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

Report on Carcinogens

Monograph on Human T-Cell Lymphotropic Virus Type 1

RoC MONOGRAPH 09

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Foreword

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

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

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

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

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

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Figures

This report has been reformatted to meet new NTP publishing requirements; its content has not changed. The proposed substance profile is no longer part of the document because it is published in the 14th Report on Carcinogens.

About This Report

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Peer Review

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

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

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

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

The panel was asked to vote on the following questions:

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

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

This RoC monograph on HTLV-1 has been revised based on NTP's review of the panel's peer-review comments. The Peer-Review Panel Report, which captures the panel recommendations for listing status of HTLV-1 in the RoC and their scientific comments, and the NTP Response to the Peer-Review Report are available on the Peer-Review Meeting webpage for human T-cell lymphotropic virus type 1 (http://ntp.niehs.nih.gov/go/38854).

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Abstract

Introduction: An estimated 90,000 to 100,000 people in the United States are infected with human T-cell lymphotropic virus type 1 (HTLV-1), an enveloped, single-stranded RNA delta-type retrovirus of the subfamily *Oncovirinae*. HTLV-1 infects T cells, mainly CD4 T cells, and transmission requires cell-to-cell contact. The three main modes of transmission are from mother to child (mainly through breastfeeding), sexual contact, and unscreened blood transfusions or organ transplants. Most HTLV-1-infected individuals are lifelong asymptomatic carriers, with only 2% to 5% developing disease. The virus was first isolated in 1979 from peripheral blood lymphocytes in a patient thought to have T-cell lymphoma.

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

Results and Discussion: NTP concluded there was sufficient evidence of HTLV-1 causing acute T cell leukemia/lymphoma (ATLL), a rare and aggressive T cell cancer. Many case series studies found consistent evidence of HTLV-1 infections in over 500 ATLL cases. Several cohort studies found higher rates of death from ATLL among HTLV-1 carriers. Some found this rate higher in men than in women. Other prospective studies found the risk of developing ATLL was greater with higher proviral load or higher anti-HTLV-1 antibody levels. Molecular studies of almost all ATLL tumors found that the virus is integrated in a monoclonal fashion, indicating infection precedes disease, and some tumors express Tax, a key HTLV-1 protein. Mechanistic studies found that Tax can immortalize T cells both in vitro and in immunodeficient mice and support the evidence from human studies. Because of the high prevalence of HTLV-1 infection (over 90%) and monoclonal integration in almost all ATLL cases, HTLV-1 monoclonal integration is part of the diagnostic definition of ATLL.

NTP Hazard Conclusion and Significance: The conclusion of the cancer hazard evaluation was that HTLV-1should be listed as *known to be a human carcinogen* in the RoC. The Secretary of Health and Human Services approved the listing of HTLV-1 in the 14th RoC. The rationale for the listing was sufficient evidence from studies in humans (epidemiological and molecular) for ATLL. Globally, HTLV-1 is estimated to be responsible for approximately 10,000 cancers per year.

Introduction and Methods

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

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

Monograph Contents

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

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

Evaluating the Evidence from Human Epidemiological Studies

The available studies of specific types of cancer for these human viruses present several challenges with respect to the evaluation of methodological strengths and limitations of the body of evidence. Large prospective cohort studies, particularly those that follow individuals for

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

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

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

Evaluating Causality of Viruses

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

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

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

Hill's Characteristics of Causality

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

Table 1. Hill's Epidemiological Characteristics for Evaluating Causality

Characteristic	Description
1. Strength of association	A strong association between a virus and a cancer increases the confidence for causality unless confounded by some other exposure. However, a weak association does not give evidence against causality.
2. Consistency	Consistent findings observed among different groups of people, in different places, circumstances, and times.
3. Specificity	A viral exposure is limited only to specific types of cancer; this is considered a weak factor because there are well-established examples in which a virus might cause several types of cancer.
4. Temporality	Exposure to the virus must occur prior to the onset of the cancer, in contrast to a "passenger infection."
5. Biological gradient	The virus is more likely to be found at the tumor site than at non-tumor sites.
6. Plausibility	This characteristic should be applied with caution because it is limited by current medical knowledge (e.g., a currently 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.

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

Source: Moore and Chang (2014).

Evaluating Mechanistic Data from Human Studies

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

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

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

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

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

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

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

Source: zur Hausen and de Villiers (2014).

Multicausality Issues

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

Application of Causality Criteria and Alternative Approaches

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

While causal criteria can be helpful, there are flaws and practical limitations that restrict their use in cancer biology (Moore and Chang 2010). Therefore, a more probabilistic approach may be more useful for determining whether or not certain viruses cause human cancers. For example, instead of trying to determine if virus A causes cancer B, the probabilistic approach examines if cancer B is more probable in the presence of virus A. Although a correlation does not imply causation, it can be argued that correlations that are strong, reproducible, and predictive have a similar value as a causative conclusion. In a similar fashion, zur Hausen and de Villiers (2014) also expressed concern over all attempts to summarize criteria for "causality" of infectious agents in cancer development and proposed replacing "causal factor" with "risk factor" and grading them according to their contribution to an individual's cancer risk. This will require a greater understanding of the complexity of factors involved and their mechanistic contribution to individual cancers.

RoC Listing Criteria

Known to Be Human Carcinogen:

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

Reasonably Anticipated to Be Human Carcinogen:

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

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

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

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

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

NTP's Approach

For each virus, NTP applied the RoC listing criteria (see text box) to the body of literature to reach the listing recommendation. The level of evidence conclusion from studies in humans considers the evidence from epidemiological studies as well as clinical and molecular studies of tissues from exposed (i.e., infected) individuals. In evaluating the mechanistic data and

determining the recommendations for its level of evidence conclusion and overall listing recommendation, NTP considered the principles outlined by Hill (1965), IARC (1997b), zur Hausen (1994; 2001; 2014), and Rothman and Greenland (2005) in its assessment of causality for the five viruses reviewed. However, these factors were not used as a strict checklist to either prove or disprove a causal association but rather as guidance to assess the level of epidemiological or molecular evidence that a virus contributes to a carcinogenic effect.

1. Properties and Detection

This section reviews the 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 and Cassar 2012; IARC 2012). HTLV-1 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 (Poiesz et al. 1980). 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 myelopathy, pulmonary infections, and elevated lymphocyte and platelet counts but not with neoplasms (IARC 1996; 2012; Murphy et al. 1997a; 1997b). 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 (IARC 1996; 2012; Jacobson and Massoud 2013). 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 surrounding 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) (IARC 1996; 2012; Jacobson and Massoud 2013). The HTLV-1 genome is about 9 kb long and contains three major genes that 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). The lipid membrane envelope is created by budding off from the host cell membrane, which has been modified 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 (IARC 2012; Schafer et al. 2015). 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 1996; 2012). 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 (IARC

2012; Jacobson and Massoud 2013). Viral gene expression is controlled by promoters and enhancers in the two LTR regions and are regulated by Tax protein. Tax regulates the expression of viral genes and some host genes that promote cell proliferation (see Section 4.3). However, Tax is immunogenic and anti-Tax immune responses lead to a decrease in Tax expression. Even with decreased expression of Tax, cell proliferation continues to be promoted by HBZ, which also can suppress Tax expression. HBZ is less immunogenic than Tax; therefore, HBZ becomes the predominant driver of cell proliferation in later stages of infection. This allows for the clonal expansion of latently infected cells.

