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Chapter 3

Leukemia and Retroviral Disease

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Additional information is available at the end of the chapter

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Abstract

Two human retroviruses, identified as the human T-cell leukemia virus type 1 (HTLV-1) and human immunodeficiency virus type 1 (HIV-1), have been shown to affect millions of people worldwide. In the context of coinfection, the impact of their interactions with respect to HTLV-1-induced adult T-cell leukemia and neurologic disease as well as HIV-1 disease progression has been an understudied area of investigation. HTLV-1/HIV-1 coinfections occur frequently, particularly in large metropolitan areas of the Americas, Africa, Europe, and Japan. The retroviruses HTLV-1 and HIV-1 share some similarities with regard to their genetic structure, general mechanisms of replication, modes of transmission, and cellular tropism; however, there are also significant differences in the details of these properties as well, and they also differ significantly with respect to the etiology of their pathogenic and disease outcomes. Both viruses impair the host immune system with HIV-1 demonstrated to cause the hallmark lethal disease known as the acquired immune deficiency syndrome (AIDS), while HTLV-1 infection has been shown to cause several different forms of T-cell leukemia. In addition, both viruses have also been shown to cause a spectrum of neurologic disorders with HIV-1 shown to cause an array of neurologic syndromes referred to as HIV-1-associated neurologic disorders or HAND, while HTLV-1 has been shown to be the etiologic agent of HTLV-1-associated myelopathy/tropical spastic paraparesis or HAM/TSP. The natural history of the coinfection, however, is different from that observed in monoinfections. Several studies have demonstrated utilizing a number of in vitro models of HTLV-1/HIV-1 coinfection that the two viruses interact in a manner that results in enhanced expression of both viral genomes. Nevertheless, there remains unresolved controversy regarding the overall impact of each virus on progression of disease caused by both viruses during the course of coinfection. Although combination antiretroviral therapy has been shown to work very effectively with respect to maintaining HIV-1 viral loads in the undetectable range, these therapeutic strategies exhibit no benefit for HTLV-1-infected individuals, unless administered immediately after exposure. Furthermore, the treatment options for HTLV-1/HIV-1-coinfected patients are very limited. In recent years, allogeneic stem cell transplantation (alloSCT) has been used for

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the treatment of leukemia. In this regard, the case of a leukemic patient positive for HIV-1 who was cured of their HIV-1 infection while treated with alloSCT for acute myeloid leukemia has also been examined with regard to impact on HIV-1 disease.

Keywords: HIV-1, HTLV-1, coinfection, ATL/ATLL, HAM/TSP

1. Introduction

HTLV-1/HIV-1 coinfection is very common among drug users, particularly in metropolitan areas [1, 2]. It is estimated that in endemic areas, 10% of HIV-1-infected patients are coinfected with HTLV-1 [3]. The frequency of HTLV-1 and HIV-1 coinfections is on the rise, especially in Africa and South America [4]. Both HTLV-1 and HIV-1 are retroviruses capable of integrating their proviral DNA genome into the host cell chromosome, thereby establishing a latent infection, both of which share quiescent $CD4^+$ T cells as their primary target. However, the life cycle, pathogenesis, and clinical syndromes of these two viruses after infection are very different within this cellular compartment [5, 6]. In the absence of therapeutic intervention, there is a striking difference in the prevalence of disease caused by the two viruses with overt clinical disease far less common after HTLV-1 infection, perhaps because HTLV-1 has existed within the human population for far longer than HIV-1 and therefore may be more highly adapted to its human host. This could explain why HTLV-1 has been shown to cause T-cell transformation and clonal expansion of immortalized cells, whereas HIV-1 induces $CD4^+$ T-cell death [7]. Since the first cases of HIV-1 were reported early in the 1980s, there has been much progress with respect to investigating the viral replication cycle, mechanisms of pathogenesis, as well as the diagnosis and treatment of HIV-1 infection. There are now more than 30 antiretroviral drugs available for the management of HIV-1 infection, with them, their modes of inhibition and novel drug discovery techniques have been reviewed previously [8]. A number of drug combinations have been shown to be quite effective with regard to reducing HIV-1 titers to undetectable levels with subsequent maintenance of this well-controlled state for many years if not decades, yet they do not cure individuals because the drugs are effective against actively replicating virus and not the latent, integrated provirus. In the absence of treatment and subsequent to the development of drug resistance, particularly in the precombination antiretroviral therapy (cART) era, HIV-1 has been shown to induce severe immunosuppression leading to AIDS with the ultimate development of opportunistic infections and cancers. In the case of HTLV-1 infection, most patients remain asymptomatic for many years before the onset of disease. In contrast to HIV-1, only a small percentage of untreated HTLV-1 carriers develop clinically apparent disease [9, 10]. HTLV-1 may cause neurologic problems, skin and inflammatory disorders, leukemia, and leukemia/lymphoma [9, 10]. The treatments available for HTLV-1-related complications are limited, and the antiretrovirals used to treat HIV-1 infection are not efficacious unless taken early after first contact with the virus [6] when viral replication is responsible for expansion in the number of infected cells as compared to expansion of infected cells by cell division with the associated integrated HTLV-1 provirus expanding within the transformed cell population in the absence of infectious HTLV-1

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production [5]. The clinical implications and the molecular interactions between HTLV-1 and HIV-1 remain understudied. The management of patients coinfected with HTLV-1/HIV-1 is clearly a challenge. Although it is well known that both HTLV-1 and HIV-1 may cause progressive diseases within the central nervous system, the focus here will center on the interaction of these two retroviruses within the immune system and more specifically examine the impact of HIV-1 infection on the leukemogenic process induced by HTLV-1 in coinfected individuals as well as the impact of HTLV-1 infection on HIV-1 disease. A summary of the epidemiology of the two viruses within the human population is shown in Table 1.

	HIV-1	**HTLV-1**
Prevalence	35 million people	20 million people
Transmission	· Sexual transmission · Parenteral transmission (blood transfusions, organ transplantation, and via infected sharp objects) · Mother to child (breast-feeding and during delivery)	· Sexual transmission · Parenteral transmission (blood transfusions, organ transplantation, and via infected sharp objects) · Mother to child (breast-feeding and during delivery)
Endemic areas	Africa, Eastern Europe, South Asia, and China	Caribbean region, Central Africa, and South Japan

Table 1. Epidemiological comparison of HTLV-1 and HIV-1 infection and disease

2. Introduction to Human T-cell Leukemia Virus type 1 (HTLV-1)

HTLV-1 is a single-stranded positive-sense RNA, a type C retrovirus, and the etiologic agent of adult T-cell leukemia (ATL) or adult T-cell leukemia/lymphoma (ATLL) and a progressive neuroinflammatory disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), with some similarities to multiple sclerosis due to the progressive destruction/loss of myelination [11] (also reviewed in [68]). It was the first human retrovirus discovered [10, 12] and isolated in the United States in the late 1970s, with parallel discoveries by investigators in Japan [13–15]. In this regard, in the United States, HTLV-1 particles were detected in fresh peripheral blood lymphocytes and in the T-cell lymphoblastoid cell lines, HUT 102 and CTLC-3, derived from a 28-year-old African American man suffering from cutaneous T-cell lymphoma [13]. At nearly the same time, the Japanese investigators isolated HTLV-1 from a series of cell lines derived from cases of adult T-cell leukemia [13, 15]. Over the years, HTLV-1 has been shown to be associated with the human population for a much longer period of time than the HIV-1 with HTLV-1 being detected in remains of a 1,500 Chilean mummy [16], while HIV-1 sequences have been detected in humans only as far back as the 1920s, many decades before its discovery in the mid-1980s. Based on extensive studies performed over the past three to four decades concerning clinical parameters, epidemiology,

molecular biology and virology, immunology, cancer biology, neurobiology, and immune- and neuropathogenesis of HTLV-1 infection, the virus appears to be much more adapted to the human population with greater than 95% of the infected individuals harboring the virus asymptomatically with only small percentages of individuals presenting with symptomatic disease in the form of leukemia or neurologic disease [9, 17]. This epidemiologic pattern is quite different than the widespread highly lethal disease of the immune and nervous systems caused by the HIV-1 in the absence of highly active antiretroviral therapy (HAART) [18] (also reviewed in [19]).

