

TECHNICAL REPORT

HUMAN T-LYMPHOTROPIC VIRUS TYPE 1: TECHNICAL REPORT

FEBRUARY 2020



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WHO commissioned the Kirby Institute, University of New South Wales, Sydney, Australia to write this document, based on a series of literature reviews and discussions held during the WHO Global Consultation on HTLV-1 on 13–15 November 2019. The review and writing team included: **Sahar Bajis**, **Rowena Bull**, **Louise Causer**, **John Kaldor**, **Nicolas Legrand**, **Marianne Martinello**, **Skye McGregor**, **Ela Naruka**, **Amrita Ronnachitand** and **Braulio Valencia** (Kirby Institute); and **Nicola Low** (University of Berne, Switzerland).

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ABBREVIATIONS

ATL	adult T-cell leukaemia/lymphoma
CCR4	C-C chemokine receptor 4
CI	confidence interval
CSF	cerebrospinal fluid
EIA	enzyme immunoassay
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAM/TSP	HTLV-1-associated myelopathy or tropical spastic paraparesis
HAU	HTLV-1-associated uveitis
HLA	human leukocyte antigen
HTLV-1	human T-lymphotropic virus type 1
IARC	International Agency for Research on Cancer
IFA	indirect immunofluorescence assays
NAT	nucleic acid testing
OR	odds ratio
PA	particle agglutination
PCR	polymerase chain reaction
RIA	radioimmunoprecipitation assay
RR	rate ratio

EXECUTIVE SUMMARY

The human T-lymphotropic virus type 1 (HTLV-1, also known as the human T-cell leukaemia virus type 1) has been shown to cause severe disease in some people infected with the virus, including adult T-cell leukaemia/lymphoma (ATL) and progressive nervous system condition known as HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP). Infection tends to be concentrated geographically, with high levels in specific geographical regions and populations. The main routes of transmission of HTLV-1 infection are sexual, parenteral (primarily through transfusion of cellular blood components) and vertically from mother to child (primarily through breastfeeding). Most high-income countries have introduced HTLV-1 screening of blood donations, but few other public health measures have been implemented to prevent infection or its effects or to manage ATL and HAM/TSP. Further, there are major gaps in the epidemiology of HTLV-1 infection, which creates difficulty in assessing its public health burden and trends.

WHO has published several technical reports on HTLV-1, including: reports from the 1988 and 1992 meetings of the WHO Western Pacific Regional Office Scientific Group on HTLV-1 Infections and Associated Diseases; an evaluation of commercial HTLV-1 test kits in 1995; and International Agency for Research on Cancer (IARC) monographs on HTLV-1 in 1996 and 2012. In 2018, a group of HTLV-1 experts and other stakeholders called upon WHO to take action on HTLV-1. Given increasing public awareness of HTLV-1 infection in some populations and interest expressed by Member States, an expert consultation was organized to review the global situation of HTLV-1 from a public health perspective. The WHO Global Consultation on HTLV-1 aimed to review existing global epidemiological, clinical and public health evidence to better understand the public health implications of HTLV-1 infection and disease, identify major gaps in knowledge requiring further research and identify possible public health measures to be undertaken. WHO commissioned literature reviews to guide the discussions during the Consultation.

This report synthesizes the findings of the literature reviews, primarily derived from information reported in peer-reviewed publications and the deliberations of the Global Consultation. It provides the most current evidence on the HTLV-1 epidemics, impact and interventions, including in epidemiology, routes of transmission, pathogenesis and disease associations, prevention interventions, diagnostics and screening, therapeutics for HTLV-1 infection and HTLV-1-associated diseases, public health interventions and national responses. It provides the most comprehensive global overview of HTLV-1 infection within the context of public health. The report concludes that there are many gaps in knowledge to fully understand the public health implications of HTLV-1 infections and a lack of effective interventions to respond effectively. It identifies the need for: standardized HTLV-1 surveillance and rapid assessment methods; guidance on HTLV-1 testing approaches and strategies; further data to define the risks of HTLV-1 transmission, including through mother-to-child transmission; integrating HTLV-1 prevention, testing and treatment interventions into broader sexually transmitted infection and communicable disease strategies, programmes and services; additional studies to better understand HTLV-1 disease manifestations and associations; and improved HTLV-1 communication strategies and tools to inform people living with HTLV-1, health-care providers and the general public.

INTRODUCTION

Background

Discovered 40 years ago as the first oncogenic human retrovirus, the human T-lymphotropic virus type 1 (HTLV-1, also known as the human T-cell leukaemia virus type 1) was shown to be the cause of an aggressive malignancy of the blood and blood-forming organs known as adult T-cell leukaemia/lymphoma (ATL). Infectious transmission of HTLV-1 occurs when the viral RNA genome from infected donor cells transfers and permanently integrates a copy of proviral DNA into the cells of a recipient host. This results in lifelong infection of the new host. Surveys of HTLV-1 prevalence have found that infection is concentrated geographically, with high levels in specific regions and populations. HTLV-1 infection was subsequently identified in the mid-1980s as the cause of a progressive nervous system condition that became known as HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP). Case investigations and epidemiological studies identified the main routes of transmission of HTLV-1 infection as sexual, parenteral (primarily through transfusion of cellular blood components) and vertically from mother to child (primarily through breastfeeding). Most high-income countries have introduced HTLV-1 screening of blood donations, but few other public health measures have been implemented to prevent infection or its effects or to manage ATL and HAM/TSP. Further, there are major gaps in the epidemiology of HTLV-1 infection, which creates difficulty in assessing its public health burden and trends.

WHO 2019 global consultation

WHO has published several technical reports on HTLV-1, including: reports from the 1988 and 1992 meetings of the WHO Western Pacific Regional Office Scientific Group on HTLV-1 Infections and Associated Diseases; an evaluation of commercial HTLV-1 test kits in 1995; and International Agency for Research on Cancer (IARC) monographs on HTLV-1 in 1996 and 2012. In 2018, a group of HTLV-1 experts and other stakeholders called on WHO to take action on HTLV-1. Given increasing public awareness of HTLV-1 infection in some populations and interest expressed by Member States, an expert consultation was organized to review the global situation of HTLV-1 from a public health perspective. The WHO Global Consultation on HTLV-1 aimed to review existing global epidemiological, clinical and public health evidence to better understand the public health implications of HTLV-1 infection and disease, identify major gaps in knowledge requiring further research and identify possible public health measures to be undertaken.

