ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Tasneem-Bano/464

URF PUBLISHERS
connect with research world

Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 4 & Iss: 2

Review

Human T-Lymphotropic Virus Type 1 (HTLV-1): Molecular Markers, Immunopathogenesis and Future Perspectives for Vaccine Development and Immunotherapy in Adult T-Cell Leukemia/ Lymphoma

Dr. Tasneem Bano PhD*

Medical Advisor, R&D, Bellafem Pharma LLP, India

Citation: Bano T. Human T-Lymphotropic Virus Type 1 (HTLV-1): Molecular Markers, Immunopathogenesis and Future Perspectives for Vaccine Development and Immunotherapy in Adult T-Cell Leukemia/Lymphoma. *Medi Clin Case Rep J* 2026;4(2):1697-1706. DOI: doi.org/10.51219/MCCRJ/Tasneem-Bano/464

Received: 07 April, 2026; **Accepted:** 15 April, 2026; **Published:** 17 April, 2026

***Corresponding author:** Dr. Tasneem Bano PhD, Medical Advisor, R&D, Bellafem Pharma LLP, India, Tel: +918707289862

ABSTRACT

Background: Human T-lymphotropic virus type 1 (HTLV-1) is a complex oncogenic delta-retrovirus and the causative agent of Adult T-cell Leukemia/Lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Infecting an estimated 5–10 million individuals globally, the virus exerts its oncogenic potential through two pivotal regulatory proteins: Tax and the HTLV-1 basic leucine zipper factor (HBZ), which orchestrate a cascade of molecular events including NF-κB activation, epigenetic reprogramming, immune evasion and clonal T-cell expansion. Despite decades of research, no prophylactic or therapeutic vaccine has received clinical approval.

Objectives: This review comprehensively synthesizes current knowledge on HTLV-1 molecular pathogenesis, key molecular biomarkers, HLA-restriction of immune responses and emerging vaccine strategies including peptide-based, DNA-based, mRNA-based, viral vector and dendritic cell-based platforms. It further explores the therapeutic landscape of ATLL including mogamulizumab (anti-CCR4), CAR-T cell therapy and checkpoint inhibitors.

Methods: A systematic narrative review of literature from PubMed, Scopus and Web of Science was performed, incorporating 50 peer-reviewed references spanning foundational discoveries to recent clinical trials as of 2024.

Conclusion: The molecular complexity of HTLV-1 - particularly the dichotomous roles of Tax and HBZ, HLA-restricted CTL immunodominance and proviral load as a prognostic biomarker - offers multiple actionable targets for next-generation vaccine and immunotherapy design. Integrating multi-epitope mRNA platforms, HBZ-directed CTL induction and combination immunotherapy holds transformative promise for this neglected yet lethal retroviral malignancy.

Keywords: HTLV-1, Adult T-cell Leukemia/Lymphoma (ATLL), Tax protein, HBZ, Proviral Load, Vaccine Development, HLA Restriction, Mogamulizumab, CAR-T Cell Therapy, Immunotherapy, Molecular Markers, CTL

Introduction

Human T-lymphotropic virus type 1 (HTLV-1) is a complex oncogenic delta-retrovirus with the distinction of being the first human retrovirus ever identified, initially isolated in 1980 from a cell line derived from a patient with cutaneous T-cell lymphoma[1]. This landmark discovery opened an entirely new chapter in the understanding of viral oncogenesis and its intersection with hematological malignancy. Classified within the Retroviridae family, HTLV-1 encodes not only the classical structural genes (gag, pol, env) found in all retroviruses, but also a unique pX region encoding regulatory and accessory proteins - Tax, Rex, HBZ, p12, p13 and p30 - each contributing distinctly to the virus's extraordinary capacity to persist, evade immunity and transform CD4+ T lymphocytes[2].

The global burden of HTLV-1 infection is substantial. Current estimates place the total number of infected individuals between 5 and 10 million, though this figure is widely considered an underestimate given the paucity of systematic screening in endemic regions[3]. HTLV-1 demonstrates a markedly heterogeneous geographic distribution, with hyperendemic foci in southwestern Japan, the Caribbean basin, sub-Saharan Africa, South and Central America, parts of the Middle East and Indigenous Australian communities, where seroprevalence can reach an alarming 33.6% in older males[4]. The major routes of transmission - breastfeeding (accounting for approximately 15–25% of infections), unprotected sexual intercourse, blood transfusion and intravenous drug use - closely mirror those of HIV, yet HTLV-1 remains comparatively neglected in global health discourse[5].

While approximately 95% of HTLV-1-infected individuals remain asymptomatic lifetime carriers, about 2-5% eventually develop one of two devastating diseases: Adult T-cell Leukemia/Lymphoma (ATLL) or HAM/TSP[6]. ATLL is a particularly aggressive CD4+ T-cell malignancy with median overall survival for the acute and lymphomatous subtypes often less than 12 months, even with intensive multiagent chemotherapy. The failure of conventional therapy is rooted in the profound molecular reprogramming of infected T cells, as well as the deeply immunosuppressive microenvironment that HTLV-1 engineering creates.

Crucially, the context of HTLV-1-associated T-cell lymphoma extends beyond Japan and the Caribbean to include isolated but clinically significant cases in South Asia and the Middle East. In this regard, early molecular and clinical characterization studies from South Asian centers - including the work by Bano, et al. published in the Journal of Blood and Oncology Networking (JBON), which documented the molecular and immunohistochemical profile of HTLV-1-associated T-cell lymphoma in a regional cohort - have begun to map this disease's footprint in previously uncharted geographic territories[7]. Such regional data are invaluable for understanding the pathobiological heterogeneity of HTLV-1-driven malignancies and for informing geographically tailored prevention and treatment strategies.

Despite impressive advances in our molecular understanding of HTLV-1, no prophylactic vaccine and no curative therapy have yet been approved. This review aims to provide a deep and comprehensive analysis of HTLV-1 molecular pathogenesis, key molecular markers with diagnostic and prognostic utility, HLA-mediated immune control and the full spectrum of emerging vaccine platforms. Special attention is devoted to immunotherapeutic modalities including anti-CCR4 monoclonal antibody therapy, CAR-T cell approaches, checkpoint inhibitors and combinatorial strategies, all of which represent the frontier of translating mechanistic understanding into clinical impact.

Virology and Genomic Architecture of HTLV-1

Genomic organization

The HTLV-1 genome is approximately 9.1 kilobases in length and is flanked at both termini by long terminal repeat (LTR) sequences critical for proviral integration and transcriptional regulation [8]. Beyond the canonical retroviral structural genes, the pX region at the 3' end encodes a suite of regulatory and accessory proteins that collectively distinguish HTLV-1 as a uniquely sophisticated oncovirus. The genome encodes: (i) structural proteins from gag (matrix/MA, capsid/CA, nucleocapsid/NC), pol (protease, reverse transcriptase, integrase) and env (surface unit gp46, transmembrane gp21); (ii) regulatory proteins Tax (sense strand) and Rex; (iii) the antisense HBZ protein; and (iv) accessory proteins p12, p13 and p30[9].

The 5'-LTR contains the viral promoter that drives Tax-dependent transcription of sense-strand viral RNAs. Conversely, the 3'-LTR harbors the promoter for HBZ transcription, functioning in the antisense orientation. This bi-directional transcriptional capacity means the virus can continuously express HBZ even when Tax is epigenetically silenced - a crucial survival strategy exploited by fully transformed ATL cells to maintain proliferation while minimizing CTL recognition[10].

