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

Peer-Review Draft:
Report on Carcinogens Monograph on
Human T-Cell Lymphotropic Virus Type 1

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Office of the Report on Carcinogens
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U.S. Department of Health and Human Services

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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), Mechanisms 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 Mechanisms 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

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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.

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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

Mechanistic Data and Other Relevant Data

Preliminary Listing Recommendation

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1 Properties and Detection

This section reviews the biology, detection, transmission, prevention, and treatment of the human T-cell lymphotropic virus type 1 (HTLV-1). The specific topics covered include the properties (Section 1.1) and detection (Section 1.2).

1.1 Properties

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

1.1.1 Family and type

Human T-cell lymphotropic virus type 1 (HTLV-1) is a delta-type retrovirus, in the subfamily *Orthoretrovirinae*, which has four types HTLV-1, HTLV-2, HTLV-3, and HTLV-4 (Gessain 2012, IARC 2012). It was the first oncoretrovirus to be discovered in humans and was isolated in 1979 from peripheral blood lymphocytes in a patient thought to have T-cell lymphoma (Jacobson and Massoud 2013). HTLV-1 is very similar to bovine leukemia virus and simian T-cell leukemia virus; all three viruses have an extra pX region in their genome containing regulatory and accessory genes (Jacobson and Massoud 2013). HTLV-2 has been associated with elevated lymphocyte and platelet counts but not with neoplasms (IARC 2012). HTLV-3 and HTLV-4 have not been associated with hematological diseases. The genomes of HTLV-1 isolated from humans in different parts of the world vary (Jacobson and Massoud 2013, IARC 2012, 1996). HTLV-1 is divided into four clades, or subtypes, with similar nucleotide sequences in specific viral genes. These include the Cosmopolitan, Japanese, African, and Melanesian clades. Humans are the natural host for HTLV-1, but other mammals (rabbits, rats, mice, and New World monkeys) have been infected experimentally.

1.1.2 Virus structure and genome

The HTLV-1 virion (80 to 100 nm diameter) consists of a lipid membrane envelope with two surface proteins, which surrounds a protein matrix, inside which is a protein capsid containing two copies of the viral single-stranded RNA (ssRNA) genome and the enzymes reverse transcriptase, integrase, and protease (see Figure 1-1) (Jacobson and Massoud 2013, IARC 2012, 1996). The HTLV-1 genome is about 9 kb long and contains three major genes, which encode multiple structural proteins (*env* and *gag* genes), enzymes (*pol* genes), regulatory proteins (Tax and Rex), and accessory proteins (p12, p13, p30, and HBZ), all of which are flanked by two long terminal repeats (LTRs) (see Figure 1-2). The lipid membrane envelope is created by budding off from the host cell membrane, which has been modifed by insertion of two viral glycoproteins produced from the *env* gene. The *env* gene produces a single protein that is cleaved by a cellular protease into gp21, which has a transmembrane domain anchoring it into the membrane envelope, and gp46, which attaches to gp21 (Schafer *et al.* 2015, IARC 2012). The *gag* gene produces a precursor protein (p53) that is cleaved by the viral protease to give rise to the matrix protein (p19), the viral capsid protein (p24), and the nucleocapsid protein (p15) (IARC 2012, 1996). The *pol* gene codes for three proteins (reverse transcriptase, integrase, and protease) that are created by frame shifts. Tax and Rex are regulatory proteins found in the pX region, near the 3' end, which produces at least four open reading frames by alternate mRNA splicing and internal initiation codons (Jacobson and Massoud 2013, IARC 2012). Accessory proteins from

the Xp genes exist (p12, p13, p30, and HBZ), but their functions are less well defined. Viral gene expression is controlled by promoters and enhancers in the two long terminal repeat (LTR) regions and are regulated by Tax protein. Both Tax and HBZ promote host cell proliferation.
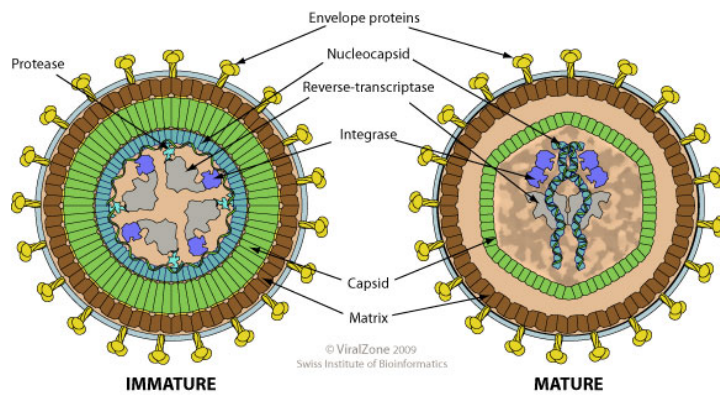
Figure 1-1. Human T-cell lymphotropic virus particle

Source: CreativeCommons.org
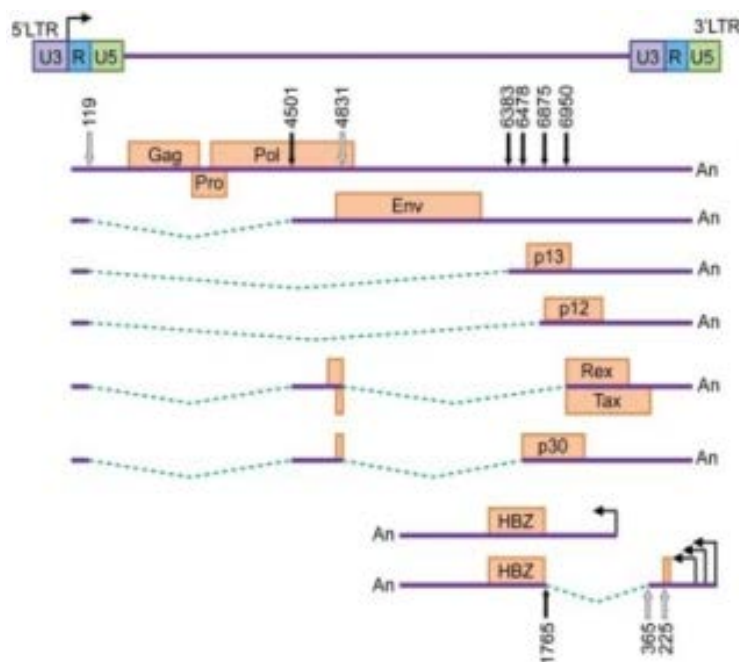
Figure 1-2. Genome schematic

Source: Creative Commons

1.1.3   Infection and replication

Free HTLV-1 viruses are unstable and not very infectious (Carpentier *et al.* 2015, Schafer *et al.* 2015, Jacobson and Massoud 2013, IARC 2012, 1996). Transmission of infection occurs through cell-to-cell contact between an infected and uninfected cell. HTLV-1 infects T cells, mainly CD4 T cells, and to a lesser extent CD8 T cells. Infection of other hematopoietic cells (dendritic cells,

monocytes, macrophages, B cells) and glial cells and endothelial cells is less efficient, though antigen-presenting cells (dendritic cells and macrophages) may play a major role in facilitating cell-to-cell transmission.

The routes of infection include the transfer of infected cells from one person to another through breast-feeding, sexual intercourse, and blood transfusions (Carpentier *et al.* 2015, Schafer *et al.* 2015, Cook *et al.* 2013). Blood transfusion is a direct route of infection. Breast-feeding and sexual intercourse, however, require the HTLV-1 infected cells to cross a mucosal epithelium. Mucosal epithelium can be traversed in several different ways (Carpentier *et al.* 2015). Infected macrophage might transmigrate through an intact epithelium, infected cells might cross through breaks in the epithelium, epithelial cells might become infected and transfer the virus to uninfected cells that come in contact with the basal end, or virions could cross the epithelial cells by transcytosis. Transcytosis occurs when virus from infected T cells are endocytosed by the epithelial cells on the apical end and then are passed to the basal end inside a vesicle, never coming in contact with the cytoplasm.

HTLV-1 viruses bind to uninfected cells by the Env protein, gp46, initially binding to cellular heparan sulfate proteoglycan and neuropilin, which induces a conformational change in gp46, exposing cellular glucose transporter 1 binding sites (Schafer *et al.* 2015, Cook *et al.* 2013, Jacobson and Massoud 2013, IARC 2012, 1996). The binding to glucose transporter 1 facilitates fusion of the viral membrane envelope with the cell membrane. Cell-to-cell transmission of HTLV-1 viruses occurs through several possible mechanisms - virological synapse, membrane-bound extracellular virus transfer, contact with infected antigen-presenting cells, and intercellular conduits (Carpentier *et al.* 2015, Schafer *et al.* 2015, Jacobson and Massoud 2013). A virological synapse is formed when cellular and viral proteins in an infected cell facilitate attachment to uninfected cells in a way that protects the virions from the surrounding environment. Extracellular viral transfer starts with viral budding, but the viral particles attach to the infected cell's membrane. The extracellular viruses can then bind to uninfected cell surfaces that come into contact with the infected cell. The close contact between antigen-presenting cells and T cells allows budding viruses to attach to the uninfected T cell. Epithelial or endothelial cells with intercellular conduits, such as gap junctions, can allow the HTLV-1 viruses to pass from the cytoplasm of an infected cell into the cytoplasm of an uninfected cell.

When the viral and cellular membranes fuse, the viral contents empty into the cytoplasm, where the matrix and capsid proteins separate, releasing the ssRNA genome, and reverse transcriptase, integrase, and protease enzymes (Schafer *et al.* 2015, Cook *et al.* 2013, Jacobson and Massoud 2013, IARC 2012, 1996). The ssRNA genome is then replicated by reverse transcriptase to a DNA genome. Reverse transcriptase is an error-prone polymerase and introduces random mutations into the viral genome. However, HTLV-1 does not go through as many rounds of replication or produce as many progeny as other retroviruses, such as human immunodeficiency virus (HIV). Instead, HTLV-1 replicates primarily along with the host cell replication and so doesn't utilize reverse transcriptase as much as HIV and has better genetic stability (Gessain 2012, Kubota 2007). The dsDNA genome is then transported into the nucleus along with integrase to integrate into the host cell genome, with only a single viral genome per host genome. From there, the virus can either remain latent and replicate clonally during mitosis along with the host cell genome or it can produce more viruses that can infect other cells through cell-to-cell contact. During virion production, viral proteins are produced and ssRNA is expressed and bind

to the cell membrane, which contains the Env proteins. The newly-formed virion buds off and sticks to the outside of the host cell or is transferred to uninfected cells. The protease enzyme inside the newly formed virion cleaves multi-gene proteins, causing the virus to mature to its infectious form (see Figure 1-1).