With the support of the Governments of Australia and Japan, two countries with high HTLV-1 prevalence in limited and specific geographical areas and populations, WHO organized the Global Consultation on 13–15 November 2019, hosted by the National Center for Global Health and Medicine, Tokyo, Japan. More than 50 participants were invited from 20 countries, representing all WHO regions. The participants included experts in basic science, epidemiology, infectious disease clinical practice, public health and the affected communities. Experts were invited from national public health and communicable disease programmes of countries with a high burden and from existing research, technical and policy networks at the national and international levels.

The participants reviewed background papers commissioned by WHO to inform the deliberations, including papers on: (1) HTLV-1 epidemiology, transmission and diagnosis; (2) the health effects of HTLV-1 infection; and (3) HTLV-1 prevention testing, treatment and care interventions and national policies and guidelines. This technical report has been developed from the background papers along with comments from Global Consultation participants and external peer reviewers.



1. GLOBAL AND REGIONAL EPIDEMIOLOGY OF HTLV-1

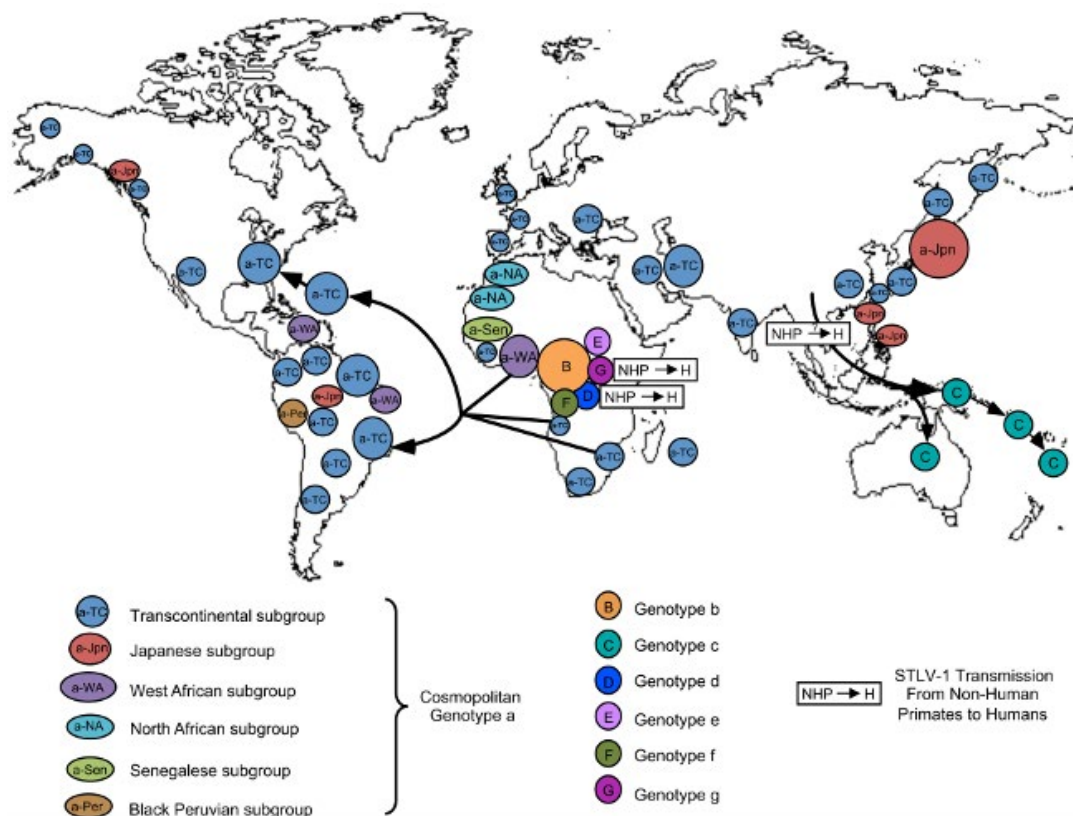
In 1977, a novel disease entity that became known as ATL was described among people in Japan (1). HTLV-1 was characterized in 1980 and identified as the cause of ATL (2). Infection with HTLV-1 was found to be endemic in Kyushu, the southern Japanese island that was also the place of origin of a high proportion of people with ATL.

After HTLV-1 was discovered, research into its distribution and epidemiological determinants was carried out across a number of countries and population groups. This research concluded that, in the countries and populations in which it is found, the distribution of HTLV-1 is quite heterogeneous, often as clusters of endemic foci situated adjacent to or even within low-prevalence populations. The mechanisms by which HTLV-1 remains largely circumscribed to specific geographical locations and population groups is not completely understood but is likely related to a founder effect (3) in which viral infection within a discrete population is sustained over time. The prevalence of HTLV-1 increases with age, and this effect is often more pronounced among women than men.

Seven HTLV-1 subtypes (A to G) have been identified, with characteristic geographical distributions via population migration (4). The “cosmopolitan” subtype A occurs globally, and the remaining subtypes are geographically localized: subtype C in Australia and Melanesia and subtypes B, D, E, F and G in Africa (5).

