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Review of current literature and evidence on Human T- Lymphotropic Virus Type 1 (HTLV-1) infection

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Preface

In Australia, there has been a marked increase in public health awareness around optimizing prevention, detection and management strategies for HTLV-1 infection, especially in Aboriginal and/or Torres Strait Islander communities, since a roundtable was convened in 2015. To address this need, the National Aboriginal Community Controlled Health Organisation (NACCHO) commissioned the Kirby Institute, UNSW Sydney with conducting a review of the latest literature on HTLV-1 to inform and support decision making, ensuring that health organisations and practitioners are equipped with the most recent data and evidence.

This initiative is elaborates on three foundational pieces of work previously undertaken by the Kirby Institute: i) *Association between HTLV-1 infection and adverse health outcomes*¹, ii) WHO HTLV-1 Technical Report (2021)², and iii) *Clinical and Public Health Implications of Human T-Lymphotropic Virus Type 1 Infection* (2022)³. Despite the publication of additional research, the current report found minimal evidence to change our understanding of HTLV-1 infection in key clinical and public health domains. Therefore, this report synthesizes the updated literature, with the evidence base gathered previously by the Kirby Institute and collaborators, and acknowledges that the evidence prior to 2021 is derived from the three documents outlined above. This approach aims to inform decision-making by not duplicating existing information and integrating longitudinal and contemporary global evidence to contextualize the information published since 2021.

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Executive Summary

HTLV-1 is a human retrovirus belonging to the subfamily Retroviridae and genus *Deltaretrovirus*, which preferentially infects CD4+ T cells (helper T cells).⁴ The viral genome is encoded on two copies of positive single-stranded RNA which undergo reverse transcription into double-stranded DNA. This DNA then integrates into the host genome as a provirus, and establishes persistent, lifelong infection.

HTLV-1 was first isolated and characterized in early 1980's.⁵ Since its discovery, epidemiological surveys have reported HTLV-1 in many regions, with high prevalence areas found in Central and West Africa, Japan, Islamic Republic of Iran, Latin America, the Caribbean, parts of Melanesia, and Australia. Where found, HTLV-1 is characterized by a marked non-uniform distribution. Typically, regions with higher prevalence are situated within or adjacent to regions with little or no infection. Despite population migration being an important factor in the detection of HTLV-1 in low prevalence areas, there is no evidence of ongoing or persistent transmission beyond regions with known high prevalence. This limited transmission has been attributed to a founder effect,⁶ where initially limited infection within a given population can, through sustained transmission over time, result in high prevalence. In addition to the substantial geographic variability, increased prevalence is strongly associated with older age, and in most populations is higher in females than males.

Initial systematic reviews were undertaken in 2018, and updated in 2023 to incorporate current evidence on the epidemiology of HTLV-1, transmission and prevention, disease associations and therapeutics. An additional narrative review was undertaken in 2023, on breastfeeding cessation and transmission in the Australian context.

Epidemiology

Unlike most retroviruses, HTLV-1 is genetically highly stable, as viral amplification occurs primarily via clonal expansion of infected cells, rather than reverse transcription. This stability is characterized by a high degree of molecular sequence conservation, and has been an important means by which phylogenetic investigation has derived insights into the divergence and global distribution of HTLV-1 subtypes.

Numerous studies have been conducted worldwide to determine the prevalence of HTLV-1 in different populations. The most common method for assessing HTLV-1 prevalence has been serological screening of pregnant women and blood donors. While testing blood donors yields large numbers, it may not reflect the general population and may preferentially select individuals at lower risk of blood-borne viral infections due to pre-selection criteria. Studies focusing on screening pregnant women provide a more accurate estimate of HTLV-1 prevalence in young and early middle-aged populations as they encompass a broader cross-section of risk factors among women of comparable age. Nevertheless, this approach is not an adequate surrogate for older adults, nor generalizable to adults in different regions and communities.

Furthermore, aside from the gaps in HTLV-1 prevalence data, there is a global deficiency in systematically collected information on HTLV-1-related diseases as outlined in the disease associations section of the report. Establishing a standardized monitoring approach for both HTLV-1 and its complications would enhance the foundation for making informed public health decisions.

Recent published studies on HTLV-1 prevalence have primarily expanded on existing knowledge within regions and populations where HTLV-1 prevalence was previously recognized. These updates include evidence, largely comprised of blood donor studies reporting low to moderate prevalence from Azerbaijan, Iran, China, Ireland, the United States, and Brazil, in particular Minas Gerais and

Mato Grosso. Several community-based studies among Brazilian Amazonian communities, report prevalences ranging from 0.1% to 0.5%.

Recent community-based studies from Central Australia report high HTLV-1 prevalence of 38.6% among adults, exceeding 49.0% among people aged over 45 years in select communities. Furthermore, a significant correlation was observed between higher HTLV-1 proviral load and increased odds of diabetes and chronic kidney disease (CKD). Recent research in Queensland, using serum samples from healthcare services and hemodialysis units alongside Australian National Cancer Registry data, found a low HTLV-1 prevalence of 0.1% and a crude ATL incidence rate of 0.025/100,000, predominantly in non-Indigenous adult men, with no HTLV-1 detected in hemodialysis samples.

Despite high local prevalence of bronchiectasis, particularly among First Nations children, a 2021 study at Royal Darwin Hospital found no association between HTLV-1 infection and bronchiectasis in children. In contrast to previous studies from Central Australia, these results suggest HTLV-1 may not be a contributing factor in the clinical profile of bronchiectasis in this particular demographic. However, further research is needed to understand the relationship between HTLV-1 and bronchiectasis.

Transmission and prevention

HTLV-1 is a cell-associated virus that preferentially infects CD4+ T-cells via cell-to-cell transmission. Cell-free infection of T-cells is inefficient, and as such, is primarily transmitted through direct contact between infected and uninfected cells via bodily fluids such as blood, breast milk, and semen. Low levels of cell-free virus have been detected in those people with HTLV-1; however, this form of transmission presents a substantially lower risk as indicated by the effectiveness of leukoreduction in preventing transmission via transfusion of cellular blood components.

The primary mechanism of HTLV-1 transmission among adults is generally considered to occur via sexual contact, as indicated by the typical age associated prevalence increases. The likelihood of transmission reportedly increases with higher partner viral loads. HTLV-1 shares transmission pathways with many other blood-borne viruses, which beyond sexual routes, include transfusion of HTLV-1 positive cellular blood components, organ transplant, as well as injecting drug use. Robust evidence on HTLV-1 transmission among people-who-inject-drugs is limited and appears more associated with HTLV-2.

Breastfeeding is the main pathway for vertical (mother-to-child) transmission, accounting for approximately 80% of these cases. Other perinatal routes pose a comparatively minor risk of transmission. While these findings are consistently reported in the literature across studies conducted in the Americas, Japan, and the Caribbean, there are no available data in the Australian context on which pathways account for the majority of cases. More research is needed to better understand HTLV-1 transmission in these settings.

It was recently identified that pregnant women who seroconvert and develop HTLV-1 antibodies during pregnancy express lower proviral loads compared to women who were HTLV-1 positive prior to pregnancy. Additionally, PVL was observed to increase with maternal age and parity number. In a related finding, a direct correlation was observed between HTLV-1 proviral load (PVL) in vaginal fluid and peripheral blood mononuclear cells (PBMCs), noting that PVL in vaginal fluid is, on average, 50 times lower than in PBMCs.

Recent meta-analysis findings indicate that short-term breastfeeding (STBF) for up to three months does not increase the risk of mother-to-child transmission (MTCT) compared to exclusive formula feeding. However, extending STBF to six months significantly raises this risk. Secondly, a prospective

cohort study found no significant difference in mother-to-child transmission rates between breastfeeding for up to three months, and exclusive formula feeding, suggesting that both feeding strategies may be equally viable for preventing vertical transmission via breastfeeding. The meta-analysis findings noted that breastfeeding cessation interventions to reduce MTCT must be balanced with the benefits of breastfeeding, to both infant and maternal health.

Breastfeeding cessation for prevention of transmission, in the Australian context

A narrative review was undertaken to inform this section of the report. While there is a need for a more thorough understanding of the epidemiology of HTLV-1 infection in Australia, the available data suggest that it is crucial to balance the prevention of HTLV-1 transmission with the protective benefits of breastmilk against common pathogens and chronic diseases that disproportionately affect Aboriginal and/or Torres Strait Islander children under 5 years old. Ongoing access to culturally sensitive nutrition education and healthcare services is required, to avoid formula feeding resulting in the concurrent introduction of non-formula beverages and potentially increase the risk of tooth decay and nutritional deficiencies. Moreover, in remote and very remote Aboriginal communities where breastfeeding is typical, discontinuing breastfeeding before 6 months of age or avoiding it altogether may lead to the disclosure of HTLV-1 status and subsequent social stigma. Additionally, in such settings, practical challenges such as the availability of sterilization equipment for bottles and unreliable access to clean water increase the risk of serious infections, and the financial burden of sustaining formula feeding throughout the first year of life may further complicate the decision-making process.

Disease associations

ATL, HAM/TSP, HTLV-1 associated uveitis, and infective dermatitis

HTLV-1 infection serves as a crucial diagnostic criterion for ATL, HAM/TSP, HAU, and infective dermatitis associated with HTLV-1. While there is increasing evidence for the impact of HTLV-1 proviral load in disease progression and other associations, the reasons behind the development of severe complications in some HTLV-1-infected individuals while the majority remain unaffected remain unclear. The incidence of HTLV-1-associated diseases varies across different geographical regions. The impact and outcome of HTLV-1 infection seem to hinge on interactions between the virus and host genetic and immunological factors. Recent studies have focused on the influence of host genetics in disease progression, and therapeutics, rather than further causal evidence for the identified diseases.

In relation to ATL, evidence of a smoldering subtype, primary cutaneous tumoral (PCT), have been strengthened in recent studies, with a poorer prognosis reported among these patients.⁷ For HTLV-1 associated uveitis, an additional study has revealed a heightened prevalence among individuals with HTLV-1 compared to their negative counterparts.⁸ There is an increasing body of research on biomarkers and prognostics of disease progression.⁹⁻¹²

All-cause mortality and other disease associations

HTLV-1 infection has been associated with an increased risk of mortality, as evidenced by the previous meta-analysis showing a pooled relative risk of 1.57 (95% confidence interval: 1.37, 1.80). This increased mortality risk cannot be solely attributed to the elevated likelihood of conditions previously linked to HTLV-1. Furthermore, it cannot be accounted for by ATL alone, despite its high case-fatality rate but low incidence. While unmeasured confounding might theoretically contribute to this mortality increase, its consistency across diverse settings and countries suggests otherwise.

Limited robust evidence exists regarding the morbidity associated with HTLV-1 that might elucidate this increase in mortality.

Limited to moderate-quality evidence indicates that individuals with HTLV-1 infection are at an elevated risk of developing certain conditions, including tuberculosis, seborrheic dermatitis, eczema, bronchitis, bronchiectasis, bronchiolitis, urinary tract infections, and lymphoma other than ATL. However, evidence for associations between HTLV-1 and other studied conditions is deemed very limited.

Additional analyses from cross-sectional studies from central Australia found an association between HTLV-1 and pulmonary disease¹³, diabetes^{14,15}, and kidney disease,^{14,15} but given study designs and low quality of evidence of association do not change the overall evidence significantly. A cross sectional study from Japan found an association between rheumatoid arthritis and HTLV-1, but again provides limited further evidence due to study design.¹⁶ In the Australian context, conflicting findings have been reported regarding the association between HTLV-1 and bronchiectasis,^{13,17} highlighting the need for further research to clarify the relationship between these conditions. A case-control study from the United States found no association between HTLV-1 status and all-cause 1-year mortality in multivariate analysis, however was limited by small study size and potential bias.¹⁸ A sub-section has also been included on cognitive impairment, with cross-sectional studies showing cognitive decline in HTLV-1 positive cases versus negative controls, and in HAM/TSP patients.

Therapeutics

Asymptomatic HTLV-1

At present, no specific treatments are recommended for individuals with asymptomatic HTLV-1 infection due to the inadequate evidence necessary for establishing clinical guidelines. Management protocols for those with HTLV-1 infection primarily entail monitoring for indications of HTLV-1-associated conditions, such as ATL or HAM/TSP, upon diagnosis and during subsequent follow-up assessments.

Recent in-vitro studies have examined the potential for new HIV antiretroviral treatments to be used in HTLV-1 treatment.^{19,20} Further in-vitro studies have aimed to determine the potential of natural anti-HTLV-1 compounds (pulp/seeds of *Akebia quinata* fruit, and bitter melon) as HTLV-1 therapeutics.²¹

Diseases associated with HTLV-1

ATL: The natural progression and prognosis of ATL vary depending on clinical subtypes, which significantly influence treatment approaches. Despite advancements in understanding its pathophysiology and therapeutic interventions, such as intensive chemotherapy regimens, aggressive forms of ATL still carry a dismal prognosis. Treatment strategies for ATL encompass "antiviral" protocols involving interferon-based therapy, multi-agent chemotherapy, and more recently, the incorporation of biologic agents. International recommendations for the management of ATL were published in 2009,²² and updated in 2019.²³ There are also several recent reviews focusing on ATL therapeutics.²⁴⁻²⁶ Rosadas et al. recently suggested that when devising therapeutic interventions for ATL, it may be necessary to take into account the distinctive regional attributes due to evidence of differential prognosis.²⁷

Further recent studies have focused on favourable outcomes with allo-HSCT in ATL patients outside Japan.²⁸⁻³⁰

No new therapeutic options for HAU were found, and studies focused on description of clinical course of infection under existing protocols.

No new therapeutic options for infective dermatitis were found.

HAM/TSP: The available evidence for the management of individuals with HAM/TSP is limited. Clinical trials have evaluated pharmacological treatments such as corticosteroids, HIV antiretrovirals, and interferon in this population, yet none have shown sustained efficacy. In 2018, the International Retrovirology Association issued guidelines for HAM/TSP management, predominantly relying on expert opinion due to the scarcity of robust data.³¹

A randomized controlled trial of corticosteroids for HAM/TSP treatment was recently published, concluding that while none of the primary endpoints achieved statistical significance, corticosteroids still had an important role to play in the treatment of HAM/TSP.³²

Epidemiology

Background

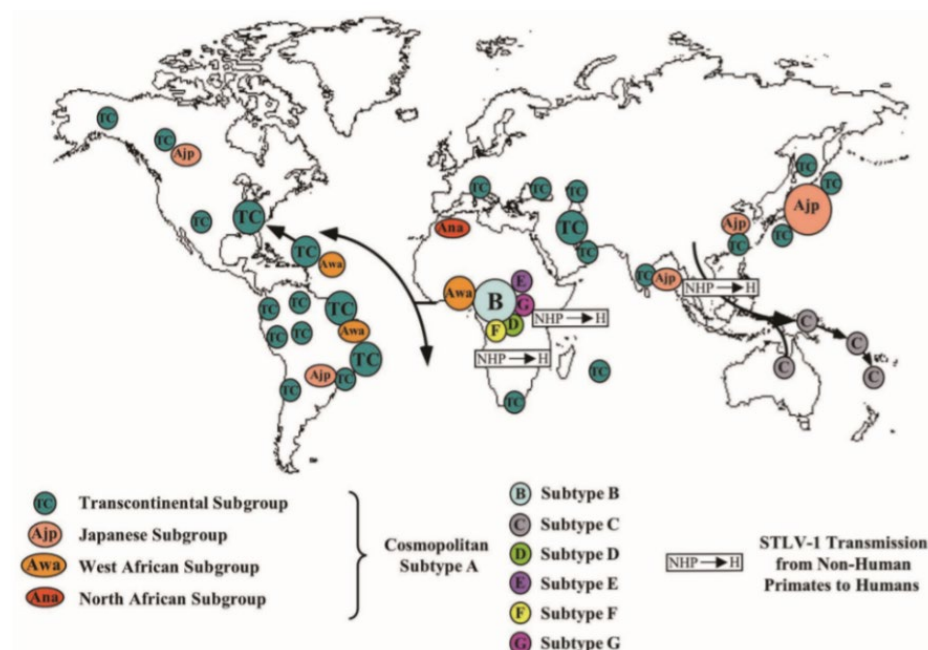
Since its identification Human T-lymphotropic virus type 1 (HTLV-1) has been recognized as an infection with a distinctive geographic distribution characterized by populations and communities with high prevalence within or near populations of low prevalence.

Countries and regions broadly regarded as having focal areas endemic for HTLV-1 include Japan, Islamic Republic of Iran, Australia, Latin America, the Caribbean, Melanesia, and West Africa. In addition to the substantial geographic variability both across and within these locations, prevalence typically increases markedly with age, and in most populations is higher in females than males.

Unlike most retroviruses, HTLV-1 is genetically stable, with viral amplification occurring primarily via clonal expansion of infected cells, rather than by reverse transcription. This high degree of sequence conservation enabled phylogenetic analyses into the divergence of the global distribution of HTLV-1 subtypes. There are seven HTLV-1 subtypes (A – G), based on the detection of nucleotide differences within specific genomic regions. The cosmopolitan subtype A occurs globally, while the remaining subtypes are geographically localised: subtypes -B, -D, -E, -F, and -G are found in Africa, while subtype-C is found only in Oceania. There is little evidence of change to the distribution of these geographic subtypes (Figure 1).³³

There is a high degree of nucleotide sequence conservation across subtypes. Isolates from Japan, the West Indies, the Americas, and Africa share 97% or greater sequence homology, while HTLV-1c, the most divergent subtype, is 92% homologous with the HTLV-1a isolate first characterized in Japan. The majority of nucleotide differences between subtypes are single point mutations that reportedly do not correlate with specific disease outcomes.

Figure 1. Geographical distribution of HTLV-1 subtypes (A–G) (adapted from Gessain et al., 2012)³³



Results

Most HTLV-1 prevalence surveys were conducted in areas or among populations with known high prevalence, including specific regions in South America, Japan, West Africa, and parts of the Caribbean. There were no new affected populations or areas identified, and there remain many key populations in which there is little or no information available on the prevalence of infection with HTLV-1. See Supplementary Material 1: Search strategies for details of search terms, bibliographic database, and results.

The following sections presents regional summaries of prevalence estimates, based primarily on data from screening of blood donors and pregnant women, supplemented by population-based surveys where available. Within-country heterogeneity in prevalence may reflect genuine regional variation, particularly for larger countries such as Brazil, or ones in which particular sub-populations are affected, such as Australia or Japan. For other countries, variation may be partially or entirely a statistical phenomenon, attributable to small numbers of detected cases and differences in study design between surveys.