The HTLV-1 virion is immunogenic and so active viral production will elicit a cytotoxic T-cell immune response (Carpentier *et al.* 2015, Cook *et al.* 2013). This results in clearing out cells that are producing virus particles, leading to a predominance of infected cells in the latent phase. During the latent phase, Tax protein promotes host cell proliferation, but Tax itself is immunogenic and will elicit a cytotoxic T-cell immune response. In order to maintain a latent infection, Tax expression must be suppressed. It has been found that Tax expression is either mutationally inactivated or epigenetically suppressed by methylation in about half of acute T cell lymphoma cases. The accessory protein HTLV-1 bZIP factor (HBZ) is constitutively expressed and can also promote host cell proliferation, but it is not as immunogenic as Tax and might not elicit an immune response against the infected cells, allowing for maintenance of clonal expansion in the latent phase.
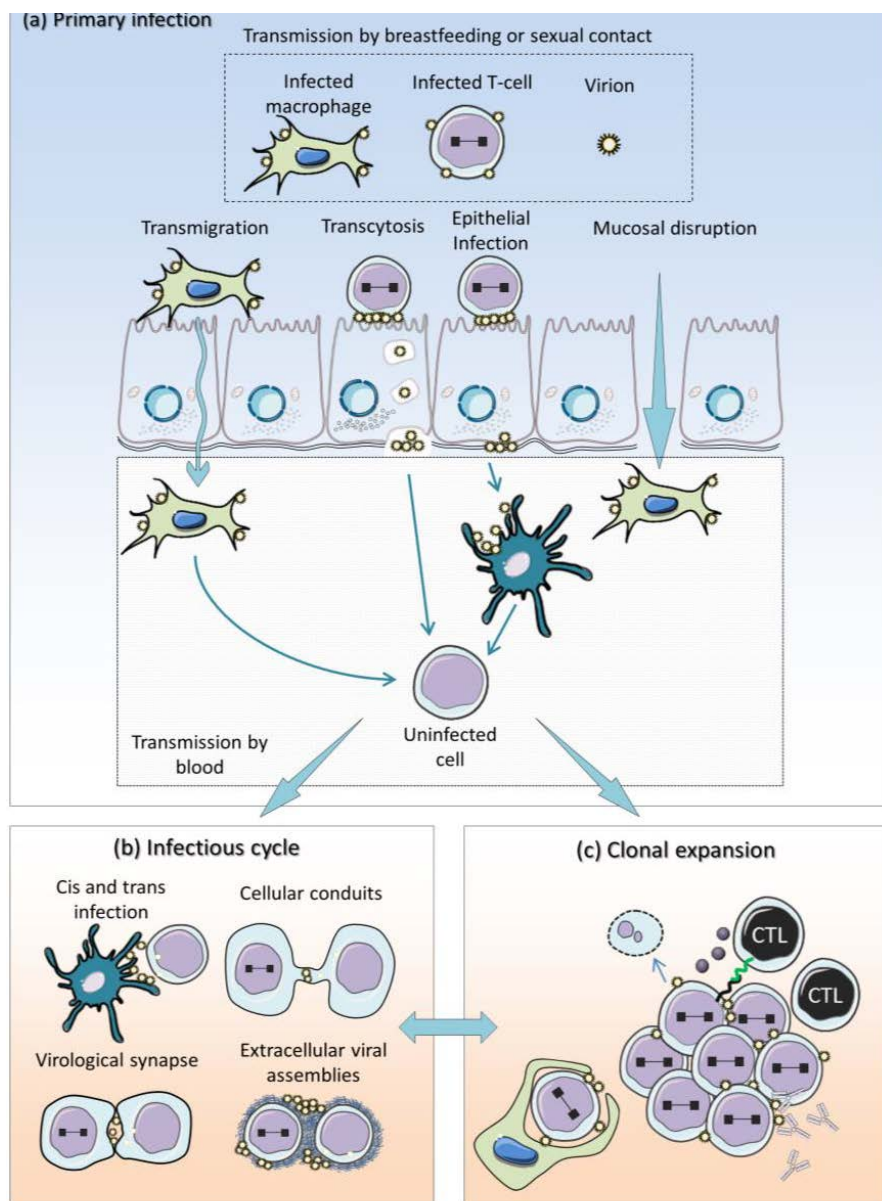
Figure 1-3. HTLV infection and replication cycle

Source: Carpentier *et al.* 2015.

1.2   Detection

HTLV-1 is rarely detected free in bodily fluids, but it is found in peripheral mononuclear blood cells in breast milk, blood, semen, and cerebral spinal fluid (Carpentier *et al.* 2015, Schafer *et al.* 2015, IARC 1996). Detection of HTLV-1 infection consists of tests to detect either a) anti-HTLV-1 antibodies, b) HTLV-1 RNA/DNA, or c) HTLV-1 in culture.

1.2.1   **Detection of anti-HTLV-1 antibodies or antigens**

HTLV-1 viral antigens are found in fluids at very low levels and are not routinely used for diagnosis (IARC 1996). Detection of anti-HTLV-1 antibodies is used to diagnose an infection. IgG anti-HTLV antibodies are produced continually during most of the HTLV infection, while IgA and IgM are produced temporarily during the beginning of the infection. Anti-HTLV antibody screening tests are usually done initially, with positive specimens then tested in a confirmatory test, which offers the ability to differentiate HTLV-1 from HTLV-2.

Screening immunoassays for HTLV-1 consist of laboratory-based tests, such as enzyme-linked immunosorbent assays (ELISA), particle agglutination assays, and immunofluorescence assays (IARC 1996). ELISA assays use either purified virions, viral peptides, or recombinant proteins, with specific peptides and recombinant proteins offering higher specificity. Particle agglutination tests use viral antigen-containing gelatin particles, which are cross-linked by anti-HTLV antibodies. Immunofluorescence tests rely on staining of HTLV-producing cell lines.

Confirmatory tests include western blot, radioimmuno-precipitation, and immunofluorescence (IARC 1996). Western blots, like ELISA, utilize purified virions. Antibodies are commonly found that are specific for Gag proteins (p19, p24, p53) and Env glycoproteins (gp21 and gp46). The strain of HTLV can be differentiated by adding synthetic viral gp46 peptides that are derived from either HTLV-1 or HTLV-2 to the western blots. A positive test for at least one Gag and one Env protein is needed for confirmation of anti-HTLV-1 antibodies. Immunofluorescence assays also can differentiate HTLV-1 from HTLV-2. The most sensitive assay is radioimmuno-precipitation, but high cost and longer time to perform curtail its use as a first-line confirmatory assay. Instead, it is more often used as a second-line test when confirmatory western blot assays give indeterminate results.

1.2.2   **Detection of RNA**

The levels of free virions in bodily fluids are much lower than those within cells, so detection of viral RNA or DNA is usually carried out on peripheral mononuclear cells in blood, semen, and breast milk (Carpentier *et al.* 2015, Schafer *et al.* 2015, IARC 1996). Detection of viral RNA requires very sensitive methods (IARC 1996). Reverse transcription-polymerase chain reaction (RT-PCR) is used to detect HTLV-1 specific *pol* and *tax* genes, as they have a lower variability among strains. Alternatively, the long terminal repeat or *env* gene can be amplified by PCR and then subjected to restriction enzyme digestion to differentiate HTLV-1 from HTLV-2. Nested PCR is more sensitive than single-round PCR and is needed to detect low levels of HTLV in some people. Viral integration into the host genome can be detected by Southern blot or inverse PCR. This allows for the quantitation of the percentage of peripheral blood cells with integrated viral genomes, which usually remain stable over many years (Cook *et al.* 2013). However, the percentage of cells with the virus varies widely among individuals. This percentage is likely determined primarily by the cytotoxic T cell response against HTLV-1 infected cells.

Some specimens show a positive result by PCR, but are negative for anti-HTLV-1 antibodies (IARC 1996). Such cases have occurred in the West India, where PCR detected small fragments of *tax* or *pol* genes, but such cases have not been reported from Japan, the Caribbean, or the United States.

1.2.3   **Detection of HTLV-1 by viral culture**

Long-term culture of peripheral blood mononuclear cells with IL-2 or co-culture with phytohemagglutinin-stimulated cord blood cells can result in virion production (IARC 1996). The cultured virions can then be detected by electron microscopy or immunofluorescence using antibodies against Env glycoprotein (gp46) or Gag proteins (p19 or p24). Gag proteins released into the culture medium can also be detected by antigen capture assay.

1.3   Summary

Human T-cell Lymphotropic Virus Type 1 (HTLV-1) is an enveloped RNA retrovirus found in T-cell lymphoma. HTLV-1 contains regulatory and accessory genes that promote proliferation of T cells, predominately CD4 T cells. HTLV-1 is unstable as a free virion and transmission requires cell-to-cell contact, with antigen-presenting cells thought to play a major role in infecting CD4 T cells. Selective pressure from anti-viral immune responses often leads to loss of expression of some regulatory genes in latently infected cells, and the immune response is thought to play a major factor in determining viral load. Detection is most commonly carried out by measurement of anti-HTLV-1 antibodies; however, measuring viral RNA or DNA or use of *in vitro* culture techniques can also be productive.

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2 Exposure

2.1   Prevalence and transmission

Most available human T-cell lymphotropic virus type 1 (HTLV-1) prevalence studies in the United States have focused on blood donor or intravenous drug user (IDU) populations (Gessain and Cassar 2012). The first detailed U.S. study conducted in more than a decade reported a seroprevalence of 0.0051% (reported as 5.1 cases per 100,000) in 2,047,740 first-time blood donors in a network of blood centers located in the western, southern, and northern United States examined over the time period of 2000 to 2009 (Chang *et al.* 2014, Cook and Taylor 2014). Previous studies reported U.S. HTLV-1 seroprevalences ranging from 0.009% to 0.025% measured in approximately 40,000 blood donors in 8 cities in geographically distinct areas and reporting that HTLV-1 was found primarily in the southeastern and southwestern United States; in 1.7 million donors at 5 U.S. blood centers during 1991 to 1995; and in approximately 21,000 individuals representing blood donors, various patient populations, and retroviral risk groups (Poiesz *et al.* 2001, Murphy *et al.* 1999, Williams *et al.* 1988). Though not as prevalent in the United States as other viruses, e.g., Epstein-Barr virus, the 104 individuals identified as seropositive of HTLV-1 by Chang *et al.* (2014) would extrapolate to approximately 16,000 persons based on the 0.0051% U.S. HTLV-1 seroprevalence rate and a 2014 U.S. population estimate of approximately 318 million people (Population Reference Bureau 2014). No analyses of HTLV-1 prevalence in blood, serum, or urine specimens from the National Health and Nutrition Examination Survey (NHANES) have been identified.