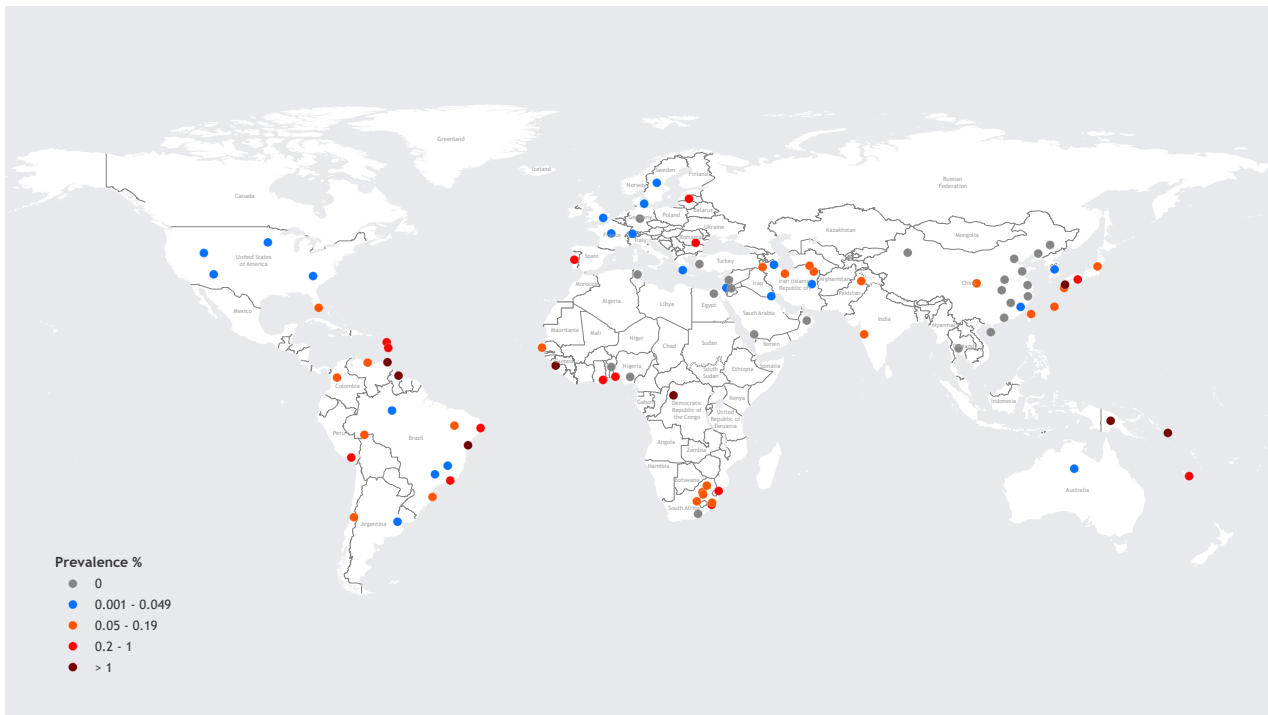
The latest global estimates for the total number of people living with HTLV-1 infection ranged from 5 million to 10 million in 2012 (latest year) (5). The scarcity of reliable data on prevalence from several highly populated countries means that the estimate is largely based on studies from known endemic regions and likely underestimates actual global numbers. Also, where prevalence data exist they may have been obtained at various times in the past, so the global picture is not built up on information of equal recency. Fig. 1–4 provide an overview of the global and regional epidemiology of HTLV-1 prevalence and distribution. The text in the remainder of the section provides a summary of the occurrence of HTLV-1 by WHO Region, along with comprehensive references to the sources of prevalence data.

Fig. 1. Geographical distribution of HTLV-1 subtypes (A–G), 2019



Geographical location and results of HTLV-1 prevalence studies

Fig. 2. Distribution and results of studies examining HTLV-1 seroprevalence among blood donors

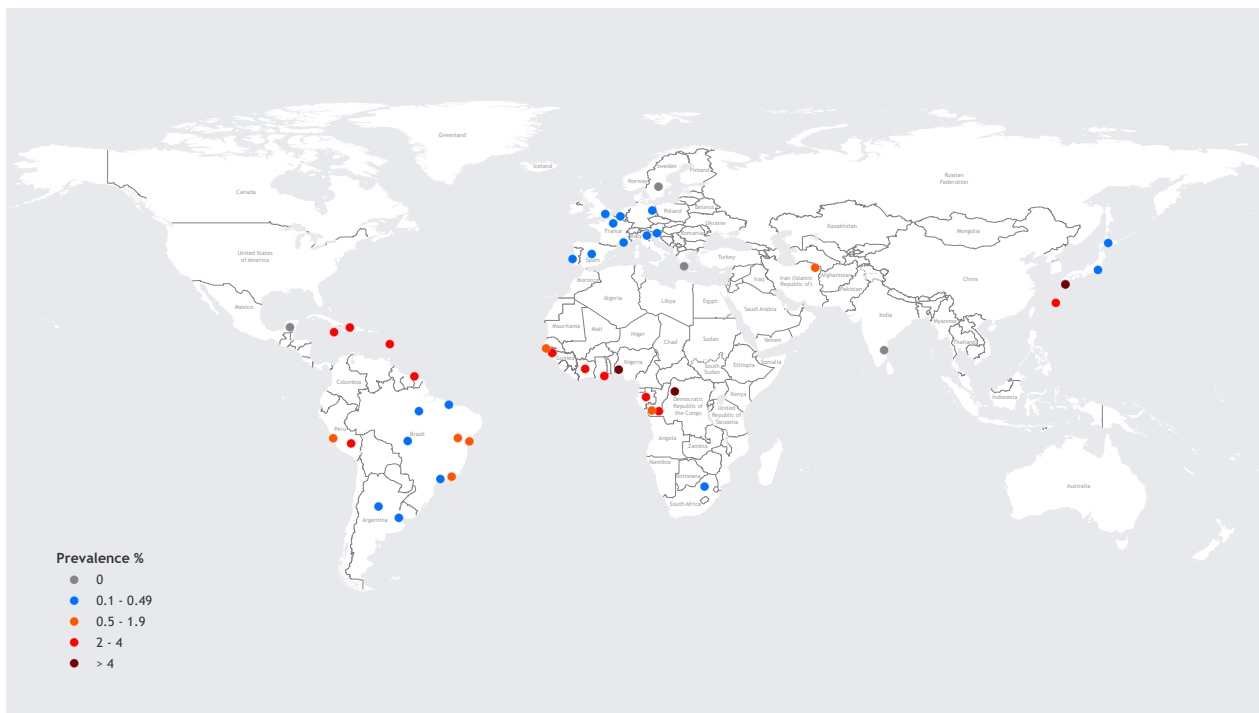


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Source: WHO, 2021

Fig. 3. Distribution and results of studies examining HTLV-1 seroprevalence among pregnant women

