverse transcriptase, integrase, and protease (see Figure 1-1) (IARC 2012a). The lipid membrane envelope is created by budding off the host cell membrane, and viral glycoproteins are situated with gp41 spanning the lipid membrane and gp120 binding to the exterior portion of gp41. The protein gp120 binds to CD4 on T cells, imparting tropism for those cells. RNA is normally very sensitive to degradation by nuclease enzymes, but the HIV-1 genome binds to nucleocapsid proteins (p6 and p7) that inhibit nuclease enzymes. The capsid is made from the p24 protein and the matrix is made from the p17 protein. Aside from these structural proteins there are three enzymes within the capsid (reverse transcriptase, integrase, and protease) and proteins *Vif*, *Vpr*, and *Nef*; the *Vif* and *Vpr* proteins help support viral replication and *Nef* is a regulatory protein that increases virulence.

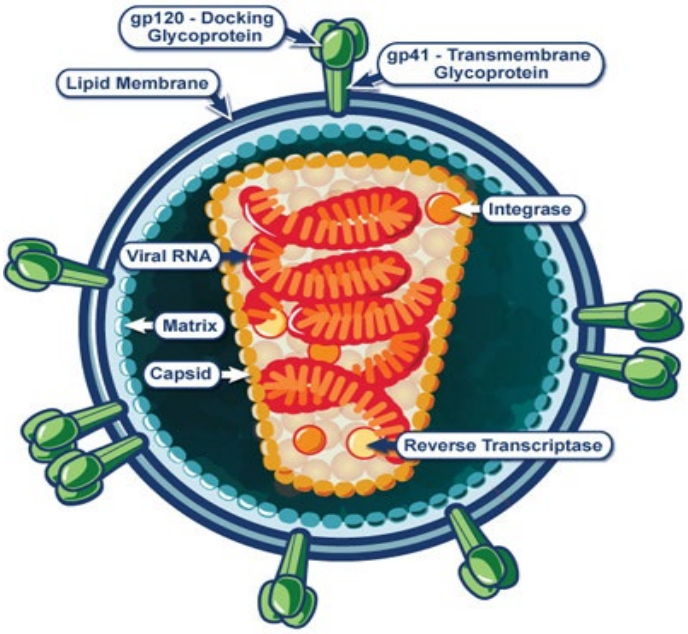

Figure 1-1. Human Immunodeficiency Virion Structure

Source: NIAID (2009). Courtesy: National Institute of Allergy and Infectious Diseases.

The HIV-1 genome is 9.8 kb long and contains three major genes, which encode multiple proteins, and six genes that encode single proteins, all of which are flanked by two long terminal repeats (LTRs) (see Figure 1-2) (IARC 1996; 2012a). The three main genes are *gag*, *pol*, and *env*. The *gag* gene produces the matrix protein (p17), viral capsid protein (p24), and two nucleocapsid proteins (p6 and p7). The *pol* gene produces reverse transcriptase, integrase, and protease; the protease is used to cleave *gag* and *pol* proteins into the individual proteins. The third main gene, *env*, encodes the two envelope proteins gp41 and gp120. The single protein genes include regulatory proteins *tat* and *rev* and accessory proteins *nef*, *vif*, *vpu*, and *vpr*. Viral gene expression is controlled by promoters and enhancers in the two long terminal repeat regions.

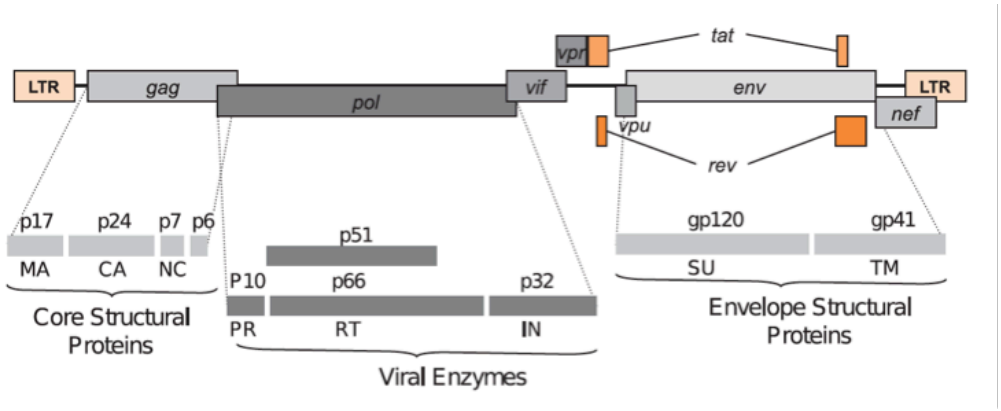

Figure 1-2. Human Immunodeficiency Virus Genome Structure

Source: IARC (2012a).

1.1.3. Life Cycle and Course of Infection

The life cycle of the virus begins with binding of the viral gp120 protein to CD4 on helper T cells (see Figure 1-3) (IARC 1996; 2012a). A co-receptor CCR5 or CXCR4 on the CD4 T-cell is also needed. Binding allows the viral envelope to fuse with the cell membrane, releasing the contents into the cell's cytoplasm. Inside the cytoplasm, the matrix and capsid fall apart and release the ssRNA genome and viral enzymes. Reverse transcriptase enzyme reads the RNA and polymerizes a complementary DNA strand. The DNA/RNA genome is then used to replicate a double-stranded DNA (dsDNA) genome. Reverse transcriptase is an error-prone DNA polymerase and introduces random mutations into the viral genome. Integrase then binds the dsDNA genome and travels to the nucleus where it integrates into the host genome, forming a stable infection. The virus can then remain latent and evade immune detection by several mechanisms, including *tat*- and *nef*-mediated suppression of major histocompatibility complex I (MHC I) expression so that CD8 T cells cannot "see" the virus or by disruption of nearby immune cells through the secretion of *tat* and *nef* proteins. During the lytic phase, viral structural genes and enzymes are expressed and ssRNA genomes are produced and bud off the cell membrane to form immature enveloped virions. Envelope proteins travel to the host cell surface through the endoplasmic reticulum. The virion then matures as the protease cleaves precursor proteins (gag and pol) into their individual proteins so they can form the matrix and capsid. CD4 cells are directly killed in large numbers or indirectly via HIV-1 disruption of cell regulation followed by apoptosis.

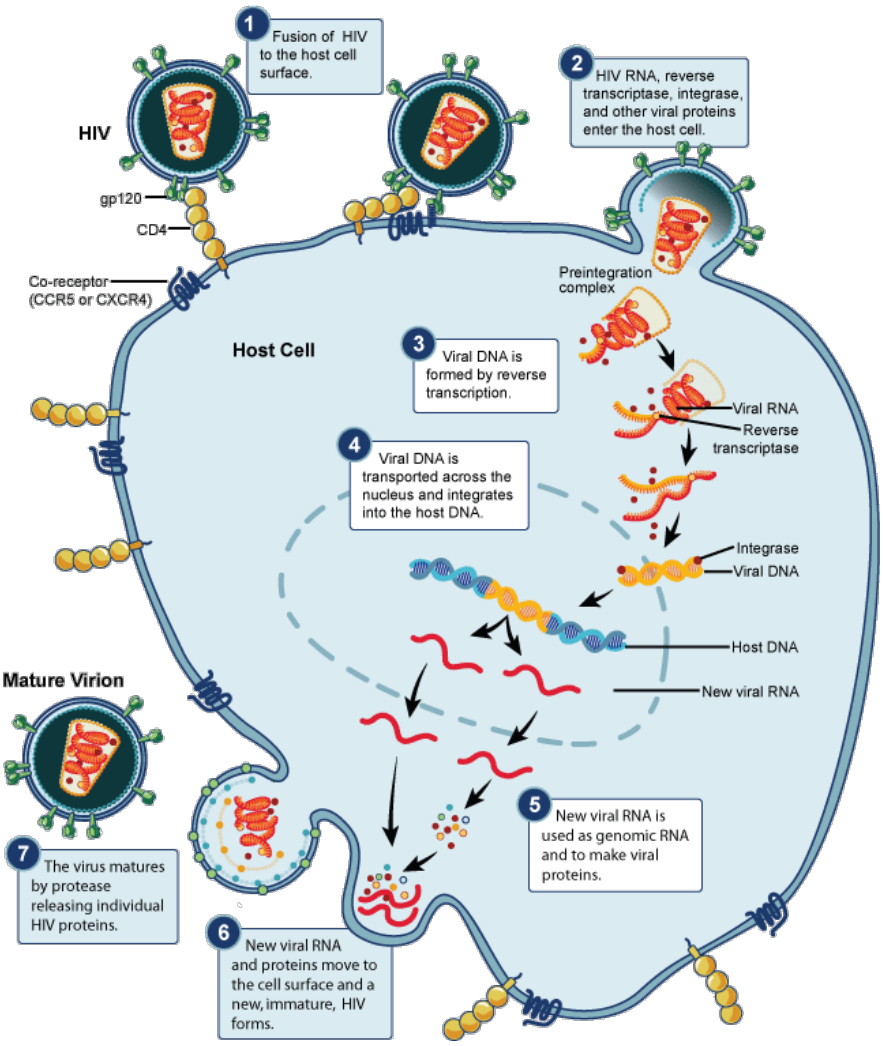

Figure 1-3. HIV-1 Replication Cycle

Source: NIAID (2009). Courtesy: National Institute of Allergy and Infectious Diseases.

HIV-1 can also infect other cells of the immune system, including B cells and monocytes and macrophages; these cells are long-lived and are not killed as a result of viral penetration and thus act as one of the body's reservoirs of HIV-1 infection. Other reservoirs include follicular dendritic cells within lymph nodes, tonsils, adenoids, and mucosa-associated lymphoid tissue (IARC 2012a).

In the symptomatic acute phase of infection, flu-like symptoms are experienced by the majority of people, typically within two to four weeks after initial infection. During the acute phase, which lasts 10 to 12 weeks, viral load and infectiousness are extremely high, with over 20 times the sexual transmission rate compared with that of the established infection period (CDC 2014b). The immune system responds with increased production of CD8 (killer) T cells and B-cell antibodies, which kill infected CD4 cells (along with other cells with HIV-1 on the cell surface), resulting in a fall in HIV-1 titers. After this acute phase, HIV-1 remains at low levels in the blood, but continues to replicate and mutate, mostly in lymphoid tissue. HIV-1 integrated into the host genome can remain undetected and can get carried to the brain by infected monocytes

and macrophages that are not killed by the virus. Most untreated individuals are latently infected for an average of 10 to 12 years before symptoms of HIV-1-related diseases appear, although the latency range varies from about 2 to over 25 years (DHHS 2015b). Several prospective studies have shown that the viral load (also referred to as the viral "set point") occurring within 6 months to a year after infection predicts strongly for the later risk of disease progression (DHHS 2015b).

1.2. Detection

HIV-1 has been detected primarily in blood and sexual fluids (semen and vaginal secretions), and in very low concentrations in other body fluids (unless contaminated by blood or sexual fluids) (IARC 1996; IARC 2012a). Detection of HIV-1 infection consists of (1) tests to detect HIV-1 antibodies and/or antigen, (2) HIV-1 RNA tests, and (3) HIV-1 culture.

1.2.1. Detection of Antibodies or Antigens in Body Fluids

Detection of anti-HIV-1 antibodies represents current infection since HIV-1 infections are considered lifelong (Cornett and Kirn 2013; IARC 1996). The rate of seroconversion (or "window period") varies from less than 1 month to 3 months in 97% of people (Hecht et al. 2011). During the window period HIV-1 antibody tests cannot detect the virus. Third generation tests detect IgG and IgM antibodies three weeks after the initial infection (Cornett and Kirn 2013; IARC 1996) and fourth generation immunoassays, available in the United States since 2010, detect a combination of capsid protein p24 antigen, IgG, and IgM, and can be used to detect HIV-1 infection as early as two weeks after infection. p24 antigen levels are short-lived and decline rapidly after the first phase of HIV-1 viremia in the days following infection until much later in the infection period.

Recommended current testing guidelines for U.S. laboratories were adopted in 2014 and consist of a sequence of tests used in combination to improve the accuracy of the laboratory diagnosis of HIV-1 based on testing of serum or plasma specimens. Previously, guidelines from the Centers for Disease Control and Prevention (CDC) for serodiagnosis of HIV-1 infections, testing for antibodies for HIV-2, and confirmation of reactive rapid antibody test results in 2004 employed only tests for HIV antibodies, such as the HIV-1 Western Blot and HIV-1 IFA. The updated recommendations include tests for HIV antigens and HIV nucleic acid based on data from high-risk populations showing that antibody testing alone can miss a high percentage of HIV infections which are detectable by virologic tests (CDC 2014b).

The updated recommendations for testing algorithms are more accurate than previous algorithms for laboratory diagnosis of acute HIV-1 and HIV-2 infections, have fewer indeterminate results and faster turnaround time for most results; and are equally accurate as previous laboratory diagnosis of established HIV-1 infection.

A panel of assays can also be used to distinguish recent from long-standing HIV-1 infections by taking advantage of the sequence of events following infection, thereby assisting in the recognition of HIV-1 incidence in cross-sectional serological studies (Murphy and Parry 2008). The relationship between different measures of HIV-1 infection over time is shown in Figure 1-4.

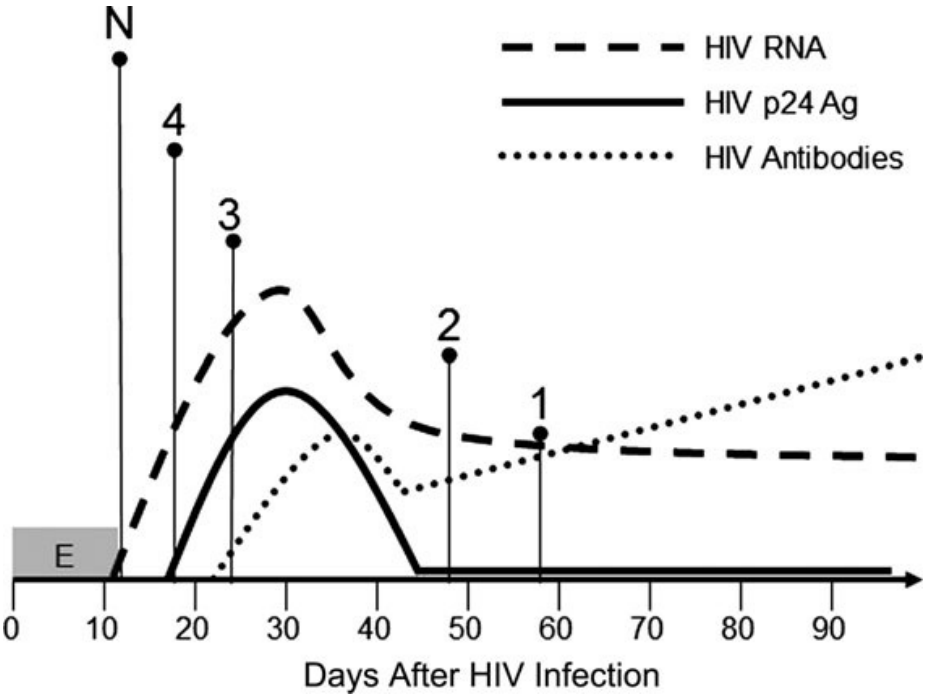

Figure 1-4. Diagnostic Markers of Human Immunodeficiency Virus (HIV) Infection

Source: Cornett and Kirn (2013).
Time to reliable positivity of first (1), second (2), third (3), and fourth (4) generation and nucleic acid amplification test (N) HIV-1 diagnostic assays superimposed on a graphical depiction of the kinetics of circulating HIV-1 RNA, p24 antigen, and HIV-1 antibodies.
Ag = antigen; E = eclipse period; HIV = human immunodeficiency virus.

1.2.2. Detection of HIV-1 RNA in Body Fluids

Nucleic acid-based testing of blood or blood cells for viral genes, predominantly HIV-I *gag,* HIV-II *gag*, HIV-*env*, or HIV-*pol*, by RT-PCR (converting HIV-1 RNA to complementary DNA by reverse transcriptase [RT] treatment and amplifying by polymerase chain reaction [PCR]) is also used to detect early infection and to measure viral load (Cornett and Kirn 2013; IARC 1996; IARC 2012a). This test can detect HIV-1 within a range of approximately two weeks to one month of infection. PCR-based assays can also measure viral load using dried blood blot samples (Smit et al. 2014). Since RT-PCR can measure viral load, it is often used to predict prognosis and the effectiveness of treatment (IARC 1996; IARC 2012a).

1.2.3. Detection of HIV-1 by Viral Culture

In some cases, immunoassays do not give meaningful results (IARC 1996). This can happen either when results are considered indeterminate, as only one of the two antibodies (anti-Gag and anti-Env) needed for a positive result were detected, or when infants less than 15-months-old are tested, as anti-HIV-1 IgG antibodies reflect maternal antibodies and not those of the infant (DHHS 2015a). Detection of HIV-1 can then be performed by culturing the HIV-1 virus and testing the culture for either the p24 antigen or reverse transcriptase activity. HIV-1 culture takes two to four weeks to perform and specialized facilities to conduct. Alternatively, infants can be tested for anti-HIV-1 IgA or IgM antibodies, which do not cross the placenta, or by PCR to detect HIV-1 RNA (Bunders et al. 2010; França et al. 2012; Palmeira et al. 2012; DHHS 2015a).

1.3. Summary

HIV-1 is an enveloped single-stranded RNA retrovirus of the subfamily *Orthoretrovirinae* and genus *Lentivirus* (IARC 2012a). HIV-1 is composed of an outer lipid membrane envelope with two surface proteins surrounding a protein matrix, inside of which is a protein capsid containing two copies of the 9.8-kb viral genome and the enzymes for viral replication, integration into host cell genetic material, and processing of viral proteins. HIV-1 infection can be detected by anti-HIV-1 antibodies, which typically take one to three months to become detectable serologically, HIV-1 antigens (p24), HIV-1 RNA (*gag*, *env*, *pol*), or by measuring HIV-1 antigen and HIV-1 RNA from in vitro culture of the virus, and which can be used if antibody detection gives indeterminate results.

2. Human Exposure

This section discusses transmission and prevalence (Section 2.1) and non-cancer diseases, prevention, and treatment for HIV-1 infection (Section 2.2).

2.1. Transmission and Prevalence

In infected people, blood, semen, and vaginal fluids contain measurable quantities of HIV-1; other body fluids, including saliva, urine, sweat, and tears, contain negligible amounts of HIV-1 (unless contaminated by blood) (IARC 1996; IARC 2012a). The transmission of HIV-1 infection occurs by direct blood-to-blood transmission or from blood or infected body fluids via mucous membranes into the bloodstream. Vertical transmission between HIV-1-infected mothers and neonates occurs *in utero* and via contamination of the neonate's mucous membranes during the birth, and/or via infected breast milk during lactation. In infected women not treated with antiretroviral prophylaxis, an estimated 15% to 25% of infants may be born with HIV-1 infection; breastfeeding may increase that risk by another 5% to 20% (Newell and Thorne 2004). Horizontal transmission occurs primarily during sexual activity, i.e., oral, anal, and vaginal sex, in which HIV-1 in infected sexual fluids crosses mucous membranes to enter the bloodstream; and by direct blood-to-blood transmission, primarily via sharing of infected needles among injection drug users, or more rarely by percutaneous transmission via, e.g., needlestick injury, or via the transfusion of infected blood (depending on the availability of effective blood supply screening programs) (IARC 2012a). Non-sexual mucous membrane or non-intact skin contact with infected blood or body fluids in, e.g., occupational healthcare or first responder settings (e.g. CDC 1987; Ippolito et al. 1999; Leiss et al. 2006) may also increase exposure and the potential risk of HIV-1 transmission, although the actual risk of infection from percutaneous or mucous membrane exposure is estimated to be less than 1% (Cardo et al. 1997).

In resource-rich countries, the two primary behavioral risk factors for transmission are the practice of unprotected sex (i.e., particularly unprotected anal sex), and the sharing of drug needles. The relative importance of these factors varies widely geographically as a function of differences in sexual practices, prevalence of injecting drug use, screening practices for the transfusion blood supply and blood donors, and the extent and effectiveness of deployed education and prevention strategies.

However, other risk factors are salient for the two-thirds of adults with HIV-1 infection living in sub-Saharan countries (UNAIDS 2013b). Unlike resource-rich countries, well over half of those infected are women, largely as a result of the high rate of multiple partners among men, and the practice of polygyny (Reniers and Watkins 2010). In addition, in contrast to North America and Europe, mother-to-child transmission, perinatally or via breastfeeding, accounts for a high proportion of HIV-1 infections (IARC 1996; IARC 2012a; UN 2001); and unsafe medical practices (e.g., injection practices), may also account for a higher proportion of infections (e.g., (IARC 2012a; Zetola et al. 2009).

Other risk factors for HIV-1 infection globally include other sexually transmitted infections, e.g., chlamydia and gonorrhea, which can increase the risk of sexually transmitted HIV-1 infection, in part by causing inflammation or rupture of mucous membranes in the vagina, vulva, penis, or anus. However, treatment or prevention interventions for other sexually transmitted diseases do

not always result in decreases in HIV-1 infection rates (see review by (Ng et al. 2011)). Other risk factors include circumcision, hormonal factors, and host immune and genetic factors (IARC 1996; IARC 2012a).

Approximately 37 million people worldwide are infected with HIV-1 and approximately 2 million were newly infected in 2013, a decline of about one-third in new infections from 2001 to 2012). There were an estimated 1.6 million AIDS-related deaths worldwide in 2012 (UNAIDS 2013c). Although subject to some uncertainty due to variations in HIV-1 screening and testing programs, the reported current prevalence and incidence of HIV-1 infection show considerable variation worldwide (Table 2-1).

Table 2-1. Global Prevalence and Incidence of HIV-1 Infection in 2014

Region	HIV-1 Prevalence	HIV-1 Incidence	Adult Prevalence Rate (%)
Sub-Saharan Africa	25.8 million (70%)	1.4 million	4.8
Asia and Pacific	5.0 million (14%)	340,000	0.2
Western/Central Europe and North America	2.4 million (7%)	85,000	0.3
Latin America	1.7 million (5%)	87,000	0.4
Eastern Europe and Central Asia	1.5 million (4%)	140,000	0.9
Caribbean	280,000 (<1%)	13,000	1.1
Middle East and North Africa	240,000 (<1%)	22,000	0.1
TOTAL	36.9 million	2.0 million	0.8

Source: Kaiser Family Foundation (2015).
Data from UNAIDS Global AIDS Report 2014 (2013b).

The current U.S. prevalence of HIV-1 infection is approximately 1.2 million, of which an estimated 13% are unaware of their infection status (CDC 2015a) (which can be confirmed by standardized testing protocols such as those recommended by the CDC (2006)). Approximately 47,350 people were newly infected with HIV-1 in 2013 (CDC 2015a). A total of approximately 660,000 people with an AIDS diagnosis have died since the start of the epidemic in 1981.

2.2. Diseases, Prevention, and Treatment

Acquired immune deficiency syndrome (AIDS) typically results from long-term untreated HIV-1 infection. The WHO classification (2007) is based on four clinical stages from primary HIV-1 infection to AIDS. Criteria for defining a confirmed case have been recently updated given new multi-test algorithms and the need to recognize early HIV infection (CDC 2014c). Cases are currently classified as Stage 0 through 3, with Stage 0 being early infection, recognized by a negative HIV test within 6 months of HIV diagnosis; and Stage 3 being AIDS. This surveillance case definition is intended primarily for monitoring the HIV infection burden, not as a basis for clinical decisions for individual patients. However, studies included in this review have not used this case definition, and therefore, this review will not refer to this staging classification.

The CDC (2015b) has identified a list of the most common opportunistic infections or related conditions for individuals living in the United States that are used to diagnose AIDS. The opportunistic infections occur more frequently and are more severe in individuals with weakened

immune systems, including people with HIV-1 infection or a CD4 count of <200/μL. Among non-cancer diseases, the most common are opportunistic infections including candidiasis, *Pneumocystis jirovecii*, cytomegalovirus disease, tuberculosis, toxoplasmosis, histoplasmosis, mycobacterium avian complex, cryptococcosis and cryptosporidiosis, which are associated with a decrease in CD4 cells and the resulting impairment of immune function. A number of AIDS-related diseases are associated with viruses or other infections, for example, human papillomavirus, herpes simplex or herpes zoster virus, cytomegalovirus, hepatitis B or C virus, Epstein-Barr virus, or Kaposi sarcoma-associated herpesvirus (CDC 2015b; IARC 1996; IARC 2012a). Hepatitis C virus infection, primarily transmitted via injection drug use, and also transmitted via sexual fluids, is estimated to occur among 25% to 30% and hepatitis B virus among 6% to 14% of HIV-1-positive people (Alter 2006). Tuberculosis, caused by *Mycobacterium tuberculosis*, is a common disease and co-infection, particularly in sub-Saharan Africa and other resource-constrained countries (IARC 1996). Chronic conditions, including HIV-1-associated nephropathy, diabetes, and cardiovascular disease, may also be more common among HIV-1-infected people compared with non-infected populations, although part of this increase in risk may result from long-term treatment with antiretroviral drugs rather than HIV-1 infection *per se* (Feeney and Mallon 2011).

Since the primary mode of HIV-1 transmission in most populations is unprotected sex, behavioral risk reduction strategies have focused on education about safer sex practices, ranging from abstinence to consistent condom use, and testing for HIV-1 status. In addition, blood-to-blood transmission risk can be decreased by education about the risk of infection from mucous membrane, percutaneous, and intravenous contact with infected fresh blood, and by the use of clean needles, particularly among high-risk populations, including sex workers, injection drug users, and infected pregnant mothers (CDC 2015d).

Effective screening of the blood supply has also reduced infection rates, along with increased penetration of HIV-1 testing programs using rapid tests (CDC 2006). Condom distribution and needle exchange programs have been instituted in some populations. The CDC reports that early HIV-1 treatment has a profound prevention benefit with 96% reduction in the risk of transmitting HIV-1 to an uninfected partner with early initiation of antiretroviral therapy (CDC 2016). Short-term post-exposure prophylaxis in which specific antiretroviral drugs are taken within 72 hours after a high-risk episode, such as sexual assault, or an accidental needlestick injury, can be instituted to prevent the establishment of HIV-1 infection, and prophylactic prevention of mother-to-child transmission including antiretroviral drugs and related precautions have been instituted (CDC 2014d). In addition, pre-exposure prophylaxis, in which uninfected high-risk subgroups take antiretroviral drugs (tenofovir disoproxil fumarate and emtricitabine) on a daily basis and are tested regularly, has undergone clinical trials in the United States and is now recommended for specific at-risk populations (CDC 2014a). Mother-to-child HIV-1 transmission risk has been greatly reduced, in some cases from up to 48% to under 2% (Newell and Thorne 2004) by the use of antiretroviral drug administration to the mother in the pre-labor and breastfeeding period and beyond, and to the infant in the immediate postnatal period and up to 14 weeks among breastfed infants (e.g., with nevirapine in combination with zidovudine), combined with Cesarean delivery in some populations; the latter can reduce infection by up to 70% (European Mode of Delivery Collaboration 1999). Updated recommendations for the prevention of mother-to-child transmission have been made by the Centers for Disease Control (CDC) (CDC 2014d).

Finally, a substantial international effort to develop an effective vaccine for HIV-1 has been made but has proved challenging (Wang et al. 2015) and no prophylactic or therapeutic vaccine is currently available (NIAID 2015).

Treatment to suppress the viral load of HIV-1 consists of five main classes of antiretroviral drugs: fusion or entry inhibitors, integrase inhibitors, protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitor, and non-nucleotide reverse transcriptase inhibitors, which are designed to block different steps in the HIV-1 replication cycle described above (Avert.org 2015a; 2015b). Two or more of these drugs, with at least two from different classes of compounds, are used in various combinations designed to disrupt viral replication at more than one stage.

Over 20 antiretroviral drugs have been developed since the development of the nucleoside reverse transcriptase inhibitor zidovudine (azidothymidine) in the mid to late 1980s (Avert.org 2015b) followed by the nucleoside reverse transcriptase inhibitors didanosine and stavudine in the early 1990s and lamivudine in 1995. These drugs were shown to be more effective in combination with zidovudine than administered alone. In 1995, the first protease inhibitor (saquinavir) was approved in the United States by the U.S. Food and Drug Administration (FDA), and in combination with one or two of the nucleoside reverse transcriptase inhibitors were considerably more effective in suppressing HIV-1 drug-resistant mutation than nucleoside reverse transcriptase inhibitors alone and thus delaying the onset of AIDS. These combination drugs are called highly active antiretroviral therapies (HAART) or combination antiretroviral therapy (cART) and are now incorporated into standard treatment guidelines (e.g. DHHS 2015b).