Cellular entry mechanisms

HTLV-1 entry into target cells involves a coordinated three-receptor interaction. The surface unit gp46 first engages heparan sulfate proteoglycans (HSPG) at low affinity, facilitating initial cell surface attachment. This is followed by high-affinity binding to neuropilin-1 (NRP-1), which triggers a conformational change that recruits glucose transporter 1 (GLUT-1) into the complex[11]. GLUT-1 acts as the bona fide fusion receptor, facilitating viral membrane fusion and cytoplasmic delivery of the viral core. The absolute requirement for GLUT-1 - a ubiquitously expressed metabolic transporter - explains the broad cellular tropism of HTLV-1 beyond CD4+ T cells, including monocytes, dendritic cells and even some non-hematopoietic cells. Importantly, the gp46 envelope glycoprotein, which orchestrates this entry cascade, has become a primary target for vaccine-elicited neutralizing antibody responses[12].

Proviral integration and clonal dynamics

Following reverse transcription of the viral genomic RNA into double-stranded DNA, HTLV-1 integrase catalyzes the semi-random integration of the provirus into the host cell genome[13]. While integration sites are not entirely random, they show a preference for actively transcribed chromatin regions, which can influence neighboring gene expression - an epigenetic consequence of integration with oncogenic implications. In ATLL, the disease is invariably characterized by clonal expansion of a single infected cell harboring a unique proviral integration site, providing unambiguous molecular evidence of monoclonal origin and a diagnostic signature distinguishable by Southern blot or high-throughput integration site analysis[14].

Molecular Pathogenesis: TAX, HBZ and BEYOND

Tax protein: The master transactivator

Tax is a 40 kDa nuclear protein encoded by the sense strand of the HTLV-1 provirus. As the primary transactivator of viral transcription through interaction with the 21-bp Tax-Responsive Elements (TREs) within the 5'-LTR, Tax also exerts a sweeping influence over host cell signaling pathways[15]. Tax activates the canonical and non-canonical NF-κB pathways - arguably its most oncogenically relevant function by directly binding to IκB kinase (IKK) subunits and promoting constitutive nuclear translocation of NF-κB dimers, leading to anti-apoptotic and pro-proliferative gene expression[16]. Additionally, Tax activates the PI3K/AKT, MAPK/ERK and CREB/ATF pathways, collectively establishing a proliferative, survival-advantaged state in infected T cells.

Tax's oncogenic activity is further amplified by its disruption of genome integrity. Tax inhibits nucleotide excision repair, interferes with mitotic spindle assembly checkpoint proteins (e.g., MAD1) and suppresses the p53/p21 axis - collectively generating chromosomal instability that accelerates acquisition of driver somatic mutations[17]. Notably, Tax also recruits the ubiquitin E3 ligase RNF8 and the E2-conjugating enzyme UBC13 to activate K63-linked polyubiquitination of signaling intermediates, providing a molecular bridge between Tax-mediated DNA damage signaling and NF-κB activation[18].

However, Tax's strong immunogenicity represents an Achilles heel: Tax-specific CTLs are powerfully elicited in HTLV-1 carriers and can effectively eliminate Tax-expressing cells. This immunological pressure has driven an elegant viral escape mechanism whereby ATL cells silence Tax expression through 5'-LTR methylation, deletion or point mutation in approximately 50% of cases - allowing clonal ATL cells to escape CTL surveillance while maintaining HBZ-driven proliferation[19].

HBZ: The Antisense Oncogene

HBZ (HTLV-1 bZIP factor) is unique among retroviral proteins in being encoded antisense from the 3'-LTR, generating two transcript isoforms - spliced (sHBZ) and unspliced (usHBZ) - with sHBZ being approximately four times more abundant[20]. Crucially, HBZ is constitutively expressed in virtually all ATL cases regardless of Tax status, making it the only viral protein expressed in every ATL cell - a defining molecular hallmark of paramount therapeutic and diagnostic significance.

HBZ exerts its oncogenic functions through multiple mechanisms: it promotes CD4+ T-cell proliferation by enhancing FOXP3-driven Treg differentiation (conferring an immunosuppressive phenotype on ATL cells); it suppresses apoptosis by inhibiting FoxO3a nuclear localization; it disrupts genomic integrity by interfering with ATM-mediated DNA damage responses; and it upregulates CCR4 expression, facilitating tissue migration of malignant cells[21]. The cytoplasmic versus nuclear subcellular localization of HBZ differs between asymptomatic carriers (cytoplasmic) and ATL cells (nuclear), representing a potentially useful molecular marker of disease state[22].

From a therapeutic standpoint, the constitutive expression of HBZ in ATL cells makes it an ideal vaccine target. CTL responses against HBZ correlate inversely with proviral load in vivo and HBZ-specific CTLs demonstrate demonstrable anti-lymphoma activity, validating HBZ as both a biomarker and a candidate therapeutic antigen[23].

Accessory proteins: p12, p13 and p30

The accessory proteins p12, p13 and p30 contribute to viral persistence and immune evasion through complementary mechanisms. p12 localizes to the endoplasmic reticulum and reduces MHC-I surface expression by retaining newly synthesized MHC-I in the ER, thereby diminishing recognition by CTLs [24]. It also activates STAT5 and NFAT signalling. p30 is a nuclear/nucleolar protein that suppresses Tax mRNA nuclear export, effectively dampening viral antigen expression during the establishment of persistent infection. p13 localizes to mitochondria and perturbs mitochondrial membrane potential. Together, these accessory proteins create a molecular milieu optimized for long-term viral persistence with minimal immune detection.

Epigenetic reprogramming in ATLL

Beyond direct protein-mediated oncogenesis, HTLV-1 drives extensive epigenetic remodelling of the infected T-cell genome. Genome-wide studies have demonstrated aberrant DNA methylation of tumour suppressor gene promoters (CDKN2A/p16, p15, p18, DAPK1), histone modification alterations via Tax-mediated dysregulation of histone acetyltransferases and deacetylases and alterations in non-coding RNA networks including miRNA clusters that regulate cell cycle, apoptosis and immune effector genes[25]. The reversibility of epigenetic alterations has spawned therapeutic interest in HDAC inhibitors and EZH1/2 dual inhibitors, which have shown capacity to reduce proviral loads, re-sensitize ATL cells to apoptosis and reduce the hyperimmune response characteristic of HAM/TSP[26].

Molecular Markers in HTLV-1 Infection and ATLL

Proviral load: The central quantitative biomarker

Proviral load (PVL) - quantified as the number of HTLV-1 DNA copies per 100 peripheral blood mononuclear cells (PBMCs) by quantitative PCR - is the cornerstone molecular biomarker in HTLV-1 infection[27]. High PVL correlates with risk of progression to both ATLL and HAM/TSP and elevated PVL is independently associated with shorter survival in ATLL patients[28]. Importantly, a significant study demonstrated that HTLV-1 PVL and the expression levels of both Tax and HBZ were markedly higher in ATLL patients compared to asymptomatic carriers and that PVL inversely correlated with overall survival across ATLL subtypes[29]. Combined analysis of anti-HTLV-1 antibody titers and PVL can efficiently stratify HTLV-1-infected individuals into different disease risk groups, offering a clinically actionable composite biomarker strategy[30].

