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

Peer-Review Draft:
Report on Carcinogens Monograph on Human Immunodeficiency Virus Type 1

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Office of the Report on Carcinogens
Division of the National Toxicology Program
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Foreword

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of HHS, has delegated responsibility for preparation of the RoC to the NTP, which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions. The most recent RoC, the 13th Edition (2014), is available at http://ntp.niehs.nih.gov/go/roc.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

Overview and Introduction

This collection of monographs on selected viruses provide cancer hazard evaluations for the following human viruses: Epstein-Barr virus, Kaposi sarcoma herpesvirus, human immunodeficiency virus-1, human T-cell lymphotropic virus-1, and Merkel cell polyomavirus for potential listing in the Report on Carcinogens (RoC). Currently, there are three human oncogenic viruses listed in the RoC: human papillomaviruses: some genital-mucosal types (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV). The five viruses covered in these monographs were selected for review for the RoC based on a large database of information on these agents, including authoritative reviews, and public health concerns for disease mortality and morbidity both in the United States and worldwide because of significant numbers of infected people.

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 epidemiology studies and evaluating the causation by viruses.

Background

The RoC draft monograph for each virus consists of the following components: (Part 1) the cancer evaluation component that reviews the relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status, and (Part 2) the draft substance profile containing the NTP's preliminary listing recommendation, a summary of the scientific evidence considered key to reaching that recommendation, and information on properties, exposure, and Federal regulations and guidelines. 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 cancer evaluation component provides the following information relevant to a RoC listing recommendation: Properties and Detection (Section 1), Exposure (Section 2), Human Cancer Hazard Evaluation for specific cancer endpoints (Section 3), Mechanistic and Other Relevant Data (Section 4), and Preliminary Listing Recommendation (Section 5). Because these viruses are primarily species-specific for humans and similar to the approach used by IARC, we are including information on studies in experimental animals in the Mechanistic and Other Relevant Data section of the monographs. 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 an independent 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.

Issues related to evaluating the evidence from human epidemiological studies

The available studies of specific cancer endpoints in the human virus studies 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, the ability to analyze dose-response relationships. However, there is the potential for misclassification of exposure in studies that measure the virus once, but with a long follow-up period as they may miss new infections. For most cancer endpoints, only cross-sectional or retrospective cohort studies or hospital or clinic-based case-control studies are available, which lack direct evidence of temporality and may lack power or adequate data on, e.g., 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.

In addition, for several rare endpoints, e.g., adult T-cell leukemia/lymphoma and human T-cell lymphotropic virus type 1, or primary effusion lymphoma and Kaposi sarcoma 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.

For several viruses, e.g., Epstein-Barr virus, the population prevalence may exceed 90%, so that cohort and case-control studies must rely on the evaluation of cancer risk using measures such as Epstein-Barr virus titer or antibody levels rather than exposed and non-exposed categories of study participants, allowing for the possibility that past or current viral level could be misclassified. In addition, for a number of these viruses, e.g., Kaposi sarcoma herpesvirus, the presence of the virus may be necessary but not sufficient to increase the risk for a specific cancer endpoint and more than one virus may be associated with risk. Thus, methodologically adequate studies should include measurement of such cofactors and consider potentially confounding factors; however, relatively few studies have measured a panel of other viruses or taken into account other cofactors. In addition, 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.

Issues related to evaluating causality of viruses

Approximately 12% of all human cancers have been attributed to viral infections; however, viruses are rarely fully oncogenic themselves and only a small percentage of infected individuals develop cancer, often decades after the initial infection (Mesri *et al.* 2014). Therefore, oncogenic viruses are generally considered necessary but not sufficient to cause cancer. Additional cofactors, such as infective organisms, chemicals, or environmental agents in conjunction with risk modifiers such as immune dysfunction or chronic inflammation can contribute to malignant transformation. 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. In addition, some cofactors produced by other organisms or agents have been shown to activate the oncogenic potential of some of these viruses. There are also other challenges that are

somewhat unique to the evaluation of the epidemiological studies (discussed below) and thus molecular evidence is often considered in the evaluation of causality.

In light of these issues, IARC monographs and several other publications have discussed 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 that health effect is eliminated or mitigated by removal of the substance.

There have been a number of attempts to develop criteria 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 of the limitations associated with strict application of the criteria in the context of virally induced cancers, some alternative approaches, and the NTP's approach for evaluating the role of select viral agents in human cancer.

Hill's characteristics for evaluation of epidemiological studies

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; 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 causality

Criterion	Description
1. Strength of association	A strong association between a virus and a cancer is most consistent with causality unless confounded by some other exposure. However, a weak association does not give evidence against causality.
2. Consistency	Consistent findings observed by different persons, in different places, circumstances and times.
3. Specificity	A viral exposure is limited to specific types of cancer (considered a weak factor because there are well-established examples in which multiple types of disease are caused by one type of exposure). However, the more specific the association, the higher the probability of a causal relationship.
4. Temporality	Exposure to the virus must occur prior to the onset of the cancer, in contrast to a "passenger infection."
5. Biologic 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.
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 2010.

Consideration of mechanistic data from studies in humans

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. Thus, in addition to the Hill characteristics, IARC (1997) also considered the following in their evaluation of Epstein-Barr virus, which are 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, and
- the expression of Epstein-Barr virus proteins.

zur Hausen (2001, 1994) also noted the difficulty of applying stringent criteria to identify human tumor viruses and proposed the following:

- the regular presence and persistence of the respective viral DNA in tumor biopsies and cell lines derived from the same tumor type,
- the demonstration of growth-promoting activity of specific viral genes or of virus-modified host cell genes in tissue culture systems or in suitable animal systems,
- the demonstration that the malignant phenotype depends on the continuous expression of viral oncogenes or on the modification of host cell genes containing viral sequences,
- epidemiological evidence that the respective virus infection represents a major risk factor for cancer development.

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

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 agent that is both necessary and sufficient for a disease to occur describes a complete causal effect. However, this is not a practical definition for infectious diseases that emerge from complex interactions of multiple factors and may be caused by more than a single agent. An important consideration regarding multicausality is that most of the identified 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 1976, zur Hausen and de Villiers 2014). Although the known oncogenic viruses belong to different virus families, they share several common traits: (1) they are often necessary but not sufficient for tumor development; (2) viral cancers appear in the context of persistent infections and occur many years to decades after acute infection; and (3) the immune system can play a deleterious or a protective role (Mesri *et al.* 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 herpesvirus and Merkel cell polyomavirus. Kaposi sarcoma 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 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 herpesvirus but not Merkel cell polyomavirus is that all clinical forms of Kaposi sarcoma require Kaposi sarcoma herpesvirus while most studies indicate that all forms of Merkel cell carcinoma do not require Merkel cell polyomavirus infection. Further, Kaposi sarcoma herpesvirus infection is uncommon in most parts of the world but was confirmed to be present in nearly all AIDS-associated Kaposi sarcoma cases, while widespread Merkel cell polyomavirus infection rate implies that it cannot be a specific causal factor for a rare cancer like Merkel cell carcinoma. In the case of Merkel cell polyomavirus, additional considerations, as suggested by IARC (1997) and zur Hausen (2001,

1994), provide molecular evidence of the association between Merkel cell polyomavirus and Merkel cell carcinoma, such as the tumor-causing form of the virus is mutated and monoclonally integrated into the tumor genome and that tumor cells require 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.

NTP's approach

For each virus, the NTP applied the RoC listing criteria (see text box) to the body of literature to reach the preliminary 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

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.

mechanistic data and determining the preliminary recommendations for its level of evidence conclusion and overall listing recommendation, the NTP considered the principles outlined by Hill, IARC, zur Hausen, and Rothman 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.

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Part 1

Draft Cancer Hazard Evaluation

Properties and Detection

Exposure

Human Cancer Studies

Mechanisms and Other Relevant Data

Preliminary Listing Recommendation

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Table of Contents

List of Tables

List of Figures

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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, was later discovered in 1986 but is confined to West Africa, often in people co-infected with both types (IARC 2012a, De Cock *et al.* 1991). 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.

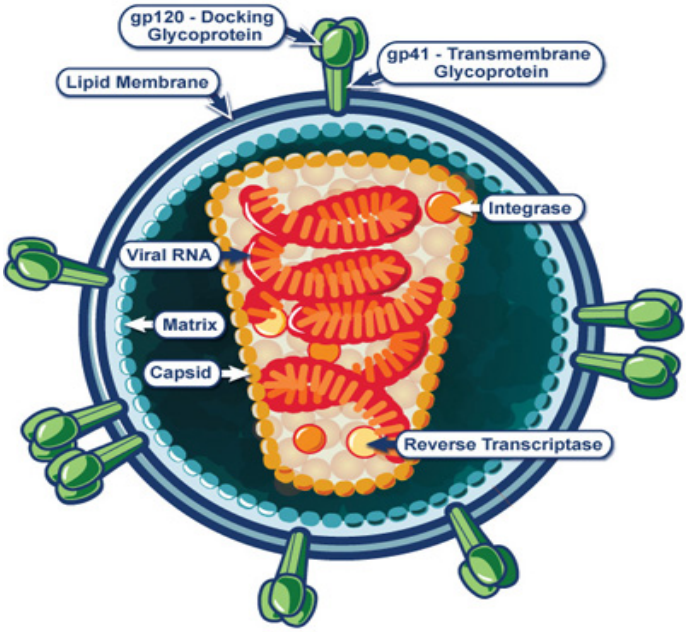

Figure 1-1. Human immunodeficiency virion structure

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 (see Figure 1-2) (IARC 2012a, 1996). 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 and the protease is used to cleave *gag* and *pol* proteins into the individual proteins. The third main gene, *env*, encodes the two envelope proteins pg41 and pg120. 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.

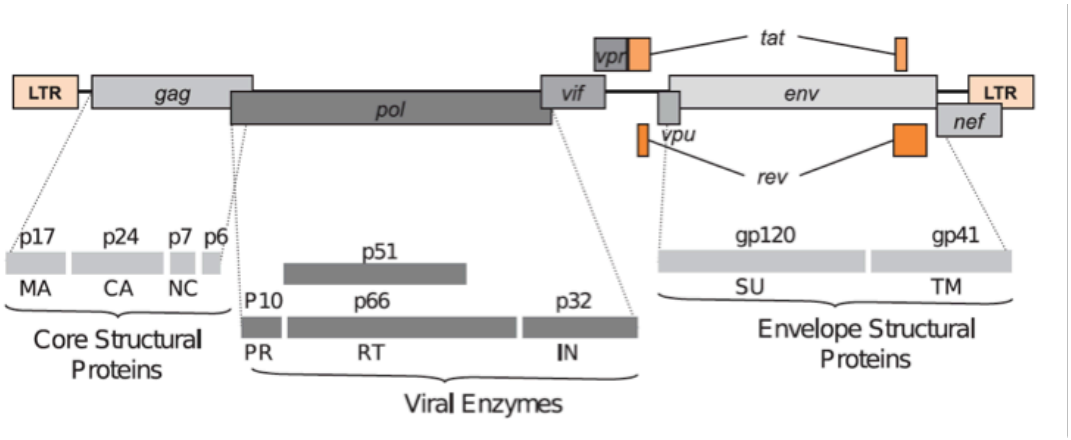

Figure 1-2. Human immunodeficiency virus genome structure

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 2012a, 1996). 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 can't "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.

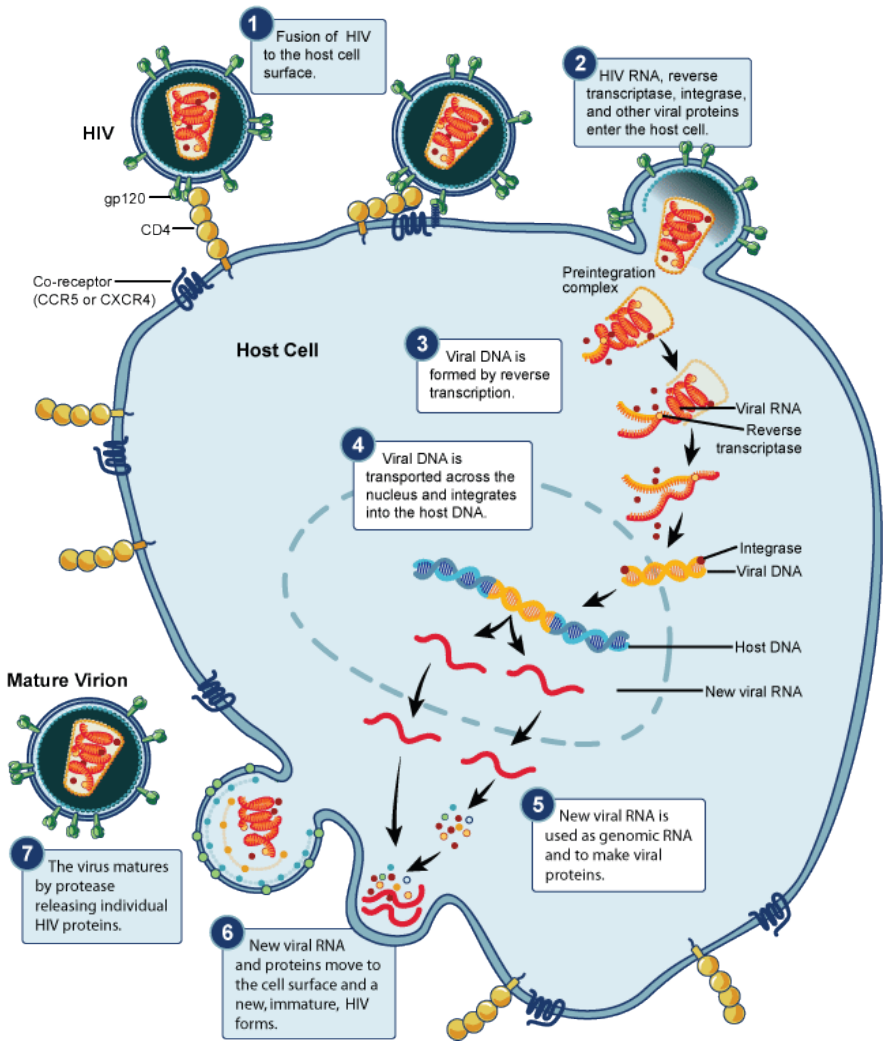

Figure 1-3. HIV-1 replication cycle

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 2014d). 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 2015a). 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 rate of disease progression (DHHS 2015a).