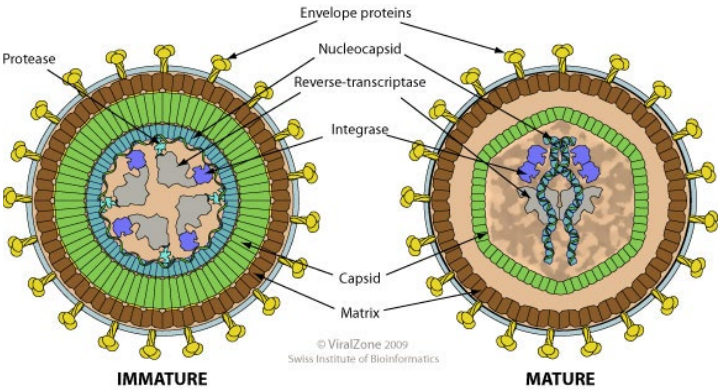

Figure 1-1. Human T-cell Lymphotropic Virus Particle

Source: CreativeCommons.org.

1.1.3. Infection and Replication

Free HTLV-1 viruses are unstable and not very infectious (Carpentier et al. 2015; IARC 1996; 2012; Jacobson and Massoud 2013; Schafer et al. 2015). Transmission of infection occurs primarily through cell-to-cell contact between an infected and uninfected cell; cell-free virus transmission has been described but it is much less efficient (Gross and Thoma-Kress 2016). 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 (Carpentier et al. 2015; IARC 1996; 2012; Jacobson and Massoud 2013; Schafer et al. 2015). In vitro studies have demonstrated that dendritic cells can be infected without cell-to-cell contact (i.e., cell-free) and a role for this route of infection has been proposed as a possible way that HTLV-1 infection is initially acquired (Gross and Thoma-Kress 2016).

HTLV-1 viruses bind to uninfected cells by the Env protein, gp46 (Cook et al. 2013; IARC 1996; 2012; Jacobson and Massoud 2013; Schafer et al. 2015), inducing a conformational change in the protein that allows it to bind to cellular glucose transporter 1 and facilitates fusion of the viral and cellular membranes. Cell-to-cell transmission of HTLV-1 viruses occurs through several possible mechanisms (Carpentier et al. 2015; Gross and Thoma-Kress 2016; Jacobson and Massoud 2013; Schafer et al. 2015) (see Figure 1-2). Cell-to-cell attachments can occur in a way that protects the virions from the surrounding environment, called a virological synapse. Extracellular viral transfer can occur when viral particles attach to the infected cell's membrane during viral budding, which can then come in contact with uninfected cells. The close contact

between virally infected antigen-presenting cells and T cells allows budding viruses to infect T cells. Epithelial or endothelial cells with intercellular conduits, such as gap junctions, can allow the virus to pass to neighboring cells.

When the viral and cellular membranes fuse, the viral contents empty into the cytoplasm releasing the ssRNA genome, along with reverse transcriptase, integrase, and protease enzymes (Cook et al. 2013; IARC 1996; 2012; Jacobson and Massoud 2013; Schafer et al. 2015). The ssRNA genome is then replicated by reverse transcriptase to a DNA genome, which integrates into the host cell genome. 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. 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), and has better genetic stability. Instead, the provirus is amplified along with the host genome during cell division (Gessain and Cassar 2012; Kubota et al. 2007). During virion production, viral proteins are produced and ssRNA is expressed and binds 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 1-2).

The HTLV-1 virion is immunogenic, 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. However, HBZ 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.

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; IARC 1996; Schafer et al. 2015). 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. Although procedures are prescribed for donor screening and tissue testing to ensure that tissues intended for human transplant are free of HTLV-1, some vascularized human organs for transplantation are excluded from testing.

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 using a supplemental test that offers the ability to differentiate HTLV-1 from HTLV-2.

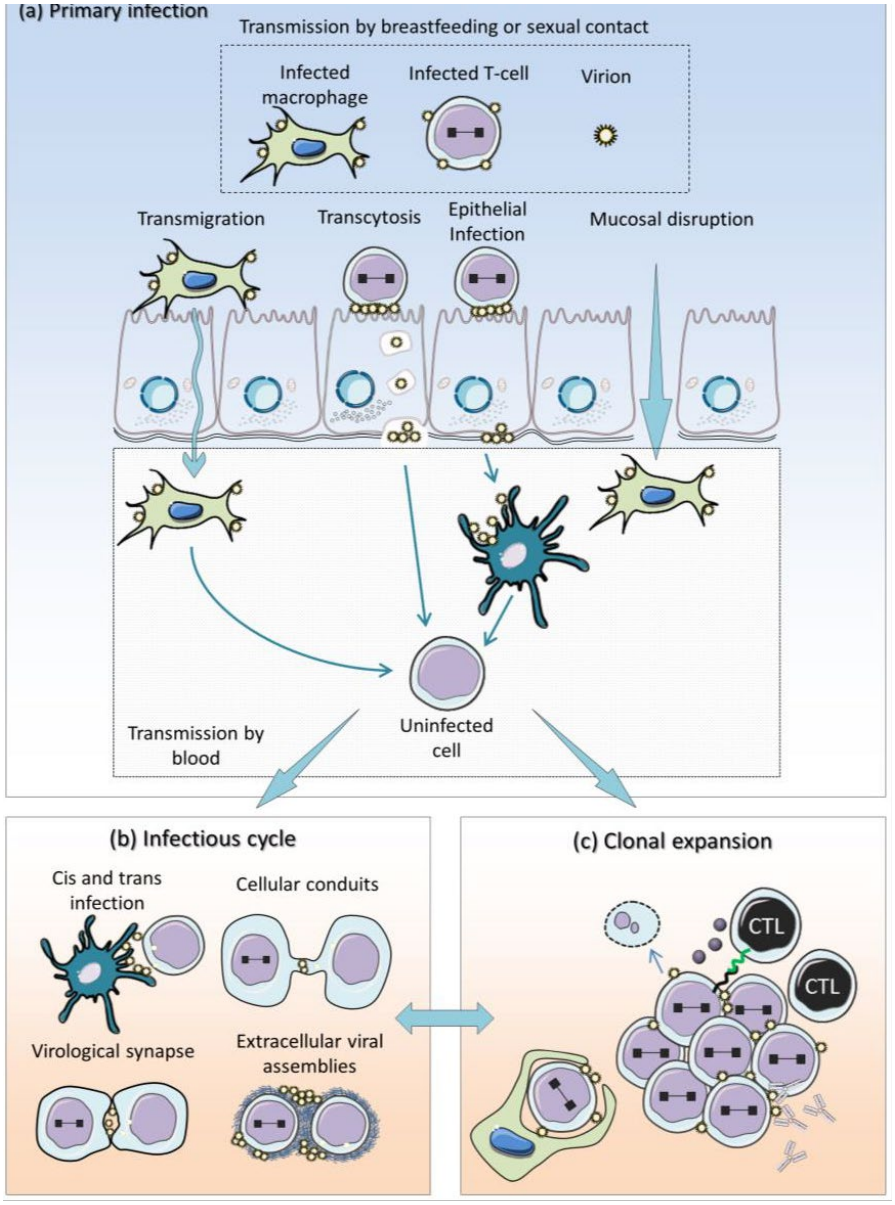

Figure 1-2. HTLV Infection and Replication Cycle

Source: Carpentier et al. (2015).

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.

Supplemental tests include western blot, immunofluorescence, and recombinant immunoblot (RIBA) (IARC 1996; Sabino et al. 1999). Both western blots and ELISA use 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. PCR is able to clarify indeterminate western blot and ELISA results, can differentiate HTLV-1 from HTLV-2 (Sabino et al. 1999) and is supplanting the western blot in usage.