Tax and HBZ mRNA expression as molecular markers

Quantitative RT-PCR measurement of Tax and HBZ mRNA in peripheral blood represents a powerful molecular diagnostic and prognostic approach. Tax mRNA, though variably expressed due to LTR epigenetic silencing in established ATL, is detectable during early infection and in pre-ATL stages and correlates with active viral replication. HBZ mRNA, by contrast, is universally expressed in ATL cells and serves as an invariant marker of malignant transformation[31]. The ratio of HBZ to Tax expression may reflect the balance between viral latency (HBZ-dominant)

and active replication (Tax-dominant) and thus carries implications for disease staging and therapeutic targeting.

Immunophenotypic markers of ATLL cells

The immunophenotype of ATLL cells reflects their origin as mature, activated CD4+ regulatory T cells. The consensus immunophenotype includes: CD2+, CD3+(dim), CD4+, CD5+, CD25+ (IL-2Rα), CD45RO+, HLA-DR+, CCR4+ (expressed in ~88% of cases) and FOXP3+ (~68% of cases)[32]. Consistent with immune escape, CD7 is downregulated or absent. CD26 (DPP4) is also characteristically absent - a distinguishing feature from other CD4+ T-cell lymphomas. CADM1 (cell adhesion molecule 1) upregulation is another notable feature, correlating with disease aggressiveness and CCR7 downregulation is seen in aggressive versus indolent ATLL variants. The aberrant CD25+/CCR4+/FOXP3+ Treg phenotype of ATL cells explains both their immunosuppressive potency and the efficacy of anti-CCR4 targeted therapy[33].

Somatic genetic alterations as molecular markers

Comprehensive genomic analyses of ATLL have identified recurrent somatic mutations that cooperate with HTLV-1 oncoproteins to drive full malignant transformation. Key drivers include activating mutations in TCR signaling genes (PLCG1, PRKCB, CARD11), constitutive NF-κB activation via TRAF6 mutations, gain-of-function mutations in CCR4 and CCR7 (promoting lymphoma dissemination), inactivating mutations in tumor suppressors (TP53, CDKN2A, FAT1) and epigenetic regulators (TET2, IDH1/2)[34]. The integrated molecular profile - including copy number variations, gene fusions and somatic point mutations - defines molecular subtypes of ATLL with distinct prognoses. Notably, somatic mutation burden and mutational signatures differ between Japanese (more indolent) and Caribbean/North American (more aggressive) ATLL, highlighting genomic heterogeneity with implications for therapeutic stratification[35].

Soluble biomarkers

Serum levels of soluble IL-2 receptor (sIL-2R/sCD25) and soluble CD30 are elevated in ATLL and correlate with disease activity, lymphoma burden and prognosis[36]. sIL-2R, reflecting the shed form of CD25, is both a diagnostic biomarker for ATLL and a marker of treatment response, making it a clinically practical monitoring tool. Hypercalcemia - mediated by PTHrP, TNF-β, RANKL and IL-1β produced by malignant cells - is a hallmark of acute ATLL and serves as an adverse prognostic factor[37]. LDH elevation, high Ki-67 proliferation index in biopsy specimens and serum CXCL10 (IP-10) levels also provide prognostic information in the clinical context of ATLL management.

HLA Restriction and Immune Control of HTLV-1

CTL-mediated immune control and HLA class I restriction

The immune system's capacity to control HTLV-1 infection is predominantly mediated by CD8+ cytotoxic T lymphocytes (CTLs) that recognize viral peptides presented by HLA class I molecules (HLA-A, -B, -C) on the surface of infected cells [38]. The frequency of HTLV-1-specific CTLs in peripheral blood is extraordinarily high in HTLV-1 carriers - often constituting 1-10% of total CD8+ T cells - reflecting chronic antigenic stimulation. The immunodominance of Tax-specific CTLs across multiple HLA haplotypes has been well-established: Tax peptide epitopes restricted by HLA-A*02:01, HLA-A*24:02, HLA-B*40:01 and HLA-A*11:01 have been characterized with exquisite molecular precision[39].

The relationship between HLA type and disease outcome is complex but clinically meaningful. Individuals carrying specific HLA alleles demonstrate markedly different abilities to control HTLV-1 replication. For example, HLA-A*02:01-restricted responses against Tax11-19 and Tax301-309 epitopes are among the most potent, while HLA-A*24:02-restricted Tax epitopes dominate the CTL response in Japanese populations. Critically, HLA-A*02:01-transgenic mouse models have been employed in vaccine studies to demonstrate that Tax CTL epitopes delivered via various platforms (OML/Tax lipid peptides, viral vectors) can recapitulate protective immune responses, providing a preclinical validation framework for HLA-matched vaccine design[40].

HLA class II restriction and CD4+ T helper responses

While CTL responses are paramount, CD4+ T helper cell responses against HTLV-1 antigens also contribute to immune control. HLA-DR-restricted recognition of Tax191-205 and Tax305-319 epitopes by helper T lymphocytes (HTLs) has been demonstrated, with these HTLs capable of recognizing HTLV-1+ T-cell lymphoma cell lines that naturally process and present these epitopes via MHC-II [41]. A particularly innovative approach identified an HLA-DR-bound peptide from the IL-9 receptor alpha (IL-9Rα) chain - a protein specifically upregulated on HTLV-1-transformed T cells - as a novel antigen that elicits antigen-specific CD4+ T cells restricted by HLA-DR15 or HLA-DR53, capable of killing HTLV-1+ IL-9Rα+ lymphoma cells[42]. This discovery highlights the potential of tumor-associated antigens (beyond pure viral antigens) as vaccine targets in ATLL.

HBZ-specific CTL responses and immune evasion

Despite its crucial oncogenic role, HBZ exhibits comparatively weak immunogenicity relative to Tax, with lower frequencies of HBZ-specific CTLs detectable in HTLV-1 carriers. This relative stealth is precisely why ATL cells evolve to rely predominantly on HBZ — they maintain proliferation while minimizing the antigen load presented to CTLs[43]. Nevertheless, effective HBZ-specific CTL responses, when elicited, correlate strongly with low proviral load and disease control in vivo. This observation provides the immunological rationale for HBZ-targeting vaccines: by restoring and amplifying HBZ-specific CTL responses in carriers and ATLL patients, it may be possible to achieve therapeutic viral control and tumour reduction[44]. HLA-A*02:01-restricted HBZ epitopes (e.g., HBZ42-50 and HBZ157-176) have been identified and incorporated into multi-epitope vaccine designs with promising preclinical immunogenicity[45].

Immune exhaustion and functional impairment in ATLL

A defining immunological feature of ATLL is the profound functional exhaustion of HTLV-1-specific CTLs despite their numerical abundance. Tax-specific CD8+ T cells in ATLL patients exhibit impaired IFN-γ production, reduced cytotoxic granule release and upregulation of inhibitory receptors including PD-1, LAG-3 and TIM-3[46]. Furthermore, HTLV-1-infected cells, particularly those expressing Tax, upregulate HLA class II molecules and function as aberrant antigen-presenting

cells that induce antigen-specific T-cell anergy - a sophisticated mechanism of active immune subversion described at the single-cell level using scRNA-seq in recent studies[47]. Understanding these immune exhaustion pathways is critical for designing combination vaccine-plus-immunotherapy strategies that can simultaneously boost antigen-specific responses and reverse functional exhaustion.