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 2012a, 1996). 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). For screening purposes, immunoassays for HIV-1 consist of laboratory-based tests, such as enzyme-linked immunosorbent assays (ELISA), also known simply as enzyme immunoassays (EIA) and point-of-care rapid tests. These tests detect immunoglobulins G and M and have a high degree of sensitivity, although the first generation tests had relatively low specificity due to contamination with non-viral antigens during the production of anti-HIV-1 antibodies. Second generation tests used recombinant HIV-1 antigens which increased specificity and were able to detect HIV-1 in blood in as little as five weeks after the initial infection. 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. Rapid screening tests for IgG and IgM antibodies using fingerprick blood samples or oral swabs have also been developed, and approved by the FDA for use in the United States since 2002. These tests qualitatively detect HIV-1 somewhat later than lab-based immunoassays and reportedly with lower sensitivity and specificity.

Both laboratory-based and point-of-care positive screening tests must be followed by a confirmatory laboratory-based Western blot immunoassay (CDC 1989) or, less frequently, by the immunofluorescence assay (IFA). The Western blot tests for IgG antibodies that bind to fixed HIV-1 proteins and is 99.3% to 99.7% sensitive and 99.7% specific, but may not be able to detect HIV-1 infection as early as the latest immunoassays (CDC 1989). The 1989 CDC screening protocol specifies the confirmation of a repeatedly positive immunoassay by Western blot or the indirect immunofluorescence assay. The most recent update to the screening guidelines (CDC 2014d; see also Cornett and Kirn 2013), use new diagnostic and confirmatory tests that are more sensitive and specific than the Western blot test.

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.

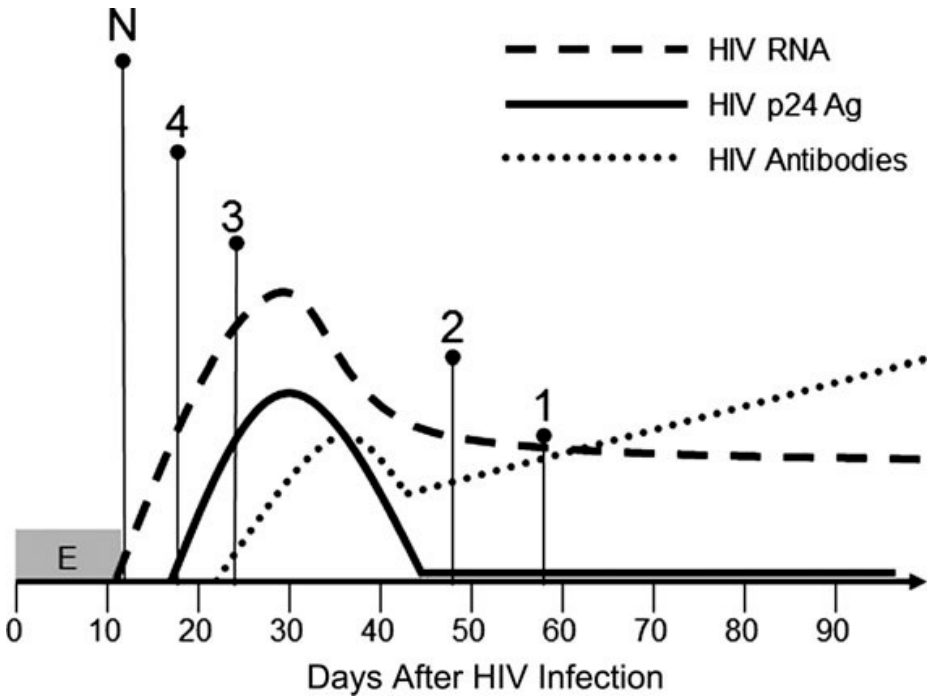

Figure 1-4. Diagnostic markers of human immunodeficiency virus (HIV) infection

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 2012a, 1996). 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 2012a, 1996).

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 2015b). 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 2010, DHHS 2015b, Palmeira 2012, Franca 2012).

1.3 Summary

HIV-1 is an enveloped single-stranded RNA retrovirus of the subfamily *Orthoretrovirinae* and genus *Lentivirus* (IARC 1996, 2012). 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.

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2 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 2012a, 1996). 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., Leiss *et al.* 2006, Ippolito *et al.* 1999, CDC 1987) 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).

The two primary behavioral risk factors for transmission in most resource-rich countries are the practice of unprotected sex, particularly unprotected anal sex, and the sharing of drug needles. However, the relative importance of these risk factors vary widely geographically, primarily as a function of differences in, e.g., sexual practices, injecting drug use, screening practices for the transfusion blood supply and blood donors, and the extent and effectiveness of deployed education and prevention strategies. Globally, approximately two-thirds of adults living with HIV-1 infection live in sub-Saharan countries, with the epicenter in South Africa (UNAIDS 2013a), and well over half of them are women, in part due to polygyny and multiple relationships among men (Reniers and Watkins 2010), although new HIV-1 infections have declined substantially (UNAIDS 2013a). 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 2012a, UN 2001, IARC 1996). Other factors such as unsafe medical, e.g., injection practices, may also account for a higher proportion of infections than in resource-rich countries (e.g., IARC 2012a, Zetola *et al.* 2009).

Other risk factors for HIV-1 infection 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 2012a, 1996).

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) and there were an estimated 1.6 million AIDS-related deaths worldwide in 2012 (UNAIDS 2013b). 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 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 (UNAIDS 2015c).

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 50,000 new HIV-1 infections are estimated to occur each year. Approximately 1.2 million people in the United States have been diagnosed with AIDS since the start of the epidemic in 1981, when the first patients with a newly identified syndrome of acquired immunity were reported, with 26,700 newly diagnosed with AIDS and 47,350 with HIV-1 in 2013. A total of approximately 660,000 people with an AIDS diagnosis have died since the start of the epidemic. About half of all people living with HIV infection are men who have sex with men. The incidence of new HIV-1 infections has remained stable over recent years, at about 50,000 per year, but varies considerably by risk group, with men who have sex with men making up about 63% of these, injecting drug users 8%, and women approximately 20% (CDC 2015a, 2012).

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. The CDC case definition (CDC 1999, 1992) includes over 20 opportunistic infections or related conditions or a CD4 count of < 200/μL (see e.g., CDC 2015b).

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 herpesvirus (CDC 2015b, IARC 2012a, 1996). Hepatitis C virus infection, primarily transmitted via injecting 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 co-infection and disease, 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, injecting drug users, and infected pregnant mothers (CDC 2015c).

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. 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 2014b). 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 2014c). 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 zidvudine), 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 2014b).

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 2015b, 2015a). 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 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 cART (combination antiretroviral therapy) and are now incorporated into standard treatment guidelines (e.g., DHHS 2015a).

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

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 injecting 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 acquired immune deficiency syndrome (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 among 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.

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3 Human Cancer

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 1992, 1985). 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, invasive 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 noted 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, oral and pharyngeal, liver, lung, and non-melanoma skin cancers. NTP provided a more comprehensive review update of cohort studies or cancer site-specific studies published since 2009.

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, and 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.

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 cancer endpoint is presented (Sections 3.2 to 3.9), other cancer sites and cancer burden are discussed in Section 3.10, followed by the potential carcinogenicity of HAART and treatments for opportunistic infections (Section 3.11), and an integration and summary of the evidence across HIV-1-related cancer endpoints (Section 3.12).

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, we identified 21 cohorts or record-linkage studies that reported risk estimates for at least three cancer sites (summarized in Table 3-1, below), as well as additional studies focusing specifically on individual cancers. For Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, invasive 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 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[1]

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
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

Reference/ Country	Study design	# with HIV or AIDS in cohort	Dates	Cancer endpoints	Comments
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 PWH	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	US HIV/AIDS Cancer Match Study cancer registry children (0-14 yrs) 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
Albini *et al.* 2013/Calabresi *et al.* 2013 Italy	Retrospective cancer registry PWH	5, 090	1999–2009	Testes, lung, NMSK(Albini) KS, NHL, HL, cervical, anal, genital, liver, lung, NMSK, ororpharynx (Calabresi)	
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

Reference/ Country	Study design	# with HIV or AIDS in cohort	Dates	Cancer endpoints	Comments
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	6459 HIV-1-positive cancer cases vs 1,816,461 HIV-1-negative cancer cases	1996–2010	HL, cervical, anal, liver, lung, oropharynx	

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

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.

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

3.2 Cancer hazard evaluation: Kaposi sarcoma

Kaposi sarcoma herpesvirus is necessary for the development of Kaposi sarcoma (see monograph on Kaposi sarcoma herpesvirus). 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 evaluating 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 mainly found in regions of sub-Saharan Africa where the Kaposi sarcoma herpesvirus seroprevalence rate is approximately 25% to 50%;
2. Classic Kaposi sarcoma, which occurs among certain southern Mediterranean populations with Kaposi sarcoma herpesvirus seroprevalence rates of 10% to 20%;
3. Iatrogenic Kaposi sarcoma, which is observed mainly among organ transplant recipients who have Kaposi sarcoma herpesvirus infection;
4. Epidemic or HIV-1/AIDS-related Kaposi sarcoma, which occurs among HIV-1-positive or AIDS populations.

In the United States, Kaposi sarcoma occurred in less than 1 per 100,000 individuals prior to the HIV-1/AIDS epidemic starting in the early 1980s, peaking at approximately 5 to 6 per 100,000 by the early1990s, prior to the advent of HAART.

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 (Rabkin and Yellin 1994, Rabkin *et al.* 1991, Bernstein *et al.* 1989, Biggar *et al.* 1989,

Biggar *et al.* 1987, Biggar *et al.* 1985) and risks were correlated with a decrease in CD4 counts (Dore *et al.* 1996, Lundgren *et al.* 1995, Veugelers *et al.* 1995, Munoz *et al.* 1993).

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 1 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 others 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 2012a, 1996): 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, 2% in intravenous drug users, 3% in transfusion recipients, 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 in the 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 2012, 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 Kasposi sarcoma herpesvirus (KSHV), 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 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 KSHV monograph).

3.2.3 Studies comparing Kaposi sarcoma in HAART and non-HAART-administered HIV-1/AIDS populations

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 (Hleyhel *et al.* 2013, Franceschi *et al.* 2010, van Leeuwen *et al.* 2009, Patel *et al.* 2008, Engels *et al.* 2006a) (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.* 2004, Carrieri *et al.* 2003, Grulich *et al.* 2001, Ives *et al.* 2001, ICHIVC 2000) and from 0.11 to 0.2 in more recent studies comparing pre-HAART with early to established HAART periods (Seaberg *et al.* 2010, Simard *et al.* 2010, Franceschi *et al.* 2008). 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 (e.g., Mbutailaye *et al.* 2003, Serraino *et al.* 2005, Clifford *et al.* 2005, Franceschi *et al.* 2008, 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 = 3.5 (3.0 to 4.8) for ≥ 10,000 copies HIV RNA/mL vs. 1.2 (0.8 to 1.7) for 501 to 9,999 copies/mL).

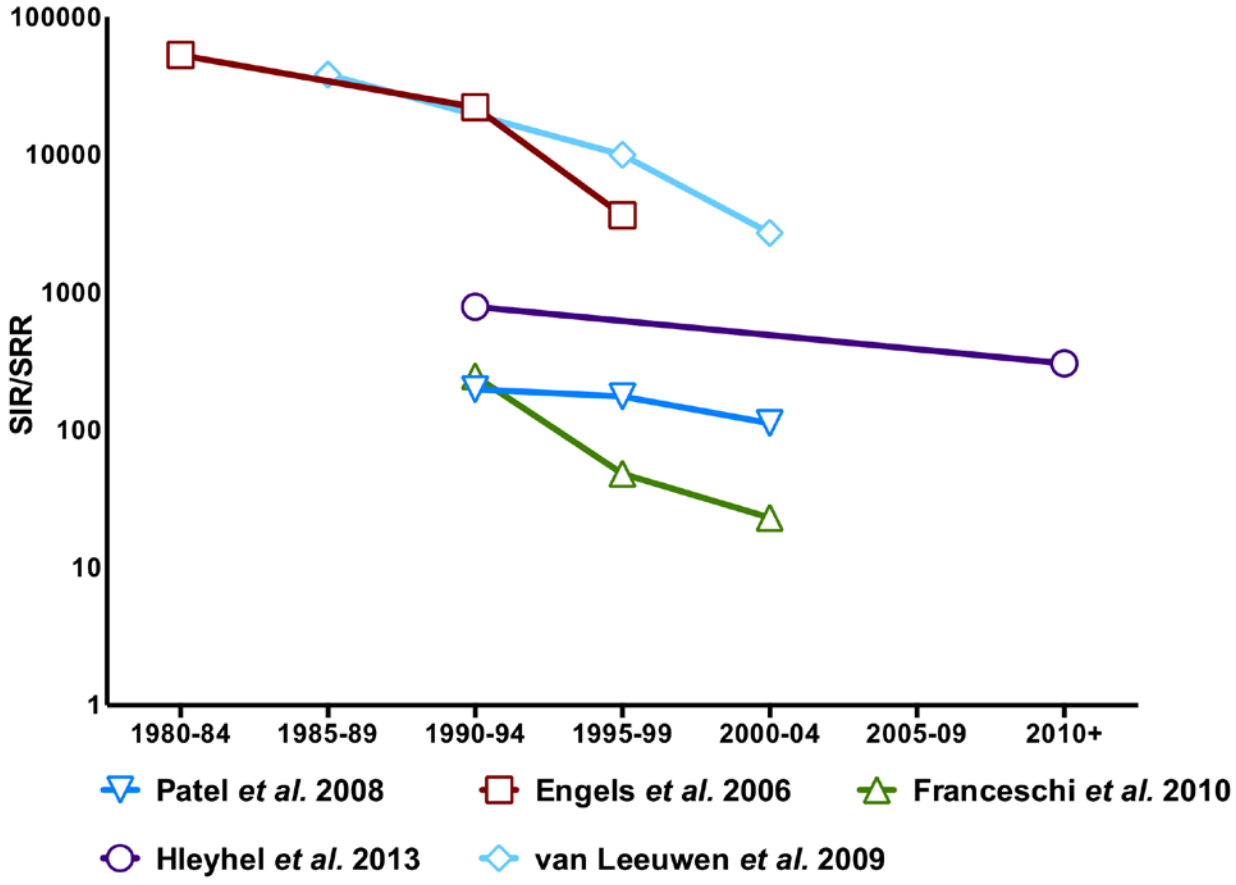

Figure 3-1. Cohort studies of Kaposi sarcoma incidence in HIV-1/AIDS populations from pre-HAART (1980 to 1996) to HAART (1996 and later) periods

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., Patel *et al.* 2014, Hleyhel *et al.* 2013, 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 2015a).

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 2012a, Kaplan 2012, IARC 1996).

In addition, T-cell lymphomas have also been evaluated among HIV-1-positive groups (IARC 2012a). Non-Hodgkin lymphoma is considered to be a late manifestation of HIV-1/AIDS infection.