1.2.2. Detection of RNA

Detection of viral RNA or DNA is usually carried out on peripheral mononuclear cells in blood, semen, and breast milk (Carpentier et al. 2015; IARC 1996; Schafer et al. 2015). 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. The amount of HTLV proviral DNA can be measured using quantitative assays based upon real-time PCR and is usually expressed as HTLV copies per peripheral blood mononuclear cell. This allows for 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.

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 in most cases, with antigen-presenting cells thought to play a major role in infecting CD4 T cells. However, cell-free infection of dendritic cells in vitro has been described. 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. Cell proliferation is promoted by Tax and HBZ. 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 of HTLV-1 is most commonly carried out by

measurement of anti-HTLV-1 antibodies. Other detection methods include measurement of viral RNA or DNA from peripheral mononuclear cells in blood, semen, and breast milk or use of in vitro culture techniques for peripheral blood mononuclear cells or cord blood cells. Specimens with positive results are further tested in a confirmatory laboratory-based Western blot immunoassay, polymerase chain reaction, immunofluorescence assay, or recombinant immunoblot assay.

2. Human 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 injection 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 (Murphy et al. 1999; Poiesz et al. 2001; Williams et al. 1988). The number of HTLV-1-infected persons in the United States has been estimated to range from 90,000 to 100,000 persons (Gessain and Cassar 2012). 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 The 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 (southwestern Japan, sub-Saharan Africa, the Caribbean islands, and parts of South America) but not all populations. For example, Gessain and Cassar (2012) based their estimates on areas with a total of 1.5 billion people that did not include China, India, or other highly populated regions in the approximately 7 billion total world population in 2012 (PRB 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 where HTLV-1 is found mainly in immigrants from endemic countries (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 routes of transmission include the transfer of infected cells from one person to another through blood transfusions, breast-feeding, and sexual intercourse (Carpentier et al. 2015; Cook et al. 2013; Schafer et al. 2015). 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 macrophages 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 their basal end, or virions could cross the epithelial cells by transcytosis. Transcytosis occurs when

virus from infected T cells is endocytosed by the epithelial cells on the apical end and then is passed to the basal end inside a vesicle, never coming in contact with the cytoplasm.

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 (Ichimaru et al. 1991). 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 sexually transmitted diseases among populations. HTLV-1 transmission via the transfusion of cellular blood products is very efficient, with transmission of at least 40% (Manns et al. 1992), and blood donors have been screened for HTLV-1 antibody in the United States since 1988. HTLV infection is also transmitted via injection drug use, although HTLV-2 is more common than HTLV-1 in this risk group (Khabbaz et al. 1992). Organ-transplantation-acquired infection has been reported in Germany (Glowacka et al. 2013) and the United States (Ramanan et al. 2014).

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 (Hino 2011; IARC 2012). 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 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). Blood screening has reduced the risk of transfusion-related transmission (McKendall 2014); screening the U.S. blood supply for HTLV-1 began in 1988 (IARC 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 2015; CDC 2015; FDA 2015); however, vaccine development efforts are ongoing (Kuo et al. 2011).

2.3. Summary

The number of human T-cell lymphotropic virus type 1 (HTLV-1)-infected persons in the United States has been estimated to range from 90,000 to 100,000 persons, indicating that a significant number of people living in the United States are exposed to (HTLV-1). Worldwide prevalence of HTLV-1 is highest in endemic areas including southwestern Japan, parts of sub-Saharan Africa, the Caribbean Islands, and South America; 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.

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 1996; 2012) 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 are included.

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 prevalent and prototype of adult T-cell leukemia/lymphoma), lymphoma type, chronic type, and smoldering type (a slow-growing type of adult T-cell leukemia/lymphoma) (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 IARC review (1996) 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 adult T-cell leukemia/lymphoma in South America, Japan, and other Asian countries (see Table 2.1 in 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 about one per thousand person years, or 2% to 4% over a lifetime post-infection (Matutes 2007; Murphy et al. 1989). 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). In Japan, 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 (Arisawa et al. 2000; Arisawa et al. 2003; Arisawa et al. 2006; Hisada et al. 2001; Stienlauf et al. 2013; Tokudome et al. 1991). Modeling data from Jamaica have not identified higher disease penetrance in HTLV-1-infected men compared to women (Murphy et al. 1991).

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 (Arisawa et al. 2002; Hisada et al. 1998a; Hisada et al. 1998b; Okayama et al. 2004). 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	3,991 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)[c]	–	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)[c]	–	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. (1998a) 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. (1998b)	Japan MCS cohort	5 cases/38 matched controls		**OR (95% CI)**	Matched on age, gender, study screens. Also adjusted for other viral markers, smoking, leukocyte count	Pre-diagnosis predictors of ATLL
			Anti-HTLV-1/level	1.6 (0.94–3.8)		
			Anti-Tax/unit	0.78		
Arisawa et al. (2002)	Japan	29 cases/158 matched controls		**OR (95% CI)**	Matched for gender, birth year, date of first blood draw	Pre-diagnosis predictors of ATLL
			sIL-2R ≥500 U/mL vs. <500 (N = 18)	20.5 (4.5–194)		
			anti-HTLV-1 titer ≥1,024 vs. <1,024 (N = 17)	2.9 (0.98–9.5)		
			anti-Tax (N = 18)	0.59 (0.15–2.0)		
Okayama et al. (2004)	Japan MCS cohort	4 cases/37 matched controls		**OR (95% CI)**	Matched for age and gender	Pre-diagnosis predictors of ATLL
			Proviral load/per 1,000 copies	1.42 (1.04–2.10)		

Studies prior to 2009 were reviewed by IARC (2012), and results shown are adapted here from IARC 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; sIL-2R = 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 at least in Japan. 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 incidence 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. Plumelle 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 (Gabet et al. 2000; Satoh et al. 2002) 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 and monoclonal integration of the virus in almost all adult T-cell leukemia/lymphoma cases, monoclonal integration is now part of the diagnostic definition of the disease (IARC 1996; 2012). 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 studies for these cancer endpoints 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 1996; 2012).

3.3.2. Solid Tumors

A small number of epidemiologic studies have investigated the association between HTLV-1 and other cancer endpoints; however, the association was not strong because most studies had few cases. Four studies, three cohort and one case-control study, have investigated the association of HTLV-1 and gastric cancer; two of which (Arisawa et al. 2003; Matsumoto et al. 2008) 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 with 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), Asou et al. (1986); Iida et al. (1988); Kamihira et al. (1994)) and two prospective cohort studies (Arisawa 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. In addition patients with liver

cancer are likely to receive blood transfusions that may result in both HTLV-1 and hepatitis infections (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 1996; 2012).

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 = hepatitis 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 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	• Although several studies reported a decreased risk of gastric cancer most studies had few cases.
Liver cancer	• Although several studies found an increased risk of liver cancer among HTLV-1-infected individuals, the body of literature is limited by small number of studies or exposed subjects and potential confounding from infection with hepatitis B or C viruses.

ATLL = Adult T-cell leukemia/lymphoma.

4. Mechanisms and Other Relevant Data

Human T-cell lymphotropic virus type 1 (HTLV-1) was the first oncogenic human retrovirus discovered (Poiesz et al. 1980; Poiesz et al. 1981; Yoshida et al. 1982). 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 background on 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), a mode-of-action evaluation (Section 4.4), and a synthesis of this information (Section 4.5).

4.1. Background

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 Section 1. Properties and Detection). 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 (Cesarman and Mesri 2007; Chang et al. 2014; Ciminale et al. 2014).