Worldwide prevalence of HTLV-1 has been variously reported as 10 million to 20 million infected persons (de Thé and Bomford 1993) or 5 million to 10 million (Gessain and Cassar 2012). However, these numbers should be considered as estimates of minimum numbers because both studies examined certain endemic regions but not all populations. For example, Gessain and Cassar based their estimates on areas with a total of 1.5 billion people that did not include China, India, and other highly populated regions in the approximately 7 billion total population in 2012 (Population Reference Bureau 2012). Prevalence varies geographically, and HTLV-1 can be found in high-endemicity clusters near regions where it may be nearly absent (Gessain and Cassar 2012, IARC 2012). Generally, highly endemic areas include southwestern Japan, parts of sub-Saharan Africa, the Caribbean Islands, and South America (IARC 2012). Seroprevalence increases with age and especially in women in these areas (Gessain and Cassar 2012). Infections have also been reported in Melanesia, Papua New Guinea, and the Solomon Islands, and among Australian aborigines (IARC 2012, Kannian and Green 2010). Prevalence is low in Europe and North America (IARC 2012).

The 3 main transmission modes for HTLV-1 are vertical, sexual, and parenteral, all of which require cell-to-cell contact (IARC 2012). The highest rates of HTLV-1 transmission are from vertical transmission via breastfeeding, and are as high as 30% in southern Japan. Risk of HTLV-1 infection in children from vertical transmission corresponds to the mother's breast milk proviral load and to breastfeeding duration. Vertical transmission occurs rarely *in utero* (e.g., during the intrauterine period or peripartum) in < 5% of cases (Hlela and Bittencourt 2014). Risk factors for sexual transmission include unprotected sex with an infected partner, multiple lifetime sexual partners, and infection with sexually transmitted diseases (STDs) (IARC 2012). Findings from one study of couples in Japan with one seropositive and one seronegative partner showed a

higher male-to-female transmission rate; however, another study in a different geographic location (Latin America) did not, possibly due in part to differences in sexual practices between genders and seroprevalence of sexual transmitted diseases among populations. HTLV-1 transmission also occurs via transfusion of cellular blood components and from needle sharing by injection drug use. Organ-transplantation-acquired infection has been reported in Germany (Glowacka *et al.* 2013).

2.2   Diseases (non-cancer), prevention, and treatment

Most HTLV-1-infected individuals are lifelong asymptomatic carriers (Cook *et al.* 2013), and only 2% to 5% of infected people develop diseases related to the virus (Hlela and Bittencourt 2014). HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), an inflammatory central nervous system disease, is the most common clinical manifestation of HTLV-1 (Fuzii *et al.* 2014). Other diseases associated with HTLV-1 include HTLV-1 uveitis, an inflammatory disorder affecting intraocular tissues (Kamoi and Mochizuki 2012), and infective dermatitis associated with HTLV-1, a chronic and recurrent eczema that occurs during childhood and rarely in adolescence or adulthood (Hlela and Bittencourt 2014).

Prenatal screening for HTLV-1 and counseling of seropositive mothers to avoid breastfeeding reduces mother-to-child transmission; in Japan, avoidance of breastfeeding by HTLV-1-infected mothers reduced transmission from 20% to 3%, and efforts to eliminate breastfeeding or reduce breastfeeding duration to less than 12 months also reduced transmission (IARC 2012, Hino 2011). Following the practices that prevent sexually transmitted infections, e.g., use of condoms and avoiding multiple and anonymous sexual partners, can reduce sexual transmission (Yoshimitsu *et al.* 2013). In addition, counseling and education of intravenous drug users (e.g., implementation of harm reduction practices) may be effective in reducing HTLV-1 infection among this population (Goncalves *et al.* 2010). Blood screening has reduced the risk of transfusion-related transmission (McKendall 2014); screening the U.S. blood supply for HTLV-1 began in 1988 (ARC 2015).

Prevention involves four major areas for actions to reduce transmission of HTLV-1: blood transfusion, sexual transmission, breastfeeding, and vaccine development (McKendall 2014). There is currently no vaccine against HTLV-1 (ACS 2015a, CDC 2015, FDA 2015); however, vaccine development efforts are ongoing (Kuo *et al.* 2011).

2.3   Summary

A significant number of people living in the United States are exposed to human T-cell lymphotropic virus type 1 (HTLV-1). The seroprevalence of HTLV-1 among blood donors in the United States from 2000 to 2009 is reported to be 0.0051% indicating that approximately 16,000 individuals living in the United States carry this virus. Worldwide prevalence of HTLV-1 is highest in endemic areas including southwestern Japan, parts of sub-Saharan Africa, the Caribbean Islands, and South America and numbers of infected persons range from 5 million to 20 million people, although the estimates generally did not include all countries. The 3 main transmission modes for HTLV-1 are vertical, sexual, and parenteral, all of which require cell-to-cell contact. The highest rates for vertical transmission involve breastfeeding, although transmission *in utero* from mother to fetus has also been reported as a possibility. Most HTLV-1 infected individuals are lifelong asymptomatic carriers and only 2% to 5% of infected people

develop diseases, such as HTLV-1 associated myelopathy/tropical spastic paraparesis, related to the virus. Prevention of HTLV-1 transmission is based on blocking the known routes of transmission, including blood transfusion, sexual transmission, and breastfeeding. Although there is currently no vaccine against HTLV-1, vaccine development efforts are ongoing.

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3 Human Cancer Studies

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus whose association with cancer has been explored in numerous studies. The NTP used the IARC monographs on HTLV-1 (IARC 2012, 1996) as a resource for key studies on cancer conducted prior to 2008 together with new studies identified between 2008 and 2015 to evaluate the scientific evidence for specific cancer endpoints for the RoC, independently of IARC's conclusions.

Only the adult T-cell leukemia/lymphoma endpoint is evaluated in depth. There are few studies on other cancer endpoints, cutaneous T-cell lymphoma, other B- and T-cell lymphomas, and gastric cancer, which are briefly reviewed. HTLV-1 detection methods varied across studies, with exposure detected primarily in tissues through particle agglutination assay, enzyme-linked immunosorbent assay (ELISA), and western blot (see Section 1.2 for more information).

The cancer hazard evaluation of HTLV-1 from human cancer studies is divided into three parts: the first (Section 3.1) summarizes the approach for selecting the literature specific to HTLV-1; the second (Sections 3.2 and 3.3) discusses the cancer hazard evaluation for specific cancer endpoints; and the last (Section 3.4) summarizes the evaluations across endpoints. The literature search strategy is described in Appendix A.

3.1   Selection of the relevant literature

A systematic literature search of major databases, citations, and other authoritative sources from 2008 to January 2015 was conducted. The literature search strategy is described in Appendix A. For this review of HTLV-1, all case-control and cohort studies (regardless of cancer endpoint) and case-series studies on the relationship between HTLV-1 and adult T-cell leukemia/lymphoma published since 2008 were included in the review.

3.2   Cancer hazard assessment: Human T-cell lymphotropic virus type 1

This section provides a brief background on adult T-cell leukemia/lymphoma, summarizes the findings for studies for each study design, discusses relevant cofactors and integrates the evidence for the association between adult T-cell leukemia/lymphoma and HTLV-1 across studies. The review consists of case-series and eight cohort studies. HTLV-1 is part of the diagnostic criteria for adult T-cell leukemia/lymphoma. As such, relative risks (odds ratios) cannot be calculated, and no case-control studies have been conducted on risk.

3.2.1   Background information

Adult T-cell leukemia/lymphoma is a rare and aggressive T-cell malignancy most commonly found in HTLV-1 endemic areas such as Japan, the Caribbean, and the Middle East. Prevalence of adult T-cell leukemia/lymphoma varies with geographic location. In Japan, adult T-cell leukemia/lymphoma incidence among HTLV-1 positive carriers has been reported as 92 per 100,000 males, and 44 per 100,000 females (Koga *et al.* 2010). In endemic areas of Japan, adult T-cell leukemia/lymphoma accounts for over 51% of all non-Hodgkin lymphomas, while the overall prevalence of adult T-cell leukemia/lymphoma in Japan (nationwide) is 7.5% of all lymphomas (Iwanaga *et al.* 2012). Other endemic areas such as the Caribbean, Central and South America, and the Middle East report low prevalence rates of disease (Iwanaga *et al.* 2012). Adult T-cell leukemia/lymphoma is rare in non-endemic areas, such as the United States, with an age-

adjusted incidence rate of 0.05 for men and 0.03 for women per 100,000 (Iwanaga *et al.* 2012, Yamamoto and Goodman 2008), although it should be noted that the majority of cases in the United States have occurred in immigrants from endemic areas (Goncalves *et al.* 2010). Adult T-cell leukemia/lymphoma prognosis is poor, with a median survival time of less than 12 months (Matutes 2007).

Based on clinicopathological features, adult T-cell leukemia/lymphoma has been classified into four major subtypes– acute type (most frequent and prototype of adult T-cell leukemia/lymphoma), lymphoma type, chronic type, and smoldering type (a slow-drowing type of ATLL) (IARC 1996).

3.2.2 Studies of HTLV-1 and adult T-cell leukemia/lymphoma

The endemic nature of adult T-cell leukemia/lymphoma was first recognized in 1977, when the first case reports were published (Uchiyama *et al.* 1977). A viral etiology for this disease was proposed (Takatsuki *et al.* 1977), and HTLV-1 was identified within a few years (Poiesz *et al.* 1980). Initial case reports and case series of adult T-cell leukemia/lymphoma, conducted in HTLV-1-endemic regions, found a very high prevalence of HTLV-1 among cases (> 90%), compared with the general population from which the cases came (see Table 5 in the 1996 IARC review of HTLV-1 for prevalence of anti-HTLV-1 individuals in adult T-cell leukemia/lymphoma (greater than 250 cases) and other lymphoma cases and controls from endemic regions). Because of this strong association seen among adult T-cell leukemia/lymphoma cases, HTLV-1 was considered the cause of adult T-cell leukemia/lymphoma. HTLV-1 infection is now considered a necessary, but not sufficient, cause of adult T-cell leukemia/lymphoma, and is part of the diagnostic criteria (IARC 1996). IARC (2012) also reviewed eight case-series studies published between 1996 and 2005 reporting on over 300 cases of HTLV-associated ATLL in South America, Japan, and other Asian countries (Table 2.1 in the 2012 IARC (2012). Proviral HTLV-1 DNA is integrated in a monoclonal fashion in all cases of adult T-cell leukemia/lymphoma (Yoshida *et al.* 1984). Clonality provides evidence that infection precedes tumor development. This correlation between adult T-cell leukemia/lymphoma and HTLV-1 complicates the epidemiological assessment of the association, as studies that traditionally produce measures of association (such as case-control studies and cohort studies) are limited.