For most studies that have provided age-specific prevalence, there is a substantial increase with age most prominently in early adulthood, typically suggestive of sexual transmission as the main driver. In some high prevalence populations, lower rates of HTLV-1 among younger age groups may reflect a decline in prevalence due to a birth cohort effect. Prevalence is generally higher among women than men in the same population. This is attributed to more efficient male-to-female sexual transmission. While this trend is globally the most common, there are exceptions.

Africa is regarded as the continent with the highest number of people living with HTLV-1 worldwide.³⁴ There is significant variance in HTLV-1 prevalence across regional and demographic levels within individual countries. High-prevalence regions have been reported in Central and West Africa, particularly in Gabon, Guinea, Cameroon, and the Democratic Republic of Congo.³⁴ Within these regions, considerable research has been conducted to describe the distribution and associated risk factors. In contrast, surveys from southern, eastern, and northern Africa generally report much lower prevalence rates. The variation in HTLV-1 prevalence across these areas remains poorly understood due to the limited number of population-based surveys conducted.³ Certain regions and specific population groups, particularly within distinct age cohorts and key demographic segments, exhibit substantially elevated prevalences.

For central and west Africa, prevalence in Cameroon varies from 1.9% and 2.6% across a broad age range.^{35,36} Recent surveys from rural communities in central Democratic Republic of Congo report prevalences between 2.9% to 3.5%, with variable rates across age groups.^{37,38} Guinea's prevalence varied from 0% in younger cohorts to 5.65% in older adults.³⁹ Studies among female sex workers in Côte d'Ivoire and the Democratic Republic of the Congo report prevalences up to 7.4% and 7.3%, respectively, with a strong age associated increase.^{40,41} Among pregnant women, prevalence varied from 0.7% in the Republic of the Congo⁴² to 5.5% in Nigeria,⁴³ with other countries reporting intermediate prevalences.

Data from East and Southern Africa indicate lower prevalence rates. Blood donor studies in Mozambique⁴⁴ and South Africa⁴⁵ report prevalences from 0.0% to 0.4%. Community based studies from South Africa, report seroprevalences of 0.2%, and 4.4% among pregnant women, with positivity increasing with age.^{46,47}

In South America, there are several known high prevalence areas and communities, particularly among select Indigenous communities in Peru⁴⁸ and Brazil,⁴⁹ and communities in French Guiana,⁵⁰ Guyana⁵¹ with African ancestry. Blood donor studies generally report low prevalence, with higher rates from Brazil,⁵² French Guyana,⁵¹ and Peru.⁵³ Among pregnant women, the available data reports

prevalences of 5.7% and 4.2% in French Guiana⁵⁴ and Haiti⁵⁰ respectively. In Brazil, prevalence among pregnant women ranged from 0.1% in Sao Paulo⁵⁵ to 0.6% in Rio de Janeiro.⁵⁶ In contrast, rates are very low in Venezuela,⁵⁷ and Argentina.⁵⁸⁻⁶⁰

Limited evidence from early studies from Canada report prevalence of 2.8% among First Nation communities in coastal British Columbia.⁶¹ The United States reports a very low prevalence among blood donors, around 0.001% to 0.02%,^{62,63} suggesting a low overall risk. There is ongoing surveillance of the blood supply due to account for higher rates among older donors and individuals from high prevalence areas.

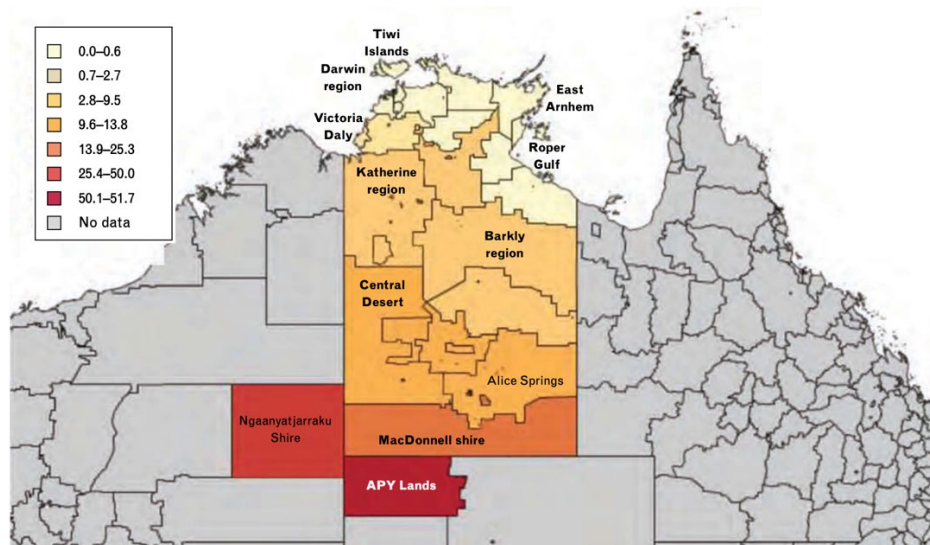
In the regions of South-East Asia and the Middle East, HTLV-1 surveillance has yielded varying, albeit lower, prevalence data. Blood donor studies across these regions range from zero in Indonesia,⁶⁴ Thailand,⁶⁵⁻⁶⁷ and several Middle Eastern nations (Jordan,⁶⁸ Lebanon,⁶⁹ Oman,⁷⁰ Saudi Arabia,⁷¹ Tunisia⁷²) to higher levels in Iran where prevalence ranges from 0.05% to 0.7%.⁷³ In Pakistan⁷⁴ and Kuwait,⁷⁵ prevalence among blood donors was 0.2% and 0.07% respectively, indicating some localized areas of HTLV-1 presence. Studies among pregnant women and community-based surveys in Indonesia, Thailand, and India consistently report no HTLV-1, aligning with findings from blood donors. The burden of HTLV-1 in Iran is more substantial with 1.5% prevalence in pregnant women and 2.1% in general population studies.⁷⁶⁻⁷⁸

Australia

Following the initial detection of HTLV-1 in Australia in the late 1980's, information on its occurrence has primarily come from blood donor and surveillance data, hospital-based cohort studies in Central Australia, and community-based studies from the same region. The epidemiology of HTLV-1 in Australia aligns closely with other well characterized countries where it is reported. Specifically, there is a marked association with increased age, and prevalence is highly variable across geographic regions and populations.

Studies have consistently reported a high prevalence among Central Australian Aboriginal communities. In the Northern Territory, the only jurisdiction where HTLV-1 is a notifiable disease, a review of all HTLV-1 serology requests from 2008 to 2011 demonstrated a marked geographic trend with test positivity increasing with proximity to Central Australia (Figure 2).⁷⁹ While blood donor studies and surveillance data on the national blood supply consistently indicate low overall prevalence,^{80,81} several community surveys from the Northern Territory, particularly in the Alice Springs region, have reported very high prevalences among Aboriginal communities, in some cases exceeding 50% among older age groups.⁸² The sex-distribution within Central Australian Aboriginal communities is different from many other HTLV-1 affected populations with higher rates atypically observed among males.

Figure 2. Geographical distribution of positive HTLV-1 serology requests (adapted from Grivas et al., 2014).⁷⁹



Six recent studies, four of which were conducted in Central Australia, report comparably high HTLV-1 prevalences. Two cross sectional studies examining the prevalence of blood borne viruses, and risk factors associated with chronic kidney disease (CKD) among hemodialysis patients, reported HTLV-1 prevalences of 28% and 36% respectively.^{15,83} In this study population, HTLV-1 antibody positivity was associated with increased age, and was higher among men compared to women. The representativeness of immunosuppressed haemodialysis patients may limit the extent to which these results can be generalized to broader populations.

Additionally, two large community-based studies were conducted in Central Australian Aboriginal communities.^{14,84} The first study assessed HTLV-1 prevalence and transmission risk factors, reporting infection rates of 3.5% in children and 36.8% in adults. Prevalence increased with age, reaching 49.3% in individuals over 45.⁸⁴ The second study examined the association between HTLV-1 infection and noncommunicable diseases. Prevalence was 38.6%, and higher HTLV-1 proviral load was significantly correlated with increased odds of diabetes and CKD.¹⁴

Despite the prevalence of conditions classically associated with HTLV-1 in Far North Queensland (FNQ), the region's HTLV-1 epidemiology remains poorly defined. Researchers reviewed all HTLV-1 serology tests requested through public health facilities in FNQ from 1999 to 2016, recording demographic and clinical data.⁸⁵ Of the 444 tests performed on 409 individuals, only four (1%) were positive for HTLV-1 infection. Three of these individuals belonged to the same family, and two were asymptomatic. This study suggests that HTLV-1 infection is uncommon in FNQ. Consequently, the high rates of bronchiectasis and other associated conditions observed in the region are likely attributable to socioeconomic determinants of health and are likely better addressed through public health policies targeting these factors. A recent retrospective cross-sectional study from QLD used serum samples from healthcare services in Brisbane, Townsville, and Cairns, and haemodialysis units in Brisbane, alongside Australian National Cancer Registry data for ATL cases.⁸⁶ The findings indicate low HTLV-1 prevalence (0.1%) among the tested samples, with two confirmed cases in Indigenous and non-Indigenous older women. No HTLV-1 was detected in haemodialysis samples. The study also reported a crude incidence rate of ATL in Queensland at 0.025/100,000, with the majority of cases incident in non-Indigenous adult men.

A study from 2021 examined bronchiectasis prevalence and severity in children and its association with HTLV-1 infection.¹⁷ Data from Royal Darwin Hospital compared clinical presentations and bronchoalveolar lavage fluid analyses from child patients diagnosed with bronchiectasis during two

separate five-year periods, 2007-2011 and 2012-2016. Findings indicated a consistent pattern of high bronchiectasis prevalence in children, disproportionately affecting First Nations children, however there were no instances of HTLV-1 infection, suggesting these factors may not contribute to bronchiectasis in this demographic.

Conclusion

Our understanding of HTLV-1 and its global and population distribution has changed little since the last major reviews. There remain significant gaps in our understanding of HTLV-1 prevalence, both within high prevalence regions and among key subpopulations generally at higher risk of blood borne viral infection. Most recent prevalence estimates have involved serological screening and blood donors, and systematically collected data on HTLV-1-associated diseases remain limited.

In Australia, HTLV-1 remains an infection of significant public health, particularly among Indigenous communities in Central Australia. The available evidence demonstrates high prevalence of infection, particularly among adults in remote communities, with transmission likely driven by a combination of sexual contact, and socioeconomic factors.

HTLV-1 transmission

Transmission routes and risk factors

Human T-Lymphotropic Virus Type 1 (HTLV-1) is primarily transmitted through direct contact between infected and uninfected target cells, a process facilitated by cell-containing bodily fluids, including blood, breast milk, and semen.⁸⁷ While individuals with HTLV-1 infection have low levels of cell-free virus, transmission in the absence of cell-containing blood components is considered a possible, yet significantly lower risk, mode of transmission.⁸⁸

Mother-to-child transmission

The probability of HTLV-1 mother-to-child transmission

Research on mother-to-child transmission of HTLV-1 emerged in the 1980s, with subsequent studies offering varied estimates of transmission probabilities. These studies employed diverse recruitment and follow-up methods, with a limited number conducting prospective analyses on transmission outcomes from birth. Transmission rate estimates ranged from 3.9% to 27.0% across 24 studies conducted in Gabon, Brazil, Japan, The Gambia, Guinea-Bissau, and Jamaica with a consensus figure of approximately 20% based on the synthesis of results across studies.⁸⁹

Mechanism of transmission

HTLV-1 antigen has been found in breast milk,⁹⁰ cord blood, and peripheral blood,⁹¹ while HTLV-1 proviral DNA has been identified in breast milk⁹² and placental tissue,⁹³ but not cord blood.⁹⁴⁻⁹⁶ While the absence of proviral DNA in cord blood strongly suggests limited, if any, intrauterine transmission, documented cases of MTCT among infants reliably reported as exclusively formula-fed (ExFF) indicates the possibility of alternative transmission routes, potentially during delivery.^{97,98} As cases of intra-uterine transmission or transmission during delivery are rare, breastfeeding is acknowledged as the primary route of MTCT of HTLV-1.^{97,99}

Factors associated with HTLV-1 transmission risk

Several studies have analysed risk factors for HTLV-1 MTCT. This review focused on biological risk factors, rather than socio-demographic factors.

Duration of breastfeeding

Evidence on the factors associated with breastfeeding mediated transmission has been derived from 13 studies across 5 countries. There are no available data upon which to draw in the Australian context. Breastfeeding was the primary route of MTCT of HTLV-1, with duration of breastfeeding as the main risk factor. The available evidence consistently indicates that breast feeding for six months or less is associated with a lower rate of transmission compared to more than six months. Transmission rates greater than 30% have been reported where breastfeeding exceeds 6 months duration (Table 1).

Recent findings from a prospective cohort study conducted in Japan from 2012 to 2015 reported a low risk of transmission (2.3%) among those breastfeeding for three months or less, which was not significantly different from that of exclusive formula feeding (RR 0.36, 95% CI: 0.12–1.2).¹⁰⁰ Similarly, a meta-analysis revealed no significant increase in transmission risk between breastfeeding for three months or less, and exclusive formula feeding (RR 0.72, 95%CI 0.30–1.77).¹⁰¹ The meta-analysis also noted that breastfeeding cessation interventions to reduce MTCT must be balanced with the benefits of breastfeeding, to both infant and maternal health.¹⁰¹

Table 1. The relationship between duration of breast feeding and the proportion of HTLV-1 mother-to-child transmission

Study	Country of research	Transmission proportion by breast-feeding duration*			Odds ratio (95%CI)	
		Group 1:	Group 2:	Group 3:	Group 1 vs 2	Group 2 vs 3
		Not breastfed	≤6 months	>6 months		
Takahashi 1991 ¹⁰²	Japan	9/158 (5.7)	4/90 (4.4)	20/139 (14.4)	1.3 (0.35, 5.9)	0.27 (0.07, 0.9)
Hirata 1992 ¹⁰³	Japan	10/78 (12.8)	7/61 (11.5)	11/36 (30.6)	1.3 (0.4, 3.8)	0.4 (0.2, 0.9)
Oki 1992 ¹⁰⁴	Japan	10/177 (5.6)	1/26 (3.8)	1/4 (25)	3.7 (0.5, 30.7)	0.12 (0.0, 2.6)
Oki 1992 ¹⁰⁴	Japan	0/7 (0)	3/67 (4.5)	19/36 (14)	0.81 (0.0, 17.3)	0.42 (0.2, 0.9)
Nakayama 1992	Japan	1/53 (2)	4/41 (10)		0.18 (0.02, 1.6)	
Wiktor 1993 ¹⁰⁵	Jamaica		1/15 (7)	4/19 (21)		0.27 (0.0, 2.7)
Takezaki 1997 ¹⁰⁶	Japan	4/162 (2.5)	2/51 (3.9)	13/64 (20.3)	0.6 (0.09, 7.1)	0.2 (0.05, 0.8)
Wiktor 1997 ¹⁰⁷	Jamaica		8/86 (9)	19/60 (32)		0.22 (0.1, 0.5)
Ureta-Vidal 1999 ¹⁰⁸	French Guyana	0/23 (0)	2/52(0.4)	17/151 (11.3)	0.4 (0.02, 9.3)	0.3 (0.07, 1.4)
Gotuzzo 2007 ¹⁰⁹	Peru		3/81 (3.7)	65/262 (24.8)		0.1 (0.03, 0.4)
Hino 2011 ¹¹⁰	Japan	29/1152 (2.5)	15/202 (7.4)	74/365 (20)	0.3 (0.2, 0.7)	0.3 (0.2, 0.6)
Masuzaki 2013 ¹¹¹	Japan	23/962 (2)	14/169 (8)		0.3 (0.1, 0.5)	
Paiva 2018 ¹¹²	Brazil		7/145 (4.8)	34/143 (23.8)		0.16 (0.07, 0.4)

Maternal proviral load

All of the five studies that examined the relationship between HTLV-1 MTCT and maternal HTLV-1 proviral load in peripheral blood and breast milk found a significant association, with a higher proportion of transmission with higher proviral load (Table 2).^{92,108,112-116} One study from Japan monitoring the course of HTLV-1 PVL among women throughout pregnancy observed a plateau during pregnancy, followed by an increase after childbirth, regardless of initial PVL levels.¹¹⁷

A recent study determined that pregnant women who undergo seroconversion, developing HTLV-1 antibodies during pregnancy, have a lower PVL compared to those who enter pregnancy already HTLV-1 positive. Additionally, PVL was found to be positively associated with increasing age and parity number.¹¹⁸

There are currently no standardized thresholds or categories for high and low proviral load, with different studies having used different thresholds.

Maternal antibody titre

All four studies that examined maternal plasma antibody titre as a risk factor for HTLV-1 MTCT found an association between higher titre and the rate of transmission (Table 2).^{107,108,113,115,116} Recently, it has been shown that during pregnancy, there is an increase in antibodies, not matched with an increase in maternal PVL. Placental transfer of antibodies may confer a protective effect, particularly in the context of short-term breastfeeding.¹¹⁹ However, the observed increase of maternal PVL post-delivery,¹¹⁷ may reduce this potentially protective effect. The apparent contradictory nature of these findings suggest further research is required to understand pathways of transmission and the protective nature of maternal HTLV-1 antibodies.

Mother-child Human Leukocyte Antigen (HLA) class I type concordance

HLA class I types are cell-surface proteins that play a crucial role in the immune system by presenting peptides to T cells helping distinguish between self and non-self cells. HLA class I type concordance refers to the matching of these types between two individuals, with higher concordance indicating a greater number of shared HLA class I types. A single study examined mother-child HLA class I type concordance and found that higher concordance between mother and child increased the risk of HTLV-1 transmission via breastfeeding.¹¹⁵ Greater concordance was hypothesised to reduce the immune system's ability to recognize and eliminate infected maternal cells, facilitating viral transmission. (Table 2).