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 (IARC 1996; Moulés et al. 2005). ATLL does not appear to arise from the largest clones but from one of the numerous small clones in carriers suggesting that other oncogenic events are important in its pathogenesis (Cook et al. 2014). 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 (Gabet et al. 2000; Satoh et al. 2002). 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 (Matsuoka and Jeang 2007; Mesri et al. 2014; 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).

Humanized mouse models are under development to further investigate adult T-cell leukemia pathogenesis from HTLV-1 infection. In the mouse model, "Human Immune System" (HIS) $Rag2^{-/-}\gamma_c^{-/-}$, HTLV-1 infected human lymphocytes from thymus and spleen expressed CD25 indicating activation, and this activation correlated with the presence of Tax mRNA and increased NF-kB expression (Villaudy et al. 2011). However, there was no evidence of humoral immunity or T-cell mediated cytotoxicity. In another model, HTLV-1-infected IBMI-huNOG mice recapitulated ATLL-like symptoms, including oligoclonal proliferation of HTLV-1-infected T cells and the presence of flower cells, as well as HTLV-1 specific immune responses (Tezuka et al. 2014).

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 (Currer et al. 2012; Matsuoka and Jeang 2007; Mesri et al. 2014; 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 (Grossman et al. 1995; Pozzatti et al. 1990; Tanaka et al. 1990; Yao and Wigdahl 2000), 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 (Currer et al. 2012; Zane and Jeang 2014).
- *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 4-1) (Rahman et al. 2012; Sampey et al. 2012).

Table 4-1. 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	Anti-apoptotic, immune evasion
		MICB	
miR-132, miR-149, miR-873	Down	P300	Increase viral transcription
		AChE	Pro-inflammatory
miR-143-p3	Up	PKA	Proliferation
		GRα	Proliferation
miR-155	Up	TP53INP1	Anti-apoptotic
		Unknown	Increase IFN-γ
miR-146a	Up	Unknown	Proliferation

Source: Sampey et al. (2012).
AChE = acetyl cholinesterase; GRα = glucocorticoid receptor alpha; MICB = major histocompatibility complex chain I chain-related B; PKA = protein kinase A; PTEN = phosphatase and tensin homolog; TP53INP1 = tumor protein P53 inducible nuclear protein 1.

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 (Borowiak et al. 2013; Matsuoka and Jeang 2007; Mesri et al. 2014).
- 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 Jeang 2007; Matsuoka and Yasunaga 2013). Table 4-2 depicts key molecular oncogenic pathways of HTLV-1.

Table 4-2. 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.

5. Overall Cancer Hazard Evaluation and 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). The body of epidemiological studies for liver cancer was judged inadequate based on several limitations such as the small number of studies or few exposed subjects. In addition, there is potential confounding from infection with hepatitis B or C viruses and no available molecular data. Epidemiological studies provided limited evidence 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 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. Summary of the 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 (1985–2005). 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. Summary of the 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 (potential confounding from infection with hepatitis B or C viruses)
Molecular (human tissue)	No available information	No available information
Level of evidence	**Limited for decreased risk**	**Inadequate**

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

References

Akbarin MM, Rahimi H, Hassannia T, Shoja Razavi G, Sabet F, Shirdel A. 2013. Comparison of HTLV-I proviral load in adult T cell leukemia/lymphoma (ATL), HTLV-I-associated myelopathy (HAM-TSP) and healthy carriers. Iran J Basic Med Sci. 16(3):208-212.

American Cancer Society (ACS). 2015. Viruses that can lead to cancer. http://www.cancer.org/cancer/cancercauses/othercarcinogens/infectiousagents/infectiousagentsandcancer/infectious-agents-and-cancer-viruses. [Accessed on 8/26/15]

American Red Cross (ARC). 2015. Blood testing. American Red Cross. http://www.redcrossblood.org/print/learn-about-blood/what-happens-donated-blood/blood-testing.

Arisawa K, Soda M, Endo S, Kurokawa K, Katamine S, Shimokawa I, Koba T, Takahashi T, Saito H, Doi H et al. 2000. Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. Int J Cancer. 85(3):319-324. http://dx.doi.org/10.1002/(SICI)1097-0215(20000201)85:3<319::AID-IJC4>3.0.CO;2-B

Arisawa K, Katamine S, Kamihira S, et al. 2002. A nested case-control study of risk factors for adult T-cell leukemia/lymphoma among human T-cell lymphotropic virus type-I carriers in Japan. Cancer Causes Control. 13:657-663. http://dx.doi.org/10.1023/A:1019511224501

Arisawa K, Sobue T, Yoshimi I, Soda M, Shirahama S, Doi H, Katamine S, Saito H, Urata M. 2003. Human T-lymphotropic virus type-I infection, survival and cancer risk in southwestern Japan: A prospective cohort study. Cancer Causes Control. 14(9):889-896. http://dx.doi.org/10.1023/B:CACO.0000003853.82298.96

Arisawa K, Soda M, Akahoshi M, Fujiwara S, Uemura H, Hiyoshi M, Takeda H, Kashino W, Suyama A. 2006. Human T-cell lymphotropic virus type-1 infection and risk of cancer: 15.4 year longitudinal study among atomic bomb survivors in Nagasaki, Japan. Cancer Sci. 97(6):535-539. http://dx.doi.org/10.1111/j.1349-7006.2006.00212.x

Asou N, Kumagai T, Uekihara S, Ishii M, Sato M, Sakai K, Nishimura H, Yamaguchi K, Takatsuki K. 1986. HTLV-I seroprevalence in patients with malignancy. Cancer. 58(4):903-907. http://dx.doi.org/10.1002/1097-0142(19860815)58:4<903::AID-CNCR2820580417>3.0.CO;2-J

Bartholomew C, Jack N, Edwards J, Charles W, Corbin D, Cleghorn FR, Blattner WA. 1998. HTLV-I serostatus of mothers of patients with adult T-cell leukemia and HTLV-I-associated myelopathy/tropical spastic paraparesis. J Hum Virol. 1(4):302-305.

Biswas HH, Kaidarova Z, Garratty G, Gibble JW, Newman BH, Smith JW, Ziman A, Fridey JL, Sacher RA, Murphy EL. 2010. Increased all-cause and cancer mortality in HTLV-II infection. J Acquir Immune Defic Syndr. 54(3):290-296. http://dx.doi.org/10.1097/QAI.0b013e3181cc5481

Borowiak M, Kuhlmann AS, Girard S, Gazzolo L, Mesnard JM, Jalinot P, Dodon MD. 2013. HTLV-1 bZIP factor impedes the menin tumor suppressor and upregulates JunD-mediated transcription of the hTERT gene. Carcinogenesis. 34(11):2664-2672. http://dx.doi.org/10.1093/carcin/bgt221

Carpentier A, Barez PY, Hamaidia M, Gazon H, de Brogniez A, Perike S, Gillet N, Willems L. 2015. Modes of human T cell leukemia virus type 1 transmission, replication and persistence. Viruses. 7(7):3603-3624. http://dx.doi.org/10.3390/v7072793

Centers for Disease Control and Prevention (CDC). 2015. List of vaccines used in United States. http://www.cdc.gov/vaccines/vpd-vac/vaccines-list.htm. [Accessed: August 26, 2015]

Cesarman E, Mesri EA. 2007. Kaposi sarcoma-associated herpesvirus and other viruses in human lymphomagenesis. Curr Top Microbiol Immunol. 312:263-287. http://dx.doi.org/10.1007/978-3-540-34344-8_10