Currently, WHO (2013) recommends as a first-line treatment for adults and adolescents one fixed dose daily pill containing two nucleoside reverse transcriptase inhibitors (tenofovir, and lamivudine or emtricitabine) and one non-nucleoside reverse transcriptase inhibitor (efavirenz). However, the availability of antiretroviral therapies, particularly the new generation of drugs, varies widely across the world (UNAIDS 2013a).

2.3. Summary

HIV-1 infection has become a global epidemic since its identification in the early 1980s, with approximately 35 million people currently infected worldwide. In the United States, approximately 1.2 million people are currently infected, representing less than 0.5% of the population, and the incidence rate has remained stable over the past decade. Transmission is primarily via blood-to-blood and sexual fluid-to-blood transmission, mostly by anal, oral, and vaginal sex; vertical transmission from mother-to-child also occurs prenatally, during birth, or via breast milk. Occupational or iatrogenic exposure via percutaneous or mucous membrane exposure to blood or transfusion of unscreened blood, organs, or blood products also occurs, although very rarely in countries with effective prevention strategies. Populations at highest risk of infection vary considerably globally, with men who have sex with men and injection drug users forming the highest risk groups in the United States, whereas women may have a higher rate of infection than men in, for example, some southern African countries. Untreated HIV-1 infection usually results in severe immune deficiency and AIDS, typically several years after initial infection. However, effective risk reduction prevention strategies, HIV-1 screening and testing practices, post-exposure prophylaxis, and highly effective antiretroviral therapies have reduced rates of both person-to-person and mother-to-child transmission and morbidity and

mortality from HIV-associated diseases in resource-rich countries, although less successfully in other countries. While HIV-1 infection may now be considered a chronic, manageable condition, infection is permanent, and efforts to develop a vaccine have thus far been unsuccessful.

3. Human Cancer Studies

Introduction

Infection with HIV-1 is associated with the death of T cells (CD-4) and severe immune suppression, which after several years in untreated individuals typically progresses to acquired immunodeficiency syndrome (AIDS), a range of immune-related opportunistic infections and related diseases (CDC 1985; CDC 1992). In addition, association of HIV-1 infection with a number of cancer endpoints, mostly those associated with co-infection with other viruses, have been investigated. The advent of highly active antiretroviral therapies (HAART) (usually defined as prescription of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor) has resulted in reductions in HIV-1 viral load and partial to complete recovery of immune function in treated patients.

The NTP used the body of knowledge published on HIV-1 in the IARC (1996; 2012a) monographs (which included studies published up to 2008) as the resource as well as any key cohort studies published after 2008 to develop its cancer assessment, which is made independently of IARC's conclusions. Key studies were those cohort studies that provide new information. Where available, IARC data tables of the effect estimates have informed the cancer hazard assessment, with links to these tables made available in the text.

The NTP focused on those cancer sites evaluated in the IARC monographs. Many of the cancers—Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, conjunctival cancer, and anal cancer—have relatively large databases, thus, NTP primarily used the studies included in the IARC monograph for its assessment, supplementing with any new information on key issues and briefly noting whether the recent studies are consistent with the studies reviewed by IARC. For other cancer sites, for which IARC identified weaknesses in the database, including genital, lip, head and neck, liver, lung, and non-melanoma skin cancers, NTP provided a more comprehensive review update of cohort studies or cancer site-specific studies published since 2008.

In the cohort and case-control studies reviewed below, HIV-1 exposure is detected primarily via serological measures and/or measures of HIV-1 RNA according to standard case definition guidelines developed by bodies such as the Centers for Disease Control (CDC) and UNAIDS for surveillance of HIV-1. These guidelines have generally been adopted worldwide (with some variations for resource-poor countries), which may rely primarily on serological rather than RNA-based detection methods. (See Section 1 for more details on HIV-1 detection methods.) AIDS is defined as a spectrum of one or more diseases specified in case definition guidelines developed by the CDC and other bodies (CDC 2014c; CDC 2015b).

The evaluation of the human cancer hazard associated with HIV-1 is divided into five parts. First, a summary of the approach for selection of the studies is provided (Section 3.1). Next, the cancer hazard evaluation for each of the 11 cancer endpoint is presented (Sections 3.2 to 3.7,), cancer burden from all cancer is discussed in Section 3.8, followed by the potential carcinogenicity of HAART and treatments for opportunistic infections (Section 3.9). An integration and summary of the evidence across HIV-1-related cancer endpoints are provided in Section 3.10.

3.1. Selection of the Relevant Literature

A literature search of major databases, citations, and other authoritative sources for literature from 2009 through August 2015 was conducted. The literature search strategy (including the databases and search terms, and other sources for identifying literature) and procedures for selecting the literature (systematic screening procedures and inclusion/exclusion criteria) are described in Appendix A.

For the evaluation of the cancer endpoints identified above, the initial search strategy was restricted to review articles identified from 2009 on, and new epidemiological studies on specific cancer sites identified in these reviews were obtained. Since most of the key cohort studies in the IARC review evaluating HIV-1 infection and cancer were published in 2008 and before, primary literature for cohort studies and meta-analyses published from 2009 to August 2015 was also identified and screened. Based on this search, 21 cohorts or record-linkage studies that reported risk estimates for at least three cancer sites were identified (summarized in Table 3-1, below), as well as additional studies focusing specifically on individual cancers. For Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, conjunctival cancer, and anal cancer, the newly identified studies were reviewed for consistency with findings reported in IARC. Summary tables for these endpoints report only relative risks from studies included in the IARC tables (see below for links to specific IARC tables), and do not include relative risks from the newer studies. For non-melanoma skin cancer, oral-related cancers, and cancers of the vagina, penis, liver, and lung summary tables were constructed based on the totality of the literature from IARC together with the most recently identified cohorts.

This review also includes cohort studies comparing the incidence of these cancer endpoints in a range of HIV-1-infected populations before and after the advent of widespread use of HAART in the mid- to late 1990s (usually defined as prescription of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor) because these studies can provide evidence to evaluate a causal relationship between HIV-1 infection and cancer risk.

Table 3-1. HIV-1/AIDS Cohorts 2009–2015 Reporting SIR/RR on Multiple (≥3) Cancer Endpoints[a]

Reference/ Country	Study Design	# with HIV or AIDS in Cohort	Dates	Cancer Endpoints	Comments
Powles et al. (2009) UK	Prospective cancer registry PWAH	11,112	1983–2007	HL, anal, liver, lung, head/neck	Incl. HAART comparisons
Silverberg et al. (2011) USA	Prospective cancer registry PWAH	20,775	1996–2008	KS, NHL, HL, anal, liver, lung, oropharynx	Kaiser enrollees vs. 215,158 HIV-1-negative enrollees
Chaturvedi et al. (2009) USA	Prospective cancer registry PWA	500,000	1990–2002	cervical, anal, genital	Incl. HAART comparisons
van Leeuwen et al. (2009) Australia	Retrospective cancer registry PWAH	20,230	1982–2004	KS, NHL, HL, anal, liver, lung, oropharynx	Incl. HAART comparisons

Reference/ Country	Study Design	# with HIV or AIDS in Cohort	Dates	Cancer Endpoints	Comments
Bedimo et al. (2009) USA	Prospective cohort PWAH	32,942	1997–2004	KS, NHL, HL, cervical, anal, liver, lung	U.S. Veterans hospital-based vs. 64,996 HIV-1-negative veterans Incl. HAART comparisons
Seaberg et al. (2010) USA	Prospective cancer registry PWAH	3,505 PWAH MSM	1984–2007	KS, NHL, HL, anal, testes, liver, lung, NMSK, oropharynx	Incl. HAART comparisons
Simard et al. (2010) USA	Prospective cancer registry PWA	263,250	1990–2006	KS, NHL, HL, cervical, anal, genital, liver, lung, oropharynx	Incl. HAART comparisons
Franceschi et al. (2010) Switzerland	Prospective cancer registry PWAH	9,429	1985–2006	KS, NHL, HL, cervical, anal, testes, liver, lung, NMSK	Incl. HAART comparisons
Vogel et al. (2011) Germany	Prospective cancer registry	1,476 PWAH	1996–2009	KS, NHL, HL, cervical, anal, liver, lung, oropharynx	Incl. HAART comparisons
Zhang et al. (2011) China	Retrospective clinical chart review	3,554	2004–2008	NHL, cervical, liver, lung	Hospital-based
Simard et al. (2012) USA	U.S. HIV/AIDS Cancer Match Study cancer registry children (0–14 yr) with AIDS	5,850	1980–2007	KS, NHL, HL, cervical, liver, lung	Subcohort of cohort reported in Simard et al. (2010) Incl. HAART comparisons
Chao et al. (2012) USA	Prospective cancer registry linkage	12,872	1996–2008	KS, NHL, HL, anal, lung	Subcohort of Kaiser enrollees (see Silverberg et al. 2011); selected endpoints + risk factors
Hleyhel et al. (2013; 2014) France	Prospective cancer registry PWAH	99,000 84,504	1992–2009 1997–2009	KS, NHL, cervical (2013) HL, anal, liver, lung (2014)	2013 study incl. HAART comparisons

Reference/ Country	Study Design	# with HIV or AIDS in Cohort	Dates	Cancer Endpoints	Comments
Albini et al. (2013)/Calabresi et al. (2013) Italy	Retrospective cancer registry PWAH	5, 090	1999–2009	Albini: testes, lung, NMSK Calabresi: KS, NHL, HL, cervical, anal, genital, liver, lung, NMSK, ororpharynx	
Franzetti et al. (2013) Italy	Retrospective cancer registry PWH	5,924	1985–2011	HL, anal, genital, liver, lung oropharynx	
Park et al. (2014) USA	Prospective PWAH VA and SEER cancer registries	38,123	1996–2008	KS, NHL, HL, cervical, anal, liver, lung, oropharynx	Incl. HAART comparisons
Akarolo-Anthony et al. (2014) Nigeria	Retrospective cancer registry PWAH	17,826	2005–2012	KS, cervical, anal, liver, NMSK, eye	Cancer registry linkage only from 2009–2012
Chen et al. (2014) Taiwan	Retrospective national insurance database PWAH	15,269	1998–2009	KS, NHL, HL, cervical, anal, testes, liver, lung, NMSK, oropharynx	
Raffetti et al. (2015) Italy	Retrospective PWAH	16,268	1986–2012	KS, NHL, HL, cervical, anal, genital, liver, lung, oropharynx	Hospital-based Incl. HAART comparisons
Castilho et al. (2015) USA, Brazil	Retrospective PWAH	2,925 Brazil 3,927 USA	1998–2010	KS, NHL, HL, cervical, anal, testes, liver, lung NMSK, oropharynx	Hospital-based Incl. HAART comparisons
Coghill et al. (2015) USA	6 States in HIV-1/AIDS Cancer Match registry mortality study PWAH	6,459 HIV-1-positive cancer cases vs. 1,816,461 HIV-1-negative cancer cases	1996–2010	HL, cervical, anal, liver, lung, oropharynx	

AIDS = acquired immunodeficiency syndrome; HIV-1 = human immunodeficiency virus type 1; HL = Hodgkin lymphoma; KS = Kaposi sarcoma; IRR = incidence rate ratio; HAART = highly active antiretroviral therapy; HL = Hodgkin lymphoma; MSM = men who have sex with men; NHL = non-Hodgkin lymphoma; NMSK = non-melanoma skin cancer; PWA = people with AIDS; PWAH = people with AIDS or HIV; RR = relative risk; SIR = standardized incidence ratio; USA = United States of America.

[a]Cancer endpoints included in the current review; some studies reported additional endpoints.

[b]Cohorts M+F unless stated (note that in most cohorts, women were approximately 10% to 25% of the total cohort, except Akarolo-Anthony et al. (2014), where women were 65% of the cohort).

3.2. Cancer Hazard Evaluation: Kaposi Sarcoma

Kaposi sarcoma-associated herpesvirus (KSHV) is necessary for the development of Kaposi sarcoma (see monograph on KSHV). Studies evaluating Kaposi sarcoma include cohort and case-control studies of HIV-1-infected or AIDS patients (status of Kaposi sarcoma unknown), cohort and case-control studies of known infection and HIV-1-infected populations that evaluated the effect of HAART on Kaposi sarcoma incidence.

3.2.1. Background Information

Kaposi sarcoma occurs in four epidemiological types (Iscovich et al. 2000):

(1) Endemic Kaposi sarcoma, which is found mainly in regions of sub-Saharan Africa where the KSHV seroprevalence rate is approximately 25% to 50%

(2) Classic Kaposi sarcoma, which occurs among certain southern Mediterranean populations with KSHV seroprevalence rates of 10% to 20%

(3) Iatrogenic Kaposi sarcoma, which is observed mainly among organ transplant recipients who have KSHV infection

(4) Epidemic or HIV-1/AIDS-related Kaposi sarcoma, which occurs among HIV-1-positive or AIDS populations

In the United States, the incidence of Kaposi sarcoma was 0.23 per 100,000 individuals prior to the HIV-1/AIDS epidemic starting in the early 1980s, peaking at approximately 5 per 100,000 by the early 1990s (and ~125 per 100,000 in San Francisco), prior to the advent of HAART. In the HAART era, the incidence of Kaposi sarcoma incidence has continued a steady decline leveling off at a plateau 0.5 per 100,000 (4.0 per 100,000 in San Francisco) in the United States SEER data 2013.

3.2.2. Cohort and Case-control Studies

In small studies from the early 1980s reviewed by IARC (1996), the relative risk of Kaposi sarcoma increased among “never married” men in comparison to the 1970s by between 19 and >5,000 (Bernstein et al. 1989; Biggar et al. 1987; Biggar et al. 1989; Rabkin et al. 1991; Rabkin and Yellin 1994) and risks were correlated with a decrease in CD4 counts (Dore et al. 1996; Lundgren et al. 1995; Muñoz et al. 1993; Veugelers et al. 1995).

IARC (2012a) reviewed a total of 23 HIV-1/AIDS cohort studies including one meta-analysis that reported standardized incidence ratios (SIR) or risk ratios (RR). Twenty-two of the studies were from Europe and the United States and one was from Uganda. The cohorts ranged from approximately 1,600 to 376,000 members and included a total of almost 25,500 cases of Kaposi sarcoma (see IARC 2012a monograph for details of study methods and findings). Findings across these studies that reported risk estimates (SIR or RR) are summarized in Table 3-2. The majority of the cohort studies were cancer registry linkage studies that reported age- and sex-adjusted SIRs. The studies varied in the calendar year in which patients were enrolled, with some studies reporting effect estimates of HIV-1-positive and/or AIDS patients prior to HAART and other studies enrolling patients from both pre- and post-HAART era, and some studies evaluating the impact of HAART on the effect estimate (discussed below). Advantages of the database were the large size of the cohorts and large numbers of exposed cases.

The studies in Europe and the United States found strong and consistent evidence of an association of HIV-1 infection or AIDS and Kaposi sarcoma with very high and statistically significant SIRs ranging from 109 to 72,700, depending in part on the stage of HIV-1 infection (with those developing AIDS generally at higher risk for Kaposi sarcoma) and the calendar period over which cases were identified. Based on studies with a total of 444,000 members and 494 cases, Grulich et al. (2007) reported an age- and sex-adjusted meta-SIR = 3640 over the period 1980 to 2002. A much lower SIR (~6) was found in the only study from Africa (Uganda) (Mbulaiteye et al. 2006) based on 105 cases found among a cohort of HIV-1-positive people or people with AIDS enrolled from 1988 to 2002. However, higher risks (ORs ranged from 47 to 91) were observed for HIV-1 infection and Kaposi sarcoma in two hospital-based case-control studies from Uganda (Newton et al. 2001) and South Africa (Stein et al. 2008); the former study included children (see IARC (2012a), Table 2.3). The risk of Kaposi sarcoma varies considerably with HIV-1 transmission group and is highest among men who have sex with men (IARC 1996; IARC 2012a): for example Beral et al. (1990) reported that among 88,739 AIDS patients in the United States, 13,616 (15%) developed Kaposi sarcoma, ranging from 21% in "homosexual or bisexual" men down to 3% in "heterosexual" men, 3% in transfusion recipients, 2% in intravenous drug users, 1% in hemophiliacs, and 1% in children infected by perinatal transmission. Similar patterns have been found in other countries with epidemic forms of Kaposi sarcoma (Beral et al. 1990).

Findings (most risks ranging from 100 to 1000s) from 16 cohort studies published after the IARC review (Akarolo-Anthony et al. 2014; Bedimo et al. 2009; Calabresi et al. 2013; Castilho et al. 2015; Chao et al. 2012; Chen et al. 2014; Franceschi et al. 2010; Hleyhel et al. 2013; Park et al. 2014; Raffetti et al. 2015; Seaberg et al. 2010; Silverberg et al. 2011; Simard et al. 2010; Simard et al. 2012; van Leeuwen et al. 2009; Vogel et al. 2011) were consistent (data not shown) with the findings from the earlier studies.

Table 3-2. Summary of HIV-1/AIDS Cohort Studies of Kaposi Sarcoma

	AIDS	HIV-1 Positive[a]	AIDS or HIV-1 Positive
RR/SIR	258–72,700[b]	192–5,600 [a]	109–3,640 [c]
Cohort size	1,659–375,933	1,950–54,780	2,574–491,048
Number of cases	6–7,028	6–3,267	17–5,936
Number of studies	8	8	6

Source: IARC (2012a), Table 2.1 and Table 2.2.
[a]Subjects with Kaposi sarcoma in the cohorts would have AIDS as this cancer is an AIDS-defining disease.
[b]All lower 95% CI > 1.0.
[b\c]Mbulaiteye et al. (2006) not included as estimates were outliers.

The major co-factor for Kaposi sarcoma is Kaposi sarcoma-associated herpesvirus, which is present in all cancer cases. Numerous studies have found strong evidence for an increased risk of Kaposi sarcoma among HIV-1-positive and Kaposi sarcoma-associated herpesvirus-infected populations; relative risks ranged from 1 to 30 for the cohort studies and 1 to 1,683 for the case-control studies (see Tables 3-1 and 3-2 in the Kaposi sarcoma-associated herpesvirus monograph).

3.2.3. Relationship with HAART

Calendar-period analyses or prospective cohort analyses, predominantly using cancer-registry linkage study designs of populations compared over pre-HAART (prior to approximately 1996), early HAART (from approximately 1996 to 2002) and established HAART (approximately 2002 and later) periods, can provide indirect evidence of an association between HIV-1 infection rates or titers and changes in Kaposi sarcoma incidence over time. (Note, however, that HAART was not widely available in many resource-poor countries such as southern Africa until the 2000s).

Five cohort studies reported SIRs or relative risks for Kaposi sarcoma decreased sharply over two or three time periods, representing pre-, early, and established HAART periods (Engels et al. 2006a; Franceschi et al. 2010; Hleyhel et al. 2013; Patel et al. 2008; van Leeuwen et al. 2009, see Figure 1) (see Figure 3-1). In addition, 10 studies reported incidence rates and/or differences in relative risks from the pre-/early to late HAART periods. Statistically significant decreases in relative risks were reported, ranging from 0.19 to 0.92 in studies comparing pre- to early HAART periods (Bedimo et al. 2009; Carrieri et al. 2003; Grulich et al. 2001; ICHIVC 2000; Ives et al. 2001) and from 0.11 to 0.2 in more recent studies comparing pre-HAART with early to established HAART periods (Franceschi et al. 2008; Seaberg et al. 2010; Simard et al. 2010). Relative risks also significantly decreased by 70% when comparing post-treatment CD4 levels of <50 cells/μL (RR = 1.0) to CD4 levels of ≥500 cells/μL (RR = 0.3). A number of other cohort studies (Clifford et al. 2005; Franceschi et al. 2008; Mbulaiteye et al. 2003; Serraino et al. 2005; Silverberg et al. 2011) also report dose-response relationships between low CD4 counts and increased risks of Kaposi sarcoma. Silverberg et al. (2011) reported a statistically significant trend between HIV-1 RNA levels and risk of Kaposi sarcoma both between HIV-1-positive and HIV-1-negative groups ($P < 0.001$) and within HIV-1-positive groups (RR = 3.8, 95% CI = 3.0 to 4.8) for ≥10,000 copies of HIV RNA/mL vs. 1.2 (95% CI = 0.8 to 1.7) for 501 to 9,999 copies/mL.

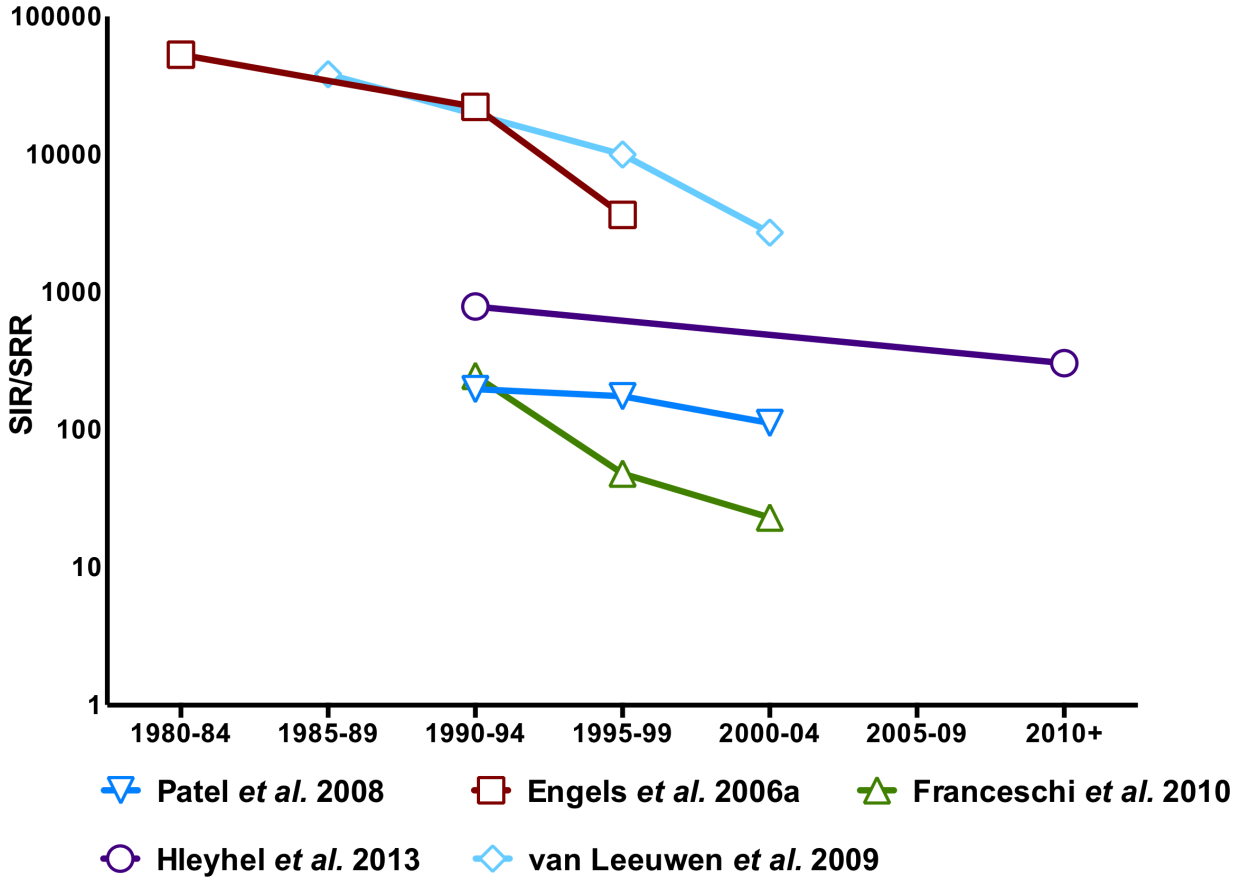

Figure 3-1. Cohort Studies of Kaposi Sarcoma Incidence in HIV-1/AIDS Populations from Pre-HAART (1980 to 1996) to HAART (1996 and Later) Periods

Overall, these cohort studies indicate rapid and substantial decreases in Kaposi sarcoma incidence rates of up to 90% among HIV-1-positive populations from the pre- or early HAART to the established-HAART period in a number of (mostly U.S. and European) countries. However, incidence rates of Kaposi sarcoma among HIV-1-positive populations remain approximately 20- to 300-fold higher than general population rates, even in the established HAART era (e.g. Hleyhel et al. 2013; Patel et al. 2014; van Leeuwen et al. 2009).

3.3. Cancer Hazard Evaluation: Non-Hodgkin Lymphoma

3.3.1. Background Information

In the United States, non-Hodgkin lymphoma, consisting of predominantly B-cell subtypes, is relatively common, with an estimated annual incidence rate of 20/100,000 and a 5-year survival rate of 70% (SEER 2015h). Approximately 4% of people with AIDS have NHL at diagnosis and at least the same proportion develop NHL during the course of illness (IARC 1996; Medscape 2016). Among HIV-infected individuals non-Hodgkin lymphoma manifests late in the progression of the infection and is most common in persons with very low CD4 counts.

Three types of aggressive B-cell lymphomas have been evaluated among HIV-1-positive/AIDS populations:

- Primary central nervous system diffuse large B-cell lymphoma (a relatively rare form of non-Hodgkin lymphoma with a current incidence rate of approximately 0.5 per 100,000 in the United States), which appears mainly among severely immunosuppressed people
- Diffuse large B-cell immunoblastic lymphoma, which is also associated with severe immunosuppression (both are uncommon when CD4 levels are close to normal (IARC (2012a)); see also review by Kaplan (2012))
- Burkitt lymphoma, which occurs at various stages of immune deficiency (IARC 1996; 2012a; Kaplan 2012)

In addition, T-cell lymphomas have also been evaluated among HIV-1-positive groups (IARC 2012a), but they constitute less than 5% of all cases of NHL among HIV-1-positive individuals.

3.3.2. Cohort and Case-control Studies

An association between HIV-1/AIDS and non-Hodgkin lymphoma incidence was first observed in cancer registry-based descriptive epidemiology studies in populations with high mortality from AIDS (Biggar et al. (1989); Harnly et al. (1988); Kristal et al. (1988); Rabkin and Yellin (1994); Ross et al. (1985), cited in IARC (1996)); these were followed by cancer registry and AIDS registry linkage studies (Coté et al. 1991; Reynolds et al. 1993) reporting 91- to 140-fold increases in non-Hodgkin lymphoma among AIDS patients compared with general population rates. Case series/cohort studies also reported increases in non-Hodgkin lymphoma risk with decreasing CD4 counts (Moore et al. (1991); Muñoz et al. (1993); Pluda et al. (1990); Pluda et al. (1993); Rabkin et al. (1992), cited in IARC (1996)).

IARC (2012a) reviewed 39 cohort studies, 21 of which reported SIRs or RRs, including the meta-analysis by Grulich et al. (2007) and 6 case-control studies, of which 3 reported SIRs or RRs (see IARC monograph for details of study methods and findings). Almost all the cohort studies were conducted in the United States or Europe and were large, involving from approximately 2,500 to over 375,000 people registered with AIDS or HIV-1 infection, and, studies that reported risks included a total of approximately 14,500 cases of non-Hodgkin lymphoma. These studies reported a wide range of SIRs or relative risks of approximately 25 to 3,600 for combined non-Hodgkin lymphoma among AIDS patients and approximately 4 to 79 among HIV-1-positive populations, depending in part on the time period over which the studies were conducted (see Table 3-1, Table 3-3). Overall, most risk estimates were between 10 and 300. One cohort study among a HIV-1-positive Ugandan population (Mbulaiteye et al. 2006) reported a lower, but statistically significant SIR of 3.6 (95% CI = 1.2 to 8.4). Eight case-control studies were reviewed by IARC (2012a), of which three (from Africa) reported risks. Statistically significant odds ratios ranging from approximately 6 to 12 were reported (Mutalima et al. 2008; Newton et al. 2001; Stein et al. 2008). The meta-analysis of over 444,000 HIV-1/AIDS patients in the United States, Europe, and Australia (Grulich et al. 2007) reported an age- and sex-adjusted meta-SIR for non-Hodgkin lymphoma of 76.7 (95% CI = 39.4 to 149, 5,295 cases) over the period 1980 to 2002.

Findings (most risks between 8 and 45 with risks up to 100 for cancers developing in the pre-HAART era) from 16 cohort studies published after the 2008 review (Albini et al. 2013; Bedimo et al. 2009; Castilho et al. 2015; Chao et al. 2012; Chen et al. 2014; Franceschi et al. 2010; Hleyhel et al. 2013; Park et al. 2014; Raffetti et al. 2015; Seaberg et al. 2010; Silverberg et al.