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 (Rabkin and Yellin 1994, Biggar *et al.* 1989, Harnly *et al.* 1988, Kristal *et al.* 1988, Ross *et al.* 1985, cited in IARC [1996]); these were followed by cancer registry and AIDS registry linkage studies (Reynolds *et al.* 1993, Cote *et al.* 1991) 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 (Munoz *et al.* 1993, Pluda *et al.* 1993, Rabkin *et al.* 1992, Moore *et al.* 1991, Pluda *et al.* 1990, 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, among studies reporting risks, included a total of approximately 14,500 cases of non-Hodgkin lymphoma. These studies report 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 and 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, Stein *et al.* 2008, Newton *et al.* 2001). 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 (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; 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 Studies comparing non-Hodgkin lymphoma in HAART and non-HAART-administered HIV-1/AIDS populations.

Reported SIRs or relative risks for non-Hodgkin lymphoma declined from approximately 134 to 7 among AIDS or combined AIDS/HIV-1 populations (Hleyhel *et al.* 2013, van Leeuwen *et al.* 2009, Franceschi *et al.* 2010, Dal Maso *et al.* 2009, Engels *et al.* 2008, Galceran *et al.* 2007, Engels *et al.* 2006a) 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, see also review by Engels *et al.* 2010b).

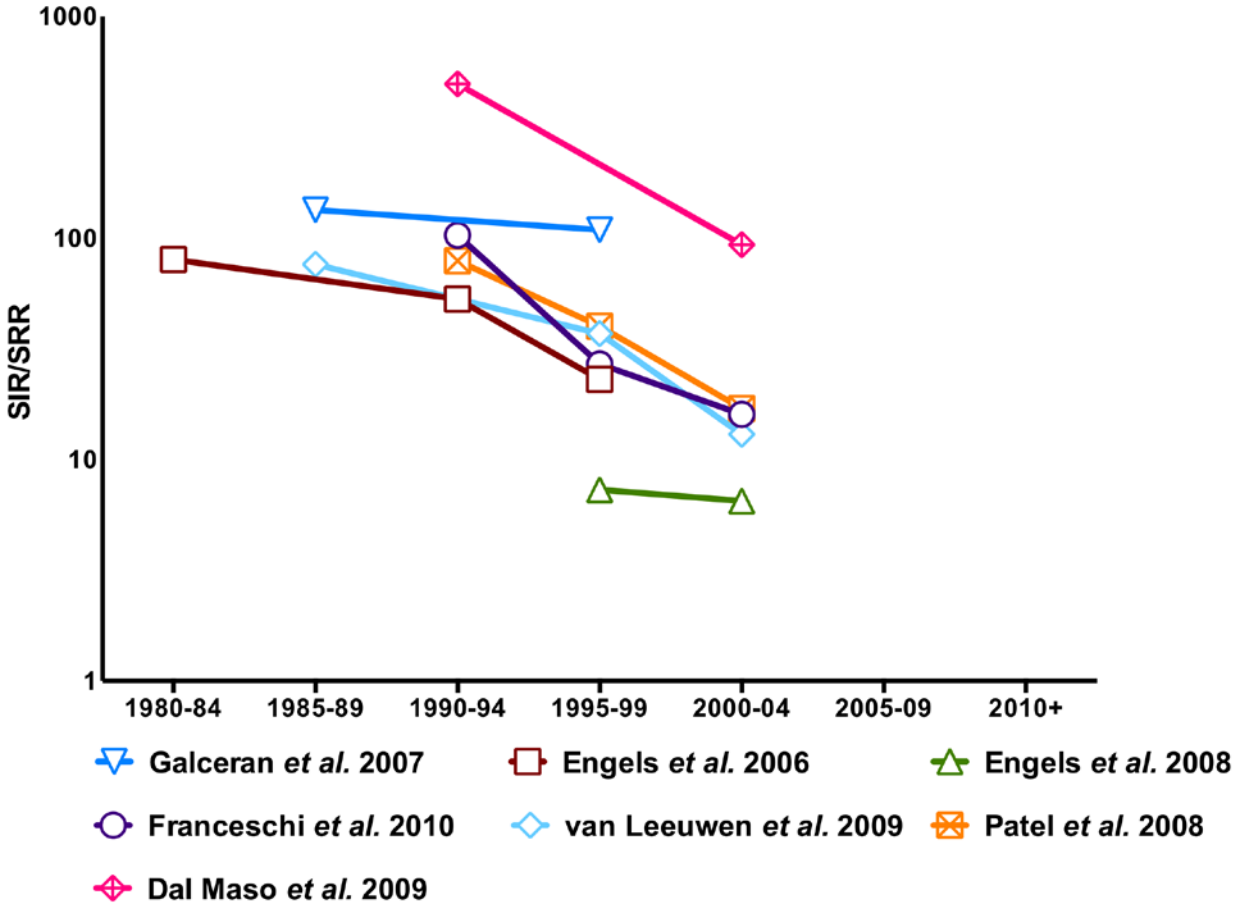

Figure 3-2. Cohort studies of non-Hodgkin lymphoma incidence in HIV-1/AIDS populations from pre-HAART (1980 to 1996) to HAART (1996 and later) periods

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 (Seaberg *et al.* 2010, Simard *et al.* 2010, Bedimo *et al.* 2004, Bhaskaran *et al.* 2004, ICHIVC 2000); 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).

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 (Polesel *et al.* 2008, Kirk *et al.* 2007).

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., Hleyhel *et al.* 2013, Franceschi *et al.* 2010, van Leeuwen *et al.* 2009, Engels *et al.* 2008, Patel *et al.* 2008), and it is now the second most common HIV-1/AIDS-related

cancer worldwide, partly as a result of declines in other HIV-1-related cancers such as Kaposi sarcoma.

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 (Engels *et al.* 2006a, Cote *et al.* 1996). Diffuse large B-cell immunoblastic lymphoma is also associated with severe immunosuppression and occurs at several hundred times the general population rate (Engels *et al.* 2006a, Engels and Goedert 2005). 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 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 (IARC 2012a, Kaplan 2012, Diamond *et al.* 2006). 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 the 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 lymphomas (SIRs of 141, 95, and 60, respectively) and a 20% decline in primary central nervous system lymphomas (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 40% of cases of Burkitt lymphoma (IARC 2012, Grulich *et al.* 2007, Gioghini *et al.* 2013, 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 herpesvirus-related lymphomas (reviewed in the accompanying monograph on Kaposi sarcoma 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 2012). However, the precise role of hepatitis B and C viruses in non-Hodgkin lymphoma risk in the presence of HIV-1 infection has not yet been fully elucidated, to our knowledge.

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, however.

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% (SEER 2015b, 2008 to 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, and indicating a preponderance of mixed cellularity and lymphocyte depletion as histological subtypes. Early cohort studies reported increases in Hodgkin lymphoma in some AIDS patients (Reynolds *et al.* 1993, Hessol *et al.* 1992, Rabkin *et al.* 1992) 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 Gruclich *et al.* (2007), and 1 case-control study of Hodgkin lymphoma that reported SIRs or RRs, conducted in the United States, Europe, and Africa (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 a relative risk of 1.6 (95% CI = 1.1 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 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 the 2008 review (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.* overlap with those of Grulich, although not all reported data for every cancer endpoint).

There is some variation in the histological type of Hodgkin lymphoma (Mounier *et al.* 2010, Carbone *et al.* 2009, Biggar *et al.* 2006, Frisch *et al.* 2001, 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 Studies comparing Hodgkin lymphoma in HAART and non-HAART-administered HIV-1/AIDS populations

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, that ranged from 0.75 to 2.7, depending in part on the periods being compared (Seaberg *et al.* 2010, Simard *et al.* 2010, Engels *et al.* 2008, Bedimo *et al.* 2004, ICHIVC 2000). 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 may have partly leveled off (see reviews by Goedert and Bower 2012, Kaplan 2012, Carbone *et al.* 2009). 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.

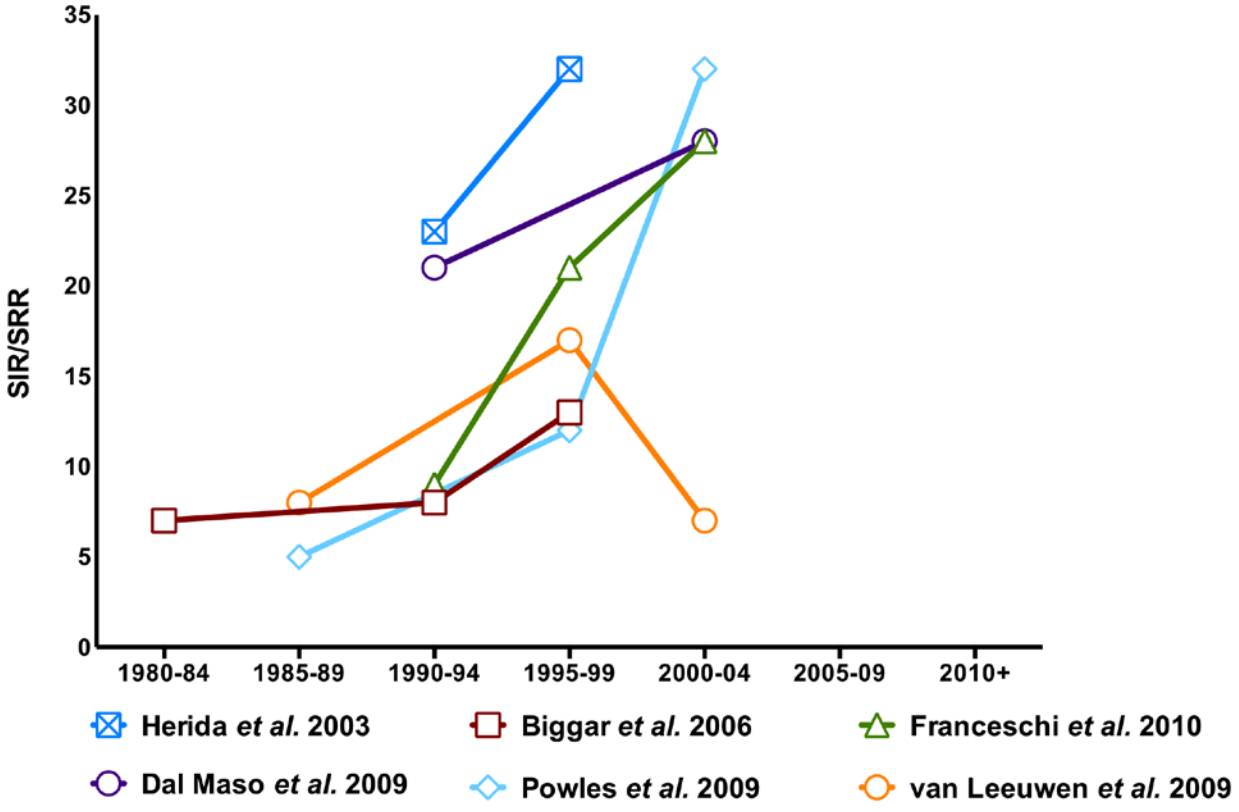

Figure 3-3. Cohort studies of Hodgkin lymphoma incidence in HIV-1/AIDS populations from pre-HAART (1980 to 1996) to HAART (1996 and later) periods

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 Goedert and Bower 2012, Sissolak *et al.* 2010, Carbone *et al.* 2009). 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 Mounier *et al.* 2010, Carbone *et al.* 2009).

3.5 Cancer hazard evaluation: Human papilllomavirus-related cancers

Three main cancer types are associated with exposure to both HIV-1 and human papillomavirus: invasive 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 Invasive cervical cancer

Background information

Invasive cervical cancer incidence rates in the United States have fallen steadily from 14.8 to 6.7 per 100,000 from 1975 to 2012 (SEER 2015c) but 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 invasive 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 invasive 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 7 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 invasive 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 fifteen cohort studies published after 2008 review (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).

Studies comparing HAART and non- or early HAART-treated HIV-1/AIDS populations and invasive cervical cancer

The effect of HAART on the risk of cervical cancer is unclear. The risk of invasive cervical cancer modestly declined during the HAART era (from the mid-1990s to late 2000s (see Figure 3-4, (IARC 2012a and reviews Denslow *et al.* 2014, Adler 2010, Palefsky 2009a) in three of four cohort studies (Hleyhel *et al.* 2013, Franceschi *et al.* 2010, Dal Maso *et al.* 1990) that reported risks estimates since the 1990's. Four large cohort studies reported non-statistically significant age-adjusted changes in SIR/RR risk over the pre-HAART to the early HAART periods from 0.8 to 1.9 (Simard *et al.* 2010, Chaturvedi *et al.* 2009, Biggar *et al.* 2007, ICHIVC 2000). In a small cohort study of approximately 2,300 HIV-1-positive women from Italy and France, no effect of HAART on cervical cancer rates was observed when treated and untreated women were compared. 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)

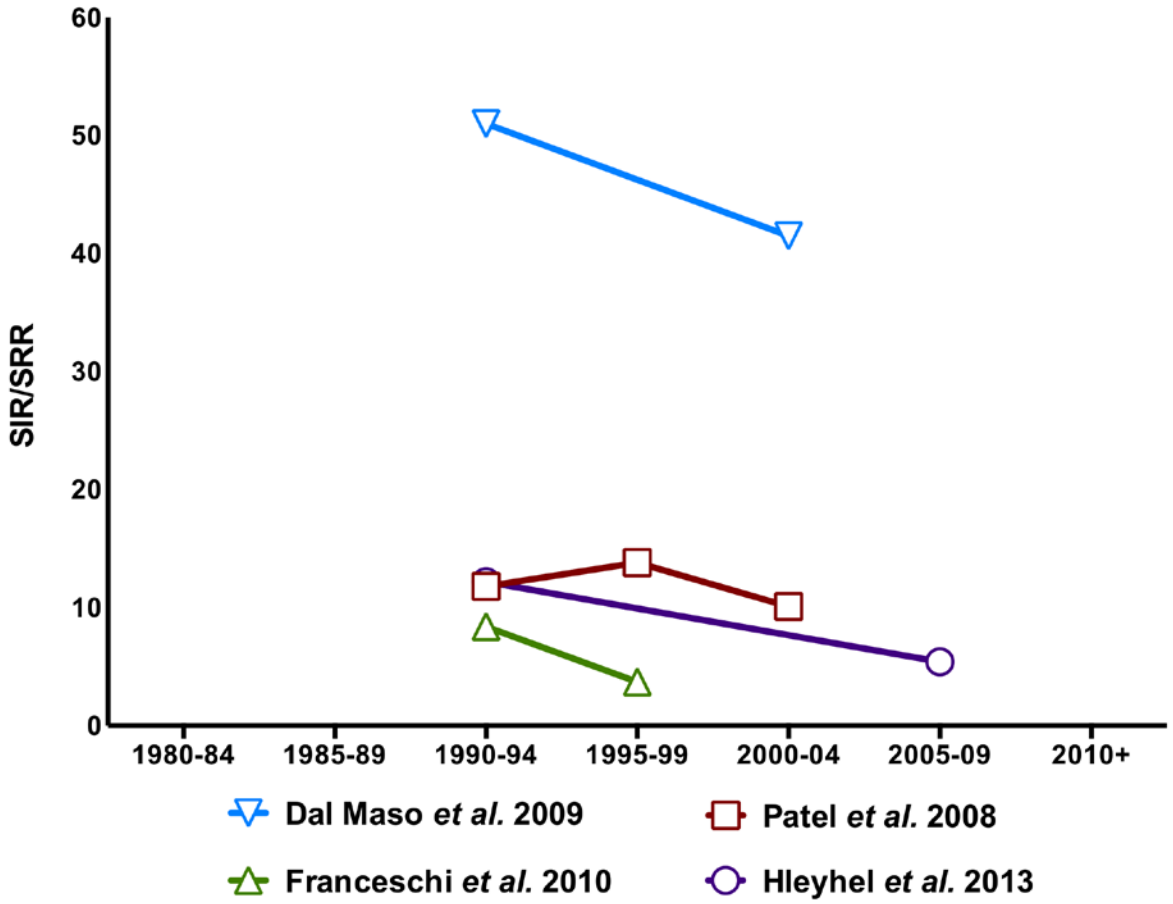

Figure 3-4. Cohort studies of invasive cervical cancer incidence in HIV-1/AIDS populations from pre-HAART (1980 to 1996) to HAART (1996 and later) periods

Cofactors

Human papillomavirus is considered necessary for the development of invasive cervical cancer, and the risk is substantially increased in the presence of HIV-1 infection (NTP 2014a, IARC 2012a, 2007 and reviews by Crosbie *et al.* 2013, Bosch *et al.* 2002). While most human papillomavirus infections are transient, a causal relationship between persistent human papillomavirus infection involving certain genital mucosal types and the development of invasive 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).