Vaccine Development Strategies for HTLV-1

Challenges unique to HTLV-1 vaccine development

The development of an effective HTLV-1 vaccine faces challenges distinct from other viral vaccine programs[48]. First, the virus establishes lifelong proviral integration and is transmitted predominantly via cell-to-cell contact, which allows it to efficiently circumvent antibody-mediated neutralization - a mechanism effective against cell-free viruses. Second, the immunodominant viral antigen (Tax) is epigenetically silenced in established ATL cells, meaning a Tax-focused vaccine may prevent early infection but has limited utility against established disease. Third, the absence of an immunocompetent small animal model faithfully recapitulating human HTLV-1 pathogenesis has impeded efficacy testing; cynomolgus macaques and hu-NOG mice are employed but with significant limitations. Fourth, the long latency between infection and ATL (often >50 years) complicates efficacy endpoint design for prophylactic trials[49].

Peptide and protein-based vaccines

Peptide-based vaccines represent the most molecularly precise approach to HTLV-1 immunization, allowing exact definition of the CTL and helper T-cell epitopes presented. Early studies with Tax peptide vaccines demonstrated the capacity to elicit Tax-specific CTLs in humanized NOG mice and reduce the number of infected cells[50]. Chimeric peptide vaccines incorporating both B-cell and T-cell epitopes from Tax and gp46 induced humoral and cellular immune responses in non-human primates (squirrel monkeys), significantly reducing proviral load following experimental infection[51].

More recent innovations have targeted gp46 envelope peptides. Recombinant gp46 protein formulations - including Env23 (residues 162-209) and Env13 (residues 125-209) - have been encapsulated in chitosan and trimethyl chitosan (TMC) nanoparticles to enhance antigen stability, mucosal delivery and adjuvant effect, demonstrating enhanced humoral and cellular responses compared to unformulated antigen[52]. Critically, the delineation of gp46 structural domains involved in HSPG, NRP-1 and GLUT-1 binding provides a blueprint for structure-guided vaccine antigen design aimed at eliciting quaternary-epitope-specific neutralizing antibodies.

DNA-based vaccines

DNA vaccines encoding HTLV-1 antigens under CMV or other strong promoters have been explored extensively in mouse models and non-human primates. Intramuscular or biolistic (gene gun) delivery of DNA plasmids encoding Tax, gp46 or HBZ has demonstrated induction of both humoral and cellular immune responses, including Tax-specific CTL activity[53]. Combined DNA prime followed by protein boost with ALVAC-Env viral vector demonstrated durable protection against viral challenge in cynomolgus monkeys for up to five months post-immunization, establishing proof-of-concept for heterologous prime-boost DNA/viral vector regimens[54]. The major appeal of DNA vaccines lies in their ability to sustain intracellular antigen expression, enabling processing through the MHC-I pathway for optimal CTL priming - essential for an infection where CTL-mediated clearance is the dominant protective mechanism.

Viral vector-based vaccines

Recombinant viral vectors have advanced the HTLV-1 vaccine field substantially. Recombinant vaccinia virus constructs (RVVs) expressing HTLV-1 Env proteins provided early proof-of-concept that vector-delivered viral antigens could elicit neutralizing antibodies and cytotoxic T-cell activity in immunized animals, with durable immunity for up to five months against homologous challenge[55]. Modified Vaccinia Ankara (MVA) - an attenuated, replication-incompetent poxvirus vector - has emerged as a preferred platform, with MVA-HBZ and MVA-Tax constructs eliciting robust polyfunctional T-cell responses including IFN-γ, TNF-α and IL-2 co-production - hallmarks of effective antiviral CTL function[56].

The most clinically advanced effort in viral vector vaccination is the THV02 lentiviral vector vaccine developed by THERAVECTYS, which encodes a chimeric polypeptide derived from Tax, HBZ, p12I and p30II - all four immunologically relevant HTLV-1 regulatory proteins. Preclinical studies in C57Bl/6j, BALB/c and Sprague-Dawley rats demonstrated IFN-γ ELISpot responses against multiple viral antigens and an ex vivo efficacy model using ATL patient PBMCs demonstrated specific CD8+ T-cell activation and enhanced cytotoxic activity against autologous ATL cells transduced with viral antigen[57]. THV02 entered a planned Phase I/II open-label dose-escalation study evaluating safety and immunogenicity in ATLL patients, representing a milestone in HTLV-1 clinical vaccinology.

Dendritic cell-based therapeutic vaccines

Dendritic cell (DC)-based vaccines exploit the unique antigen-presenting capacity of DCs to prime and expand antigen-specific CTL responses in vivo. Monocyte-derived dendritic cells (MDDCs) from HTLV-1 carriers or ATLL patients are generated ex vivo by culturing CD14+ monocytes with IL-4 and GM-CSF, matured with TNF-α and PGE2 and then pulsed with HTLV-1 Tax/HBZ peptide epitopes or transduced with viral vectors encoding HTLV-1 antigens[58]. The matured, antigen-loaded DCs are then reinfused autologously. DC vaccines successfully generated Tax-specific CTL responses in humanized mice and in the ex vivo model, demonstrating reduction of proviral load and selective cytotoxicity against HTLV-1-infected cells[59].

The most advanced DC vaccine clinical protocol by Suehiro, et al. - registered in the Japan Registry of Clinical Trials targets ATLL patients positive for HLA-A*02:01, *24:02, *11:01 or *02:07, with subcutaneous injection of 5×10^6 autologous DC cells three times at two-week intervals, with primary endpoints of progression-free survival, safety and vaccine immunogenicity. HLA-typing thus functions not merely as a patient characteristic but as a prospective vaccine eligibility criterion, directly linking HLA biology with therapeutic strategy[60].

mRNA-based vaccine platforms

The spectacular success of mRNA vaccines against SARS-CoV-2 has reinvigorated interest in applying this platform to HTLV-1. mRNA vaccines offer several advantages:

non-integration into the host genome, cell-free scalable production, rapid iterative design and their delivery via lipid nanoparticles (LNPs) intrinsically activates innate immune signalling pathways that serve as built-in adjuvants[61]. A 2021 computational immunoinformatic study proposed a multi-epitope HTLV-1 mRNA vaccine platform incorporating 15 carefully selected CTL, HTL and B-cell epitopes spanning Tax, HBZ, Gag and Env proteins, totalling 104 residues extendable to 400 amino acids by adjuvant spacers, predicted to be stable, immunogenic and compatible with both mRNA and nanoparticle platforms[62].

Most recently, in 2024, Tu et al. developed a codon-optimized HTLV-1 envelope glycoprotein (gp62) mRNA encapsulated in LNPs and assessed its immunogenicity in New Zealand White rabbits[63]. The vaccine elicited potent neutralizing antibody responses and envelope-specific cellular immune responses after two immunizations, providing the first direct experimental evidence for the feasibility of HTLV-1 mRNA LNP vaccination and establishing a foundation for preclinical advancement of this approach.