2011; Simard et al. 2010; Simard et al. 2012; van Leeuwen et al. 2009; Vogel et al. 2011; Zhang et al. 2011) were consistent with the findings from the earlier studies (data not shown).

Table 3-3. Summary of HIV-1/AIDS Cohort Studies of Non-Hodgkin Lymphoma

	AIDS	HIV-1 Positive[a]	AIDS or HIV-1 Positive
RR/SIR	24.6–3,600	3.6–79.4	72.8–3,640
Cohort size	1,659–375,933	2,566–57,350	2,574–444,172
No. cases	52–2,852	5–675	82–3,344
No. of studies	8	8	5

Source: IARC (2012a), Table 2.4 and Table 2.5.
All lower 95% CI > 1.0.
[a]Subjects with non-Hodgkin lymphoma in these cohorts would have AIDS as this cancer is an AIDS-defining disease.

3.3.3. Relationship with HAART

Reported SIRs or relative risks for non-Hodgkin lymphoma declined from approximately 134 to 7 among AIDS or combined AIDS/HIV-1 populations (Dal Maso et al. 2009; Engels et al. 2006a; Engels et al. 2008; Franceschi et al. 2010; Galceran et al. 2007; Hleyhel et al. 2013) and from 97 to 6.5 among HIV-1-positive populations (Engels et al. 2008; Patel et al. 2008) from the pre-/early HAART era to the established HAART era (see Figure 3-2, also see review by Engels et al. (2010)).

Studies reporting changes in relative risks (rather than absolute risk) indicate declines of approximately 30% to 80% from the pre-HAART to early HAART period and from 70% to 80% from the pre-/early HAART to the established HAART era (Bedimo et al. 2009; Bhaskaran et al. 2004; ICHIVC 2000; Seaberg et al. 2010; Simard et al. 2010). AIDS patients appear to have experienced a greater decrease in risk than HIV-1-positive patients.

In two French/Italian studies comparing treated with non-treated groups in the same study population, the relative risk of non-Hodgkin lymphoma was 0.2 among treated vs. untreated patients (Carrieri et al. 2003); similarly, the SIR was approximately half as large (SIR = 35) among treated patients as that among untreated patients (SIR = 72) (Serraino et al. 2007).

In prospective studies reporting on the course of non-Hodgkin lymphoma risk among individual patients, the administration of HAART appears to result in a decrease in risk within months of starting treatment (Kirk et al. 2007; Polesel et al. 2008).

Despite a clear decline in the HAART era, the overall risk of non-Hodgkin lymphoma among people with AIDS and HIV-1 remains on average 10- to 15-fold higher than that of the general population (see e.g. Engels et al. 2008; Franceschi et al. 2010; Hleyhel et al. 2013; Patel et al. 2008; van Leeuwen et al. 2009), and it is now the most common HIV-1/AIDS-related cancer in the United States, partly as a result of declines in other HIV-1-related cancers such as Kaposi sarcoma (Robbins et al. 2015).

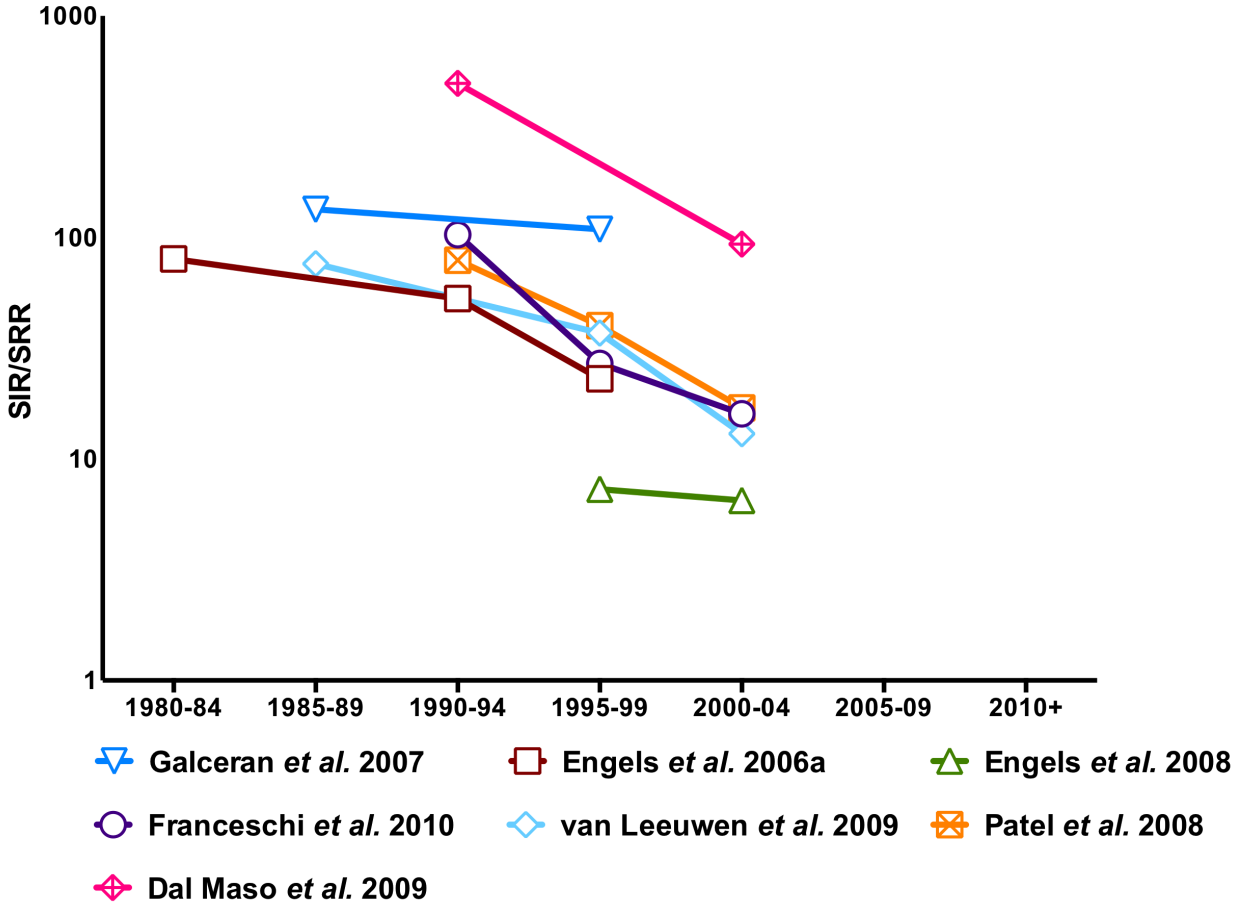

Figure 3-2. Cohort Studies of Non-Hodgkin Lymphoma Incidence in HIV-1/AIDS Populations from Pre-HAART (1980 to 1996) to HAART (1996 and Later) Periods

3.3.4. Non-Hodgkin Lymphoma Subtypes

Primary central nervous system diffuse large B-cell lymphoma occurs several thousand times more frequently in HIV-1-positive populations than in the general population and is associated with severe immunosuppression (Coté et al. 1996; Engels et al. 2006a). Diffuse large B-cell immunoblastic lymphoma is also associated with severe immunosuppression and occurs at several hundred times the general population rate (Engels and Goedert 2005; Engels et al. 2006a). Burkitt lymphoma, as noted above, occurs at varying stages of immunosuppression and at 50 to 100 times the general population rate. As reviewed in the accompanying Kaposi sarcoma-associated herpesvirus monograph, HIV-1 infection is associated with an increased risk of two rare forms of lymphoma, primary effusion lymphoma, and multicentric Castleman disease. Finally, a 15-fold increase in T-cell lymphoma has been identified in HIV-1-positive patients (Biggar et al. 2001).

There is evidence from studies reporting non-Hodgkin lymphoma subtypes that both diffuse large B-cell primary central nervous system lymphoma and diffuse large B-cell immunoblastic lymphoma have declined substantially, but Burkitt lymphoma and low to intermediate grade diffuse large B-cell lymphoma incidence do not appear to have declined (Diamond et al. 2006; IARC 2012a; Kaplan 2012). The ICHIVC (2000) study of almost 48,000 HIV-1-positive people

reported decreases of approximately 50% in diffuse B-cell primary central nervous system lymphoma and immunoblastic lymphoma, but no change in Burkitt lymphoma, during the HAART era; a similar pattern was observed in the Swiss HIV-1 cohort (Polesel et al. 2008). Over three periods reflecting pre-HAART era, early-HAART era, and late-HAART era, Engels et al. (2006a) also reported a 30% decline in diffuse large B-cell lymphomas (SIRs of 98, 64, and 30, respectively), with a 43% decline in immunoblastic lymphoma (SIRs of 141, 95, and 60, respectively) and a 20% decline in primary central nervous system lymphoma (SIRs of 5,000, 4,850, and 1,020, respectively), but no decrease in Burkitt lymphoma (SIRs of 57, 53, and 50, respectively).

3.3.5. Cofactors

Some specific subtypes of non-Hodgkin lymphoma among HIV-1-positive populations have been associated with Epstein-Barr virus in some but not all cases (see e.g.`, review by (Carbone et al. 2009)). Epstein-Barr virus is found in almost all cases of HIV-1-associated primary central nervous system lymphoma, approximately 40% of cases of large-cell immunoblastic lymphoma, and approximately 30% of cases of Burkitt lymphoma (Gloghini et al. (2013); Grulich et al. (2007); IARC (2012a); Stefan et al. (2011) see also accompanying monograph on Epstein-Barr virus). In addition, increasing Epstein-Barr virus titers have been reported among HIV-1-positive people following HIV-1 infection, with decreases in Epstein-Barr virus titers observed among HIV-1-positive patients successfully treated with HAART (IARC 2012a). Apart from Kaposi sarcoma-associated herpesvirus-related lymphomas (reviewed in the accompanying monograph on Kaposi sarcoma-associated herpesvirus), the risks of which are also increased in HIV-1-positive and Epstein-Barr virus-positive populations, associations of non-Hodgkin lymphoma with other oncoviruses have not been clearly demonstrated (IARC 2012a) and one study found reported hepatitis B virus antibodies in 78% of HIV-1-positive patients with non-Hodgkin lymphoma (Burbelo et al. 2012). Hepatitis B and C infections occur more frequently among HIV-1-positive populations (Nunnari et al. 2012) and are risk factors for non-Hodgkin lymphoma; IARC concluded that there is sufficient evidence for hepatitis C and limited evidence for hepatitis B virus and non-Hodgkin lymphoma from studies in IARC (2012a). However, a role of hepatitis B and C viruses in non-Hodgkin lymphoma risk in the presence of HIV-1 infection has not been elucidated.

Co-infection with human T-cell lymphotropic virus type 1 has been found to be in the range of 5% to 27% in populations highly endemic for human T-cell lymphotropic virus type 1 (Araujo et al. 2002; Dezzutti and Lal 1999). While there are case reports of adult T-cell leukemia/lymphoma in patients infected with both HIV-1 and human T-cell lymphotropic virus type 1, there does not appear to be an increased incidence of adult T-cell leukemia/lymphoma in co-infected persons (Dhasmana and Taylor 2014).

Other risk factors impact non-Hodgkin lymphoma risk, depending on the subtype, including other causes of immune suppression (transplants or specific autoimmune diseases and allergies), as well as some environmental and occupational exposures. Smoking and alcohol consumption, however, are not strongly associated with non-Hodgkin lymphoma risk. Data are insufficient to evaluate whether such factors directly interact with HIV-1 infection to increase risk and/or act as confounders in studies comparing non-Hodgkin lymphoma cancer risk among HIV-1-positive vs. HIV-1-negative populations.

3.4. Cancer Hazard Evaluation: Hodgkin Lymphoma

3.4.1. Background Information

In the United States, Hodgkin lymphoma occurs relatively infrequently, with an estimated annual incidence rate of 2.7/100,000 and a 5-year survival rate of approximately 86% (NCI 2015f, 2008-2012 data). The age-specific risk for Hodgkin lymphoma is bimodal, with peaks among the young and the elderly and lowest risks among 40- to 59-year-olds (Goedert and Bower 2012). There are four major histological types: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted.

3.4.2. Cohort and Case-control Studies

IARC (1996) described a series of five case series and descriptive studies in which Hodgkin lymphoma was first reported in HIV-1-infected persons, indicating a preponderance of mixed cellularity and lymphocyte depletion as histological subtypes. Early cohort studies reported increases in Hodgkin lymphoma in some AIDS patients (Hessol et al. 1992; Rabkin et al. 1992; Reynolds et al. 1993) but not in all studies (Lyter et al. 1995; Ragni et al. 1993).

IARC (2012a) (see IARC monograph tables for details on study methods and findings) reviewed 23 cohort studies of HIV-1 infection and/or AIDS patients, including a meta-analysis by Grulich et al. (2007), and 1 case-control study of Hodgkin lymphoma conducted in the United States, Europe, and Africa that reported SIRs or RRs, (see IARC monograph for study methods and findings) (Table 3-4). The individual cohort studies were large, with study populations ranging from approximately 1,200 to over 375,000 people with AIDS or HIV-1 infection, and represent approximately 2,280 cases of Hodgkin lymphoma. These studies, conducted in the United States, Europe, and Australia, reported statistically significant increases in risk ranging from approximately 4 to 38 among HIV-1-positive/AIDS patients vs. HIV-1-negative populations. One case-control study was identified; Stein et al. (2008) reported an odds ratio (OR) of 1.6 (95% CI = 1.0 to 2.7) among 30 cases of Hodgkin lymphoma with HIV-1 infection in a South African hospital-based study. Based on 444,172 HIV-1-positive/AIDS patients and 802 cases, Grulich et al. (2007) reported an age- and sex-adjusted meta-SIR = 11.3 (95% CI = 8.4 to 14.4) for the period 1980 to 2002.

Findings from 18 cohort studies published after 2008 (Bedimo et al. 2009; Calabresi et al. 2013; Castilho et al. 2015; Chao et al. 2012; Chen et al. 2014; Coghill et al. 2015; Franceschi et al. 2010; Franzetti et al. 2013; Hleyhel et al. 2014; Park et al. 2014; Powles et al. 2009; Raffetti et al. 2015; Seaberg et al. 2010; Silverberg et al. 2011; Simard et al. 2010; Simard et al. 2012; van Leeuwen et al. 2009; Vogel et al. 2011) were consistent with the findings (most risks between 4 and 38) from the earlier studies (data not shown). In addition, Shiels et al. (2009) reported a meta-SIR of 11 (95% CI = 8.8 to 15) based on 643 cases (note that 6 of the total of 13 studies included by Shiels et al. (2009) overlap with those of Grulich et al. (2007), although not all reported data for every cancer endpoint).

There is some variation in the histological type of Hodgkin lymphoma (Biggar et al. 2006; Carbone et al. 2009; Frisch et al. 2001; Mounier et al. 2010; Rapezzi et al. 2001; Serraino et al. 1993). According to a meta-analysis of 17 studies by Rapezzi et al. (2001), the risk for mixed cellularity (RR = 3.2, 95% CI = 2.6 to 3.8) and lymphocyte-depleted subtypes (RR = 6.3, 95%

CI = 4.5 to 8.8) is statistically significantly higher in HIV-1-positive patients than in HIV-1-negative populations, whereas lymphocyte predominance and nodular sclerosis types were not statistically significantly different in the two groups. The relative proportions of subtypes may also be altered among HAART-treated populations who develop Hodgkin lymphoma (Carbone et al. 2009).

Table 3-4. Summary of HIV-1/AIDS Cohort Studies of Hodgkin Lymphoma

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR	7.6–28.4[a]	5.6–38[a]	3.6–20.7[a]
Cohort size	1,659–375,933	1,255–57,350	2,574–444,172
No. cases	6–173	2–38	2–802
No. of studies	7	9	7

Source: IARC (2012a), Table 2.7 and Table 2.8.
[a]All lower 95% CI > 1.0 except Allardice et al. (2003).

3.4.3. Relationship with HAART

The risk of Hodgkin lymphoma has increased during the HAART era, although part of this increase may be attributable to the aging of surviving HIV-1/AIDS populations. SIRs in the pre-HAART era (up to 1995 to 1996) ranged from 5 to 23; by the later HAART period (approximately 2000 onward), SIRs had generally increased, ranging from 13 to 32 (see Figure 3-3). Relative risks following the advent of HAART ranged from 0.75 to 2.7, depending in part on the periods being compared (Bedimo et al. 2009; Engels et al. 2008; ICHIVC 2000; Seaberg et al. 2010; Simard et al. 2010). In addition, an earlier study by Clifford et al. (2005) reporting on a Swiss HIV-1/AIDS cohort from 1985 to 2005, found a doubling of risk among HAART-treated patients (SIR = 36) vs. those untreated prior to cancer diagnosis (SIR = 11), whereas Bohlius et al. (2011), reporting on a combined cohort of approximately 40,170 HIV-1-positive patients from 16 European cohorts (1998 to 2006), found no difference in risk between HAART and non-HAART-treated patients (hazard ratio = 1.0). Some recent studies of current HAART use and Hodgkin lymphoma risk suggest that the risk might have partly leveled off (see reviews by Carbone et al. 2009; Goedert and Bower 2012; Kaplan 2012). Nevertheless, the risk of Hodgkin lymphoma appears to have remained 5- to 25-fold higher among people with HIV-1/AIDS than in the general population.

The level of risk was not related to baseline or nadir CD4 levels, but declined significantly with the most recently measured CD4 level [>350 cells/μL vs. <50 cells/μL: RR = 0.2 (95% CI = 0.1 to 0.6)] (Bohlius et al. 2011).

3.4.4. Cofactors

Hodgkin lymphoma is strongly associated with Epstein-Barr virus infection (see accompanying monograph on Epstein-Barr virus), and in HIV-1-positive people, up to 80% to 100% of tissues have been reported to be infected with Epstein-Barr virus (Glaser et al. 2003), compared with less than 50% among HIV-1-negative Hodgkin lymphoma cases (Biggar et al. 2006); see also review by (Carbone et al. 2009; Goedert and Bower 2012; Sissolak et al. 2010). HIV-1-Hodgkin lymphoma appears to be an Epstein-Barr virus-related lymphoma expressing Epstein-Barr virus-

encoded latent membrane protein 1 (LMP-1) (IARC (2012a); also see Carbone et al. (2009); Mounier et al. (2010)).

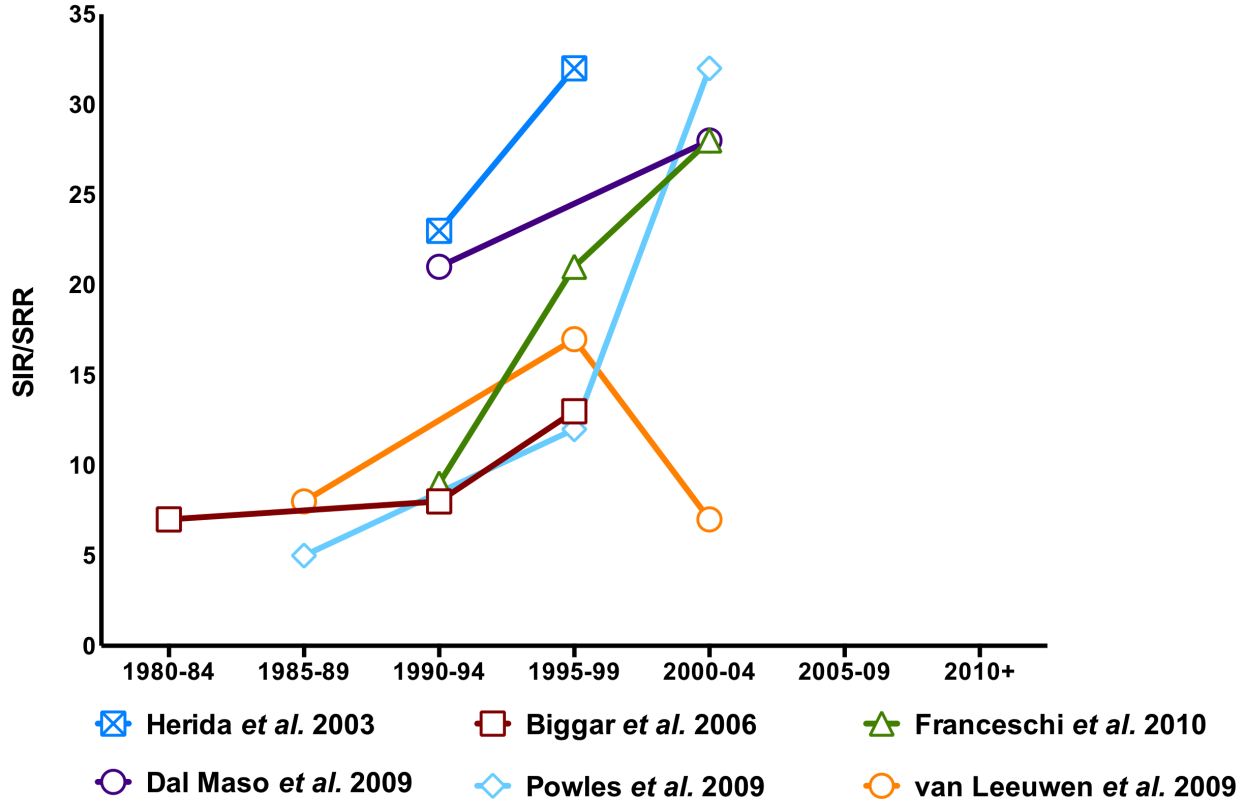

Figure 3-3. Cohort Studies of Hodgkin Lymphoma Incidence in HIV-1/AIDS Populations from Pre-HAART (1980 to 1996) to HAART (1996 and Later) Periods

3.5. Cancer Hazard Evaluation: Human Papillomavirus-related Cancers

Three main cancer types are associated with exposure to both HIV-1 and human papillomavirus: cervical cancer (see Section 3.5.1), invasive anal cancer (see Section 3.5.2), and genital cancers (see Section 3.5.3).

3.5.1. Cervical Cancer

Background Information

Cervical cancer incidence rates in the United States have fallen steadily from 14.8 to 6.7 per 100,000 from 1975 to 2012 (NCI 2015b); however, they remain high in developing countries, e.g., in sub-Saharan Africa, where the incidence is approximately 31 per 10,000 women (Louie et al. 2009), in part due to a lack of screening, sexually transmitted infection (STI) prevention, or human papillomavirus vaccination programs.

Cohort and Case-control Studies

A total of 17 cohort studies including the meta-analysis by Grulich et al. (2007) and 2 case-control studies of cervical cancer reporting SIR or RR were reviewed by IARC (2012a). The

populations in the cohort studies were large, ranging from approximately 1,659 to 375,933 women with HIV-1/AIDS and including 977 cases of cervical cancer (one study by Patel et al. (2008) did not state the number of cases). The two case-control studies of people with HIV-1 in Africa, from Uganda (Newton et al. 2001) and South Africa (Stein et al. 2008), both reported non-statistically significant relative risks of 1.6, based on 257 exposed cases.

The cohort studies of cervical cancer reviewed by IARC reported risks ranging from 1 to over 40 among HIV-1-positive women vs. HIV-1-negative women, with most excess risks in developed countries of between 3 and 22 (Table 3-5), depending on factors such as availability of human papillomavirus screening, human papillomavirus vaccination and treatment programs, availability of HAART, and competing causes of death (IARC 2012a). A meta-analysis of seven of these cohorts by Grulich et al. (2007) reported an age- and sex-adjusted meta-SIR = 5.8 (95% CI = 3.0 to 11.3) for the period 1980 to 2002 based on 104 cases.

Table 3-5. Summary of HIV-1/AIDS Cohort Studies of Cervical Cancer

	AIDS	HIV-1 Positive[a]	AIDS or HIV-1 Positive
RR/SIR	2.9–51[a]	1.0–14.6[a]	1.7–21.8[b]
Cohort size	1,659–375,933	2,141–57,350	2,574–444,172
No. cases	9–84	2–137	1–355
No. of studies	5	7	5

Source: IARC (2012a), Table 2.10 and Table 2.11.
[a]Subjects with cervical cancer in these cohorts would have AIDS as this cancer is an AIDS-defining disease.
[b]All lower 95% CI > 1.0, with the exception of Goedert et al. (1998), Allardice et al. (2003), Newnham et al. (2005).

Findings from the 15 cohort studies published after 2008 (Akarolo-Anthony et al. 2014; Bedimo et al. 2009; Calabresi et al. 2013; Castilho et al. 2015; Chaturvedi et al. 2009; Chen et al. 2014; Coghill et al. 2015; Franceschi et al. 2010; Hleyhel et al. 2013; Park et al. 2014; Raffetti et al. 2015; Simard et al. 2010; Simard et al. 2012; Vogel et al. 2011; Zhang et al. 2011) were consistent with the findings (risks mostly between 2 and 18) from the earlier studies (data not shown).

Relationship with HAART

The effect of HAART on the risk of cervical cancer is not clear. HAART appeared to have little impact on decreasing the risk of cervical cancer in HIV-infected women based on reviews of studies comparing rates from the pre-HAART era to the early HAART era (Adler 2010; Denslow et al. 2014; IARC 2012a; Palefsky 2009). Large cohort studies have reported no change or statistically insignificant decreases or increases in SIR/RRs in the range of 0.8 To 1.9 from the pre-HAART to HAART periods (Biggar et al. 2007; Chaturvedi et al. 2009; ICHIVC 2000; Serraino et al. 2007; Simard et al. 2010).

Some studies have reported that patients with a higher CD4+ cell count and receiving HAART had a lower risk of cervical cancer (Abraham et al. 2013; Guiguet et al. 2009; Leitao et al. 2008; Patel et al. 2008), while others report no apparent association with CD4+ cell counts (Biggar et al. 2007; Chaturvedi et al. 2009; Frisch et al. 2000). Chaturvedi et al. (2009) hypothesized that high cervical cancer mortality in the pre-HAART era may have masked the association of immunosuppression with cervical cancer, and that prolonged survival with incomplete immunocompetence among those with very low CD4+ counts at diagnosis provided time for

cancer to develop. Many of the studies that reported no significant effect of HAART on the risk of cervical cancer were registry studies that used aggregate data and did not compare risk at the individual level and could not account for the increased life expectancy of HIV-1 patients receiving HAART (Dugué et al. 2013; Gravitt and Kirk 2010).

Current invasive cervical cancer risks among HIV-1-infected women generally remain elevated compared with general population rates and among people treated with HAART (Patel et al. 2014).

Cofactors

Human papillomavirus is considered necessary for the development of cervical cancer, and the risk is substantially increased in the presence of HIV-1 infection (IARC (2007; 2012a); NTP (2014a) and reviews by Bosch et al. (2002); Crosbie et al. (2013)). Almost all cervical cancers are caused by human papillomavirus (CDC 2015c). While most human papillomavirus infections are transient, a causal relationship between persistent human papillomavirus infection involving certain genital mucosal types and the development of cervical cancer has been well established in virtually all populations around the world that have been studied. Both human papillomavirus and HIV-1 are sexually transmitted, and the two infections frequently occur together (IARC 2012a). The primary evidence for an indirect effect of HIV-1 infection for cervical cancer is that HIV-1-positive women from various populations are more likely to be human papillomavirus positive than HIV-1-negative women, and more likely to have persistent and multiple infections, and more likely to have one or more of the human papillomavirus genotypes that are considered to be high risk for progression to invasive cervical cancer (IARC (2012a); NTP (2003) see also, e.g., Desruisseau et al. (2009) and reviews by De Vuyst et al. (2013), Denny et al. (2012), Adler (2010)). Abnormal cervical cytology as a result of HPV infection and an increased risk of progression of cervical lesions has been associated with low CD4+ counts in multiple studies (Denslow et al. 2014).

Other risk factors may impact cervical cancer risk, including other causes of immune suppression (transplants or autoimmune disease), end-stage renal disease, chronic inflammation, oral contraceptive use, and, most strongly, smoking (see e.g., reviews by (Dugué et al. 2013; Fernandes et al. 2015; Gadducci et al. 2011)).

3.5.2. Cancer Evaluation: Invasive Anal Cancer

Background Information

In the United States, anal cancer is rare, accounting for 0.4% of all incident cancers. The annual incidence rate is approximately 1.8 per 100,000, based on 2008 to 2012 SEER rates. However, over the past 10 years, anal cancer incidence rates have been increasing on average 2.2% per year, and the risk in men is approaching the risk in women (1.5/100,000 in men and 2.0/100,000 women per year based on 2008 to 2012 cases), which is largely attributed to increased rates of HIV (NCI 2015e).