2.1. HTLV-1 genetic architecture and viral replication

The HTLV-1 genome comprises four main genetic components that include gag, pol, env, and pX sequences (Figure 1). The gag, pol, and env genes encode the structural proteins and enzymatic proteins, with a 5 and 3 long terminal repeat (LTR) at each end of the genome, typical of all viruses in the Retroviridae family. Gag proteins have been designated the group-specific antigens, which encode the inner virion structural components such as matrix, capsid, and nucleocapsid. The pro and pol genes encode the protease, integrase, and viral RNA-dependent DNA polymerase or reverse transcriptase, respectively, and the env gene that encodes the viral surface and transmembrane envelope proteins [63]. What makes HTLV-1 unique compared to other retroviruses is the pX region. This region encodes multiple accessory and regulatory proteins that give HTLV-1 its unique phenotype, one of which is the multifunction oncoprotein Tax. Tax has been shown to alter the course of gene expression at a number of points during the course of viral infection and in this regard has been shown to regulate viral replication, modulate cellular gene expression, induce inflammation, and block apoptosis to pinpoint just a few, with many of its functions being identified by Tax mutagenesis [20]. More importantly, this protein is known for its ability to transform T lymphocytes into cancerous leukemic cells, as described in the following sections. HTLV-1 infection of susceptible cells via transmission involving transfer of virus from an infected cell to an uninfected cell occurs very efficiently as a result of specific cell–cell interactions and less efficiently from cell-free viral particle-driven transmission [21–23]. The replication cycle of HTLV-1 begins with the interaction between the viral Env glycoproteins and the specific cellular receptor proteins. At least three cellular receptors have been found to facilitate viral attachment and entry into the cell, and these include the glucose transporter 1 (GLUT1) [24, 25], neuropilin-1 (NRP-1) [26–28], and heparan sulfate proteoglycans (HSPG) [29–31]. During the membrane fusion process and after entry of the viral capsid into the cytoplasm, the viral genomic RNA is reverse transcribed into DNA, by the viral particle-associated reverse transcriptase. During the process of reverse transcription, the newly synthesized proviral DNA is transported to the nuclear membrane. After the translocation of the proviral DNA into the nucleus, it is subsequently integrated into the host cell chromosomal material, which is catalyzed by the activity of the viral-encoded, particle-associated integrase. Following integration, the transcription of viral RNAs and the translation of viral proteins are carried out by host machinery with the subsequent assembly of viral particles and release of infectious virions into the extracellular environment.

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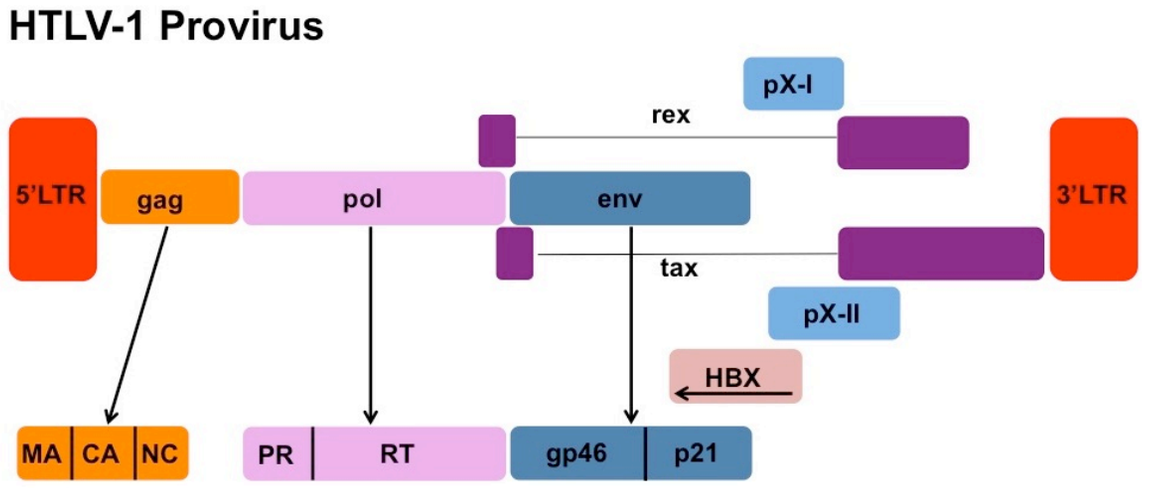

Figure 1. HTLV-1 genomic architecture. A schematic representation of the proviral genome organization, open reading frames, and viral products of HTLV-1. The organization of the ~9-kb genome is depicted along with the genes and their transcriptional splicing.

2.2. HTLV-1 infectivity, transmission, and pathogenesis

Although the tropism of HTLV-1 may not represent a direct representation of cells that can be infected *in vivo*, studies performed *in vitro* are often performed to get an approximation regarding the cell types that may be targeted by a virus during the course of *in vivo* infection. If proven susceptible and productive for viral replication, these cell types may then be used for virus propagation or studies concerning viral pathogenesis. In this regard, during *in vitro* propagation of HTLV-1, a wide variety of non-T-cell types have been shown to be susceptible to viral infection, including human primary endothelial cells [32], monocytes [33], microglial cells [33], B cells [34], mammary epithelial cells [35], and dendritic cells (DCs) [36], although the relative level of viral production between the different cell types was shown to differ greatly. In parallel with these observations, HTLV-1 infection *in vivo has* been shown to occur primarily in $CD4^+$ T-cell subsets and to a lesser extent in $CD8^+$ T cells in both asymptomatic and symptomatic HTLV-1-infected patients [37]. Furthermore, Koyanagi and colleagues [37] demonstrated HTLV-1 tropism for $CD8^+$ T cells, monocytes, and B cells in the majority of the asymptomatic HTLV-1-positive individuals studied, as well as in patients with HTLV-1-related ATL or HAM/TSP. Other groups have also confirmed these observations and have reported that HTLV-1 also infects macrophages [37], DCs [38], synovial fluid cells [39], and astrocytes [40] among others when the target cells are examined *in vivo*. Perhaps of great importance in the pathogenesis of HTLV-1-associated neurologic disease is the penetration of the virus into the bone marrow compartment with increasing numbers of HTLV-1 DNA^+/RNA^-progenitor cells detected in patients suffering from HAM/TSP as compared to patients with ATL [41], thus further demonstrating another layer of complexity with respect to target cell identification that likely involves latency, immune invasion, and adaptation to the host.

HTLV-1 has been shown to be transmitted primarily via three routes: (i) mother-to-child transmission [42], (ii) sexual intercourse [43], and (iii) parenteral transmission. The vertical

transmission of HTLV-1 from mother to child occurs via the transfer of maternally infected lymphocytes to the fetus or newborn through the placenta [44], during delivery [45, 46], or by breastfeeding [47]. Sexual transmission is a common route of HTLV-1 transmission. Sexual transmission of HTLV-1 occurs more efficiently from male to female than from female to male. This might be due in part to the higher numbers of HTLV-1-infected lymphocytes found in semen than in vaginal secretions [48]. The parenteral transmission of HTLV-1 includes blood or cellular blood products transferred during the transfusion process [49], organ transplantation [50], and possibly percutaneous exposure of the virus via sharing of contaminated objects such as razor blades and needles, particularly among drug users and healthcare workers [48]. Parenteral transmission represents a large proportion of infected individuals. Regardless of how the virus is acquired, the infected cells produce numerous progeny virion. Particularly in the case of T lymphocytes, they too are activated and clonally proliferate, further driving the expansion and number of cells harboring provirus DNA.

2.3. Cancers and other diseases associated with HTLV-1 infection

Currently, there are approximately 20 million individuals living with HTLV-1 worldwide [7]. In highly endemic regions such as the Caribbean Basin, Central Africa, and southern Japan, more than 1% of the population is infected with HTLV-1 (reviewed in [51] and [52]). Approximately 95% of the individuals infected with HTLV-1 remain as asymptomatic carriers throughout their lives [9, 17]. As previously indicated, HTLV-1 is the etiological agent for causing two distinct disease phenotypes, ATL and HAM/TSP, the first involving a $CD4^+$ T-cell malignancy and the second involving a progressive neurological disease. Interestingly, the specific response of the immune system to the virus seems to influence which clinical manifestation presents and likely includes other factors such as route of transmission, host genetics, and perhaps aspects of viral genetics.

Less than 5% of the HTLV-1-infected individuals develop ATL after a long period of latency, which in some cases can be greater than 50 years [53]. ATL is more prevalent in men than in women with a median onset age of 55 years. ATL can present as four overlapping clinical manifestations that are broken down into smoldering, chronic, acute, and lymphoma [54, 55]. Approximately 5% of the patients with ATL have been shown to develop the smoldering type of disease presenting with a number of minor symptoms with leukemic cells infiltrating the skin causing surface lesions leading to a breach in the epithelial layer of the skin [56]. It has been estimated that 20% of the HTLV-1-positive patients will develop a chronic form of the disease. These patients experience similar manifestations as individuals with smoldering ATL, but they also develop abnormalities in their viscera, leading to impairment of spleen, liver, and lymphatic functions as well as a slight increase in the levels of leukemic cells [54].