The estimated lifetime risk of an HTLV-1 carrier developing adult T-cell leukemia/lymphoma is 6% in men and 2% in women. Adult T-cell leukemia/lymphoma occurs most frequently in adults, 20 to 40 years after initial HTLV-1 infection, though average age at onset differs by region, with an average age of 40 in Central and South America, and an average age of 60 in Japan (Iwanaga *et al.* 2012). High proviral load is an independent risk factor for development of adult T-cell leukemia/lymphoma (Akbarin *et al.* 2013, Iwanaga *et al.* 2012).

HTLV-1 positivity is part of the diagnostic criteria for adult T-cell leukemia/lymphoma and, as such, studies of risk compared to non-exposed individuals have not been conducted. All cases in the included studies below are HTLV-1 positive, and no negative controls are available. Eight cohort studies have been conducted on predictors of disease, risk of disease among HTLV-1 carriers, and mortality rate. Six of these cohort studies have been in Japan, where HTLV-1 is endemic, while two newer studies have been conducted in the United States (Biswas *et al.* 2010) and in Israel (Stienlauf *et al.* 2013). Adult T-cell leukemia/lymphoma mortality rates (per

100,000) among HTLV-1 carriers ranged from 35.8 to 190.5 while adult T-cell leukemia/lymphoma incidence rates (per 100,000) ranged from 57.4 to 137.7 (Table 3-1). There is evidence of greater adult T-cell leukemia/lymphoma incidence, and mortality, among men than women; six of the eight studies reported incidence and/or mortality rates to be higher for men than women (Stienlauf *et al.* 2013, Arisawa *et al.* 2006, Arisawa *et al.* 2003, Hisada *et al.* 2001, Arisawa *et al.* 2000, Tokudome *et al.* 1991). IARC (2012) noted these differences, but whether they existed outside of Japan was unknown.

Four nested case-control analyses, nested within prospective HTLV-1 cohorts, have investigated both viral and serological predictors of adult T-cell leukemia/lymphoma on a small number of incident cases (Okayama *et al.* 2004, Arisawa *et al.* 2002, Hisada *et al.* 1998b, Hisada *et al.* 1998a). These studies found that higher proviral load, higher antibody titers, and a higher prevalence of soluble interleukin-2 receptor-α were more likely to lead to an adult T-cell leukemia/lymphoma diagnosis (Table 3-1). For more details, see Table 2.4 in IARC (2012).

Table 3-1. Summary of studies of HTLV-1 and adult T-cell leukemia/lymphoma

Study	Country/ population Enrollment period	Population size (HTLV+) Age Follow-up	Exposure group (# cases/deaths)	Findings (95% CI)	Covariates	Comments
Cohort HTLV-1 carriers[a]						
Tokudome *et al.* 1991	Japan 1984–1987	3991 Men: 1,797 Women: 2,194 Age ≥ 40 Follow-up 1984–1989	Death from ATLL Men: 3 Women: 2	Crude mortality rate/100,000: 68.1 (12.8–201.7) 35.8 (3.4–131.5)		Higher risk of HTLV among men
Iwata *et al.* 1994	Japan 1984–1990	503 Age ≥ 30 Follow-up 1992–1997	Death from ATLL 2	Crude mortality rate/100,000: 77		Higher risk of HTLV among men
Arisawa *et al.* 2000	Japan 1985–1996	[2,973] Men: [1,242] Women: [1,731] Age 35–82 Follow-up 1985–1995	Incidence cases of ATLL Men: 24 Women: 16 Men Women	Cases/100,000 PY: 137.7 (88.3–204.9) 57.4 (32.8–93.2) Total lifetime risk (30–79 years): 6.6 (3.8–9.2) 2.1 (1.0–3.1)	Age adjusted	Higher risk of HTLV among men

Study	Country/ population Enrollment period	Population size (HTLV+) Age Follow-up	Exposure group (# cases/deaths)	Findings (95% CI)	Covariates	Comments
Hisada *et al.* 2001	Japan 1984–1997	550 Age 64–83 Follow-up 1984–1997	Death from ATLL Men: 4 Women: 2 Men Women	Crude mortality rate/100,000 PY 190.5 (51.9–487.7) 51.7 (6.3–186.8) Adjusted mortality rate/100,000 PY 209.1 (57.0–535.2) 60.9 (7.4–219.9)	Adjusted rate based on PY of observation attributable to perinatal transmission	Higher risk of HTLV-1 among men
Arisawa *et al.* 2003	Japan 1985–1992	Men: 1,852 Women: 2,284 Age 40–69 Follow-up 1993–2000	Deaths from ATLL Total: 10 Men: 8 Women: 2	Crude mortality rate/100,000 125 (60–230)[+]		Higher risk of HTLV-1 among men
Arisawa *et al.* 2006	Japan 1985–1987	Men: 1,078 Women: 1,655 Age 39–92 Follow-up 1985–2001	Incident case of ATLL Total: 2 Men: 1 Women: 1	Crude incidence rate/100,000 PY 71 (9–255)[+]		Higher risk of HTLV-1 among men
Biswas *et al.* 2010	USA 1990–1992	155 Ages ≥ 8 Follow-up 1992–2009	Deaths from ATLL 1	NA		

Study	Country/ population Enrollment period	Population size (HTLV+) Age Follow-up	Exposure group (# cases/deaths)	Findings (95% CI)	Covariates	Comments
Stienlauf *et al.* 2013	Israel 1995–2009	90 Average age: 50.2 Average follow up 9.2 ± 6 years	Incidence of ATLL Total: 3 Men: 2 Women: 1	Crude incidence rate/100 HTLV-1 carrier-years: 0.37 (0.13–1.08)		
Nested case-control studies in HTLV-1 cohorts[b]						
Hisada *et al.* 1998b 1988–1991	Japan Miyazaki Cohort Study	Cases 215/Controls 215	**Ably +** High proviral load (N = 64) Male gender (N = 81) **Ably ++** High proviral load (N = 18) Male gender (N = 30) **Males:** Ably+ (N = 25) Ably++ (N = 9) **Females:** Ably+ (N = 27) Ably++ (N = 9)	**OR (95% CI)** 8.9 (4.1–19.5) 1.5 (0.73–3.1) 19.7 (6.9–56.1) 2.8 (1.0–7.8) High proviral load 15.5 (0.33–6.6) 30.2 (4.4–209.5) 5.5 (2.0–15.2) 18.1 (4.1–80.6)	High proviral load adjusted for age, gender, leukocyte categories. Male gender adjusted for age, proviral load, leukocyte category Gender Ably ORs adjusted for age, leukocyte categories	Pre-diagnosis predictors of ATLL

Study	Country/ population Enrollment period	Population size (HTLV+) Age Follow-up	Exposure group (# cases/deaths)	Findings (95% CI)	Covariates	Comments
Hisada *et al.* 1998a	Japan MCS cohort	5 cases/38 matched controls	Anti-HTLV-1/level Anti-tax/unit	**OR (95% CI)** 1.6 (0.94–3.8) 0.78	Matched on age, gender, study screens. Also adjusted for other viral markers, smoking, leukocyte count	Pre-diagnosis predictors of ATLL
Arisawa *et al.* 2002	Japan	29 cases/158 matched controls	sIL-2R ≥ 500U/mL vs. < 500 (N = 18) anti-HTLV-1 titer ≥ 1024 vs. < 1024 (N = 17) anti-tax (N = 18)	**OR (95% CI)** 20.5 (4.5–194) 2.9 (0.98–9.5) 0.59 (0.15–2.0)	Matched for gender, birth year, date of first blood draw	Pre-diagnosis predictors of ATLL
Okayama *et al.* 2004	Japan MCS cohort	4 cases/ 37 matched controls	Proviral load/per 1000 copies	**OR (95% CI)** 1.42 (1.04–2.10)	Matched for age and gender	Pre-diagnosis predictors of ATLL

Studies prior to 2009 were reviewed by IARC (2012), and are adapted here from IARC tables (Table 2.2 and Table 2.4).

Ably = flower cell-like abnormal lymphocytes; ATLL = adult T-cell leukemia/lymphoma; CI = confidence interval; HAM/TSP = HTLV-1 associated myelopathy/tropical spastic paraparesis; NA = not available; OR = odds ratio; PY= person years; sIL2S = soluble interleukin-2 receptor-α.

[ ] = population calculated from proportions of seropositivity.

[a]Some HIV carriers identified from screening.

[b]Viral and serum immune markers.

[c]Reported in the article as rate per 1,000.

3.2.3   **Host susceptibility and cofactors**

Several host susceptibility characteristics have been suggested as potential risk factors for adult T-cell leukemia/lymphoma among HTLV-1 carriers. As discussed above (Table 3-1), male carriers of HTLV-1 appear to be at increased risk for development of adult T-cell leukemia/lymphoma compared with female carriers. Additionally, the risk of developing adult T-cell leukemia/lymphoma is suspected to be associated with early and/or mother-to-child HTLV-1 infection, which may play a role in the development of adult T-cell leukemia/lymphoma. One study in the Caribbean found that almost all mothers of adult T-cell leukemia/lymphoma cases were HTLV-1 positive; all the patients were breastfed. (Bartholomew *et al.* 1998). Two studies have suggested that there may be differences in the viral and immune markers between Jamaican and Japanese HTLV-1-carriers and non-carriers, which could in part help explain differences in adult T-cell leukemia/lymphoma seen between the two populations (reviewed by IARC 2012).

There is evidence in the literature that co-infection with the parasitic roundworm *Strongyloides stercoralis* (threadworm) is an effect modifier of HTLV-1 and adult T-cell leukemia/lymphoma. Pulmelle *et al*. (1997) reported adult T-cell leukemia/lymphoma patients who were also positive for *S. stercoralis* were younger at diagnosis than those infected with HTLV-1 alone. Two additional studies (Satoh *et al.* 2002, Gabet *et al.* 2000) found that HTLV-1 carriers who were co-infected with *S. stercoralis* had substantially higher HTLV-1 proviral loads, compared with those infected with HTLV-1 only. This evidence suggests *S. stercoralis* may increase risk of adult T-cell leukemia/lymphoma in HTLV-1 carriers. (For more details, see Table 2.11 in IARC 2012.)