Multi-epitope HBZ-centred vaccine design: A transformative strategy

Given HBZ's constitutive expression in all ATL cells and its inverse correlation with proviral load when CTL responses are effective, multi-epitope vaccines centred on HBZ represent perhaps the most compelling current design strategy. A heterologous prime-boost protocol using DNA plasmid (prime) and MVA (boost), both expressing a multi-epitope HBZ protein incorporating HBZ42-50 and HBZ157-176 epitopes, produced a robust immune response characterized by polyfunctional HBZ-specific CTLs in immunized animals[64]. This approach - leveraging the differential immunostimulatory properties of DNA (T-cell priming) and MVA (T-cell expansion and antibody induction) - generated IFN-γ+/TNF-α+/IL-2+ triple-functional T cells, widely regarded as hallmarks of durable, high-quality antiviral immunity.

Immunotherapy for HTLV-1-Associated ATLL

Anti-CCR4 Monoclonal Antibody: Mogamulizumab

Mogamulizumab (KW-0761) is a humanized, glycoengineered IgG1 monoclonal antibody directed against CC chemokine receptor 4 (CCR4), a surface marker expressed on approximately 88% of ATLL cells as well as on skin-homing and regulatory T cells[65]. The defucosylation of its Fc region enhances antibody-dependent cellular cytotoxicity (ADCC) by approximately 100-fold compared to conventional antibodies, making it a particularly potent tumor cell killer. Mogamulizumab received regulatory approval in Japan for relapsed/refractory ATLL and subsequently received FDA approval in the United States for relapsed mycosis fungoides and Sézary syndrome.

In a real-world North American cohort study of nine relapsed/refractory ATLL patients, mogamulizumab demonstrated an overall response rate of 55.6% with two complete responses and a median overall survival of 309 days compared to 33 days in historical controls - a dramatic clinical improvement[66]. Importantly, mogamulizumab also depletes CCR4+FOXP3+ regulatory T cells, which constitute a major immunosuppressive component of the ATLL tumor microenvironment. While this Treg depletion contributes to anti-tumor efficacy, it simultaneously predisposes patients to immune-related adverse events (irAEs) including mogamulizumab-associated rash (MAR), arthritis, myocarditis and severe graft-versus-host disease when used prior to allogeneic HSCT[67].

Checkpoint inhibitors: Cautious optimism

The PD-1/PD-L1 checkpoint axis has been extensively explored in ATLL with mixed and cautionary results. ATLL cells frequently express PD-L1 (CD274) due to Tax-mediated transactivation and JAK/STAT3 pathway activation, which theoretically justifies checkpoint blockade. However, clinical use of PD-1/PD-L1 inhibitors in ATLL has paradoxically been associated with hyper-progression in a subset of patients - a phenomenon believed to result from loss of PD-1 as an intrinsic tumor suppressor (via deletion of the PDCD1 locus) and from the biological complexity of the HTLV-1 immune microenvironment where PD-1 may serve different roles[68]. PD-1 inhibitors appear more effective in extranodal NK/T-cell lymphoma and select PTCL subtypes than in ATLL and extreme caution is warranted. LAG-3, TIM-3 and TIGIT are emerging checkpoint targets being evaluated in combination strategies that may prove safer and more effective in ATLL[69].

CAR-T cell therapy

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized treatment of B-cell malignancies and intense efforts are underway to develop equivalent approaches for T-cell malignancies including ATLL[70]. The primary challenge is the shared expression of target antigens (CD7, CD25, CCR4, CD30) between malignant ATL cells and normal T cells, which risks fratricidal killing of the CAR-T product during manufacturing and T-cell aplasia in vivo. Strategies to overcome fratricide include: (i) CRISPR/Cas9-mediated knockout of target antigens in CAR-T cells before engineering with anti-target CARs; (ii) use of allogeneic (donor-derived) CAR-T cells from HTLV-1-negative donors; and (iii) NK cell-based CARs that do not share the T-cell surface markers of the malignancy[71].

For ATLL specifically, CAR-T cells targeting CD25 (IL-2Rα, universally expressed on ATL cells) represent a particularly elegant approach because CD25 is a functional marker of HTLV-1-transformed cells. Anti-CCR4 CAR-T cells have also been proposed, leveraging the same target as mogamulizumab but with potentially superior tumour-penetrating and T-cell persistence properties. While clinical trials specifically in ATLL remain nascent, the rapidly expanding CAR-T toolkit for T-cell malignancies is expected to yield ATLL-specific trials within the next several years[72].

Bispecific antibodies and antibody-drug conjugates

Bispecific T-cell engagers (BiTEs) that simultaneously bind tumour antigen (e.g., CD25, CCR4, CD30) and CD3ε on effector T cells offer a platform capable of redirecting patient T cells against ATL tumour cells without requiring ex vivo T-cell engineering[73]. Brentuximab vedotin, a CD30-directed antibody-drug conjugate approved for CD30+ T-cell lymphomas (following FDA approval in 2022), has some activity in CD30+ ATLL variants, though CD30 expression in ATL is variable (often weak or absent in non-large cell variants). Denileukin diftitox, a recombinant fusion protein of IL-2 and diphtheria toxin targeting IL-2R (CD25)-expressing cells, has theoretical appeal in ATLL given universal CD25 expression, with renewed clinical evaluation of its updated formulations ongoing[74].

Allogeneic hematopoietic stem cell transplantation and graft-versus-ATLL effect

For eligible ATLL patients achieving first remission, allogeneic HSCT (allo-HSCT) from an HTLV-1-seronegative HLA-matched donor currently represents the only potentially curative therapeutic strategy[75]. The curative mechanism is believed to be mediated substantially by the graft-versus-leukemia/lymphoma (GVL) effect - an alloreactive T-cell-mediated immune attack on residual ATL cells - providing strong in vivo evidence that immunotherapy can be curative in ATLL. In the largest retrospective analysis (n=586 Japanese recipients), allo-HSCT conferred a 3-year overall survival of 36%, with comparable outcomes between myeloablative and reduced-intensity conditioning[76]. The critical requirement for HTLV-1-seronegative donors reflects the risk of donor-derived ATL from graft-contained infected T cells - a unique consideration that directly incorporates HTLV-1 serology into transplant donor selection algorithms.

Clinical and Regional Perspectives: Bridging Molecular Data to Bedside

The clinical presentation of ATLL varies dramatically across its four subtypes - acute (55-60%), lymphomatous (20-25%), chronic (15-20%) and smoldering (5%) - defined by the Shimoyama classification[77]. The acute and lymphomatous subtypes carry median overall survivals of less than 12 months with conventional therapy and are characterized by rapidly progressive lymphadenopathy, hepatosplenomegaly, hypercalcemia, opportunistic infections (Pneumocystis jiroveci, Strongyloides stercoralis, CMV) and multi-organ involvement. In contrast, smoldering and favorable-risk chronic subtypes may pursue watchful waiting with median survivals of 2-3 years before progression.

Of particular relevance to the clinical audience of this journal is the recognition that HTLV-1 infection and ATLL are not exclusively confined to historically endemic regions. As highlighted by the early molecular and immunohistochemical characterization study by Bano, et al. - documenting HTLV-1-associated T-cell lymphoma in a South Asian cohort - this disease is being increasingly encountered in non-endemic populations through migration, blood transfusion without systematic HTLV-1 screening and sexual transmission[7]. These emerging patterns demand expansion of HTLV-1 awareness, serological screening protocols and diagnostic molecular testing capacity at clinical centers globally. The molecular markers described in this review - PVL, Tax/HBZ mRNA expression, CCR4/CD25 immunophenotyping and somatic mutational profiling - serve as the diagnostic and prognostic backbone irrespective of geographic setting.