Table 2: Biological risk factors for mother-to-child transmission of HTLV-1

Risk factor	Study	Country of research	Risk factor category	Transmission	Odds ratio (95%CI)
Maternal proviral load	Van Tienen 2011 ¹¹⁴	Guinea-Bissau	Undetectable 0.6–1.4 log ₁₀ copies/10 ⁵ 1.5–2.4 > 2.4	0/13 (0%) 1/14 (7%) 5/11 (45%) 8/16 (50%)	3.5 (1.6-7.7)
	Ureta-Vidal 1999 ¹⁰⁸	French Guiana	≤500 >500	2/78 (3%) 17/111 (15%)	6.9 (1.5-30.7)
	Paiva 2018 ¹¹²	Brazil	<100 copies/10 ⁴ ≥100 copies/10 ⁴		2.3 (1.2-4.5)
	Biggar 2006 ¹¹⁵	Jamaica	<2.20 log ₁₀ copies/10 ⁶ 2.20-3.10 ≥3.11	2/58 (3%) 10/50 (20%) 13/35 (37%)	2.6 (1.6-4.3) per log ₁₀ increase
	Hisada 2002 ¹¹⁶	Jamaica	N.A.		1.9 (1.1-3.4) per quartile
Maternal antibody titre	Biggar 2006 ¹¹⁵	Jamaica	<1000 1000-4000 4001-10000 >10000	1/37 (3%) 3/38 (8%) 10/38 (26%) 14/42 (33%)	3.1 (1.7-5.6) per log ₁₀ increase
	Hisada 2002 ¹¹⁶	Jamaica	N.A.		2.2 (1.0-3.3) per quartile
	Ureta-Vidal 1999 ¹⁰⁸	French Guiana	≤1/320 1/640 ³1280	1/81 (1.2%) 5/48 (10.4%) 15/83 (18%)	2.2 (1.4-3.6)
Mother-child HLA class I type concordance	Biggar 2006 ¹¹⁵	Jamaica	3	12/93 (13%)	1.0 (Ref)
			4	12/53 (23%)	1.8 (0.8-4.0)
			5	3/12 (25%)	2.8 (0.8-9.9)
			6	1/4 (25%)	4.1 (0.5-32.5)

Sexual transmission

Mechanism of sexual transmission

HTLV-1 DNA have been detected in cervico-vaginal secretions,^{97,120} and HTLV-1 antibodies have been detected in both cervico-vaginal secretions and semen.⁸⁷ Recent findings demonstrated a correlation between HTLV-1 proviral load (PVL) levels in vaginal fluid and peripheral blood mononuclear cells (PBMCs), noting that PVL in vaginal fluid is on average 50 times lower than in PBMCs. It was observed that PVL remained undetectable in vaginal fluid for approximately one-third of the study participants, predominantly asymptomatic carriers. This study suggests that the closely corresponding levels of PVL in serum and vaginal fluid can serve as proxies for each other, providing an alternative method for monitoring PVL, and broaden screening potential.¹²¹

HTLV-1 risk factors related to sexual activity

Cross sectional serosurveys (Table 3) have investigated prevalence of HTLV-1 among populations often considered to be at higher risk of sexually transmitted infection, including sex workers,^{88,122-124} and men who have sex with men.¹²² Another group recruited into surveys is comprised of the sexual partners of people with HTLV-1 infection.¹²⁵⁻¹²⁸ Few studies included comparative prevalence data for the corresponding population considered at lower risk for sexually transmitted infections. Without a comparator group, definitive conclusions regarding elevated prevalence in specific populations are not possible. While reports from the 1990s indicated substantially higher prevalence among female sex workers in Peru with prevalences ranging from 13.7% to 21.8%, surveys from Brazil and Japan reported substantially lower rates in similar populations. Higher prevalence has been most notable among sexual partners of people with HTLV-1 infection, particularly female partners of males with HTLV-1.

Table 3: Cross sectional studies of HTLV-I sexual transmission risk and associated risk factors

Study	Country of research	Study Period	Study Population	HTLV-1 prevalence (%)
Bellei 1996 ¹²⁴	Brazil	1987 - 1990	Female sex worker	2.8
			Male clients	2.0
Paiva 2017 ¹²⁹	Brazil	2013 -2015	Partners of people with HTLV-1	M: 55.7 F: 65.2
Diaz 2009 ¹³⁰	Cuba	Not stated	Sexual contacts of blood donors with HTLV-1	M: 9 F: 53
Murphy 1989 ¹³¹	Jamaica	1986	STI clinic attenders	5.7
Nakashima 1995 ⁸⁸	Japan	-	Female sex workers	5.1
			STI clinic attender M	2.8
			STI clinic attender F	5.7
			Blood donors M	1.4
			Blood donors F	2.2
Wignall 1992 ¹²³	Peru	1987-1988	Female sex workers	21.8

			Pregnant women	3.1
Zurita 1997 ¹²²	Peru	Not stated	Female sex workers	13.7
			MSM	6.2
Alarcon 2006 ¹³²	Peru	1996-1997	Pregnant women	1.7
Blas 2013 ¹³³	Peru	2010	Indigenous women	5.9
Sullivan 1993 ¹²⁷	USA	1989-1991	Sexual contacts of HTLV-1+ donors	28.1
Kaplan 1996 ¹²⁸	USA	1990- 1991	Sexual contacts of blood donors with HTLV-1	M 20.2
				F 37.5

In these cross-sectional studies, factors associated with higher HTLV-1 seropositivity related to sexual activity included history of condomless sex,¹²⁸ earlier age at first sex,¹³² and having a higher number of sex partners.¹³¹ There have also been reports investigating the association between a presence or history of other sexually transmitted infections (Table 4), particularly those that result in ulceration, such as syphilis and herpes simplex virus.^{88,122,123,128,131} One study from the French West Indies found a positive association between a history of having had a sexually transmitted infection and HTLV-1 transmission.¹³⁴ Among sex workers in Peru, sex during menses and vaginal douching pre- and post-intercourse were identified as risk factors.¹²² Some studies found no association with number of sexual partners.^{122,130} Among Indigenous Peruvian women, the sexual behaviours of male sex partners were identified as risk factors.¹³³

As with similar studies conducted in the 1980's that evaluated the association between HIV and other sexually transmitted infections, it is difficult, if not impossible, to distinguish between the hypothesis that sexually transmitted infections are a co-factor for HTLV-1 transmission, and the alternative explanation that both HTLV-1 and other sexually transmitted infections are driven by shared sexual behavior as the common causal factor.

The observed association in most studies of HTLV-1 seropositivity and age is consistent with sexual transmission,^{122,123,126,131-133,135} but does not provide direct evidence. It may be expected that if sexual transmission was the cause of a substantial proportion of infections, prevalence would increase sharply in late adolescence, and then plateau in older age. There are few age-specific analyses of population-based prevalence surveys that might be used to answer this question.

Table 4: Studies evaluating association between sexually transmissible infection and HTLV-1

Study	Country of research	Study Population	STI risk factor	OR (95% CI)
Bellei 1996 ¹²⁴	Brazil	Female sex workers Male clients	History of STI	1.6 (0.6 - 4.5)
Murphy 1989 ¹³¹	Jamaica	STI clinic attender	Penile sores/ulcers, Syphilis – Male Syphilis – Female	2.13 (1.05 - 4.33) 3.56 (1.24 - 10.22) 2.12 (1.12 - 3.99)
Nakashima 1995 ⁸⁸	Japan	Female sex workers STI clinic attenders Blood donors	Any history of STI Syphilis (female, non-sex worker Gonorrhoea (female, non-sex worker Gonococcal urethritis (male)	p < 0.001 p < 0.05 p < 0.05 p < 0.05
Wignall 1992 ¹²³	Peru	Female sex worker Pregnant women	Syphilis	1.78 (1.05 – 3.04)
Zurita 1997 ¹²²	Peru	High-risk: Sex worker MSM	History of STI (Gonorrhoea, syphilis, ulcer)	p = 0.00005
Kaplan 1996 ¹²⁸	USA	Sexual contacts of HTLV-1 donors	Gonorrhoea Syphilis Herpes Urethritis	No significant associations

Abbreviation: MSM, men who have sex with men; STI, sexual transmission infection

Transmission in couples or sexual partners of people with HTLV-1

Prospective cohort studies evaluating transmission risk in couples are limited (Table 5)^{126,135} and blood donor populations (USA).¹²⁵ In these longitudinal studies, transmission occurs more efficiently from male to female than from female to male. This is supported in cross-sectional sero-discordant partner studies which found male negativity to be more common than female negativity.^{126,128,130,135} Longer relationship duration of sero-discordant couples,^{126,128} and older age of seropositive male partner have also been associated with a higher risk of transmission.¹²⁶ Higher proviral load is a risk factor in both cross-sectional, and longitudinal studies,^{124-126,128} and presence of antibodies to the viral oncoprotein (anti-Tax)¹²⁶ observed as an additional risk-factor for sexual transmission.

Between 2011 and 2018, a retrospective cohort study of 57,323 pregnant women found that 0.054% had seroconverted from anti-HTLV-1 antibody negative to positive. Seroconversion incidence was 17.5 per 100,000 person-years during this seven-year span.¹³⁶

Table 5: Cohort studies evaluating sexual transmission risk

Study	Country of research	Study Period	Study Population	HTLV-1 transmission (%)
Kajiyama 1986 ¹³⁵	Japan		Married couples	M to F = 60 F to M = 0.4
Stuver 1992 ¹²⁶	Japan	1984-1989	Married couples	Discordant = 7.5 Seronegative = 0.14
Roucoux 2005 ¹²⁵	USA	1990-2003	Sexual contacts of donors with HTLV-1	Overall = 0.9 M to F = 1.2 F to M = 0.4

HTLV-1 transmission through blood and blood products

Rate of HTLV-1 transmission due to transfusion of blood products

In the 1980's, evidence of HTLV-1 transmission occurring through transfusion of cell-containing blood products emerged. In contrast to those receiving acellular blood products, these early investigations observed a substantially higher HTLV-1 prevalence among patient populations that required blood for conditions such as neonatal complications (2%), thalassemia (6%), sickle cell anemia (4%), and hemodialysis patients (20%).¹³⁷⁻¹³⁹ In these studies, transmission rates due to blood transfusion from a donor with HTLV-1 ranged from 28 to 63% and provided evidence that transmission occurred primarily, if not exclusively, through blood products containing cellular components (Table 6).¹⁴⁰⁻¹⁴²

Table 6: Transmission of HTLV-1 through blood or blood products from positive donors

Study	Country of research	Study Period	Blood product	HTLV-1 transmission (%)
Okochi 1984 ²¹⁶	Japan	1981-1983	Whole blood; packed red cells; platelet concentrates	63
			Fresh frozen plasma	0
Donegan 1994 ²²²	USA	1984-1985	Platelets	86
			Red cells	30
			Acellular	0
Manns 1992 ²²¹	Jamaica	1987-1988	Cellular	44
			Acellular	0
Kleinman 1993 ²²⁰	USA	1983-1989	Platelets	40
			Red cells	28

Risk factors for blood transfusion HTLV-1 transmission**Duration of storage of blood donor units**

Shorter duration of storage of blood has been associated with increased risk of transmission, likely due to the reduction of lymphocyte viability in older units of blood (Table 7).¹⁴⁰⁻¹⁴²

Table 7: Factors associated with transmission of HTLV-1 through blood and blood products

Risk factor	Study	Country of research	Duration of storage (days)	HTLV-1 transmission (%)	Odds ratio (95%CI)
Duration of storage	Manns 1992 ¹⁴¹	Jamaica	≤6	20/31 (64.5%)	6.34 (1.83-21.92)
			>6	6/26 (21.1%)	
	Kleinman 1993 ¹⁴⁰	USA	≤14	9/19 (47%)	
			>14	0/15 (0%)	
	Donegan 1994 ¹⁴²	USA	0-5	1/1 (100%)	
			6-10	2/7 (29%)	
			11-20	0/1 (0%)	
			21-25	N/A	
			≥26	0/1 (0%)	
Immuno-suppressive therapy	Manns 1992 ¹⁴¹	Jamaica		4/24 (25%)	12.2 (0.95-156.0)

Use of immunosuppressive therapy

A study from Jamaica found an association between the use of immunosuppressive therapy by recipients and HTLV-1 seroconversion following exposure to HTLV-1 positive blood products, with an adjusted odds ratio of seroconversion of 12.2 (95%CI 0.95-156.0), adjusted for recipient's sex and donor unit storage time).¹⁴¹

Injecting drug use as a risk factor

Injecting drug use has been shown to be a risk factor for HTLV-1 infection in multiple analyses.¹⁴³⁻¹⁴⁶ A number of studies have described HTLV-1 prevalence among people who inject drugs (Table 8)^{145,147-151}

Table 8: Risk factors for blood contact HTLV-1 transmission

Risk factor	Study author, year, and location	Risk factor category	HTLV-1 prevalence	Odds ratio (95%CI)
Injecting drug use	Etzel, 2001 Brazil	Injecting drug use	19/119 (15.9%)	2.99
		No injecting drug use	11/378 (2.9%)	
Injecting drug use	Khabbaz, 1990 United States	Injecting drug use	65/600 (10.8%)	5.0 (2.8-8.7)
		No injecting drug use	15/620 (2.4%)	
		Partner injecting drug use	42/389 (10.8%)	2.5 (1.6-3.9)
		Partner non-injecting drug use	39/834 (4.7%)	

HTLV-1 transmission through tissue transplant

The review returned 12 studies relating to transmission of HTLV-1 via tissue transplant. Most of the literature on HTLV-1 transmission via organ transplant is in the form of case reports related to an infected donor and one or more recipients (Table 9). A review published in 2012 summarised HTLV-1 clinical manifestations in solid-organ transplant patients (both HTLV-1 negative and positive pre-transplantation), noting limited development of HTLV-1 associated disease, but also a lack of long-term follow up studies.¹⁵²

There has been one longitudinal study of HTLV-1 transmission following tissue transplant, involving 99 kidney transplants in Japan between 2000 and 2014.¹⁵³ Of the eight HTLV-1 negative individuals who received HTLV-1 positive kidney donations, seven (87%) acquired the infection.

Table 9: HTLV-1 transmission associated with tissue transplant

Study	Year of publication	Type of study	Tissue	Country of research	HTLV-1 transmission detail
Remesar ¹⁵⁴	2000	Case report	Kidney	Argentina	
Kikuchi ¹⁵⁵	2000	Case report	Bone marrow	Japan	Sibling donor with known HTLV-1 status
Nakatsuji ¹⁵⁶	2000	Case report	Kidney	Japan	
Gonzalez-Perez ¹⁵⁷	2003	Case report	Kidney, liver, cornea	Spain	3 positive recipients (2 kidney, 1 liver)
Zarranz Imirizaldu ¹⁵⁷	2003	Case report	Kidney, liver	Spain	3 positive recipients from single donor
Yara ¹⁵⁸	2009	Case report and review	Lung	Japan	
Yamauchi ¹⁵³	2019	Retrospective cohort study	Kidney	Japan	87% transmission rate (7/8)

Prevention of HTLV-1 transmission

Current evidence on preventing HTLV-1 infection primarily stems from observational studies investigating risk factors for transmission. Limited evidence has emerged beyond observations following the implementation of specific preventive interventions.

Methods and results

Methods of this component of the review, including search strategy, are described in detail in Supplementary Material 1: Search Strategies. This section reports the outcomes of the review as they relate to strategies for the prevention of transmission by specific routes of infection.

Prevention of mother-to-child transmission

Breastfeeding cessation

Findings from three studies show that children who were breast fed are significantly more likely to have acquired HTLV-1 than children who were formula fed. In 2008, a 20-year evaluation of breast feeding cessation in the Nagasaki prefecture in Japan, showed the incidence of HTLV-1 infection among formula fed children was significantly lower than that in breast fed children.¹⁵⁹ Among breast fed children, the incidence was lower among children who were breastfed for less than six months than children breast fed long-term (≥ 6 months).¹⁵⁹ Combining the use of breast milk with infant formula (mixed feeding) has been considered as an alternate approach to reduce the risk of mother to child transmission by limiting the amount of exposure. It was noted that this method of feeding can affect the permeability of the intestinal mucosa and thereby the risk of transmission. Currently, no studies have specifically examined the effects of mixed feeding on transmission outcomes.¹⁶⁰

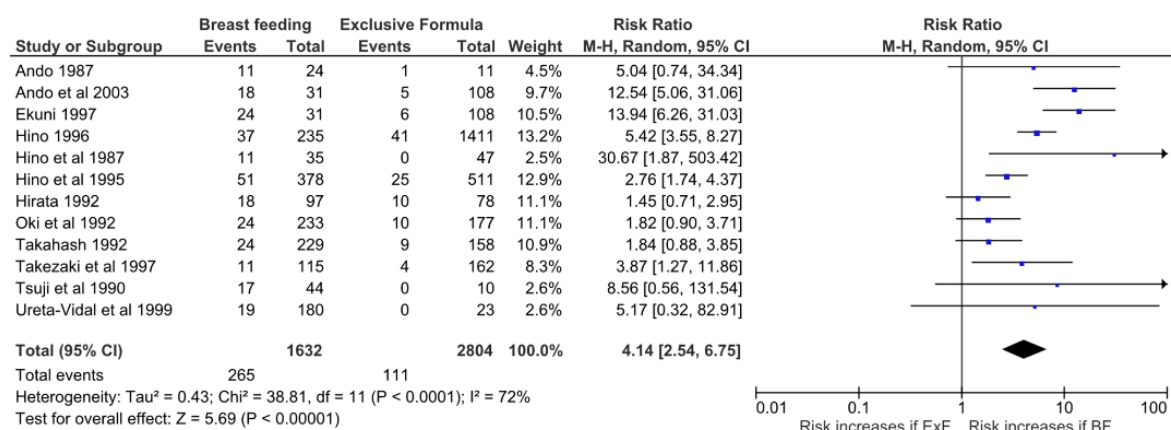
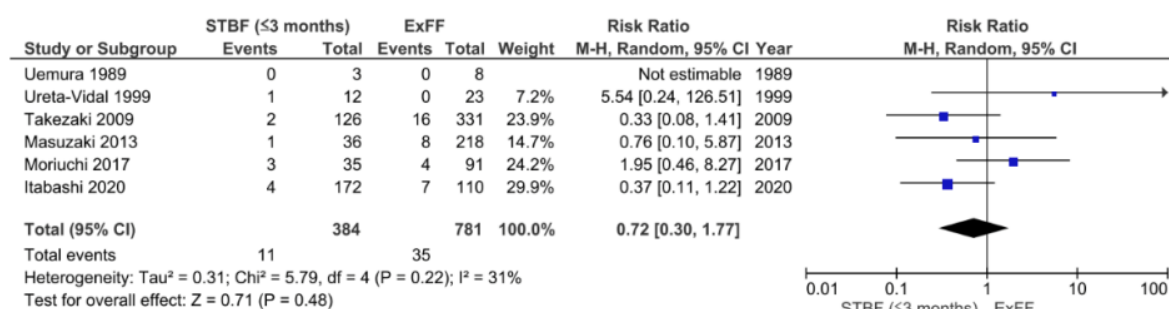


Figure 3: HTLV-1 infection by feeding method in children born to carrier mothers (adapted from Itabashi, 2021)¹⁰¹

The forest plot displaying the comparative risk of HTLV-1 infection among infants breastfed by HTLV-1-positive mothers with those exclusively formula-fed. Risk Ratios (RR) and their 95% Confidence Intervals (CIs) for each study are denoted by boxes and lines, respectively. The meta-analytic pooled RR, synthesizing these individual estimates, is encapsulated by the central black diamond.