In the acute phase of ATL, the disease progresses quickly, and patients exhibit generalized swelling of the lymph nodes, elevated calcium and lactate dehydrogenase levels, impairment of liver and spleen function, skin lesions, bone wounds, and release of cytokines by malignant cells. All of these abnormalities cause patients to experience fever, cough, malaise, dehydration, lethargy, shortness of breath, and inflammation of the lymph nodes. About 55% of patients with ATL experience the acute form of the disease. Furthermore, around 20% of the

ATL cases are of the lymphoma type, and they experience inflammation of the lymph nodes, with no evidence of leukemic cells in the periphery, and general suppression of their immune system function as summarized in Figure 2. The survival rate associated with ATL from the time of first disease manifestations is approximately 24.3, 10.2, and 6.2 months for the chronic, lymphoma, and acute types, respectively [55]. The actual process of transforming T lymphocytes and developing ATL is dependent on the HTLV-1 oncoprotein Tax in part as well as a number of other factors indicated above.

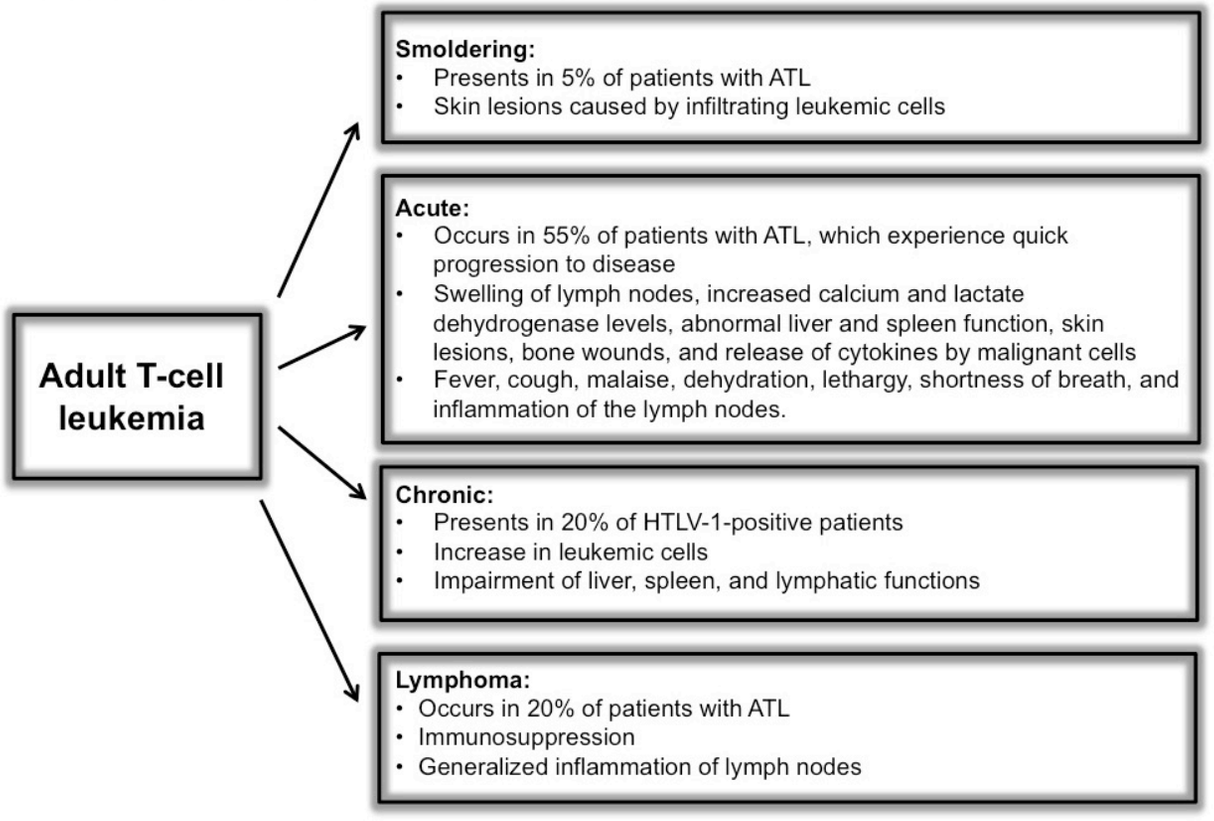

Figure 2. Summary of pathogenic forms of HTLV-1-induced leukemia. A summary of disease outcomes and symptomatology during the course of HTLV-1-induced leukemia.

Like most other RNA viruses, due to the constraints of genome size, as compared to larger DNA viruses, the proteins they encode usually have multiple functions. The multifunction oncoprotein Tax is a 353 amino acid phosphoprotein that is a transcriptional activator of the LTR, and the protein is primarily responsible for transformation of T lymphocytes. It has been shown that selected domains of Tax are responsible for interacting with the host transcription factors NF-κB, ATF/CREB, Sp1, Ets-1, and many others in conjunction with their cognate binding sites. This leads to enhanced chromatin remodeling, transactivation of the LTR, activation of host genes, and enhanced viral gene expression. More importantly in the process of cellular transformation is its chronic activation of signaling pathways (JAK/STAT), expression of cytokines and their receptors (IL-2, IL-2Rα), and interaction with cellular tumor suppressors (p53) and cell cycle kinases and regulators (p15, p16, and p21), to name a few, all

of which increase the probability of uncontrolled cell division and transformation exhaustively reviewed [10, 57, 58]. As of now, it is not fully understood how and why Tax, which is a strong inducer of transformation, only induces ATL in 5% of infected individuals. This could be, in part, the immune system efficiently removing infected cells and/or combating Tax with specific host restriction factors. Additionally, Tax has been shown to be secreted from infected cells and have bystander effects, such as pro-inflammatory cytokines and the infiltration of Tax-specific $CD8^+$ T cells into the CNS, thus playing a part in HAM/TSP [59–64].

HTLV-1 infection also causes HAM/TSP, a neuroinflammatory disorder that mostly affects the spinal cord and brain due to chronic proinflammatory cytokines, the destruction of myelin, and the cells that secrete it, oligodendrocytes [64–66]. It was first thought that there might be a hormonal component regulating HAM/TSP, as it occurs more frequently and progresses more rapidly in women than in men, particularly if the first signs of disease occur before menopause [67]. The onset of HAM/TSP usually happens after 20–30 years of latency [4], and the average age in which patients experience the first signs of disease is about 43 years of age [68]. The early phase of HAM/TSP is presented with a profound inflammatory response resulting in lower back pain, weakness in the lower limbs, and impairment of urinary and sexual functions. Eventually, a chronic degenerative disorder develops characterized by the progressive loss of myelin in the thoracic and lumbar regions of the spinal cord [67]. Damage to the central nervous system (CNS) also occurs in patients with HAM/TSP, likely mediated by particular cells of the immune system such as $CD4^+$ T cells, $CD8^+$ T cells, DCs, and cells of the monocyte–macrophage lineage. For instance, it has been proposed (28) that at least three mechanisms participate in the process of myelin degradation that occurs in HAM/TSP: (i) direct injury caused by $CD8^+$ T cells, (ii) damage mediated by an uncontrolled cytokine storm, and (iii) an autoimmune response. Previous studies have shown that infiltrating activated Tax-specific $CD8^+$ cytotoxic T lymphocytes (CTLs) in the peripheral blood and cerebrospinal fluid (CSF) induced lysis of HTLV-1-infected cells triggering a pro-inflammatory cytokine storm. There is evidence that HTLV-1 has been found in the CNS. The release of pro-inflammatory factors such as TNF-α and IFN-γ secreted by activated $CD8^+$ CTLs injures the CNS. Further damage may occur as a result of the molecular mimicry between the Tax protein and the neuronal antigen heterogeneous ribonuclear protein-A1 (hnRNP-A1), which may cause an autoimmune response [69].

Both HTLV-1 and HIV-1 have been shown to penetrate the bone marrow to varying degrees during the course of monoinfection, and it is assumed to be the case during the course of coinfection with both viruses but less information is available in this regard. Clearly, the relative penetration of the two viruses into the bone marrow compartment during the course of coinfection may have dramatic effects on HTLV-1- and HIV-1-induced pathogenesis and disease caused by either viruses, and these pathogenic processes will also be a subject of this review. These interactions may periodically alter the balance between immune control and HTLV-1 infection, and the periodic imbalance has also been associated with the etiology of other inflammatory diseases such as arthropathy, pulmonary alveolitis, uveitis, dermatitis, Sjögren's syndrome, Behçet's disease, thyroid disease, prostatitis, cystitis, hepatitis, polymyositis, arthritis, and a sarcoidosis-like disorder [67].

3. Introduction to HIV-1 infection, pathogenesis, and disease

In 1981, the first cases of AIDS were reported in the United States. At the beginning of the epidemic, AIDS was first identified in homosexual men and drug users. However, the epidemic rapidly spread to the general population primarily by heterosexual intercourse [70]. In 1983, a retrovirus was isolated at the Pasteur Institute in France from a lymph node biopsy from a homosexual man with lymphadenopathy presenting with AIDS-like symptoms [71]. Almost in parallel at the National Cancer Institute in Bethesda, United States, the same virus was identified from samples of patients suffering from AIDS [72]. In 1986, the virus was named the human immunodeficiency virus (HIV) and demonstrated to be the causative agent of AIDS [73].