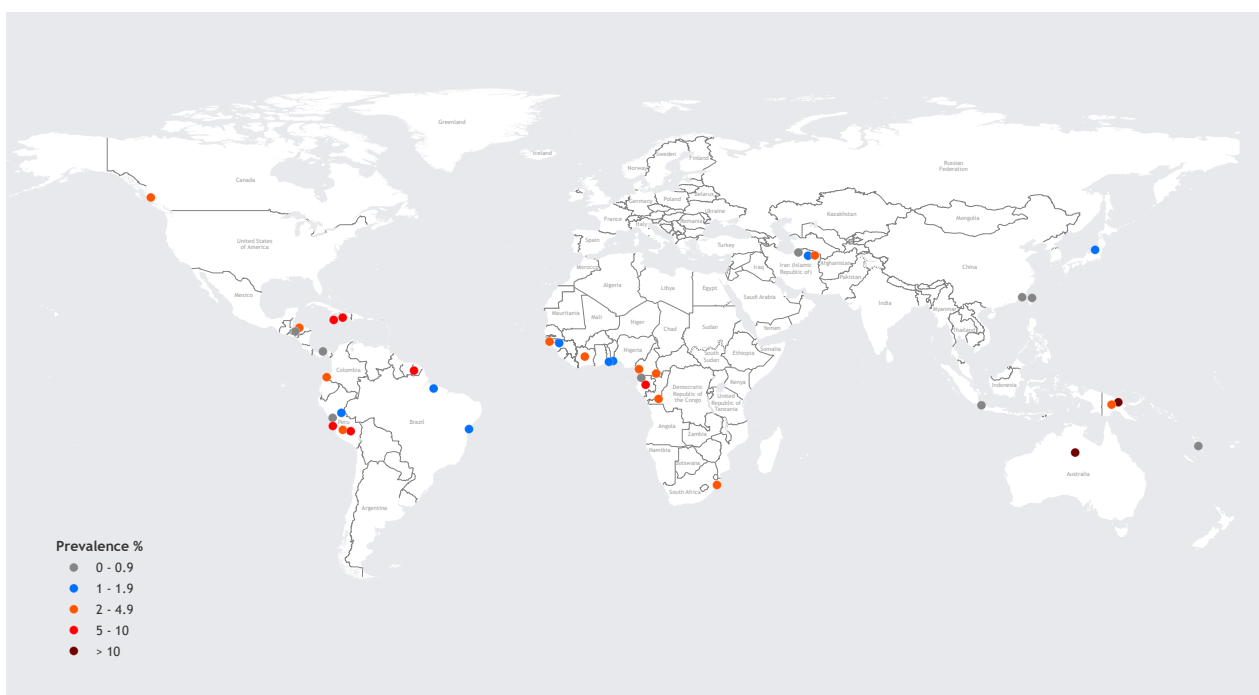


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Source: WHO, 2021

Fig. 4. Distribution and results of studies examining HTLV-1 seroprevalence in general populations



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Source: WHO, 2021

WHO African Region

Although the burden of HTLV-1 infection in many areas in the WHO African Region remains largely unknown, particularly in the north and east, it most likely represents the largest endemic area for HTLV-1 worldwide. Data are most complete for central and western Africa. Several countries are reported as having endemic HTLV-1, with high levels of prevalence in populations and geographical foci found in Cameroon, the Democratic Republic of the Congo, Gabon, Ghana and Guinea-Bissau. The prevalence data are largely derived from studies of blood donors and pregnant women, with a smaller number of community survey prevalence studies, typically focusing on areas and populations with known high prevalence.

In western Africa, prevalence data are available for Benin, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Senegal and Togo. The prevalence ranges from 0% to 1.2% in blood donor studies (6–12), 1.2% to 2.2% in studies of pregnant women (13–17), and 1% to 3.6% in community surveys (9,17–22). Blood donor and antenatal serosurveys with generally less than 1000 individuals tested indicate that HTLV-1 is present in Nigeria (7,10,12,16). Countries in western Africa lacking reliable HTLV-1 prevalence data include Algeria, Burkina-Faso, Cabo Verde, Liberia, Mali, Mauritania, Niger and Sierra Leone.

The prevalence of HTLV-1 in central Africa is similar, with reported ranges from 0.3% to 8.7% in the general population (23–30), and 2.0–4.6% among pregnant women (31–34) in Cameroon, the Democratic Republic of the Congo, Equatorial Guinea and Gabon. In Gabon, the epidemiology of HTLV-1 has been well characterized, with numerous studies reporting high prevalence, especially in the eastern provinces, where it exceeds 11% in the general population (24,26). Community samples from rainforest regions in Cameroon report levels of 1.3% HTLV-1 positivity in Bantu communities and 2.9% HTLV-1 positivity in Bakola Pygmy communities (27,29). The prevalence of HTLV-1 in the Democratic Republic of the Congo was 3.1–4.6% among blood donors, pregnant women and general population samples, with higher levels among sex workers (3.2% and 7.3%) (28,31,33,35). Pregnant women in Congo have comparatively lower levels of HTLV-1 (0.7%), although far fewer prevalence data are available there (34). Countries in central Africa with no published HTLV-1 prevalence data include Angola, Central African Republic, Chad and Sao Tome and Principe.

In southern Africa, HTLV-1 data are limited to studies from South Africa. Prevalence varied, from 0.12% among blood donors to 0.2% among pregnant women and 1.6% among asymptomatic hospital patients (33,36,37).

In general population studies, the prevalence was 2.6% (38). Countries in Southern Africa with no available HTLV-1 prevalence data include Botswana, Eswatini, Lesotho and Namibia.

Available data for eastern Africa, limited to Ethiopia, Mozambique and Rwanda, indicate prevalence lower than elsewhere in Africa, ranging between 0% and 1.8% among blood donor (39), community-based (40) and outpatient surveys (41,42). Reliable data are lacking for many countries, including: Burundi, Comoros, Djibouti, Eritrea, Kenya, Madagascar, Malawi, Mauritius, Seychelles, Somalia, South Sudan, Uganda, United Republic of Tanzania, Zambia and Zimbabwe and the French Department of Mayotte.

WHO Eastern Mediterranean Region

The overall prevalence of HTLV-1 in the WHO Eastern Mediterranean Region is generally low, with zero cases reported in blood donor studies from Egypt, Jordan, Lebanon, Oman, Saudi Arabia and Tunisia (43–50). A prevalence of 0.07% was reported for both outpatient cohorts in Egypt and blood donors in Kuwait (51,52). Recent evidence indicates the presence of HTLV-1 in Pakistan, with 0.2% prevalence among blood donors (53) and cases among residents of the United Kingdom of Pakistani origin (54). Although few data exist for Iraq, there are reports of people with ATL and HTLV-1-positive blood donor cases of Iraqi origin in Israel (55).

In this Region, the epidemiology of HTLV-1 has been most extensively studied in the Islamic Republic of Iran, where infection is described as a significant health problem, especially in the north-eastern provinces of Golestan and Razavi Khorasan, which have reported prevalence among the general population ranging from 0.3% to 2.6% (56–58). The seroprevalence among blood donors ranges from 0.05% to 0.72% (59–64).

No HTLV-1 prevalence data are available for Afghanistan, Bahrain, Djibouti, Iraq, Libya, Morocco, Qatar, Somalia, Sudan, Syria, United Arab Emirates, West Bank and Gaza Strip and Yemen.