Chang YB, Kaidarova Z, Hindes D, Bravo M, Kiely N, Kamel H, Dubay D, Hoose B, Murphy EL. 2014. Seroprevalence and demographic determinants of human T-lymphotropic virus type 1 and 2 infections among first-time blood donors--United States, 2000-2009. J Infect Dis. 209(4):523-531. http://dx.doi.org/10.1093/infdis/jit497

Ciminale V, Rende F, Bertazzoni U, Romanelli MG. 2014. HTLV-1 and HTLV-2: Highly similar viruses with distinct oncogenic properties. Front Microbiol. 5:398. http://dx.doi.org/10.3389/fmicb.2014.00398

Cook LB, Elemans M, Rowan AG, Asquith B. 2013. HTLV-1: Persistence and pathogenesis. Virology. 435(1):131-140. http://dx.doi.org/10.1016/j.virol.2012.09.028

Cook LB, Melamed A, Niederer H, Valganon M, Laydon D, Foroni L, Taylor GP, Matsuoka M, Bangham CR. 2014. The role of HTLV-1 clonality, proviral structure, and genomic integration site in adult T-cell leukemia/lymphoma. Blood. 123(25):3925-3931. http://dx.doi.org/10.1182/blood-2014-02-553602

Cook LB, Taylor GP. 2014. HTLV-1 and HTLV-2 prevalence in the United States. J Infect Dis. 209(4):486-487. http://dx.doi.org/10.1093/infdis/jit558

Currer R, Van Duyne R, Jaworski E, Guendel I, Sampey G, Das R, Narayanan A, Kashanchi F. 2012. HTLV tax: A fascinating multifunctional co-regulator of viral and cellular pathways. Front Microbiol. 3:406. http://dx.doi.org/10.3389/fmicb.2012.00406

de The G, Bomford R. 1993. An HTLV-I vaccine: Why, how, for whom? AIDS Res Hum Retroviruses. 9(5):381-386. http://dx.doi.org/10.1089/aid.1993.9.381

Fuzii HT, da Silva Dias GA, de Barros RJ, Falcao LF, Quaresma JA. 2014. Immunopathogenesis of HTLV-1-assoaciated myelopathy/tropical spastic paraparesis (HAM/TSP). Life Sci. 104(1-2):9-14. http://dx.doi.org/10.1016/j.lfs.2014.03.025

Gabet AS, Mortreux F, Talarmin A, Plumelle Y, Leclercq I, Leroy A, Gessain A, Clity E, Joubert M, Wattel E. 2000. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. Oncogene. 19(43):4954-4960. http://dx.doi.org/10.1038/sj.onc.1203870

Gessain A, Cassar O. 2012. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol. 3(NOV). http://dx.doi.org/10.3389/fmicb.2012.00388

Giam CZ, Jeang KT. 2007. HTLV-1 Tax and adult T-cell leukemia. Front Biosci. 12:1496-1507. http://dx.doi.org/10.2741/2163

Glowacka I, Korn K, Potthoff SA, Lehmann U, Kreipe HH, Ivens K, Barg-Hock H, Schulz TF, Heim A. 2013. Delayed seroconversion and rapid onset of lymphoproliferative disease after transmission of human T-cell lymphotropic virus type 1 from a multiorgan donor. Clin Infect Dis. 57(10):1417-1424. http://dx.doi.org/10.1093/cid/cit545

Goncalves DU, Proietti FA, Ribas JG, Araujo MG, Pinheiro SR, Guedes AC, Carneiro-Proietti AB. 2010. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 23(3):577-589. http://dx.doi.org/10.1128/CMR.00063-09

Gross C, Thoma-Kress AK. 2016. Molecular mechanisms of HTLV-1 cell-to-cell transmission. Viruses. 8(3):74. http://dx.doi.org/10.3390/v8030074

Grossman WJ, Kimata JT, Wong FH, Zutter M, Ley TJ, Ratner L. 1995. Development of leukemia in mice transgenic for the tax gene of human T-cell leukemia virus type I. Proc Natl Acad Sci U S A. 92(4):1057-1061. http://dx.doi.org/10.1073/pnas.92.4.1057

Hill AB. 1965. The environment and disease: Association or causation? Proc R Soc Med. 58(5):295-300. http://dx.doi.org/10.1177/003591576505800503

Hino S. 2011. Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): The ATL Prevention Program Nagasaki. Proc Jpn Acad Ser B Phys Biol Sci. 87(4):152-166. http://dx.doi.org/10.2183/pjab.87.152

Hisada M, Okayama A, Shioiri S, Spiegelman DL, Stuver SO, Mueller NE. 1998a. Risk factors for adult T-cell leukemia among carriers of human T-lymphotropic virus type I. Blood. 92(10):3557-3561. https://doi.org/10.1182/blood.V92.10.3557

Hisada M, Okayama A, Tachibana N, Stuver SO, Spiegelman DL, Tsubouchi H, Mueller NE. 1998b. Predictors of level of circulating abnormal lymphocytes among human T-lymphotropic virus type I carriers in Japan. Int J Cancer. 77(2):188-192. http://dx.doi.org/10.1002/(SICI)1097-0215(19980717)77:2<188::AID-IJC3>3.0.CO;2-M

Hisada M, Okayama A, Spiegelman D, Mueller NE, Stuver SO. 2001. Sex-specific mortality from adult T-cell leukemia among carriers of human T-lymphotropic virus type I. Int J Cancer. 91(4):497-499. http://dx.doi.org/10.1002/1097-0215(20010215)91:4<497::AID-IJC1044>3.0.CO;2-A

Hlela C, Bittencourt A. 2014. Infective dermatitis associated with HTLV-1 mimics common eczemas in children and may be a prelude to severe systemic diseases. Dermatol Clin. 32(2):237-248. http://dx.doi.org/10.1016/j.det.2013.11.006

Ichimaru M, Ikeda S, Kinoshita K, Hino S, Tsuji Y. 1991. Mother-to-child transmission of HTLV-1. Cancer Detect Prev. 15(3):177-181.

Iida S, Fujiyama S, Yoshida K, Morishita T, Shibata J, Sato T, Nishimura Y. 1988. The seroprevalence of anti-HTLV-1 antibodies in patients with various liver diseases. Hepatogastroenterology. 35(5):242-244.

International Agency for Research on Cancer (IARC). 1996. Human T-cell lymphotropic viruses. In: Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses. Lyon, France: International Agency for Research on Cancer. p. 261-390.

International Agency for Research on Cancer (IARC). 1997a. Epstein-Barr virus. In: Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8. Lyon, France: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. p. 47-373.

International Agency for Research on Cancer (IARC). 1997b. Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8. In: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: International Agency for Research on Cancer. p. 549.

International Agency for Research on Cancer (IARC). 2012. Human T-cell lymphotropic viruse type 1. In: Biological Agents. Lyon, France: International Agency for Research on Cancer. p. 315-340.

Iwanaga M, Watanabe T, Yamaguchi K. 2012. Adult T-cell leukemia: A review of epidemiological evidence. Front Microbiol. 3:322. http://dx.doi.org/10.3389/fmicb.2012.00322

Iwata K, Ito S, Saito H, Ito M, Nagatomo M, Yamasaki T, Yoshida S, Suto H, Tajima K. 1994. Mortality among inhabitants of an HTLV-I endemic area in Japan. Jpn J Cancer Res. 85(3):231-237. http://dx.doi.org/10.1111/j.1349-7006.1994.tb02087.x

Jacobson S, Massoud R. 2013. Human T-cell lymphotropic virus type 1 infection. Birkhauser Advances in Infectious Diseases. Basel, Switzerland: Springer. p. 183-207.