3.2.4   **Integration of the evidence across studies**

Because of the high prevalence of HTLV-1 infection in almost all adult T-cell leukemia/lymphoma cases it is now part of the diagnostic definition of the disease. In addition, proviral HTLV-1 DNA is integrated in a monoclonal fashion in all cases of adult T-cell leukemia/lymphoma. Among HTLV-1 carriers, cohort studies are suggestive of an increased risk of disease and mortality in males compared with females. Four nested case-control studies among HTLV-1 carriers found high proviral loads, higher antibody titers, and higher prevalence of soluble interleukin-2 receptor-α to be strong pre-diagnosis predictors of adult T-cell leukemia/lymphoma. Co-infection with *S. stercoralis* may increase the risk of adult T-cell leukemia/lymphoma in HTLV-1 carriers.

3.3   **Cancer hazard evaluation**

3.3.1   **Other lymphomas/leukemias**

The IARC (2012) review of these studies and HTLV-1 is available in the supplemental tables 2.6, 2.7, and 2.8 of IARC (2012), along with Table 5 in the IARC (1996) review.

Early evidence presented by one study (Pancake *et al.* 1996) was suggestive of an association between cutaneous T-cell lymphoma and HTLV-1 based on the presence of HTLV-1 proteins or antibodies to proteins in 60 cutaneous T-cell lymphoma patients. However, 6 case-series studies, reviewed by IARC (2012), from multiple locations throughout the world, could not replicate the results of this study. These studies, which included 2 to 127 patients, did not detect HTLV-1

DNA (integrated) in tumor tissue or antibody in serum from patients with cutaneous T-cell lymphoma (IARC 2012, Table 2.6). No new studies on this association have been published since the last review.

Several case series have examined HTLV-1 infection in cases of B- and T-cell lymphomas; however, there was very little evidence of HTLV-1 involvement in these lymphomas in the published case series reviewed by IARC (2012). Thomas *et al.* (2010) studied 53 patients with large granular lymphocytic leukemia (a T-cell leukemia) and 10,000 healthy volunteer blood donors as non-matched controls. No large granular lymphocytic leukemia cases, and only one control, were positive for HTLV-1 (IARC 2012, Table 2.7). One study (Marin *et al.* 2002) found some evidence of T-cell lymphoma cases among HTLV-1 carriers; however, the authors stated that these might have been cases of adult T-cell leukemia/lymphoma. Gastric lymphomas of T-cell origin were also investigated as having HTLV-1 involvement. Some cases of HTLV-1-positive gastric lymphoma cases were reported; however, results were generally negative, and adult T-cell leukemia/lymphoma presenting as gastric lymphoma could not be ruled out (IARC 2012, Table 2.8) (Sakata *et al.* 2001, Shimada-Hiratsuka *et al.* 1997). Findings for other types of lymphomas/leukemias were limited to one or two studies per cancer endpoint (IARC 2012, 1996).

3.3.2   **Solid tumors**

A small number of epidemiologic studies have investigated the association between HTLV-1 and other cancer endpoints. Four studies, three cohort and one case-control study, have investigated the association of HTLV-1 and gastric cancer; two of which (Matsumoto *et al.* 2008, Arisawa *et al.* 2003) were reviewed by IARC (2012). These studies all found a decreased risk for gastric cancer among those who were HTLV-1 positive. Three cohort studies in Japan found the relative risks of gastric cancer among individuals who were HTLV-1 positive to be 0.42 (95% CI = 0.17 to 0.99; 1 exposed case) (Arisawa *et al.* 2003), 0.62 (non-significant; 95% CI and exposed cases not reported) (Arisawa *et al.* 2006), and an odds ratio (OR) = 0.38 (95% CI = 0.21 to 0.70; 14 exposed cases) (Matsumoto *et al.* 2008). The latter study found that *Helicobacter pylori* positivity was lower ($P = 0.07$) in the HTLV-1-positive group (61.7%) compared to the negative group (71.6%) suggesting that HTLV-1 might reduce the risk of *H. pylori* infection. In a recent case-control study of 201 gastric cancer patients in Iran, Tahaei *et al.* (2011) found the OR for gastric cancer among HTLV-1 positive was 0.27 (95% CI = 0.03 to 2.43) based on one exposed case.

Several studies, including four case-control studies (Okayama *et al.* 1995, reviewed by IARC 1996, Kamihira *et al.* 1994, Iida *et al.* 1988, Asou *et al.* 1986) and two prospective cohort studies (Ariswa *et al.* 2003, 2006) have reported positive associations with liver cancer although the interpretation is complicated by limitations of the studies (see Table 3-2). All of the studies were conducted in Japan where there are major risks factor for liver cancer of hepatitis B (HBV) and C (HCV) viruses and thus it is unclear whether HTLV-1 could be a possible co-factor or is a confounder. One study of HCV-infected cases and controls suggested that HTLV-1 increases the risk of HCV-associated liver cancer in men (Kamihira *et al.* 1994). In case-control studies, it is unclear whether HTLV-1 is a possible risk factor for liver cancer or if the development of the malignancy contributes to expression of HTLV-1 latent infection (Asou *et al.* 1986). In the cohort studies, the risk of liver cancer grew with increasing HTLV-1 antibody in the cohort study

of Japanese atomic bomb survivors (Arisawa *et al.* 2006), which had an adequate follow-up (15 to 16 years). Relative risk was not statistically significant in the second cohort study; however, the follow-up was short (6 to 7 years) (Arisawa *et al.* 2003).

Findings for other types of solid tumors were limited to one or two studies per cancer endpoint (IARC 2012, 1996).

Table 3-2. Summary of studies of HTLV-1 and liver cancer

Study Country	Population	HTLV-1 positivity	OR or RR (95% CI); exposed cases	Comments
Case-control studies				
Asou *et al.* 1986 Japan	33 cases 22,726 controls (health survey)	NR[a] 2.98%	SIR (observed/ expected[b]) 2.6 (5/1.94)	Excluded cases with history of blood transfusion; higher risk of all malignancy
Iida *et al.* 1988 Japan	40 cases 62,000 local blood donors	17.5% 4.7% $P < 0.001$	NR	6/7 cases had history of transfusion
Kamihira *et al.* 1994 Japan	181 cases 77,540 local blood donors	20.4% 3.8%	NR	Significant association between HTLV-1 and HCV infection in controls
Okayama *et al.* 1995 Japan	43 HCV- positive cases (33 men and 10 women) HCV-positive chronic hepatitis	30.2% 9.5%	***Men*** 12.8 (3.3–52.3); 11 ***Women*** 1.3 (0.7–10.1); 2	Adjusted for age History of transfusion similar between cases and controls
Prospective cohort studies				
Arisawa *et al.* 2003 Japan	4,136 Hospital outpatient or check up without cancer 1985–1992	Men 22.9% Women 26.2%	***Mortality*** 1.2 (0.64–2.4); 14 Incidence 1.4 (0.79–2.7); 17	Adjusted for sex, age, smoking and drinking habits, history of blood transfusion, and motive for examination Short follow up (mean 7.6 years)
Arisawa *et al.* 2006 Japan	2,728 Atomic bomb survivors 1985–1987	Men 8.2% Women 8.5%	***Incidence*** 2.1 (1.0–4.6); 8	Adjusted for sex, age, smoking and drinking habits Average follow up 15.4 years

HCV = hepatitic C virus; NR = not reported; OR = odds ratio; RR = risk ratio; SIR = standardized incidence ratio.
[a]HTLV-1 positivity for all cancers with blood transfusion 26% and without blood transfusion 15%.
[b]Expected numbers of cases based on age and sex distribution in the healthy individuals.

3.4   Synthesis across cancer endpoints

A summary of the evidence for HTLV-1 infection and the different cancer endpoints from epidemiological studies is provided in Table 3-3. The preliminary level of evidence from cancer studies in human also considers studies of tissues from humans in addition to epidemiological studies and is provided in Section 5.

Table 3-3. Summary of HTLV cancer endpoints and strength of the epidemiological evidence

Cancer endpoint	Strength of evidence
Adult T-cell leukemia/lymphoma	• Infection with HTLV-1 is part of the diagnostic criteria of ATLL. • Consistent evidence across multiple studies. • Prospective studies and clonality indicate that infection precedes diagnosis.
Cutaneous T-cell lymphoma	• Inconsistent evidence in multiple case series. • No epidemiologic studies available.
Gastric Cancer	• Epidemiological evidence suggests a decreased risk although most studies had few cases.
Liver Cancer	• Consistent evidence of increase risk but bias and limitations cannot be adequately ruled out.

ATLL = Adult T-cell leukemia/lymphoma.

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4 Mechanisms and Other Relevant Data

Human T-cell lymphotropic virus type 1 (HTLV-1) was the first oncogenic human retrovirus discovered (Yoshida *et al.* 1982, Poiesz *et al.* 1981, Poiesz *et al.* 1980). It has been established as the causal factor in adult T-cell leukemia/lymphoma as its presence is a part of the diagnostic criteria for this cancer (IARC 1996).

This section provides a brief introduction to HTLV-1 biology and the clinical characteristics of adult T-cell leukemia/lymphoma (Section 4.1), the role of risk modifiers (Section 4.2), adult T-cell leukemia/lymphoma pathogenesis (Section 4.3), and a synthesis of this information (Section 4.4).

4.1 Introduction

Adult T-cell leukemia/lymphoma is a malignancy defined, in part, by the presence of HTLV-1, and develops only in some HTLV-1-infected people. The retrovirus infects primarily CD4+ T cells, incorporates into the cellular DNA, and becomes a life-long infection (see Properties, Section 1). The cancer latency period can be 40 to 60 years long and a small percentage (3% to 5%) of carriers will develop adult T-cell leukemia/lymphoma in their lifetime (Mortreux *et al.* 2003). The virus is endemic to Japan, Central and South America, the Caribbean and sub-Saharan Africa, and is also found in some parts of the United States (Chang *et al.* 2014, Ciminale *et al.* 2014, Cesarman and Mesri 2007).

HTLV-1 infects cells primarily by cell-to-cell contact and is poorly infectious as a free virion (Jacobson and Massoud 2013). The primary mode of transmission of HTLV-1 is from mother to child through breast milk; however, it can also be transmitted by blood or blood products or sexual contact (IARC 1996). The virus has been detected in dendritic cells, monocytes, endothelial cells, and B and T lymphocytes (Yao and Wigdahl 2000).