Exclusive formula feeding versus short-term breastfeeding

In one recent cohort study from Japan, an analysis comparing rates of mother-to-child transmission found no significant difference between mothers who breast-fed for 3 months or less, compared to those who opted for exclusive formula feeding.¹⁰⁰



Breast milk freeze-thaw method

While formula feeding has been shown to be extremely effective in reducing mother-to-child transmission (MTCT) of HTLV-1, it is recognized that breast feeding has considerable benefits for infants, particularly in settings where the capacity to sterilize bottles is inadequate and social determinants of health impact on the availability and affordability of formula, clean water, and reliable electricity supply. The freeze-thaw method has been proposed as an alternative for the prevention of transmission of HTLV-1 to allow infant consumption of breast milk, because it effectively eliminates cells infected with HTLV-1.

Studies conducted in 1986¹²⁰ and 1989¹⁶¹ demonstrated the effectiveness of the freeze-thaw method in eliminating infected cells in vitro and preventing transmission to infants during the 12 months of follow-up. However, the authors acknowledged the potential impracticality of this method in certain settings. Notably, no further studies on the freeze-thaw method for HTLV-1 prevention have been published since.

Delivery-based prevention

Recently, caesarean section has been suggested as a delivery method to reduce the risk of transmission during childbirth by limiting exposure to maternal blood.¹⁶² The effectiveness of this approach is unclear due to limited and inconclusive evidence. Additionally, the absence of HTLV-1 provirus in cord blood suggests that the impact on transmission risk via caesarean section may be limited.

Prevention of HTLV-1 transmission through blood and blood products

Studies from Japan, the United States, and Brazil have demonstrated the significant reduction in the rates of transfusion related transmission following the implementation of blood screening programs (Table 10). In Japan, there was a substantial decrease from 53.6% to 0.9% following the implementation of screening in 1987. Similarly, in the United States, HTLV-1 prevalence declined from 0.0039% to 0% post-screening. Further evidence from Brazil supports these findings, reporting reduced prevalence after introducing improved screening methods, including second-generation passive agglutination and ELISA testing. A recent study from Brazil conducted a community-based serological screening study, complemented by counseling and referrals for medical care. Out of 1,572 screened individuals, six (0.38%) tested positive, with pre-1993 blood transfusions—before mandatory HTLV screening in Brazil—as the main risk factor.¹⁶³

Table 10: Impact of screening on HTLV-1 transmission through blood products

Study	Country of research	Study design	HTLV-1 screening	Prior to screening	Post implementation of screening
Kamihira et al. 1987 ¹⁶⁴	Japan	Before and after comparison	PA	53.6%	0.9% (n=1)*
Nelson et al. 1992 ¹⁶⁵	United States	Before and after comparison	ELISA and confirmatory WB/RIPA	0.0039% (n=2)	0.0%
Inaba et al. 1999 ¹⁶⁶	Japan	Prospective cohort	Second generation PA	-	0.021% (n=1)**
Dias-Bastos et al. 2010	Brazil	Retrospective	ELISA	0.4%	<0.1%

*One seroconversion occurred, due to blood being used from a different donation centre that did not screen;

**Follow-up of patient did not confirm whether seroconversion was due to transfusion

Leucodepletion aims to reduce HTLV-infected lymphocytes below the virus' minimum infectious load. While the minimum leucocyte threshold required for transmission to occur remains uncertain with estimates ranging widely, France saw a reduction in transfusion-transmitted HTLV risk from 1 in 20 million to 1 in 178 million donations after transitioning from HTLV testing alone, to HTLV testing in combination with leucodepletion.¹⁶⁷ Similarly, a lookback study from the United Kingdom reviewing HTLV (both 1 and 2) seroconversion in patients receiving blood products from HTLV positive donors, revealed a 93% decrease in HTLV transfusion transmission with leucodepleted

components compared to those without leucodepletion.¹⁶⁸ As HTLV-1 is almost always cell-associated, leucoreduction may be as effective as blood donation screening.¹⁶⁹ A large-scale lookback study in Ireland, analyzing over 3 million donations (n = 3,666,253) from 1996 to 2020, focused on the likelihood of leucodepletion failure, and HTLV testing strategies, detected six (0.00016%) positives first-time blood donors, with no cases since 2011.¹⁷⁰

Prevention of sexual transmission

The available evidence for preventing sexual transmission of HTLV-1 have principally been derived from observational studies evaluating specific routes of transmission, and have lacked information on population-level effects.³ While this review found no specific studies addressing preventive strategies for sexual transmission, given that infected lymphocytes are detected in semen and vaginal fluid, it is generally considered that condom use may decrease the risk of sexual transmission among HTLV-1 sero-discordant couples.

Therapeutic prevention

There are no chemoprophylactic interventions available for preventing HTLV-1 infection acquisition.¹⁷¹ While there is an emerging interest in testing and repurposing HIV pre- and post-exposure prophylaxis for the prevention of HTLV-1 transmission, no clinical trials of anti-retroviral therapy has been conducted to evaluate the reduction of HTLV-1 infection or PVL in the context of asymptomatic or chronic disease. In some clinical settings, opinion-based guidelines suggest the use of AZT/raltegravir as post-exposure prophylaxis within 72 hours of a needlestick injury, and continuing treatment for one month. The effectiveness of this approach has not yet been verified, as all anti-retroviral studies on HTLV have involved individuals with established infections.¹⁷²

Impact of breastfeeding cessation and HTLV-1 infection in the Australian context

A narrative review was undertaken to inform this section of the report, summarizing available evidence and key peer reviewed publications. The Australian National Feeding Guidelines recommend exclusive breastfeeding until approximately 6 months old, and the introduction of solids at around the same age while continuing breastfeeding,¹⁷³ with the World Health Organization Guidelines recommending continuing to breastfeed up to two years or beyond.¹⁷⁴ A systematic review from 2023, found that breastfeeding was recognized by Aboriginal Torres Strait Islander communities and mothers as important,¹⁷⁵ and the 2018–19 National Aboriginal and Torres Strait Islander Health Survey found that a higher proportion of Indigenous children than non-Indigenous children aged 0–2 were breastfed for at least one month to <6 months (30% versus 19%).¹⁷⁶ However, geographical variations in breastfeeding uptake have been previously reported, with Aboriginal women living in remote and very remote Australia (92%) being more likely to breastfeed than their peers in urban settings (84%).¹⁷⁶

Most data on mother-to-child-transmission of HTLV-1 comes from studies conducted in Japan, Latin America, and the Caribbean (see [Transmission](#) section).¹⁷⁷ In brief, HTLV-1 transmission risk via breastmilk increases with the duration of breastfeeding. In Japan, the MTCT transmission rate for HTLV-1 has been reported to be 2.3% in infants breastfed for less than 3 months and unlikely to be different than the observed among bottle fed infants.¹⁰⁰ In Brazil, transmission rates for breastfeeding duration greater than 12 months have been estimated at 24% (OR 6.15; 95%CI 2.62–14.41), and between 24 and 36 months, at 50%.¹⁷⁸

No population-based studies have estimated the proportion of vertically transmitted cases of HTLV-1 in Australia. However, a cross-sectional analysis using data from the National Cancer Registry suggests that adult T cell leukemia (ATL) is a rare outcome (crude incidence rate between 0.021/100 000 person years, 95% CI 0.015 to 0.029; 92% of cases occurred in non-Aboriginal people).⁸⁶ Since ATL can be a proxy for HTLV-1 acquired during childhood,¹⁷⁹ this may suggest that mother-to-child-transmission is not common in the Australian context, however in the absence of robust data, this should be interpreted with caution.

While a more comprehensive picture of the epidemiology of HTLV-1 infection in Australia is needed (as noted in the [Epidemiology](#)), the current evidence suggests transmission via breastfeeding to be uncommon and given the extensive benefits of breastfeeding, there is likely to be insufficient evidence to support breastfeeding cessation.

Formula feeding may lead to concomitant introduction of sweetened beverages and potentially, tooth decay.¹⁷⁵ In addition, in remote and very remote Aboriginal communities where breastfeeding is a well-established practice, its cessation before 6 months old or overall avoidance may lead to disclosure of HTLV-1 status and subsequent stigma. Incorrect usage of commercial milk formula may have unintended negative consequences including baby growth faltering, failure to thrive, or conversely, excessive weight gain.¹⁸⁰ In some settings, unreliable access to power may impact on bottle sterilization. Social determinants of health also impact on appropriate formula feeding with poverty and marginalization, contributing to formula feeding throughout the first year of life not being financially sustainable.¹⁷⁵

The impact of breastfeeding on child health and maternal health

Multiple research studies and reviews have assessed the impact of breastfeeding on infant and maternal health, with comprehensive 2016 and updated 2023 review series from the Lancet examining impacts on infant and maternal health.^{181,182} Benefits for infant health include:

- Lower rates of infectious illness and mortality, including sudden infant death syndrome
- Lower incidence of dental malocclusions
- Longer breastfeeding duration contributes to improved cognitive outcomes
- Breastfeeding may also have a protective effect against obesity or diabetes later in life

For maternal health, benefits of breastfeeding include:

- Improvements in birth spacing
- Prevention of breast cancer
- Potential reduction in risk of diabetes and ovarian cancer

A recent systematic review on breastfeeding and maternal mental health also found the benefits of breastfeeding supported maintenance of psychological health of the mother.¹⁸³ They also emphasized the importance of support mechanisms to support maternal feeding choices including individualized care, which is also relevant for the context of breastfeeding recommendations for HTLV-1 in Australia.

Economic cost of formula feeding

While no recent Australian studies have assessed the cost of formula feeding, a 2023 analysis from the United States found that in their first year of life, infants would generally consume between 269 and 340kg of formula with cost estimates of between USD1200 and USD2800 per year.¹⁸⁴

Formula shortages have occurred in the past and may impact on infant feeding practices. In 2005, the discovery that around 20 Chinese manufacturers had added melamine (a whitening agent) to breast milk substitutes to increase protein levels, resulted in formula shortages in Australia.¹⁸⁵ Similarly, supply chain issues due to the COVID-19 pandemic also resulted in formula shortages. While these examples are extraordinary, formula shortages are not unprecedented and need to be considered as a potential economic, health, and social costs in infant feeding guidelines.

Social considerations in breastfeeding cessation

There is evidence to suggest that early cessation of exclusive breastfeeding has social and cultural impacts and contributes to postpartum depression¹⁸⁶, feelings of loneliness, isolation, grief, and failure.¹⁸⁷ Additionally, in a recent cohort study, approximately 8% of mothers who chose short-term breastfeeding as a strategy to mitigate transmission, continued to breastfeed to 6 months due to challenges around ceasing breastfeeding.¹⁰⁰ It was recommended that women choosing short-term breastfeeding should receive preemptive on the challenges of short term breastfeeding and support to reduce extended breastfeeding. In a study from the United States, women reported little or no stigma if they chose not to breastfeed, versus mothers who were unable to breastfeed, who experienced internalized stigma.¹⁸⁸ This study is not generalizable to the Australian or Aboriginal and Torres Strait Islander context but highlights the need to understand the possible impacts on mothers, of breastfeeding cessation, and the critical role of structured support in enabling women to make feeding choices appropriate to their circumstances and in the context of HTLV-1 status.

Health Consequences

Introduction and overview

Most people living with HTLV-1 infection remain asymptomatic. However, there are also established severe and potentially fatal diseases associated with HTLV-1 infection. These include adult T-cell leukaemia /lymphoma (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), which were recognised prior to the discovery of HTLV-1. Their significant association with HTLV-1 led to their categorization as uniquely caused by HTLV-1. Clinical research after this categorisation, has sought to determine associations between HTLV-1 infection and several other clinical conditions. Sub-groups of two other diseases, infective dermatitis and HTLV-1 associated uveitis (HAU) have been added to the list of diseases that require the presence of HTLV-1 infection as a diagnostic criterion.

Recently, an increase in interest in the prevention and treatment of HTLV-1 infection and its complications has emphasised the need for robust evidence on the health consequences of HTLV-1 infection.¹⁸⁹ Building on prior publications this section of the report presents the evidence on the incidence and factors associated with the development and progression of ATL, HAM/TSP, HAU and infective dermatitis among people with HTLV-1 infection; and presents an evaluation of the association between HTLV-1 infection, all-cause mortality and other adverse health outcomes. See Supplementary Material 1: Search Strategies, for details of search terms, and results.

The first part of this section presents a summary of previous and updated evidence from cohort and population-based surveillance studies on incidence and factors associated with development and progression of ATL, HAM/TSP, HAU, and infective dermatitis, the four conditions for which the presence of HTLV-1 infection is a necessary diagnostic criterion. Each condition is presented separately, and the results are preceded by a summary of the epidemiological and biological evidence in support of the causal role of HTLV-1 infection in the pathogenesis of the specific disease. The second section examines the association between HTLV-1 infection and health outcomes other than these four conditions.

ATL, HAM/TSP, HAU and infective dermatitis

HTLV-1 infection is a necessary criterion for the diagnosis of ATL, HAM/TSP, HAU and infective dermatitis associated with HTLV-1. In this report, results on the incidence and factors associated with the development and progression of ATL, HAM/TSP, HAU and infective dermatitis are presented, based on previous work¹⁻³ with updated literature from 2021 to 2023. The summary and synthesis of results is presented separately for each HTLV-1 disease association (Table 11). Following the discovery of HTLV-1 40 years ago, there have been progressive insights into the pathogenesis of ATL and HAM/TSP and advances in knowledge of T cell function, but it remains unclear as to why some people living with HTLV-1 infection develop these severe recognized disease related complications while the majority do not. The incidence of HTLV-1 associated disease is not uniform, with differences noted across geographic regions. The impact and outcome of HTLV-1 infection appears to depend on interactions between the virus and host genetic and immunological factors.

Table 11: Epidemiological and biological evidence for diseases associated with HTLV-1 infection

	Epidemiological evidence				Biological evidence	
	Case reports or case series	Cross-sectional studies	Case control studies	Cohort studies	HTLV-1 identified in lesions	Animal model
Adult T cell leukaemia-lymphoma	Yes 190-192	Yes 193	Yes 193-195	Yes 196-199	Yes 5,191,192,200-202	Yes 203-205
HTLV-1 associated myelopathy	Yes 206-208	Yes 209-212	Yes 213	Yes 214-217	Yes 206-208,218-220	Yes 221,222
HTLV-1 associated uveitis	Yes 223-231	Yes 8,223-229,232-237	Yes 213,238	Yes 217	Yes 227,239,240	Yes 241
Infective dermatitis associated with HTLV-1	Yes 242-247	Yes 248	Yes 249	Yes 250,251		

Adult T cell leukaemia-lymphoma

ATL is a mature T-cell malignancy associated with HTLV-1 infection. According to criteria developed by Shimoyama *et al*, there are four clinical subtypes: acute, lymphomatous, chronic, and smoldering.²⁵² The more aggressive subtypes, acute and lymphomatous, represent the majority of ATL cases. Clinical presentation depends upon ATL subtype. People may present with a range of symptoms, including lymphadenopathy, hepatosplenomegaly, hypercalcemia, and involvement of the skin, lung, bones, and other organs. Features particularly associated with ATL are thirst (due to hypercalcaemia) and skin involvement (nodules, plaques, or a generalised papular rash). Opportunistic infections may manifest due to immunosuppression as a consequence of dysfunctional HTLV-1–infected T cells.

More recently, it has also been suggested that smoldering subtype should be further split to differentiate patients who present nodules or tumours in the skin without lung involvement, named primary cutaneous tumoral (PCT) form of ATL.⁷ The same prospective study of 143 ATL patients,

found a median survival time of 20 months for PCT patients (n=6), lower than for smoldering patients (109 months, n=35).

Table 10: Clinical subtypes, presentation and survival among people with ATL in Japan (2000 – 2011)

Subtype	Proportion of ATL cases	Clinical presentation	Median survival (months)	Four-year overall survival
Acute	50%	Acute leukaemia High serum LDH	8.3	11%
Lymphomatous	26%	Lymphadenopathy <1% ATL cells in peripheral blood	10.6	16%
Chronic	14%	$\geq 4 \times 10^9$ lymphocytes/L in peripheral blood Elevated LDH (1.5-2x ULN) Lung, skin, or liver involvement (with no other extra-nodal sites) Absence of hypercalcemia	31.5	36%
Smoldering	11%	$<4 \times 10^9$ lymphocytes/L Normal LDH (<1.5 ULN) No lymphadenopathy Lung or skin involvement (with no other extra-nodal sites) Absence of hypercalcemia	55.0	52%

Collated from ^{253,254}, see also ²⁵⁵

Summary of evidence in support of the causal role of HTLV-1 in ATL

- In 1979, HTLV-1 was first isolated from a patient with a cutaneous T cell malignancy in the United States.⁵ The suggestion that HTLV-1 may be involved in the pathogenesis of ATL (previously recorded in Japan) were prompted by similarities with the clinical presentation and abnormal T cell morphology.¹⁹⁰ The causal link was soon established.²⁰¹ In 1996, the International Agency for Research on Cancer concluded that HTLV-1 was carcinogenic to humans.²⁵⁶ As the specific cluster of pathological features of ATL are not seen in people without HTLV-1 infection, the disease is effectively defined by the presence of infection.
- The epidemiological and biological evidence in support of HTLV-1 infection being necessary for the pathogenesis of ATL includes:
 - Identification of HTLV-1 provirus integrated in tumors cells of ATL²⁰¹
 - Cord blood T lymphocytes infected with HTLV-1 *in vitro* exhibit characteristics of T cell lines established previously from patients with ATL^{257,258}
 - Anti-HTLV-1 antibodies detected in the majority of patients diagnosed with ATL¹⁹⁶⁻²⁰⁰
 - High prevalence of ATL in regions in which HTLV-infection is endemic, including familial clusters of HTLV-1 infection and ATL cases^{200,259-261}
 - Absence of a disease that resembles ATL among people who are HTLV-1 seronegative²⁶²

While the causal role of HTLV-1 infection in the pathogenesis of ATL has been established, additional factors associated with development of ATL are less clear. Case reports and series of ATL have been published from many countries in both HTLV-1 endemic and non-endemic regions, but data are sparse outside of Japan, a country in which approximately 1000 new cases of ATL are reported each year.²⁵⁴ Within Japan, there is considerable geographic variation in ATL incidence, with higher

incidence seen in HTLV-1 endemic regions. See Supplementary Material (Table 5, Table 6, Table 7, Table 8, Table 9) and Schierhout et al¹, Legrand et al³ and WHO² for details of studies included.