WHO European Region

In the WHO European Region, the prevalence of HTLV-1 among blood donors is generally low, ranging from 0 to 0.006% in Denmark, France, Germany, Greece, Israel, Sweden, Switzerland, Turkey and the United Kingdom (55,65–73). Higher prevalence among blood donors has been reported from Latvia, Portugal, Romania and Turkmenistan, with prevalence ranging from 0.2% to 0.64% (74–77). The prevalence in studies of pregnant women ranges from 0% to 0.04% in Belgium, Germany, Greece, Italy, Portugal, Slovenia, Spain, Sweden and the United Kingdom, with a higher prevalence reported in Paris, France (0.1%) (70,78–81).

In this region, population migration plays an important role in the detection of HTLV-1 in individuals originating from, or with ancestry from endemic areas (typically western Africa and the Caribbean), and in some cases, albeit less frequently, in their sexual partners. In France, more than 80% of positive samples in large-scale blood donor and antenatal screening studies are from individuals originating from or with sexual partners from the Caribbean, western Africa and the French Territories of the Americas (68,78). Similarly, in the United Kingdom, the HTLV-1 prevalence among women born in the Caribbean (1.4%) was significantly greater than that among women born in the United Kingdom (0.03%) (82). Romania, as the notable exception, represents the only true endemic country in the European Region for reasons that are still unknown (76). In addition, a significant proportion of the positive cases detected in blood donor studies in Israel are derived from Romanian donors (55).

Countries for which no reliable HTLV-1 prevalence data are available include Albania, Andorra, Austria, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czechia, Finland, Hungary, Iceland, Ireland, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Montenegro, North Macedonia, Norway, Poland, Republic of Moldova, Russian Federation, San Marino, Serbia, Slovakia, Ukraine and the Vatican.

WHO Region of the Americas

The prevalence and distribution of HTLV-1 in the WHO Region of the Americas vary greatly. In North America, HTLV-1 data have largely been derived from blood donor studies indicating low prevalence (83). Positivity is higher among people of African and Asian descent (83–85). Although cases of ATL and HTLV-1-associated nervous system disease are reported, they are typically diagnosed among individuals originating from endemic regions in the Caribbean (85). Recent estimates for first-time blood donors report prevalence ranging from 0.001% for people younger than 30 years to 0.02% in people older than 70 years (83). A general population survey found prevalence of 2.8% among First Nation Canadians in coastal British Columbia (86).

In South America, regions and population groups with high burdens of HTLV-1 infection include the city of Salvador, Brazil (87,88), Tumaco, Colombia (89), the Noir-Marron people in French Guiana (90–93), the Shipibo-Conibo and Quechua peoples in Peru (94–96) and the non-mestizo population of Honduras (97). In these populations, prevalence ranges between 2% and 8%. Overall, the prevalence in blood donor studies ranges between 0.01% and 0.1% in Brazil (98–103), Argentina (104), Colombia (105), the Bolivarian Republic of Venezuela (106), Chile (107) and 0.2% to 1% in Martinique (108,109), Guadeloupe (110) and Peru (111). Higher prevalence in blood donors is reported in Guyana (1.3%) and Trinidad and Tobago (1.5%) (112).

In studies of pregnant women, the prevalence ranged from 0.1% to 2.4% in Argentina (113,114), Brazil (115–122), Peru (123,124) and Martinique (125,126). Positivity in pregnant women was highest in Jamaica (127–129), Haiti (92,130) and French Guiana (90,92,93), ranging from 2% to 5.7%.

In community surveys, prevalence ranged from 0.26% to 6.7 in Brazil, Colombia, French Guiana, Haiti, Honduras, Jamaica, Panama and Peru (86,87,89,91,94–97,124,131–138). The prevalence was highest in Peru (94,124), Haiti (136), Jamaica and French Guiana (91). Mexico has no reported positive cases in surveys of pregnant women, healthy volunteers and other groups (139,140).

Countries in the Region of the Americas for which there are no reliable prevalence data include Antigua and Barbuda, Bahamas, Barbados, Belize, Plurinational State of Bolivia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, United States of America, Uruguay and the Bolivarian Republic of Venezuela.

WHO South-East Asia Region

HTLV-1 prevalence in the WHO South-East Asia Region is low, with no cases detected in blood donor and general population cohorts from Indonesia and Thailand (141–143) and 0.14% among blood donors in India (144). There are case reports of ATL in India (145). However, the availability of reliable data, given the population size, is currently insufficient to accurately describe the epidemiology of HTLV-1 in India. Most countries of the Region have substantial gaps in data on the distribution and burden of infection of HTLV-1.

Countries in which no HTLV-1 prevalence studies have been performed include Bangladesh, Bhutan, Maldives, Myanmar, Nepal, Sri Lanka and Timor-Leste.

WHO Western Pacific Region

HTLV-1 is found in several countries in the WHO Western Pacific Region, with multiple focal areas of high prevalence in Australia, Papua New Guinea, Solomon Islands and south-western Japan.

The prevalence in blood donor studies ranged from 0.007% to 0.6% in Australia (146), China (147–150), Japan (151,152), Republic of Korea (153–155) and the French territory of New Caledonia (156), with higher levels reported in the Solomon Islands (0.7% and 2%) (157,158).

In community surveys, the prevalence ranged from 0.5% to 0.7% in Taiwan, China (159), Vanuatu (160) and Kinmen County, China (161). High prevalence in community samples is reported in Papua New Guinea's Madang province (14%) (162,163) and among Central Australia's indigenous population (31%). In these communities, prevalence exceeding 40% has been reported in older age groups (163,164).

In Japan, the overall prevalence of HTLV-1 among pregnant women was 0.16% and varied significantly by region, with greater positivity in the south-western island of Kyushu (0.6%), intermediate (0.35%) in Otaru and 0% in Asahikawa, Ishikari, Tomakomai, Abashiri and Shin-Hidaka (165). The HTLV-1 prevalence among pregnant women in the Tokyo area was at the lower end of this range (0.08%) (166). The prevalence among blood donors in Japan also varied significantly by geographical location, from 0.06% in eastern Japan to 1.95% in Kyushu (151).

Countries in the Western Pacific Region without reliable prevalence data include Brunei Darussalam, Cambodia, Cook Islands, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, New Zealand, Niue, Palau, Philippines, Samoa, Singapore, Tonga, Tuvalu and Viet Nam.