The HTLV-1 RNA genome integrates into cellular DNA using viral reverse transcriptase and integrase enzymes (Jacobson and Massoud 2013). The provirus is amplified primarily via monoclonal proliferation of infected CD4+ cells using the host DNA polymerase. Thus, copy numbers of the virus in an individual increase through mitosis of infected cells and not through viral reverse transcriptase (IARC 1996). Clonally expanded T cells carry the latent HTLV-1 infection, and adult T-cell leukemia/lymphoma originates from the clonal population of cells (Moules *et al.* 2005, IARC 1996). Details of adult T-cell leukemia/lymphoma risk modifiers and oncogenesis are presented in Section 4.2.

4.2 Risk modifiers

The mechanism to explain why some HTLV-1 carriers develop adult T-cell leukemia/lymphoma is not completely understood; however, it is known that host immune status affects viral infection and maintenance of a proviral carrier state (Matsuoka and Jeang 2007). In general, there is evidence that perturbations in immune surveillance and factors influencing immune status can affect proviral load (number of cells infected) and factors that allow stimulation of T-cell proliferation that can lead to this aggressive cancer (Mortreux *et al.* 2003). Therefore, control of T-cell proliferation in asymptomatic carriers would be important for prevention of adult T-cell leukemia/lymphoma (Mortreux *et al.* 2003).

Another potential risk modifier is *Strongyloides stercoralis* (threadworm) infection because it can enhance the progression of HTLV-1 infection by increasing the number of lymphocytes infected and shortening the latency period of adult T-cell leukemia/lymphoma development. *S. stercoralis* infection has been shown to induce a mitogenic T-cell response via activation of the IL-2/IL-2R cytokine system (Satoh *et al.* 2002, Gabet *et al.* 2000). The degree of infected T-cell proliferation correlates with the frequency of somatic mutations and accounts for the decreased latency period (Mortreux *et al.* 2003). A chronic carrier state of *S. stercoralis* infection can last for decades but can become a hyperinfection due to decreased immunosurveillance with HTLV-1 infection (Marcos *et al.* 2008, Satoh *et al.* 2002). In general, patients with co-infections are younger than those without parasite co-infection (Weatherhead and Mejia 2014).

4.3   Adult T-cell leukemia/lymphoma pathogenesis

Adult T-cell leukemia/lymphoma develops in two stages. In the first stage, Tax, a viral protein, induces polyclonal proliferation of infected T cells; in the second stage, Tax expression is eliminated or reduced by the host's cytotoxic T lymphocytes. Tax is highly immunogenic and cells expressing this protein would be more likely to be eliminated by the host immune system. In the absence of Tax expression, continued cell proliferation may continue through HTLV-1 bZip (HBZ) RNA and protein production and through host oncogenic alterations such as with p16^{INK4A} and *p53* tumor suppressor genes resulting in clonal selection and lymphomagenesis (Mesri *et al.* 2014, Matsuoka and Jeang 2007, Satou *et al.* 2006). Tax is expressed in about 40% of adult T-cell leukemia/lymphoma cases; lack of expression is due to deletions, epigenetic changes in the 5′ long terminal repeat (5′-LTR), and genetic changes in the *Tax* sequence (Giam and Jeang 2007, Matsuoka 2005). However, HBZ gene expression is conserved in adult T-cell leukemia/lymphoma and correlates with proviral load (Zhao and Matsuoka 2012).

4.3.1   *Tax* gene and protein

Tax is a gene unique to HTLV that produces a pleiotropic *trans*-acting viral protein. It contributes to HTLV-1 oncogenesis by affecting both viral and host functions. Research has shown that Tax affects cell cycle, cell proliferation, DNA repair, and cell survival pathways, and triggers genetic instability (Mesri *et al.* 2014, Currer *et al.* 2012, Matsuoka and Jeang 2007, Mortreux *et al.* 2003). In addition, Tax has been shown to immortalize T cells both *in vitro* and *in vivo* in the absence of other viral factors (Yao and Wigdahl 2000, Grossman *et al.* 1995, Pozzatti *et al.* 1990, Tanaka *et al.* 1990), and the malignant transforming ability of Tax has been demonstrated *in vitro* in the Rat-1 fibroblast cell line in a soft-agar assay and *in vivo* in nude mice (IARC 2012).

Although Tax promotes cell-cycle progression and plays a role in tumor initiation, it is debated whether Tax alone is sufficient for cell immortalization because, although Tax enables increased expression of IL-2, Tax alone does not enable transition to IL-2 independent growth so it is thought that other factors are involved (Currer *et al.* 2012).

Some of the key cancer pathways promoted by Tax are listed below.

- *Constitutive activation of NF-κB*. Tax interacts with the NF-κB family of transcription factors leading to increased expression of IL-2, IL-2 receptor and IL-6 (Currer *et al.* 2012). NF-κB proteins are involved with T-cell proliferation, growth, and survival and

constitutive expression occurs with some viruses and some cancers (Cesarman and Mesri 2007, Yoshida 2001).

- *Post-translational modification*. Tax both undergoes and promotes post-translational modification of cellular proteins essential for interaction with various host cell proteins, such as NF-κB, and for translocation to different compartments within the cell (Currer *et al.* 2012).

- *Cell-cycle promotion and cell survival*. Tax disrupts cell-cycle checkpoints through interactions with cell-cycle proteins, promoting cell proliferation and prevention of apoptosis (Currer *et al.* 2012).

- *Promotion of genetic instability*. Tax also localizes at the centrosome during the mitosis phase of the cell cycle, suggesting that Tax has a role in promoting aneuploidy (Zane and Jeang 2014, Currer *et al.* 2012).

- *Promotion of DNA damage and inhibition of DNA repair*. Tax has been shown to produce reactive oxygen species within human cells, which can directly result in DNA damage (Kinjo *et al.* 2010). In addition, Tax has been shown to interfere with multiple DNA repair mechanisms: excision repair, mismatch repair, non-homologous end joining, and DNA damage response signaling leading to genomic instability (Currer *et al.* 2012).

Further, Tax interactions may play a role in cellular transformation; of particular interest is the role of miRNAs in cellular transformation. Although HTLV-1 does not produce viral miRNAs, Tax has been shown to modulate host miRNAs (Moles and Nicot 2015). Tax can regulate the effects of host miRNA promoting cell proliferation, survival, and immune evasion (Mesri *et al.* 2014). Tax down-regulates miRNAs that target p300 mRNA increasing viral transcription and also has been found to modulate other host miRNAs thus controlling host mRNA transcription (see Table 4-2) (Rahman *et al.* 2012, Sampey *et al.* 2012).

Table 4-2. Regulation of host miRNA by HTLV-1 infected cells

Host miRNA	Direction of regulation	mRNA affected	Resultant biological effect
miR-21	Up	PTEN	Anti-apoptotic
miR-93	Up	P21 MICB	Anti-apoptotic, Immune evasion
miR-132, miR-149, miR-873	Down	P300 AChE	Increase viral transcription Pro-inflammatory
miR-143-p3	Up	PKA GRα	Proliferation Proliferation
miR-155	Up	TP53INP1 Unknown	Anti-apoptotic Increase IFN-γ
miR-146a	Up	Unknown	Proliferation

Source: Sampey *et al.* 2012.

4.3.2   HTLV-1 bZip protein (HBZ)

HBZ gene is on the complementary DNA strand to *tax*. HBZ promotes T-cell proliferation in its mRNA form and suppresses *tax*-mediated viral transcription in its protein form (Zhao and

Matsuoka 2012). HBZ is expressed, in addition to Tax, by HTLV-1 in infected cells and is essential for continuous expansion and immortalization of adult T-cell leukemia/lymphoma cells (IARC 2012). Unlike Tax, HBZ is not immunogenic and expression continues with Tax down-regulation allowing for survival of Tax-negative cells (IARC 2012).

Some of the key cancer pathways affected by HBZ are listed below.

- It sustains proliferative signaling. Knock-down of HBZ in adult T-cell leukemia/lymphoma cells decreases the growth of these cells (Satou *et al.* 2006).
- It enables replicative immortality and activation of invasion and metastasis. HBZ activates hTERT expression, which is supportive of cell immortalization. hTERT expression is important for activation of telomerase expression leading to cell immortalization and is also related to clinical aggressiveness of leukemias and other malignancies (Mesri *et al.* 2014, Borowiak *et al.* 2013, Matsuoka and Jeang 2007).
- It promotes cell proliferation and resists cell death. HBZ RNA promotes transcription of E2F, a cell-cycle promoter, and activates transcription of *JUND*, *JUN* and *ATF* prosurvival genes (Mesri *et al.* 2014, Satou *et al.* 2006).
- Several host transcription factors bind HBZ protein, modulating their transcriptional activity. Signaling pathways are related to T-cell differentiation, immune response, and growth (Zhao and Matsuoka 2012).
- It promotes immune evasion. HBZ inhibits CD4 T-cell responses by suppression of the IFN-γ promoter, resulting in impaired host immunity *in vivo* (Zhao and Matsuoka 2012).

4.4   Mode-of-action evaluation

HTLV-1 oncogenesis results from Tax-mediated dysregulation of host replication and survival pathways (Mesri *et al.* 2014). However, the current understanding is that the effect of HTLV-1 Tax expression alone is not sufficient for cell immortalization (Currer *et al.* 2012), HBZ expression as well as mutations in host genes, are important factors leading to immortalization and malignant transformation of infected cells (Matsuoka and Yasunaga 2013, Matsuoka and Jeang 2007). Table 4-3 depicts key molecular oncogenic pathways of HTLV-1.

Table 4-3. Cancer hallmarks associated with HTLV-1 infection and adult T-cell leukemia/lymphoma

Viral Gene	Pathways	Cancer hallmark
Tax	NFκB	Proliferation, growth, survival
Tax	CREB	Regulates CPB/p300; transcriptional factor regulation
Tax	PI3K	Promotes cell survival and growth
Tax	DDR	Inhibits DNA damage response and interacts with mitotic spindle
HBZ	c-jun	Promotes cell survival
HBZ	E2F	Promotes cell proliferation
HBZ	Activates *htert*	Enables replicative immortality

Source: Mesri *et al.* 2014.