Kamihira S, Yamada Y, Sohda H, Atogami S, Tomonaga M, Egawa S, Fujii M, Chifu K. 1994. Human T-lymphotropic virus type-I influence on hepatotropic virus infections and the subsequent development of hepatocellular carcinoma. Cancer Detect Prev. 18(5):329-334.

Kamoi K, Mochizuki M. 2012. HTLV-1 uveitis. Front Microbiol. 3(Article 270):1-4.

Kannian P, Green PL. 2010. Human T lymphotropic virus type 1 (HTLV-1): Molecular biology and oncogenesis. Viruses. 2(9):2037-2077. http://dx.doi.org/10.3390/v2092037

Khabbaz RF, Onorato IM, Cannon RO, Hartley TM, Roberts B, Hosein B, Kaplan JE. 1992. Seroprevalence of HTLV-1 and HTLV-2 among intravenous drug users and persons in clinics for sexually transmitted diseases. N Engl J Med. 326(6):375-380. http://dx.doi.org/10.1056/NEJM199202063260604

Kinjo T, Ham-Terhune J, Peloponese JM, Jr., Jeang KT. 2010. Induction of reactive oxygen species by human T-cell leukemia virus type 1 tax correlates with DNA damage and expression of cellular senescence marker. J Virol. 84(10):5431-5437. http://dx.doi.org/10.1128/JVI.02460-09

Koga Y, Iwanaga M, Soda M, Inokuchi N, Sasaki D, Hasegawa H, Yanagihara K, Yamaguchi K, Kamihira S, Yamada Y. 2010. Trends in HTLV-1 prevalence and incidence of adult T-cell leukemia/lymphoma in Nagasaki, Japan. J Med Virol. 82(4):668-674. http://dx.doi.org/10.1002/jmv.21738

Kubota R, Hanada K, Furukawa Y, Arimura K, Osame M, Gojobori T, Izumo S. 2007. Genetic stability of human T lymphotropic virus type I despite antiviral pressures by CTLs. J Immunol. 178(9):5966-5972. http://dx.doi.org/10.4049/jimmunol.178.9.5966

Kuo C-WS, Mirsaliotis A, Brighty DW. 2011. Antibodies to the envelope glycoprotein of human T cell leukemia virus type 1 robustly activate cell-mediated cytotoxic responses and directly neutralize viral infectivity at multiple steps of the entry process. J Immunol. 187(1):361-371. http://dx.doi.org/10.4049/jimmunol.1100070

Manns A, Wilks RJ, Murphy EL, Haynes G, Figueroa JP, Barnett M, Hanchard B, Blattner WA. 1992. A prospective study of transmission by transfusion of HTLV-I and risk factors associated with seroconversion. Int J Cancer. 51(6):886-891. http://dx.doi.org/10.1002/ijc.2910510609

Marcos LA, Terashima A, Dupont HL, Gotuzzo E. 2008. Strongyloides hyperinfection syndrome: An emerging global infectious disease. Trans R Soc Trop Med Hyg. 102(4):314-318. http://dx.doi.org/10.1016/j.trstmh.2008.01.020

Marin O, Hasui K, Remondegui C, Sato E, Aye MM, Takenouchi N, Izumo S, Tajima K. 2002. Adult T-cell leukemia/lymphoma in Jujuy, north-west Argentina. Pathol Int. 52(5-6):348-357. http://dx.doi.org/10.1046/j.1440-1827.2002.01356.x

Matsumoto S, Yamasaki K, Tsuji K, Shirahama S. 2008. Human T lymphotropic virus type 1 infection and gastric cancer development in Japan. J Infect Dis. 198(1):10-15. http://dx.doi.org/10.1086/588733

Matsuoka M. 2005. Human T-cell leukemia virus type I (HTLV-I) infection and the onset of adult T-cell leukemia (ATL). Retrovirology. 2:27. http://dx.doi.org/10.1186/1742-4690-2-27

Matsuoka M, Jeang KT. 2007. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat Rev Cancer. 7(4):270-280. http://dx.doi.org/10.1038/nrc2111

Matsuoka M, Yasunaga J. 2013. Human T-cell leukemia virus type 1: Replication, proliferation and propagation by Tax and HTLV-1 bZIP factor. Curr Opin Virol. 3(6):684-691. http://dx.doi.org/10.1016/j.coviro.2013.08.010

Matutes E. 2007. Adult T-cell leukaemia/lymphoma. J Clin Pathol. 60(12):1373-1377. http://dx.doi.org/10.1136/jcp.2007.052456

McKendall RR. 2014. Neurologic disease due to HTLV-1 infection. Handb Clin Neurol. 123:507-530. http://dx.doi.org/10.1016/B978-0-444-53488-0.00024-9

Mesri EA, Feitelson MA, Munger K. 2014. Human viral oncogenesis: A cancer hallmarks analysis. Cell Host Microbe. 15(3):266-282. http://dx.doi.org/10.1016/j.chom.2014.02.011

Moles R, Nicot C. 2015. The emerging role of miRNAs in HTLV-1 infection and ATLL pathogenesis. Viruses. 7(7):4047-4074. http://dx.doi.org/10.3390/v7072805

Moore PS, Chang Y. 2010. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat Rev Cancer. 10(12):878-889. http://dx.doi.org/10.1038/nrc2961

Moore PS, Chang Y. 2014. The conundrum of causality in tumor virology: The cases of KSHV and MCV. Semin Cancer Biol. 26:4-12. http://dx.doi.org/10.1016/j.semcancer.2013.11.001

Mortreux F, Gabet AS, Wattel E. 2003. Molecular and cellular aspects of HTLV-1 associated leukemogenesis in vivo. Leukemia. 17(1):26-38. http://dx.doi.org/10.1038/sj.leu.2402777

Moulés V, Pomier C, Sibon D, Gabet AS, Reichert M, Kerkhofs P, Willems L, Mortreux F, Wattel E. 2005. Fate of premalignant clones during the asymptomatic phase preceding lymphoid malignancy. Cancer Res. 65(4):1234-1243. http://dx.doi.org/10.1158/0008-5472.CAN-04-1834

Murphy EL, Hanchard B, Figueroa JP, Gibbs WN, Lofters WS, Campbell M, Goedert JJ, Blattner WA. 1989. Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. Int J Cancer. 43(2):250-253. http://dx.doi.org/10.1002/ijc.2910430214

Murphy EL, Figueroa JP, Gibbs WN, Holding-Cobham M, Cranston B, Malley K, Bodner AJ, Alexander SS, Blattner WA. 1991. Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. I. Demographic determinants. Am J Epidemiol. 133(11):1114-1124. http://dx.doi.org/10.1093/oxfordjournals.aje.a115824

Murphy EL, Fridey J, Smith JW, Engstrom J, Sacher RA, Miller K, Gibble J, Stevens J, Thomson R, Hansma D et al. 1997a. HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected blood donors. The REDS investigators. Neurology. 48(2):315-320. http://dx.doi.org/10.1212/WNL.48.2.315

Murphy EL, Glynn SA, Fridey J, Sacher RA, Smith JW, Wright DJ, Newman B, Gibble JW, Ameti DI, Nass CC et al. 1997b. Increased prevalence of infectious diseases and other adverse outcomes in human T lymphotropic virus types I- and II-infected blood donors. Retrovirus Epidemiology Donor Study (REDS) Study Group. J Infect Dis. 176(6):1468-1475. http://dx.doi.org/10.1086/514143

Murphy EL, Watanabe K, Nass CC, Ownby H, Williams A, Nemo G. 1999. Evidence among blood donors for a 30-year-old epidemic of human T lymphotropic virus type II infection in the United States. J Infect Dis. 180(6):1777-1783. http://dx.doi.org/10.1086/315139

National Toxicology Program (NTP). 2015. Handbook for preparing the report on carcinogens monographs. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Institute of Environmental Health Sciences, Division of the National Toxicoogy Program, Office of the Report on Carcinogens. https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf.