There are two types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), which are genetically and morphologically related viruses that share similarities in their mechanisms of replication and transmission. However, HIV-1 and HIV-2 differ in clinical disease progression and geographical distribution. HIV-1 leads to overt disease much faster than HIV-2, with world-wide distribution, whereas HIV-2 infections are more prevalent in West Africa [74]. HIV-1 is divided into four genetically different groups: M (main), O (outlier), N (non-M, non-O), and P. The group M, which accounts for 98% of the HIV-1 cases worldwide, is further classified into nine subtypes, with subtype B being the most prevalent within North America [75].

3.1. HIV-1 genetic architecture, entry, and viral replication

HIV-1 is also a type C retrovirus that belongs to the genus lentivirus. On a genomic level, HIV-1 is similar to HTLV-1 in a number of aspects. They both contain 5 and 3 LTR and gag, pol, and env genes. However, HIV-1 lacks the pX region and encodes for other accessory proteins that have some overlapping function with those of HTLV-1. HIV-1 proviral DNA encodes for the accessory proteins Tat, Vpu, Nef, Vif, Rev, and Vpr (Figure 3) [6, 76]. Tat is similar in function to Tax in the sense it can transactivate the LTR but does not function in cell transformation. Similarly, both Rev and Rex function to export unspliced and singly spliced RNAs from the nucleus. While HIV-1 shares sequence similarity at the genome level, it has been shown to utilize a different receptor for entry.

The HIV-1 envelope glycoprotein gp120 is the trimeric spike on the surface of the virion that has been shown to mediate attachment to the host target cells by engaging the CD4 receptor embedded in the plasma membrane. Subsequent structural changes mediate the exposure and interaction of the V3 region of gp120 to the chemokine coreceptors, either CXCR4 or CCR5 (although others have also been identified to facilitate this process as well), depending on V3 sequence and charge, and mediate fusion of the viral plasma membrane with the host cell membrane. Once the particle has been internalized, the capsid and associated viral enzymes and RNA remain associated in the cytoplasm in a capsid-like structure, where the viral reverse transcriptase continues to be transcribed from viral RNA to DNA (a process that is likely initiated as the viral particle interfaces with the cell surface proteins involved in viral entry). As the reverse transcription process continues to completion, the capsid structure transitions to a preintegration complex (PIC) containing the reverse transcriptase, integrase, capsid, and

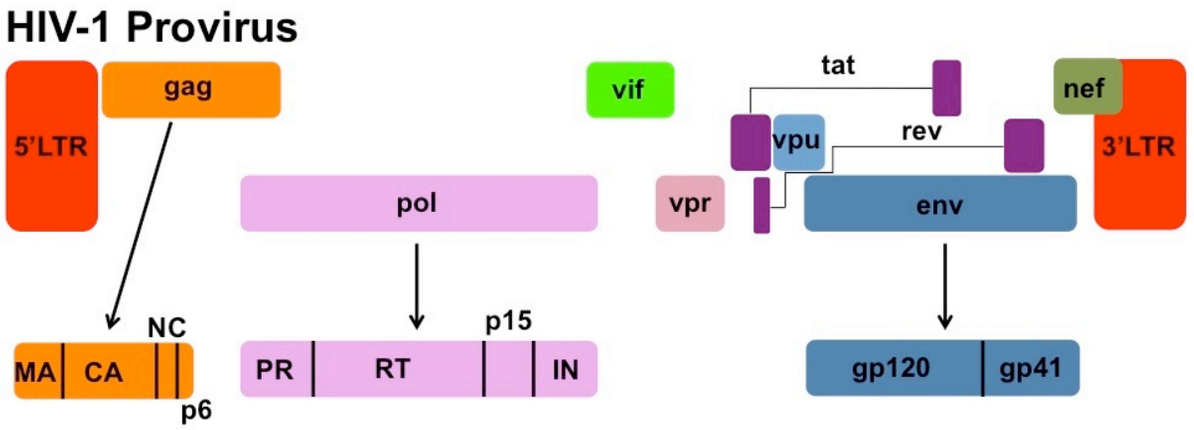

Figure 3. HIV-1 genomic architecture. A schematic representation of the proviral genome organization open reading frame and viral products of HIV-1. The organization of the ~10-kb genome is depicted along with the genes and their transcriptional splicing.

Vpr, and this structure has been shown to be transferred to the nuclear membrane. After entry into the nucleus, the proviral DNA genome is integrated into the host cell chromosome, with recent studies characterizing integration site preference and how it changes with disease progression [77–79]. Once integrated, the proviral DNA becomes part of the cellular chromatin environment and subjected to host machinery involved in the processes of transcription and translation. In conjunction with a number of cellular transcription factors and the viral transactivator proteins Tat and Vpr, transactivation directed by the LTR-driven contained within the integrated provirus is initiated and used as a template for the transcription of viral genomic RNAs and viral mRNAs with the subsequent translation of these viral mRNA into structural, enzymatic, and accessory proteins. From there, the viral polyproteins an proteins are recruited and aggregate primarily in the vicinity of the plasma membrane, resulting in the formation and release of mature infectious virions as previously reviewed [80, 81].

3.2. HIV-1 infectivity, transmission, and pathogenesis

As a result of studies performed in cell lines and primary human cells cultured *in vitro*, transplanted human cells maintained *in vivo* in engineered animals, and primary cells examined in an *ex vivo* experimental environment, HIV-1 has been shown to most efficiently infect activated $CD4^+$ T cells [82], although these cells do not need to be activated in order for infection to occur [83]. Both HIV and HTLV-1 share $CD4^+$ T cells as their cell target, which was further demonstrated by complementation viral envelopes for each other [84]. In addition to the $CD4^+$ T-cell compartment, a number of other human cellular compartments are infected by HIV-1, including cells of the monocyte–macrophage lineage, some subsets of dendritic cells, microglial cells and astrocytes within the brain, hematopoietic progenitor cells, and endothelial cells lining the blood-brain barrier [85, 86].

Studies performed *in vitro* have shown that all HIV-1 isolates infect activated peripheral blood mononuclear cells (PBMCs). Some isolates are able to infect $CD4^+$ T-cell lines, T-cell leukemia

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cell lines, and monocyte-derived macrophages (MDMs). The target cell population and coreceptor utilization seems to change during disease progression, and the once clear distinction between CXCR4-utilizing or X4 versus the CCR5-utilizing or R5 viruses as compared to the designations referred to as T-tropic and M-tropic now seems to be also guided by the relative utilization of different levels of the CD4 receptor present on T cells and cells of the monocyte–macrophage lineage [87]. During the acute phase of infection and to a lesser extent at later times during the course of disease, primarily due to cART combating replication competent virus, HIV-1 infects $CD4^+$ T-cell populations, with the resting memory $CD4^+$ T cells establishing a latent HIV-1 reservoir. The majority of activated and infected $CD4^+$ T cells will be eliminated, and during this T-cell depletion phase, a portion of the activated $CD4^+$ T cells will undergo a reprogramming of transcription and translation to allow them to survive and differentiate into a resting memory cell phenotype. This resting memory $CD4^+$ T-cell can contribute to the latent reservoir because it was infected and then differentiated into a resting memory cell or as the cell was differentiated into a memory cell it became infected; regardless of the mode of infection, the HIV-1 provirus survives, along with a substantial number of defective proviral genotypes [78, 79]. Because memory $CD4^+$ T cells live for many years, with a predicted half-life of 44 months [79, 88], these cells maintain one of the critical latent reservoirs of HIV-1 and a complicating factor in the pursuit to identify an effective means to cure the HIV-1-infected individual by a new generation of treatment strategies. However, there are very likely a number of additional cellular reservoirs that facilitate the persistence of HIV-1 during prolonged cART. For example, cells of the monocyte–macrophage lineage in the peripheral blood and other lymphoid tissues, resident macrophages of the central nervous system, astrocytes, DCs, follicular dendritic cells (FDCs), hematopoietic progenitor cells (HPCs) in the bone marrow, and specialized epithelial cells within the kidney likely play a role in maintaining HIV-1 during clinical latency prior to the start of any form of therapy despite ongoing immune surveillance and after the start of cART [85]. Each of these cell types present a unique challenge with respect to a cure based on the IR rate of cell turnover, the relative proviral genome transcriptional competency, the innate capacity of the virus to move out of the reservoir, the continued production of infected cells from infected precursors, and the poor drug penetrating ability into these physiological niches, with resting memory $CD4^+$ T cells and cells within the brain and bone marrow being prime examples.