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 Fernandes *et al.* 2015, Dugue *et al.* 2013, 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 1.8/100,000, based on 2008 to 2012 SEER rates (SEER 2015d).

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.* (1993).

A total of 17 cohort studies reporting SIR or RR were reviewed by IARC (2012), representing approximately 1,670 cases. No case-control studies were identified by IARC. The cohort studies report substantial increases in anal cancer among HIV-1-positive men, particularly men having sex with men, but increases in risk are 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 confirm 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.* (1999).

Studies comparing invasive anal cancer in HAART vs. non- or early-HAART-treated HIV-1/AIDS populations

There is no consistent evidence as to whether HAART itself either increases or decreases the risk for this cancer. 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, and four studies reporting changes in relative risk report 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 (Seaberg *et al.* 2010, Simard *et al.* 2010, Diamond *et al.* 2005, ICHIVC 2000). However, record linkage registry studies of HIV-1/AIDS cases in the United States (Engels *et al.* 2008, Hessol *et al.* 2007, Engels *et al.* 2006a, Simard *et al.* 2010, Seaberg *et al.* 2010), 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. 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

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 (IARC 2012a, Hessol *et al.* 2009). While 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 (Coutlee *et al.* 2012, Stanley *et al.* 2012, Hessol *et al.* 2009) are correlated with the risk of both human papillomavirus and HIV-1 infection, 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 2008-2012, 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 (SEER 2015e); the incidence of penile cancer is approximately 0.7 per 100,000 men per year (Sewell *et al.* 2015).

Cohort and case-control studies of genital cancer

The available database on HIV-1 infection and human papillomavirus-related genital cancers has expanded since the IARC (2012) 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 cancer and 6.8, 95% CI = 4.2 to 11, 16 infected cases from 3 studies for 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 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 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.* 2005, Newhahn *et al.* 2006, Long *et al.* 2008, Patel *et al*. 2009, 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.* 2006 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 (Simard *et al.* and Chaturvedi *et al*.) might be of overlapping populations.

Two studies evaluated cancer risk among people with AIDS in the United States with potentially overlapping populations (Simard *et al.* 2010, Chaturvedi *et al.* 2006), one of which conducted detailed analysis on human papillomavirus-related tumors (Chaturvedi *et al.* 2006) 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 estimate 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 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 cancer.

3.5.4 Oral cancers

Background information

Oral cancer includes both oropharyngeal cancers (cancers of the soft palate and uvula, tonsils, osterior 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 2008-2012, the number of new cases of oral cancers combined was 11.0 per 100,000 men and women per year, and represent 2.8% of all new cancers per year (SEER 2015f).

Cohort and case-control studies of oral cancer

The IARC 2012 monograph on HIV-1 infection and oral 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 monography 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.* also included separate estimates for oropharyngeal cancer (mSIR = 1.9, 95% CI = 1.4 to 2.6) based on 108 cases.

Since the IARC 2012 review and the meta-analysis by Shiels *et al.* (2009), the available database on HIV-1 infection and oral cancers has expanded considerably. Approximately thirteen new cohort studies have reported estimates for oral cancers (excluding studies of head and neck 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 cancers among HIV-1 infected individuals were available from 21 studies including both those reviewed in IARC and new studies conducted. Risks reported in these studies ranged from SIR/RRs of 1.1 to 5.3. In addition, SIR/RR estimates from three studies conducted outside of these geographic areas range from 1.7 to 22.1. Due to small numbers of these relatively rare tumors, studies often report estimates for combined cancer sites, and/or for specific oral cancer sites (see Table 3-8): 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 cancers*

	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: IARC 2012; Shiels *et al.* 2009; Grulich *et al.* 2007; 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; Newnham *et al.* 2005; 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.
*Several studies report more than one anatomical site or site grouping.

The heterogeneity of disease, the unmeasured heterogeneity of risk factors, and the potentially distinct etiologic pathways for oral 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. HIV infected individuals are known to have a high prevalence of co-infection with HPV16 (Kreimer *et al.* 2004; Beachler *et al.* 2012), an established cause of oropharyngeal and oral cavity carcinomas (IARC 2007; Gillison *et al.* 2008). Stein *et al.* (2014) reported, based on a systematic review of the prevalence of human papillomavirus in oropharyngeal squamous-cell carcinoma, that in the United States approximately 65% of tumors are human papillomavirus positive. Multiple investigations show that HIV-1-infected persons 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 *et al.* 2012).

It has been hypothesized that human papillomavirus-associated cancers and human papillomavirus-nonassociated 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-nonassociated cancers are more likely to be associated with tobacco and alcohol use which are also elevated among HIV infected individuals (Gillison *et al.* 2008). Registry studies conducted cannot precisely distinguish between human papillomavirus-associated and human papillomavirus -non-associated cancer. Risk factors such as common sexual behaviors, the proportion of men who have sex with men and heterosexuals and other behavioral risk factors related to the proportion of human papillomavirus related oral cancers likely vary across cohorts (Pickard *et al.* 2012; Kreimer *et al.* 2013). Findings regarding decreased oral transmission of human papillomavirus from males to males compared to oral transmission from females to males may help explain the modest increase in risk measured in the HIV/AIDS cohorts (which are largely men who have sex with men), compared to HPV-associated cancers such as cervical or anal cancers (Beachler and D'Souza 2014). Two studies found higher risks of oral cancer among heterosexual men compared to men who have sex with men.

Clifford *et al.* 2005; Chaturvedi *et al.* 2009). These data are consistent with the male predominance of these 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 oropharyngeal cancer 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 and found that oral human papillomavirus acquisition appears to be increased by oral sex and with 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.* 2014b).

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 (SEER 2015g). Hepatocellular carcinoma is the most common form of liver cancer, occurring among 5 to 10/100,000 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. The 5-year survival rate is less than 20%. 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

Nineteen cohort, one nested case-control, and two case-control studies reporting risks were reviewed by IARC (2012); since 2009, 39 additional cohort studies were identified (excluding prospective patient series). Studies reviewed by IARC (2012) 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 to 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 2012, Table 2.23 and studies since IARC 2012: Powles *et al.* 2009; Bedimo *et al.* 2009; van Leeuwen *et al.* 2009; Seaberg *et al.* 2010; Simard *et al.* 2010; Franceschi *et al.* 2010; Silverberg *et al.* 2011; Sarasbuddhe *et al.* 2012; Park *et al.* 2014; Raffetti *et al.* 2015; Castilho *et al.* 2015; Chen *et al.* 2014; Coghill *et al.* 2015; Franzetti *et al.* 2013; Hleyel *et al.* 2014; Kramer *et al.* 2015; MacDonald *et al.* 2009; Shiels *et al.* 2009; Simard *et al.* 2012; Vogel *et al.* 2011; and 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: Kramer *et al.* 2015; Di Benetto *et al.* 2014; Vogel *et al.* 2011; MacDonald *et al.* 2009; Sahasrabuddhe *et al.* 2012; McGinnis *et al.* 2006. Deng *et al.* 2009 meta-analysis examined hepatitis C virus patients with and without HIV-1.

*All lower 95% CI > 1.0 except Dal Maso *et al.* (2003); Grulich *et al.* 1999, 2002; Mbulaiteye *et al.* 2006; Serraino *et al.* 2000; and Coghill *et al.* 2015.

3.6.3 Studies comparing hepatocellular carcinoma in HAART and non- or early-HAART-treated HIV-1/AIDS populations.

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 (Hessol *et al.* 2007, Sahasrabuddhe *et al.* 2012, Curry 2013). 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 infection rates, or other risk factors for hepatocellular carcinoma (Hessol *et al.* 2007, IARC 2012, Curry 2013). 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).

3.6.4 Cofactors

Hepatocellular carcinoma is causally linked to both hepatitis B virus and to hepatitis C virus infection (see IARC 2012, RoC 2014b.c). 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 (Engels *et al.* 2002a, Clifford *et al.* 2008).

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. Few studies have measured the seroprevalence

of hepatitis C or B 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-infected patients (Henderson *et al.* 2010; Tradati *et al.* 1998, Kramer *et al.* 2005 as reviewed by Deng *et al.* 2009) 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 and HIV-1 co-infected patients (incidence ratio 1.97).

3.7 Cancer hazard evaluation: Non-melanoma skin cancer

3.7.1 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 (American Cancer Society 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 (American Cancer Society 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 6 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.

3.7.2 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 (2012). 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 (Zhao *et al.* 2015; Shiels *et al.* 2009), with two of the cohort studies having been published prior to the IARC publication (Grulich *et al.* 2002; and Cooksley *et al.* 1999). Most of the reported risks in the cohort studies ranging 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 as 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) 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[1]

	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. cases	6	3–70	2–570
No. of studies	1	6	12

Source: IARC, 1996, IARC 2012a, Table 2.17 and studies since IARC 2012:Francheschi *et al.* 2010; Lanoy *et al.* 2009; Silverberg *et al.* 2013; Chen *et al.* 2014; Albini *et al.* 2013; Crum-Cianflone *et al.* 2015; and Grulich *et al.* 2002, Zhao *et al.* 2015 and Shiels *et al.* 2009 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.
[1]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.

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 log10 copies/mL, hazard ratio [HR] = 1.75 [95% CI = 1.42 to 2.14]). This finding provides some evidence of the link between HIV-1 viremia 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.* 2004).

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

3.7.3 Cofactors

Since the last IARC review (2012) and shortly after the discovery of Merkel cell virus, two cohort studies and one case-control study have been identified that report increased risks of Merkel cell carcinoma among HIV-1-positive populations (Lanoy *et al.* 2009, 2010, Izikson *et al.* 2011) 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 (Tolstov *et al.* 2011, Wieland *et al.* 2011, Wieland and Kreuter 2011, Fukomoto *et al.* 2013), however, and no studies have been identified to date that have measured Merkel cell virus among HIV-1-positive Merkel cell carcinoma cases, with the exception of one case study (Li *et al.* 2013).

3.8 Cancer hazard evaluation: Cancers not known to be associated with oncoviruses in HIV-1/AIDS populations.

3.8.1 Conjunctival cancer

Three early case-control studies from Africa (Ateenyi-Agaba 1995, Newton *et al.* 1995, Kestelyn *et al.* 1990, 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 and based on a total of 158 cases, reported increased relative risks of 12 to 24 for conjunctival cancer in HIV-1-positive populations (Newton *et al.* 2001, Waddell *et al.* 1996, Ateenyi-Agaba 1995, Kestelyn *et al.* 1990; 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) (Mbulaiteye *et al.* 2006). In addition, three large cancer registry linkage studies of people with AIDS or HIV-1 in the United States (Guech-Ongey *et al.* 2008, Frisch *et al.* 2000, Goedert and Cote 1995) 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.* (2003) 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) 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 by Guench-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.

3.8.2 Cofactors

While ambient ultraviolet light has been postulated as a cofactor (IARC 2012a), its interaction with HIV-1 status is unclear. No role for co-infection with human papillomavirus of the mucosal type has been identified, but a role for 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.

3.9 Cancer hazard evaluation: 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 (SEER 2015h). 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.

3.9.1 Overview of epidemiological studies

Twenty-two cohort studies and one case-control study were reviewed by IARC (2012) (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 Section 3.9.2.

Table 3-12. Summary of HIV/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

*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.
Source: IARC (1996), IARC (2012), Table 2.21, and studies since IARC 2012: Powles *et al.* 2009; Bedimo *et al.* 2009; van Leeuwen *et al.* 2009; Seaberg *et al.* 2010; Simard *et al.* 2010; Franceschi *et al.* 2010; Silverberg *et al.* 2011; Park *et al.* 2014; Raffetti *et al.* 2015; Castilho *et al.* 2015; Albini *et al.* 2013; Coghill *et al.* 2015; Crothers *et al.* 2011; Franzetti *et al.* 2013; Hleyhel *et al.* 2014; Levine *et al.* 2010; Sigel *et al.* 2012; Vogel *et al.* 2011.
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 6 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.* 2013a, Winstone *et al.* 2013) (see Section 4 for a discussion on the relationship between immunosuppression, CD4 cells and lung cancer).

3.9.2 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 or 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. Nevertheless, there are some differences between the profile of lung cancer observed in the HIV-1-positive population compared with cases in the general population; 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 are observed in fewer cases (6% to ~9%) (Chaturvedi *et al.* 2007, Engels *et al.* 2006b); small-cell lung cancer has a much stronger association with smoking than does adenocarcinoma (Chaturvedi *et al.* 2007, Engels *et al.* 2006b, Lubin and Blot 1984).

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 is an independent risk factor for lung cancer. Table 3-13 provides details on these studies and Figure 3-5 shows the risk estimates from these studies.

Table 3-13. Summary of HIV-1 cohorts 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.* 2006b 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 calculate risk estimates using extreme scenarios (100% smoking and double RR for lung cancer and smoking)
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 year/day; also conducted analysis or cumulative pack yr.
Shiels *et al.* 2010	Prospective cohort: Incidence ALIVE cohort (same as Kirk 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

Reference Location	Design/Population/ Enrollment dates	Smoking methods
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 bacteria pneumonia Sensitivity analysis overestimate 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 years, 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.