Cohort and Case-control Studies of Invasive Anal Cancer

IARC (1996) reviewed two early U.S. cancer registry linkage studies of AIDS patients in which an SIR of 3.5 (95% CI = 1.3 to 7.5) was reported for anorectal cancer by Reynolds et al. (1993)

and relative risks of 84.1 (95% CI = 46.4 to 152) among men having sex with men, and 37.7 (95% CI = 9.4 to 151) among other men were reported for anal cancer by Melbye et al. (1994).

A total of 17 cohort studies reporting SIR or RR were reviewed by IARC (2012a), representing approximately 1,670 cases. No case-control studies were identified by IARC. The cohort studies reported substantial increases in anal cancer among HIV-1-positive men, particularly men having sex with men, but increases in risk were also reported among HIV-1-positive women, compared to HIV-1-negative groups or the general population (IARC 2012a). In addition, cases may occur at a younger age among HIV-1-positive compared with HIV-1-negative populations (IARC 2012a). These cohort studies conducted in the United States, Europe, or Australia, including the meta-analysis by Grulich et al. (2007), were reviewed by IARC, which reported a range of SIRs or RRs from approximately 6.8 to 222, with most studies reporting risk between 10 and 39 (IARC 2012a) (see Table 3-6). Twenty-one studies conducted since the IARC review confirmed these findings with most studies reporting higher risk estimates ranging from 20 to over 100. Shiels et al. (2009) reported a meta-SIR of 28 (95% CI = 21 to 35), based on 253 cases. In addition, Machalek et al. (2012) conducted a meta-analysis of 53 studies of anal cancer among men who have sex with men and reported an approximately 9-fold higher risk of anal cancer among HIV-1-positive compared with HIV-1-negative men. The risk of anal cancer was also increased among HIV-1-negative men who have sex with men compared with the general population (Machalek et al. 2012).

Table 3-6. Summary of HIV-1/AIDS Cohort Studies of Invasive Anal Cancer

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR	6.8–37.9[a]	9.2–222[a]	28.8–37.1[a]
Cohort size	3,616–375,933	2,566–57,350	12,104–444,172
No. cases	1–214	5–61	6–303
No. of studies	6	7	4

Source: IARC (2012a), Table 2.13 and Table 2.14.
[a]All lower 95% CI > 1.0 except Grulich et al. (2007).

Relationship with HAART

The risk of anal cancer in the HAART era appears to be increased. An early U.K. clinical study of HAART-treated vs. untreated patients (Bower et al. 2004) reported a doubling of risk from approximately 0.4 to 0.9 cases per 1,000 person-years. Four studies reported increases in anal cancer risk from the pre- to the early or established HAART era ranging from 1.5 to 274, with most between 1.5 and 6 (Diamond et al. 2005; ICHIVC 2000; Seaberg et al. 2010; Simard et al. 2010), and studies by Piketty et al. (2008), Patel et al. (2008), and Hessol et al. (2007) reported increased risks in the HAART era. However, record-linkage registry studies of HIV-1/AIDS cases in the United States(Engels et al. 2006a; Engels et al. 2008; Hessol et al. 2007), Switzerland (Clifford et al. 2005) and Australia (van Leeuwen et al. 2009) reported inconsistent changes in SIRs over two to three time periods between the pre-and established HAART era. In the largest study of human papillomavirus-associated cancers Chaturvedi et al. (2009) found that the incidence of invasive anal cancer was 104% higher in the HAART era than in the pre-HAART era (RR = 2.03, 95% CI = 1.54 to 2.68), and that low CD4 counts at diagnosis during the HAART era were associated with significantly increased anal cancer incidence. Such

observed increases in anal cancer incidence may be due to the fact that mortality among individuals with a low CD4 T-cell count during the pre-HAART era may have masked an association between immunosuppression and the risk of human papillomavirus-related invasive anal cancer; the increased survival during the HAART era may provide adequate time for progression of premalignant lesions to invasive cancers (Chaturvedi et al. 2009).

Overall, current risks of anal cancer among HIV-1-positive populations, particularly among men who have sex with men, remain 30 to 140 times higher than general population rates (Franceschi et al. 2010; Powles et al. 2009; van Leeuwen et al. 2009).

Cofactors

Approximately 91% of anal cancers are considered to be human papillomavirus-associated (CDC 2015c). Human papillomavirus infection of the anal canal is highly prevalent among both HIV-1-positive people and transplant recipients, and is also observed in the large majority of invasive anal cancer cases in both men and women (Hessol et al. 2009; IARC 2012a). Anal cancer and anal intraepithelial neoplasia incidence is highest among HIV-1-positive men who have sex with men where anal human papillomavirus infection is almost universal, chronic, and characterized by multiple human papillomavirus subtypes; however, human papillomavirus infection and anal cancer are also more common in HIV-1-positive women than HIV-1-negative women (Engels 2009). A high percentage of HIV-1-infected individuals co-infected with human papillomavirus also have an increased risk of developing many human papillomavirus-associated cancers, including oropharyngeal cancers (Gillison 2009; Park et al. 2016). Other risk factors for precancerous anal intraepithelial neoplasias and subsequent risk of invasive anal cancer, which include a history of receptive anal intercourse, genital warts, and smoking (Coutlée et al. 2012; Hessol et al. 2009; Stanley et al. 2012) are correlated with the risk of both human papillomavirus and HIV-1 infection; however, the degree of interaction between these factors and the risk of anal cancer in HIV-1-positive populations is not clear.

3.5.3. Genital Cancers

Background Information

Genital cancers include vaginal/vulvar cancer in women and penile cancer in men. In the United States based on age-adjusted data from SEER 2008 to 2012, the number of new cases of vulvar cancer was 2.4 per 100,000 women per year, and accounts for 0.3% of all incident cancers (NCI 2015d); the incidence of vaginal cancer is 0.7 per 100,000 women per year (CDC 2016); the incidence of penile cancer is 0.8 per 100,000 men per year (CDC 2016).

Cohort and Case-control Studies

The available database on HIV-1 infection and human papillomavirus-related genital cancers has expanded since the IARC (2012a) review. The working group considered the database to be limited as it was based primarily on a meta-analysis of only two studies of vaginal/vulvar cancer (mRR = 6.5, 95% CI = 4.1 to 10.2) and three studies of penile cancer (mRR = 4.4, 95% CI = 2.8 to 7.1), each with relatively few (less than 25) infected cases (Grulich et al. 2007). (Two of the studies in the analysis for each cancer might have been on overlapping populations.) A subsequent meta-analysis (Shiels et al. 2009), which included some of the same studies, reported similar risks for both cancer endpoints (mRRs = 9.4, 95% CI = 4.9 to 18, 25 infected cases from

four studies on vaginal/vulvar cancer and 6.8, 95% CI = 4.2 to 11, 16 infected cases from 3 studies on penile cancer) based on relatively few infected cases.

Since the 2009 meta-analysis, four additional cohort studies conducted in the United States and Europe that reported risk estimates for vaginal/vulvar cancer (totaling over 150 cases) and four studies for penile cancer (totaling over 65 cases) among HIV-1-infected individuals or people with AIDS were identified (Park et al. (2014) for penile only, Franzetti et al. (2013) for vaginal/vulvar only and Raffetti et al. (2015), Simard et al. (2010), Chaturvedi et al. (2009) for both cancer sites). (Two studies may report on overlapping populations and overlap with earlier studies). In general, these studies have more infected cases than the earlier studies. All studies, most of which used the general population as the comparison group, found statistically significantly increased SIRs (mostly ranging from 4 to 28) for both cancers. A study of HIV-1-infected and uninfected veterans found a statistically significant elevated incidence rate ratio (IRR) for penile cancer (Park et al. 2014). A summary of the findings across all studies (prior to and after the 2009 meta-analysis) are provided in Table 3-7.

Table 3-7. Summary of HIV-1/AIDS Cohort Studies of Genital Cancers

	Penile	Vulva/vagina
RR/SIR (range)	4–28	5–27[a]
No. cases/study	1–29 (in situ)	1–123 (in situ)
No. of studies[b]	6	7

Source: Long et al. (2008), Mbulaiteye et al. (2006), Newnham et al. (2005), Patel et al. (2008), Chaturvedi et al. (2009), Dal Maso et al. (2009), Simard et al. (2010), Park et al. (2014), Franzetti et al. (2013), Raffetti et al. (2015). Does not include Engels et al. (2006a) and Frisch et al. (2001) since those population are thought to have been updated by Simard et al. 2010.
[a]RR of 69 based on one case; 5 is based on invasive cancer only.
[b]Two studies (Chaturvedi et al. 2009; Simard et al. 2010) might be of overlapping populations.

Approximately 75% of vaginal cancers, 69% of vulvar cancers, and 63% of penile cancers are considered to be human papillomavirus associated (CDC 2012). Two studies evaluated cancer risk among people with AIDS in the United States with potentially overlapping populations (Chaturvedi et al. 2009; Simard et al. 2010), one of which conducted a detailed analysis of human papillomavirus-related tumors (Chaturvedi et al. 2009) primarily related to indicators of immunosuppression. For each cancer type, higher risks were found for in situ cancer (~20-fold) compared with invasive cancer (~5-fold) and in general, similar risk estimates were found across the different HIV-1 risk groups (such as injection drug users, heterosexual, unknown, and men having sex with men for penile cancer), which may help rule out potential confounding from lifestyle behaviors.

Simard et al. (2010) reported higher risk in the HAART era compared with pre-HAART for both cancer types. Both studies of people with AIDS found evidence to suggest that the risk of genital cancers is higher at longer time periods after AIDS onset compared to shorter time periods with the strongest association with vaginal/vulvar cancer although the time period after AIDS onset differed between the two studies. In addition, the risk of vaginal/vulvar cancer increased during the time period 5 years prior to AIDS onset to 5 years after AIDS onset. Among women who developed AIDS during the HAART era, low CD4 counts at AIDS onset was associated with the risk of developing in situ and invasive cancer of the vagina or vulva 28 to 60 months after AIDS onset. These findings are consistent with a link between prolonged HIV-related

immunosuppression, which would allow increased risks from co-infection with human oncogenic papillomaviruses—the major co-factor. Other concerns are similar to those mentioned for anal and cervical cancer.

3.5.4. Oral-related Cancers

Background Information

Oral-related cancers include both oropharyngeal cancers (cancers of the soft palate and uvula, tonsils, posterior pharyngeal wall and the base of the tongue), and oral cavity cancers (cancers of the lips, floor of the mouth, buccal mucosa, gingiva, hard palate, and the mobile part of the tongue). In the United States based on age-adjusted data from 2008 to 2012, the number of new cases of oral-related cancers combined was 11.0 per 100,000 men and women per year, and represent 2.8% of all new cancers per year (NCI 2015g).

Cohort and Case-control Studies of Oral-related Cancer

The IARC (2012a) monograph on HIV-1 infection and oral-related cancers provided limited information about the risks, including reference to one meta-analysis based on five studies of the risk of lip cancer and of oral cavity/pharyngeal cancers in HIV-1/AIDS-positive individuals showing increased risks of cancer (mSIR = 2.80, 95% CI = 1.91 to 4.11, and mSIR = 2.32, 95% CI = 1.65 to 3.25, respectively) (Grulich et al. 2007). A meta-analysis conducted by Shiels et al. (2009), including some of the same studies reported by Grulich et al. (2007), published after the IARC monograph, reported meta-SIRs for lip and oral cavity/pharynx together (mSIR = 2.2, 95% CI = 1.0 to 4.7) based on 84 cases. Shiels et al. (2009), also included separate estimates for oropharyngeal cancer (mSIR = 1.9, 95% CI = 1.4 to 2.6) based on 108 cases.

Since the IARC (2012a) review and the meta-analysis by Shiels et al. (2009), the available database on HIV-1 infection and oral-related cancers has expanded considerably. Approximately 13 new cohort studies have reported estimates for oral-related cancers (Calabresi et al. 2013; Castilho et al. 2015; Chaturvedi et al. 2009; Chen et al. 2014; Coghill et al. 2015; Franzetti et al. 2013; Park et al. 2014; Raffetti et al. 2015; Seaberg et al. 2010; Silverberg et al. 2011; Simard et al. 2010; van Leeuwen et al. 2009; Vogel et al. 2011).

Overall, estimates of oral-related cancers among HIV-1 infected individuals were available from 21 studies including both those reviewed in IARC and new studies published since the IARC (2012a) review. Risks (SIR/RRs) reported in these studies ranged from 1.1 to 5.3, with most studies reporting risks in the range of 2 to 4. SIR/RR estimates from two studies which were conducted outside of these geographic areas reported elevated risks of tongue/tonsil cancers in the range of 11 to 22. Due to small numbers of these relatively rare tumors, studies often report estimates for combined cancer sites, and/or for specific oral-related cancer sites (see Table 11): oral cavity and oropharyngeal cancers combined, oropharyngeal cancers, tongue and/or tonsil cancers, and oral cavity cancers (lip and/or oral cavity).

Table 3-8. Summary of Studies of HIV-1/AIDS Cohort of Oral-related Cancers[a]

	Oral Cavity/Pharyngeal Cancers	Oropharyngeal Cancers	Tongue and/or Tonsil Cancer	Oral Cavity Cancer
RR/SIR (range)	1.1–4.1	1.1–5.4	1.7–22.1	1.1–8.5
No. cases/study	2–260	2–108	2–54	4–30
No. of studies[b]	14	7	7	7

Source: Calabresi et al. (2013); Castilho et al. (2015); Chaturvedi et al. (2009); Chen et al. (2014); Clifford et al. (2005); Coghill et al. (2015); Engels et al. (2008); Franzetti et al. (2013); Frisch et al. (2001); Grulich et al. (2002); Grulich et al. (2007); IARC (2012a); Newnham et al. (2005); Park et al. (2014); Raffetti et al. (2015); Seaberg et al. (2010); Shiels et al. (2009); Silverberg et al. (2011); Simard et al. (2010); van Leeuwen et al. (2009); Vogel et al. (2011).
[a]Several studies report more than one anatomical site or site grouping.

Cofactors

Population-level incidence of human papillomavirus-positive oropharyngeal cancers has increased by 225% (95% CI = 208% to 242%) from 1988 to 2004 (from 0.8 per 100,000 to 2.6 per 100,000), and incidence for human papillomavirus-negative cancers declined by 50% (95% CI = 47% to 53%; from 2.0 per 100,000 to 1.0 per 100,000) (Chaturvedi et al. 2011). In a systematic review of the prevalence of human papillomavirus in oropharyngeal squamous-cell sarcoma worldwide which sought to determine whether human papillomavirus is driving the increase in incidence of oropharyngeal cancers, Stein et al. (2015) reported that prevalence of human papillomavirus-positive oropharyngeal squamous-cell sarcoma in North America increased in the 1990s, rose dramatically from 2000 to 2004 and plateaued at about 65% through approximately 2012.

HIV-1-infected individuals are known to have a high prevalence of co-infection with HPV16 (Beachler et al. 2012; Kreimer et al. 2004), an established cause of oropharyngeal and oral cavity carcinomas (IARC 2007). Among HIV-1 infected persons compared to the general population in the United States, multiple investigations show that they have a higher oral human papillomavirus DNA prevalence (20% to 45%), and a higher oncogenic oral human papillomavirus DNA prevalence (12% to 26%) than a sample of the U.S. population (Gillison 2009).

This heterogeneity of disease, the unmeasured heterogeneity of risk factors, and the potentially distinct etiologic pathways for oral-related cancer subtypes complicate the interpretation of these modest risks. Many reports combine oropharyngeal and oral cavity cancer, or report on the broader category of head and neck cancers.

It has been hypothesized that human papillomavirus-associated cancers and human papillomavirus-non associated cancers have distinct risk factor profiles: sexual behavior, particularly increased numbers of oral sexual partners, is a risk factor for human papillomavirus and human papillomavirus-associated cancers; while human papillomavirus-non-associated cancers are more likely to be associated with tobacco and alcohol use, which are also elevated among HIV-1-infected individuals (Gillison et al. 2008). Registry studies have not been able to precisely distinguish between human papillomavirus-associated and human papillomavirus-non-associated cancer. Furthermore, it is likely that risk factors such as common sexual behaviors, the proportion of men who have sex with men and heterosexuals in a cohort, and other

behavioral risk factors related to human papillomavirus-related oral-related cancers, vary across cohorts (Kreimer et al. 2013; Pickard et al. 2012). Unlike HPV1-associated cancers (e.g., cervical or anal cancer), oral transmission of human papillomavirus from males to males has decreased compared with oral transmission from females to males, which may also help explain the modest increase in risk measured in the HIV/AIDS cohorts which are largely men who have sex with men (Beachler and D'Souza 2013). In addition, Chaturvedi et al. (2009) found higher risks of oropharyngeal cancer among heterosexual men compared to men who have sex with men. These data are consistent with the male predominance of human papillomavirus-related cancers and their increase in men compared with women as the prevalence of heterosexual men is much greater than that of men who have sex with men (Gillison et al. 2015).

The role of tobacco and alcohol in combination with HIV-1 and human papillomavirus infections has not been widely investigated. However, Silverberg et al. (2011), in a study estimating the risk of oral cavity and pharynx cancers in HIV-1-positive and negative individuals, controlled for smoking which resulted in a reduction in the SIR from 1.9 to 1.4. Also, the interrelationship of risk factors among HIV-1-infected individuals was recently explored in a natural history study of human papillomavirus among HIV-1-positive and HIV-1-negative individuals, which found that oral human papillomavirus acquisition appears to be increased by oral sex and by the severity of immunosuppression as measured by CD4 counts, while the risk of oral human papillomavirus persistence, necessary for carcinogenesis, is likely to be increased by older age, male sex, and cigarette smoking (Beachler et al. 2014).

3.6. Cancer Hazard Evaluation: Hepatocellular Carcinoma

3.6.1. Background Information

Liver cancer is relatively uncommon in the United States; the annual number of combined liver and intrahepatic bile duct cancers was an estimated 8 per 100,000 in 2015 (NCI 2015a). Hepatocellular carcinoma is the most common form of liver cancer, occurring among 5 to 10 per 100,000 population in the United States (Altekruse et al. 2014), with several recognized and overlapping risk factors, including alcohol abuse, non-alcoholic steatohepatitis, intravenous drug use, cirrhosis, diabetes, and hepatitis B and C virus infection. HIV-1 infection has been reported to be associated with an increase in intrahepatic apoptosis, activation and fibrosis, and gastrointestinal permeability (Crane et al. 2012).

3.6.2. Cohort and Case-control Studies

Eighteen cohort, one nested case-control, and two case-control studies reporting risks were reviewed by IARC (2012a); since 2009, 21 additional cohort studies were identified (excluding prospective patient series). Studies reviewed by IARC (2012a) reported increases in the risk of hepatocellular carcinoma compared with the general population among U.S., European, or Australian populations of between approximately 1.9 and 50, with most estimates between 2 and 16 (see IARC Table 2.23). Studies published from 2009 through August 2015 reported risks ranging from approximately 2 to 31 with most between 2 and 11; 2 studies reported no observed cases. In addition, the meta-analyses by Grulich et al. (2007) (7 studies) and by Shiels et al. (2009) (11 studies), reported meta-SIR for hepatocellular carcinoma of 5.2 (95% CI = 3.3 to 8.2) based on 133 cases, and 5.6 (95% CI = 4.0 to 7.7) based on 171 cases, respectively (see summary Table 3-9).

Shiels et al. (2009) included seven studies of liver cancer among patients with AIDS and without AIDS in their meta-analysis and reported that the risk of hepatocellular carcinoma among patients with AIDS was 6.5 (95% CI = 3.6 to 12), while the risk among patients without AIDS was 3.9 (95% CI = 2.6 to 5.6), supporting the association between decreased immune function and increased risk of liver cancer.

Table 3-9. Summary of HIV-1/AIDS Cohort Studies of Hepatocellular Carcinoma

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR*	3.3–4.5	1.0–16.5	1.7–11
Cohort size	1,659–375,933	2,566–84,504	1,476–615,150
No. cases	1–95	2–174	2–366
No. of studies	9	11	19

Source: IARC (1996), IARC (2012a), Table 2.23 and studies since IARC (2012a): Bedimo et al. (2009); Castilho et al. (2015); Chen et al. (2014); Coghill et al. (2015); Franceschi et al. (2010); Franzetti et al. (2013); Hleyhel et al. (2014); Kramer et al. (2015); McDonald et al. (2009); Park et al. (2014); Powles et al. (2009); Raffetti et al. (2015); Sahasrabuddhe et al. (2012); Seaberg et al. (2010); Shiels et al. (2009); Silverberg et al. (2011); Simard et al. (2010); Simard et al. (2012); van Leeuwen et al. (2009); Vogel et al. (2011); Zhang et al. (2011). References not reporting SIR or RR and outliers (Akarolo-Anthony et al. 2014) were excluded. Findings of studies conducted among populations of hepatitis C virus positives or which also adjusted for hepatitis C virus in models are discussed in the text: Di Benedetto et al. (2014); Kramer et al. (2015); McDonald et al. (2009); McGinnis et al. (2006); Sahasrabuddhe et al. (2012); Vogel et al. (2011). The Deng et al. (2009) meta-analysis examined hepatitis C virus patients with and without HIV-1.
*All lower 95% CI > 1.0 except Coghill et al. (2015); Dal Maso et al. (2003); Grulich (1999); Grulich et al. (2002); Mbulaiteye et al. (2006); Serraino et al. (2000).

3.6.3. Relationship with HAART

The role of HAART on hepatocellular carcinoma risk has yet to be clearly established. Calendar-period analyses indicate that hepatocellular carcinoma risk has increased in the HAART era (Curry 2013; Hessol et al. 2007; Sahasrabuddhe et al. 2012). In the Shiels et al. (2009) meta-analysis, the SIR for liver cancer in the HAART era was slightly higher than in the pre-HAART era (ratio of SIRs: 1.25, 95% CI = 0.49 to 3.24). Merchante et al. (2013) reported that the incidence of hepatocellular carcinoma among HIV-1/hepatitis C virus-positive patients increased from 0.2 to 2.8 per 1,000 person-years (based on 82 cases of hepatocellular carcinoma) from the early to established HAART era (2000 to 2009). Observed increases may at least partly be due to increased survival or possible changes in alcohol consumption, hepatitis B or C virus infection rates, or other risk factors for hepatocellular carcinoma (Curry 2013; Hessol et al. 2007; IARC2012a). In contrast to this, some follow-up studies of individual HIV-1-infected patients reported either a lack of association (e.g., Serraino et al. 2007), or a reduction in relative risk among HAART-treated patients (Hessol et al. 2007) or since the advent of HAART (Limketkai et al. 2012).

Several studies have found the risk of hepatocellular carcinoma to be associated with the degree of immunosuppression at HIV-1 diagnosis, as measured by CD4 cell count (Engels et al. 2008) (Kramer et al. 2015; Silverberg et al. 2011; Vogel et al. 2011), suggesting a role for HIV-1-induced immunosuppression. However, observations of low CD4 counts with liver cancer are sensitive to the timing of the count either at AIDS diagnosis or at enrollment; one study evaluating time-dependent measures of CD4 found that liver cancer was unrelated to longer exposure to CD4 counts of <200 cells/μL (Kesselring et al. 2011), while another study (Guiguet

et al. 2009) measuring recent low CD4 count found that this metric was the best predictor of liver cancer incidence.

3.6.4. Cofactors

Hepatocellular carcinoma is causally linked to both hepatitis B virus and hepatitis C virus infection (see IARC 2012a; 2014b; NTP 2014c). Overall, approximately 25% of HIV-1-positive people in the United States and also in Europe are estimated to be co-infected with hepatitis C virus and 9% with hepatitis B virus (Nunnari et al. 2012). Hepatitis C virus infection is highly prevalent among groups with parenterally acquired HIV-1 infection, notably hemophiliacs and injection drug users (between 80% and 95%) and substantially less (3% to 15%) among other groups, i.e., non-injection drug-using men who have sex with men and other men and women (Clifford et al. 2008; Engels et al. 2002a).

Concerns remain as to the extent to which these viruses are cofactors or confounders of observed associations between HIV-1 infection and hepatocellular cancer, and the extent to which observed increases in risk of hepatocellular carcinoma among HIV-1-infected populations is attributable to co-infection with hepatitis B or C virus. Few studies have measured the seroprevalence of hepatitis B or C virus among HIV-1/AIDS individuals, but several cohort studies have reported a lack of association between HIV-1 status and the risk of hepatocellular carcinoma among hepatitis C virus-infected patients (Henderson et al. (2010); Kramer et al. (2005) as reviewed by Deng et al. (2009); Tradati et al. (1998)) or after adjustment for hepatitis C virus infection (McGinnis et al. 2006). Di Benedetto et al. (2014) observed that hepatitis C infection alone was associated with a higher incidence of hepatocellular carcinoma than among hepatitis C virus and HIV-1 co-infected patients (incidence ratio 1.97).

3.7. Cancer Hazard Evaluation: Cancers Not Known to Be Associated with Other Viruses

Three main cancer types which are not known to be associated with other viruses are evaluated below: non-melanoma skin cancer (see Section 3.7.1), conjunctival cancer (see Section 3.7.2), and lung cancers (see Section 3.7.3).

3.7.1. Non-melanoma Skin Cancer

Background Information

Non-melanoma skin cancer is the most common cancer in the United States; with 3.5 million new cases per year, the incidence rate exceeds that of all other cancers combined (ACS 2015). Two primary subtypes have been identified: squamous-cell carcinoma and basal-cell carcinoma (the most common form). While most forms of in situ non-melanoma skin cancer are readily treatable and are not included in cancer statistics, an estimated 2,000 deaths per year in the United States have been attributed to this form of cancer (in contrast to melanoma with 9,000 deaths per year (ACS 2015).

A rare form of basal-cell carcinoma, Merkel cell carcinoma, has been identified in association with the recently identified Merkel cell polyomavirus since 2008 and is associated with approximately 80% of these cancers (see accompanying monograph on Merkel cell polyomavirus). One cohort study of AIDS patients prior to this date (Engels et al. 2002b)

specifically identified Merkel cell carcinoma in this population, and reported a relative risk of 13.4 (95% CI = 4.9 to 29.1) based on six cases. The proportion of basal-cell carcinomas previously observed in studies of HIV-1-infected populations that are attributable to Merkel cell carcinoma and Merkel cell polyomavirus co-infection has not been clearly established to date.

Cohort and Case-control Studies

Eight cohort studies and one case-control study of non-melanoma skin cancer in HIV-1-positive populations were reviewed by IARC (2012a). The cohort studies, all from the United States or Europe, reported risks ranging from 2.8 to 20, based on 130 cases. Since the IARC review (2012a), eight cohort studies and two additional meta-analyses were identified (Shiels et al. 2009; Zhao et al. 2015), with two of the cohort studies having been published prior to the IARC publication (Cooksley et al. 1999; Grulich et al. 2002). Most of the reported risks in the cohort studies ranged from 1.5 to 6 but were up to 20 in a few studies (see Table 3-10). There is some overlap of studies included in the three meta-analyses, with meta-SIR values ranging from 2.8 to 4.1 based on a total of 851 cases. The most recent meta-analyses by Zhao et al. (2015) was limited to the six studies published between 2003 and 2013 that only collected data on cancer incidence through cancer registries to ensure unbiased comparisons of the incidence rates from the cohorts with the general population. All the studies in this meta-analysis reported statistically significant risk estimates and the meta-risk was 2.76 (95% CI = 2.55 to 2.98) based on 570 cases. In addition, a case-control study from South Africa (Stein et al. (2008), reviewed by IARC (2012a)) reported a statistically significant odds ratio of 2.6 among 15 exposed cases.

Table 3-10. Summary of HIV-1/AIDS Cohort Studies of Non-melanoma Skin Cancer[a]

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR*	13.4	1.75–19.6	1.5–14.9
Cohort size	309,365	2,238–33,190	2,574–497,142
No. of cases	6	3–70	2–570
No. of studies	1	6	12

Source: IARC (1996), IARC (2012a), Table 2.17 and studies since IARC (2012a): Albini et al. (2013); Chen et al. (2014); Crum-Cianflone et al. (2015); Franceschi et al. (2010); Grulich et al. (2002); Lanoy et al. (2009); Shiels et al. (2009); Silverberg et al. (2013); Zhao et al. (2015) meta-analyses. References not reporting SIR or RR were excluded.

*All lower 95% CI > 1.0 except Dal Maso et al. (2003), RR = 1.5 (0.8–2.5); and Lanoy et al. (2010), RR = 2.3 (0.94–5.67) for Merkel cell carcinoma.

[a]Includes non-melanoma skin cancer, not otherwise specified, except for Engels et al. (2002b) study of Merkel cell carcinoma; Lanoy et al. (2009) study of Merkel cell carcinoma (NS), sebaceous carcinoma, and appendageal carcinoma; and Silverberg et al. 2013 study of basal-cell and squamous-cell carcinomas.