4.5   Synthesis

HTLV-1 infection is necessary but not sufficient for cancer development since not everyone infected with this virus develops adult T-cell leukemia/lymphoma. Host, environmental, and viral factors are all determinants. The viral protein Tax induces polyclonal proliferation of infected T-cells but it is also highly immunogenic. Tax-negative cells survive since HBZ RNA and protein and host mutations support cell survival and can lead to cell immortalization. Alterations in host genes, such as mutations or deletions in tumor suppressor genes *p53* and *p16,* can lead to increased genetic instability and malignant transformation. Although the HTLV-1 genes *tax* and *HBZ* are key in the oncogenic process, host and environmental factors such as immunosuppression or T-cell proliferation in HTLV-1 carriers can increase viral load and push clonal selection to malignancy.

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5   Preliminary Listing Recommendation

Human T-cell lymphotropic virus type 1 (HTLV-1) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on epidemiological and molecular studies showing that it causes adult T-cell leukemia/lymphoma in humans, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans (Table 5-1). Epidemiological studies also provide limited evidence of a causal association for liver cancer and for a decreased risk for gastric cancer; however, no molecular data were available for these cancer sites (Table 5-2).

Data are inadequate to evaluate the association between HTLV-1 and cutaneous T-cell lymphoma, which has inconsistent evidence from epidemiological studies and no available evidence from molecular studies.

The following tables provide the preliminary level of evidence recommendations for the carcinogenicity of HTLV-1 for each endpoint from studies in humans, including the key data from both epidemiological and molecular studies in humans.

Table 5-1. Evidence for HTLV-1 and adult T-cell leukemia/lymphoma from human studies

Types of studies	Adult T-cell leukemia/lymphoma (ATLL)
Epidemiological	
Positive associations	Original link established by case reports/case series; over 550 cases primarily from Japan and South America (1985 to 2005).
	HTLV-1 carriers developed ATLL
	(8 cohorts).
	Risk higher with higher viral load or proviral load in 4 case-control studies nested in HTLV-1 cohort studies.
Molecular (human tissue)	
Clonality	Monoclonal
% HTLV-1 infected tumors	> 90%
HTLV-1 protein expression	40% Tax, 100% HBZ
Other	Diagnostic criteria for ATLL
Level of evidence	**Sufficient**

ATLL = adult T-cell leukemia/lymphoma; HBZ = HTLV-1 basic leucine zipper factor; HTLV = human T-cell lymphotropic virus; NA = not available.

Table 5-2. Evidence for HTLV-1 and gastric and liver cancer from human studies

Types of studies	Gastric cancer	Liver cancer
Epidemiological		
Positive associations	Decreased risks in 3 cohort and 1 case-control study. *Helicobacter pylori* positivity lower in HTLV-1 group compared with negative group.	Positive associations in all studies (4 case-control and 2 cohort studies); most not significant and modest ORs. Bias and confounding cannot be ruled out.
Molecular (human tissue)	No available information	No available information
Level of evidence	**Limited for decreased risk**	**Limited**

HTLV = human T-cell lymphotropic virus; OR = odds ratio.

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Glossary

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

Case report: Detailed descriptions of a few patients or clinical cases (frequently, just one sick person) with an unusual disease or complication, uncommon combinations of diseases, an unusual or misleading semiology, cause, or outcome (maybe a surprising recovery). They often are preliminary observations that are later refuted. They cannot estimate disease frequency or risk (e.g., for lack of a valid denominator).

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).

Codon: A specific sequence of three consecutive nucleotides that is part of the genetic code and that specifies a particular amino acid in a protein or starts or stops protein synthesis.

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.

Hyperinfection: Infection by large numbers of organisms as a result of immunologic deficiency.

Immunoassay: A laboratory technique that uses the binding between an antigen and its homologous antibody to identify and quantify the specific antigen or antibody in a sample.

Inverse polymerase chain reaction: A variant of polymerase chain reaction used to amplify and clone unknown DNA that flanks one end of a known DNA sequence and for which no primers are available. Inverse PCR is useful in identifying flanking DNA sequences of genomic inserts. Similar to other PCR methods, inverse PCR amplifies target DNA using DNA polymerase.

microRNA: small, non-coding RNA molecules approximately 22 nucleotides in length that act post translationally in a regulatory role to target messenger RNAs for cleavage or translational expression.

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

Nude mouse (athymic nude mouse): A type of laboratory mouse that is hairless, lacks a normal thymus gland, and has a defective immune system because of a genetic mutation. Athymic nude

mice are often used in cancer research because they do not reject tumor cells, from mice or other species.

Open reading frame: A portion of a DNA molecule that, when translated into amino acids, contains no stop codons.

Parenteral: By some other means than through the gastrointestinal tract; the parenteral route of infection involves breaks in the skin such as cuts and scrapes, puncture wounds, bites and burns.

Polyclonal: Pertaining to or designating a group of cells or organisms derived from several cells.

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.

Smoldering type adult T-cell leukemia/lymphoma

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.

Abbreviations

5′-LTR	5′ long terminal repeat
Ably	flower cell-like abnormal lymphocytes
ATLL	Adult T-cell leukemia/lymphoma
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
DNA	deoxyribonucleic acid
DOT	Department of Transportation
dsDNA	double-stranded DNA
ELISA	enzyme-linked immunosorbent assays
FDA	Food and Drug Administration
HAM/TSP	HTLV-1 associated myelopathy/tropical spastic paraparesis
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HBZ	HTLV-1 bZIP factor
HTLV	human T-cell lymphotropic virus-1
IARC	International Agency for Research on Cancer
IDU	intravenous drug user
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2	interleukin 2
LTR	long terminal repeat

miRNA	microRNA
mRNA	messenger RNA
NA	not available
NF-κB	nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NR	not reported
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PCR	polymerase chain reaction
PY	person years
RNA	ribonucleic acid
RR	relative risk
RT-PCR	reverse transcriptase-prolymerase chain reaction
ssRNA	single-stranded RNA
SIR	standardized incidence ratios
sIL2S	soluble interleukin-2 receptor-α
STD	sexually transmitted disease
USA	United States of America

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 Human T-lymphotrophic Virus (HTLV). 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 HTLV through 12/2008, so PubMed, Web of Science and Scopus were searched for new information about HTLV from > 2008 to August 2015. Table 1 highlights the general concepts searched with selected example terms. To review all the terms used, please refer the to full search strings below.

Table A-1. Major topics searched

Topics	Example terms
Human T-lymphotrophic virus type 1	Human T-lymphotrophic virus type 1(Mesh), Adult T-cell leukemia-lymphoma virus 1, Human T-cell leukemia virus 1, HTLV
General Cancer	Neoplasm(s), Tumor(s), leukemia, cancer(s)
Study types Epidemiology Terms	case control, ecological studies, follow-up study cohort, Epidemiologic Studies (Mesh), epidemiology (Subheading)
Mechanistic Terms	Mode of action, Mechanism

The literature for HTLV was searched without using narrowing terms within the bibliographic databases. The results were then processed in EndNote to remove duplicates and conduct a second level of searching for the relevant major topics, before being transferred to DistillerSR for screening.
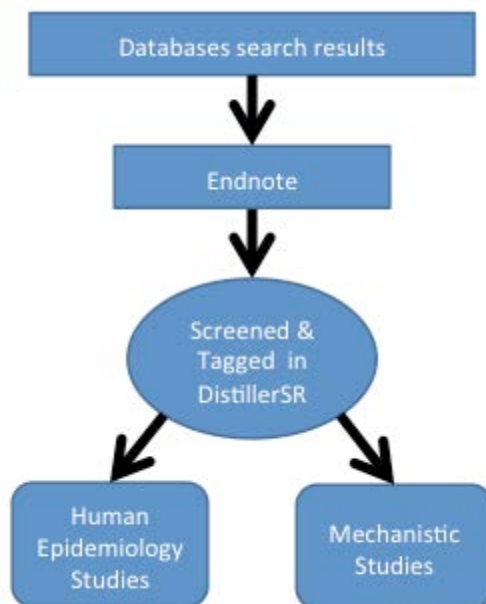
Figure A-1: Literature Processing Flow

The bibliographic database search results (5,239) 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 searched were also included. Tagging in DistillerSR categorized the useful articles into Human Epidemiologic literature (40) or Mechanistic literature (193).

Search strings for HTLV-1 Searches

PubMed: 2010-2015

"Human T-lymphotrophic virus type 1"[MeSH] OR "Human T-lymphotrophic virus type 1" OR "HTLV-1" OR "HTLV" OR "Human T-cell leukemia virus 1" OR "Adult T-cell leukemia-lymphoma virus 1"

Scopus and WOS: 2010-2015

"Human T-lymphotrophic virus type 1" OR "HTLV-1" OR "HTLV" OR "Human T-cell leukemia virus 1" OR "Adult T-cell leukemia-lymphoma virus 1"

Endnote searching:

Cancer* OR Neoplas* OR Tumor* OR Lymphoma* OR Leukemia*

Epidemiol* OR Case report OR Case control OR Case series OR Case referent OR Cohort OR Registry

Mode of action OR Mechanism

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Part 2

Draft Profile

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Human T-Cell Lymphotropic Virus Type 1

CAS No.: none assigned

Known to be a human carcinogen[1]

Also known as HTLV-1

Carcinogenicity

Human T-cell lymphotropic virus type 1 (HTLV-1) is *known to be a human carcinogen* based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological and molecular studies, which show that HTLV-1 causes adult T-cell leukemia/lymphoma (ATLL), and on supporting mechanistic data. There is also limited evidence for an association with liver cancer.

HTLV-1 is a retrovirus that can integrate into the genome of CD4 T lymphocytes. Most carriers of this virus do not get cancer; however, 2% to 4% of carriers develop ATLL. The genetic signature of the virus in this T-cell cancer is monoclonal, over 90% of the cancer cells are infected with HTLV-1, and oncogenic viral proteins are produced (IARC 2012), indicating that the viral infection preceded the cancer.

Cancer Studies in Humans

Most of the human cancer studies on HTLV-1 have evaluated ATLL, a rare and aggressive T-cell malignancy most commonly found in areas where HTLV-1 is endemic, such as Japan, the Caribbean, and the Middle East. The only other cancer end points for which the data were sufficient to evaluate an association with HTLV-1 were liver cancer and stomach (gastric) cancer. Findings for other solid tumors were limited to one or two studies (Matsumoto *et al.* 2008).