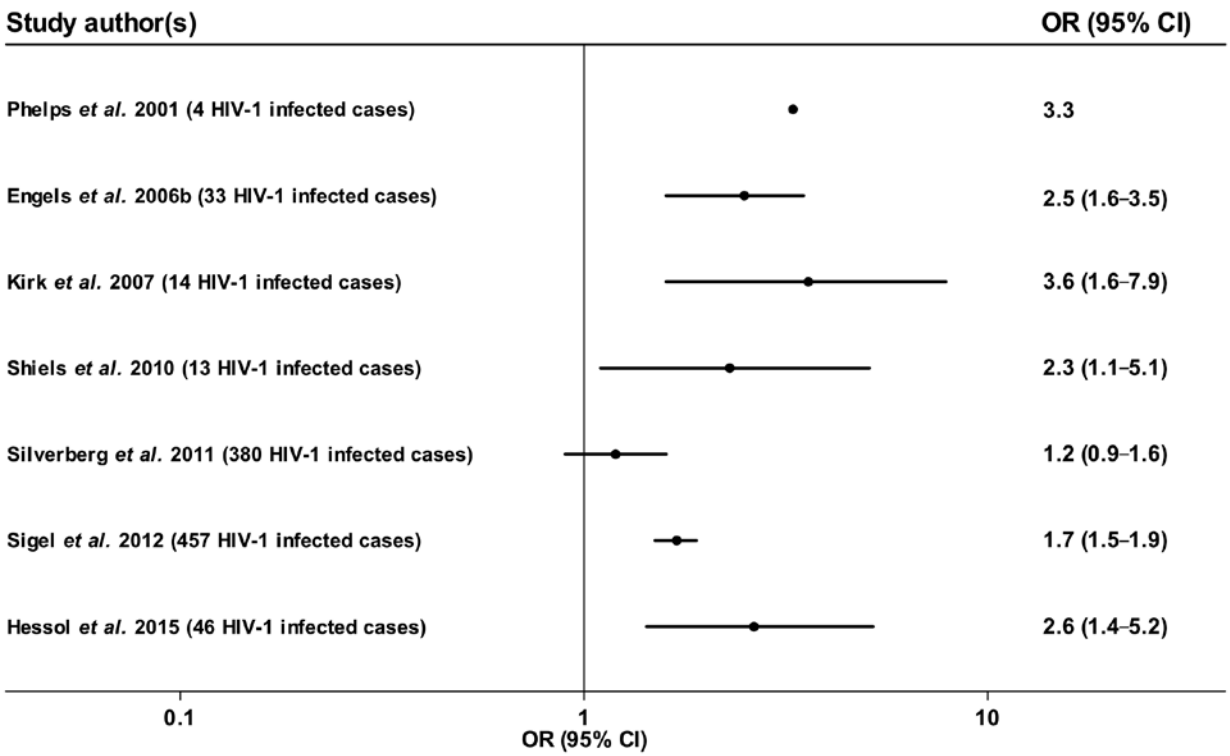

Figure 3-5: Relative risks for lung cancer from studies adjusting for smoking

Note: the forest plot doesn't contain the study by Chaturvedi *et al.* (2007) because it does 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.* (2006b) 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. 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 evidence for an association between HIV-1 infection and lung cancer. The fifth study that 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) (Kirk *et al.* 2007, Shiels *et al.* 2011, Hessol *et al.* 2015); (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.* 2011); (4) one study had large numbers of HIV-1 infected cases (Sigel *et al.* 2012); and (5) in a study which 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 number 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 explains 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, this study does not provide convincing evidence to negate the conclusion that the excess of lung cancer among HIV-1-infected populations cannot be entirely explained by smoking.

The combined analysis of the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) found the highest risk among HIV-1 patients with AIDS-related pneumonia damage in the entire cohort period and analysis restricted to the HAART era, suggesting that the HIV-1-related pulmonary damage and inflammation may be responsible for

the excess lung cancer although a case-control study nested 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) (Clifford *et al.* 2012).

3.10 Other cancer sites and cancer burden

As mentioned in the introduction, the NTP evaluation was based on the body of evidence from an authoritative evaluation by IARC, 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 cancers in the United States has increased in the HAART era as the population of HIV-1-infected individuals expands and ages (Shiels *et al.* 2011). 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.* 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.* Risk estimates for most cancer endpoints were between 1 and 2; 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 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 two-fold increased risk of non-AIDS related cancers not related to viral infection compared with the general population. A study in Denmark found find that HIV-1-infected individuals had almost three-fold 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 Shields meta-analysis cancers with elevated risks (such as leukemia and multiple myeloma) were not included. An Italian study (Franzetti *et al.* 2013) have also found increased in non-AIDS related cancers (as a group) as well as an increased 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 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.

3.11 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 *in utero* and postnatal gavage studies of 3′-azido-3′-deoxythymidine, and a mixture of 3′-azido-3′-deoxythymidine, lamivudine, and nevirapine in genetically modified F1 $p53^{+/-}$ mice. NTP (2013a,b) reported that 3′-azido-3′-deoxythymidine alone or in combination produced liver cancer in the male offspring. In another 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 2013c). 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 addition, a U.K. study of cancer outcomes among people with AIDS or HIV-1 was the first (to our knowledge) to report 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); two subsequent studies (Chao *et al.* 2012, Bruyand *et al.* 2015a) found no association between non-AIDS-defining cancers and nucleoside reverse transcriptase inhibitors treatment, but a marginal increase in anal cancer in association with the long-term administration of protease inhibitors.

3.12 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-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, Shiels *et al.* 2011a, Kesselring *et al.* 2011), which might account for some observed differences in risk over time. In addition, the time of starting and duration of antiretroviral treatment may 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 (Schneider *et al.* 2008, CDC 1992, CDC 1985). 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 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.

3.12.1 Infection-related cancers including AIDS-defining malignancies

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 virus-infected populations (also see accompanying monograph on Kaposi sarcoma 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 C or B are cofactors or confounders of the observed associations. In most studies the seroprevalence of hepatitis C or B among HIV-1/AIDS individuals is not measured, but in those that have measured Hepatitis C, individuals with Hepatitis C and cirrhosis were twice as likely to develop hepatocellular carcinoma than those co-infected with hepatitis C and HIV-1. Modest positive associations are found between HIV-1 and oral cancers; however, the heterogeneity of these cancers, as well as the unmeasured heterogeneity of risk factors, and potentially distinct etiologic pathways for oral 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 HPV 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 2012). 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 invasive 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 on 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 Cofactor	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		100	3–25	←→
Anus	HPV	> 90	9–350	←→
Kaposi sarcoma	KSHV	100	100–10,000s	↓
NHL (all)	EBV/KSHV	Varies by subtype*	10–300	Varies by subtype*
Hodgkin lymphoma (all)	EBV	> 80	4–38	↑
Oral cancer	HPV	65	2–4	←→
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 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.

3.12.2 Other cancers not known to be infection-related

There is consistent evidence of an up to 12-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 cofactor. 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; 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-analyses (Zhao *et al*. 2015) on six studies, published between 2003 and 2013, that collected data on cancer incidence through cancer registers 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). Some studies have a found a stronger risks for Merkel cell carcinoma suggesting a subset of the cancers may be infection related.

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4 Mechanistic and Other Relevant Data

It is clear that HIV-1-positive individuals are at an increased risk of developing cancer and that HIV integrates its DNA into hundreds of sites in the host genome (Maldarelli *et al.* 2014, Borges *et al.* 2014, 2013, IARC 2012). However, there is very little evidence that the transformed tumor cells harbor integrated HIV-1 proviruses, thus, generally ruling out the known direct carcinogenic mechanism of insertional activation of proto-oncogenes (Borges *et al.* 2013, IARC 2012a, Craigie and Bushman 2012, IARC 1996). 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-positive individuals, as well as in organ transplant patients (Shiels *et al.* 2011a, Engels *et al.* 2011, Bruyand *et al.* 2009, Grulich *et al.* 2007, Penn 1988, 1986, Penn and Starzl 1973), 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 infection of additional cells, it has no effect on infected cells and is a critical obstacle for curing HIV infection (Maldarelli *et al.* 2014). Studies of HIV-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 in specific genes that promote cell survival and expansion. Although, most studies have not shown evidence that HIV integration contributes directly to cell transformation and malignancy, a few studies have reported that a small number of lymphomas harbor HIV proviruses integrated at defined sites (Shiramizu *et al.* 1994, Herndier *et al.* 1992). Perhaps prior attempts to detect HIV DNA in cancers examined only a small portion of the HIV genome and missed HIV 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).

Approximately 70% of cancers in the HIV-1-positive population have a known infectious cause compared with only 12% in the HIV-1-negative population according to one estimate (Silverberg *et al.* 2009). HIV-1 infection is thought to increase the risk of cancer by indirect mechanisms, primarily through immunodeficiency and reduced immune surveillance (Silverberg *et al.* 2011, Silverberg *et al.* 2009). These and other possible mechanisms 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 (Shiels *et al.* 2011a, Engels *et al.* 2011, Shackelford and Pagano 2007). As noted in Section 3, co-infection with the oncogenic viruses Kaposi sarcoma 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

Increased incidences of non-AIDS-defining malignancies have been reported in both the AIDS and the HIV-1-only-infected populations and show that an important part of the cancer burden (approximately 29% in 34 U.S. states) occurs in people with HIV-1 only (Shiels *et al.* 2011a). In contrast to AIDS-defining malignancies discussed above, the estimated number of non-AIDS-defining malignancies increased by approximately 3-fold from the pre-HAART era (1991 to 1995) compared with the post-HAART era (2001 to 2005) and was mainly driven by the growth and aging of the AIDS population. 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).

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 cancer, liver cancer, and non-melanoma skin cancers) (Vaccher *et al.* 2014, Shiels *et al.* 2011a, Bedimo *et al.* 2009, Engels 2009, Silverberg *et al.* 2009, Patel *et al.* 2008, Frisch *et al.* 2000). The risk for these cancer types in the HIV-1+ 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, Engels 2009). 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, UV radiation) are thought to play a significant role in the excess cancer risk (Shiels *et al.* 2011a, Silverberg *et al.* 2011, Engels 2009, Silverberg and Abrams 2007).

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 suggest 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 (Silverberg *et al.* 2009, Grulich *et al.* 2007). 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 may have oncogenic effects via synergism with other oncogenic viruses, disruption of cell-cycle regulation, inhibition of tumor suppressor genes, promotion of chromosome instability, inhibition of DNA repair, and 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 of 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 complete story because the risk of these cancers remains elevated even after HAART therapy.

Kaposi sarcoma

HIV-1 co-infection, and to a lesser extent, iatrogenic immunosuppression, are important cofactors and increase the risk of developing Kaposi sarcoma in a Kaposi sarcoma virus-infected person by several orders of magnitude (see Section 3.2.3 and KSHV monograph). 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).

The number of cases of Kaposi sarcoma in the U.S. AIDS population declined from the pre-HAART era to the post-HAART era (see Section 3.2.3). However, intermittent HAART or interruptions of HAART for 3 months or more were associated with an increased risk of Kaposi sarcoma (Franceschi *et al.* 2008, Silverberg *et al.* 2007). HAART therapy may reduce the incidence of Kaposi sarcoma indirectly through improved immune surveillance, or directly by inhibiting tumor development (Silverberg *et al.* 2007, Sgadari *et al.* 2003). For example, protease inhibitors used in HAART inhibit KSHV replication and possess anti-angiogenic and other anti-tumor properties that can impair growth and persistence of Kaposi sarcoma (Gantt *et al.* 2014, 2011). 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 and are no longer declining (IARC 2012a, Shiels *et al.* 2011b).

Several large cohort studies in the United States and Europe have reported that current CD4+ cell count (significant trend for increasing relative risk with decreasing recent CD4+ count), current viral load (HIV-1 RNA), and absence of HAART are important risk factors for Kaposi sarcoma (Silverberg *et al.* 2011, Clifford and Franceschi 2009, Guiguet *et al.* 2009, Franceschi *et al.* 2008, Silverberg *et al.* 2007). In studies that reported CD4 levels or HIV-1 RNA, low CD4 or high viral levels were correlated with increased risk of Kaposi sarcoma (e.g., Silverberg *et al.* 2011, Clifford *et al.* 2005, Serraino *et al.* 2005, Mbulaiteye *et al.* 2003). 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, Patel *et al.* 2014, Hleyhel *et al.* 2013). These data strongly support HIV-induced immunosuppression and co-infection with Kaposi sarcoma virus as a primary mode of action for Kaposi sarcoma (see also Kaposi sarcoma virus monograph).

Non-Hodgkin lymphoma

Most cases of non-Hodgkin lymphoma are of the B-cell phenotype and are frequently associated with Epstein-Barr virus infection (IARC 2012a). The increased risk of non-Hodgkin lymphoma in HIV-1-positive patients compared with the general population is mainly due to chronic B-cell activation and impaired immunosurveillance against Epstein-Barr virus (Petrara *et al.* 2013). Chronic B-cell activation is a well-documented consequence of HIV-1 infection, and a significant association between B-cell activation-associated biomarkers (e.g., the CXCL13 chemokine and its receptor CXCR5, and miR-21) and AIDS-related non-Hodgkin lymphoma risks has been reported (Sekar *et al.* 2014, Hussain *et al.* 2013).

As with Kaposi sarcoma, non-Hodgkin lymphoma risk is increased in immunosuppressed populations and has been recognized as an AIDS-defining clinical condition since 1985 (IARC 2012a). The available evidence indicates that HIV-1-induced immunosuppression and depletion of CD4+ T cells results in dysregulated proliferation of B lymphocytes and enhancement of the oncogenic effects of infectious agents (IARC 2012a, Engels 2007). However, there is increasing evidence that HIV-1 may directly induce B-cell activation and malignant transformation via HIV-1 envelope glycoprotein gp120, or matrix protein p17, or by incorporation of CD40L expressed by activated T cells (Gloghini *et al.* 2013).

Although there are many subtypes of non-Hodgkin lymphoma, three have been specifically associated with HIV-1/AIDS. These include primary brain lymphoma, large-cell immunoblastic lymphoma, and Burkitt lymphoma (Gloghini *et al.* 2013, Engels 2007, Eltom *et al.* 2002). Incidences of primary brain lymphoma and diffuse large B-cell 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 virus 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 virus 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.

Temporal trends in the incidence rate and number of non-Hodgkin lymphoma cases during the pre- and post-HAART periods are similar to those reported for Kaposi sarcoma but declined less due to the higher background rate of non-Hodgkin lymphoma in the general population (see Section 3.3.3).The relationship between CD4 and/or HIV-1 RNA levels in populations receiving HAART can be shown by both the apparent correlation between the decline in 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 shown in several large cohort studies (Silverberg *et al.* 2011, Clifford and Franceschi 2009, Guiguet *et al.* 2009, Silverberg *et al.* 2007). These data strongly support HIV-1-induced immunosuppression and co-infection with Epstein-Barr virus as a primary mode of action (also see Epstein-Barr virus monograph).