Relationship with HAART

Crum-Cianflone et al. (2015), based on a substudy of 2,238 HIV-1-infected adults within the U.S. Military HIV Natural History Study (NHS) who initiated HAART between 1996 and 2012, found that viremia was associated with non-melanoma skin cancers (time-updated HIV-1 RNA, per $\log_{10}$ copies/mL, hazard ratio [HR] = 1.75 [95% CI = 1.42 to 2.14]). This finding provides some evidence of the link between HIV-1viremia and non-melanoma skin cancers and lends support to control of viremia in limiting the risk of cancer among HIV-1 patients after HAART initiation. This is consistent with the finding of a statistically significant trend ($P < 0.001$) that was observed with decreasing recent CD4 counts in a cohort study of HIV-1-positive and 36,821 HIV-1-negative patients in the United States (Silverberg et al. 2013).

In contrast to transplant recipients, in whom substantial increases in predominantly squamous-cell carcinoma of the skin have been reported, basal-cell carcinomas appear to predominate (Bedimo et al. 2009).

The meta-analysis by Zhao et al. (2015) reported similar risk estimates for studies in the pre-HAART era (2.11, 95% CI = 1.44 to 3.2, 3 studies) and the post-HAART era (2.01, 95% CI = 1.33 to 3.04, 4 studies).

Cofactors

Since the last IARC review (2012a) and shortly after the discovery of Merkel cell polyomavirus, two cohort studies and one case-control study have been identified that reported increased risks of Merkel cell carcinoma among HIV-1-positive populations (Izikson et al. 2011; Lanoy et al. 2009; Lanoy et al. 2010) and also diminished survival of Merkel cell carcinoma patients (Paulson et al. 2013). There is limited evidence to date as to whether infection with HIV-1 increases the risk of Merkel cell polyomavirus infection (Fukumoto et al. 2013; Tolstov et al. 2011; Wieland and Kreuter 2011; Wieland et al. 2011), however, and no studies have been identified to date that have measured Merkel cell polyomavirus among HIV-1-positive Merkel cell carcinoma cases, with the exception of one case study (Li et al. 2013). Merkel cell carcinoma is primarily attributed to Merkel cell polyomavirus and HIV-1-induced immunodeficiency increases the risk (see Merkel cell polyomavirus monograph at https://ntp.niehs.nih.gov/go/797227).

The elevated risk of non-melanoma skin cancer in the HIV-1-positive population is largely limited to Caucasians and suggests that exposure to solar ultraviolet radiation is an important co-factor in the general population.

3.7.2. Conjunctival Cancer

Background

Squamous-cell carcinoma of the conjunctiva is a rare cancer of the ocular surface with an incidence rate that varies geographically from 0.02 to 3.5 per 100,000 depending on the latitude of the population studied (Sun et al. 1997; Yang and Foster 1997). The incidence of squamous-cell carcinoma of the conjunctiva has been estimated to be 8.4 per 10^6 based on an analysis of the U.S. NIH-AARP Diet and Health study (Emmanuel et al. 2012).

Cohort and Case-control Studies

Three early case-control studies from Africa (Ateenyi-Agaba 1995; Kestelyn et al. 1990; Newton et al. 1995), reviewed by IARC (1996), reported statistically significant increases in risk of conjunctival cancer among HIV-1-positive cases of 8 to 13. Four cohort and two additional case-control studies were reviewed by IARC (2012a) (see summary Table 3-11), and two meta-analyses were identified since 2008. Case-control studies in African countries, reviewed by IARC (2012a) and based on a total of 158 cases, reported increased relative risks of 12 to 24 for conjunctival cancer in HIV-1-positive populations (Ateenyi-Agaba (1995); Kestelyn et al. (1990); Newton et al. (2001); Waddell et al. (1996); see IARC (2012a), Table 2.20), although one cohort study in Uganda involving 6 cases of conjunctival cancer reported a lower rate (SIR = 4.0, 95% CI = 1.5 to 8.7) SIR = 4.0, 95% CI = 1.5-8.7 (Mbulaiteye et al. 2006). In addition, three large cancer registry linkage studies of people with AIDS or HIV-1 in the United

States (Frisch et al. 2000; Goedert and Coté 1995; Guech-Ongey et al. 2008) reported very similar age-, sex-, year- and/or race-adjusted relative risks of approximately 12 to 15, based on a total of 26 cases, rates that were almost identical to those observed in the African studies cited above. Incidence rates appear to have increased substantially around the period that the HIV-1 epidemic spread in these countries (IARC 2012a). In two meta-analyses conducted among studies up to 2013, Carreira et al. (2013) reported a meta-relative risk for ocular surface squamous-cell carcinoma of 8.1 (95% CI = 5.3 to 12.3), and Gichuhi et al. (2013) reported a meta-odds ratio of 6.2 (95% CI = 4.8 to 7.9) in association with HIV-1 infection. There are few data on the effects of antiretroviral treatment: one case study reported a regression of this cancer in a woman commensurate with beginning HAART and improved CD4 counts (Holkar et al. 2005), but a subsequent study in the United States (Guech-Ongey et al. 2008) reported a similar 12-fold increase in risk in both the pre-and post-HAART period.

Table 3-11. Summary of HIV-1/AIDS Cohort Studies of Conjunctival Cancer

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR	13–15	_	4–12
Cohort size	50,050–309,365	_	12,607–491,048
No. cases	4–7		6–15
No. of studies	2		2

Source: IARC (2012a), Table 2.19 and Table 2.20.
All lower CI > 1.0.

Cofactors

The risk of squamous-cell carcinoma of the conjunctiva is higher in males and in whites and is correlated to ultraviolet radiation (Sun et al. 1997; Yang and Foster 1997); however, the interaction of ultraviolet light with HIV-1 status is unclear (IARC 2012a). In Africa, the incidence is rising rapidly in conjunction with the rising HIV/AIDS pandemic and is affecting young persons (around 35 years of age) and women; it is suggested that this increase is related to the co-existence of the HIV-1/AIDS pandemic, high human papillomavirus exposure, and solar radiation in the region. In the United States, squamous-cell carcinoma of the conjunctiva risk in persons with HIV-1/AIDS is higher in persons aged ≥50 years, of Hispanic ethnicity and who resided in the southern low altitude states (Guech-Ongey et al. 2008). Squamous-cell carcinoma of the conjunctiva has also been shown to be elevated in persons post kidney transplant, implicating immunosuppression (Vajdic et al. 2007).

Human papillomavirus infections of the conjunctiva of the eye are more common than previously appreciated (Angeletti et al. 2008; Ateenyi-Agaba et al. 2006; Mincione et al. 1992; Reszec and Sulkowski 2005; Tabrizi et al. 1997; Waddell et al. 2003).

No definitive role for co-infection with human papillomavirus of the mucosal type has been identified, but a role for co-infection with human papillomavirus of cutaneous types has been reported (Gichuhi et al. 2014). An approximately 3-fold increase in risk was associated with this human papillomavirus subtype in a meta-analysis (Carrieri et al. 2003). Smoking, allergies, vitamin A deficiency, and other risk factors do not appear to affect risk among HIV-1-positive populations (Gichuhi et al. 2013), but data are limited.

HAART does not appear to reduce the incidence of squamous-cell carcinoma of the conjunctiva (Guech-Ongey et al. 2008). SIRs in the pre- and post-HAART eras were similar at 12.0 (95% CI = 5.5 to 22.8) and 12.6 (95% CI = 4.6 to 27.4), respectively ($P = 0.79$). Holkar et al. (2005) reported, however, one case of ART causing tumor regression in an otherwise inoperable case.

3.7.3. Lung Cancer

In the United States, lung cancer incidence accounts for approximately 13% of new cancers, at an incidence rate of approximately 59 per 100,000, based on 2008 to 2012 rates (NCI 2015c). Lung cancer has a latency of approximately 20 years or longer and is now the leading cause of death among HIV-1-positive populations in the United States, accounting for almost 30% of cancer deaths.

Overview of Epidemiological Studies

Twenty-two cohort studies and one case-control study were reviewed by IARC (2012a) (excluding two small clinical follow-up studies). Since the IARC report, 24 additional cohort studies and 1 meta-analysis were identified. None of the studies reviewed by IARC controlled for smoking; but several cohorts since that time have considered smoking in their analyses. Table 3-12 includes both studies that have and have not controlled for smoking; studies that controlled for smoking are discussed in Table 3-13.

Table 3-12. Summary of HIV-1/AIDS Cohort Studies of Lung Cancer

	AIDS	HIV-1 Positive	AIDS or HIV-1 Positive
RR/SIR*	1.63–3.9	1.28–8.9	1.1–15.9
Cohort size	1,659–397,927	871–84,504	2,086–625,716
No. cases	4–531	3–517	4–1,016
No. of studies	9	18	21

Source: IARC (1996), IARC (2012a), Table 2.21, and studies since IARC (2012a): Albini et al. (2013); Bedimo et al. (2009); Castilho et al. (2015); Coghill et al. (2015); Crothers et al. (2011); Franceschi et al. (2010); Franzetti et al. (2013); Hleyhel et al. (2014); Levine et al. (2010); Park et al. (2014); Powles et al. (2009); (Raffetti et al. 2015); Seaberg et al. (2010); Sigel et al. (2012); Silverberg et al. (2011); Simard et al. (2010); van Leeuwen et al. (2009); Vogel et al. (2011).
*All lower 95% CI > 1.0 except Goedert et al. (1998), Grulich et al. (2002), Serraino et al. (2007), van Leeuwen et al. (2009), Silverberg et al. (2011), and Castilho et al. (2015) for Brazil subcohort.
Studies not reporting SIR or RR or which were outliers were excluded.

Most of the studies were conducted in the United States or Europe, spanning both the pre-and post-HAART era; together, the 48 studies reported SIRs or RRs ranging from 1.1 to 15.9, with most risks between 1.5 and 6. In a meta-analysis of cohorts in six countries by Grulich et al. (2007), the lung cancer risk among HIV-1-positive populations was 2.7 (95% CI = 1.9 to 3.9, 1,016 cases). A similar risk estimate (2.6, 95% CI = 2.1 to 3.1) was found in a 2009 meta-analysis of 13 studies (847 cases). This analysis also found higher risk in women (SIR = 3.8, 95% CI = 2.5 to 5.9, 6 studies) compared to men (SIR = 1.9, 95% CI = 1.4 to 2.7, 7 studies).

The effect of HAART on lung cancer rates appears to be limited, according to evidence from studies of individually treated patient populations. In the 2009 meta-analysis, SIRs were regressed based on HAART era, AIDS status, and sex. Statistically significant SIRs were found for both the pre-HAART era (SIR = 2.0; 95% CI = 1.2 to 3.3) and HAART era (SIR = 3.5, 95% CI = 2.6 to 4.6) although somewhat higher for the HAART era. Risks were also higher among

patients with AIDS (SIR = 5.1, 95% CI = 4.0 to 6.4, 5 studies) compared with those without AIDS (SIR = 1.5, 95% CI = 0.82 to 2.6, 5 studies) and in women (SIR = 3.8, 95% CI = 2.5 to 5.9, 6 studies) compared to men (SIR = 1.9, 95% CI = 1.4 to 2.7, 7 studies).

A relationship between nadir CD4 or viral load and lung cancer risk has been reported in some studies but not others (Lambert et al. 2013; Winstone et al. 2013) (see Section 4 for a discussion on the relationship between immunosuppression, CD4 cells, and lung cancer).

Evaluation of Potential Confounding from Smoking

Many of the cohort or record-linkage studies calculated risk estimates (SIR) using expected numbers from the general population and did not have information on adjust for smoking. Because smoking is two to three times more prevalent among HIV-1-positive people (40% to 70%) compared with the general population in Western countries (~20% to 40%), there are concerns that the increases observed for lung cancer and HIV-1 infection could be explained by smoking. However, there are some differences between the profile of lung cancer observed in the HIV-1-positive population compared with cases in the general population; that is, lung cancer in the HIV-1-positive population is more frequently diagnosed when locally advanced or metastatic, diagnosed at a younger age, more aggressive with higher rates of relapse, and has a decreased progression-free survival time (Ruiz 2010). Although all major lung cancer subtypes are elevated, lung adenocarcinoma is the most prevalent subtype observed in the HIV-1-positive population (34% to ~50%) while small-cell carcinomas, which have a stronger association with smoking (Chaturvedi et al. 2007; Engels et al. 2006b; Lubin and Blot 1984), are observed in fewer cases (6% to ~9%) (Chaturvedi et al. 2007; Engels et al. 2006b).

The most informative studies for evaluating the relationship between HIV-1 and smoking are eight cohort studies (several published after the IARC review) that have calculated risk estimates in models that adjusted for or modeled smoking habits, using hypothetical smoking scenarios. The collective evidence from these studies is that smoking does not explain all the excess risk among HIV-1-positive people or people with AIDS, suggesting that HIV-1 might be an independent risk factor for lung cancer. Table 3-13 provides details on these studies and Figure 3-4 shows the risk estimates from these studies.

Table 3-13. Summary of HIV-1 Cohort Studies and Lung Cancer That Adjusted for Smoking

Reference Location	Design/Population/ Enrollment Dates	Smoking Methods
Phelps et al. (2001) USA	Prospective cohort: Incidence HIV-1-infected and HIV-1 uninfected women (with HIV-1 risk behavior) multicenter 1993–1995	Similar smoking history in HIV-1+ and HIV-1– populations (>80%) Controlled for smoking use. CD4 counts, age
Engels et al. (2002b) Baltimore, USA	Retrospective cohort: Incidence Single clinic (Moore Clinic HIV-1); comparison Detroit 1989–2003	Smoking data available for 1/3 of cohort Indirect adjustment by dividing the observed SIR by a bias factor Also calculated risk estimates using extreme scenarios (100% smoking and double RR for lung cancer and smoking)

Reference Location	Design/Population/ Enrollment Dates	Smoking Methods
Chaturvedi et al. (2007)	HIV-1/AIDS cancer match study: Incidence 1980–2002	Modeling assuming 80% or 60% smokers
Kirk et al. (2007)	Prospective cohort: Mortality ALIVE cohort; HIV-1-infected (without AIDS) and HIV-1 injection drug users 1988–2000	Smoking habits similar in HIV-1-infected and non-infected subjects (>80%) Adjusted for pack-yr/day; also conducted analysis or cumulative pack-yr.
Shiels et al. (2010)	Prospective cohort: Incidence ALIVE cohort (same as Kirk et al. 2007) 1988–2000	Adjusted for average packs/day
Silverberg et al. (2011)	Health delivery system HIV-1 and non-HIV-1: Incidence 1980–2000	Tobacco use higher in HIV-1-positive (42.5%) than non-HIV-1-infected subjects Adjusted for smoking at baseline (ever tobacco use), and alcohol/drug abuse, sex, age, race, overweight, calendar year and region
Sigel et al. (2012)	Veterans aging cohort/HIV-1 and non-HIV-1 infected: Incidence 1997–2008	Smoking habits in HIV-1-infected (48%) and non-infected (46%) people were significantly different. Smoking status, adjusted for age, COPD, and bacterial pneumonia Sensitivity analysis overestimates smokers, i.e., all HIV-1 former and never smokers as current smokers and also stratified analysis by smoking status
Hessol et al. (2015)	WIHS (women) and MAC (men) USA; both HIV-1 and non-HIV-1 subjects: Incidence 1994–1995; 2001–2002 WIHS 1984–1985; 1987–1991; 2001–2003 MAC	Smoking pack-yr, Also adjusted for age, race, history of injection drug use, education level, BMI, and history of asthma, calendar time, HAART use, and prior clinical AIDS diagnosis

BMI = body mass index; COPD = chronic obstructive pulmonary disease; MAC = Multicenter AIDS Cohort Study; RR = relative risk; WIHS = Women Interagency HIV Study.

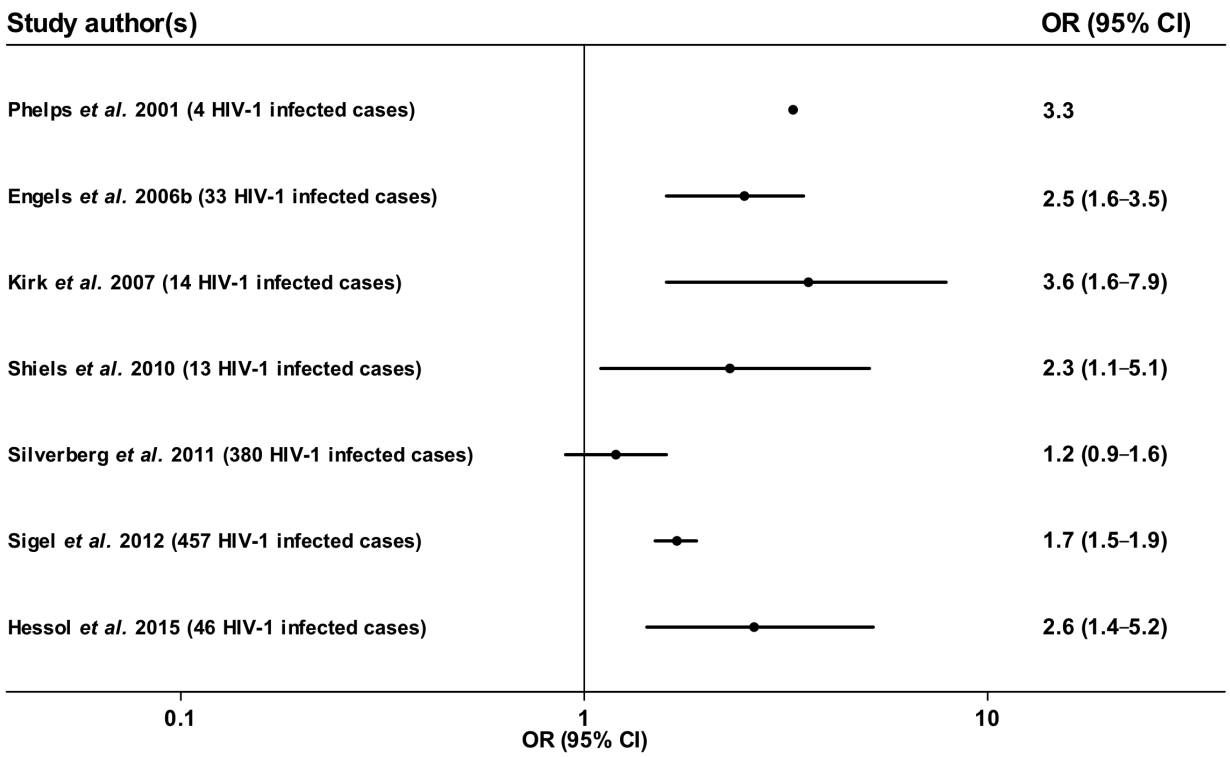

Figure 3-4. Relative Risks for Lung Cancer from Studies Adjusting for Smoking

Note: the forest plot does not contain the study by Chaturvedi et al. (2007) because that publication did not report risk estimates for the entire cohort.

Two studies modeled smoking bias using data from large cohorts. Chaturvedi et al. (2007), evaluated data from lung cancers among people with AIDS from the HIV/AIDS Cancer Match Study in the United States, and found statistically significant predicted lung cancer risks for men 59 years or younger and women 49 years or younger but not among older age groups in models assuming 80% and 60% smoking; no predicted risk estimates were reported for the entire cohort. Engels et al. (2006a) also found statistically significant risks for lung cancer after indirectly adjusting for smoking using a smoking bias factor based on smoking data for a subset of the HIV-1 cohort from a large urban clinic. The findings remain robust in analyses assuming extreme scenarios, 100% smoking and double the risk of lung cancer from smoking. However, in the absence of individual smoking data, residual confounding from smoking cannot be completely ruled out.

The remaining six studies calculated lung cancer risk using HIV-1-uninfected subjects as the comparison group and adjusted for smoking using data on individual smoking behaviors. In smoking-adjusted analyses, five of the six studies found elevated risks for lung cancer, four of which were statistically significant elevated risks for lung, providing limited evidence for an association between HIV-1 infection and lung cancer. The fifth study, which reported a statistically non-significant increase in smoking-adjusted lung cancer risk, had inadequate statistical power because of small numbers of HIV-1 infected cases (Phelps et al. 2001). The strength of the evidence is based on these factors: (1) three studies adjusted for smoking using quantitative measures of smoking (i.e., the amount smoked per day or over time), which is

considered to be more informative (i.e., greater confidence in ruling out residual confounding) than analyses using qualitative smoking data (e.g., smoking status or ever use of tobacco) (Hessol et al. 2015; Kirk et al. 2007; Shiels et al. 2011a); (2) studies were conducted in different populations, e.g., men and women veterans, injection drug users (see Table 3-13); (3) studies included both incidence and mortality data (Kirk et al. 2007; Shiels et al. 2011a); (4) one study had large numbers of HIV-1-infected cases (Sigel et al. 2012); and (5) in a study that conducted a sensitivity analysis overestimating smoking status (i.e., assumed all HIV-1 infected persons were smokers), the relative risk remained significant, albeit attenuated (IRR = 1.2, 95% CI = 1.1 to 1.4), and an elevated risk, which approached significance, was found among non-smokers (Sigel et al. 2012).

The limitations of this database include the fact that the number of studies is limited and there are relatively small numbers of cases in most studies; two studies evaluated mortality and incidence in the same cohort (ALIVE Cohort). Silverberg et al. (2011) found only a small, statistically non-significant, smoking-adjusted RR in a cohort of HIV-1-infected and uninfected patients based on insurance data, suggesting that smoking may explain the excess risk. Advantages of this study are the large number of subjects; however, in the analyses for adjusting for smoking, baseline ever use of tobacco was somewhat limited and the study adjusted for variables that have not been clearly linked to lung cancer risk (e.g., overweight and alcohol use). In addition, the study found statistically significant smoking-adjusted RRs (~2-fold) among subjects with the highest HIV-1 RNA titer (>10,000 copies/mL) or lowest CD4 cells levels (≤ 200 cells/μL). Overall, provides some limited support for the conclusion that the excess lung cancer risk among HIV-1-infected populations is not entirely explained by smoking.

AIDS-related pneumonia has been investigated as a risk factor for lung damage and lung cancer with unclear findings. The combined analysis of the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) cohorts found the highest risk of lung cancer among HIV-1 patients with AIDS-related pneumonia damage. This finding was observed throughout the full follow-up period, as well as when the analysis was restricted to the HAART era, suggesting that the HIV-1-related pulmonary damage and inflammation may be responsible for the excess lung cancer. A nested case-control study within the HIV-1 cohort did not find an association with history of AIDS and pulmonary disease after adjusting for smoking; all cases and controls in the study were HIV-1 positive in this study (Clifford et al. 2012).

3.8. Cancer Burden from HIV from All Cancers

As mentioned in the introduction, the NTP evaluation was based on the body of evidence from an authoritative evaluation by IARC (2012a), and thus the NTP evaluation was focused on those cancer endpoints that IARC considered in its evaluation. There is evidence that HIV-1/AIDS-infected individuals have higher cancer incidence for many cancer endpoints compared with the general public (Robbins et al. 2015), and the estimated number of cases of non-AIDS-defining cancers in the United States has increased by approximately 3-fold from the pre-HAART era (1991 to 1995) to the post-HAART era (2001 to 2005) as the population of HIV-1-infected individuals expands and ages (Shiels et al. 2011a). An important part of the cancer burden (approximately 29% in 34 U.S. states) occurs in people with HIV-1 only. In a large meta-analysis, the risk of developing a non-AIDS-defining cancer was 2-fold greater in HIV-1-positive individuals compared with the general population and was greater in men than in women; however, no substantial differences were observed by HAART era (Shiels et al. 2009).

Due largely to HAART therapy, non-AIDS-defining malignancies now account for more morbidity and mortality than AIDS-defining malignancies (Silverberg and Abrams 2007). The risks for Hodgkin lymphoma, lung cancer, anogenital cancer, oral-related cancer, liver cancer, and non-melanoma skin cancers in the HIV-1-positive population are substantial or increasing and account for about half of the non-AIDS-defining cancers reported in the United States (Shiels et al. 2011a). However, it is not clear for some endpoints whether the increases in these cancers are related to HIV-1 infection or other behaviors or confounders that might be more common in HIV-1-infected individuals compared with the general public.

The 2009 meta-analysis by Shiels et al. (2009) of non-AIDS-defining cancer and HIV-1 infection or AIDS also found statistically significant increases in risk for cancer endpoints not evaluated in the monograph (such as melanoma, kidney, stomach, brain, testes, oropharynx, leukemia, and multiple myeloma (now called plasma-cell myeloma), which were all based on more than 70 cases and at least three studies) in addition to the sites evaluated in the monograph. Further, newer cohort studies published since 2009 (those listed in Table 3-1) appear to have a pattern of findings consistent with those reported by Shiels et al. (2009). Risk estimates for most cancer endpoints were between 1.0 and 2.0; little was known about potential confounders and there was evidence of heterogeneity across studies. A subsequent meta-analysis found a statistically significant meta-risk for melanoma and HIV-1 infection or AIDS of 1.50 (95% CI = 1.12 to 2.01) among studies that controlled for ethnicity in the post-HAART era (Olsen et al. 2014).

Many of the newer cancer endpoints identified in the Shiels et al. (2009) analysis are ones that are not thought to be related to co-infection with other viruses, and several studies have calculated risk estimates for groups of cancers. For example, Albini et al. (2013) found that HIV-1-infected individuals had approximately twofold increased risk of non-AIDS-related cancers not related to viral infection compared with the general population. A study in Denmark found that HIV-1-infected individuals had almost threefold elevated risk collectively of smoking-related cancers (primarily lung and head and neck combined) after adjusting for smoking (Helleberg et al. 2015). However, the latter analysis combined specific cancers with increased and decreased risks, and in the Shiels et al. (2009) meta-analysis cancers with elevated risks (such as leukemia and multiple myeloma) were not included. An Italian study (Franzetti et al. 2013) has also found an increase in non-AIDS\-related cancers (as a group) as well as an increase in the spectrum of cancer endpoints.

Robbins et al. (2015) estimated that the excess cancer burden in the United States in 2010 (over 3,900 cases), of which 54% were AIDS-defining cancers (which were reviewed in the IARC 2012a monograph), and 46% were non-AIDS-defining, of which most were from lung, liver, and Hodgkin lymphoma (which are reviewed in this monograph). While it is beyond the scope of the monograph to evaluate all cancer endpoints potentially associated with HIV-1/AIDS infection, this evaluation considered endpoints thought to contribute to greater than 90% of the excess cancer risk.

3.9. HAART and Treatments for Opportunistic Infections

The number of antiretroviral drugs used to treat HIV-1 infection has increased substantially over the past 30 years. Few data are available pertaining to the potential carcinogenicity of these drugs or of a wide array of pharmaceutical and other therapies used in the treatment of specific opportunistic infections, particularly after long-term use. In studies in experimental animals, 3′-

azido-3′-deoxythymidine has been shown to induce chromosomal damage, gene mutations, and cancer following direct or transplacental exposures (Witt et al. 2007). In addition, elevated frequencies of micronucleated red blood cells were found in human infants exposed *in utero* to 3′-azido-3′-deoxythymidine (Witt et al. 2007). NTP (2013b; 2013c) reported that 3′-azido-3′-deoxythymidine alone or in combination produced liver cancer in the male offspring. In a NTP *in utero* and postnatal cancer study, a mixture of 3′-azido-3′-deoxythymidine, lamivudine (also called 3TC), and nevirapine produced an increased incidence of subcutaneous skin neoplasms in male $B6C3F_1$ offspring (NTP 2013a). IARC (2000) has classified zidovudine (also known as azidothymidine or AZT) and zalcitabine (also known as dideoxycytidine or DDC) as possibly carcinogenic to humans based on sufficient evidence in animals.

In human studies, a U.K. study of cancer outcomes among people with AIDS or HIV-1 reported an increase in non-AIDS-defining cancers, particularly Hodgkin lymphoma, among people with AIDS or HIV-1 treated with non-nucleoside reverse transcriptase inhibitors, which include nevirapine (Powles et al. 2009). However, Chao et al. (2012) reported no increased risk in non-AIDS-defining cancers among HIV-1-positive users of non-nucleoside reverse transcriptase inhibitors, although in this paper long-term use of protease inhibitors were linked with a marginally increased risk of anal cancer, but not with any other non-AIDS-defining cancers. Bruyand et al. (2015) found no increased risk of lung cancer among persons with HIV who smoked and used protease inhibitors. Thus, at this time, data are insufficient to conclude that either non-nucleoside reverse transcriptase inhibitors or protease inhibitors are associated with increased risk of non-AIDS-defining cancers in HIV-1-positive persons.