Okayama A, Maruyama T, Tachibana N, Hayashi K, Kitamura T, Mueller N, Tsubouchi H. 1995. Increased prevalence of HTLV-I infection in patients with hepatocellular carcinoma associated with hepatitis C virus. Jpn J Cancer Res. 86(1):1-4. http://dx.doi.org/10.1111/j.1349-7006.1995.tb02979.x

Okayama A, Stuver S, Matsuoka M, et al. 2004. Role of HTLV-1 proviral DNA load and clonality in the development of adult T-cell leukemia/lymphoma in asymptomatic carriers. Int J Cancer. 110:621-625. http://dx.doi.org/10.1002/ijc.20144

Pancake BA, Wassef EH, Zucker-Franklin D. 1996. Demonstration of antibodies to human T-cell lymphotropic virus-I tax in patients with the cutaneous T-cell lymphoma, mycosis fungoides, who are seronegative for antibodies to the structural proteins of the virus. Blood. 88(8):3004-3009. http://dx.doi.org/10.1182/blood.V88.8.3004.bloodjournal8883004

Plumelle Y, Gonin C, Edouard A, Bucher BJ, Thomas L, Brebion A, Panelatti G. 1997. Effect of Strongyloides stercoralis infection and eosinophilia on age at onset and prognosis of adult T-cell leukemia. Am J Clin Pathol. 107(1):81-87. http://dx.doi.org/10.1093/ajcp/107.1.81

Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. 1980. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A. 77(12):7415-7419. http://dx.doi.org/10.1073/pnas.77.12.7415

Poiesz BJ, Ruscetti FW, Reitz MS, Kalyanaraman VS, Gallo RC. 1981. Isolation of a new type C retrovirus (HTLV) in primary uncultured cells of a patient with Sézary T-cell leukaemia. Nature. 294(5838):268-271. http://dx.doi.org/10.1038/294268a0

Poiesz BJ, Papsidero LD, Ehrlich G, Sherman M, Dube S, Poiesz M, Dillon K, Ruscetti FW, Slamon D, Fang C et al. 2001. Prevalence of HTLV-I-associated T-cell lymphoma. Am J Hematol. 66(1):32-38. http://dx.doi.org/10.1002/1096-8652(200101)66:1<32::AID-AJH1004>3.0.CO;2-3

Population Reference Bureau (PRB). 2012. 2012 world population data sheet. Washington, DC. http://www.prb.org/pdf12/2012-population-data-sheet_eng.pdf. [Accessed: August 26, 2015]

Pozzatti R, Vogel J, Jay G. 1990. The human T-lymphotropic virus type I tax gene can cooperate with the ras oncogene to induce neoplastic transformation of cells. Molecular and cellular biology. 10(1):413-417. https://doi.org/10.1128/mcb.10.1.413-417.1990

Rahman S, Quann K, Pandya D, Singh S, Khan ZK, Jain P. 2012. HTLV-1 Tax mediated downregulation of miRNAs associated with chromatin remodeling factors in T cells with stably integrated viral promoter. PLoS One. 7(4):e34490. http://dx.doi.org/10.1371/journal.pone.0034490

Ramanan P, Deziel PJ, Norby SM, Yao JD, Garza I, Razonable RR. 2014. Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient--case report and literature review. Am J Transplant. 14(10):2417-2421. http://dx.doi.org/10.1111/ajt.12849

Rothman KJ, Greenland S. 2005. Causation and causal inference in epidemiology. Am J Public Health. 95 Suppl 1:S144-S150. http://dx.doi.org/10.2105/AJPH.2004.059204

Sabino EC, Zrein M, Taborda CP, Otani MM, Ribeiro-Dos-Santos G, Sáez-Alquézar A. 1999. Evaluation of the INNO-LIA HTLV I/II assay for confirmation of human T-cell leukemia virus-reactive sera in blood bank donations. J Clin Microbiol. 37(5):1324-1328. http://dx.doi.org/10.1128/JCM.37.5.1324-1328.1999

Sakata H, Iwakiri R, Koyama T, Yoshida T, Okamoto K, Miyazaki K, Mizuguchi TM, Kudo S, Tokunaga O, Fujimoto K. 2001. Human T-cell lymphotropic virus-associated primary gastric lymphoma. Dig Dis Sci. 46(7):1381-1386. http://dx.doi.org/10.1023/A:1010667232366

Sampey GC, Van Duyne R, Currer R, Das R, Narayanan A, Kashanchi F. 2012. Complex role of microRNAs in HTLV-1 infections. Front Genet. 3:295. http://dx.doi.org/10.3389/fgene.2012.00295

Satoh M, Toma H, Sugahara K, Etoh K, Shiroma Y, Kiyuna S, Takara M, Matsuoka M, Yamaguchi K, Nakada K et al. 2002. Involvement of IL-2/IL-2R system activation by parasite antigen in polyclonal expansion of CD4(+)25(+) HTLV-1-infected T-cells in human carriers of both HTLV-1 and S. stercoralis. Oncogene. 21(16):2466-2475. http://dx.doi.org/10.1038/sj.onc.1205329

Satou Y, Yasunaga J, Yoshida M, Matsuoka M. 2006. HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. Proc Natl Acad Sci U S A. 103(3):720-725. http://dx.doi.org/10.1073/pnas.0507631103

Schafer G, Blumenthal MJ, Katz AA. 2015. Interaction of human tumor viruses with host cell surface receptors and cell entry. Viruses. 7(5):2592-2617. http://dx.doi.org/10.3390/v7052592

Shimada-Hiratsuka M, Fukayama M, Hayashi Y, et al. 1997. Primary gastric T-cell lymphoma with and without human T-lymphotropic virus type 1. Cancer. 80:292-303. http://dx.doi.org/10.1002/(SICI)1097-0142(19970715)80:2<292::AID-CNCR18>3.0.CO;2-P

Stienlauf S, Yahalom V, Shinar E, Sidi Y, Segal G, Schwartz E. 2013. Malignant diseases and mortality in blood donors infected with human T-lymphotropic virus type 1 in Israel. Int J Infect Dis. 17(11):e1022-1024. http://dx.doi.org/10.1016/j.ijid.2013.03.012

Tahaei SM, Mohebbi SR, Fatemi SR, Mohammadi P, Malek FN, Azimzadeh P, Almasi S, Mirsattari D, Zali MR. 2011. Low frequency of human T-cell lymphotropic virus 1 antibodies in Iranian gastric cancer patients in comparison to controls. Asian Pac J Cancer Prev. 12(9):2447-2450.

Takatsuki K, Matsuoka M, Yamaguchi K. 1977. Adult T-cell leukemia in Japan. In: Seno S, Takaku S, Irino S, editors. Topics in Hematology. Amsterdam: Excerpta Medica. p. 73-77.