Invasive cervical cancer

Cervical cancer can be regarded as a rare complication of human papillomavirus infection (Helmerhorst and Meijer 2002). 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 (IARC 2012a, Clifford and Franceschi 2009). The relative risk of cervical cancer in HIV-1-positive women varies from country to country (with higher risk observed in developing countries [see Section 3]), the magnitude of the excess risk is lower than for Kaposi sarcoma or non-Hodgkin lymphoma. HIV-1-positive women are more likely to be human papillomavirus-positive than HIV-1-negative women in various populations, more likely to have persistent and multiple infections, and 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; see also, e.g., Desruisseau *et al.* (2009) and reviews by De Vuyst *et al.* 2013, Denny *et al.* 2012, Adler 2010). Prior human papillomavirus infection may also increase the probability of HIV-1 infection (Einstein and Phaeton 2010).

Although an increased risk of cervical cancer has been reported in studies of immunosuppressed HIV-1/AIDS and organ transplant patients, these cases represent only a small fraction of all cervical cancer cases (Denslow *et al.* 2014, Dugue *et al.* 2013, Clarke and Chetty 2002, Penn 1988). Unlike other AIDS-defining malignancies, immunosuppression is important but not an essential factor in the development of cervical cancer (Dugue *et al.* 2013, Clarke and Chetty 2002 and see reviews by Denslow *et al.* 2014, Adler 2010). 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).

There is no clear association with CD4+ cell counts. Some studies reported that patients with a higher CD4+ cell count and receiving HAART had a lower risk of cervical cancer (Guiguet *et al.*

2009, Leitao *et al.* 2008, Patel *et al.* 2008) (Abraham *et al.* 2013), while others reported no apparent association with CD4+ cell counts (Chaturvedi *et al.* 2009, Biggar *et al.* 2007, Frisch *et al.* 2000). However, many of the studies that reported no significant effect of HAART on the risk of cervical cancer were ecological 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 on HAART (Dugue *et al.* 2013, Gravitt and Kirk 2010). Thus, the relationship of cervical cancer with HIV-1-related immunosuppression is difficult to establish because the association, compared with Kaposi sarcoma and non-Hodgkin lymphoma, is much weaker and the dose-response relationships with CD4+ levels are not as defined (Clifford and Franceschi 2009).

Frisch *et al.* (2000) reported that the overall risk for *in situ* cervical 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). 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-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 (Fernandes *et al.* 2015, Dugue *et al.* 2013).

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 (Kesselring *et al.* 2011, Reekie *et al.* 2010, Engels 2009, 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 remains 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 cancer (human papillomavirus), and liver cancer (hepatitis B and hepatitis C viruses) (Engels 2009, Gillison *et al.* 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 (Vaccher *et al.* 2014, Shiels *et al.* 2009). 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 *et al.* 2014, Ipp and Zemlin 2013). Thus, the increased incidence in HIV-1-positive individuals could reflect a high prevalence of known cancer risk factors, 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 cancer, liver cancer, and non-melanoma skin cancers.

Hodgkin lymphoma

Persons with HIV-1/AIDS of all age groups have a 4- to 38-fold increased risk of developing Hodgkin lymphoma compared with the general population (see Section 3). 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 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 2012c, 1997). 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 *et al.* 2009).

Although Hodgkin lymphoma incidence increases among people diagnosed with AIDS (see Section 3), some studies reported that incidence rates unexpectedly increased among the HIV-1-positive population during the HAART era (Engels 2009, Biggar *et al.* 2006, Frisch *et al.* 2001). 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 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 (Reekie *et al.* 2010, Clifford *et al.* 2009, Fontas *et al.* 2009). These studies reported increased risk with declining CD4+ count; however, the differences were not significant in another study (Clifford *et al.* 2009). Thus, the relationship between Hodgkin lymphoma risk and the degree of HIV-1-related immunodeficiency is perhaps more complex, but 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 are the most common (Ruiz 2010, Engels 2009, Kirk *et al.* 2007). Even with HAART treatment,

HIV-1 still increases inflammatory mediators, deregulates cell proliferation and apoptosis, and induces oxidative stress (Almodovar 2014) and the increased risk has not decreased substantially with HAART (Engels 2009, Kirk *et al.* 2007, Engels *et al.* 2006b, Clifford *et al.* 2005).

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 (Ruiz 2010, Engels 2009, Chaturvedi *et al.* 2007, Kirk *et al.* 2007, Engels *et al.* 2006b), while other studies reported an inverse relationship of CD4+ count and lung cancer incidence (Silverberg *et al.* 2011, Reekie *et al.* 2010, Guiguet *et al.* 2009). A meta-analysis of cancer incidence in HIV-1/AIDS patients and organ transplant patients reported similar risks of lung cancer in both populations and suggests a causal role for immunosuppression (Grulich *et al.* 2007). However, Grulich *et al.* suggested that CD4+ count at AIDS diagnosis might be an insensitive measure of immune deficiency. Two potential HIV-1-related immunologic mechanisms associated with lung cancer risk include repeated lung infections and chronic pulmonary inflammation (Ruiz 2010, Engels *et al.* 2008). 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). Kirk *et al.* (2007) reported trends of increased lung cancer risk with preexisting lung disease; however, the sample size was small and associations of lung cancer with preexisting lung disease in HIV-1-positive populations have not been fully investigated.

Other possible risk factors have been suggested; however, experimental support is limited for all of them. These include different patterns of tobacco use (e.g., heavier smoking or smoking at an earlier age); illicit drug use that causes chronic lung damage; 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 (Kirk *et al.* 2007, Wistuba *et al.* 1998, el-Solh *et al.* 1997). 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. A possible mechanism of HIV-1-induced genomic instability is an interaction between HIV-1 and endogenous retrotransposable type 1 long-interspersed nuclear (L1) elements (Jones *et al.* 2013). This study showed that HIV-1-infection enhanced L1 retrotransposition in an immortalized line of human T lymphocytes (Jurkat cells) and resulted in accumulation of L1 DNA in primary CD4+ lymphocytes.

Anogenital and oral cancers

The HIV-infected population has an increased risk for all known human papillomavirus-associated cancers relative to the general population (Gillison 2009). 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. Anal cancer and anal interepithelial 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). The risks of anal interepithelial 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).

However, since the advent of HAART therapy, there has been no consistent reduction in anal interepithelial neoplasia/anal cancer incidence as might be expected if immunosuppression was an overriding factor (Engels 2009, Gillison 2009, Cameron et al 2008, Chin-Hong and Palefsky 2002). 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 interepithelial 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 interepithelial neoplasia I lesions to anal interepithelial neoplasia II, anal interepithelial neoplasia III, and finally to cancer. Thus, HAART therapy would not be expected to affect the natural history of anal interepithelial neoplasia II or anal interepithelial 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). 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.

The evidence for the effect of immunosuppression on the risk of oral cancers has been inconsistent, with some studies reporting higher risk among those with lower CD4 counts (Engels *et al.* 2008; Clifford *et al.* 2005; Silverberg *et al.* 2011) and others reporting reduced risk with reduced CD4 counts (Chaturvedi *et al.* 2009). The role of HAART on the risk of oral 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 recent practice in high income countries is to provide HAART to those with higher CD4 cell counts (Beachler *et al.* 2014).

Liver cancer

HIV-associated immunosuppression may be important in modulating the hepatotropic virus driven progression of liver disease (see Section 3.6). Among HCV-infected individuals,

coinfection with HIV is associated with increased risk of chronic liver disease and hepatocellular carcinoma (Mallet *et al.* 2011, Graham *et al.* 2001). In addition, the course of hepatitis C virus infection is more aggressive and the prognosis poorer among HIV-1-positive than HIV-1 negative populations (Nunnari *et al.* 2012, Gelu-Simeon 2014, Sahasrabuddhe 2012).

In addition to potential indirect effects on hepatocellular carcinoma risk through improvements in immune reconstitution and survival, HAART is known to have some direct hepatotoxic effects, which are amplified among HIV-positive patients chronically infected with HBV or HCV (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 (Feeney and Mallon 2011b, Joshi *et al.* 2011, Bongiovanni and Tordato 2007).

Non-melanoma skin cancers

Non-melanoma skin cancers include two very common subtypes, basal-cell and squamous-cell carcinoma, and two very rare subtypes, Merkel cell and sebaceous carcinoma (Engels 2009). Chronic exposure to solar UV radiation is a major risk factor for all skin cancer subtypes. Although many cancer registries do not include basal-cell and squamous-cell subtypes, the available data indicate that immunosuppressed transplant patients and HIV-1+ individuals have an increased risk of all subtypes of non-melanoma skin cancer. However, the risk was higher in transplant recipients than in people with HIV-1/AIDS and while most cases in transplant recipients were squamous-cell carcinoma, basal-cell carcinoma is the primary subtype in the HIV-1/AIDS and general population (IARC 2012, Grulich *et al.* 2007). Some data suggest that immunosuppression may alter the phenotype of non-melanoma skin cancer to a more aggressive squamous-cell skin cancer (Engels 2009). The elevated risk of non-melanoma skin cancer in the HIV-1+ population is largely limited to Caucasians and suggests that exposure to solar UV radiation is an important cofactor as in the general population. Merkel cell carcinoma is primarily attributed to Merkel cell polyomavirus and HIV-1-induced immunodeficiency increases the risk (see Merkel cell polyomavirus Monograph). HIV-1-induced immunodeficiency could possibly increase the risk for basal-cell and squamous-cell carcinoma by reduced immunosurveillance for malignant cells.

4.2.3 Evidence that HIV-1 causes cancer

As discussed in the Overview and Introduction section, it is often difficult to identify oncogenic viruses by applying stringent criteria such as Hill's epidemiological considerations for causality (Moore and Chang 2010, zur Hausen 2001, Moore and Chang 2014). HIV-1 DNA is not generally found in tumor cells, there is no evidence that HIV-1 or any of its transcripts can transform cells, and there is no evidence that the malignant phenotype depends on the continuous expression of viral oncogenes (IARC 2012a). This is in contrast to viruses that are directly oncogenic. Nevertheless, the epidemiological data (see Section 3) provide support for several of the Hill considerations including strength of association (high risk estimates), consistency across studies, specificity (especially for AIDS-defining cancers), temporality (virus infection precedes the cancer in prospective studies), and a dose-response effect based on HIV-1 titer or CD4+ levels and serological evidence of HIV-1 infection. Studies conducted pre- and post-HARRT also showed significant changes in cancer incidence, particularly for Kaposi sarcoma and non-Hodgkin lymphoma.

4.3 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-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 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 (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 on cancer incidence through immune dysregulation, a direct oncogenic effect of HIV-1, activated inflammatory pathways, and 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 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.

Epidemiological data provide support for a causal role of HIV-1 in carcinogenesis based on strength of association, consistency, specificity, temporality, and dose response.

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5 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, invasive cervical cancer (see Table 5.1); Hodgkin lymphoma, invasive anal cancer, genital cancers (see Table 5.2); conjunctival cancer, non-melanoma skin cancer, and lung 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 liver cancer and oral cancer (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.

Table 5-1. Preliminary level of evidence recommendations 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 to 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).

Cancer	Level of evidence	Evidence and viral cofactors
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 significant 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.
Invasive cervical cancer	**Sufficient**	***Epidemiological evidence*** Consistent evidence of increased risk Statistically significant elevated RR found in almost all (at least 17) cohort studies Increased risks 2 to 25 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 to 50) compared to HIV-1-infected populations (mostly ranged from ~3 to 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 herpesvirus; mRR = relative risk from a meta-analysis; RR = relative risk.
[a]Numbers in epidemiological studies based on IARC 1996, 2012a.

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 invasive 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, thus, increasing the risk of opportunistic infections, particularly by oncogenic viruses as seen with these malignancies.

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. Preliminary level of evidence conclusions 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 to 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-Hodgkin lymphoma cases co-infected with EBV.
Anal cancer	**Sufficient**	***Epidemiological evidence***
		Consistent evidence of increased risk
		Statistically significant RR (mostly ranging from 9 to 39 with a few studies with risk ranging from 60 to ~350) found in at least 19 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

Cancer	Level of evidence	Evidence and viral co-factors
Genital (vulvar, vaginal, penile) cancers	**Sufficient**	***Epidemiological evidence*** Vaginal 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 to 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
Oral cancer	**Limited**	***Epidemiological evidence*** Consistent evidence of modest increased risk across various groupings of oral cancers (e.g., oropharynx, oral cavity/pharyngeal, oral cavity, or lip, tongue, tonsil) in at least 19 studies (most risks between 2 and 4) compared to general population based primarily on HIV cohort registry studies. mSIR = 2.3 (1.65 - 3.25) N = 238 HIV-1-infected cases from 4 studies (Grulich *et al.* 2007) Most studies do not account for disease and risk factor heterogeneity which suggest distinct tumor types – HPV-associated and HPV-nonassociated; in additions, unmeasured variations in sexual behaviors and other risk factors (such as smoking) across cohorts which influence the proportion of HPV-associated cancers may account for the moderate risk of oral cancers. Inconsistent evidence of the effect of immunosuppression and the effects of HAART on risk of oral 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 to 16) in at least 40 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 (Shiels

Cancer	Level of evidence	Evidence and viral co-factors
		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 immune deficiency syndrome; EBV = Epstein-Barr virus; 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 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. Preliminary level of evidence conclusions 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 12 to 15) 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 1.5–6 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	**Sufficient**	Consistent evidence for increase risk At least 48 cohort studies, most of which reported statistically significant RRs (between 1.5–6). 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 all the excess risk: 7/8 cohort studies that controlled for smoking or modeled bias from smoking found elevated risks for smoking; 6/7 were statistically significant.

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, Shiels *et al.* 2011a, Engels 2009, 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). Several possible risk factors for lung cancer with HIV-1 include different patterns of tobacco use (e.g., heavier smoking or smoking at an earlier age in the HIV+ population); illicit drug use that causes chronic lung damage; interaction of the effects of HIV-1 with tobacco use; lower levels of antioxidants in HIV-1-positive individuals; 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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6 References

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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).

Cofactor: 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 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 3 or more HIV drugs from at least 2 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 amount 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) that the body settles at 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.

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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
DNA	deoxyribonucleic acid
DLBCL	diffuse large B-cell lymphoma
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
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVMA	HIV Medicine Association
HPV	human papillomavirus
HUD	Department of Housing and Urban Development
IARC	International Agency for Research on Cancer
IFA	immunofluorescence assay
HAART	highly active antiretroviral therapies

HR	hazard ratio
HHS	Department of Health and Human Services
IgG	immunoglobulin G
IgM	immunoglobulin M
IRR	incidence rate ratio
KSHV	Kaposi sarcoma 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 Toxicolog 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

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.