3.10. Summary and Integration across Cancer Endpoints

A large body of cohort studies, including some very large prospective cohorts of HIV-1-positive and AIDS patients followed up for cancer incidence from the early AIDS epidemic onwards, are available to evaluate the association of HIV-1 and cancer endpoints. A smaller number of case-control studies have also been conducted on specific cancer endpoints. Indirect evidence of the effect of HIV-1 on cancer risk can also be evaluated from studies comparing HAART to non-HAART-treated groups or pre- to established HAART era cohorts, but complicating factors include a higher prevalence of traditional cancer risk factors (e.g., smoking, alcohol use) among those infected with HIV-1; an increased age-related cancer incidence associated with the increased lifespan of the HIV-1-positive population treated with HAART; limited data on the mutagenicity or carcinogenicity of the multiple drugs used in HAART (i.e., conflicting data that some HAART agents or classes may be associated with cancer); differences or changes in screening practices for HIV-1-related disease; and limited data on the seroprevalence of oncogenic viruses in HIV-positive populations (Borges et al. 2013; Kesselring et al. 2011; Shiels et al. 2011a), which might account for some observed differences in risk over time. In addition, the time of starting and duration of antiretroviral treatment might affect cancer risk.

AIDS-defining malignancies are included in the broader category of AIDS-defining clinical conditions and include Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer (CDC 1985; 1992; Schneider et al. 2008). Non-AIDS-defining cancers include a broad spectrum of neoplasms for which HIV-1-positive persons have an elevated risk and for which HIV-1 infection may play an etiologic role (Engels 2009). These neoplasms represent an increasingly important source of morbidity and mortality in the HIV-1-positive population. Non-AIDS-defining cancers have been grouped according to whether they are “infection related” (or not)

(Gopal et al. 2014; Patel et al. 2014). There are limitations to this classification scheme (Gopal et al. 2014), in large part due to etiologic heterogeneity within groups (for example, cervical cancer is classified as an AIDS-defining cancer while anal cancer is not, despite etiologic commonalities) and secondly because, while some oncoviruses (e.g., Kaposi-sarcoma-associated herpesvirus) are closely associated with specific cancers in HIV-1-infected populations, some (e.g., Epstein-Barr virus) are associated only with a proportion of specific cancer types. In addition, relatively few studies of HIV-1/AIDS populations have been conducted using valid and reliable panels of serological or pathological tests for other oncoviruses.

3.10.1. Infection-related Cancers including AIDS-defining Malignancies

Approximately 40% (95% CI = 39 to 42) of cancer cases occurring in HIV-infected people in the United States are attributable to infectious agents compared with 4% in the general U.S. population (de Martel et al. 2015). Kaposi sarcoma, non-Hodgkin lymphoma, and, especially in men, anal cancer are the most important of these. In contrast, in the general U.S. population, infection-related cancers are largely noncardia gastric, liver, and cervical cancers.

There is consistent evidence from a large body of cohort and case-control studies that HIV-1 substantially increases the risk of the three cancers classified as AIDS-defining: Kaposi sarcoma in Kaposi sarcoma-associated virus-infected populations (also see accompanying monograph on Kaposi sarcoma-associated virus); non-Hodgkin lymphoma, in particular primary central nervous system lymphoma, and Burkitt lymphoma, in some cases in association with Epstein-Barr virus (see also accompanying monograph on Epstein-Barr virus); and cervical cancer in human papillomavirus-infected populations.

In addition, there is consistent evidence that HIV-1 infection increases the risk of anal and other genital cancers in association with human papillomavirus co-infection, and Hodgkin lymphoma, associated with Epstein-Barr virus co-infection. While there is consistent evidence that HIV-1 infection increases the risk of hepatocellular carcinoma, concerns remain as to the extent to which hepatitis B or C virus is a co-factor or confounder of the observed associations. In most studies the seroprevalence of hepatitis B or C virus among HIV-1/AIDS individuals is not measured, but in those that have measured hepatitis C virus, individuals with hepatitis C virus and cirrhosis were twice as likely to develop hepatocellular carcinoma than those co-infected with hepatitis C virus and HIV-1.

Modest positive associations are found between HIV-1 and oral-related cancers; however, the heterogeneity of these cancers, as well as the unmeasured heterogeneity of risk factors, and potentially distinct etiologic pathways for oral-related cancer subtypes complicate the interpretation of these modest risks. However, based on limited evidence from natural history studies, HIV-1 may increase the risk of becoming infected with human papillomavirus or having a recurrence.

Since the widespread introduction of HAART, the spectrum and pattern of a number of cancers associated with HIV-1 infection has changed considerably (IARC 2012a).Although the estimated number of all AIDS-defining infection-related cancers decreased by approximately 3-fold following HAART therapy, the risk of Kaposi sarcoma (3,640-fold), non-Hodgkin lymphoma (77-fold), and cervical cancer (6-fold) remained significantly increased in AIDS patients compared with the general population (Shiels et al. 2011b). Among other, non-AIDS-defining

infection-related cancers, up to a 3-fold upward trend in Hodgkin lymphoma has been observed over the HAART era and the patterns for cancer of the liver and anus are not clear.

A summary of the range of risks for selected cancers with other viruses as cofactors is presented in Table 3-14, below.

Table 3-14. Summary of Risk Estimates and Effects of HAART for Selected Viral-related Cancers in HIV-1-positive Populations

Cancer	Viral Co-factor	Prevalence in HIV-1-Associated Tumors (%)	Range of Relative Risks in HIV/AIDS vs. HIV-1-Negative Populations	Effect of HAART on Risk of Cancer
Cervix	HPV	100	2–22	← →
Anus	HPV	>90	10–100	↑
Kaposi sarcoma	KSHV	100	100–10,000s	↓
NHL (all)	EBV/KSHV	Varies by subtype*	10–300	↓overall but varies by subtype*
Hodgkin lymphoma (all)	EBV	>80	4–38	↑
Oral-related cancer	HPV	65	2–4[a]	← →
Liver (HCC)	HBV/HCV	>90	2–16	← →

Columns 1–3 from Table 1 in Gopal et al. (2014); range of relative risks (excluding extreme outliers) and HAART effects are summarized from present monograph.
EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HPV = human papillomavirus; KSHV = Kaposi sarcoma-associated herpesvirus; NHL = non-Hodgkin lymphoma. ↑ = risk increase in HAART era; ↓ = risk decrease in HAART era; ← → = no overall change or inconsistent change in risk in HAART era.
*For NHL subtypes, risks of diffuse large B-cell primary CNS lymphoma and immunoblastic lymphoma have decreased, but Burkitt lymphoma risk remains unchanged.
[a]Some oral-related cancer sites including tonsil/tongue have been associated with risks in the range of 11 to 22.

3.10.2. Other Cancers Not Known to Be Infection Related

There is consistent evidence of a 6 to 8-fold increase in conjunctival cancer in HIV-1-positive populations, primarily in African countries, based on a limited number of studies; ambient ultraviolet light has been postulated as a co-factor. There is also consistent evidence for an association with lung cancer based on numerous studies showing statistically significant increases of 1.5 to 6 in lung cancer. Smoking prevalence is higher within the HIV-1 population and explains part of the risk; however, studies controlling for smoking or modeling smoking have found a 2-fold increase suggesting that smoking does not explain all the excess risk. Statistically significant increased risks of non-melanoma skin cancers among HIV-1-infected individuals have also been reported in numerous cohort studies. A meta-analysis (Zhao et al. 2015) on six studies, published between 2003 and 2013, that collected data on cancer incidence through cancer registries to ensure unbiased comparisons of the incidence rates from the cohorts and the general population, found a risk estimate of 2.76 (95% CI = 2.55 to 2.98).

4. Mechanisms and Other Relevant Data

It is clear that HIV-1-positive individuals are at an increased risk of developing cancer and that HIV-1 integrates its DNA into hundreds of sites in the host genome (Borges et al. 2013; Borges et al. 2014; IARC 2012a; Maldarelli et al. 2014). However, there is very little evidence that the transformed tumor cells harbor integrated HIV-1 proviruses, which generally rules out the known direct carcinogenic mechanism of insertional activation of proto-oncogenes (Borges et al. 2013; Craigie and Bushman 2012; IARC 1996; 2012a). Furthermore, HIV-1 infection alone does not induce cell transformation, and none of its encoded proteins are directly oncogenic (IARC 2012a). Most cancers associated with HIV-1 are infection related; therefore, HIV-1-related immune dysregulation is an important factor.

This section identifies some of the basic characteristics and risk factors associated with HIV-1-induced cancers (Section 4.1), reviews the experimental and biological evidence for the proposed modes of action and the evidence for cancer causation (Section 4.2), and provides a synthesis of the information (Section 4.3).

4.1. Characteristics and Risk Factors

Although immunosuppression is clearly associated with an increased risk of cancer in HIV-1-positive individuals, as well as in organ transplant patients (Bruyand et al. 2009; Engels et al. 2011; Grulich et al. 2007; Penn and Starzl 1973; Penn 1986; 1988; Shiels et al. 2011a), immunosuppression alone does not completely explain the incidence and spectrum of tumors observed in the HIV-1-positive populations pre- and post-HAART (see Section 3). Although HAART improves immune function and lowers HIV-1 viral load, it only partially normalizes the enhanced inflammation associated with HIV-1 (Borges et al. 2014). Further, while HAART therapy blocks HIV-1 infection of additional cells, it has no effect on infected cells and is a critical obstacle for curing HIV-1 infection (Maldarelli et al. 2014). Studies of HIV-1-infected populations show that after long-term HAART therapy, many of the infected cells that persist have undergone clonal expansion and were selected because they harbor integrated HIV-1 in specific genes that promote cell survival and expansion. Although, most studies have not shown evidence that HIV-1 integration contributes directly to cell transformation and malignancy, a few studies have reported that a small number of lymphomas harbor HIV-1 proviruses integrated at defined sites (Herndier et al. 1992; Shiramizu et al. 1994). Perhaps, prior attempts to detect HIV DNA in cancers examined only a small portion of the HIV-1 genome and missed HIV-1 proviruses with large deletions (proviruses that cause murine and avian tumors often contain large deletions) (Maldarelli et al. 2014). Thus, the mechanisms for HIV-1-induced cancer are complex and incompletely understood (Borges et al. 2013).

In a retrospective cohort study conducted in California (1996 to 2007) that included >20,000 HIV-1-infected and >200,000 HIV-1-uninfected adults, approximately 70% of cancers in the HIV-1-positive population had a known infectious cause compared with only 12% in the HIV-1-negative population (Silverberg et al. 2009). HIV-1 infection is thought to increase the risk of cancer primarily through immunosuppression and reduced immune surveillance (Silverberg et al. 2009; Silverberg et al. 2011). However, the data suggest that immunosuppression is not the only mechanism. Possible mechanisms or modes of action associated with AIDS-defining

malignancies and non-AIDS-defining malignancies are briefly discussed in Sections 4.1.1 and 4.1.2, respectively.

4.1.1. AIDS-defining Malignancies

Oncogenic viral infections are usually kept under control by the host immune system; however, the risk of virus-associated malignancies dramatically increases in immunosuppressed populations (Engels et al. 2011; Shackelford and Pagano 2007; Shiels et al. 2011a). As noted in Section 3, co-infection with the oncogenic viruses Kaposi sarcoma-associated herpesvirus, Epstein-Barr virus, and oncogenic subtypes of human papillomavirus are associated with Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancers, respectively. Overall, the data support a mechanism in which an HIV-1-impaired immune system cannot adequately suppress oncogenic viruses, resulting in an increased risk of infection-related cancer.

The declining incidence of HIV-1/AIDS combined with improved immune function from HAART therapy has significantly reduced the mortality of AIDS patients, predominantly due to a decrease in opportunistic infections, including at least a partial decrease in incidence rate and cases of some AIDS-defining malignancies and prolonged survival among HIV-1-positive individuals. As a consequence, the numbers of non-AIDS-defining malignancies have increased and are discussed in the following section.

4.1.2. Non-AIDS-defining Malignancies

Although non-AIDS-defining malignancies include numerous infection-related and infection-unrelated cancers, this evaluation focuses on several types that show a particularly strong association with HIV-1 infection (Hodgkin lymphoma, lung cancer, anogenital cancer, oral-related cancer, liver cancer, and non-melanoma skin cancers) (Bedimo et al. 2009; Engels 2009; Frisch et al. 2000; Patel et al. 2008; Shiels et al. 2011a; Silverberg et al. 2009; Vaccher et al. 2014). The risk for these cancer types in the HIV-1-positive population are substantial or increasing and account for about half of the non-AIDS-defining cancers reported in the United States (Shiels et al. 2011a). Immunodeficiency, inflammation, co-infections (e.g., hepatitis B and C viruses, human papillomaviruses, Epstein-Barr virus) and traditional risk factors (e.g., smoking, alcohol, age, ultraviolet radiation) are thought to play a significant role in the excess cancer risk (Engels 2009; Shiels et al. 2011a; Silverberg and Abrams 2007; Silverberg et al. 2011).

4.2. Mode of Action and Evidence for Cancer Causation

The primary mode of action of HIV-1 is progressive depletion of CD4+ T lymphocytes, which are responsible for helper functions in cell-mediated immunity (Clifford and Franceschi 2009). Therefore, HIV-1 increases the risk of cancer primarily through immunodeficiency and reduced immune surveillance, thus increasing the risk of opportunistic infections, particularly by oncogenic viruses.

Two primary lines of evidence support an indirect mechanistic link between HIV-1 infection and cancer. First, the pattern of increased risk for cancer in HIV-1/AIDS and immunosuppressed transplant recipients is similar and suggests that immune deficiency, rather than other cancer risk factors, is largely responsible (Grulich et al. 2007). Second, the vast majority of cancers in the HIV-1/AIDS population are infection related and are likely to become increasingly important

complications of long-term HIV-1 infection (Grulich et al. 2007; Silverberg et al. 2009). However, evidence is emerging that HIV-1 viral load and direct oncogenic effects of HIV-1 contribute to the increased cancer risk in the HIV-1/AIDS population (Borges et al. 2014). Evidence for a direct oncogenic effect of HIV-1 includes studies that showed cumulative and/or current plasma HIV-1 RNA levels were independently associated with an increased risk of AIDS-defining malignancies or that HIV-1 Tat and Vpr proteins might have oncogenic effects via synergism with other oncogenic viruses through disruption of cell-cycle regulation, inhibition of tumor suppressor genes, promotion of chromosome instability, inhibition of DNA repair, and by promoting effects of exogenous carcinogens (Borges et al. 2014; Bruyand et al. 2009; Guiguet et al. 2009).

This section briefly reviews the experimental evidence for possible modes of action for AIDS-defining and non-AIDS-defining malignancies and the evidence for a causal association between HIV-1 and cancer.

4.2.1. AIDS-defining Malignancies

All three of the AIDS-defining malignancies are infection related with clear links to HIV-1-induced immunosuppression, especially for Kaposi sarcoma and non-Hodgkin lymphoma (Pinzone et al. 2015; Shiels et al. 2011a). However, immunosuppression is not the only factor because the risk of these cancers remains elevated even after HAART therapy.

Kaposi Sarcoma

These data strongly support HIV-1-induced immunosuppression and co-infection with Kaposi sarcoma-associated herpesevirus as the primary modes of action for Kaposi sarcoma (see also monograph for Kaposi sarcoma-associated herpesvirus). The primary evidence that HIV-1 is indirectly linked to Kaposi sarcoma is that the risk of developing Kaposi sarcoma is higher in people co-infected with HIV-1 and Kaposi sarcoma-associated herpesvirus compared to individuals infected with Kaposi sarcoma-associated herpesvirus only (see Section 3.2.3 and the monograph for Kaposi sarcoma-associated herpesvirus). Studies also show that HIV-1 and Kaposi sarcoma virus can enhance each other's replication and that the HIV-1 Tat protein enhances Kaposi sarcoma virus entry into endothelial cells (IARC 2012a). Within the HIV-1-infected/AIDS population, many studies have shown that Kaposi sarcoma incidence has decreased in the post-HAART era; it increases with decreasing CD4+ cell count and increasing HIV-1 viral load (see Section 3). In addition, studies reporting CD4 and/or HIV-1 RNA levels in populations receiving HAART indicate that the decline in risk appears to be correlated with improvements in CD4 counts or decreases in viral titer (Castilho et al. 2015; Hleyhel et al. 2013; Patel et al. 2014). Further, chronic immunosuppressive therapy is associated with an increased risk of developing Kaposi sarcoma in organ transplant recipients (Engels et al. 2011).

HAART therapy may reduce the incidence of Kaposi sarcoma indirectly through improved immune surveillance, or directly by inhibiting tumor development (Sgadari et al. 2003; Silverberg and Abrams 2007). For example, protease inhibitors used in HAART inhibit Kaposi sarcoma-associated herpesevirus replication and possess anti-angiogenic and other anti-tumor properties that can impair growth and persistence of Kaposi sarcoma (Gantt and Casper 2011; Gantt et al. 2014). Although antiviral therapy initially resulted in a rapid and substantial reduction in the incidence rate and number of Kaposi sarcoma cases, they remain significantly

elevated above the general population rate and are no longer declining (IARC 2012a; Shiels et al. 2011b).

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma risk is increased in immunosuppressed populations and has been recognized as an AIDS-defining clinical condition since 1985 (IARC 2012a). As with Kaposi sarcoma, the primary evidence that HIV-1 is an indirect causal factor of non-Hodgkin lymphoma is the increased incidence of this disease in the HIV-1/AIDS population. Most cases of non-Hodgkin lymphoma are of the B-cell phenotype and are frequently associated with Epstein-Barr virus infection (IARC 2012a).

HIV-1 contributes to lymphomagenesis through two indirect mechanisms: (1) impaired immunosurveillance and loss of immunoregulatory control against Epstein-Barr virus and (2) promotion of chronic B-cell activation due to HIV-1-mediated immune dysfunction (Petrara et al. 2013). Chronic B-cell activation is a well-documented indirect consequence of HIV-1 infection that is driven by abnormal production of B-cell stimulatory cytokines (e.g., IL-6, IL-10, IFN-α, and TNF), miR-21, and chronic antigenic stimulation (Gloghini et al. 2013; Petrara et al. 2013; Sekar et al. 2014). Several studies have shown that certain B-cell stimulatory cytokines and other markers of immune activation (e.g., CXCL13, C-reactive protein, soluble CD23, CD27, and CD30) are elevated several years before the diagnosis of systemic AIDS-associated non-Hodgkin lymphoma (Hussain et al. 2013; Sekar et al. 2014).

In addition to indirect mechanisms, there is growing evidence that HIV-1 virions can contribute to B-cell activation and malignant transformation via direct interaction with B cells (Gloghini et al. 2013). The potential relevance of HIV virions in the development of AIDS-associated non-Hodgkin lymphoma is supported by evidence showing that the cumulative duration of HIV-1 viremia is predictive of lymphoma development (Zoufaly et al. 2009). HIV-1 Tat expression in lymphoid tissue of transgenic mice induced B-cell lymphoma and production of lymphoma-associated cytokines (Kundu et al. 1999). HIV-1 envelope glycoprotein gp120 activates B cells and induces class switch combinations via up-regulation of activation-induced cytidine deaminase (AID) (Epeldegui et al. 2010; He et al. 2006). AID is a DNA-modifying enzyme that is normally expressed exclusively in germinal center B cells and is believed to play a central role in the development of B-cell non-Hodgkin lymphoma via immunoglobulin heavy chain gene (IgH) class switch recombination and somatic hypermutation (Epeldegui et al. 2007; Epeldegui et al. 2010). CD40 ligand (CD40L or CD154), an immune stimulatory molecule expressed by activated T cells, is also incorporated into HIV-1 virions and stimulates B cells via the interaction of CD40L with CD40 resulting in expression of the AID gene, elevated cytokine secretion, as well as CD71 (a marker of cellular activation) and CD10 (a marker for immature germinal center B cells) (Epeldegui et al. 2010). Thus, AID-expressing B cells have an activated germinal center phenotype and HIV virions can induce AID expression in B cells by direct CD40L:CD40 stimulation without the requirement for infection. AID also increases the frequency of the *c-myc*:*IgH* translocation via errors in class switch recombination (a hallmark of Burkitt lymphoma) and induces DNA double-strand breaks in Ig genes and other loci, thus, leading to genomic instability (Epeldegui et al. 2007; Epeldegui et al. 2010). Thus AID over-expression results from chronic B-cell hyperactivation associated with HIV-1 infection and/or direct induction by HIV-1 virions (Epeldegui et al. 2010; He et al. 2006). AID expression in peripheral blood mononuclear cells was markedly elevated in subjects who later developed

AIDS-non-Hodgkin lymphoma compared to AIDS and HIV-1-negative controls (Epeldegui et al. 2007). AID expression also differs according to non-Hodgkin lymphoma subtype (see Section 3.3.4 for discussion of subtypes). The highest levels were measured in those who developed Burkitt lymphoma while AID over-expression was not seen in subjects who developed central nervous system (CNS) lymphoma.

As discussed in Section 3.3.4, several subtypes of non-Hodgkin lymphoma have been strongly associated with HIV-1/AIDS. These include primary brain lymphoma, large-cell immunoblastic lymphoma, and Burkitt lymphoma (Eltom et al. 2002; Engels 2007; Gloghini et al. 2013). Incidences of primary brain lymphoma and diffuse large B-cell immunoblastic lymphoma show a strong correlation with the severity of immune deficiency and are rarely seen when CD4+ cell counts are maintained at relatively normal levels (IARC 2012a). In contrast, Burkitt lymphoma can occur at any level of immune deficiency. Epstein-Barr virus is present in virtually all AIDS-related cases of primary brain lymphoma, 40% of large B-cell lymphoma cases, and 30% of Burkitt lymphoma cases. In people with HIV-1, Epstein-Barr viral loads are increased from the early stages of HIV-1 infection (Piriou et al. 2004). Fan et al. (2005) reported that high plasma Epstein-Barr viral load was found in people with Epstein-Barr virus-positive but not Epstein-Barr virus-negative AIDS lymphoma, and viral loads fell with successful therapy.

The relationships between AIDS-defining cancers and CD4+ cell counts and/or HIV-1 RNA levels in populations receiving HAART are shown by both the apparent correlation between the decline in non-Hodgkin lymphoma and improvements in CD4+ counts or decreases in viral titer (Castilho et al. 2015; Hleyhel et al. 2013) or by the increasing risk of non-Hodgkin lymphoma as the CD4+ cell count falls and viral replication rises (Clifford and Franceschi 2009; Guiguet et al. 2009; Silverberg and Abrams 2007; Silverberg et al. 2011). However, response to HAART differs among the lymphoma subtypes (Epeldegui et al. 2007). (See Section 3.3 for a discussion of cancer risk related to HAART). Mechanistic differences may partially explain the variable responses of the non-Hodgkin lymphoma subtypes to HAART. Virtually all CNS lymphomas are Epstein-Barr virus positive, have a low frequency of *c-myc*:*IgH* translocations, occur in people with low levels of CD4+ T cells, and are associated with the loss of immunoregulatory control of Epstein-Barr virus-infected B cells (Martínez-Maza and Breen 2002). However, less than half of AIDS-associated Burkitt lymphoma cases are EBV positive, are not correlated with CD4 cell counts, and are characterized by chronic B-cell hyperactivation and *c-myc*:*IgH* translocations. These data support HIV-1-induced immunosuppression, co-infection with Epstein-Barr virus, and chronic B-cell activation as likely modes of action contributing to non-Hodgkin lymphoma in the HIV-positive population (also see monograph for Epstein-Barr virus).

Cervical Cancer

Cervical cancer was recognized as an AIDS-defining cancer in 1993 and HIV is an indirect causal factor; the principal risk factor for cervical cancer is human papillomavirus. HIV-1 and human papillomavirus are both sexually transmitted; therefore, co-infection is common and HIV-1 increases the probability that human papillomavirus infection will persist and induce cervical cancer (Clifford and Franceschi 2009; IARC 2012a). Prior human papillomavirus infection may also increase the probability of HIV-1 infection (see review by (Einstein and Phaëton 2010)).

The relationship of cervical cancer with HIV-1-related immunosuppression is difficult to establish because the associations with HAART and CD4+ levels are unclear and may depend on the time period when CD4+ was measured (Clifford and Franceschi 2009, see Section 3.5.1).

Several studies have reported that the overall risk for in situ cervical cancer is significantly increased in AIDS patients. Frisch et al. (2000) reported that relative risk for in situ cervical cancer increased during a 10-year period spanning AIDS onset (5 years before and 5 years after the date of AIDS onset), which suggests that advancing immunosuppression may lead to gradual loss of control over human papillomavirus-related infection. It is uncertain if other risk factors for cervical cancer (e.g., iatrogenic immune suppression, autoimmune disease, end-stage renal disease, chronic inflammation, oral contraceptive use, smoking, poor diet) interact with HIV-1 infection to increase cancer risk (Dugué et al. 2013; Fernandes et al. 2015).

Although immunosuppression is important, it is not an essential factor in the development of cervical cancer (Clarke and Chetty 2002; Dugué et al. 2013). The data suggest that HIV-1 alters the natural history of human papillomavirus, resulting in decreased regression rates and rapid progression to high-grade lesions and an aggressive phenotype (Clarke and Chetty 2002). The more aggressive behavior of HIV-1-positive cervical cancers has been attributed to progression through the microsatellite instability pathway rather than through loss of heterozygosity associated with HIV-1-negative cervical cancer. Further, HIV-1 proteins are thought to enhance the effectiveness of human papillomavirus proteins and may contribute to cell-cycle disruption. Advanced stages of HIV-1 infection correlate with cumulative human papillomavirus prevalence and increased rates of progression of cervical disease (see e.g. Abraham et al. 2013; Chaturvedi et al. 2009; Singh et al. 2009).

4.2.2. Non-AIDS-defining Malignancies

Due to improvements in HIV-1 therapy that have prolonged survival and decreased the incidences of AIDS-defining malignancies, non-AIDS-defining malignancies represent a growing fraction of the overall cancer burden in HIV-1-positive people (Engels 2009; Kesselring et al. 2011; Reekie et al. 2010; Shiels et al. 2009). However, the evidence is limited for specific modes of action by which HIV-1 infection causes these malignancies. HIV-1-induced immunodeficiency is likely a key mode of action as evidenced by the fact that many of the non-AIDS-defining malignancies are infection related. Furthermore, the short-term risk of infection-related non-AIDS malignancies is strongly associated with current CD4 cell count (Achhra et al. 2014; Kesselring et al. 2011). In particular, three of the most prevalent non-AIDS-defining cancers are associated with oncogenic viruses: Hodgkin lymphoma (Epstein-Barr virus), anogenital and oral-related cancer (human papillomavirus), and liver cancer (hepatitis B and hepatitis C viruses) (Engels 2009). Risks for these cancers are also elevated among organ transplant patients and provides further support for immunosuppression in their etiology (Grulich et al. 2007).

It is also likely that the HIV-1-positive population is disproportionately infected with oncogenic viruses. Although no data suggest that non-AIDS-defining malignancies are pathologically distinct from their counterparts observed in the general population, they tend to occur at twice the rate in the HIV-1-positive population (Shiels et al. 2009; Vaccher et al. 2014). HIV-1 infection also activates biomarkers of inflammation (IL-6, C-reactive protein) and coagulation (D-dimer) that are associated with an increased risk of both infection-related and infection-unrelated cancer (Borges et al. 2013; Neuhaus et al. 2010). Plasma levels of these biomarkers remained elevated even after HIV-1 RNA levels were suppressed with antiretroviral therapy. The strongest association was found for plasma levels of IL-6. Chronic inflammation as well as HIV-1-specific and generalized responses to infection contribute to chronic and aberrant

activation of the immune system and are key driving forces in the loss of CD4+ cells, progression to AIDS, and other complications including cancer (Ipp and Zemlin 2013; Ipp et al. 2014). Thus, the increased incidence in HIV-1-positive individuals could reflect an independent effect of HIV-1 on progression of cancer or a biological interaction of HIV-1 with the known risk factors (Engels 2009). This section reviews mechanistic data for the following non-AIDS-defining malignancies: Hodgkin lymphoma, lung cancer, anogenital and oral-related cancer, liver cancer, and non-melanoma skin cancers.

Hodgkin Lymphoma

Several lines of evidence (e.g., excess risk in patients with congenital immunodeficiencies or iatrogenic immunosuppression, and spontaneous remission in some patients when immunosuppressive therapy was discontinued) indicate that the excess risk of Hodgkin lymphoma among HIV-1/AIDS is directly related to immunosuppression. Further, Epstein-Barr virus is more prevalent among Hodgkin lymphoma cases that are HIV-1 positive compared with those that are HIV-1 negative and suggests that loss of immune control of latent Epstein-Barr virus infection is the underlying mode of action (IARC 1997; 2012b). Most Hodgkin lymphoma cases in HIV-1/AIDS patients are strongly associated with Epstein-Barr virus (i.e., mixed cellularity or lymphocyte-depleted forms) while the nodular sclerosis form predominates in the general population (Clifford and Franceschi 2009).