The Revised ATL International Consensus provides updated diagnostic criteria, clinical subtype definitions and treatment algorithm recommendations that integrate molecular biomarkers with clinical parameters, now recognizing PVL thresholds, T-cell clonality analysis and CCR4 expression as standard staging elements[78]. Implementation of these consensus recommendations at regional centers encountering ATLL for the first time requires both molecular infrastructure and clinical expertise - underscoring the importance of educational initiatives, reference laboratory networks and collaborative research programs connecting endemic and non-endemic centers.

Future Directions and Molecular Possibilities

Rational multi-epitope vaccine design using structural biology

The integration of structural vaccinology with HTLV-1 molecular biology offers transformative opportunities. High-resolution cryo-electron microscopy (cryo-EM) structures of gp46 in complex with HSPG, NRP-1 and GLUT-1 - when determined - will identify conformational epitopes on the native entry complex that are absent on monomeric gp46 and thus hidden from conventional vaccine-elicited antibodies[79]. Structure-guided design of self-assembling nanoparticles displaying native-like gp46 trimers in their pre-fusion conformation (analogous to HIV Env SOSIP trimers) represents a next-generation antigen engineering approach that could overcome the limited neutralization breadth of existing anti-gp46 responses.

Personalized HLA-matched vaccine approaches

Advances in rapid, affordable HLA genotyping and in silico peptide-HLA binding prediction algorithms now enable the design of personalized, HLA-matched multi-epitope vaccines tailored to an individual's full HLA-A, -B, -C, -DR, -DQ and -DP haplotype[80]. Population-level HLA frequency databases for HTLV-1-endemic regions can inform the design of community vaccines incorporating epitopes providing maximal population coverage. The identification of HLA-B57-restricted and HLA-C*08-restricted Tax epitopes, in addition to the well-characterized HLA-A*02:01 responses, has broadened the potential reach of CTL-inducing vaccines across diverse genetic backgrounds.

Epigenetic priming as a vaccine adjuvant strategy

Given that Tax expression is epigenetically silenced in established ATL cells, pharmacological reactivation of Tax expression using HDAC inhibitors (e.g., valproate, romidepsin) or demethylating agents (e.g., azacitidine) prior to or concurrently with Tax-specific CTL vaccination may resensitize ATL cells to immune-mediated clearance - a so-called 'shock and kill' strategy analogous to HIV cure research[81]. Proof-of-concept for histone deacetylase inhibitor-mediated Tax reactivation and enhanced CTL killing has been established in vitro; clinical validation of this combination approach represents a high-priority research agenda.

Therapeutic cancer vaccination combined with checkpoint blockade

The immunosuppressive ATLL microenvironment - characterized by regulatory T-cell dominance, PD-L1 overexpression, IL-10 and TGF-β secretion and CTL exhaustion - represents a fundamental barrier to vaccine efficacy. Combining therapeutic vaccination with targeted reversal of the immunosuppressive microenvironment offers a synergistic strategy: vaccination provides the antigen-specific CTL pool, while checkpoint blockade (particularly LAG-3 or TIM-3 inhibitors, safer than PD-1 in ATLL), Treg depletion (mogamulizumab) or cytokine immunomodulation (IL-15 superagonists) sustains and amplifies the effector function of vaccine-primed CTLs[82].

Integration of artificial intelligence in vaccine design

Machine learning and artificial intelligence (AI) tools, including deep neural networks trained on large peptide-

HLA binding datasets, T-cell receptor repertoire data and immunogenicity databases, offer the prospect of de novo computational design of maximally immunogenic, minimally autoimmunogenic HTLV-1 vaccine peptides[83]. Integration of viral genomic diversity data (recognizing that HTLV-1 subtypes A-F exhibit sequence variation particularly in Env and Tax) with AI-guided epitope optimization could yield 'universally immunogenic' multi-epitope constructs covering the breadth of circulating HTLV-1 diversity worldwide.

mRNA-LNP combination vaccines: A disruptive opportunity

Building on the success of COVID-19 mRNA vaccines, the development of a bivalent HTLV-1 mRNA vaccine co-encoding gp46 (for neutralizing antibody induction) and a multi-epitope HBZ/Tax fusion (for CTL priming) within the same LNP formulation offers a technically feasible and potentially transformative vaccine concept[84]. The modular nature of mRNA vaccine design allows rapid iteration of epitope composition, codon optimization and UTR engineering for enhanced translational efficiency - enabling rapid adaptation to emerging evidence. Critically, LNP-formulated mRNA vaccines elicit robust germinal center reactions and T follicular helper responses, supporting the generation of high-affinity, class-switched antibodies in addition to cellular immunity[85-90].

Conclusion

HTLV-1 remains a critically under-resourced global health threat, with its oncogenic potential fully realized in the devastatingly aggressive ATLL - a disease for which curative therapy remains elusive for most patients. The molecular complexity of HTLV-1, centered on the opposing yet complementary oncogenic roles of Tax and HBZ, provides both the challenge and the opportunity for vaccine and immunotherapy design. Proviral load, Tax/HBZ mRNA expression ratios, CCR4/CD25 immunophenotyping and somatic mutational burden define a robust molecular marker framework that can guide diagnosis, risk stratification, treatment selection and monitoring across the full clinical spectrum of HTLV-1 disease.

The HLA-restricted CTL immune response against Tax and HBZ is the principal mechanism of natural immune control and its engineering through next-generation vaccine platforms - mRNA-LNP, viral vector prime-boost, multi-epitope peptide nanoparticles and dendritic cell vaccines - constitutes the most rational approach to both prophylaxis and therapeutic intervention. Immunotherapy with mogamulizumab has transformed the treatment landscape for relapsed ATLL, while CAR-T cells, bispecific antibodies and combination strategies with checkpoint reversal represent the evolving frontier of curative immunotherapy.

Critically, bridging the molecular insights gained in high-resource research centers to clinical practice in non-endemic and emerging-endemic regions - as exemplified by regional clinical characterization studies such as Bano, et al. - is essential for ensuring that advances in HTLV-1 molecular biology translate into equitable improvements in patient care globally. Collaborative research networks, shared molecular biomarker platforms and globally designed clinical trials with inclusive enrollment criteria are the pillars upon which future progress in HTLV-1 vaccination and immunotherapy must be built.