A range of risk factors for development of ATL among people with HTLV-1 infection have been reported. In the cohort studies included in previous systematic reviews, there was evidence of an association with male sex and older age from multiple sources, and with higher HTLV-1 proviral load. Evidence from case-control studies has also suggested that HTLV-1 proviral load and other host and viral factors may modulate risk of ATL, including HLA type, level of soluble interleukin-2 receptor, and HTLV-1 antibody titre; both the level of soluble interleukin-2 receptor and HTLV-1 antibody titre are likely to be related to HTLV-1 proviral load.^{193,263-265}

There is a long latency period between HTLV-1 infection and ATL. Age at diagnosis of ATL appears to differ by population. In Japan, people diagnosed with ATL were typically older than 60 years²⁶⁶ with an increase in age at diagnosis over time^{267,268}, while in Jamaica, mean age at diagnosis was 43 years.^{195,269} A cross-sectional study from Japan has reported a decrease in ATL diagnoses over time, with an increase in age at diagnosis, attributed to the decrease in HTLV-1 among younger people.²⁶⁷ From the included population-based modelling studies, it has been assumed that longer duration of infection (>20 years) and younger age at acquisition (i.e. in infancy or childhood) increases the risk of development of ATL. This increased risk is thought to be driven by several factors, including genetic and epigenetic mutations, and immune evasion. As persistence of HTLV-1 occurs via clonal expansion of infected cells, longer infection duration allows more time for clonal expansion and therefore the accumulation mutations capable of malignant transformation.^{270,271} While it has been claimed in the literature that ATL seldom develops in individuals infected in adulthood, the absence of robust studies examining this leaves the question unresolved.

Ongoing research is required to evaluate the burden of disease related to ATL and the impact of HTLV-1 proviral load and other risk factors for ATL.

HTLV-1-associated myelopathy/tropical spastic paraparesis

HTLV-1 associated myelopathy/tropical spastic paraparesis (known as HAM/TSP) is a chronic inflammatory disease of the central nervous system, characterized by progressive spastic weakness of the lower limbs, lower back pain, and bowel and bladder dysfunction. Clinical examination typically demonstrates muscle weakness, hyperreflexia, and clonus in the lower limbs, along with extensor plantar response and a spastic gait.² Cerebrospinal fluid (CSF) examination may show a mild pleocytosis, HTLV-1 antibodies, and a mild to moderate increase in protein concentration.

A definitive diagnosis of HAM/TSP requires the following:^{272,273}

1. A non-remitting progressive spastic paraparesis with sufficiently impaired gait to be perceived by the patient. Sensory symptoms may be present, but a discrete sensory level should not be evident. Urinary and anal sphincter symptoms or signs may be present.
2. Antibodies to HTLV-1 in the serum and CSF (confirmed by western blot) and/or positive PCR for HTLV-1 in blood and/or CSF
3. Spinal cord imaging and other appropriate investigations to rule out alternate causes of progressive paraparesis

Summary of evidence in support of causal role of HTLV-1 in HAM/TSP

- In 1985, it was proposed that HTLV-1 was associated with a chronic progressive myelopathy of previously unknown aetiology, referred to as tropical spastic paraparesis.^{206,208,274} A similar clinical entity was described in Japan in 1986, and was labelled HTLV-1 associated myelopathy.²⁰⁷ It was determined that these were the same conditions, and the disease was referred to as

HAM/TSP. The original diagnostic criteria were suggested by the World Health Organisation in 1988.²⁷³

- The epidemiological and biological evidence in support of a causal role for HTLV-1 infection in the pathogenesis of HAM/TSP includes:
 - Isolation of HTLV-1 from CSF in people diagnosed with HAM/TSP^{207,220}
 - Intrathecal synthesis of HTLV-1 antibodies²⁰⁷
 - Detection of the HTLV-1 proviral DNA in involved tissues^{218,219}
 - Oligoclonal expansion of HTLV-1-specific cytotoxic T lymphocytes in the CSF²⁷⁵
 - Development of HAM/TSP after blood transfusion from an HTLV-1-infected donor to an HTLV-1-seronegative recipient^{45,276}
 - A significantly higher HTLV-1 proviral load among people diagnosed with HAM/TSP compared with people with asymptomatic HTLV-1 infection²¹²

Among people with HTLV-1 infection, the lifetime risk of HAM/TSP may be lower than the other major disease association, ATL. In Japan, the cumulative lifetime risk of HAM/TSP for people acquiring HTLV-1 at birth was estimated to be 0.23%, with a lower risk among men (0.18%) than woman (0.26%).²¹⁶ Risk of HAM/TSP decreased for people acquiring HTLV-1 infection later in life; for those acquiring HTLV-1 at age 20, age 30, age 40 and age 50, lifetime risk of HAM/TSP was 0.17%, 0.14%, 0.11%, and 0.08%, respectively. In Jamaica and Trinidad, the cumulative lifetime risk of HAM/TSP among people with HTLV-1 was 1.3% in men and 1.8% in women.²¹⁴ However, it is worth noting that wide confidence intervals highlight the uncertainty of these estimates and the different methods of case finding (for example active versus passive) may impact on the findings. The mechanisms underlying disease development in HAM/TSP and ATL appear to be distinct, with infrequent published reports of people diagnosed with both HAM/TSP and ATL. HAM/TSP appears to be associated with substantial morbidity and disability. Unlike ATL, in most cases, HAM/TSP does not appear to directly contribute to mortality, although there is insufficient evidence to robustly evaluate the effect of HAM/TSP on life expectancy.

Like ATL, HTLV-1 proviral load appears to be a key factor in disease onset and progression. Evidence comes from both cohort and case-control studies.²⁷⁷⁻²⁸² Olindo et al²⁷⁸ performed a case-control study to examine the impact of HTLV-1 proviral load on HAM/TSP disease progression. One hundred consecutive patients with HAM/TSP were enrolled, along with 34 people with asymptomatic HTLV-1 infection. On the basis of disability score and symptom duration among the 100 participants with HAM/TSP, the authors labelled 38 people as “rapid” progressors and 62 as “slow” progressors. Of note, the authors’ classification of progression was subjective, related to an affected individuals’ self-reported clinical course, and could not account for duration of HTLV-1 infection. Among people with asymptomatic HTLV-1 infection, mean HTLV-1 proviral load was 182 per 1,000 PBMCs (SD 25); among people with HAM/TSP, mean HTLV-1 proviral load was 1079 per 1,000 PBMCs (SD 967). HTLV-1 proviral load was higher among those with “rapid” disease progression compared to those with “slow” disease progression (rapid progressor: 1465 per 1000 PBMCs [SD 989]; slow progressor: 843 per 1000 PBMCs [SD 879]). In people with HAM/TSP, HTLV-1 proviral load was independent of age at enrolment, age at disease onset, symptom duration, and other HTLV-1 disease manifestations. The risk of HAM/TSP may also be moderated by the degree of HTLV-1-specific cytotoxic T lymphocyte response²⁸³ and HLA type^{282,284}, both of which may impact HTLV-1 proviral load.

Cross-sectional studies have also studied factors associated with progression. A recent study from Boostani et al, demonstrated that HTLV-1 proviral load was significantly higher among those with HAM/TSP, compared to asymptomatic HTLV-1 carriers.²⁸⁵ A study from Brazil found that vitamin D deficiency may play a role in disease progression.²⁸⁶

Other markers of progression have been identified recently, with a HAM-like phenotype in asymptomatic HTLV-1 carriers described in a study from the UK, with T-cell activation markers

(CD4/CD25, CD4/HLA-DR, CD8/CD25 & CD8/HLA-DR) and β 2-microglobulin potentially identifying a proportion of asymptomatic carriers at high risk of developing HAM.²⁸⁷

Additional work needs to be done to evaluate the epidemiology and factors associated with development and progression of HAM/TSP. Implementation of strategies to reduce HTLV-1 acquisition may reduce the burden of HTLV-1 associated disease, with declining incidence of HAM/TSP seen among the general population in Martinique corresponding with decreasing HTLV-1 seroprevalence among first time blood donors.²⁸⁸

HTLV-1 associated uveitis (HAU)

The third clinical condition to be associated with HTLV-1 was uveitis. The first evidence emerged in Japan in 1989, with case reports suggesting a possible association between HTLV-1 infection and various ocular symptoms.²⁸⁹ This was followed by epidemiological, clinical, and laboratory evidence for the causal role of HTLV-1 in uveitis.

The pathogenesis of HAU, as with other HTLV-1-associated inflammatory diseases, is thought to be related to lymphocyte-driven inflammation mediated by infected CD4+ T cells. HTLV-1 infected lymphocytes have been identified in the aqueous humour of the eye, and cytokine production by these infected T cells appears to be responsible for the intraocular inflammation in patients with HAU.

Summary of evidence in support of causal role of HTLV-1 in HAU

- The epidemiological and biological evidence in support of a causal role for HTLV-1 infection in the pathogenesis of uveitis includes:
 - Higher seroprevalence of HTLV-1 among people with uveitis of unknown aetiology, compared to people with uveitis of defined aetiology or people with other eye diseases (age- and sex-matched controls)^{8,227,238}
 - A significantly higher HTLV-1 proviral load among people diagnosed with HAU compared with people with asymptomatic HTLV-1 infection²¹³
 - Detection of HTLV-1 antibodies and proviral DNA in the eyes of people with uveitis^{223,227,233,239,240}
 - Accumulation of HTLV-1-infected lymphocytes in the eye²⁴⁰
 - Production of inflammatory cytokines by HTLV-1 infected lymphocytes in the eye²³⁹
 - Absence of HTLV-1 antibodies and proviral DNA in the aqueous humor of the eye among people with HTLV-1 infection and uveitis of another aetiology or people with HTLV-1 infection and no ocular manifestations^{290,291}

Results for HAU

HTLV-1 associated uveitis appears to be uncommon and robust epidemiological data are limited. There is insufficient evidence available to comment on the incidence of HAU among people living with HTLV-1 infection, with only one small cohort study identified.

The prevalence of HAU among people with uveitis has been evaluated in cross-sectional studies. Consecutive patients who attended the outpatient uveitis clinic of 36 university hospitals for the first time between 1 June 2009 and 31 May 2010 in Japan were enrolled.²³⁵ Of 3,830 patients enrolled, 29 (0.8%) were diagnosed with HAU. The proportion with HAU in the Kyushu area (3.1 %) was higher than remainder of the country. The proportion with HAU in the 2009-2010 survey was similar to results obtained in a national survey conducted in 2002 involving 41 hospitals (n=3060; HAU, 1.1%).²³⁶

Studies from Japan (cross-sectional and retrospective cohort studies) have recorded the clinical features and visual outcomes of people diagnosed with HAU, but have not rigorously examined factors associated with disease progression.^{231,292,293} In these studies, diagnosis of HAU relied on positive HTLV-1 serology and exclusion of other causes of uveitis; serological or molecular testing for HTLV-1 on vitreous samples was not performed to confirm the diagnosis. This is a limitation of many published studies. From the evidence available, women were more likely to be diagnosed with HAU than men,²⁹⁴ and cases of HAU have been documented in adults and children (age at diagnosis, range 7 – 83 years).²⁹⁴ Cases were predominantly classified as intermediate uveitis, with unilateral or bilateral involvement. Blurred vision and ‘floaters’ were common at initial presentation. Many patients experienced a single bout of mild to moderate uveitis which resolved within weeks.

While the prognosis of HAU appeared to be generally favorable, recurrence and sight-threatening complications occurred, including retinochoroidal degeneration, glaucoma, and corticosteroid-induced cataracts.²²⁶ In one cohort of 112 patients with HAU,²⁹² recurrence of uveitis was seen in 52%; 12 patients were diagnosed with more than six episodes, with the interval between episodes ranging from two weeks to 10 years. Ocular complications included cataracts (n=22), persistent vitreous opacities (n=17), and glaucoma (n=16). In another cohort of 70 patients with HAU,²⁹³ recurrent episodes were noted in 37%, with a mean interval of 16 months (range, 1-250 months), with visual complications including cataracts and retinochoroidal degeneration.

HAU can occur as an isolated disorder, or in association with other HTLV-1 related diseases. ATL and HAM/TSP have been reported infrequently in people both before and after the diagnosis of HAU.^{226,292,293} In three retrospective cohort studies comprising a total of 203 people with HAU,^{231,292,293} 12 were diagnosed with HAM/TSP, and two were diagnosed with ATL.

There remain gaps in research in terms of evaluating the incidence of HAU, and the burden of disease, and factors associated with the development of it.

Infective dermatitis

In 1966, a pattern of severe exudative eczema in 17 Jamaican children was described, characterized by crusting around the nostrils, ears, and scalp, followed by a generalized fine papular rash. The condition responded quickly to treatment with antibiotics and topical steroids.²⁴⁷ In 1990, la Grenade *et al* reported a series of 14 Jamaican children with infective dermatitis, all of whom had antibodies to HTLV-1.²⁴² In 1998, la Grenade *et al* performed a case-control study comparing the clinical, pathological, and immunological features of infective dermatitis (n=50; male 40%; age range, 1-32) and atopic dermatitis (n=35; male 49%; age range, 1-36).²⁴⁹ All (100%) patients with infective dermatitis had antibodies to HTLV-1, compared with 14% of those with atopic dermatitis. Median HTLV-1 antibody titre was substantially higher among people with infective dermatitis (1:36827) compared to those with atopic dermatitis (1:1580). Other features were similar between groups, with frequent colonization with *Staphylococcus aureus* or beta-haemolytic streptococci (infective dermatitis, 49%; atopic dermatitis, 30%). Skin biopsy revealed changes consistent with chronic dermatitis, which were indistinguishable between the groups.

There is no supportive evidence from animal models nor has HTLV-1 been identified in typical skin lesions. The histological characteristics of infective dermatitis are not distinctive. Differentiating infective dermatitis from other skin conditions, including atopic and seborrheic dermatitis, relies on clinical assessment. Among 60 children in South Africa screened for infectious dermatitis related to HTLV-1 (based on clinical phenotype), 27 (45%) were HTLV-1 seronegative, with most having HIV-related seborrheic dermatitis.²⁹⁵

The epidemiological and biological evidence in support of a causal role for HTLV-1 infection in the pathogenesis of infective dermatitis includes:

- High seroprevalence of anti-HTLV-1 antibodies among children diagnosed with infective dermatitis^{242,249}
- A significantly higher HTLV-1 proviral load among people diagnosed with infective dermatitis compared with people with asymptomatic HTLV-1 infection.²⁴⁸

The incidence and burden of disease related to infective dermatitis among people with HTLV-1 is unknown. Very few case series with limited numbers of patients have been published describing the characteristics of infective dermatitis associated with HTLV-1, with case series consisting of less than or equal to 50 patients (Jamaica, n=50; Brazil, n=42; South Africa, n=19).^{249,295,296} Of note, in the study from Brazil, two cases of infectious dermatitis were in children who were HTLV-1 antibody negative and HTLV-1 PCR positive; molecular testing was performed given the clinical phenotype. As with other HTLV-1 disease associations, there may be marked geographic variation. Cases of infectious dermatitis have been reported predominantly in tropical regions in which HTLV-1 is endemic, such as Jamaica, Trinidad, and Brazil; with few cases reported in Japan.

There may be an association with infective dermatitis and future development of HTLV-1 related disease. There are case reports of adults with ATL or HAM/TSP who have had a history of infectious dermatitis in childhood.^{243,248,251,296-301} In a study from Brazil, of a series of 42 patients with infectious dermatitis, 20 (48%) were diagnosed with HAM/TSP in childhood or adolescence, and one was diagnosed with ATL as an adult.^{296,302} As with ATL and HAM/TSP, a higher HTLV-1 proviral load has been demonstrated among people with infective dermatitis than in people with asymptomatic HTLV-1 infection.²⁴⁸ In addition, people with infectious dermatitis may have increased rate of infection of new clones and an increased number of existing HTLV-1 positive clones, which could contribute to the high HTLV-1 proviral load and contribute to the risk of ATL.³⁰³ Similar to other inflammatory

conditions associated with HTLV-1, infective dermatitis appeared to be characterised by an exacerbated Th1 immune response.²⁴⁸

Biomarkers and prognostics for progression to known disease associations

Risk factors for progression to known disease associations include higher proviral load (ATL, HAM/TSP, infective dermatitis) older age (ATL, HAM/TSP), cigarette smoking (ATL), and female sex (HAM/TSP).

As summarized in Taylor et al,³⁰⁴ a number of studies^{215,305,306} have found that higher PVL is associated with HAM/TSP, when compared with asymptomatic carriers, and higher PVL pre-dated or was associated with disease progression.^{215,306,307} More severe HAM/TSP disease has also been associated with higher PVL.³⁰⁵ In a cohort in Brazil, children with infective dermatitis had higher PVL than asymptomatic carriers, however higher PVL was not indicative of progression to HAM/TSP.³⁰⁷ Studies from Japan have also shown higher PVL in ATL patients compared to asymptomatic carriers,³⁰⁸ and higher baseline PVL in individuals progressing to ATL.¹⁹⁹

Recent studies have also focused on potential biomarkers to identify risk of disease progression.^{9,10} One study found that an oligoclonality score, a measure expressing the number of clonal populations of HTLV-1 infected cells, could serve as a clinically useful prognostic and diagnostic index. HTLV-1 positive asymptomatic patients who did not develop ATL during >7 years' follow-up all had an oligoclonality index (OCI) flow less than 0.770. In contrast, those with an OCI-flow exceeding 0.770 were more than seven times more likely to develop disease compared to all patients, and five times more likely to develop ATL than patients with a PVL >4%. A retrospective cross-sectional epigenetic study of over 400 samples detected epigenetic alterations of Fragile Histidine Triad Diadenosine Triphosphatase in ATL patients, which may be useful for screening for early identification of ATL risk.¹¹

Prognostic models have been developed to determine risk of mortality and progression to ATL using conditional inference trees, the ATLL-GELL, by including serum lactate dehydrogenase (LDH) and the Eastern Cooperative Oncology Group (ECOG) performance status. Preliminary findings suggest the model provided better risk stratification and low- vs high-risk categories for ATLL progression.¹² Research to validate these models is currently underway.