It has been suggested that HIV-1 can be transmitted via free virus or HIV-1-infected cells present in infected blood and body fluids that enter the blood stream of an uninfected individual. The three routes of HIV-1 transmission are (i) via sexual intercourse, (ii) from mother to child, and (iii) parenteral transmission [76]. Sexual transmission is the most common mode of HIV-1 transmission and accounts for the 80% of infections in adults [89] and includes vaginal, anal, and oral unprotected sex between an infected individual and his or her uninfected partner. The risk of HIV-1 transmission is higher between homosexual men as compared to the risk during heterosexual intercourse and individuals whom engage in high risk behaviors [90]; however, this trend can be steadily reduced by prophylactic antiviral use and educating the public. Parenteral transmission of HIV-1 is usually associated with the transfusion of contaminated blood, transplant of infected organs, and sharing of infected sharps, needles, or syringes [76]. Mother-to-child HIV-1 transmission occurs during pregnancy,

delivery, or breastfeeding. The presence of higher levels of HIV-1 RNA in blood/body fluids of the infected host has been associated with greater probabilities of transmission [91].

3.3. Diseases caused by HIV-1

According to the World Health Organization (WHO), by the end of 2013, there were 35 million people living with HIV worldwide, and 1.5 million people died as a consequence of AIDS-associated diseases [92]. The course of HIV-1 infection consists of three phases of disease: primary or acute, asymptomatic/chronic, and AIDS. After 2 weeks of initial exposure to HIV-1, approximately 50–70% of the infected patients experience nonspecific symptoms that do not last for more than 4 weeks. These symptoms include increase in body temperature, sore throat, cephalea, joint and muscle pain, general discomfort, and weight loss. Around 70% of patients will develop a rash on trunk and face [6]. This is followed by a long-term period (in many individuals, this highly variable period has been thought to be longer than 10 years but may be altered by many host and comorbidity factors) of asymptomatic chronic infection [93]. This phase is marked by a loss of $CD4^+$ T cells at an annual rate of 30 to 60 cells/mm^3 [6]. HIV-1 titers in the peripheral blood, and antibodies to HIV-1 become readily detectable [76]. Most patients do not present major symptoms; however, some experience tiredness and swollen lymph nodes. Less than 1% of patients in this phase develop AIDS within a period of 1–2 years. The more advanced disease symptoms begin when the $CD4^+$ T-cell levels drop below 500 cell/mm^3. During this stage, HIV-1-infected patients become immunocompromised, developing opportunistic infections such as oral candidiasis, pneumococcal infections, tuberculosis, and infections caused by the herpes simplex and varicella zoster viruses. When the CD4 counts decrease below 200 cells/mm^3, they are clinically diagnosed as having progressed to AIDS. Here HIV-1-infected patients are at high risk of serious diseases like systemic fungal infections, toxoplasma encephalitis, and cryptococcal meningitis, reactivation of other latent viruses such as cytomegalovirus (CMV), and other opportunistic infections, [94], which is primarily due to the decrease in T-cell count. AIDS patients are also susceptible to developing AIDS- and non-AIDS-defining cancers. Kaposi sarcoma (KS) induced by human herpes virus 8 and non-Hodgkin's lymphoma are two examples of AIDS-defining cancers. Importantly, the incidence of AIDS-defining cancers and opportunistic infections in HIV-1-infected patients has dropped since the introduction in 1996 of the highly active antiretroviral therapy (HAART) for the treatment of HIV-1 in North America, Europe, and Australia [95]. In contrast, the frequency of non-AIDS-defining cancers such as cervical and anal cancer caused by human papilloma virus, liver cancer, Hodgkin's lymphoma, lung cancer, and prostate cancer has increased among the HIV-1-infected population [95].

4. Impact of HIV-1 on HTLV-1 disease progression

The effect that HIV-1 has on the progression of HTLV-1 infection remains controversial, as there are very few studies that have directly examined the process interaction. However, it is likely that the periods of immunosuppression observed during the course of HIV-1 disease include the first 3–6 months of the primary infection, a time when the $CD4^+$ T-cell compartment

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is acutely targeted by HIV-1, the period involving the transition from asymptomatic clinical latency to symptomatic disease prior to therapeutic intervention, and last during the final progressive decrease in the $CD4^+$ T-cell count prior to the availability of therapy or after the development of drug resistance without the availability of alternative therapies, which may very likely alter the course of primary HTLV-1 infection, the development and control of ATL, or the etiology and progression of HAM/TSP. Although HIV-1 has not been shown to infect bone marrow stem cells, it has been shown to infect more differentiated progenitor cells. In addition, HTLV-1 has also been shown by Jacobson and coworkers [96] to penetrate the bone marrow compartment with the detection of HTLV-1 DNA in the absence or presence of detectable transcription. Given these observations, it is possible that HIV-1 infection of similar cell populations in the bone marrow may impact HTLV-1 gene expression programming and alter the functional course of these cell populations with respect to the development and control of ATL and HAM/TSP.

4.1. Incidence of HAM/TSP among HTLV-1/HIV-1-coinfected patients

Much knowledge of viral coinfection and HAM/TSP has come from longitudinal and cross-sectional studies of patient cohorts. While much still needs to be understood on a molecular biologic and immunologic level, these human studies are invaluable with respect to identifying correlations that allow one to develop experimental designs to explore mechanistic avenues to determine the role of virus–virus interactions. Based on these studies, it was determined that less than 2% of the individuals were infected with HTLV-1 develop HAM/TSP [97, 98]. Previous studies have suggested that HIV-1 increases the risk of HAM/TSP in HTLV-1/HIV-1-coinfected individuals. For example, the incidence of HAM/TSP is 9.7% among HTLV-1/HIV-1-coinfected individuals in a cohort of patients from New Orleans, Louisiana. These patients did not present with AIDS, and their $CD4^+$ T-cell levels were normal or slightly elevated [99]. The occurrence of myelopathy in HTLV-1/HIV-1-coinfected individuals was estimated in a case-control study in Rio de Janeiro, Brazil. The results indicated that 73% of the coinfected patients and 16% of the patients infected with only HIV-1 developed myelopathy [100]. Another group reported that the prevalence of HAM/TSP among HTLV-1/HIV-1-coinfected patients in Brazil was 8% [101]. Schutte and coworkers [102] observed in a cohort of patients in Pretoria, South Africa, that HTLV-1/HIV-1-coinfected individuals were prone to developing HAM/TSP at an earlier age than when infected with HTLV-1. Furthermore, the period of time in which the coinfected patients remained asymptomatic was shorter than the monoinfected patients (less than 3 years) [102]. Furthermore, Casseb and colleagues [101] demonstrated that the levels of HTLV-1 proviral DNA load in coinfected patients with HAM/TSP were five times higher than in asymptomatic coinfected individuals. HTLV-1 proviral DNA levels in PBMCs varied during the course of HTLV-1 infection [103]. High proviral DNA levels [104] along with the replication or migration of HTLV-1-infected lymphocytes to the CNS have been associated with the development of HAM/TSP [103]. Indeed, Bassi et al. [105] proposed the use of HTLV-1 proviral DNA loads as a diagnostic tool for the early detection of HAM/TSP. In this regard, other studies have established the lower limits of detection of HTLV-1 proviral DNA, and these efforts facilitated studies to distinguish between asymptomatic HTLV-1-infected patients and HAM/TSP patients. With regard to coinfection, studies have reported that HIV-1 infection increased

the HTLV-1 proviral DNA levels in HTLV-1-infected patients. Yet, Césaire and colleagues [106] found no difference between the levels of HTLV-1 proviral DNA in the coinfected patients compared to those infected with only HTLV-1. Even without understanding the molecular mechanism of how one retrovirus influences pathology and disease, what is obvious is the strong association of HAM/TSP and HTLV-1/HIV-1 coinfection (Table 2).