Biggar et al. (2006) analyzed Hodgkin lymphoma incidence rates in relation to CD4+ counts and found some evidence that incidence was lower with severe immunosuppression than with moderate immunosuppression. These data suggest that the association between CD4+ count at the time of AIDS onset and Hodgkin lymphoma risk has an "inverted U" shape (i.e., risk increased with a decline in CD4+ count to 225 to 249 cells/mm^3 but then risk declines as the CD4+ count declines further). Thus, a possible explanation for the increase in Hodgkin lymphoma risk since the advent of HAART therapy (see Section 3.4) is that treatment of severely immunodeficient cases could raise CD4+ counts to a level that puts them at greatest risk of developing Hodgkin lymphoma (immune reconstitution syndrome). However, more recent studies that looked at CD4+ count as a predictor of Hodgkin lymphoma risk reported no evidence that Hodgkin lymphoma incidence decreased at CD4+ counts less than 200 cells/mm^3 or that risk was increased in the setting of improved immunity (Clifford and Franceschi 2009; Fontas et al. 2009; Reekie et al. 2010). These studies reported increased risk with declining CD4+ count; however, the differences were not significant in another study (Clifford and Franceschi 2009). Thus, the relationship between Hodgkin lymphoma risk and the degree of HIV-1-related immunodeficiency is perhaps more complex and not as strong as observed for Kaposi sarcoma or non-Hodgkin lymphoma.

Lung Cancer

Lung cancer is the most common non-AIDS-defining malignancy in the HIV-1-positive population in developed countries with an elevated risk of all major lung cancer subtypes (i.e., adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma) although adenocarcinoma is the most common (Engels 2009; Kirk et al. 2007; Ruiz 2010). The role of HIV-1 viral load and immunodeficiency in lung cancer is uncertain. Neither viral load nor CD4+ cell count was strongly associated with lung cancer risk in some studies (Chaturvedi et al. 2007; Engels et al. 2006b; Engels 2009; Kirk et al. 2007; Ruiz 2010), while other studies reported an inverse relationship of CD4+ count and lung cancer incidence (Guiguet et al. 2009; Reekie et al. 2010;

Silverberg et al. 2011). Even with HAART treatment, HIV-1 still increases inflammatory mediators, deregulates cell proliferation and apoptosis, and induces oxidative stress in the lung (Almodovar 2014) and the increased risk of lung cancer has not decreased substantially with HAART (Clifford et al. 2005; Engels et al. 2006b; Engels 2009; Kirk et al. 2007). Two potential HIV-1-related immunologic mechanisms associated with lung cancer risk include repeated lung infections and chronic pulmonary inflammation (Engels et al. 2008; Ruiz 2010). The pro-tumorigenic function of several proinflammatory cytokines (e.g., TNFα, IL-6, IL-8) as regulators of tumor-associated inflammation are well established (Grivennikov and Karin 2011; Pine et al. 2011).

The HIV-1-infected population is prone to respiratory infections that could increase the risk of lung cancer (Almodovar 2014). Other potential mechanisms have been suggested; however, experimental support is limited for all of them. These include interaction of the effects of HIV-1 (e.g., expansion of the pool of alveolar macrophages, abnormally high levels of proinflammatory cytokines, and chronic inflammation of lower respiratory tract) with tobacco use; lower levels of antioxidants in HIV-1-positive individuals; or amplification of the effects of other infectious agents (Engels et al. 2006b). There is limited experimental evidence that HIV-1 *tat* gene product can modulate growth-related genes in human lung epithelial cells; although, amplification of HIV-1 sequences in lung carcinoma tissues has not been demonstrated (el-Solh et al. 1997; Kirk et al. 2007; Wistuba et al. 1998). However, Wistuba et al. (1998) reported that microsatellite alterations were significantly increased in HIV-1-associated lung carcinomas compared to lung carcinomas in HIV-1-indeterminate subjects and reflected widespread genomic instability.

Anogenital and Oral-Related Cancers

The primary cause of anal cancer is persistent infection with oncogenic subtypes of human papillomavirus; however, the role of HIV-1-related immunosuppression in promoting anal cancer development has been more difficult to establish. Overall, the risk of invasive anal cancer appears to be increasing in the post-HAART era (see Section 3.5.2).

The risks of anal intraepithelial neoplasia and anal cancer increase with decreasing CD4+ count among HIV-1-positive individuals (Chaturvedi et al. (2009); Hessol et al. (2009); also see reviews by Pernot et al. (2014); Tong et al. (2014); Zaleski and Turiansky (2010)). It is possible that as HIV-1-induced immunosuppression progresses (as measured by lower CD4+ cell counts), attenuation of human papillomavirus-specific immunity results in the development of anal intraepithelial neoplasia I followed by a sustained high-level expression of human papillomavirus proteins and genomic instability. Consequently, genomic instability could be the driving force toward progression of anal intraepithelial neoplasia I lesions to anal intraepithelial neoplasia II, anal intraepithelial neoplasia III, and finally to cancer. HAART therapy would not be expected to affect the natural history of anal intraepithelial neoplasia II or anal intraepithelial neoplasia III. In support of this model, Frisch et al. (2000) reported that the overall risk for in situ anogenital cancer was significantly increased in AIDS patients and the relative risk increased during a 10-year period spanning AIDS onset (5 years before and 5 years after the date of AIDS onset). (A similar pattern was observed for in situ cervical cancer). The overall risk for invasive anogenital cancers was also significantly elevated in AIDS patients; however, the risk changed little during the 10 years spanning AIDS onset. Increasing relative risk for in situ cancers spanning the time of AIDS onset suggests that advancing immunosuppression leads to gradual loss of control over human papillomavirus infection while the lack of a similar increase for

invasive human papillomavirus-associated cancer suggests that late-stage cancer invasion is not greatly influenced by immune status. In addition, Meys et al. (2010) proposed that persistent or emergent human papillomavirus disease in the HIV-1-positive population might represent persistent or modulated immunodysregulation after HAART and could be a form of immune reconstitution-associated disease or immune restoration inflammatory syndrome.

A high percentage of HIV-1-infected infected individuals are co-infected with human papillomavirus and have an increased risk of developing many human papillomavirus-associated cancers, including oral-related cancers (Gillison 2009; Park et al. 2016). Molecular and epidemiological data show that cancers that arise from the lingual and palatine tonsils within the oropharynx show the strongest association with human papillomavirus. HIV-1 appears to affect the natural history of human papillomavirus infection by increasing the risk of both incident infection and prevalent infection compared to HIV-1-negative individuals (Beachler et al. 2012; Beachler et al. 2015). HIV-1 Tat and gp120 proteins have been reported to disrupt the tight junction in the oral-related mucosa and may facilitate human papillomavirus infection. Further, as noted above for cervical cancer, some HIV-1 proteins (e.g., Tat, rev) are thought to enhance the effectiveness of human papillomavirus proteins (e.g., E6, E7) and may contribute to cell-cycle disruption and a more aggressive phenotype (Clarke and Chetty 2002).

Although the effects of immunosuppression on the risk of oral-related cancers is not completely understood, the available data suggest that immunosuppression contributes to increased persistence or progression of oral human papillomavirus infection (Beachler et al. 2012). Oral-related cancers are elevated among chronically immunosuppressed populations including HIV-1-infected individuals and solid organ transplant patients (Beachler and D'Souza 2013; Giagkou et al. 2016); however, some studies report higher risk with lower CD4 counts or higher HIV-1 viral load (Beachler et al. 2015; Engels et al. 2008; Silverberg et al. 2011) while others do not (Chaturvedi et al. 2009; Clifford et al. 2005). The role of HAART on the risk of oral-related cancer has also been inconsistent, with some studies reporting no differences and others reporting modest decreases in risk; however, many of these results are prone to confounding by indication since those receiving HAART are likely to be more immunosuppressed, although the recent practice in high income countries is to provide HAART to those with higher CD4 cell counts (Beachler et al. 2014).

Liver Cancer

The role of HIV-1-associated immunosuppression in liver cancer is not well understood but immunosuppression is likely an important factor modulating the hepatotropic virus driven progression of liver disease, including cancer (Mallet et al. 2011). Hepatocellular carcinoma and other liver diseases are among the primary causes of non-AIDS-related death in people infected with HIV-1, and there is significantly elevated risk of severe liver disease in persons who are co-infected with HIV-1 and hepatitis C virus compared to persons infected with hepatitis C virus alone (Graham et al. 2001; Mallet et al. 2011). In addition, the course of hepatitis C virus infection is more aggressive, the prognosis is poorer, and the efficacy of antiviral therapy is reduced in HIV-1-positive compared to HIV-1 negative populations (Gelu-Simeon et al. 2014; Nunnari et al. 2012; Sahasrabuddhe et al. 2012). HIV-1/hepatitis C virus-co-infected people have very weak CD4 and CD8 responses, and even after the CD4+ cell count recoveries following HAART, these responses are not restored (Gelu-Simeon et al. 2014). The role of HAART on hepatocellular carcinoma risk has not been clearly established with most studies reporting a

slightly higher incidence in the HAART era (see Section 3.6.3). Although HAART therapy would be expected to improve immune control of hepatitis B virus or hepatitis C virus infection, the increase in liver cancer may be at least partially explained because increased survival of HIV-1-infected individuals also prolongs the duration of chronic liver disease (Sahasrabuddhe et al. 2012). Although hepatitis C virus or hepatitis B virus co-infection is common within the HIV-infected population, and is highly prevalent among people that acquired HIV-1 through blood transfusions or injection drug use (see Section 3.6.4), it is unclear whether HIV-1 infection directly increases the likelihood of hepatocellular carcinoma in viral hepatitis (Nunnari et al. 2012).

In addition to immunosuppression, other general mechanisms include increased inflammation and fibrosis in the liver of HIV-1/hepatitis C virus-co-infected compared to hepatitis C virus-monoinfected people (Gelu-Simeon et al. 2014). One mechanism contributing to increased inflammation is the accumulation of cytotoxic CD8+ T cells in the liver. There is also some evidence that the HIV-1 viral proteins Tat and gp120 may play a role via promotion of type I collagen and proinflammatory cytokines that activate hepatic stellate cells and promote fibrosis (Gelu-Simeon et al. 2014; Nunnari et al. 2012). Other risk factors for chronic liver disease and liver cancer that are more common among HIV-1-infected populations than the general population include excessive alcohol consumption, obesity, diabetes, and non-alcoholic steatohepatitis (Sahasrabuddhe et al. 2012).

HAART is also known to have some direct hepatotoxic effects, which are amplified among HIV-1-positive patients chronically infected with hepatitis B or C virus (Sulkowski et al. 2000). Lipodystrophy syndrome, which is associated with certain HAART regimens, may be accompanied by insulin resistance, increasing the risk for nonalcoholic steatohepatitis and, consequently, for cirrhosis and hepatocellular carcinoma (Bongiovanni and Tordato 2007; Feeney and Mallon 2011; Joshi et al. 2011).

Non-melanoma Skin Cancers

Although many cancer registries do not include detail on non-melanoma skin cancer subtypes, the available data indicate that HIV-1-positive individuals have an increased risk of all subtypes of non-melanoma skin cancer. Some data suggest that immunosuppression may alter the phenotype of non-melanoma skin cancer to a more aggressive squamous-cell skin cancer (Engels 2009). HIV-1-induced immunodeficiency could possibly increase the risk for basal-cell and squamous-cell carcinoma by reduced immunosurveillance for malignant cells.

Merkel cell carcinoma is primarily attributed to Merkel cell polyomavirus and HIV-1-induced immunodeficiency increases the risk (see Merkel cell polyomavirus monograph at https://ntp.niehs.nih.gov/go/797227).

Conjunctival Cancers

Mechanisms for HIV-1-induced conjunctival cancers in combination with solar ultraviolet radiation are not completely understood.

4.2.3. Synthesis

Although the mechanisms for HIV-1-induced cancer are not completely understood, most AIDS-defining and non-AIDS-defining malignancies have a known infectious cause and are similar to

the patterns observed in immunosuppressed transplant recipients. Therefore, the data support an indirect mechanistic link between HIV-1 infection and cancer (i.e., failure to suppress infection by oncogenic viruses and/or impaired immune surveillance of transformed cells). However, there is increasing evidence that direct oncogenic effects of HIV-1 may contribute to the increased cancer risk in the HIV-1/AIDS population. While it is clear that HIV integration can lead to clonal expansion and persistence of HIV-1-infected cells, its relationship to cancer is unclear and warrants further investigation.

The primary causes of the three AIDS-defining malignancies (Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma) are co-infection with the oncogenic viruses: Kaposi sarcoma-associated virus, Epstein-Barr virus, and oncogenic subtypes of human papillomavirus. Overall, the data support a mechanism in which an HIV-1-impaired immune system cannot adequately suppress or clear oncogenic viruses, resulting in an increased risk of infection-related cancer. Although HAART has dramatically decreased the incidences of Kaposi sarcoma and non-Hodgkin lymphoma, these malignancies remain elevated in the HIV-1-positive population. While the incidence rates of cervical cancer in AIDS patients in the United States have declined, the number of cases has continued to increase (due primarily to an increased number of women in the AIDS population) with little evidence that HAART decreases the risk. Thus, it is clear that immunosuppression alone does not completely explain the incidence and spectrum of tumors observed in the HIV-1-positive populations pre- and post-HAART. In addition to an indirect effect of HIV-1 on cancer incidence through immune dysregulation, chronic B-cell activation, and activated inflammatory pathways, HAART toxicity may play a role in the increased risk.

Although non-AIDS-defining malignancies include a broad spectrum of infection-related and infection-unrelated cancers, Hodgkin lymphoma, lung, anogenital, and liver cancers account for about half of the non-AIDS-defining cancers reported in the United States. In addition to these cancers, risk factors and mechanistic data for non-melanoma skin cancer and oral-related cancers were also reviewed. In contrast to AIDS-defining malignancies, non-AIDS-defining malignancies have increased in the post-HAART era and are largely attributed to growth and aging of the HIV-1-positive population. Immunodeficiency, inflammation, co-infections with oncogenic viruses (e.g., Epstein-Barr virus, hepatitis B virus, hepatitis C virus, and human papillomavirus), and traditional risk factors (e.g., smoking, alcohol abuse, and age) play a primary role or contribute to the excess of non-AIDS-defining malignancies.

5. Overall Cancer Hazard Evaluation and Preliminary Listing Recommendation

Human immunodeficiency virus type 1 (HIV-1) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on epidemiological studies showing that HIV-1 increases the risk of Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer (see Table 5-1); Hodgkin lymphoma, invasive anal cancer, genital cancers (see Table 5-2); conjunctival cancer, non-melanoma and skin cancer(see Table 5-3) in humans, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence of a causal association for cancers of the liver, lung, and oropharynx (see Table 5-2).

These cancer sites include both AIDS-defining and non-AIDS-defining cancers and include a broad spectrum of malignancies for which HIV-1-positive persons have an elevated risk over the general population. In addition, an estimated 70% of cancers in the HIV-1-positive population have a known infectious cause compared with only 12% in the HIV-1-negative population. The evidence from studies in humans establishing links for various cancer sites and supporting mechanisms are discussed below and organized according to the following groups: AIDS-defining cancers, non-AIDS-defining cancers that are infection related, and non-AIDS-defining cancers that are not believed to be infection related.

5.1. AIDS-defining Cancers

This section summarizes the preliminary level of evidence recommendations from studies in humans (Section 5.2.1) and supporting mechanistic data. (Section 5.2.2).

5.1.1. Level of Evidence from Studies in Humans

The preliminary level of evidence recommendations from studies in humans and the rationale for those recommendations for the three AIDS-defining cancers are provided in Table 5-1.

5.1.2. Mechanistic Evidence

The primary mode of action of HIV-1 is progressive depletion of CD4 T lymphocytes, which are responsible for helper functions in cell-mediated immunity (Clifford and Franceschi 2009). With Kaposi sarcoma and non-Hodgkin lymphoma, there is an increased cancer risk with decreases in CD4 T lymphocytes; however, the evidence with cervical carcinoma is less clear. Treatment with drugs (HAART) that specifically prevent HIV-1 replication and CD4 T-cell depletion diminishes the cancer risk for Kaposi sarcoma and non-Hodgkin lymphoma. Therefore, HIV-1 increases the risk of cancer primarily through immunodeficiency and reduced immune surveillance; therefore, increasing the risk of opportunistic infections, particularly by oncogenic viruses as seen with these malignancies.

Table 5-1. Summary of the Evidence for AIDS-defining Cancers[a]

Cancer	Level of Evidence	Evidence and Viral Cofactors
Kaposi sarcoma	**Sufficient**	***Epidemiological evidence***
		Consistent evidence of increased risk.
		Statistically significant very high RRs reported in over 35 cohort studies from western countries.
		Increased risks ranged from 100s to 10,000s.
		Dose response with HIV-1 titers.
		Statistically significantly decreased RR in HAART era (0.19–0.92) vs. pre- or early HAART supports findings.
		Viral co-factor: KSHV
		All cases occur in KSHV-infected individuals.
		HIV-1 and KSHV (HIV-1 Tat protein enhances KSHV entry into cells).
Non-Hodgkin lymphoma	**Sufficient**	***Epidemiological evidence***
		Consistent evidence of increased risk.
		Statistically significant high RR in over 35 cohort studies.
		Increased risks 10 to ~300 fold in most studies.
		mRR = 77 (95% CI = 39–149) 5,295 cases from 6 studies (Grulich et al. 2007).
		Statistically significantly decreased RR in HAART era (30%–80%) vs. pre- or early HAART and associated decreased viral titers supports finding.
		Viral co-factor: EBV
		EBV infection in some but not all non-Hodgkin lymphoma subtypes.
Cervical cancer	**Sufficient**	***Epidemiological evidence***
		Consistent evidence of increased risk.
		Statistically significantly elevated RR found in most of at least 30 cohort studies.
		Increased risks 2–22 fold in most studies.
		mRR = 5.8 (95% CI = 3–11.3); 104 HIV-1-infected cases from 6 studies (Grulich et al. 2007).
		RR higher in people with AIDS (mostly ranged from ~3–50) compared to HIV-1-infected populations (mostly ranged from ~3–15).
		Viral co-factor: HPV
		Oncogenic HPV necessary.

AIDS = acquired immune deficiency syndrome; EBV = Epstein-Barr virus; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; HPV = human papillomavirus; KSHV = Kaposi sarcoma-associated herpesvirus; mRR = relative risk from a meta-analysis; RR = relative risk.
[a]Numbers in epidemiological studies based on IARC (1996; 2012a).

5.2. Non-AIDS-defining Cancers That Are Thought to Be Infection Related

This section summarizes the preliminary level of evidence recommendations from studies in humans (Section 5.2.1) and supporting mechanistic data (Section 5.2.2).

5.2.1. Preliminary Level of Evidence Recommendation from Studies in Humans

The preliminary level of evidence recommendations from studies in humans and the rationale for those recommendations for the four non-AIDS-defining cancers related to infections are provided in Table 5-2.

Table 5-2. Summary of the Evidence for Non-AIDS-defining Cancers: Infection Related[a]

Cancer	Level of Evidence	Evidence and Viral Co-factors
Hodgkin lymphoma	**Sufficient**	***Epidemiological evidence*** Consistent evidence of increased risk. Statistically significant RRs ranging from ~4–38 in over 40 large cohort studies. Elevated risks found among people with AIDS compared to people with HIV-1 without AIDS. mRR = 11 (95% CI = 8.4–14.4); 5,295 cases from 6 studies. (Grulich et al. 2007). mRR = 11 (95% CI = 8.5–15); 643 cases from 6 studies (Shiels et al. 2009). ***Viral co-factor***: EBV 80%–100% of HIV-1-Hodgkin lymphoma cases co-infected with EBV.
Anal cancer	**Sufficient**	***Epidemiological evidence*** Consistent evidence of increased risk. Statistically significant RR (mostly ranging from 10–100 with a few studies with risk ranging from 60–~350) found in at least 38 cohort studies. Risks higher among people with AIDS compared to HIV-1-infected individuals without AIDS. mRR = 28.8 (95% CI = 21.6–38.3); 303 cases from 6 studies (Grulich et al. 2007). mRR = 28 (95% CI = 21–35); 243 cases from 8 studies (Shiels et al. 2009). ***Viral co-factor***: HPV Oncogenic HPV present.
Genital (vaginal/vulvar, penile) cancers	**Sufficient**	***Epidemiological evidence*** Vaginal/vulvar cancer: Consistent evidence of increased risk in at least 7 cohort studies, most reporting statistically significant risks ranging from 5 to 27; one study had over 123 cases. RR lower for invasive cancer compared to in situ cancers, but still elevated (RR = ~5). mSIR = 9.4 (95% CI = 4.9–18) 25 cases; 4 studies (Shiels et al. 2009). Positive association with CD4 levels at AIDS onset. Penile cancer: Consistent evidence of increased risk in at least 6 cohort studies, most reporting statistically significant risks ranging from 4–28. RR lower for invasive cancer compared to in situ cancers, but still elevated (RR = ~5). mSIR = 6.8 (95% CI = 4.2–11); 16 cases; 3 studies (Shiels et al. 2009). ***Viral co-factor***: HPV

Cancer	Level of Evidence	Evidence and Viral Co-factors
Oral-related cancer	**Limited**	***Epidemiological evidence*** Consistent evidence of modest increased risk across various groupings of oral-related cancers (e.g., oropharynx, oral cavity/pharyngeal, oral cavity) in at least 21 studies (most risks between 2 and 4) compared to general population based primarily on HIV cohort registry studies. mSIR = 2.3 (95% CI = 1.65–3.25); N = 238 HIV-1-infected cases from 4 studies (Grulich et al. 2007). Most studies do not account for disease heterogeneity (e.g., distinct tumor types or sites, HPV associated and HPV nonassociated), and potential confounders or unmeasured variations in sexual behaviors and other risk factors (e.g., smoking) across cohorts. Inconsistent evidence of the effect of immunosuppression and the effects of HAART on risk of oral-related cancer. ***Viral co-factor***: HPV Oncogenic HPV necessary in some types of cancer.
Liver cancer	**Limited**	***Epidemiological evidence*** Consistent evidence of increased risk (hepatocellular carcinoma). Most were statistically significant RRs (mostly ranging from 2–16) in at least 39 large cohort studies. Risks higher among people with AIDS compared to HIV-1-infected individuals without AIDS. mSIR = 5.2 (95% CI = 3.3–8.2); 133 cases from 7 studies (Grulich et al. 2007). mSIR = 5.6 (95% CI = 4.0–7.7); 171 cases from 11 studies studies (Shiels et al. 2009). ***Viral co-factor***: HCV It is unclear whether HCV is a co-factor or confounder. Some studies have either not found an excess risk for liver cancer or have found a doubling of risk of HCC in men with cirrhosis and hepatitis C compared to those co-infected with HCV and HIV.

AIDS = acquired immunodeficiency syndrome; EBV = Epstein-Barr virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; mRR = relative risk from a meta-analysis; mSIR = standardized incidence ratio from a meta-analysis; RR = relative risk.
[a]Numbers in epidemiology studies based on IARC (1996; 2012a), except for liver and genital cancers.

5.2.2. Mechanistic Evidence

Non-AIDS-defining cancers that are thought to be infection related include a broad spectrum of cancers related to opportunistic cancers from co-infections with human papillomavirus (anogenital and oral-related cancers), Epstein-Barr virus (Hodgkin lymphoma), hepatitis B virus, or hepatitis C virus (liver cancer). In contrast to AIDS-defining malignancies, some non-AIDS-defining malignancies have increased in the post-HAART era and are largely attributed to increased survival and aging of the HIV-1-positive population. In addition, the risk of infection-related non-AIDS-defining cancers is also strongly associated with immunosuppression as measured by current CD4 cell count (Clifford and Franceschi 2009; Franceschi et al. 2008; Silverberg et al. 2007). The mechanistic data suggest that the increased incidence of infection-related non-AIDS-defining cancers in HIV-1-positive individuals could reflect a high prevalence of known cancer risk factors (e.g., infection with oncogenic viruses, tobacco use, alcohol, aging),

an independent effect of HIV-1 on progression of cancer, or a biological interaction of HIV-1 with the known risk factors (Engels 2009).

5.3. Non-AIDS-defining Cancers: Not Known to Be Infection Related

This section summarizes the preliminary level of evidence recommendations from studies in humans (Section 5.3.1) and supporting mechanistic data (Section 5.3.2).

5.3.1. Preliminary Level of Evidence Recommendation from Studies in Humans

The preliminary level of evidence recommendations from studies in humans and the rationale for those recommendations for the three non-AIDS-defining cancers that are not linked to infections are summarized in Table 5-3.

Table 5-3. Summary of the Evidence for Non-AIDS-defining Cancers: Not Infection Related[a]

Cancer	Level of Evidence	Epidemiological Evidence
Conjunctival cancer	**Sufficient**	Consistent evidence of increased risk. Statistically significant RR (mostly between 6 and 8) in 4 large cohort studies and in 4 case-control studies (150 cases). ***Potential co-factor***: Ultraviolet radiation
Non-melanoma skin cancer	**Sufficient**	Consistent evidence of increased risk. At least 19 studies, most of which reported statistically significant RR (ranging between 1.5 and 6 with a few studies ranging up to 20) in over 15 cohorts. Risks found in HIV-1-infected and AIDS population. mRR = 2.76 (95% CI = 2.55–2.98); 6 cohorts. (Diagnosis verified via cancer registry.) Significant association with HIV-1 RNA in blood in one study.
Lung cancer	**Limited**	Consistent evidence for increased risk. At least 48 cohort studies, most of which reported statistically significant RRs (between 1.5 and 6). mRR = 2.7 (95% CI = 1.9–3.9); 7 studies, 1,016 cases (Grulich et al. 2007). mRR = 2.6 (95% CI = 2.1–3.1); 13 studies, 847 cases (Shiels et al. 2009). Smoking explains some but not all the excess risk; residual confounding may be present. 7/8 cohort studies that controlled for smoking or modeled bias from smoking found elevated risks for smoking; 6/7 were statistically significant. Mechanism not known; does not appear to be related to immunosuppression.

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; mRR = relative risk from a meta-analysis; RR = relative risk.
[a]Numbers in epidemiology studies based on IARC (1996; 2012a) except for skin and lung cancers.

5.3.2. Mechanistic Evidence

In addition to immunodeficiency, inflammation, and traditional risk factors (e.g., smoking, alcohol abuse, exposure to ultraviolet radiation, and age) may play a primary role or contribute to the excess of non-AIDS-defining cancers (Borges et al. 2013; Engels 2009; Shiels et al. 2011a; Silverberg and Abrams 2007). With conjunctival and non-melanoma skin cancers, exposure to ultraviolet radiation coupled with immunosuppression may have a role. A couple of studies have shown an association between HIV-1 infection and Merkel cell carcinoma, a rare type of skin cancer, and thus a viral component may be important for those specific types of skin cancer. Merkel cell carcinoma is associated with immunosuppression from HIV-1 or tissue transplants (Lanoy et al. 2010). In addition, case series studies on conjunctival cancer with HIV-1 have reported very low CD4 T-cell counts (~100/mm^3). Mechanisms for lung cancer are not known but may involve interactions interaction of the effects of HIV-1 with tobacco use; lower levels of antioxidants in HIV-1-positive individuals; chronic lung damage, or amplification of the effects of other infectious agents but experimental support is limited. Finally, there is some limited evidence of decreased risk of these cancers post-HAART although toxicity and genotoxicity of drugs used in HAART therapy may also be a risk factor for these cancers (Borges et al. 2014).

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Glossary

AIDS-defining clinical condition: Any HIV-related illness included in the Centers for Disease Control and Prevention's (CDC) list of diagnostic criteria for AIDS. AIDS-defining conditions include opportunistic infections and cancers that are life threatening in a person with HIV.

Calendar-period analysis: A method of monitoring patient survival in which the most recent survival experience is quantified for patients diagnosed in various years up to the most recent calendar year C, but only survival experience during a particular recent calendar period P (ending at the end of C) is included in the analysis.

Capsid: The protein coat surrounding the nucleic acid of a virus.

Case series: A collection of subjects (usually, patients) with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, exposure, or diagnostic procedure. A case series does not include a comparison group and is often based on prevalent cases and on a sample of convenience. Common selection biases and confounding severely limit their power to make causal inferences.

Case-comparison study (case-control study, case referent study): The observational epidemiological study of persons with the disease (or another outcome variable) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and non-diseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and non-diseased).