Issues in information on global HTLV-1 prevalence

Although many reports have been published on the prevalence of HTLV-1 in various populations across the world, many countries still have ill-defined or undetermined HTLV-1 prevalence. Further, as described in Section 3, laboratory methods for screening and diagnosing HTLV-1 infection have been diverse and changed over time, limiting the validity of geographical and time series analysis. There have been relatively few population representative surveys with reasonable sample sizes.

Although testing blood donors provides large numbers, it may not be representative of the population as a whole and indeed favour the selection of individuals at lower risk of bloodborne viral infections compared with antenatal or population-based studies. Testing pregnant women probably provides a more accurate estimate of HTLV-1 prevalence among young and early middle-aged adults but may not be an adequate surrogate for older adults, who typically have higher rates of HTLV-1 than younger cohorts of the same population.

In addition to the gaps in HTLV-1 prevalence data, there is a global lack of systematically collected information on the HTLV-1-related diseases described in detail in Section 4. A standardized approach to monitoring both HTLV-1 and its complications will provide a strengthened basis for public health decision-making.

2. HTLV-1 TRANSMISSION

HTLV-1 is understood to be transmitted primarily through direct contact between infected and uninfected target cells, via cell-containing bodily fluids including blood, breast-milk and semen. Although an individual with HTLV-1 infection has very little cell-free virus present, transmission of HTLV-1 in this manner is considered possible (168). Several studies have examined the transmission of HTLV-1 or risk factors associated with HTLV-1 transmission with no prevention intervention, using various epidemiological designs. Two recent systematic reviews have been published on mother-to-child transmission of HTLV-1 (169,170), with the 2019 review by Rosadas & Taylor (170) comprehensively covering this topic.

Mother-to-child transmission

The first studies reporting the mother-to-child transmission of HTLV-1 were published in the 1980s, with multiple studies since reporting estimated transmission probabilities (Table 1). These studies have used a variety of methods to recruit and follow up participants, with relatively few being prospective investigations of outcomes among children from the time of delivery. The estimated transmission rates have ranged from 3.9% to 27.0%, with 20% being the consensus figure following the consultation.

TABLE 1. MOTHER-TO-CHILD HTLV-1 TRANSMISSION RATE

Medical eligibility criteria category summary table for contraception and HIV			
Study	Country of research	Study period	HTLV-1 transmission (%)
Paiva et al. (171)	Brazil	2006–2016	14.2
Ureta-Vidal et al. (172)	French Guiana	1991–1993	9.7
Nyambi et al. (173)	Gabon	1987–1991	17.5
Del Mistro et al. (15)	Gambia	Not specified	22.0
Van Tienen et al. (174)	Guinea-Bissau	2004	25.0
Hamedi et al. (175)	Islamic Republic of Iran	Not specified	16.6
Biggar et al. (176)	Jamaica	1989–1990	17.0
Li et al. (177)	Jamaica	Not specified	22.0
Hisada et al. (178)	Jamaica	1989–1990	18.0
Wiktor et al. (179)	Jamaica	1989–1992	18.0
Wiktor et al. (180)	Jamaica	1983–1985	23.0
Kashiwagi et al. (181)	Japan	1986–1991	12.8
	Japan	1995–1999	3.2
Takahashi et al. (182)	Japan	1985–1990	8.5
Tsuji et al. (183)	Japan	Not specified	21.0
Kusuhara et al. (184)	Japan	1968–1983	15.4
Ando et al. (185)	Japan	1983–1985	46.0
Hino et al. (186)	Japan	Not specified	17.0
Monplaisir et al. (187)	Martinique	Not specified	27.0
Gotuzzo et al. (188)	Peru	1989–2003	19.0

Source: adapted from Rosadas & Taylor (170).

The mechanism of transmission has been investigated through testing various types of specimens. HTLV-1 antigen has been detected in breast-milk (189), cord blood and peripheral blood (190). HTLV-1 proviral DNA has been found in breast-milk (177) and placental tissue (191). Other studies have looked for proviral DNA in cord blood but not found it (173,183,186). The totality of evidence suggests that mother-to-child HTLV-1 transmission occurs primarily through breastfeeding, with limited evidence of intrauterine transmission or transmission during delivery (192,193). This conclusion is based on the lack of detection of proviral DNA in cord blood and the small number of transmission events recorded in infants who were reliably reported to be exclusively formula fed. Intrauterine and intrapartum exposure may present a non-negligible risk of HTLV-1 transmission, but this contribution appears limited compared with breastfeeding (169,193).

Several studies have analysed risk factors for mother-to-child HTLV-1 transmission. Breastfeeding for six months or less was associated with a low rate of transmission, while breastfeeding for more than six months greatly increased the risk, with transmission rates exceeding 30% reported in long-term breastfeeding (179,180,182,194–197).

Studies that examined the relationship between mother-to-child HTLV-1 transmission 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 (171,172,174,176–178,198). Maternal antibody titre has also been found to be a risk factor for HTLV-1 transmission (172,176,178,179,198).

Sexual transmission

Sexual transmission has been investigated in various ways. Some studies have reported seroprevalence among populations that might be considered to be at higher risk of sexually transmitted infections and investigated sexual risk factors associated with HTLV-1 seropositivity. Another group of studies reported on couples or sexual partners involving HTLV-1-seropositive individuals to determine the transmission risk and co-factors associated with transmission. Most studies were cross-sectional and were predominantly conducted in South America and the Caribbean.

HTLV-1 has been detected in cervical secretions (193,199) and seminal fluid (167). Cross-sectional serosurveys (Table 2) have investigated the prevalence of HTLV-1 among populations often considered to be at higher risk of sexually transmitted infections, including sex workers (124,168,200,201) and men who have sex with men (124). Another group recruited into surveys comprises the sexual partners of people with HTLV-1 infection (202–205). Few studies included comparisons with prevalence in corresponding populations that would be considered to be at lower risk of sexually transmitted infections. In the absence of such comparisons, studies cannot definitively conclude that a specific population has an elevated prevalence of HTLV-1 infection. Two reports from the 1990s of female sex workers in Peru strongly suggested that this population was at higher risk, with prevalence of 21.8% and 13.7%, whereas the surveys of sex workers from Brazil and Japan showed much lower figures. Most strikingly, elevated prevalence was reported among the sexual partners of people with HTLV-1 infection, especially the female partners of men with HTLV-1.