Viral protein	Effect on HIV-1 infection	Effect on HTLV-1 infection
Tat	Transactivator protein that enhances viral transcription; can be secreted and cause apoptosis in uninfected bystander cells	Some studies have suggested that there is minimal effect by Tat on HTLV-1 infection; other studies have suggested that HIV-1 Rev is the protein that potentially enhances gene expression; some studies have shown that HIV-1 does not affect proviral load in PBMCs; there has been a link between coinfection and increased risk to develop HAM/TSP and ATL
Tax	Has been shown to be overexpressed in HTLV-1/HIV-1 coinfection; promotes nuclear transport of the reverse transcribed HIV-1 DNA; stimulates HIV-1 via activation of NF-κB (both alone and synergistically with Tat); has been shown to interact with CCR5, a major coreceptor of HIV-1, although a role in disease progression is controversial	Transactivator protein that enhances viral transcription; largely implicated in the oncogenic potential of HTLV-1; can be secreted from infected cells resulting in bystander effects such as upregulation of cytokines and chemokines, and infiltration of Tax specific $CD8^+$ T cells, which can influence HAM/TSP

Table 2. Points of intersection between HTLV-1 and HIV-1

The levels of $CD4^+$ T-cell counts and HTLV-1 disease progression in HTLV-1/HIV-1 coinfection were evaluated in a study conducted in Brazil by Casseb and coworkers. One hundred and fifty HTLV-1-infected patients were enrolled in the study; 27 of them were coinfected with HIV-1, and 15 of the coinfected patients had already reported an AIDS-defining event. $CD4^+$ T-cell counts were higher in coinfected individuals with AIDS than in HIV-1-monoinfected patients (median = 189 cells/mm^3 and 89 cells/mm^3, respectively; $p = 0.036$). Moreover, five of the coinfected subjects who had AIDS and three of the coinfected patients without AIDS showed signs of HAM/TSP. Three of the eight patients with signs of HAM/TSP also developed an opportunistic infection. Importantly, the incidence of HAM/TSP in coinfected patients with AIDS was 20 times higher than those infected with only HTLV-1 infection. These results supported previous observations that HTLV-1/HIV-1 coinfection was associated with a higher probability of a more severe HTLV-1 infection along with an increase in the levels of $CD4^+$ T cells [3]. These results have suggested the possibility that HTLV-1 may inhibit HIV-1 replication with a subsequent increase in $CD4^+$ T-cell counts, thereby enhancing HTLV-1 disease progression. Based on these observations, current research has centered on a more in-depth molecular analysis with respect to how HTLV-1 and HIV-1 impact each other during the course of dual infection.

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5. Impact of HTLV-1 on HIV-1 disease progression

The influence of HTLV-1 infection on the development of AIDS in HIV-1-coinfected patients is not well understood. Several studies have indicated that HTLV-1 infection promotes HIV-1 replication, accelerating the development of AIDS, while other reports have shown that HTLV-1 actually inhibits HIV-1 infection [4]. The conflicting results reported are likely due in part to the diverse antiretroviral regimens used to treat HTLV-1/HIV-1-coinfected patients [104]. In addition, the timing with respect to the introduction of the second virus (HTLV-1 or HIV-1) may have great impact on HIV-1 replication and disease.

Prior to the HAART era, Bartholomew and colleagues [107] reported the results of a study conducted in Trinidad with 40 HIV-1-positive homosexual men, 6 of them coinfected with HTLV-1. The coinfected individuals were severely immunocompromised compared to the HIV-1-monoinfected patients. Irrespective of sex and $CD4^+$ T-cell counts, a retrospective case-control study performed in Bahia, Brazil, showed that people living with HTLV-1/HIV-1 coinfection exhibited a shorter lifespan than HIV-1-monoinfected patients. The mean survival time for controls was 2,430 days, whereas for HTLV-1/HIV-1-coinfected patients, it was 1,849 days, with a $p = 0.02$ when comparing the two groups [108]. The reduced survival was also observed in children [109].

Scapellato and colleagues [110] reported that in HTLV-1/HIV-1-coinfected patients naive to treatment, $CD4^+$ T-cell counts were higher in the coinfected patients than in HIV-1-monoinfected patients at the time of an AIDS-defining illness. A case-control study to characterize the phenotype of $CD4^+$ T cells during HTLV-1/HIV-1 coinfection was conducted with 701 HAART-naïve, HIV-1-positive African adults. Within this patient cohort, 29 patients were found to be coinfected with HTLV-1. Each coinfected patient was matched by age and sex with two HIV-1-monoinfected individuals. The study also included unmatched healthy controls. $CD4^+$ T-cell levels, markers of $CD4^+$ T-cell activation, and HIV viral load were the parameters used to assess HIV-1 disease progression. The results showed that coinfected patients exhibited higher levels of $CD4^+$ T cells (median = 525 cells/mm^3 and 274 cell/mm^3, respectively; $p < 0.05$) with higher levels of expression of the activation markers CD25 and CD45RO and lower expression levels of CD45RA and CD62L (markers of naïve T cells) in coinfected individuals as compared to monoinfected individuals. Furthermore, coinfected patients exhibited an increase in HIV-1 proviral DNA load as compared to monoinfected subjects. Despite the normal or higher levels of $CD4^+$ T cells, coinfected patients still progressed to AIDS [111]. These observations imply that HTLV-1 infection enhances HIV-1 progression via loss of naïve $CD4^+$ T cells, with an overall increase in total $CD4^+$ T cells and an increase in HIV-1 viral load, key features with respect to the development of AIDS. The lymphocytosis observed in coinfected patients might have been caused by the Tax oncoprotein encoded by HTLV-1. Tax inhibits the cellular mechanisms involved in DNA repair and induces cell transformation and immortalization [111, 112].

The impact of HTLV-1 on the immune response during coinfection with HIV-1 was evaluated using quiescent PBMCs from HTLV-1/HIV-1-coinfected patients as well as from HIV-1 and HTLV-1-monoinfected individuals. The Th1 cytokine pathway appeared to be overstimulated

during HTLV-1/HIV-1 coinfection, as PBMCs from coinfected patients produced increased levels of IL-2 and IFN-γ compared to PBMCs from HIV-1 and HTLV-1-monoinfected individuals. These results implied that overproduction of Th1 cytokines during the course of HTLV-1/HIV-1 coinfection could be augmenting the overall negative impairment of the immune system induced by HIV-1 [113], which normally influences a Th2 response during chronic infection. Curiously, the correction to a Th1 response does not seem to correct for the shortened lifespan and a possible increase in progression to AIDS. It should be noted that there was obviously patient-to-patient variability, differences in phenotype depending on viral genotypes, and the length of time involving mono or dual infection.

6. Molecular interactions between HTLV-1 and HIV-1

To this point, we have discussed the impact that HIV-1 has on HTLV-1 disease progression, particularly on the occurrence of HAM/TSP, as well as the effect of HTLV-1 on HIV-1 infection. Clearly, HTLV-1/HIV-1 coinfection alters the course of disease caused by either virus along as assessed by proviral DNA loads, $CD4^+$ T-cell death and proliferation assessments, and overall immunologic assessment, pathogenesis, and disease indicates that the presence of both viruses negatively impacts human health as compared to the presence of either virus alone. Based on these observations, investigators have also explored the molecular interactions between HTLV-1 and HIV-1 that could be influencing the development of HTLV-1 disease or HIV/AIDS during HTLV-1/HIV-1 coinfection. *In vitro* experiments involving superinfection with the HIV-1 molecular clone $HIV\text{-}1_{IIIB}$ on two HTLV-1-transformed cell lines, MT2 (an HTLV-1-producer cell line) and 81-66/45 cell line (an HTLV-1 nonproducer cell line), have demonstrated that HIV-1 infection activates HTLV-1 and increases the levels of HTLV-1 proviral DNA in both HTLV-1-transformed cell lines [114]. Additional studies performed by Zsabó and colleagues [115] have shown that *in vitro* HTLV-1/HIV-1 coinfection of macrophages by both viruses results in increased replication of both viruses. The presence of the HTLV-1 Tax protein promoted nuclear transport of the newly reverse transcribed HIV-1 DNA, whereas the mechanism by which HIV-1 infection enhanced HTLV-1 gene expression did not appear to involve the HIV-1 Tat protein.

In a tripartite coculture assay using Jurkat T cells transfected with an HTLV-1LTR-driven reporter construct designated Jurkat/HTLV-1-Luc with a chronically infected HTLV-1 cell line, HTLV-1-MT2, that has also been infected with $HIV\text{-}1_{IIIB}$ via cell-to-cell transfer of virus from $HIV\text{-}1_{IIIB}$-infected H9 cells, Sun and coworkers demonstrated that HIV-1 infection induced an 80-fold increase in LTR-dependent HTLV-1 gene expression. It was also demonstrated that the increase in transcriptional activation of HTLV-1 genes occurred in a mechanism that was dependent on the HTLV-1 Tax protein, the HIV-1 gp120/gp41 complex, and CD40. These results suggested that HIV-1 infection promoted the development of syncytium among the cell lines examined in these studies, thereby acting as a channel for HTLV-1 Tax to translocate from the HTLV-1-infected MT2 cells to the HTLV-1-LTR-Jurkat cells, thereby providing an explanation as to how coinfection with HIV-1 and HTLV-1 may transactivate the LTR of latent provirus in neighboring cells [116]. Using an *in vitro* model of HTLV-1/HIV-1 coinfection, Roy

and colleagues confirmed that HIV-1 virus alone or the accessory protein Tat can enhance HTLV-1 gene expression. Culturing the NO-HTLV-1 cell line, an HTLV-1-infected cell line established by exposure of the cells to an HTLV-1 clinical isolate, in the presence of cell-free HIV-1 virion alone (HIV-1_{IIIB}), doubled the amount of HTLV-1 gene expression [117–119]. Additionally, the NO-HTLV-1 cells were exposed to recombinant HIV-1 Tat protein alone, subsequently resulting in an increase in the expression of HTLV-1 matrix protein expression (p. 19). Furthermore, the majority of HTLV-1-infected cells colocalized with HIV-1 virions, indicating HLTV-1 gene expression and transactivation, was dependent and correlated with the presence of HIV-1 virion or Tat [2].