Therapeutic interventions in managing HTLV-1 infection and HTLV-1 associated disease

Therapeutic interventions for asymptomatic HTLV-1 infection

Of the included studies, two were related to asymptomatic HTLV-1 infection. The characteristics of individual studies are presented in Supplementary Material (Table 34); of the two studies, one was a single-arm pilot study evaluating raltegravir, and one was a randomised control trial evaluating green tea extract.

HIV antiretroviral therapy

Reverse-transcriptase inhibitors and integrase strand transfer inhibitors

First-generation nucleoside analogue reverse transcriptase inhibitors (NRTI), such as zidovudine and lamivudine, and the HIV integrase strand transfer inhibitor (INSTI), raltegravir, were noted to have *in vitro* activity against HTLV-1, but this has not been demonstrated *in vivo*.^{309,310} Recent *in vitro* and cell-to-cell infection models have suggested that elvitegravir, dolutegravir and bictegravir are more potent than raltegravir (with bictegravir having greatest activity; EC₅₀ 0.30 ± 0.17 nM).³¹¹ A recent study in 2021, evaluated efficacy of a new INSTI (cabotegravir - approved by the FDA for HIV treatment) against HTLV1 infection *in vitro*. Cabotegravir blocked HTLV1 transmission in tissue culture, displaying an IC₅₀ of 77.8 ± 22.4 nM.¹⁹ One study evaluated naphthyridines with substituents in position 6 as most potent against HTLV-1, with XZ450 having highest efficacy *in vitro*.²⁰ This should strongly encourage the establishment of a new standard of HTLV-1 treatment – particularly for pre-exposure prophylaxis and prevention of mother-to-child transmission.

Evidence evaluating use of HIV antiretroviral therapy among people with asymptomatic HTLV-1 infection is extremely limited. A pilot study of five people with HTLV-1 infection (asymptomatic, n=3; HAM/TSP, n=2; median HTLV-1 proviral load at baseline, 758 copies per 1000 PBMCs) in Spain found no substantial reduction in HTLV-1 proviral load after treatment with raltegravir for six months.³¹² While a transient decline was noted in the two participants with HAM/TSP, the HTLV-1 proviral load rebounded while on treatment to pre-treatment levels within the six-month study period. No changes in the HTLV-1 proviral load were noted in the three participants with asymptomatic HTLV-1 infection.

Other drugs or therapeutics

Green tea extract

A pre-clinical study suggested that polyphenols from green tea could hinder growth of T cells in people with ATL and asymptomatic HTLV-1 infection by suppressing the expression of the HTLV-1 pX gene.³¹³ A subsequent randomized (1:1) control trial among people with asymptomatic HTLV-1 infection, found that HTLV-1 proviral load did not change markedly in the group who received green tea extract powder (equivalent to 10 cups of regular green tea; n=37) compared with controls (n=46). In the control group, green tea consumption among participants was unclear. On subgroup analysis of those with an HTLV-1 proviral load above the median (18 copies per 1000 PBMCs), HTLV-1 proviral load declined at six months in those randomized to green tea extract (n=16; mean proviral load at baseline: 67, SD 49; mean change: -20, SD 39) and remained stable in controls (n=26; mean proviral load at baseline: 73, SD 53; mean change: +3, SD 37). The clinical significance of these findings is uncertain, and available evidence is insufficient to determine the effect of green tea extract on HTLV-1 proviral load among people with asymptomatic HTLV-1 infection.

Natural anti HTLV-1 compounds

Another study used HTLV-1 infected T-cell line, MT2, to find anti-HTLV-1 natural compounds, saponins A and B, from the extract of the pulp/seeds of *Akebia quinata* fruit, found to enhance Gag

aggregation, induce the abnormal cleavage of Gag, suppress virion release, and preferentially kill HTLV-1 infected cells.²¹ Another study analysed the alcoholic extract GC-MS of the *Momordica Charantia* (Bitter Melon) and was shown to have effective antiviral properties.³¹⁴

Discussion on treatment for asymptomatic HTLV-1 infection

No treatment is currently recommended for people with asymptomatic HTLV-1 infection, with insufficient evidence on which to base clinical recommendations.

While there is increasing evidence of the utility of PVL in determining severity or risk of progression,^{304,315} there is currently no single biological marker or clinical feature which predicts development or quantifies risk of HTLV-1 associated disease. Further studies are required to provide evidence of this. Improvements in risk prediction would assist in clinical management (to stratify people with HTLV-1 infection during follow up), and in research design (to determine appropriate and clinically meaningful endpoints).

Pharmacological interventions for ATL

The natural history and prognosis of ATL varies by clinical subtype and impacts on management. Aggressive subtypes of ATL continue to have a poor prognosis, despite developments in pathophysiology and therapeutics. Treatment strategies for ATL include “antiviral” regimens (with interferon-based therapy) and multi-agent chemotherapy, with the more recent addition of biologic agents. The complex presentation of ATL can make assessment of response to treatment difficult, but response criteria are necessary to interpret and standardize clinical trials. International recommendations for the management of ATL were originally published in 2009,²² and were updated in 2019.²³ Given the scarcity of data, these recommendations are based primarily on expert opinion, and recommend that where available, people with ATL should be considered for enrolment in a clinical trial. There are also several recent reviews focusing on ATL therapeutics.²⁴⁻²⁶

Table 11: Clinical response criteria in ATL

Response	Definition
Complete response	Disappearance of all clinical, microscopic, and radiographic evidence of disease for at least four weeks <i>Lymph nodes:</i> Regression to normal size (≤ 1.5 cm in their greatest transverse diameter) or regression to ≤ 1.0 cm if previously involved nodes were 1.1 to 1.5 cm <i>Peripheral blood:</i> Absolute lymphocyte count $<4 \times 10^9/L$ and $<5\%$ abnormal lymphocytes (“flower cells”)
Unconfirmed complete response	$\geq 75\%$ reduction in tumor size, but with a residual mass after treatment AND absolute lymphocyte count $<4 \times 10^9/L$ for at least four weeks
Partial response	$\geq 50\%$ reduction in measurable disease without the appearance of new lesions AND $\geq 50\%$ reduction in absolute abnormal lymphocyte count for at least four weeks
Stable disease	Failure to attain complete response or partial response, but without evidence of progressive disease
Progressive disease	<i>Peripheral blood:</i> $\geq 50\%$ increase from nadir in number of “flower cells” AND absolute lymphocyte count $\geq 4 \times 10^9/L$. <i>Other sites:</i> $\geq 50\%$ increase from nadir in measurable disease or appearance of new lesions (excluding skin).

Adapted from Tsukasaki et al²²

The overall response reported in clinical trials is a composite of participants with complete response and partial response.

Of the included studies, 23 were related to ATL. For ATL, the characteristics of individual studies are presented in Supplementary Material Table 35 for interferon-based therapy and Supplementary Material Table 36 for chemotherapeutic and biological agents; of the 23 studies, three were randomised trials and 20 were single-arm studies.

Interferon-based therapy for ATL

“Antiviral” therapy (interferon in combination with zidovudine) has been demonstrated to induce remission and improve survival in cases of acute, chronic, and smouldering ATL. The first pilot study

among people with ATL at a single-centre study in Japan, evaluating the efficacy and safety of interferon-beta and interferon-gamma, was published in 1987.³¹⁶ Of the six patients who received interferon-beta, three (50%) achieved a partial response, and of the five patients who received interferon-gamma, one (20%) achieved a complete response and two (40%) achieved a partial response (overall response, 60%). However, duration of response and survival was short (interferon-beta, survival range: 0.5 - >14 months; interferon-gamma, survival range: 1.5-5 months).

Subsequently, five phase II single-arm open-label studies have evaluated the efficacy and safety of interferon-based therapy among people with ATL,³¹⁷⁻³²¹ including a total of 71 patients (acute or lymphoma subtype, n=57; chronic subtype, n=14) (Supplementary Material Table 35). In three small trials evaluating efficacy and safety of interferon plus zidovudine among people with untreated and relapsed or refractory aggressive ATL, overall response ranged from 17% to 76% (complete response, 6% to 53%), with median survival between six and 13 months.³¹⁷⁻³¹⁹ Of reported adverse events, dose-dependent and reversible myelosuppression was most common. Two additional studies assessed the efficacy and safety of arsenic trioxide, interferon and zidovudine, both of which noted substantial toxicity with the addition of arsenic.^{320,321} No randomised trials evaluating interferon-based therapy among people with ATL have been performed.

Current clinical trial evidence for efficacy of interferon-based therapy is limited. Given the small sample size in individual studies and lack of a randomized control trial, retrospective cohort studies assessing treatment outcomes among people with ATL have been performed.^{322,323} In the largest cohort to date, Bazarbachi *et al*³²² undertook a retrospective analysis of 254 people with ATL treated between 1995 and 2008 with one of three regimens: 1) antiviral therapy (interferon-alpha plus zidovudine and/or other HIV antiretroviral therapy), 2) chemotherapy, and 3) chemotherapy followed by antiviral therapy. Of those with available survival data and a record of first-line therapy (n=207), five-year overall survival rates were 46% for patients who received first-line antiviral therapy (n=75), 20% for patients who received first-line chemotherapy (n=77), and 12% for patients who received first-line chemotherapy followed by antiviral therapy (n=55). Among people with acute, chronic, and smoldering subtypes, improved five-year survival was seen in those who received first-line antiviral therapy, whereas chemotherapy promoted better outcomes in people with lymphoma subtype. In those with acute ATL, achievement of complete remission with antiviral therapy resulted in 82% five-year survival. Antiviral therapy in chronic and smoldering ATL resulted in 100% five-year survival. A retrospective study from Brazil indicated that ATL with cutaneous involvement had improved overall survival compared to non-cutaneous, with higher response rates with combination zidovudine and interferon-alpha compared to chemotherapy.³²⁴ While these retrospective analyses suggest benefit, selection bias cannot be excluded. In contrast, a retrospective study from France (n=47) found high rates of infection and fungal infections in acute ATL patients receiving interferon-alpha and zidovudine and chemotherapy, and modified institutional guidelines to not recommend interferon-alpha and zidovudine for ATL aggressive subtypes.³²⁵

International consensus guidelines propose that interferon-alpha and zidovudine may be regarded as primary treatment options for individuals diagnosed with symptomatic smoldering ATL, as well as for those with favorable or unfavorable chronic ATL, and acute ATL.²³ The outcomes of a phase III clinical trial comparing interferon-alpha and zidovudine with 'watchful waiting' in people with indolent ATL (JCOG1111C) underway in Japan will contribute further evidence.

Chemotherapeutic and biologic agents for ATL

Use of combination chemotherapy for treatment of ATL

A phase III multicenter open-label randomized trial (JCOG9801) was conducted in Japan among individuals with untreated aggressive ATL. This trial compared the efficacy of two multi-agent chemotherapy regimens: vincristine, cyclophosphamide, doxorubicin, prednisolone-doxorubicin,

ranimustine, prednisolone-vindesine, etoposide, carboplatin, prednisolone (VCAP-AMP-VECP; utilizing a dose-intensified modified LSG15 protocol) and bi-weekly cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP).³²⁶ Superior efficacy was observed with VCAP-AMP-VECP (complete response rate: 40%) compared to bi-weekly CHOP (complete response rate: 25%). However, the median survival was only 13 months. A subsequent propensity score analysis involving transplant-eligible ATL patients who received either VCAP-AMP-VECP (n=947) or CHOP (n=513) suggested that the VCAP-AMP-VECP regimen was the preferred first-line therapy for patients with aggressive ATL in intermediate- and high-risk groups.³²⁷ The crude probabilities of two-year overall survival in the VCAP-AMP-VECP and CHOP groups were 40% and 45% in the low-risk group, 32% and 22% in the intermediate-risk group, and 17% and 6% in the high-risk group.

According to international consensus recommendations, intensive chemotherapy is advised as first-line therapy for individuals diagnosed with lymphoma-type ATL.²³ Expert consensus has outlined specific chemotherapy regimens for this purpose.²³ In Japan, recommended chemotherapy protocols encompass VCAP-AMP-VECP (modified LSG15) and EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin). Outside of Japan, favored chemotherapy regimens include CHOP, CHOEP (cyclophosphamide, vincristine, doxorubicin, etoposide, and prednisolone), dose-adjusted EPOCH, and hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine).

Use of biological agents for treatment of ATL

ATL is characterized by the proliferation of malignant CD4+ CD25+ T cells in the peripheral blood, lymph nodes, and other tissues. ATL cells have characteristic phenotypic features (CD3+ dim, CD4+, CD7-, CD8-, and CD25+). In addition, most ATL cells are CD52+ and almost all (≥90%) over-express C-C chemokine receptor 4 (CCR4). These immunophenotypic markers are useful for diagnosis and for targeted therapeutic intervention.

Mogamulizumab

Mogamulizumab, a first-in-class humanized anti-CCR4 monoclonal antibody, was approved in Japan for the treatment of relapsed or refractory ATL in 2012, and subsequently for chemotherapy-naïve CCR4-positive ATL.

In a phase II open-label single-arm trial in Japan, people with relapsed aggressive CCR4-positive ATL (acute, lymphoma, or unfavourable chronic subtype) received mogamulizumab.³²⁸ Complete and overall response were 31% and 50%, respectively. Median progression-free survival was 5.2 months, and median overall survival was 13.7 months.

In a subsequent phase II multicentre randomized trial conducted in Japan, people with untreated aggressive CCR4-positive ATL were assigned (1:1) to receive chemotherapy (modified LSG15) plus mogamulizumab (arm A) or chemotherapy alone (modified LSG15; arm B).³²⁹ Of 54 people randomised, 53 were treated (arm A: 29; arm B: 24). Complete response in arms A and B was 52% (95%CI 33, 71) and 33% (95%CI 16, 55), respectively. Overall response in arms A and B was 86% (95%CI 63, 96) and 75% (95%CI 53, 90), respectively. By ATL subtype, overall response was 55% in arm A and 29% in arm B for acute, 50% for arm A and 43% in arm B for lymphoma, and 33% in arm A and 0% in arm B for unfavourable chronic. Median progression-free survival was 259 days (95%CI 197, –) for arm A and 192 days (95%CI 147, –) for arm B. One-year overall survival was 65% in arm A and 80% in arm B. The most common treatment-related adverse events in each arm were myelosuppression (neutropenia, thrombocytopenia, leukopenia, lymphopenia, anaemia) and febrile neutropenia. There was one treatment-related death, which was not related to mogamulizumab. There were two deaths (septic shock, haemorrhagic cystitis) in arm A during treatment and follow up, with no deaths in arm B. These results suggest that mogamulizumab with mLSG15 may be appropriate for treatment of newly diagnosed aggressive ATL.

Outside of Japan, Phillips *et al* performed a phase II randomized (2:1) study evaluating the efficacy and safety of mogamulizumab compared with chemotherapy (investigators' choice) among people with relapsed or refractory aggressive ATL (acute, lymphoma, and unfavourable chronic subtypes) in the USA, Europe, and Latin America.³³⁰ Patients who progressed in the investigator's choice arm were permitted to cross over to mogamulizumab. Overall response rate was 11% (95%CI 4, 23) in the mogamulizumab arm and 0% (95%CI 0, 14) in the chemotherapy arm. The most common treatment-related adverse (grade ≥ 3) events with mogamulizumab were infusion-related reaction (9%) and thrombocytopenia (9%). In this trial, relapsed or refractory ATL had a very poor prognosis, regardless of treatment regimen.

Lenalidomide

One phase II study evaluated the efficacy and safety of lenalidomide monotherapy in patients with relapsed or recurrent ATL.³³¹ People (aged 20 years and older) with acute, lymphoma, or unfavorable chronic subtype ATL who had received one or more prior courses of systemic chemotherapy and had evidence of relapse or recurrence were eligible. In total, 26 participants received oral lenalidomide 25mg daily until disease progression or unacceptable toxicity. Overall response rate was 42% (95%CI 23, 63; 11/26), with four complete responses and one unconfirmed complete response. The median progression-free survival and overall survival were 3.8 and 20.3 months, respectively. Myelosuppression was the most common adverse event, with reversible grade 3 or 4 neutropenia (65%), leukopenia (38%), lymphopenia (38%), and thrombocytopenia (23%). The efficacy and safety profile would suggest that further evaluation of lenalidomide in the management of ATL should be considered.

In Japan, mogamulizumab and lenalidomide are licensed for use in relapsed or refractory aggressive ATL. Outside of Japan, mogamulizumab is approved for treatment of T cell malignancies by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Allogenic haematopoietic stem cell transplantation for ATL

There are no prospective randomised trials to support use of allogenic haematopoietic stem cell transplantation (allo-HSCT) in ATL. Case series and retrospective cohort studies of allo-HSCT after chemotherapy for aggressive ATL suggested improvements in overall survival, but with substantial transplantation-related morbidity and mortality.^{29,332-339} Fuji *et al* conducted a retrospective analysis of clinical outcomes among people diagnosed with aggressive ATL in Japan between 2000 and 2013.³³⁷ Criteria for inclusion included: age ≤ 70 years, aggressive ATL (acute or lymphoma subtype), and receipt of intensive multi-agent chemotherapy as first-line therapy. Overall, 2553 patients (median age, 59 years; range, 20-70) from 99 institutions in Japan were included. Clinical subtype was acute-type in 1817 and lymphoma-type in 737. Allo-HSCT was performed in 996 patients (39%). The probabilities of 2-year overall survival after diagnosis were 45% (95%CI 42, 48) in those who underwent allo-HSCT and 20% (95%CI 18, 23) in those who did not undergo allo-HSCT. Age and disease status at transplant appeared to influence overall survival, with improved 2-year overall survival in patients who were younger and had a complete response at time of allo-HSCT.

More recent studies have determined favourable outcomes with allo-HSCT in ATL patients outside Japan.²⁸ A single centre retrospective study included 100 ATLL patients from North America, demonstrating that allogenic stem-cell transplantation is a valid treatment option in some ATL patients, with 40% of patients alive after 5 years.^{29,30} The same study found 1-year relapse incidence was 80% for patients that received autologous stem-cell transplantation (n=5).

Clinical trials evaluating allo-HSCT in this setting have been proposed. Risk stratification and development of a prognostic index would guide clinicians in identifying those patients who may benefit from early allo-HSCT.

ATL and geographic region

Recent studies suggest that ATL cases by different geographic regions of descent, specifically North American, Japanese, and Latin American, may be clinically distinct, with poorer prognosis observed in Latin American and Caribbean cases.³⁴⁰⁻³⁴⁵ Rosadas et al. recently suggested that when devising therapeutic interventions for ATL, it may be necessary to take into account the distinctive regional attributes.²⁷

Discussion on treatment for ATL

Despite advances in pathophysiology and therapeutics (including use of intensive chemotherapy regimens), aggressive subtypes of ATL continue to have a poor prognosis. Limited success has been demonstrated with the therapeutic interventions studied. In addition, side effects related to therapy and dose-limiting toxicity are common, with myelosuppression the predominant adverse event.