Co-factor: A factor that activates or enhances the action of another entity such as a disease-causing agent. Cofactors may influence the progression of a disease or the likelihood of becoming ill.

Diagnostic criteria: The specific combination of signs, symptoms, and test results that a clinician uses to identify a person as representing a case of a particular disease or condition.

Enzyme immunoassay: An assay that uses an enzyme-bound antibody to detect an antigen. The enzyme catalyzes a color reaction when exposed to substrate.

Highly active antiretroviral therapy: Treatment regimens that stop or slow the HIV virus from reproducing and keep HIV disease from progressing. The usual HAART regimen combines three or more HIV drugs from at least two different classes. HAART may also be referred to as combination antiretroviral therapy (cART) or antiretroviral therapy (ART).

Horizontal transmission: The spread of an infectious agent from one individual to another, usually through contact with bodily excretions or fluids, such as sputum or blood, which contains the agent.

Latent phase: A phase of the virus life cycle during which the virus is not replicating.

Lytic phase: A phase of the virus life cycle during which the virus replicates within the host cell, releasing a new generation of viruses when the infected cell lyses.

Monoclonal: Pertaining to or designating a group of identical cells or organisms derived from a single cell or organism.

Percutaneous transmission: Exposure through any break in intact skin, whether from sharps injury (e.g., needlesticks) or other types of tissue trauma.

Point-of-care rapid test: A type of HIV antibody test used to screen for HIV infection. A rapid HIV antibody test can detect HIV antibodies in blood or oral fluid in less than 30 minutes. A positive rapid HIV antibody test must be confirmed by a second, different antibody test (a positive Western blot) for a person to be definitively diagnosed with HIV infection.

Polymerase chain reaction: A laboratory technique used to produce large amounts of specific DNA fragments. Polymerase chain reaction is used for genetic testing and to diagnose disease.

Post-exposure prophylaxis: Short-term treatment started as soon as possible after high-risk exposure to an infectious agent, such as HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV). The purpose of post-exposure prophylaxis (PEP) is to reduce the risk of infection. An example of a high-risk exposure is exposure to an infectious agent as the result of unprotected sex.

Pre-exposure prophylaxis: An HIV prevention method for people who are HIV negative and at high risk of HIV infection. Pre-exposure prophylaxis involves taking a specific combination of HIV medicines daily and is even more effective when it is combined with condoms and other prevention tools.

Prospective cancer registry linkage study: A forward-looking analytic epidemiological study that matches identification of cohort members to identification of patients in a population-based cancer registry or registries to determine if cohort members have been diagnosed with cancer. Cancer registries ideally include reports of all incident cancers in a local population identified as soon as possible after first diagnosis. Typically, the principal sources for these reports are the hospitals or cancer centers serving the population.

Provirus: An inactive viral form that has been integrated into the genes of a host cell. For example, when HIV enters a host CD4 cell, HIV RNA is first changed to HIV DNA (provirus). The HIV provirus then gets inserted into the DNA of the CD4 cell. When the CD4 cell replicates, the HIV provirus is passed from one cell generation to the next, ensuring ongoing replication of HIV.

Time-trend descriptive study: An epidemiological study based on group-level data in which comparisons are made between groups to help draw conclusions about the effect of an exposure on different populations. Observations are recorded for each group at equal time intervals (e.g., monthly). Types of measurements may include prevalence of disease, levels of pollution, or mean temperature in a region.

Titer: A laboratory measurement of the concentration of a substance in a solution (e.g., an antibody titer measures the presence and number of antibodies in the blood).

Vertical transmission: The transmission of infection from one generation to the next (e.g., from mother to infant prenatally, during delivery, or in the postnatal period via breast milk).

Viral set point: The viral load (HIV RNA) within a few weeks to months after infection with HIV. Immediately after infection, HIV multiplies rapidly, and a person's viral load is typically very high. After a few weeks to months, this rapid replication of HIV declines and the person's viral load drops to its set point.

Window period: The time period from infection with HIV until the body produces enough HIV antibodies to be detected by standard HIV antibody tests. The length of the window period varies depending on the antibody test used. During the window period, a person can have a negative result on an HIV antibody test despite being infected with HIV.

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AZT	azidothymidine
BMI	body mass index
BOP	Bureau of Prisons
cART	combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DHHS	Department of Health and Human Services
DHS	Department of Homeland Security
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DoD	Department of Defense
DOT	Department of Transportation
dsDNA	double-stranded DNA
DVA	Department of Veterans Affairs
EBV	Epstein-Barr virus
EIA	enzyme immunoassays
ELISA	enzyme-linked immunosorbent assays
FDA	Food and Drug Administration
HAART	highly active antiretroviral therapies
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HHS	Health and Human Services
HIV	human immunodeficiency virus
HIVMA	HIV Medicine Association
HPV	human papillomavirus
HR	hazard ratio
HUD	Department of Housing and Urban Development

IARC	International Agency for Research on Cancer
IFA	immunofluorescence assay
IgG	immunoglobulin G
IgM	immunoglobulin M
IRR	incidence rate ratio
KSHV	Kaposi sarcoma-associated herpesvirus
L1	type 1 long-interspersed nuclear elements
LMP1	latent membrane protein 1
MAC	Multicenter AIDS Cohort Study
mRR	relative risk from a meta-analysis
mSIR	standardized incidence ratio from a meta-analysis
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PCR	polymerase chain reaction
PHS	Public Health Service
RNA	ribonucleic acid
RR	relative risk
RT	reverse transcriptase
SEER	Surveillance, Epidemiology, and End Results Program
SIR	standardized incidence ratios
ssRNA	single-stranded RNA
STI	sexually transmitted infection
WHO	World Health Organization
WIHS	Women Interagency HIV Study

Appendix A. Literature Search Strategy

Table of Contents

Tables

Figures

The objective of the literature search approach is to identify published literature that is relevant for evaluating the potential carcinogenicity of the HIV-1virus. As discussed in the Viruses Concept Document (https://ntp.niehs.nih.gov/ntp/roc/concept_docs/2014/virusesconcept_508.pdf), the monograph relies on the IARC monograph and studies published since the monograph (new studies). The literature search strategy was used to identify new human cancer studies and recent reviews of mechanistic data.

A.1. General Approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for the individual viruses of interest, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases. IARC used literature found by searching PubMed for HIV-1 through 12/2008, so new information for these viruses were searched in PubMed from >2008 to August 2015.

The large and complex body of literature for HIV-1 was searched using narrowing terms for the relevant major topics within the bibliographic database. The results were then processed in EndNote to remove duplicates before being transferred to DistillerSR for screening. Table A-1 highlights the general concepts searched with selected example terms. To review all the terms used, please refer to the full search strings below.

Table A-1. Major Topics Searched

Topics	Example Terms
Human immunodeficiency virus	"HIV," "human immunodeficiency virus," "acquired immunodeficiency virus," "HIV Infections"(MESH), "HIV-1"(MESH)
General cancer	Neoplasms(MESH), tumor(s), leukemia
Relevant cancers	Oral cancers, genital cancers, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma
Study types	Case control, ecological studies, follow-up study
Epidemiology terms	Cohort, epidemiologic studies (MESH), epidemiology (Subheading)
Mechanistic terms	Mechanism of action, Key event, etiology (subheading)
Genetox terms	Aneuploidy, DNA-Adduct, DNA-synthes*, gene expression

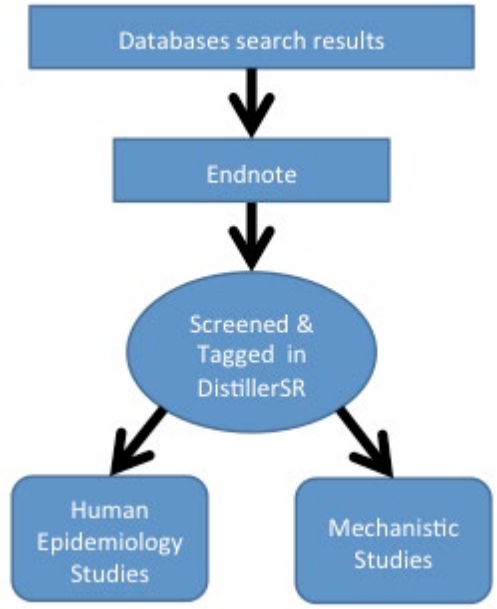

Figure A-1. Literature Processing Flow

The wealth of literature in the subject of HIV lead to a focus on review literature. For mechanistic studies, a focus on the most recent reviews (2013 to 2015) allowed for an understanding of the most current advances in understanding the carcinogenic mechanism of HIV. To ensure full coverage of the non-AIDS-defining cancers, a specific search for cohort studies in primary literature was also conducted.

The bibliographic database search results (2,294) were processed in EndNote then imported into DistillerSR for first and second tier screening. Relevant studies found through the citations of review articles and other secondary search processes were also included. Tagging in DistillerSR categorized the useful articles into Human Epidemiologic literature (674) or Mechanistic literature (499).

A.2. Search Strings for HIV Searches

A.2.1. Cohort Studies (Primary Literature)

PubMed: 2009–2015

"HIV"[Ti] OR "HIV"[Other Term] OR "human immunodeficiency virus"[Ti] OR "human immunodeficiency virus"[Other Term] OR "HIV Infections"[mh] OR "HIV-1"[mh] OR "HIV"[Mesh:noexp] OR "acquired immunodeficiency virus"[tiab]

AND

cohort[tiab] OR Cohorts[tiab] OR cancer-registry[tiab] OR registries[tiab]

AND

Journal Article[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]

AND

List of general cancer terms (see Section A.2.2).

A.2.2. Relevant Cancers and Epidemiology

PubMed: 2009–2015, Reviews only

"HIV Infections"[Mesh] OR "HIV"[Mesh:NoExp] OR "HIV-1"[Mesh] OR "HIV"[Title/Abstract] OR "HIV"[Other Term] OR "AIDS"[Title/Abstract] OR "AIDS"[Other Term] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunodeficiency virus"[Other Term])

AND

("Mouth Neoplasms/epidemiology"[Mesh] OR "Mouth Neoplasms/etiology"[Mesh] OR "Mouth Neoplasms/pathology"[Mesh] OR "Mouth Neoplasms/diagnosis"[Mesh] OR "Pharyngeal Neoplasms/epidemiology"[Mesh] OR "Pharyngeal Neoplasms/etiology"[Mesh] OR "Pharyngeal Neoplasms/pathology"[Mesh] OR "Pharyngeal Neoplasms/diagnosis"[Mesh] OR "Carcinoma, Hepatocellular/epidemiology"[Mesh] OR "Carcinoma, Hepatocellular/etiology"[Mesh] OR "Carcinoma, Hepatocellular/pathology"[Mesh] OR "Carcinoma, Hepatocellular/diagnosis"[Mesh] OR "Lung Neoplasms/epidemiology"[Mesh] OR "Lung Neoplasms/etiology"[Mesh] OR "Lung Neoplasms/pathology"[Mesh] OR "Lung Neoplasms/diagnosis"[Mesh] OR "Genital Neoplasms, Female/epidemiology"[Mesh] OR "Genital Neoplasms, Female/etiology"[Mesh] OR "Genital Neoplasms, Female/pathology"[Mesh] OR "Genital Neoplasms, Female/diagnosis"[Mesh] OR "Genital Neoplasms, Male/epidemiology"[Mesh] OR "Genital Neoplasms, Male/etiology"[Mesh] OR "Genital Neoplasms, Male/pathology"[Mesh] OR "Genital Neoplasms, Male/diagnosis"[Mesh] OR "Anus Neoplasms/epidemiology"[Mesh] OR "Anus Neoplasms/etiology"[Mesh] OR "Anus Neoplasms/pathology"[Mesh] OR "Anus Neoplasms/diagnosis"[Mesh] OR "Uterine Cervical Neoplasms/epidemiology"[Mesh] OR "Uterine Cervical Neoplasms/etiology"[Mesh] OR "Uterine Cervical Neoplasms/pathology"[Mesh] OR "Uterine Cervical Neoplasms/diagnosis"[Mesh] OR "Hodgkin Disease/epidemiology"[Mesh] OR "Hodgkin Disease/etiology"[Mesh] OR "Hodgkin Disease/pathology"[Mesh] OR "Hodgkin Disease/diagnosis"[Mesh] OR "Lymphoma, Non-Hodgkin/epidemiology"[Mesh] OR "Lymphoma, Non-Hodgkin/etiology"[Mesh] OR "Lymphoma, Non-Hodgkin/pathology"[Mesh] OR "Lymphoma, Non-Hodgkin/diagnosis"[Mesh] OR "Sarcoma, Kaposi/epidemiology"[Mesh] OR "Sarcoma, Kaposi/etiology"[Mesh] OR "Sarcoma, Kaposi/pathology"[Mesh] OR "Sarcoma, Kaposi/diagnosis"[Mesh] OR "Neoplasms/epidemiology"[Mesh] OR "Neoplasms/etiology"[Mesh] OR "Neoplasms/pathology"[Mesh] OR "Neoplasms/diagnosis"[Mesh]OR carcinogen*[Title/Abstract] OR carcinogen*[Other Term] OR tumor*[Title/Abstract] OR tumor*[Other Term] OR cancer[Title/Abstract] OR cancer[Other Term] OR cancers[Title/Abstract] OR cancers[Other Term]OR cancerous[Title/Abstract] OR cancerous[Other Term] OR "Kaposi sarcoma"[Title/Abstract] OR "Kaposi sarcoma"[Other Term] OR "Non-Hodgkin lymphoma"[Title/Abstract] OR "Non-Hodgkin lymphoma"[Other Term] OR "Hodgkin Lymphoma"[Title/Abstract] OR "Hodgkin Lymphoma"[Other Term] OR "Cervix cancer?"[Title/Abstract] OR "Cervix cancer?"[Other Term] OR "cervical cancer?"[Title/Abstract] OR "cervical cancer?"[Other Term] OR "Anal Cancer?"[Title/Abstract] OR "Anal Cancer?"[Other Term] OR "penis cancer?"[Title/Abstract] OR "penis cancer?"[Other

Term] OR “penile cancer?”[Title/Abstract] OR “penile cancer?”[Other Term] OR “lung cancer?”[Title/Abstract] OR “lung cancer?”[Other Term] OR “liver cancer?”[Title/Abstract] OR “liver cancer?”[Other Term] OR “hepatocellular carcinoma?”[Title/Abstract] OR “hepatocellular carcinoma?”[Other Term] OR “lip cancer?”[Title/Abstract] OR “lip cancer?”[Other Term] OR “oral cancer?”[Title/Abstract] OR “oral cancer?”[Other Term] OR “pharyngeal cancer?”[Title/Abstract] OR “pharyngeal cancer?”[Other Term] OR “Pharynx Cancer?”[Title/Abstract] OR “Pharynx Cancer?”[Other Term] OR lymphoma[Title/Abstract] OR lymphoma[Other Term] OR “leukemia”[Title/Abstract] OR “leukemia”[Other Term] OR “multiple myeloma”[Title/Abstract] OR “multiple myeloma”[Other Term] OR “lymphohematopoietic cancer?”[Title/Abstract] OR “lymphohematopoietic cancer?”[Other Term] OR lymphomas[Title/Abstract] OR lymphomas[Other Term] OR leukemias[Title/Abstract] OR leukemias[Other Term] OR “multiple myelomas”[Title/Abstract] OR “multiple myelomas”[Other Term] OR “lymphohematopoietic cancers”[Title/Abstract] OR “lymphohematopoietic cancers”[Other Term]) AND (“Epidemiologic Studies”[Mesh] OR “epidemiology”[Subheading] OR “cohort?”[Title/Abstract] OR “cohort?”[Other Term] OR “case control”[Title/Abstract] OR “case control”[Other Term] OR “cohorts”[Title/Abstract] OR “cohorts”[Other Term] OR “ecological study”[Title/Abstract] OR “ecological study”[Other Term] OR “follow-up study”[Title/Abstract] OR “follow-up study”[Other Term] OR “ecological studies”[Title/Abstract] OR “ecological studies”[Other Term] OR “follow-up studies”[Title/Abstract] OR “follow-up studies”[Other Term] OR “occupational exposure?”[Title/Abstract] OR “occupational exposure?”[Other Term] OR “Worker?”[Title/Abstract] OR “Worker?”[Other Term] OR “Epidemiologic Methods”[Mesh] OR “occupational exposures”[Title/Abstract] OR “occupational exposures”[Other Term] OR “Workers”[Title/Abstract] OR “Workers”[Other Term])

A.2.3. Mechanism

PubMed: 2013–2015, Reviews only

(“HIV”[Ti] OR “HIV”[Other Term] OR “human immunodeficiency virus”[Ti] OR “human immunodeficiency virus”[Other Term] OR “HIV Infections”[mh] OR “HIV-1”[mh] OR “HIV”[Mesh:NoExp] OR “acquired immunodeficiency virus”[tiab]) OR ((immunocompromised[tiab] OR “immunocompromise”[tiab] OR immune-suppressed[tiab] OR immune-suppression[tiab]))

AND

((cytotoxicities[tiab] OR Cytotoxicity[tiab] OR adverse-outcome-pathway*[tiab] OR Ames test[tiab] OR Aneuploid[tiab] OR Aneuploidy[tiab] OR angiogenesis[tiab] OR biomarkers[tiab] OR Cell-proliferation[tiab] OR Chromosom*[tiab] OR chronic-inflammation[tiab] OR chronically inflamed[tiab] OR Clastogen*[tiab] OR Comet-assay[tiab] OR Crosslink[tiab] OR Cytogenesis[tiab] OR Cytogenetic[tiab] OR Cytogenic[tiab] OR Cytotoxic[tiab] OR Cytotoxin[tiab] OR DNA-protein-crosslink*[tiab] OR DNA protein crosslinks[tiab] OR DNA-Adduct*[tiab] OR DNA-damag*[tiab] OR DNA-inhibit*[tiab] OR DNA-promot*[tiab] OR DNA-Repair[tiab] OR DNA-Repair inhibition [tiab] OR DNA-synthes*[tiab] OR down-regulate[tiab] OR down-regulated[tiab] OR down-regulating[tiab] OR down-regulation[tiab] OR down-regulator[tiab] OR epigenetic*[tiab] OR etiology[tiab] OR gene-Activation [tiab] OR gene-expression[tiab] OR Genetic-toxicology[tiab] OR Germ-line-mutation[tiab] OR

Immunologic-Cytotoxicity [tiab] OR Key Event*[tiab] OR Key-Event[tiab] OR Mechanism-of-action[tiab] OR Mechanisms-of-action[tiab] OR Micronuclei[tiab] OR Micronucleus[tiab] OR Mode-of-action[tiab] OR modes-of-action[tiab] OR Molecular-Initiating-Event*[tiab] OR Mutagenic[tiab] OR Mutagenicity[tiab] OR Mutagens[tiab] OR neoplastic-cell-transform*[tiab] OR Oncogenes[tiab] OR Oncogenesis[tiab] OR Oncogenic[tiab] OR Oxidative-damage*[tiab] OR Oxidative-damage[tiab] OR Oxidative-stress[tiab] OR Oxidative-stress*[tiab] OR pathogenesis[tiab] OR Polyploid[tiab] OR Polyploidy[tiab] OR Strand-break*[tiab] OR toxic-pathway*[tiab] OR Toxicity-Pathway*[tiab] OR transcriptional-activat*[tiab] OR tumor-inhibition[tiab] OR tumor-promot*[tiab] OR tumor-promotion[tiab] OR Unscheduled-DNA-synthes*[tiab] OR up-regulate[tiab] OR up-regulated[tiab] OR up-regulating[tiab] OR up-regulation[tiab] OR up-regulator[tiab] OR miRNA[tiab] OR microRNA[tiab] OR SiRNA[tiab] OR small-inhibitory-RNA[tiab] OR Small-interfering-RNA[tiab] OR non-coding-RNA[tiab]))

AND

List of general cancer terms (see Section A.2.4).

A.2.4. Cancer Terms

Neoplasms[mh] OR “American Cancer Society”[mh] OR “angiogenesis inducing agents”[mh] OR “antibodies, neoplasm”[mh] OR “antigens, neoplasm”[mh] OR “carcinogenicity tests”[mh] OR “carcinogens”[mh] OR clonal evolution[mh] OR “clonal evolution” OR “dna, neoplasm”[mh] OR “genes, neoplasm”[mh] OR leukostasis[mh] OR myelodysplastic-myeloproliferative diseases[mh] OR neoplasm proteins[mh] OR “neoplastic processes”[mh] OR “neoplastic stem cells”[mh] OR “oncogene fusion”[mh] OR “oncogenic viruses”[mh] OR “oncolytic viruses”[mh] OR “polyomavirus”[mh] OR “rna, neoplasm”[mh] OR “SEER program”[mh] OR “tumor lysis syndrome”[mh] OR “tumor markers, biological”[mh] OR AACR OR AJCC [tw] OR (ASCO NOT fungi) OR IARC OR “National Cancer Institute” OR AGCUS [tw] OR ASCUS [tw] OR ATLL [tw] OR CIN [tw] OR CLL [tw] OR CMML [tw] OR CMPD [tw] OR ECCL [tw] OR EGIST [tw] OR FMTC [tw] OR GLNH [tw] OR HNPCC [tw] OR HNSCC [tw] OR HPV [tw] OR HSIL [tw] OR ICD O [tw] OR JCML [tw] OR JMML [tw] OR LGLL [tw] OR MGUS [tw] OR MLH1[tw] OR MPD [tw] OR MSH2[tw] OR NSCLC [tw] OR RAEB [tw] OR RCMD [tw] OR SCLC [tw] OR VOD [tw] OR Neoplasm-Antibod*[tiab] OR Tumor Antibod*[tiab] OR Neoplasm-Antigen*[tiab] OR Tumor-Antigen*[tiab] OR SEER-program[tiab] OR carcinogenicity-test*[tiab] OR leukostasis[tiab] OR 5q syndrome [tw] OR BCR ABL [tw] OR c erbB 2 [tw] OR c erbB2 [tw] OR carney complex [tw] OR cone biopsy [tw] OR denys drash [tw] OR essential thrombocythemia [tw] OR estrogen receptor negative [tw] OR estrogen receptor positive [tw] OR li fraumeni [tw] OR meigs syndrome [tw] OR mycosis fungoides [tiab] OR peutz jeghers [tiab] OR sentinel lymph node[tiab] NOT biopsy[tiab] OR sezary syndrome [tiab] OR struma ovarii [tiab] OR zollinger ellison [tiab] OR aberrant-crypt-foci [tiab] OR Aberrant-crypt-focus[tiab] OR ((anti-n-methyl-d-aspartate [tiab] OR anti-nmda[tiab]) AND encephalitis[tiab]) OR (barrett [tiab] AND esophagus [tiab]) OR (gestational [tiab] AND trophoblastic [tiab]) OR (microsatellite [tiab] AND instability [tiab]) OR (paget [tiab] AND (breast [tiab] OR nipple [tiab])) OR (WAGR [tiab] AND syndrome [tiab]) OR acanthoma [tw] OR acanthomas [tw] OR acrochordon [tw] OR acrochordons [tw] OR acrospiroma [tw] OR acrospiromas [tw] OR adamantinoma [tw] OR adamantinomas [tw] OR adenoacanthoma [tw] OR adenoacanthomas [tw] OR adenoameloblastoma [tw] OR adenoameloblastomas [tw] OR adenocanthoma [tw] OR adenocanthomas [tw] OR

adenocarcinoma [tw] OR adenocarcinomas [tw] OR adenofibroma [tw] OR adenofibromas [tw] OR adenolipoma [tw] OR adenolipomas [tw] OR adenolymphoma [tw] OR adenolymphomas [tw] OR adenoma [tw] OR adenomas [tw] OR adenomatosis [tw] OR adenomatous [tw] OR adenomyoepithelioma [tw] OR adenomyoepitheliomas [tw] OR adenomyoma [tw] OR adenomyomas [tw] OR adenosarcoma [tw] OR adenosarcomas [tw] OR adenosis [tw] OR aesthesioneuroblastoma [tw] OR aesthesioneuroblastomas [tw] OR ameloblastoma [tw] OR ameloblastomas [tw] OR amyloidoses [tw] OR amyloidosis [tw] OR anaplasia [tw] OR androblastoma [tw] OR androblastomas [tw] OR angioblastoma [tw] OR angioblastomas [tw] OR angioendothelioma [tw] OR angioendotheliomas [tw] OR angioendotheliomatosis [tw] OR angiofibroma [tw] OR angiofibromas [tw] OR angiofibrosarcoma [tw] OR angiogenesis factor [tw] OR angiokeratoma [tw] OR angiokeratomas [tw] OR angioleiomyoma [tw] OR angioleiomyomas [tw] OR angiolipoma [tw] OR angiolipomas [tw] OR angioma [tw] OR angiomas [tw] OR angiomatosis [tw] OR angiomyolipoma [tw] OR angiomyolipomas [tw] OR angiomyoma [tw] OR angiomyomas [tw] OR angiomyxoma [tw] OR angiomyxomas [tw] OR angioreticuloma [tw] OR angioreticulomas [tw] OR angiosarcoma [tw] OR angiosarcomas [tw] OR apudoma [tw] OR apudomas [tw] OR argentaffinoma [tw] OR argentaffinomas [tw] OR arrhenoblastoma [tw] OR arrhenoblastomas [tw] OR astroblastoma [tw] OR astroblastomas [tw] OR astrocytoma [tw] OR astrocytomas [tw] OR astroglioma [tw] OR astrogliomas [tw] OR atypia [tw] OR baltoma [tw] OR basiloma [tw] OR basilomas [tw] OR biochemotherapies [tw] OR Birt-Hogg-Dube [tw] OR blastoma [tw] OR blastomas [tw] OR Buschke-Lowenstein [tw] OR cachexia [tw] OR cancer [tw] OR cancerous [tw] OR cancers [tw] OR carcinogen [tw] OR carcinogenesis [tw] OR carcinogenic [tw] OR carcinogens [tw] OR carcinoid [tw] OR carcinoma [tw] OR carcinomas [tw] OR carcinomatosis [tw] OR carcinosarcoma [tw] OR carcinosarcomas [tw] OR cavernoma [tw] OR cavernomas [tw] OR cementoma [tw] OR cementomas [tw] OR cerbB2 [tw] OR ceruminoma [tw] OR ceruminomas [tw] OR chemodectoma [tw] OR chemodectomas [tw] OR cherubism [tw] OR chloroma [tw] OR chloromas [tw] OR cholangiocarcinoma [tw] OR cholangiocarcinomas [tw] OR cholangiohepatoma [tw] OR cholangioma [tw] OR cholangiomas [tw] OR cholangiosarcoma [tw] OR cholesteatoma [tw] OR cholesteatomas [tw] OR chondroblastoma [tw] OR chondroblastomas [tw] OR chondroma [tw] OR chondromas [tw] OR chondrosarcoma [tw] OR chondrosarcomas [tw] OR chordoma [tw] OR chordomas [tw] OR chorioadenoma [tw] OR chorioadenomas [tw] OR chorioangioma [tw] OR chorioangiomas [tw] OR choriocarcinoma [tw] OR choriocarcinomas [tw] OR chorioepithelioma [tw] OR chorioepitheliomas [tw] OR chorionepithelioma [tw] OR chorionepitheliomas [tw] OR choristoma [tw] OR choristomas [tw] OR chromaffinoma [tw] OR chromaffinomas [tw] OR cocarcinogenesis [tw] OR collagenoma [tw] OR collagenomas [tw] OR comedocarcinoma [tw] OR comedocarcinomas [tw] OR condyloma [tw] OR condylomas [tw] OR corticotropinoma [tw] OR corticotropinomas [tw] OR craniopharyngioma [tw] OR craniopharyngiomas [tw] OR cylindroma [tw] OR cylindromas [tw] OR cyst [tw] OR cysts [tw] OR cystadenocarcinoma [tw] OR cystadenocarcinomas [tw] OR cystadenofibroma [tw] OR cystadenofibromas [tw] OR cystadenoma [tw] OR cystadenomas [tw] OR cystoma [tw] OR cystomas [tw] OR cystosarcoma [tw] OR cystosarcomas [tw] OR dentinoma [tw] OR dentinomas [tw] OR dermatofibroma [tw] OR dermatofibromas [tw] OR dermatofibrosarcoma [tw] OR dermatofibrosarcomas [tw] OR dermoid [tw] OR desmoid [tw] OR desmoplastic [tw] OR dictyoma [tw] OR dysgerminoma [tw] OR dysgerminomas [tw] OR dyskeratoma [tw] OR dyskeratomas [tw] OR dysmyelopoiesis [tw] OR dysplasia [tw] OR dysplastic [tw] OR ectomesenchymoma [tw] OR ectomesenchymomas [tw] OR elastofibroma [tw] OR

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