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.

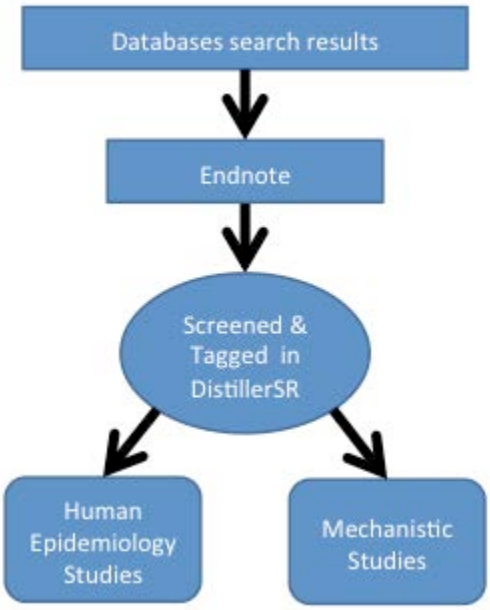
The large and complex body of literature for HIV-1 was searched using narrowing terms for the relevant major topics within the bibliographic database. The results were then processed in EndNote to remove duplicates before being transferred to DistillerSR for screening. Table 1 highlights the general 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

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.

Figure A-1: Literature Processing Flow



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 (187) or Mechanistic literature (81).

Search strings for HIV searches

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 below)

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])

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 below)

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] O □ 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

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Part 2

Draft Profile

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Human Immunodeficiency Virus Type 1

CAS No.: none assigned

Known to be a human carcinogen[1]

Also known as HIV-1

Carcinogenicity

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, invasive cervical cancer, Hodgkin lymphoma, invasive anal cancer, genital cancers (vaginal/vulvar and penile cancers), conjunctival eye cancer, non-melanoma skin cancer, and lung cancer, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence for an association between HIV-1 infection and oral and liver cancer.

Discussion of these cancer end points is organized based on whether they are acquired immunodeficiency syndrome (AIDS)-defining cancers (i.e., cancers that are considered to be diagnostic criteria for AIDS) or are infection-related non-AIDS-defining cancers (i.e., caused by opportunistic coinfection with other viruses) (CDC 1992, Gopal *et al.* 2014, Patel *et al.* 2014). The three AIDS-defining cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical carcinoma) and the majority of the non-AIDS-defining cancers (Hodgkin lymphoma, anal cancer, genital cancers, oral cancer, and liver cancer) have been shown to be associated with coinfection with other viruses. Viral coinfections have not been identified for lung cancer, non-melanoma skin cancer, or conjunctival eye cancer; however, a role for viral coinfection is likely for one type of non-melanoma skin cancer (Merkel cell carcinoma).

The excess cancer burden of HIV-1-related cancers in the United States in 2010 was estimated to be over 3,900 cases (Robbins *et al.* 2015), constituting an important public health impact. Several studies have reported increased risks for non-AIDS-defining cancers (as a group) as well as for other specific cancer endpoints in recent years (Shiels *et al.* 2009, Albini *et al.* 2013, Helleberg *et al.* 2015, Franzetti *et al.* 2013), and the spectrum of endpoints not thought to be infection related has expanded. However, approximately 90% of the HIV-1-related excess cancers identified in the Robbins *et al*. study are for endpoints described in this profile.

AIDS-Defining Cancers

There is credible evidence for associations between HIV-1/AIDS and Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer based on consistent findings of statistically significant moderate to very high increased risk in numerous epidemiological studies in different populations. The evidence for each cancer end point comes primarily from over 30 cohort studies with relatively large numbers of HIV-1/AIDS cases, in which HIV-1/AIDS increased the risk of Kaposi sarcoma by 100s- to 10,000s-fold, the risk of non-Hodgkin lymphoma by 10- to 300-fold, and the risk of invasive cervical cancer by 3- to -25 fold (IARC 2012, and see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph) in most of the studies. Although many of the studies compared cancer incidence between HIV-1/AIDS

[1]NTP preliminary listing recommendation proposed for the RoC.

patients and the general population, the overwhelming strength of the associations of these cancers with HIV-1/AIDS eliminates concern about potential confounding by non-viral agents.

These data support a mechanism of carcinogenesis in which an HIV-1-impaired immune system cannot adequately suppress or clear oncogenic viruses, resulting in an increased risk of infection-related cancer. The oncogenic viruses involved are Kaposi sarcoma herpesvirus for Kaposi sarcoma, Epstein-Barr virus for non-Hodgkin lymphoma, and oncogenic human papillomaviruses for invasive cervical cancer. HIV-1-related immunosuppression results from a progressive depletion of $CD4^+$ T lymphocytes, which serve a helper function in cell-mediated immunity (Clifford and Franceschi 2009). Dose-response relationships have been observed between low CD4 counts and increased risk of Kaposi sarcoma (e.g., Silverberg *et al.* 2011, Clifford *et al.* 2005, Serraino *et al.* 2005, Mbulaiteye *et al.* 2003). Silverberg *et al.* (2011) also reported a positive dose-response relationship between high HIV-1/RNA levels and an increase in risk of Kaposi sarcoma. Depletion of CD4 cells has also been associated with an increase in risk of non-Hodgkin lymphoma (IARC 2012a, Engels 2007), but no clear association with decreasing CD4 cell counts has been observed for invasive cervical cancer.

Highly active antiretroviral therapy (HAART), which reduces the level of HIV-1 in the blood, has dramatically decreased the risk of Kaposi sarcoma and non-Hodgkin lymphoma, supporting the link between HIV-1 infection and increased risk of these cancers. However, the risks remain higher among HIV-1-infected individuals than among non-HIV-1-infected individuals (Shiels *et al.* 2011a,b). The effect of HAART is less clear for invasive cervical cancer; some but not all studies have found decreased risks since the advent of HAART. The excess of invasive cervical cancer in HIV-1-positive individuals, due in large part to increasing survival and numbers of women with HIV-1/AIDS, remains a public health concern. Immunosuppression alone clearly does not completely explain the incidences and spectrum of cancers observed among HIV-1-infected individuals either before or after the advent of HAART. Although HAART improves immune function and lowers HIV-1 viral load, it only partially normalizes the increased inflammation associated with HIV-1 infection, suggesting that activated inflammatory pathways contribute to the increased cancer risk (Borges *et al.* 2013, 2014).

Non-AIDS-Defining Cancers Thought To Be Infection-Related

There is credible evidence of an association between HIV-1/AIDS and Hodgkin lymphoma, invasive anal cancers, vaginal/vulvar cancer, and penile cancer, based on consistent findings of statistically significant moderate to high increased risks in numerous epidemiological studies in different populations.

The evidence for Hodgkin lymphoma comes primarily from over 40 cohort studies, some with large numbers of HIV-1-infected patients, all of which reported positive associations, with excess risk of 4- to 38-fold (IARC 2012, and see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph). The risks of Hodgkin lymphoma are strongly associated with immunosuppression, as measured by CD4 cell counts, and similar to AIDS defining cancers, result in increases in infection-related (i.e., Epstein-Barr virus) cancer (Silverberg *et al.* 2007, Clifford and Franceschi 2009). However, the risk of Hodgkin lymphoma has increased with the advent of HAART, in part because of the growth and aging of the HIV-1-positive population. In addition, the toxicity of some of the antiretroviral drugs used in HIV-1/AIDS treatment may be a cancer risk factor (Borges *et al.* 2014).

Invasive anal and genital cancers are related to co-infection with human papillomaviruses. Over 20 cohort studies of HIV-1 infected people or people with AIDS have reported an increased

risk (mostly 10- to 39-fold) for invasive anal cancer (IARC 2012, and see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph). The risk of invasive anal cancer is also related to low CD4 cell count (Silverberg *et al.* 2007, Chaturvedi *et al.* 2009, Clifford and Franceschi 2009, Hessol *et al.* 2009). The evidence for the rarer cancers of the vagina/vulva and penis is based on 6 to 7 studies, all of which reported positive associations, with excess risk mostly ranging from 4- to almost 30-fold (Mbulaiteye *et al.* 2006, Newnham *et al.* 2006, Long *et al.* 2008, Patel *et al*. 2008, Chaturvedi *et al.* 2009, Dal Maso *et al.* 2009, Simard *et al.* 2010, Franzetti *et al.* 2013, Park *et al.* 2014, Raffetti *et al.* 2015). In general, similar risk estimates for penile cancer were found across different HIV-1 risk groups (i.e., injection drug users, heterosexuals, those with unknown risk factors, and men having sex with men), which may help rule out potential confounding by lifestyle behaviors (Chaturvedi *et al.* 2009). In one study, the risk of vaginal/vulvar cancer was associated with CD4 levels at AIDS diagnosis, and statistically significant increasing trends in risk were observed across the ten-year period from five years before to five years after AIDS onset, suggesting an association with prolonged immunosuppression (Chaturvedi *et al.* 2009). The relationship between cancer risk for these endpoints and HAART is unclear.

There is limited evidence for a credible association between HIV-1 infection and oral cancer, based on evidence from at least 19 cohort studies showing an association (most studies reported an excess risk of 2 to 4) of HIV-1 with oral cancers as a group (oral-cavity and oropharyngeal cancers) and specific oral cancers (such as cancer of the tongue and lip) (see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph). The heterogeneity of disease, the unmeasured heterogeneity of risk factors, and the potentially distinct etiologic pathways for oral cancer subtypes complicate the interpretation of these modest risks. Based on differences in risk-factor profiles and the high prevalence of HPV DNA in oropharyngeal cancers, distinct pathways for HPV-related and non-HPV-related oral cancer have been hypothesized (Gillison *et al.* 2008). Differences in the transmission of HPV between males and between males and females may explain the modest increase in risk measured in the HIV/AIDS cohorts, as cohorts may differ with respect to common sexual behaviors and other risk factors related to the proportion of HPV-related oral cancer (Beachler and D'Souza 2013). Tobacco smoking and alcohol consumption may also be potential confounders; tobacco smoking is higher among HIV-1 populations than in the general population, which is the comparison group in most studies. In the only study identified that evaluated tobacco smoking, HIV-1 infection, and oropharyngeal cancer in HIV-1-positive and negative individuals, controlling for smoking resulted in a reduction in the SIR from 1.9 to 1.4 (Silverberg *et al.* 2011). The evidence for the effect of immunosuppression on the risk of oral cancer is inconsistent, with some studies reporting higher risk among individuals with lower CD4 cell counts (Clifford *et al.* 2005, Engels *et al.* 2008, Silverberg *et al.* 2011, Beachler *et al.* 2014) and some reporting lower risk (Chaturvedi *et al.* 2009).

Epidemiological studies (at least 40 cohort studies) provide limited evidence of an increased risk (2- to 16-fold) of liver cancer (hepatocellular carcinoma, or HCC) among HIV-1-positive individuals (and see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph). In the United States, hepatitis B virus (HBV) and hepatitis C virus (HCV) are more common among HIV-1-infected individuals than in the general public. Although evidence suggests that progression to end-stage liver disease occurs faster in individuals coinfected with HIV-1 and HBV/HCV, there is limited evidence to assess whether HIV-1 is a surrogate for HBV/HCV exposure or whether HIV-1 contributes to increased cancer

incidence through immunosuppression that facilitates the oncogenic effects of HBV and HCV. Some studies investigating the risk of HCC among individuals coinfected with HIV-1 and HCV have found no increased risk associated with HIV-1 coinfection, arguing against a causal role for HIV-1 (Tradati *et al.* 1998, McGinnis *et al.* 2006, Kramer *et al.* 2005, Henderson *et al.* 2010, Di Benedetto *et al.* 2013). However, a recent cohort study found a higher risk of HCC in men with hepatitis C and cirrhosis than in those infected only with HIV-1 (Di Benedetto *et al.* 2014). Furthermore, several studies have found the risk of HCC to be associated with the degree of immunosuppression at HIV-1 diagnosis, as measured by CD4 cell count (Engels *et al.* 2008, Silverberg *et al.* 2011, Vogel *et al.* 2011, Kramer *et al.* 2015). Overall, the extent to which coinfection with HIV-1 increases the risk of HCC with HBV or HCV infection or with alcohol use remains to be clearly established.

Non-AIDS-Defining Cancers Not Known To Be Infection-Related

Epidemiological studies provide credible evidence for associations between HIV-1/AIDS and conjunctival eye cancer, non-melanoma skin cancer, and lung cancer, based on consistent findings of statistically significant moderate to high increased risks in numerous epidemiological studies in different populations.

The evidence for an association of HIV-1 with conjunctival eye cancer comes from at least four cohort studies and four case-control studies (IARC 2012, and see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph) that reported positive associations, with risks ranging between 12 and 15 in most of the studies.

Increased risks of non-melanoma skin cancer associated with HIV-1 have been reported in over 15 studies, mostly ranging between 1.5- and 6-fold, but up to 20-fold in a few studies (see section 3, Human Cancer Studies, in the Cancer Hazard Evaluation Component of the NTP monograph). A meta-analysis (Zhao *et al*. 2015) based on six cancer registry linkage cohort studies of people with HIV-1/AIDS published between 2003 and 2013 reported a meta-relative risk of 2.76 (95% confidence interval = 2.55 to 2.98). Additional support for an association comes from a cohort study within the U.S. Military HIV Natural History Study, which found that HIV-1 RNA was associated with an increased risk of non-melanoma skin cancer (Crum-Cianflone *et al.* 2015). The most common form of non-melanoma skin cancer is basal-cell carcinoma. A rare form of basal-cell carcinoma, Merkel cell carcinoma, is caused by Merkel cell polyomavirus and has been found at an increased incidence in HIV-1-infected individuals (Engels *et al.* 2002). However, the contribution of Merkel cell polyomavirus to the increased risk of non-melanoma skin cancer associated with HIV-1 is not known.

A positive association between HIV-1 and lung cancer has been reported in the majority of studies (at least 48), most of which report statistically significant increased risks of approximately 1.5- to 6-fold. It has been suggested that tobacco smoking could explain the excess risk, because many of these studies compared lung cancer incidence between HIV-1-infected cohorts and the general population, where the prevalence of smoking is typically much lower (20% to 40%) than among HIV-1-infected individuals (40% to 80%). However, almost all studies that controlled for smoking (Phelps *et al.* 2001, Engels *et al.* 2006, Kirk *et al.* 2007, Shiels *et al.* 2010, Sigel *et al.* 2012, Hessol *et al.* 2015) or modeled smoking bias (Charturvedi *et al.* 2007) found at least 2-fold increased risks of lung cancer incidence or mortality, most of which were statistically significant. In addition, one study (Silverberg *et al.* 2011) reported smoking-adjusted statistically significant increased risks among those HIV-1-infected subjects with the highest viral loads (HIV-1 RNA titer > 10,000 copies/mL) or lowest CD4 cell levels

(≤ 200 cells/μL, the cut-off CD4 level for an AIDS diagnosis), although not among the total HIV-1-infected population. The evidence indicates that tobacco smoking does not explain all of the excess risk of lung cancer in HIV-1 populations, and therefore supports a credible association between HIV-1 infection and increased lung cancer risk.