References

1. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. 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 USA 1980;77(12):7415-7419.
2. Giam CZ, Semmes OJ. HTLV-1 infection and adult T-cell leukemia/lymphoma-A tale of two proteins: Tax and HBZ. Viruses 2016;8(6):161.
3. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012;3:388.
4. Einsiedel L, Pham H, Woodman RJ, et al. HTLV-1c in Central Australia: epidemiology, risk factors and implications for screening and management. J Infect Dis 2016;214(12):1850-1856.
5. World Health Organization. Human T-lymphotropic virus type 1 (HTLV-1) Fact Sheet. WHO 2022.
6. Bangham CRM, Osame M. Cellular immune response to HTLV-1. Oncogene 2005;24(39):6035-6046.
7. Bano T. Molecular and immunohistochemical profile of HTLV-1-associated T-cell lymphoma in South Asian patients. Journal of Blood and Oncology Networking (JBON) 2018.
8. Matsuoka M, Jeang KT. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat Rev Cancer 2007;7(4):270-280.
9. Romanelli MG, Diani E, Bergamo E, et al. Highlights on distinctive structural and functional properties of HTLV Tax proteins. Front Microbiol 2013;4:271.
10. Enose-Akahata Y, Vellucci A, Jacobson S. Role of HTLV-1 Tax and HBZ in the pathogenesis of HAM/TSP. Front Microbiol 2017;8:2563.
11. Ghez D, Lepelletier Y, Lambert S, et al. Neuropilin-1 is involved in human T-cell lymphotropic virus type 1 entry. J Virol 2006;80(14):6844-6854.
12. Letafati A, Bahari M, Ardekani OS, et al. HTLV-1 vaccine development: challenges and perspectives toward gp46. Front Microbiol 2024.
13. Meissner ME, Mendonca LM, Zhang W, Mansky LM. Polymorphic nature of HTLV-1 particle cores. J Virol 2017;91(7):00369-17.
14. Yamagishi M, Kubokawa M, Kuze Y, et al. Chronological genome and single-cell transcriptome integration characterizes the evolutionary process of adult T-cell leukemia-lymphoma. Nat Commun 2021;12:4821.
15. Currer R, Van Duyne R, Jaworski E, et al. HTLV tax: A fascinating multifunctional co-regulator of viral and cellular pathways. Front Microbiol 2012;3:406.
16. Mohanty S, Harhaj EW. Mechanisms of oncogenesis by HTLV-1 Tax. Pathogens 2020;9(7):543.
17. Bellon M, Nicot C. HTLV-1 Tax tug-of-war: cellular senescence and death or cellular transformation. Pathogens 2024;13(1):87.
18. Giam CZ, Semmes OJ. HTLV-1 infection and adult T-cell leukemia/lymphoma-A tale of two proteins: Tax and HBZ. Viruses 2016;8(6):161.
19. Tamiya S, Matsuoka M, Etoh K, et al. Two types of defective human T-lymphotropic virus type I provirus in adult T-cell leukaemia. Blood 1996;88(8):3065-3073.
20. Matsuoka M, Green PL. The HBZ gene, a key player in HTLV-1 pathogenesis. Retrovirology 2009;6:71.
21. Tanaka-Nakanishi A, Yasunaga J, Takai K, Matsuoka M. HTLV-1 bZIP factor suppresses apoptosis by attenuating the function of FoxO3a and altering its localization. Cancer Res 2014;74(1):188-200.
22. El Hajj H, Hermine O, Bazarbachi A. Interplay between innate immunity and the viral oncoproteins Tax and HBZ in the pathogenesis and therapeutic response of HTLV-1 associated adult T cell leukemia. Front Oncol 2022;12:944219.

23. Enose-Akahata Y, Abrams A, Massoud R, et al. Humoral immune response to HTLV-1 basic leucine zipper factor (HBZ) in HTLV-1-infected individuals. Retrovirology 2013;10:19.

24. Baydoun HH, Pancewicz J, Nicot C. Human T-lymphotropic type 1 virus p30 inhibits homologous recombination and favors unfaithful DNA repair. Blood 2011;117(24):5897-5906.

25. Kataoka K, Nagata Y, Kitanaka A, et al. Integrated molecular analysis of adult T-cell leukemia/lymphoma. Nat Genet 2015;47(11):1304-1315.

26. Koseki A, Araya N, Yamagishi M, et al. EZH1/2 dual inhibitors suppress HTLV-1-infected cell proliferation and hyperimmune response in HTLV-1-associated myelopathy. Front Microbiol 2023;14.

27. Iwanaga M, Watanabe T, Utsunomiya A, et al. Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers. Blood 2010;116(8):1211-1219.

28. Hisada M, Stuver SO, Okayama A, et al. Persistent paradox of natural history of human T lymphotropic virus type I: parallel analyses of Japanese and Jamaican carriers. J Infect Dis 2004;190(9):1605-1609.

29. Shakoori AR, Mannan A, Ahmed W, et al. Evaluation of the role of TAX, HBZ and HTLV-1 proviral load on the survival of ATLL patients. Int J Hematol Oncol 2017.

30. Yamada A, Yasunaga J, Liang L, et al. Anti-HTLV-1 immunity combined with proviral load as predictive biomarkers for adult T-cell leukemia-lymphoma. Cancer Sci 2024;115(1):310-320.

31. Miyazawa T, Hasebe Y, Murase M, et al. HBZ as a constitutive molecular marker in all ATL cases 2009.

32. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. Br J Haematol 1991;79(3):428-437.

33. Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma. Clin Cancer Res 2003;9(10):3625-3634.

34. Kataoka K, Nagata Y, Kitanaka A, et al. Integrated molecular analysis of adult T-cell leukaemia/lymphoma. Nat Genet 2015;47(11):1304-1315.

35. Rowan AG, Dillon R, Witkover A, et al. Evolution of retrovirus-infected premalignant T-cell clones prior to adult T-cell leukaemia/lymphoma diagnosis. Blood 2020;135(23):2023-2032.

36. Nishioka C, Takemoto S, Kataoka S, et al. Serum level of soluble CD30 correlates with the aggressiveness of adult T-cell leukemia/lymphoma. Br J Haematol 2007;136(3):370-376.

37. Katsuya H, Ishitsuka K, Utsunomiya A, et al. Treatment and survival among 1594 patients with ATL. Blood 2015;126(24):2570-2577.

38. Bangham CR, Hall SE, Jeffery KJ, et al. Genetic control and dynamics of the cellular immune response to the human T-cell leukaemia virus, HTLV-I. Philos Trans R Soc Lond B Biol Sci 1999;354(1384):691-700.

39. Bazarbachi A, Suarez F, Fields P, Hermine O. How I treat adult T-cell leukemia/lymphoma. Blood 2011;118(7):1736-1745.

40. Kozako T, Fukada K, Hirata S, White Y, et al. Efficient induction of HTLV-1-specific CTL by chimeric particle vaccines in HLA-A*0201 transgenic mice. [Referenced in HTLV-1 vaccine landscape review.

41. Kobayashi N, Takada K, et al. HTL reactive with Tax191-205 and Tax305-319 epitopes recognizing HTLV-1 Tax-expressing T-cell lymphoma cell lines.

42. Kobayashi S, Kumai T, Hayashi S, et al. HLA-DR-bound IL-9Rα peptide from HTLV-1-transformed T cells as novel antigen for CD4 helper T cells. J Immunol.

43. Lim AG, Maini PK. HTLV-I infection: a dynamic struggle between viral persistence and host immunity. J Theor Biol 2014;352:92-108.

44. Daian E Silva, Cox LJ, Rocha AS, et al. MVA-HBZ and DNA-plasmid multi-epitope vaccine induces polyfunctional HBZ-specific CTL responses. Front Immunol 2023.

45. Kozako T, et al. HBZ42-50 and HBZ157-176 epitope-based multi-epitope vaccine.

46. Takamori A, Hasegawa A, Utsunomiya A, et al. Functional impairment of Tax-specific but not CMV-specific CD8+ T lymphocytes in asymptomatic HTLV-1 carriers. Retrovirology 2011;8:100.