With respect to the interactions between HTLV-1 and HIV-1 that affect HIV-1 expression, Leung and coworkers [120] first reported that the HTLV-1 Tat protein stimulates HIV-1 via activation of NF-κB. Later, studies by Böhnlein and colleagues [121] confirmed that in vitro HTLV-1/HIV-1 coinfection assays indicated that HTLV-1 enhanced HIV-1 expression utilizing a mechanism dependent on HTLV-1 Tax. These experiments revealed that HTLV-1 Tax protein stimulates T cells and promotes transcriptional activation of the HIV-1LTR via interaction with the cellular protein HIVEN86A. Additional studies indicated that HTLV-1 Tax also works synergistically with HIV-1 Tat to increase HIV-1 via stimulation of NF-κB [122]. Culturing HTLV-1-producing MT2 cells with HIV-1 isolates from quiescent $CD4^+$ T cells from HIV-1-infected patients treated with HAART upregulated HIV-1 expression. HTLV-1 Tax or the Env glycoprotein alone was sufficient to induce HIV-1 replication [123].

7. Treatments for HIV-1 and HTLV-1 infections

The current approach to effectively treat HIV-1-infected patients involves the use of a combination of antiretroviral drugs that inhibit a number of steps within the HIV-1 replication cycle, including the reverse transcription process, integration, and proteolytic processing of structural polyproteins, thereby reducing the production of mature infectious HIV-1 virions that involves the HIV-1-encoded protease [124]. By 2011, the FDA had approved 26 antiretrovirals for the treatment of HIV-1 [6] with now more than 30 agents approved for use in humans to treat HIV-1 infection [8]. The rationale of using highly active antiretroviral therapy (HAART) or also referred as combination antiretroviral therapy (cART) in HIV-1-infected individuals has been to minimize the development of drug-resistant virus while effectively reducing the viral load to undetectable levels for prolonged periods of time, in essence, the establishment of a manageable chronic disease. As mentioned previously, although cART reduced actively replicating virus, it does not remove active or defective integrated and latent provirus. To affectively "cure" and HIV-infected individual, every copy of proviral DNA must be removed. Recently, much attention has been focused on purging and excising the latent reservoir by the shock and kill method (HDAC inhibitors) and gene-editing enzymes (zinc-finger nucleases, TALENS and CRISPR/Cas9) [125–128], as previously reviewed [129, 130]. The shock and kill strategy has involved reactivating latent virus reservoirs from resting memory $CD4^+$ T cells with this process leading to a contraction in the size of the reservoir post activation in combination with cART therapy that leads to the destruction of the activated cell and the prevention

of infection of uninfected T cells. Additional therapeutic strategies have recently focused on the use of gene-editing systems involving protein-based enzymes that have been designed to seek out specific HIV-1 proviral DNA sequences and induce double-stranded DNA breaks that can induce nucleotide deletions and removal of whole gene segments [126, 130]. Many of these techniques are in basic discovery phases for the treatment of infected cells with the goal of eliminating integrated provirus. These technologies hold great promise to eliminate integrated retroviral genetic information thereby curing the infected cell.

In the case of HTLV-1 infection, reverse transcriptase inhibitors stop HTLV-1 replication *in vivo* but can only prevent infection if they are taken immediately after first contact with the virus [131, 132]. The current therapeutic options for HTLV-1 infection consist of a number of chemotherapeutic agents for lymphoma and the combination of zidovudine and interferon-α (IFN-α) for the management of acute, smoldering, and chronic ATL. The clinical management of ATL continues to be challenging because it has been shown to be a highly lethal type of cancer resistant to many of the currently available anticancer drugs (Figure 4) [124]. In 1996, Borg and colleagues [133] successfully treated and caused cancer rejection in an Afro-Caribbean female with ATL using a combination of chemotherapeutic agents (cyclophosphamide, doxorubicin, and etoposide) and allogeneic bone marrow stem cell transplantation (alloSCT). In the case of people older than 50 years, alloSCT treatment is given with low doses of chemotherapeutic drugs. Retrospective studies indicate that 30–40% of ATL patients who have undergone alloSCT treatment become long-term survivors [134]. The use of the humanized defucosylated antiCCR4 antibody in patients with ATL has also had promising results [135, 136] with HAM/TSP [137]. Concurrently, the treatment for HAM/TSP and its secondary effects involves the use of spasmolytic drugs, prednisone, danazol [138], valproic acid [139], prosultiamine [140], IFN-α [141–143], IFN-β-1a [144–146], or vitamin B1 [147].

The management of HTLV-1/HIV-1 coinfection can be challenging due to the lack of efficacy of antiretroviral therapy with respect to the inhibition of HTLV-1 replication as well as the disparate effects one therapy or compound may have on the other virus. One of the drugs commonly used for HTLV-1 infection is IFN-α. However, the clinical benefits of IFN-α for HIV-1-infected patients are controversial. *In vitro*, IFN-α downregulates HIV-1 replication in macrophages and T cells and halts the formation of mature HTLV-1 virions. Importantly, IFN-α treatment induces caspase-3-mediated apoptosis of HTLV-1/HIV-1_{IIIB}-coinfected MT-4 cells, but not HTLV-1-monoinfected MT-4 cells. Interestingly, IFN-α treatment did not affect HTLV-1 infectivity but markedly reduced HIV-1 replication, with an approximately 1000-fold decrease in HIV-1 p24 antigen expression [124]. These immediate differential affects on therapy of these two viruses also project a possible role of coinfection in influencing ATL and HAM/TSP prominence and therapeutic strategy for treatment.

The incidence of ATL in HTLV-1/HIV-1-coinfected individuals has not been widely reported yet. Shibata and colleagues reported a case involving a 43-year-old African American male with ATL that was positive for both HTLV-1 and HIV-1. The patient underwent three phases of treatment achieving at least 12 months of remission. The first stage consisted of daunorubicin, prednisone, and vincristine. Then the patient was placed on *cis*-platinum, etoposide, cytosine arabidoside, and dexamethasone. During the third phase, the patient was treated with

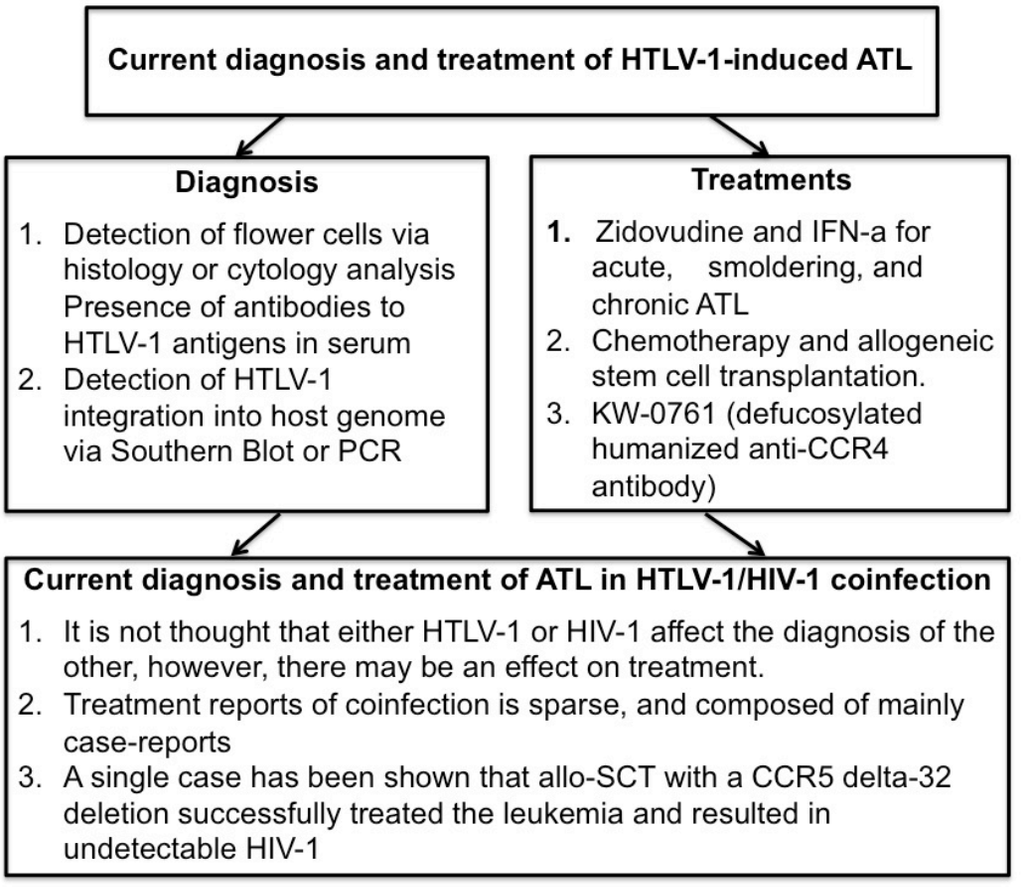

Figure 4. Current diagnosis and treatment of HTLV-1-induced ATL. Summary of criteria used to diagnose previously identifiable forms of ATL and a brief overview of currently available treatments are shown.

zidovudine. PCR analysis of PBMCs detected HTLV-1 in 1/1,000 cells and HIV-1 in a similar fraction [148].