Mechanisms of carcinogenicity for these non-infection-related non-AIDs-defining cancers are unclear but (as with the AIDS-defining cancers) may be related to immunodeficiency and inflammation. In addition, traditional risk factors (e.g., smoking, alcohol abuse, exposure to ultraviolet radiation, and age) may play a primary role in or contribute to the excess of non-AIDS-defining cancers (Silverberg and Abrams 2007, Engels 2009, Shiels *et al.* 2011a, Borges *et al.* 2014). There is emerging evidence for a direct oncogenic effect of HIV-1 and some of its proteins. For example, some studies show that plasma HIV-1 viral load is independently associated with increased risk of cancer and that the HIV-1 envelope glycoprotein gp120, matrix protein p17, tat, and Vpr proteins may have oncogenic effects (Bruyand *et al.* 2009, Guiguet *et al.* 2009, Gloghini *et al.* 2013, Borges *et al.* 2014).

Biological Properties

HIV-1 is an enveloped single-stranded RNA retrovirus of the subfamily *Orthoretrovirinae* and genus *Lentivirus* (IARC 1996, 2012). 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.

Lentivirus infections are typically characterized by a long delay before emergence of symptoms (IARC 1996, 2012, DHHS 2015). HIV-1 predominantly infects CD4 cells, and also infects other cells of the immune system, including B cells, monocytes, macrophages, and follicular dendritic cells (IARC 1996, 2012). The immune system responds with increased production of CD8 (killer) T cells and B-cell antibodies that kill infected CD4 cells and other white blood cells with HIV-1 on their cell surface. CD4 cells are also killed by viral replication and disruption of cell regulation. After an initial peak of infection, the amount of HIV-1 in the peripheral blood is reduced (IARC 1996, 2012, CDC 2014c). The virus can then remain at low levels for 2 to 25 years, averaging about a decade, and can evade immune detection by several mechanisms, including production of proteins that prevent the immune system from detecting the virus.

Detection

HIV-1 was first identified as the virus associated with acquired immune deficiency in 1983. It has been detected primarily in blood and sexual fluids (semen and vaginal secretions) and in very low concentrations in other body fluids, including saliva, urine, sweat, and tears (unless they have been contaminated by blood or sexual fluids) (IARC 1996, 2012). The most common detection methods have been based on detecting anti-HIV-1 antibodies by enzyme-linked immunosorbent assay, with confirmation by laboratory-based Western blot immunoassay or immunofluorescence assay for HIV-1 antibodies (CDC 1989). HIV-1 antibodies typically are not measurable by these methods until one to three months after infection (Hecht *et al.* 2011). A number of more rapid and sensitive methods have been developed for screening and confirmation of HIV-1 antibodies (Cornett and Kirn 2013, CDC 2014a). Infections can also be detected by measuring HIV-1 antigens (p24), HIV-1 RNA (*gag*, *env*, *pol*), or, if antibody

detection gives indeterminate results, by measuring HIV-1 antigens or RNA from *in vitro* culture of the virus (IARC 1996, 2012, Cornett and Kirn 2013). RNA-based detection methods can measure HIV-1 viral load, and some methods can use dried blood samples (Smit *et al.* 2014).

Exposure

A significant number of people living in the United States are exposed to HIV-1. The current U.S. prevalence of HIV-1 infection is approximately 1.2 million people, of whom an estimated 13% are unaware of their infection status.

Transmission

HIV-1 infection can be transmitted both horizontally and vertically (from mother to child). Horizontal transmission occurs primarily during sexual activity (oral, anal, or vaginal), when HIV-1 in infected sexual fluids crosses mucous membranes to enter the bloodstream. Somewhat less frequently, infection can occur by direct blood-to-blood transmission, primarily via sharing of needles among injection drug users or more rarely by percutaneous transmission via, for example, needlestick injury or the transfusion of infected blood (depending on the availability of effective blood supply screening programs) (IARC 2012). Contact of non-sexual mucous membranes or non-intact skin with infected blood or body fluids in, for example, occupational healthcare or first-responder settings may also increase exposure and the potential risk of HIV-1 transmission (CDC 1987, Ippolito *et al.* 1999, Leiss *et al.* 2006); however, the risk of infection from percutaneous or mucous-membrane exposure is estimated to be less than 1% (Cardo *et al.* 1997). Transmission from HIV-1-infected mothers to children occurs *in utero* and via contamination of the child's mucous membranes during birth or via infected breast milk during lactation.

The two primary behavioral risk factors for transmission in most developed countries are the practice of unprotected sex, particularly unprotected anal sex, and the sharing of drug needles. Other risk factors for HIV-1 infection 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 of other sexually transmitted diseases does not always result in decreased HIV-1 infection rates (reviewed by Ng *et al.* 2011). Other risk factors include circumcision, hormonal factors, and host immune and genetic factors (IARC 1996, 2012).

Studies of HIV-1 and AIDs incidence

Approximately 50,000 new HIV-1 infections are estimated to occur in the United States each year (CDC 2015b). Although the incidence of new HIV-1 infections has remained stable over recent years, incidence varies considerably by risk group; men who have sex with men account for about 63% of new infections, injection drug users for 8%, and women for about 20% (CDC 2012, 2015b). HIV-1 infection status can be confirmed by standardized testing protocols such as those recommended by the Centers for Disease Control and Prevention (CDC 2006). AIDS typically results from long-term untreated HIV-1 infection. Approximately 1.2 million people in the United States have been diagnosed with AIDS since the start of the epidemic in 1981, when the first patients with a newly identified syndrome of acquired immunodeficiency were reported; 26,700 people were newly diagnosed with AIDS and 47,350 with HIV-1 in 2013. A total of approximately 660,000 people with an AIDS diagnosis have died since the start of the epidemic. About half of HIV-1 infections are among men who have sex with men.

Diseases (Non-Cancer), Prevention, and Treatment

The World Health Organization (WHO 2007) classifies four clinical stages of infection from primary HIV-1 infection to AIDS. The CDC case definition for AIDS (CDC 1992, 1999) includes over 20 opportunistic infections or related conditions or a CD4 cell count of less than 200/μL and results in impairment of immune function (CDC 2015c). Among non-cancer diseases associated with HIV-1 infection, the most common are opportunistic infections, including candidiasis, pneumocystis pneumonia (caused by *Pneumocystis jirovecii*), cytomegalovirus disease, tuberculosis, toxoplasmosis, histoplasmosis, mycobacterium avian complex, cryptococcosis, and cryptosporidiosis. A number of AIDS-related diseases are associated with viruses or other infections (e.g., human papillomavirus) (IARC 1996, 2012, CDC 2015c). Some chronic conditions (e.g., HIV-1-associated nephropathy) more common among HIV-1-infected than non-infected people may be due in part to long-term treatment with antiretroviral drugs, rather than to HIV-1 infection *per se* (Feeney and Mallon 2011).

With respect to prevention, behavioral risk reduction strategies include education about safer sex practices (e.g., abstinence, consistent condom use, and testing for HIV-1 status), education about the risk of infection from mucous membrane, percutaneous, and intravenous contact with infected fresh blood, and the use of clean needles, particularly among high-risk populations, including sex workers, injection drug users, and infected pregnant mothers (CDC 2015a).

Effective screening of the blood supply and increased implementation of HIV-1 testing programs using rapid tests have reduced infection rates (CDC 2006). Short-term post-exposure prophylaxis can be instituted to prevent the establishment of HIV-1 infection (CDC 2014c), and pre-exposure prophylaxis is now recommended for specific at-risk populations (CDC 2014b). Mother-to-child HIV-1 transmission risk has been greatly reduced by administration of antiretroviral drugs to the mother beginning before labor and continuing through breastfeeding (Newell and Thorne 2004) and to the infant in the immediate postnatal period and up to 14 weeks among breastfed infants, combined with Cesarean delivery in some populations (UNAIDS 2013).

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 inhibitors, and non-nucleoside reverse-transcriptase inhibitors, which are designed to block different steps in the HIV-1 replication cycle (NIAID 2013). Combinations of these drugs (e.g., protease inhibitors and nucleoside reverse-transcriptase inhibitors) (called highly active antiretroviral therapy or combination antiretroviral therapy) are now incorporated into standard treatment guidelines (e.g., DHHS 2015).

A substantial international effort to develop an effective vaccine for HIV-1 has proved challenging (Wang *et al.* 2015), and no prophylactic or therapeutic vaccine is currently available (NIAID 2015). The National Institute of Allergy and Infectious Diseases website provides updated information on HIV vaccine research.

Regulations

Bureau of Prisons (BOP)

The BOP manages infectious diseases in the confined environment of a correctional setting through a comprehensive approach that includes HIV-1 testing.

The BOP may place an inmate who tests positive for HIV-1 in controlled housing status when there is reliable evidence that the inmate may engage in conduct posing a health risk to another person.

Victims of severe forms of human trafficking in federal custody shall receive necessary medical care and other assistance, including free optional testing for HIV-1 and other sexually transmitted diseases in cases involving sexual assault or trafficking into the sex industry.

Department of Defense (DoD)

If required by an agreement or local requirements, HIV-1 testing for deployment of contractors authorized to accompany the force in applicable contingency operations must occur within 1 year before deployment. The Combatant Command surgeon should be consulted in all instances of HIV-1 seropositivity before medical clearance for deployment.

Military health system personnel who provide or coordinate medical care for victims of sexual assault under the Sexual Assault Prevention and Response Program are required to consult with the victim, once clinically stable, regarding further healthcare options, including testing, prophylactic treatment options, and follow-up care for possible exposure to HIV-1 and other sexually transmitted diseases or infections.

Department of Health and Human Services (DHHS)

Designated states under the Substance Abuse Prevention and Treatment Block Grant program (i.e., any state whose rate of cases of AIDS is 10 or more per 100,000 individuals) must make early intervention services for HIV-1 disease, including testing to confirm the presence of the disease, available to individuals undergoing treatment for substance abuse.

Department of Homeland Security (DHS)

Aliens applying for temporary resident status or adjustment from temporary to permanent resident status are required to submit the result of a serologic test for HIV-1 virus.

Any alien inadmissible under Section 212(a)(1)(A)(i) of the Immigration and Nationality Act, as amended by the Immigration Reform and Control Act of 1986, because of HIV-1 infection may be issued a B-1 (business visitor) or B-2 (visitor for pleasure) nonimmigrant visa and be authorized for temporary admission into the United States for a period of 30 days subject to conditions in 8 CFR 4(f)(2).

Department of Housing and Urban Development (HUD)

HUD implements programs (e.g., Housing Opportunities for Persons with AIDS, Shelter Plus Care) designed to provide rental assistance for permanent housing and supportive services (including health care) for low-income individuals with HIV-1/AIDS and homeless persons with disabilities, including HIV-1/AIDS, and their families.

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Department of Veterans Affairs (DVA)

For any record maintained in connection with the performance of any program or activity relating to infection with HIV-1, information may be disclosed to a Federal, State, or local public health authority charged with protection of the public health under Federal or State law, and to which Federal or State law requires such disclosure, if a qualified representative of such authority has made a written request for such record pursuant to such law for a purpose authorized by such law.

A physician or professional counselor may disclose information indicating that a patient is infected with HIV-1 to the spouse of the patient or to an individual whom the patient has (during the process of counseling or of HIV-1 testing) identified as being a sexual partner of the patient.

Food and Drug Administration (FDA)

Since May 2015, 21 CFR 606, 610, 630, 640, and 660 prescribe procedures, including recordkeeping, donor screening and notification, blood and blood component testing, and product labeling, to guard against the spread of HIV-1 through donation of blood, serum, or plasma.

21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of HIV-1.

21 CFR 864 identifies class designations (Class I, II, or III) of analyte-specific reagents (e.g., analytes intended as components in tests intended for use in the diagnosis of HIV-1/AIDS) that determine the type of premarketing submission or application required for FDA clearance to market.

21 CFR 866 identifies the *in vitro* HIV-1 drug resistance genotype assay (a device intended for use in detecting HIV-1 genomic mutations that confer resistance to specific anti-retroviral drugs, as an aid in monitoring and treating HIV-1 infection) as a Class II medical device with special controls (i.e., a guidance document) requiring premarket notification for FDA clearance to market.

Patient examination and surgeon's gloves must be sampled and tested for leaks and other visual defects to reduce the risk of transmission of HIV-1.

The labeling of over-the-counter vaginal contraceptive and spermicide drug products containing nonoxynol 9 as the active ingredient must contain warnings that these products do not protect against the transmission of HIV-1/AIDS, may increase the risk of getting HIV-1/AIDS from an infected partner, and should not be used by individuals who have HIV-1/AIDS or are at high risk for HIV-1/AIDS.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Public Health Service (PHS)

Programs or practitioners engaged in opioid treatment of individuals with an opioid agonist treatment medication must provide counseling on preventing exposure to and transmission of HIV-1 disease for each patient admitted or readmitted to maintenance or detoxification treatment.

Organs from individuals infected with HIV-1 may be transplanted only into individuals who are infected with HIV-1 before receiving such organ(s) and (A) are participating in clinical research approved by an institutional review board (as defined in 45 CFR Part 46, as amended) or (B) a determination under Section 377E(c) of the Public Health Service Act, as amended has been published that participation in such clinical research is no longer a requirement for transplants of organs from individuals infected with HIV-1.

Serologic testing for HIV-1 is required for aliens over 15 years of age who are applying for immigrant visas; are students, exchange visitors, or other applicants for non-immigrant visas required by a United States consular authority to have a medical examination; are outside the United States applying for refugee status; or are in the United States applying for adjustment of their status under the immigration statute and regulations.

Guidelines

Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)

The CDC, NIH, and HIVMA have issued federally approved HIV-1/AIDS medical practice guidelines (NIH 2015).

Department of Defense (DoD)

DoD Instruction 6485.01 establishes policy, assigns responsibilities, and prescribes procedures for the identification, surveillance, and management of members of the military services infected with HIV-1 and for prevention activities to control transmission of HIV-1.

Department of Health and Human Services (DHHS)

DHHS has issued guidance regarding enrollment of children with disabilities (including HIV-1, AIDS-related complex, or AIDS) in Head Start programs. The guidance includes direction in the event that a child with disabilities presents a problem involving biting or bodily fluids.

Food and Drug Administration (FDA)

The FDA has issued numerous guidance documents prescribing procedures (e.g., use of standardized labels, abbreviated donor screening questionnaires) for reducing the risk of virus transmission by blood and blood products (FDA 2015).

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