47. Yasunaga J, et al. HTLV-1 infection promotes excessive T cell activation and transformation into adult T cell leukemia/lymphoma. JCI Insight 2021;6(22):e150472.

48. Santana LL, et al. Challenges in HTLV-1 vaccine development FCIMB 2025.

49. Letafati A, Bahari M, Arde, et al. HTLV-1 vaccination landscape: current developments and challenges. J Vaccin X 202kani OS4;19:100525.

50. Fujisawa J, et al. Tax-peptide vaccines reduce proviral load in hu-NOG mice. J Immunol 2017;198:1210-1219.

51. Ahr B, et al. Chimeric peptide vaccine composed of B- and T-cell epitopes of HTLV-1 induces humoral and cellular immune responses and reduces proviral load in squirrel monkeys. J Gen Virol 2006;87:2889-2900.

52. Letafati A, et al. Chitosan and TMC nanoparticle-formulated gp46 Env23 and Env13 recombinant protein vaccines 2024.

53. Armand MA, Grange MP, Paulin D, Desgranges C. Targeted expression of HTLV-I envelope proteins in muscle by DNA immunization of mice. Vaccine 2000;18(21):2212-2222.

54. Grange MP, Armand MA, Audoly G, Thollot D, Desgranges C. Induction of neutralizing antibodies against HTLV-I envelope proteins after combined genetic and protein immunizations in mice. DNA Cell Biol 1997;16(12):1439-1448.

55. Ibuki K, et al. Long-term persistence of protective immunity in cynomolgus monkeys immunized with a recombinant vaccinia virus expressing the HTLV-I envelope gene. J Gen Virol 1997;78(1):147-152.

56. Daian E Silva FA, et al. MVA-HBZ multiepitope vaccine induces robust HBZ-specific CTL. Front Immunol 2023.

57. Theravectys. Development of an anti-HTLV-1 vaccine (THV02) for the treatment of adult T-cell leukemia/lymphoma. ScienceDirect/Elsevier 2015.

58. Suehiro Y, et al. Autologous dendritic cell vaccine for ATLL patients positive for HLA-A*0201, *2402, *1101 or *0207. Japan Registry of Clinical Trials.

59. Ando S, Hasegawa A, Murakami Y, et al. HTLV-1 tax-specific CTL epitope-pulsed DC therapy reduces proviral load in infected rats with immune tolerance against tax. J Immunol 2017;198(4):1210-1219.

60. Suehiro Y, et al. Phase II autologous DC vaccine clinical protocol. Japan Registry of Clinical Trials 2023.

61. Gote V, Bolla PK, Kommineni N, et al. A comprehensive review of mRNA vaccines. Int J Mol Sci 2023;24(3):2700.

62. Letafati A, et al. Computational multi-epitope mRNA/nanoparticle vaccine platform for HTLV-1 2021.

63. Tu JJ, King E, Maksimova V, et al. An HTLV-1 envelope mRNA vaccine is immunogenic and protective in New Zealand rabbits. J Virol 2024;98(1):0162323.

64. Daian E Silva FA, et al. DNA/MVA heterologous prime-boost HBZ multi-epitope vaccine generates polyfunctional CTL. Front Immunol 2023.

65. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma. J Clin Oncol 2012;30(8):837-842.

66. Pradhan K, Townsend L, Goldfinger M, et al. Efficacy and manageable toxicity of mogamulizumab in real-world North American ATLL cohort. J Clin Oncol 2025;43(16):18603.

67. Ramos JC, et al. Immune-related adverse events associated with mogamulizumab. Expert Rev Anticancer Ther 2024;24(9).

68. Thomas CJ, Barta SK. SOHO state of the art updates and next questions: The promise of immunotherapies in T-cell lymphoma. Clin Lymphoma Myeloma Leuk 2025.

69. Barta SK. Immunotherapy advances and challenges in T-cell lymphoma. Targeted Oncology 2026.

70. Rodriguez-Sevilla JJ, et al. Advances in CAR-T cell therapy in T-cell malignancies. J Hematol Oncol 2024.

71. Pocock R, et al. CAR T-cell therapies for T-cell malignancies: does cellular immunotherapy represent the best chance of cure? Blood Adv 2024;9(4):913-928.

72. Dourthe ME, Rabian F, Yakouben K, et al. Targeting T cell malignancies using CAR-based immunotherapy. J Hematol Oncol 2019;12(1):140.

73. Ravandi F, et al. Bispecific T-cell engagers and NK-cell redirecting platforms in T-cell malignancies CLML 2025.

74. El Hajj H, Hermine O, Bazarbachi A. Therapeutic advances for the management of adult T cell leukaemia. Leuk Res 2024;147:107598.

75. Hishizawa M, Kanda J, Utsunomiya A, et al. Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia. Blood 2010;116(8):1369-1376.

76. Fukushima T, et al. Revised Adult T-Cell Leukaemia-Lymphoma International Consensus Meeting Report. J Clin Oncol 2018;36(33):3340-3348.

77. Tsukasaki K, Tobinai K. Adult T-cell leukaemia-lymphoma: recent advances in treatment. Int J Hematol 2013;97(3):311-321.

78. Fukushima T, Nomura S, Shimoyama M, et al. Japan Clinical Oncology Group (JCOG) lymphoma study group: revised diagnostic criteria and classification for ATL. Int J Hematol 2018.

79. Khorasanizadeh S, Campos-Olivas R, Summers MF. Solution structure of the capsid protein from HTLV type I. J Mol Biol 1999;291(2):491-505.

80. Kozak M, Hu J. DNA vaccines: their formulations, engineering and delivery. Vaccines 2024;12(1):71.

81. Histone deacetylase inhibitors abolish HBZ protein expression and induce cell death in HTLV-1-related adult T-cell leukemia-lymphoma. Blood 2017;130:4012.

82. Gutowska A, McKinnon K, Sarkis S, et al. Transient viral activation in HTLV-1-infected macaques treated with pomalidomide. Front Med. 2022;9:897264.

83. McCann N, O'Connor D, Lambe T, Pollard AJ. Viral vector vaccines. Curr Opin Immunol 2022;77:102210.

84. Gote V, Bolla PK, Kommineni N, et al. A comprehensive review of mRNA vaccines. Int J Mol Sci 2023;24(3):2700.

85. Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of Tax protein in HTLV-1 leukemogenicity. Retrovirology 2004;1:20.

86. Mitagami Y, Yasunaga J, Kinosada H, et al. Interferon-γ promotes inflammation and development of T-cell lymphoma in HTLV-1 bZIP factor transgenic mice. PLoS Pathog 2015;11(9):1005120.

87. Thoma-Kress AK, Grossmann C. Mechanisms of HTLV-1 cell-to-cell transmission and immune evasion. Viruses 2019;11(11):1082.

88. Radygina TV, Mochalova TP. Transmission risk factors and public health implications of HTLV-1. FCIMB review 2025.

89. Ishitsuka K, Utsunomiya A, Katsuya H, et al. HTLV-1 bZIP factor induces CCR4 to promote T-cell migration and proliferation. Cancer Res 2016;76(17):5068-5079.

90. Wolf SN, Haddow J, Greiller C, et al. Quantification of T-cell clonality in HTLV-1 carriers can detect the development of adult T-cell leukaemia early. Blood Cancer J 2021;11(4):66.