While overall response rates are over 50% for many of the therapeutic strategies evaluated for aggressive ATL, responses appear to be short, with relapse of disease within weeks to months. Negative prognostic factors include poor performance status at diagnosis, age over 40 years, extensive disease, hypercalcemia, and a high serum lactate dehydrogenase.²²

Allogenic haematopoietic stem cell transplantation can prolong survival, but there are few appropriate candidates because of age, availability of a stem cell source, lack of adequate response to primary therapy, and absence of effective agents in the relapsed or refractory setting.

As noted in international consensus guidelines, recent therapeutic strategies involving biological agents and intensive multi-agent chemotherapy may signal better outcomes.³⁴⁶ Given the uncertainties about treatment options, all people with ATL should be considered for enrolment in a clinical trial, if available.

Therapeutic interventions for HAM/TSP

HAM/TSP can result in substantial morbidity. Unfortunately, the evidence-base for management of people living with HAM/TSP is extremely limited. Treatments assessed in clinical trials among people with HAM/TSP include corticosteroids, HIV antiretrovirals, and interferon. So far, no agent has demonstrated lasting benefit.

The International Retrovirology Association published guidelines for the management of HAM/TSP in 2018, with most of the recommendations limited to expert opinion.³¹ Of included studies, 21 were related to HAM/TSP. The characteristics of individual studies are included in Supplementary Material Table 37; of the 21 studies, four were randomised trials and 17 were single-arm studies. Pharmaceutical agents evaluated in the management of HAM/TSP are divided into those that are postulated to impact on pathogenesis (disease-modifying therapy), and those that are for symptomatic management, and are presented within each category in alphabetical order.

Agents postulated to alter disease course of HAM/TSP

Corticosteroids

While use of corticosteroids is common in clinical practice and recommended in an international consensus statement,³¹ only one placebo-controlled study has been conducted to evaluate efficacy in the management of HAM/TSP. Much of the data regarding use of corticosteroids for HAM/TSP stems from case series and cohort studies.³⁴⁷⁻³⁵⁰ In addition, while efficacy has not been rigorously examined, the side effects of long-term corticosteroid therapy are well known.

Pulsed methylprednisolone

Two small pilot studies evaluated pulsed methylprednisolone among people with HAM/TSP, including a total of 32 participants in Brazil and the UK.^{347,351} In the first pilot study, Duncan *et al*

evaluated intravenous methylprednisolone 500 mg daily for five days among people with HAM/TSP.³⁴⁷ There was limited short term benefit in pain and spasticity, with no effect on sphincter dysfunction or sensory loss. In a subsequent single arm open trial, Araujo *et al* assessed the efficacy of high-dose intravenous methylprednisolone 1 g daily for five days in patients with “progressive” HAM/TSP (mean duration of disease 7.3 years; mean EDSS score 4.5).³⁵¹ There was very limited and transient benefit, with only one patient having any sustained benefit (for up to two months after therapy). This patient had the shortest duration of disease (5 months). There was no improvement in sphincter disturbance or sensory loss.

Current evidence regarding use of pulsed intravenous methylprednisolone in HAM/TSP is limited. In addition to the small pilot trials, cohort studies evaluating pulsed methylprednisolone among people with HAM/TSP have been published, and have been cited to support its use.^{348,350,352} The available data would suggest that any benefit of pulsed methylprednisolone is transient and limited to pain and spasticity.

Prednisolone

Retrospective observational studies have been published and are used to support a role for corticosteroids in the management of people with HAM/TSP, despite their limitations and significant risk of bias. As one example, in a retrospective cohort study, Coler-Reilly *et al* compared clinical outcomes among people with HAM/TSP who received low-dose oral prednisolone (n=57; mean 4.8mg/day) versus those who remained untreated (n=29; mean follow up, 3.4 years).³⁴⁹ Overall mean change in Osame Motor Disability Score (OMDS) per year was -0.13 in the corticosteroid group and +0.12 in the untreated group.³⁴⁹

More recently a randomized controlled trial comparing prednisolone with placebo among people with HAM/TSP (HAMLET-P: HTLV-1 Associated myelopathy/tropical spastic Paraparesis Multicentre Exploratory Double Blind Randomised Trial of Prednisolone) has been completed. The RCT included 38 HAM patients (8 with rapidly and 30 with slowly progressing walking disabilities).³² Randomisation for rapid progressors was 1:1 to receive a 3-day course of methylprednisolone in addition to oral prednisolone therapy, vs no methylprednisolone. All four patients with methylprednisolone achieved the primary outcome of a composite of ≥ 1 -grade improvement in the Osame Motor Disability Score or $\geq 30\%$ improvement in the 10 m walking time (10 mWT) at week 2, with only 1 in 4 doing so for the non-methylprednisolone group (p=0.14). For slow progressors, randomization was for 1:1 oral prednisolone or a placebo. In the examination of slow progressors, the primary outcome of median changes in 10 mWT were -13.8% (95% CI: -20.1—7.1; p < 0.001) and -6.0% (95% CI: -12.8—1.3; p = 0.10) with prednisolone and placebo, respectively (p for between-group difference = 0.12). While the authors noted that the primary outcomes did not reach statistical significance, the study data more broadly supported the benefit of corticosteroid therapy.

While corticosteroids have been the mainstay of therapy, available evidence for their use in HAM/TSP remains limited. Further clinical trials to address efficacy and safety of corticosteroid use among people with HAM/TSP should be considered.

Cyclosporin

Cyclosporin is a calcineurin antagonist, which blocks the action of calcineurin in activated T cells. This prevents production of interleukin-2 and other cytokines which stimulate T cell proliferation and differentiation.

One small open label pilot study evaluated up to 48 weeks of cyclosporin among people diagnosed with recent onset (duration of disease <2 years) or progressive HAM/TSP (n=7).³⁵³ Five patients showed evidence of clinical improvement, and two patients restarted cyclosporin during follow-up after relapse. However, four patients met criteria for clinical failure by 48 weeks. Available clinical

trial data regarding use of cyclosporin among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Heparin

Investigators hypothesized that heparin would affect activated T cell trafficking into the central nervous system and inhibit inflammation. In a small uncontrolled open-label trial (n=10), investigators assessed the impact of heparin among people with HAM.³⁵⁴ Duration of the disease at enrolment and degree of motor disability varied widely. Patients were administered intravenous heparin 5,000 units or 10,000 units daily for nine to 93 days. In six of seven ambulant patients, motor function appeared to improve with reduction in timed walk test (both on the flat and using stairs). All participants reported subjective improvement, with decreased spasticity. Available clinical trial data regarding use of heparin among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

HIV antiretroviral drugs

Reverse-transcriptase inhibitors

As with asymptomatic HTLV-1 infection, *in vitro* data or case reports of clinical improvement or reduction in HTLV-1 proviral load with lamivudine or zidovudine ignited interest in the effectiveness of HIV antiretroviral therapy among people with HAM/TSP.

A small randomized double-blind placebo-controlled trial investigated the effects of zidovudine-lamivudine over a six-month period in individuals with HAM/TSP (n=16).³⁵⁵ There was no discernible clinical response observed, nor any variance detected in proviral load, T cell activation, or proliferation. In another small open-label study (n=6), individuals with HAM/TSP were administered tenofovir disoproxil fumarate, yielding no alterations in HTLV-1 proviral load, timed walk test results, or visual analogue pain scores.³⁵⁶

Integrase strand transfer inhibitors

A pilot study of five people with HTLV-1 infection (asymptomatic, n=3; HAM/TSP, n=2) in Spain did not show a substantial reduction in HTLV-1 proviral load after six months of treatment with raltegravir.³¹² While a transient decline was noted in the two participants with HAM/TSP, the HTLV-1 proviral load rebounded on treatment to pre-treatment levels within the six-month study period.

Interferon-alpha and interferon-beta

Six clinical trials evaluating the efficacy and safety of interferon (interferon-alpha, n=5; interferon-beta, n=1) among people with HAM/TSP were identified, including one double-blind randomised trial.³⁵⁷ In this randomised trial (n=48), participants were randomised to three different doses of interferon-alpha for 28 days. A dose-dependent response was noted, with improved therapeutic response seen with higher doses of treatment.³⁵⁸

Post-marketing surveillance was performed to investigate the safety and efficacy of interferon-alpha for HAM/TSP (n=167).³⁵⁹ Efficacy at four weeks, defined as “modest to markedly improved” and “mildly improved” symptoms, was reported in 66%. Factors associated with efficacy were OMDs at baseline, duration of illness, and stage of illness. Sustained improvement of OMDs for at least five months after cessation was seen in 11 of 30 evaluable patients. Forty-six serious adverse events were reported.

Methotrexate

A retrospective cohort study (conference abstract) reported on use of methotrexate in 13 people with HAM, and suggested that 10-metre walk test and pain reduced with treatment.³⁶⁰

Monoclonal antibodies specific for IL-2 receptor (anti-Tac)

It is believed that the potential mechanism of action of anti-Tac monoclonal antibodies in HAM/TSP involves the selective reduction of activated T cells and a decline in the HTLV-1 proviral load within peripheral blood lymphocytes. Results from one small open-label pilot study (n=9) demonstrated no significant clinical response.³⁶¹ Available clinical trial data regarding use of anti-Tac monoclonal antibodies among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Mogamulizumab

In one uncontrolled phase I/IIa trial (n=21), Sato *et al* examined the safety and efficacy of mogamulizumab, an humanized anti-CCR4 monoclonal antibody, in patients with glucocorticoid-refractory HAM/TSP.³⁶² All participants were maintained on less than 10mg of prednisolone per day. In the phase I dose-escalation study, dose-dependent reductions in the frequency of CCR4+ cells, HTLV-1 proviral load, and inflammatory markers in the CSF (CXCL10, neopterin) were observed. The reduction in HTLV-1 proviral load and inflammatory markers were maintained in the phase IIa extension of the study (n=19). At week 24 of the phase IIa study, the mean reduction in HTLV-1 proviral load was 46% (95% CI 29, 64), and the mean reduction in the neopterin concentration in CSF was 45% (95% CI 30, 60). Clinical measure improved and were sustained through to week 24. Mean global-assessment scores reduced, from 75.7 (95% CI 67.8, 83.6) on day 0 to 53.7 (95% CI 43.6 to 63.8) at week 24. The Modified Ashworth Scale score decreased in 15 of 19 patients (79%), and the OMDS decreased in 6 of 19 (32%), with improvements in motor function more likely in those with shorter duration of disease (<10 years) and mild disability (OMDS <5). Long term follow-up for these study participants is ongoing (UMIN000019942). Further clinical trials are required to determine the utility of mogamulizumab in the management of HAM/TSP. A randomized placebo-controlled clinical trial could be considered to evaluate efficacy.

Agents evaluated for symptomatic management in HAM/TSP

Danazol

Danazol, an androgenic steroid, has been used for symptomatic management of bladder and bowel symptoms resulting from spinal cord involvement in HAM/TSP. The impact of danazol on the underlying neurologic deficit is unclear. Initial case series suggested that danazol may have a favourable effect; in a small series of six patients, two patients who had been in a wheelchair became ambulant, three had decreases in spasticity, and two had resolution of urinary incontinence.³⁶³

One published placebo-controlled trial by Boostani *et al* evaluated the efficacy of danazol (n=38) or placebo (n=33) for 24 weeks among people with HAM/TSP in Iran.³⁶⁴ In the intervention arm, participants were prescribed danazol 200 mg per day for two weeks, followed by 400 mg per day for 22 weeks. The investigators reported that the mean difference in motor disability grading between baseline and after six months of therapy in the intervention arm was 0.89, and “near 0” in the placebo group. However, insufficient data were presented to critique their claims. Available clinical trial data regarding use of danazol among people with HAM/TSP are limited, unclear, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Mirabegron

A prospective observational study from Japan found that urinary catheterization and mirabegron (a β 3-adrenergic agonist for overactive bladder symptoms)³⁶⁵ improved HAM/TSP bladder dysfunction.³⁶⁵

Lactobacillus

One single-arm open-label pilot study evaluated *Lactobacillus casei* strain Shirota from fermented milk (twice daily for four weeks) among people with HAM/TSP (n=10).³⁶⁶ Improvements in spasticity (modified Ashworth Scale scores) and urinary symptoms were reported after receipt of *Lactobacillus casei*. No adverse effects were observed. Available clinical trial data regarding use of *Lactobacillus* sp among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Pentosan polysulfate

A small open-label single arm trial (n=12) assessed the efficacy of pentosan polysulfate in patients with HAM/TSP with duration of disease ranging between 3 and 52 years.³⁶⁷ Three patients received concomitant therapy; one patient received interferon-alpha plus prednisolone, and two received prednisolone only. Improvements in lower-extremity motor function were reported. Available clinical trial data regarding use of pentosan polysulfate among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Pentoxifylline

Pentoxifylline is a xanthine derivative with vasodilatory properties. One small open-label trial (n=15) assessed pentoxifylline for four weeks among people with HAM/TSP.³⁶⁸ Motor disability, especially spasticity, reportedly improved in 13 patients, and spontaneous proliferation of peripheral blood mononuclear cells was suppressed in 14. Available clinical trial data regarding use of pentoxifylline among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Prosultiamine

The thiamine derivative, prosultiamine, may improve motor function in some people with HAM/TSP. One single-arm open-label trial (n=24) examined the effects of prosultiamine for 12 weeks among people with HAM/TSP.³⁶⁹ In the majority, there was reportedly a reduction in spasticity and

an improvement in walk time and urodynamic parameters. The HTLV-1 proviral load in peripheral blood decreased by 15% compared with pre-treatment levels. Available clinical trial data regarding use of prosultiamine among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Valproic acid

One single-arm open-label trial (n=19) assessed the efficacy and safety of valproic acid for 24 months among people with HAM/TSP.³⁷⁰ No significant change was noted in HTLV-1 proviral load on-treatment. Overall, mean neurological scores and timed walk tests did not appear to alter significantly. However, eight of 19 patients discontinued treatment before 24 months. Timed walk tests worsened in three patients, which were attributed to adverse drug effects including drowsiness and tremor; this was reversible after stopping treatment. Side effects were common including drowsiness (52%), tremor (47%), gastrointestinal upset (37%), vertigo (26%), and alopecia (10%). Available clinical trial data regarding use of valproic acid (sodium valproate) among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Vitamin C

In one open-label pilot study (n=7), the efficacy of intermittent high-dose oral vitamin C 35-40mg/kg/day was examined among people with HAM/TSP.³⁷¹ Six patients had improvement in disability score by 2 or more grades, and the seventh demonstrated an improvement of one grade. Overall, the mean disability score decreased from grade 7.1 to grade 3.6, after 9.7 months of therapy. Available clinical trial data regarding use of vitamin C among people with HAM/TSP are very limited, subject to bias, and insufficient to evaluate the impact of this intervention among people with HAM/TSP.

Discussion on treatment for HAM/TSP

There is no high-quality evidence to support use of any pharmacological intervention in the management of HAM/TSP. There are difficulties in developing an evidence-base for management of HAM/TSP. Given the low incidence of the disease and the occurrence of cases in resource limited settings, performing randomized clinical trials is challenging. Clinical trials need to be designed with appropriate, accurate and clinically meaningful endpoints, including reproducible measurements of disease severity to assess the impact of treatment.

In guidelines published by the International Retrovirology Association in 2018,³¹ the authors highlight the need for quality data to guide management and a validated clinical classification system to assist healthcare providers in management decisions, improve prognostication, and standardize clinical trial assessment and reporting. In guidelines prepared by the International Retrovirology Association, the expert panel recommended that people with HAM/TSP are classified by speed of disease progression into “rapid progressors”, “slow progressors”, and “very slow progressors”.³¹ The definitions and suggested criteria are largely subjective. Prior to adoption, these definitions require validation. However, these sub-classifications do highlight the varied natural history of HAM/TSP, and the inherent difficulties in developing management guidelines if natural history is not well defined and individual patient differences are not accounted for.

Given the uncertainties about treatment options, all patients with HAM/TSP should be considered for enrolment in a clinical trial, if available, regardless of severity and duration of disease.

HTLV-1 infection, all-cause mortality, and other possible disease associations

In addition to the diseases designated as “HTLV-1 associated” (whereby HTLV-1 infection is necessary for the diagnosis), a number of other diseases have been investigated for potential associations with HTLV-1 infection (See [Table 14](#), and Supplementary Material). It is important to note that once the presence of HTLV-1 becomes a necessary diagnostic criterion for a disease entity, it is no longer possible to study the extent of the population-level association between that entity and HTLV-1 infection. Results are drawn from a recently published articles,^{2,3,372} with an additional search for the 2021-2023 period. Studies were excluded if they did not have an HTLV-1 negative comparison group, although such studies (particularly where outcomes amongst people with high compared to low proviral load are compared) make an important contribution to the argument for causality for some conditions.