Furthermore, Hütter and colleagues used alloSCT to treat a 40-year-old white male who suffered from acute myeloid leukemia and was also HIV-1-positive. The patient received the transplant from an HLA-matched donor who was homozygous for the CCR5 delta32 deletion. Importantly, a homozygous 32-bp deletion in the CCR5 allele has been shown to confer long-term resistance to HIV-1 infection with CCR5-utilizing viruses but not CXCR4-utilizing viruses. The patient was infected with HIV-1 more than 10 years earlier and had received cART for the previous 4 years. At the time of his leukemia, he was asymptomatic with respect to HIV disease. Initially, the patient was treated with chemotherapy, after which time he suffered from a rebound in his HIV-1 viral load and a relapse in his leukemia. At this time, he received the alloSCT, which successfully treated the leukemia. In addition, the patient stopped taking the cART and his HIV-1 viral loads were undetectable. After 20 months of follow-up, this patient was free of both the HIV-1 infection and the leukemia [149]. While these *in vitro* and *in vivo* studies and clinical trials have revealed a great deal of information about co- and monoinfection of HTLV-1/HIV-1-infected individuals, much more research is needed to help manage these lifelong chronic infections.

8. Summary and concluding remarks

We have discussed a number of diseases caused by infection with two common human retroviruses, HTLV-1 and HIV-1, alone or within the context of coinfection. As previously shown by epidemiological studies, coinfection with these two viral pathogens occurs frequently among illicit drug users, and its incidence is on the rise particularly in regions around the world where both viruses are endemic. Although HTLV-1 and HIV-1 are both retroviruses and as such share a number of genomic structural features, similar events within the replication cycle, and common modes of transmission, the overall pathogenic outcomes and the associated diseases they cause are very different except, for the most part, they all occur within the context of the immune and nervous systems with other end organs also involved. Additional information relevant to epidemiology, virology, immunology, immune- and neuropathogenesis, diagnosis, molecular mechanisms of disease, treatment, and clinical management are also discussed within the context of mono- and coinfection with these two important human retroviruses. Despite large bodies of information available concerning the molecular pathogenesis and disease resulting from monoinfections, there is much less information concerning the molecular interactions between HTLV-1 and HIV-1 replication machinery as well as the implications each virus has on disease progression resulting from the pathogenic outcomes when both viruses are replication in the same cells or neighboring cells within the same tissue compartment. Clearly, studies of HTLV-1/HIV-1 coinfection have been complicated by the fact that most of these studies have been conducted after the initiation of cART for suppression of HIV-1 infection (although many of the coinfection studies have been performed in countries where delivery of optimal cART has been difficult). With regard to the molecular interactions between the two viruses, even though both viruses target $CD4^+$ T cells, HIV-1 infection usually results in lytic replication in activated T-cell populations, whereas HTLV-1 infection usually results in more limited replication and gene expression and ultimately induces clonal expansion of selected $CD4^+$ T-cell populations. Interestingly, the bone marrow compartment is penetrated by both HTLV-1 and HIV-1 during the course of disease; the penetration of this compartment appears to seed each virus into different cellular compartments [41, 85, 150]. With respect to HIV-1, the stem cell population within this compartment appears to be spared of viral infection with virus only seeded into more committed or differentiated progenitor cell compartments. The binding of HIV-1 particles to stem cells has been shown to alter their functional properties despite the absence of detectable levels of viral entry into stem cells. However, following HTLV-1 infection, there appears to be differential gene expression within cellular compartments within the bone marrow with much greater numbers of DNA^+RNA^+ progenitor cells in individuals suffering from HAM/TSP as compared to individuals with ATL where there are far fewer DNA^+RNA^+ progenitor cells [61, 64]. The significance of these molecular interactions within the context of bone marrow cell populations remains unresolved during the course of monoinfections and remains to be examined in HTLV-1/HIV-1 coinfections. The interaction of both viruses with the bone marrow compartment during the course of mono- and coinfection within the same or different bone marrow-infected cell populations will likely play an important role in the pathogenesis of diseases caused by both viruses. Clearly, studies with a greater number of larger coinfection cohorts will be required to

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approach defining molecular mechanisms, diagnosis, treatment, prevention, and overall clinical management of diseases caused by HTLV-1/HIV-1 coinfection. It would also seem important to obtain a better understanding concerning the relationship between the timing of HIV-1 infection relative to the course of HTLV-1-induced disease. Interestingly and perhaps relevant to thinking about this problem is the epidemiologic data suggesting that individuals that suffer from ATL as compared to HAM/TSP are more likely to have been infected by mucosal membrane exposure early in life often as a result of vertical transmission of HTLV-1 as compared to a blood stream exposure of the virus as a result of IV transmission associated with illicit drug abuse [151]. Clearly, the immunosuppression that occurs as a result of primary HIV-1 infection and later during the course of disease with individuals that first seek medical attention for symptoms consistent with HIV-1 disease prior to the start of cART may have great impact on the initial phases of HTLV-1 disease depending on the size and functionality of the T-cell compartment during the primary HTLV-1 infection. If these predictable periods of immunosuppression occur at critical phases of already ongoing HTLV-1-induced disease, the impact of HIV-1 on the course of HTLV-1 disease could be significant whether the individual is headed toward neuroinflammatory or leukemic disease. Clearly, these interactions will pose significant challenges with respect to the clinical management of HTLV-1-induced disease, while HTLV-1 infection could alter the course of HIV-1 disease depending on what impact the neuroinflammatory state associated with the development of HAM/TSP may have on HIV-1 infection of the $CD4^+$ T-cell compartment and what impact of polyclonal or monoclonal expansion of the $CD4^+$ T-cell compartment associated with HTLV-1-induced leukemogenesis may have on productive HIV-1 infection and replication in these T-cell compartments. Finally, the discussion of an HIV-1-positive patient suffering from ATL and another case with an HIV-1-positive patient with acute myeloid leukemia with respect to the impact of bone marrow stem cell replacement therapy on controlling HTLV-1-induced cancer and impact on ongoing HIV-1 disease was examined. In both cases, HIV-1 disease was well controlled at the time of the bone marrow transplant. Interestingly, they both achieved remission of the leukemia, and the HIV-1 and HTLV-1 titers of the first case were very low after treatment, and in the second case, the HIV-1 infection has been apparently cured. This is clearly a better understanding of the molecular interactions between HTLV-1 and HIV-1 and their respective host cell targets with regard to cellular coinfection or cellular interactions altered by viral coinfection of different cellular compartments.

The clinical management of HTLV-1 and HIV-1 mono- and HTLV-1/HIV-1 coinfection will be greatly enhanced by the identification of additional druggable viral or cellular targets to enhance the effective long-term clinical management of HTLV-1- and HIV-1-induced disease outcomes stemming from monoinfections (long-term suppression of viral gene expression in either case with minimal impact of viral infection on host cell function) prior to the encounter of the second virus. A second therapeutic approach will involve curing HTLV-1- and HIV-1-infected patients by elimination of susceptible target cell populations by targeted elimination of cellular receptor epitopes rendering normally susceptible cells refractile to viral infection while maintaining the normal cellular function of these host cell proteins. In parallel with these types of experimental studies, additional types of experimentation will involve the eradication of HTLV-1 and HIV-1 infections by site-specific excision of integrated HTLV-1 and HIV-1

proviral DNA with minimal off target impact on host cell function. Clearly, this is exciting technology with great promise to completely eliminate latent or persistent viral infections without having to activate latent viral gene expression to kill latently infected cells [125–130, 152]. The goal of eliminating both defective and completely functional HIV-1 and HTLV-1 will likely be very critical since it is entirely possible that nonactivatable defective proviruses may still be able to drive the expression of viral proteins (gp120, Tat, Vpr, and Nef) that may cause detrimental effects to neighboring or distant cells in the absence of lytic infectious virus production. Many challenges await this experimental approach, including the exact nature of existing viral reservoirs, the genetic variability of the latent virus, and the delivery of excision technologies to tissue-specific reservoirs, including memory $CD4^+$ T-cell subpopulations, specific cell populations within the monocyte–macrophage lineage, as well as cell populations within the brain and other tissues. Perhaps central to basic and translational science is the development of tomorrow's translational solutions to today's challenges leading to effective solutions to clinical problems.

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