TABLE 2. 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 et al. (201)	Brazil	1987–1990	Female sex worker Male clients	2.8 2.0
Paiva et al. (206)	Brazil	2013–2015	Partners of people with HTLV-1	Men: 55.7 Women: 65.2
Diaz et al. (207)	Cuba	Not specified	Sexual contacts of blood donors with HTLV-1	Men: 9 Women: 53
Murphy et al. (208)	Jamaica	1986	Sexually transmitted infection clinic attenders	5.7
Nakashima et al. (168)	Japan		Female sex workers	5.1
			Men attending a sexually transmitted infection clinic	2.8
			Women attending a sexually transmitted infection clinic	5.7
			Male blood donors	1.4
			Female blood donors	2.2
Wignall et al. (200)	Peru	1987–1988	Female sex workers	21.8
			Pregnant women	3.1
Zurita et al. (124)	Peru	Not specified	Female sex workers	13.7
			Men who have sex with men	6.2
Alarcon et al. (209)	Peru	1996–1997	Pregnant women	1.7
Blas et al. (94)	Peru	2010	Indigenous women	5.9
Sullivan et al. (204)	USA	1989–1991	Sexual contacts of HTLV-1 positive donors	28.1
Kaplan et al. (205)	USA	1990–1991	Sexual contacts of blood donors with HTLV-1	Men: 20.2 Women: 37.5

These cross-sectional studies have found several factors related to sexual activity associated with higher HTLV-1 seropositivity, including a history of unprotected sex (205), earlier age at first sex (209) and a higher number of partners (208). Associations have also been reported with the presence or history of other sexually transmitted infections, especially those causing genital ulcers, including syphilis and herpes simplex virus (124,168,200,205,208). One study from the French Territories of the Americas found a positive association between a history of having had a sexually transmitted infection and HTLV-1 transmission (210). Among sex workers in Peru, sex during menses and vaginal douching pre- and post-intercourse were identified as risk factors (124). Some studies found no association with the number of sexual partners (124,207). Among indigenous Peruvian women, the sexual behaviour of male sexual partners was identified as a risk factor (94).

Like similar studies that have been conducted to assess associations between HIV and other sexually transmitted infections since the 1980s, it is difficult, if not impossible, to distinguish the hypothesis that other sexually transmitted infections are a co-factor for HTLV-1 transmission from the alternative explanation that both HTLV-1 and other sexually transmitted infections are driven by sexual behaviour as the common causal factor.

The observed association in most studies of HTLV-1 seropositivity and age is consistent with sexual transmission (94,124,200,203,208,209,211) but does not provide direct evidence. It might be expected that, if sexual transmission causes a substantial proportion of infections, the 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.

Few prospective longitudinal studies have assessed the transmission risk among couples. Those that have been conducted are in high-endemicity regions of Japan (203,211) and blood donor populations in the United States of America (202). Transmission from men to women has been observed to occur more efficiently than from women to men in these longitudinal studies as well as in some cross-sectional partner studies that found male negativity to be more common than female negativity in serodiscordant couples (203,205,207,211). Longer duration of a couple's relationship (203,205) and older age of a seropositive male partner have also been associated with a higher risk of transmission (203). Higher proviral load was a risk factor for transmission (201–203,205) in both cross-sectional and longitudinal studies.

HTLV-1 transmission through blood, blood products and tissue transplantation

The first study reporting transmission of HTLV-1 from blood transfusion appeared in 1984 (212). Evidence of transmission via blood products emerged through studies that found elevated HTLV-1 prevalence in populations requiring blood products because of neonatal complications (2%), thalassaemia (6%) and sickle cell anaemia (4%) and people on haemodialysis (20%) compared with populations receiving either non-cellular components or controls with no history of blood transfusion (213–215). Several studies have reported rates of transmission from transfusion of blood from a donor with HTLV-1 (Table 3) and provided estimates in the range of 28–63%. The initial studies determined

that transmission only occurred through blood products containing cellular components (216–218). Most of the literature on HTLV-1 transmission via organ transplant is in the form of case reports related to a donor with HTLV-1 and one or more recipients (219–225).

There has been one longitudinal study of HTLV-1 transmission following tissue transplant, involving 99 kidney transplants in Japan between 2000 and 2014 (224). Of the eight HTLV-1-negative individuals who received HTLV-1-positive kidney donations, seven (87%) acquired the infection.

Shorter duration of storage of blood has been associated with increased risk of transmission, likely because of the reduced lymphocyte viability in older blood units (216–218).

Injecting drug use

Several analyses have shown that injecting drug use is a risk factor for HTLV-1 infection (226–229). Several studies have described the HTLV-1 prevalence among people who inject drugs (228,230–234).

Other routes of transmission

There have been reports of higher than expected rates of HTLV-1 infection among people tested after a member of the same household is diagnosed with HTLV-1 but no specific evidence for routes of transmission other than those described above (235). Religious practices involving self-flagellation have been associated with clusters of HTLV-1 in Australia and the United Kingdom (54,236).

TABLE 3. TRANSMISSION OF HTLV-1 THROUGH BLOOD OR BLOOD PRODUCTS FROM POSITIVE DONORS

Study	Country of research	Study period	Blood product	HTLV-1 prevalence (%)
Okochi et al. (212)	Japan	1981–1983	Whole blood; packed red cells; platelet concentrates	63
			Fresh frozen plasma	0
Manns et al. (217)	Jamaica	1987–1988	Cellular	44
			Non-cellular	0
Kleinman et al. (216)	USA	1983–1989	Platelets	40
			Red cells	28
Donegan et al. (218)	USA	1984–1985	Platelets	86
			Red cells	30
			Non-cellular	0

3. TESTING FOR HTLV-1 SCREENING AND DIAGNOSIS

Assays used to detect HTLV-1 infection

Over the past three decades, a number of methods have been used to detect HTLV-1 infection. Under current testing strategies, detection generally requires anti-HTLV reactive test results in two or even three assays. Most of the assays used to detect HTLV-1 are immunoassays and rely on detecting anti-HTLV-1 antibodies. The enzyme immunoassay (EIA) that uses recombinant proteins as the antigen is most commonly used for epidemiological surveys and blood and transplant screening because of its simplicity and potential for high throughput. Other less commonly used immunoassays are gelatin particle agglutination (PA) and HTLV-infected cell culture–based indirect immunofluorescence assays (IFA) that use viral lysate as the antigen. However, the ultimate ascertainment of HTLV-1 positivity often requires a confirmatory test from another group of tests that detect antibody responses to specific HTLV-1 antigens.