The epidemiological and molecular studies demonstrate a credible association between HTLV-1 infection and ATLL. Infection with HTLV-1 is one of the diagnostic criteria for ATLL. The original link between HTLV-1 infection and ATLL came from case reports and case series that found consistent evidence of HTLV-1 infection in ATLL cases; over 550 HTLV-1 associated cases of ATLL have been reported in case-series studies published between 1985 and 2005 (IARC 1996, 2012). In addition, eight cohort studies were identified, including six studies conducted in Japan (see section 3, Human Cancer Studies, Cancer Hazard Evaluation Component, IARC 2012), one study in the United States (Biswas *et al.* 2010), and one study in Israel (Stienlauf *et al.* 2013). The findings of these studies suggest a greater risk of disease and mortality in male than in female HTLV-1 carriers. In four nested case-control studies in HTLV-1 cohorts (Hisada *et al.* 1998a,b, Arisawa *et al.* 2002, Okayama *et al.* 2004), the risk of developing ATLL was greater with higher proviral load or higher anti-HTLV-1 antibody levels. Prospective studies and detection of HTLV-1 clonality in tumors indicate that infection precedes diagnosis of ATLL. In addition, studies of human cells demonstrate that a key HTLV-1 transactivator gene, *Tax*, can immortalize T cells both *in vitro* and *in vivo* in the absence of other viral factors (IARC 2012).

Epidemiological studies provide limited evidence for a causal association between HTLV-1 infection and liver cancer. The database consists of four case-control studies (Asou *et al.* 1986, Iida *et al.* 1988, Kamihira *et al.* 1994, Okayama *et al.* 1995) and two prospective cohort studies

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[1]NTP preliminary listing recommendation proposed for the RoC

(Arisawa *et al.* 2003, 2006) measuring HTLV-1 seropositivity. All studies found either higher prevalence of HTLV-1 seropositivity among liver-cancer patients than among control subjects or elevated risk estimates for liver cancer with HTLV-1 infection. Most of the findings were statistically significant; however, chance, bias, and confounding could not be ruled out as potential explanations for the results. All of the studies were conducted in Japan, where the major risk factors for liver cancer are hepatitis B and C viruses (HBV and HCV); it therefore is unclear whether HTLV-1 could be a cofactor in liver carcinogenesis or was a confounding factor in the studies. One study of HCV-infected case and control subjects suggested that HTLV-1 increased the risk of HCV-associated liver cancer in men (Kamihira *et al.* 1994). In addition, it is unclear whether HTLV-1 is a possible risk factor for liver cancer or whether the development of liver cancer contributes to expression of latent HTLV-1 infection (Asou *et al.* 1986). The numbers of HTLV-1-infected liver-cancer patients in the studies were small, and follow-up was short in one of the cohort studies (Arisawa *et al.* 2003).

Three cohort studies and one case-control study have investigated the association between HTLV-1 and stomach cancer (Arisawa *et al.* 2003, 2006, Matsumoto *et al.* 2008, Tahaei *et al.* 2011). Relative risks or odds ratios less than 1 (i.e., a decreased risk of stomach cancer in HTLV-infected individuals) were found in all studies, most of which included few HTLV-1-infected stomach-cancer patients. In one study, antibodies to *Helicobacter pylori* (a major risk factor for stomach cancer) were lower among HTLV-1 carriers than in the non-carrier group, suggesting that HTLV-1 might reduce the risk of *H. pylori* infection.

Studies on Mechanisms of Carcinogenesis

Tax is an HTLV-1 protein that affects multiple oncogenic pathways. Tax interacts with the NF-κB family of transcription factors, leading to increased expression of interleukin 2 (IL-2), IL-2 receptor, and IL-6 (Currer *et al.* 2012). NF-κB proteins are involved in T-cell proliferation, growth, and survival. Tax also affects DNA repair and triggers genetic instability (Currer *et al.* 2012). It is highly immunogenic and normally is held in check by the host immune system. However, in individuals with a weakened immune response, Tax expression can initiate and promote cancer. At cancer stage, Tax expression may be reduced or eliminated as a result of changes in the *Tax* gene; however, another HTLV-1 viral protein, HTLV-1 bZIP factor (HBZ), and host oncogenic alterations, such as mutations of the $p16^{INK4A}$ and $p53$ tumor-suppressor genes, result in clonal selection and cell proliferation of the leukemia/lymphoma (see Section 4, Mechanisms and Other Relevant Data, Cancer Hazard Evaluation Component).

Biological Properties

HTLV-1 is an enveloped single-stranded RNA (ssRNA) delta-type retrovirus of the subfamily Oncovirinae originally found in T-cell lymphoma (IARC 1996, 2012, Jacobson and Massoud 2013). HTLV-1 is composed of an outer lipid membrane envelope with two surface proteins (Schafer *et al.* 2015, IARC 2012) enclosing a protein matrix, which surrounds a protein capsid containing two copies of a 9-kb viral ssRNA genome (IARC 2012, 1996, Jacobson and Massoud 2013). The three main viral genes are *gag*, which encodes matrix and capsid proteins, *pol*, which encodes reverse transcriptase, integrase, and protease, and *env*, which encodes the envelope proteins. Single-protein genes encode the regulatory proteins Tax and Rex and the accessory proteins p12, p13, p30, and HBZ. Viral gene expression is controlled by promoters and enhancers in the two long terminal repeat regions.

The HTLV-1 virion is immunogenic, so active viral production will elicit a cytotoxic T-cell anti-HTLV-1 immune response (Cook *et al.* 2013, Carpentier *et al.* 2015), which is thought to be responsible for controlling viral load. During the latent phase, Tax promotes host cell proliferation. However, Tax itself is immunogenic; for a latent infection to be maintained, Tax expression is suppressed, and host cell proliferation is maintained by HBZ, which is less immunogenic than Tax, allowing for clonal expansion of latently infected cells.

Detection

HTLV-1 is rarely detected free in bodily fluids, but is found in peripheral mononuclear blood cells in breast milk, blood, semen, and cerebrospinal fluid (IARC 1996, Carpentier *et al.* 2015, Schafer *et al.* 2015). Detection is most commonly through measurement of anti-HTLV-1 antibodies, but can also involve measurement of viral RNA or DNA in peripheral mononuclear blood cells (allowing measurement of viral load) or *in vitro* culture of the virus. Initial anti-HTLV-1 antibody screening tests are performed by several different methods, and specimens with positive results are further tested in a confirmatory laboratory-based Western blot immunoassay or immunofluorescence assay (IARC 1996). If the confirmatory test gives indeterminate results, the more sensitive and more expensive radioimmunoprecipitation assay can be performed. The percentage of cells infected with HTLV-1 is determined primarily by the cytotoxic T-cell response against HTLV-1 infected cells and varies widely among individuals (Cook *et al.* 2013).

Exposure

Prevalence studies measuring antibodies to HTLV-1 have shown that a significant number of people in the United States are exposed to HTLV-1.

Transmission

Transmission of HTLV-1 requires cell-to-cell contact, as the virus is unstable outside of cells. The three main transmission modes are vertical (mother to child), sexual, and parenteral (through a break in the skin) (IARC 2012). HTLV-1 infects T cells, mainly CD4 T cells (helper T cells) and, to a lesser extent, CD8 T cells (cytotoxic T cells); other hematopoietic cells can be infected as well (IARC 1996, 2012, Jacobson and Massoud 2013, Carpentier *et al.* 2015, Schafer *et al.* 2015). The highest rates of HTLV-1 transmission are via breastfeeding, and risk depends on the proviral load of the mother's breast milk and on breastfeeding duration. Vertical transmission occurs rarely *in utero* (e.g., during the intrauterine period or peripartum in less than 5% of cases) (Hlela and Bittencourt 2014). Risk factors for sexual transmission include unprotected sex with an infected partner, multiple lifetime sexual partners, and infection with sexually transmitted diseases (IARC 2012). HTLV-1 transmission also occurs via transfusion of cellular blood components and needle-sharing by injection drug users.

Seroprevalence Studies

Most HTLV-1 prevalence studies in the United States have focused on blood donor or injection drug user (IDU) populations (Gessain and Cassar 2012). A detailed study of HTLV-1 prevalence in the United States conducted from 2000 to 2009 reported a seroprevalence of 0.0051% (5.1 cases per 100,000) among blood donors in the United States indicating that approximately 16,000 individuals living in the United States carry this virus (Chang *et al.* 2014, Cook and

Taylor 2014). Previous studies reported U.S. HTLV-1 seroprevalence ranging from 0.009% to 0.025% (Williams *et al.* 1988, Murphy *et al.* 1999, Poiesz *et al.* 2001). No analyses of HTLV-1 prevalence in blood, serum, or urine specimens were identified from the National Health and Nutrition Examination Survey.

Diseases (Non-Cancer), Prevention, and Treatment

Most HTLV-1-infected individuals are lifelong asymptomatic carriers (Cook *et al.* 2013); only 2% to 5% of infected people develop diseases related to the virus (Hlela and Bittencourt 2014). HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP, a chronic and progressive inflammatory disease of the central nervous system) is the most common clinical manifestation of HTLV-1 (Fuzii *et al.* 2014). Other diseases associated with HTLV-1 include HTLV-1 uveitis (eye inflammation) (Kamoi and Mochizuki 2012) and infective dermatitis associated (Hlela and Bittencourt 2014).

Prevention involves reducing transmission of HTLV-1 via breastfeeding, sexual transmission, and blood transfusion (McKendall 2014). Prenatal screening for HTLV-1 and counseling of seropositive mothers to avoid breastfeeding reduces mother-to-child transmission (Hino 2011, IARC 2012). Following practices that prevent sexually transmitted infections, such as using condoms and not having multiple or anonymous sexual partners, can reduce sexual transmission of HTLV-1 (Yoshimitsu *et al.* 2013). Counseling and education of injection drug users (e.g., implementation of harm-reduction practices) may be effective in reducing HTLV-1 infection among this population (Goncalves *et al.* 2010). Screening of the U.S. blood supply for HTLV-1, which began in 1988 (ARC 2015), has reduced the risk of transfusion-related transmission (McKendall 2014). There is no vaccine against HTLV-1 (ACS 2015, CDC 2015, FDA 2015b), although vaccine development efforts are ongoing (Kuo *et al.* 2011).

Regulations

Department of Transportation (DOT)

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

Food and Drug Administration (FDA)

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 HTLV-1 through donation of blood, serum, or plasma (except testing for source plasma). (The risk of HTLV-1, a highly cell-associated pathogen, is sufficiently mitigated by plasma-derivative manufacturing steps, including validated viral inactivation and removal procedures. These manufacturing procedures therefore obviate the need to test individual donations of source plasma for HTLV-1.)

21 CFR 1271 prescribes 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 HTLV-1.

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.

Guidelines

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 2015a).

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