Tanaka A, Takahashi C, Yamaoka S, Nosaka T, Maki M, Hatanaka M. 1990. Oncogenic transformation by the tax gene of human T-cell leukemia virus type I in vitro. Proc Natl Acad Sci U S A. 87(3):1071-1075. http://dx.doi.org/10.1073/pnas.87.3.1071

Tezuka K, Xun RZ, Tei MM, Ueno T, Tanaka M, Takenouchi N, Fujisawa J. 2014. An animal model of adult T-cell leukemia: humanized mice with HTLV-1-specific immunity. Blood. 123(3):346-355. http://dx.doi.org/10.1182/blood-2013-06-508861

Thomas A, Perzova R, Abbott L, Benz P, Poiesz MJ, Dube S, Loughran T, Ferrer J, Sheremata W, Glaser J et al. 2010. LGL leukemia and HTLV. AIDS Res Hum Retroviruses. 26(1):33-40. http://dx.doi.org/10.1089/aid.2009.0124

Tokudome S, Maeda Y, Fukada K, Teshima D, Asakura T, Sueoka E, Motomura Y, Kusumoto Y, Imamura Y, Kiyokawa T et al. 1991. Follow-up of asymptomatic HTLV-I carriers among

blood donors in Kyushu, Japan. Cancer Causes Control. 2(2):75-78. http://dx.doi.org/10.1007/BF00053124

U.S. Food and Drug Administration (FDA). 2015. Complete list of vaccines licensed for immunization and distribution in the U.S. Silver Spring, MD. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm. [Accessed: August 26, 2015]

Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. 1977. Adult T-cell leukemia: Clinical and hematologic features of 16 cases. Blood. 50(3):481-492. http://dx.doi.org/10.1182/blood.V50.3.481.481

Villaudy J, Wencker M, Gadot N, Gillet NA, Scoazec JY, Gazzolo L, Manz MG, Bangham CR, Dodon MD. 2011. HTLV-1 propels thymic human T cell development in "human immune system" Rag2-/- gamma c-/- mice. PLoS Pathog. 7(9):e1002231. http://dx.doi.org/10.1371/journal.ppat.1002231

Weatherhead JE, Mejia R. 2014. Immune response to infection with Strongyloides stercoralis in patients with infection and hyperinfection. Current Tropical Medicine Reports. 1(4):229-233. http://dx.doi.org/10.1007/s40475-014-0032-9

Williams AE, Fang CT, Slamon DJ, Poiesz BJ, Sandler SG, Darr WF, Shulman G, McGowan EI, Douglas DK, Bowman RJ et al. 1988. Seroprevalence and epidemiological correlates of HTLV-I infection in U.S. blood donors. Science. 240(4852):643. http://dx.doi.org/10.1126/science.2896386

Yamamoto JF, Goodman MT. 2008. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002. Cancer Causes Control. 19(4):379-390. http://dx.doi.org/10.1007/s10552-007-9097-2

Yao J, Wigdahl B. 2000. Human T cell lymphotropic virus type I genomic expression and impact on intracellular signaling pathways during neurodegenerative disease and leukemia. Front Biosci. 5:D138-168. http://dx.doi.org/10.2741/Yao

Yoshida M, Miyoshi I, Hinuma Y. 1982. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A. 79(6):2031-2035. http://dx.doi.org/10.1073/pnas.79.6.2031

Yoshida M, Seiki M, Yamaguchi K, Takatsuki K. 1984. Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia virus in the disease. Proc Natl Acad Sci U S A. 81(8):2534-2537. http://dx.doi.org/10.1073/pnas.81.8.2534

Yoshida M. 2001. Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. Annu Rev Immunol. 19:475-496. http://dx.doi.org/10.1146/annurev.immunol.19.1.475

Yoshimitsu M, Kozako T, Arima N. 2013. Prevention of human T-cell lymphotropic virus infection and adult T-cell leukemia. T-Cell Leukemia — Characteristics, Treatment and Prevention. Rijeka, Croatia: InTech. p. 105-118.

Zane L, Jeang KT. 2014. HTLV-1 and leukemogenesis: Virus-cell interactions in the development of adult T-cell leukemia. Recent Results Cancer Res. 193:191-210. http://dx.doi.org/10.1007/978-3-642-38965-8_11

Zhao T, Matsuoka M. 2012. HBZ and its roles in HTLV-1 oncogenesis. Front Microbiol. 3:247. http://dx.doi.org/10.3389/fmicb.2012.00247

zur Hausen H. 1994. Molecular pathogenesis of cancer of the cervix and its causation by specific human papillomavirus types. Curr Top Microbiol Immunol. 186:131-156. http://dx.doi.org/10.1007/978-3-642-78487-3_8

zur Hausen H. 2001. Oncogenic DNA viruses. Oncogene. 20(54):7820-7823. http://dx.doi.org/10.1038/sj.onc.1204958

zur Hausen H, de Villiers EM. 2014. Cancer "causation" by infections--individual contributions and synergistic networks. Semin Oncol. 41(6):860-875. http://dx.doi.org/10.1053/j.seminoncol.2014.10.003

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: A slow-growing type of adult T-cell leukemia/lymphoma characterized by less than 5% neoplastic lymphocytes in the peripheral blood, absence of lymphadenopathy and hypercalcemia, and occasional skin or pulmonary lesions.

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
AchE	acetyl cholinesterase
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
GRα	glucocorticoid receptor alpha
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	injection drug user
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2	interleukin 2
LTR	long terminal repeat
MICB	major histocompatibility complex chain I chain-related B
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
PKA	protein kinase A
PTEN	phosphatase and tensin homolog
PY	person years
RNA	ribonucleic acid
RR	relative risk
RT-PCR	reverse transcriptase-polymerase chain reaction
ssRNA	single-stranded RNA
SIR	standardized incidence ratios
sIL2S	soluble interleukin-2 receptor-α
STD	sexually transmitted disease
TP53INP1	tumor protein P53 inducible nuclear protein 1
USA	United States of America

Appendix A. Literature Search Strategy

Table of Contents

Tables

Figures

The objective of the literature search approach is to identify published literature that is relevant for evaluating the potential carcinogenicity of the human T-lymphotropic 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.

A.1. General Approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for the individual viruses of interest, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases. IARC used literature found by searching PubMed for HTLV through 12/2008, so PubMed, Web of Science and Scopus were searched for new information about HTLV from >2008 to August 2015. Table A-1 highlights the general concepts searched with selected example terms. To review all the terms used, please refer to the full search strings below.

Table A-1. Major Topics Searched

Topics	Example Terms
Human T-lymphotropic virus type 1	Human T-lymphotropic 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	Case control, ecological studies, follow-up study
Epidemiology terms	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.

The bibliographic database search results (909) 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 (77) or Mechanistic literature (269).

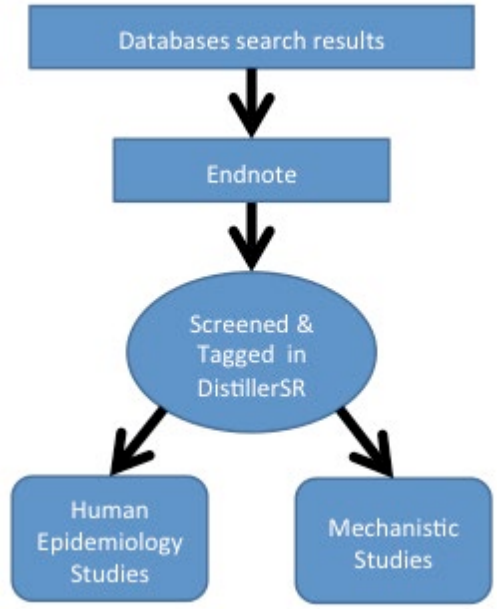

Figure A-1. Literature Processing Flow

A.2. Search Strings for HTLV-1 Searches

PubMed: 2010–2015

"Human T-lymphotropic virus type 1"[MeSH] OR "Human T-lymphotropic 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-lymphotropic 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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