All-cause mortality

HTLV-1 infection was associated with an increase in all-cause mortality, with a pooled relative risk of 1.57 (95% CI 1.37-1.80) (Figure 4, Table 14). Consistency between the results of individual studies was high across geographic areas. The association was slightly stronger among men. An age gradient was apparent in the single study providing age disaggregation, with a relative risk of 3.80 (95%CI 1.70, 8.50) for those aged 15-29 years and 1.20 (95%CI 0.90, 1.50) for those aged 60 and older.¹ The higher observed risk of death in younger people may be due to fewer competing health risks and causes of death.¹

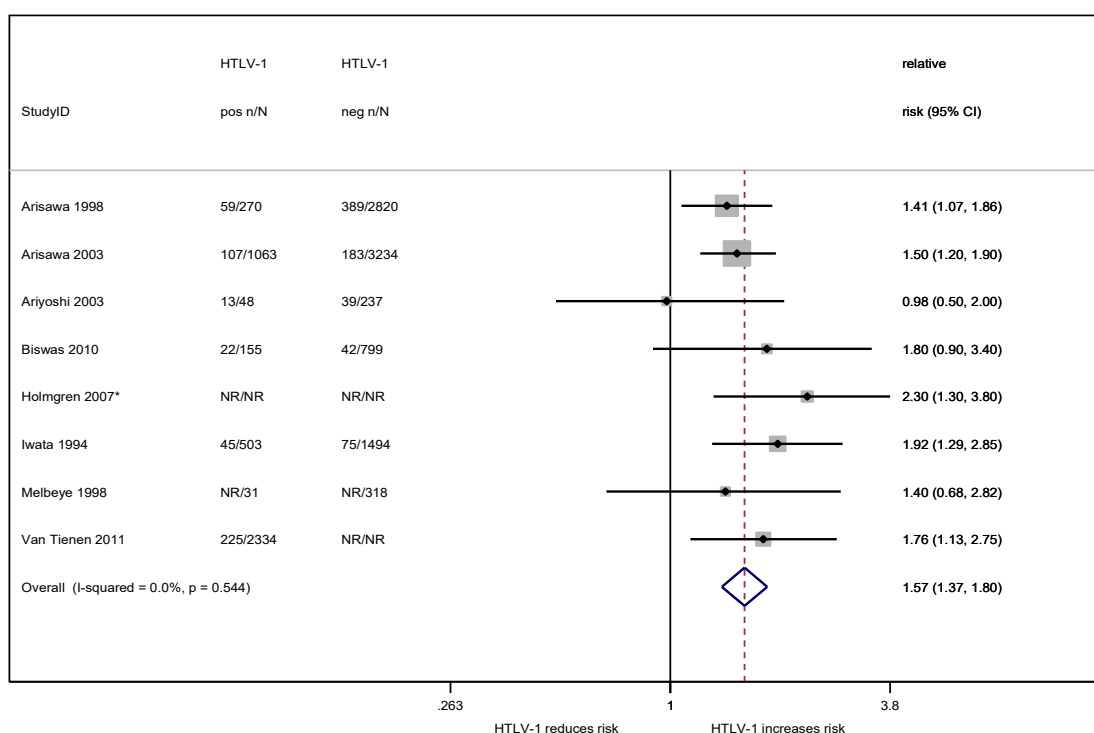


Figure 4: Meta-analysis of the association between HTLV-1 and deaths from all causes: multivariate adjusted relative risks from eight cohort studies¹

Table 12: HTLV-1 infection, all-cause mortality, and possible disease associations: Adapted from Schierhout et al¹

Overall summary of meta-analysis of studies showing significant associations between disease or death and HTLV-1 infection. *There were two further inflammatory conditions, Crohn's disease and ulcerative colitis and one other condition – renal disease, which reported statistically significant associations with HTLV-1 or substantially increased risk, but effects are not shown here on the basis of <5 participants with these conditions †As determined by study authors ‡ Strength of association, based on modification of GRADE criteria. Colour corresponds with strength of association.

Condition*	RR or OR (95% CI)	Number of studies	Location of studies	Studies used for summary estimate	Strength of association GRADE‡
Mortality					
All-cause mortality	1.57 (1.37;1.80)	9	Japan, Guinea-Bissau, United States	8 ^{196,197,373-378}	STRONG
Inflammatory conditions					
Seborrheic dermatitis (adults)	3.95 (1.99-7.81)	2	Brazil	2 ^{244,379}	LIMITED
Seborrheic dermatitis (children)	4.70 (1.70-13.20)	1	Jamaica	1 ³⁸⁰	LIMITED
Eczema (children)	3.10 (1.20-7.90)	1	Jamaica	1 ³⁸⁰	LIMITED
Rheumatoid arthritis	2.8 (1.8-4.6)	1	Japan	1 ³⁸¹	LIMITED
Arthritis	2.84 (1.51-5.33)	1	USA	1 ³⁸²	VERY LIMITED
Sjogren's syndrome	3.25 (1.85-5.70)	2	Brazil, Japan	2 ^{383,384}	LIMITED
Fibromyalgia	9.14 (2.42-34.52)	1	Brazil	1 ³⁸⁵	VERY LIMITED
Bronchiectasis, bronchitis, bronchiolitis†	2.90 (2.0-4.3)	3	Australia	1 ³⁸⁶	LIMITED

Asthma (males)	3.4 (1.2-3.3)	1	Japan	1 ³⁸⁷	VERY LIMITED
Cancer other than ATL					
Lymphoma other than ATL	2.76 (1.36-5.62)	1	Japan	1 ³⁸⁸	LIMITED
Liver cancer	1.49 (0.97-2.30)	3	Japan	3 ^{197,198,389}	LIMITED
	1.46 (0.85-2.51)	2	Japan	2 ^{388,390}	
Gastric cancer	0.45 (0.28-0.71)	3	Japan	3 ^{197,198,391}	VERY LIMITED
Cervical cancer	8.30 (0.83-82.90)	1	Japan	1 ¹⁹⁷	VERY LIMITED
	3.59 (0.68-19.11)	1	Jamaica	1 ³⁹²	
Infectious diseases					
Tuberculosis	2.30 (1.60-4.10)	1		1	MODERATE
	2.04 (1.36-3.06)	6	Brazil, Guinea-Bissau, United States, Japan,	6 ^{387,393-397}	
Kidney and bladder infections	2.32 (1.50-3.59)	2	United States	1 ³⁸²	LIMITED
	1.80 (1.0-3.2)	1	United States	1 ³⁹⁶	
Dermatophyte infection	3.32 (1.5-7.35)	1	Brazil	1 ³⁷⁹	VERY LIMITED
Community acquired pneumonia	1.36 (1.00-1.85)	1	Japan	1 ³⁹⁸	VERY LIMITED
Strongyloides hyperinfection syndrome	120 (11.43-1259)	1	Peru	1 ³⁹⁹	VERY LIMITED

Conditions classed as inflammatory

Respiratory disease

The strength of evidence for an association between HTLV-1 and bronchiectasis, bronchitis and bronchiolitis remains limited, and further research is required. The strength of evidence for an association between HTLV-1 and asthma remains very limited.

Two case control studies^{386,400} undertaken in central Australia within the same hospital population, with some overlap in study subjects found statistically significant associations between HTLV-1 and radiologically-confirmed bronchiectasis, bronchitis and bronchiolitis. The first examined bronchiectasis alone and found HTLV-1 infection was the main predictor (aRR of 1.4, 95%CI 1.19-2.84).⁴⁰⁰ The 2018 study found bronchiectasis, bronchitis and bronchiolitis were more common among participants with HTLV-1 infection (aOR 2.9, 95%CI 2.00-4.30). In contrast, two US cohort studies in overlapping populations of blood donors did not find statistically significant associations with bronchitis, ascertained by self-report of a physician-diagnosis.^{382,401} In small cross-sectional study from central Australia (n=27), seven adults with HTLV-1 infection had 'chronic lung disease' which was diagnosed by a physician blinded to HTLV-1 status, with no cases amongst those without HTLV-1.⁴⁰⁰ There was no adjustment for age or other potential confounders due to insufficient data. A recent cross-sectional study from central Australia (n=579) found a strong association between high HTLV-1 proviral load (≥ 1000 copies per 10^5 PBLs) and pulmonary disease (clinical findings, radiological evidence of bronchiectasis/bronchiolitis, or moderate-severe expiratory airflow limitation on spirometry) (aOR 14.4 95%CI 4.99-41.69).¹³ An analysis of children with bronchiectasis attending Darwin hospital found no cases of HTLV-1 among 299 children tested, concluding that HTLV-1 was unlikely to play a role in Aboriginal children with bronchiectasis.¹⁷

Evidence related to asthma comes from a cross-sectional study conducted in Japan, which found HTLV-1 infection was significantly associated with a self-reported diagnosis of asthma among men, but not women. A single cohort study undertaken in children reported no association between clinician-diagnosed asthma and HTLV-1.⁴⁰²

Other potentially inflammatory conditions

HTLV-1 was associated with seborrheic dermatitis⁴⁰² (pooled OR 3.95; 95%CI 1.99, 7.81; see Supplementary Material Figure 4) and Sjögren's syndrome (pooled OR 3.5; 95%CI 1.85, 5.70; Supplementary Material Figure 5). Rheumatoid arthritis, fibromyalgia, and ulcerative colitis all showed significant associations with HTLV-1, with effect estimates adjusted for age (Table 24, Table 27, Supplementary Material).

Cancer

In five cohort studies, the association between HTLV-1 and cancer (excluding ATL) at any site^{197,198,401} and the following specific sites was assessed: breast,¹⁹⁸ bladder,¹⁹⁸ cervix and uterus,¹⁹⁷ colon and rectum,^{197,198} liver,^{197,198,389} lung,^{197,198} oropharynx,¹⁹⁸ oesophagus,¹⁹⁸ pancreas,¹⁹⁸ prostate,¹⁹⁸ stomach,^{197,198,403} and thyroid.¹⁹⁸ In five case-control studies (Supplementary Material), the association between HTLV-1 and cancer (excluding ATL) at any site^{388,390} and the following specific sites was assessed: biliary tract,^{388,390} cervix,^{392,404} colon and rectum,^{388,390} liver,^{388,390} lung,^{388,390} oesophagus,^{388,390,405} pancreas,³⁹⁰ and stomach.^{388,390} In one cross-sectional study (Table 32, Supplementary Material), the association between HTLV-1 and cancer (excluding ATL) at any site was assessed.³⁹⁶ The strength of evidence for an association between HTLV-1 and cancer (excluding ATL) at any site, was very limited or limited.

The association between HTLV-1 and lymphoma other than ATL was examined in one case-control study.³⁸⁸ The odds of developing lymphoma other than ATL was 2.76 times higher in people with

HTLV-1 (OR 2.76; 95%CI 1.36, 5.62; one case-control study) compared with people who were HTLV-1 negative (Supplementary Material). The strength of evidence for an association between HTLV-1 and lymphoma other than ATL was limited.

In a Japanese study, people with HTLV-1 infection were less likely than those without HTLV-1 to develop gastric cancer (RR 0.45; 95%CI 0.28, 0.71; three cohort studies) (Figure 6, Supplementary Material).^{197,198,403} There was no adjustment for carcinogenic factors, namely *H. pylori* infection, smoking, and alcohol consumption; notably, participants with HTLV-1 infection were less likely to have concurrent *H. pylori* infection.^{197,198,403} The strength of evidence for an association between HTLV-1 and gastric cancer was very limited.

Infectious diseases

In four cohort studies (Table 33, Supplementary Material), the association between HTLV-1 and the following infectious diseases was assessed: tuberculosis (n=1),⁴⁰⁶ community-acquired pneumonia (n=3),^{382,401,402} genitourinary infections (n=2),^{382,401} upper respiratory tract infections (n=2),^{401,402} Candida vulvovaginitis (n=1),⁴⁰¹ otitis media (n=1),⁴⁰² and mucocutaneous herpes simplex virus (HSV) infection (n=1).⁴⁰¹ In five case-control studies, the association between HTLV-1 and the following infectious diseases was assessed: tuberculosis (n=3),³⁹³⁻³⁹⁵ community-acquired pneumonia (n=1),³⁹⁸ and *Strongyloides* hyperinfection syndrome (n=1).³⁹⁹ In five cross-sectional studies, the association between HTLV-1 and the following infectious diseases was assessed: tuberculosis (n=3),^{387,396,397} community-acquired pneumonia (n=3),^{387,396,397} genitourinary infection (n=1),³⁹⁶ viral hepatitis (n=1),³⁹⁷ mucocutaneous HSV infection (n=1),³⁹⁶ and dermatophyte infection (n=2).^{244,379}

Tuberculosis

An association between tuberculosis and HTLV-1 was identified in 7 studies,^{387,393,394,396,397,407} with a pooled odds of developing tuberculosis 2.25 times higher in people with HTLV-1 (OR 2.25, 95%CI 1.48, 3.43) than HTLV-1 negative participants. A single cohort study reported a relative risk of developing tuberculosis of 2.50 (95%CI 1.60, 4.10) (Table 33, Supplementary Material).⁴⁰⁸

Urinary tract infection

Evidence for an association between HTLV-1 and urinary tract infection derived from three studies based on the same cohort in the United States, and was assessed as limited.³⁹⁶ The risk of a self-reported urinary tract infection among people with HTLV-1 was 2.32 times that of people without HTLV-1 (RR 2.32, 95%CI 1.50, 3.59), at 4.3 years of follow up. A recent cross-sectional study from central Australia among haemodialysis (HD) patients found that men with a high proviral load had an increased risk of urinary tract infection before HD (aOR: 5.15, 95% CI: 1.62, 16.40; p = 0.006).¹⁵

Strongyloides hyperinfection syndrome and symptomatic strongyloidiasis

Symptomatic strongyloidiasis and *Strongyloides* hyperinfection syndrome was investigated in one study each. A hospital-based case control study in Peru found a substantially and statistically significantly increased risk for *Strongyloides* hyperinfection syndrome associated with HTLV-1, although with a large confidence interval.³⁹⁹ In a small community cross-sectional study in central Australia, there were two cases of symptomatic strongyloidiasis in the 22 people with HTLV-1, and no symptomatic strongyloidiasis in those without HTLV-1.⁴⁰⁹ A retrospective hospital based study from the United States found that HTLV-1 was strongly associated with strongyloidiasis (aOR 261 [95% CI: 132-517]).

Studies have also examined *Strongyloides* positivity and HTLV-1. A cross-sectional study from central Australia found *Strongyloides* seropositivity was higher among the HTLV-1 negative group compared to the HTLV-1 positive group. *Strongyloides* seropositivity was lower among participants with lower HTLV-1 PVL compared to the HTLV-1 negative comparator group (aOR 0.55 [95%CI 0.32-0.95], p=0.031).⁴¹⁰ Another recent study from Brazil found that HTLV-1 positive individuals living in poor

sanitary conditions were more likely to develop severe forms of *Strongyloides*⁴¹¹ with poor sanitation being linked to *Strongyloides* infection in general.⁴¹²

Infectious skin conditions

Two cross-sectional studies suggested a weak association between HTLV-1 and dermatophyte infection (Table 35, Supplementary Material).^{244,379} Other studies and reviews, that did not meet the formal review inclusion criteria, have high occurrence of skin disorders among people with HTLV.^{413,414}

Other conditions

“Chronic liver disease” was reported in a cohort study from Japan,³⁸⁹ and collected, but not reported in a cross-sectional study.³⁸⁷ Two cross-sectional studies that utilised self-report, presented the proportion with diabetes, and two studies reported on renal disease. Associations with HTLV-1 did not reach statistical significance in any of these studies.^{389,396} Two further cross-sectional studies from Central Australia found that diabetes and chronic kidney disease were associated with people with HTLV-1 high-proviral load, compared to HTLV-1 negative participants¹⁴ and that diabetes was associated with HTLV-1 infection among patients with chronic kidney disease.¹⁵ HTLV-1 infection was associated with a reduced risk of acute kidney injury in an unadjusted analysis, but when adjusted for sex, residence, smoking, alcohol consumption, diabetes, BSI, UTI, pneumonia and HTLV-1 serostatus it was no longer significant (aOR 0.64 [95%CI 0.36-1.14], p=0.131).

Cognitive impairment

Several studies have examined cognitive impairment, quality of life or psychosocial conditions. One study found significant differences in episodic memory recall, executive function and fine motor dexterity between HTLV-1 positive participants and controls.⁴¹⁵ A cross-sectional study from Brazil found higher cognitive impairment (attention and motor skills) with people with HAM/TSP.⁴¹⁶ A further cross-sectional study from Iran, observed similar outcomes, with cognitive deficits in asymptomatic HTLV-1 infection and HAM/TSP patients.⁴¹⁷ A cross-sectional study from Brazil found that cognitive decline was greatest in individuals with HAM, with HTLV-1 asymptomatic carriers having cognitive ageing similar to that of a negative comparator group of blood donors.⁴¹⁸

Discussion on the diseases not associated by definition with HTLV-1

Schierhout et al reported that HTLV-1 infection was associated with an increased risk of death (meta-analysis; pooled RR 1.57; 95%CI 1.37, 1.80).¹ This increase in mortality is not explained by the increased risk of conditions that have been studied in association with HTLV-1. It is also not explained by ATL, which while having a high case-fatality rate, has a low incidence. Schierhout et al postulated that although unmeasured confounding may be responsible for the mortality increment identified, this is unlikely given the consistency in the mortality associations across very different settings in diverse geographic locations. There is little robust evidence examining the morbidity associated with HTLV-1 that might explain this increase in mortality.

There is evidence of limited to moderate quality suggesting that people living with HTLV-1 infection have an increased odds of developing the following conditions: tuberculosis; seborrheic dermatitis; rheumatoid arthritis; eczema; bronchitis, bronchiectasis and bronchiolitis; urinary tract infection; and lymphoma other than ATL.¹ Evidence for an association between HTLV-1 and all other conditions studied was assessed to be very limited.¹

Few robust epidemiologic studies of HTLV-1 disease associations have been identified, with the studies that have been published being geographically restricted, limiting their application to guidelines in other settings.^{1,2} HTLV-1 mediated chronic inflammation could contribute to the development of many of the possible disease associations reported. Reported reviews have not identified epidemiological studies elucidating the relationship between HTLV-1 and major global causes of morbidity and mortality, including cardiovascular, cerebrovascular and metabolic disease.^{1,2} Inflammation is pivotal in the pathogenesis of atherosclerosis.⁴¹⁹ Increased carotid intima media thickness among adults with HTLV-1 in Japan⁴²⁰ and Iran⁴²¹ has led to the suggestion that HTLV-1 mediated inflammation might contribute to coronary artery disease. The clinical conditions responsible for the increased risk of non-neoplastic disease among people with HTLV-1 may therefore be diverse, and could be further influenced by environmental, behavioural and genetic factors.

It is worth considering that the impact of HTLV-1 on adverse health outcomes is probably less pronounced in older individuals, owing to elevated baseline levels of mortality and morbidity stemming from other causes, as evidenced by studies that presented outcome data stratified by age. Moreover, many regions with endemic HTLV-1 also suffer from significant public health disparities, complicating the discernment of HTLV-1's additional contribution to an already substantial burden of illness and premature mortality in these settings.

A significant limitation of current epidemiologic studies is the lack of risk stratification by HTLV-1 proviral load, as this allows for a clearer understanding of differing disease risk for different sub-groups of people with HTLV-1. A range of studies have reported poorer outcomes among those with high proviral load.^{196,374,386,422} And while several studies showed the risk of disease development to be higher among those with high proviral load, risk factors for high proviral load are uncertain.⁴²³

The focus on controlled studies, meant that case series were excluded, such as those of polymyositis^{424,425} that while useful to contribute to initial identification of entities possibly associated with HTLV-1, do not provide a means to calculate a measure of risk conferred by HTLV-1. For the same reason, studies were excluded if they did not have an HTLV-1 negative comparison group, although such studies (particularly where outcomes amongst people with high compared to low proviral load are compared) make an important contribution to the argument for causality for some conditions.

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