The main confirmatory assays are the western blot, radioimmunoprecipitation assay (RIA) and line immunoassay. There are also several qualitative or quantitative molecular-based methods, primarily via detection of HTLV-1 nucleic acid sequences by polymerase chain reaction (PCR). Since the introduction of nucleic acid testing (NAT) technology, the sensitivity of western blot as a gold standard has been increasingly questioned. The lack of a standard set of criteria for western blot positivity has further complicated the diagnosis of HTLV-1.

Specimen types used for testing are mostly sera and plasma for the immunoassays and peripheral blood mononuclear cells for the PCRs. A few reports tested assays on urine, cerebrospinal fluid, breast-milk and saliva. Because PCR requires DNA extracted from either whole blood or peripheral blood mononuclear cells, it may require recalling the patient if the appropriate specimen was not obtained at the initial testing.

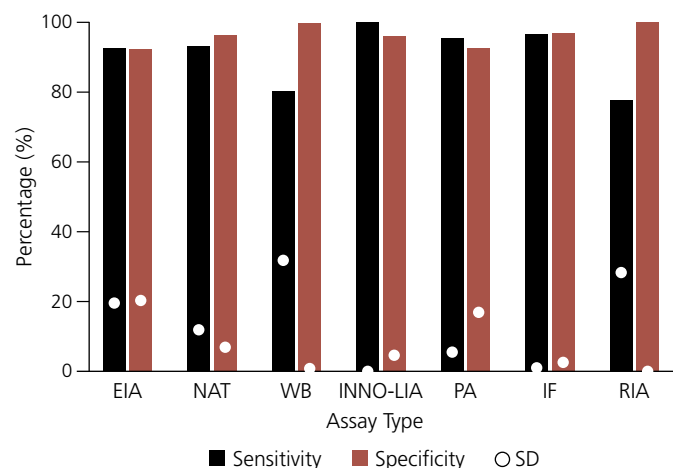
Sensitivity and specificity of HTLV-1 serology assays

Sixty-five articles, using a range of methods and sample sizes, have reported on the performance of the various HTLV-1 assays (Fig. 5) (237–301).

Analysis of the sensitivity data available in the literature indicated that the line immunoassay (INNO-LIA HTLVI/II SCORE, Fujirebio Europe, Belgium) had the highest reported sensitivity (100%), followed by IFA (96.9%), PA (95.6%), NAT (93.1%) and EIA (92.5%). The sensitivity was much lower for western blot (80.2%) and RIA (77.8%).

The order of specificity of the assays from highest to lowest was RIA (100%), western blot (99.7%), IFA (96.9%), NAT (96.2%), line immunoassay (96.1%), PA (92.5%) and EIA (92.2%). The literature shows that there has been substantial evolution in the recombinant proteins and antigens targeted for detection of HTLV-1 and their method of isolation, which has resulted in improved specificity. For example, the more recently developed EIAs have added recombinant proteins to improve assay specificity (270), although it is still lower than for the other assays. Consequently, current practice has maintained the requirement for multiple assays to be performed to confirm HTLV positivity, usually two EIAs and then a western blot or line immunoassay or NAT.

Fig. 5. Sensitivity and specificity results for the commonly used HTLV-1 assays



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Jacob F et al. (270)

Metanalysis of sensitivity and specificity data extracted from 165 results published in 65 articles. The bar graphs indicate the mean value and standard deviation calculated for the sensitivity (black) and specificity (grey) for each assay type. EIA: enzyme immunoassay; PCR: polymerase chain reaction; WB: western blot; INNO-LIA: line immunoassay; PA: particle agglutination; IF: immunofluorescence; and RIA: radioimmunoprecipitation assay.

Issues in HTLV-1 diagnosis

Seroconversion and indeterminate test results

The time to seroconvert to HTLV-1 can be protracted and has been reported to be as long as 65 days, although delayed seroconversion for several years has been reported (302). Infants have been reported to seroconvert within 1–3 years of age (173,303). Nevertheless, these time periods were determined with older assays and whether the newer assays are more sensitive and can detect seroconversion earlier has not yet been determined. There have also been reports of delayed or partial seroconversion among immunocompromised people (304,305).

Western blot positivity requires reactivity to multiple HTLV antigens, which potentially results in a large number of specimens with indeterminate results because only a subset of viral proteins is detected. The proportion of indeterminate results reported in the literature ranges from 0% to as high as 68% (251,306). Follow-up of people with western blot–indeterminate results indicated that, for some people, positive (251,307–309) or negative (310,311) status will be confirmed with a follow-up sample, whereas in others, the indeterminate status can be sustained for a long time (309).

Several studies that have investigated western blot–indeterminate specimens, later confirmed by other methods to be HTLV negative, have identified several factors associated with false reactivity, including: (1) cross-reactivity with other HTLV types 2–4 (312,313); (2) cross-reactivity with *Plasmodium falciparum*, especially the gp21 protein (314–316); and (3) non-specific cross-reactivity with other pathogens or self-proteins (317). These factors are all highly prevalent outside high-income countries and may account for the high proportion of indeterminate test results in such settings (251,306).

For western blot–indeterminate results among people found to be positive for HTLV-1 DNA, an association has been shown between low proviral loads and mutations, including large deletions, that prevent viral protein production (318).

Proposed changes to testing strategies for HTLV-1 infection

National guidelines for testing exist and are quite varied (319,320). Part of the reason for diversity in testing algorithms is that few assays have been approved by the United States Food and Drug Administration (FDA). The MP Diagnostics HTLV Blot 2.4 (MP Biomedicals, Singapore) is the most commonly used FDA-approved assay, but as yet no NAT assay has been approved.

Several studies have proposed transitioning from using western blot for confirmation in routine testing to using line immunoassay or NAT (321), which also can be used to generate proviral load results, a potential prognostic marker for HTLV disease progression (282,322–324). As noted above, a limitation with NAT is the need to acquire and store cellular samples.

Testing strategies might need to differ according to context. For example, in countries with low endemicity, a test of lower sensitivity might be acceptable for organ donations if rapid turnaround time is the main goal. Multiple assays add significant cost (discussed further below) and lead to losing donor tissue and organs if HTLV test results are delayed. Nevertheless, for people with suspected HTLV-associated disease, additional confirmatory testing such as proviral load is essential.

Cost as a consideration in testing algorithm design

An important consideration for deciding on the best testing algorithm is the cost of the screening assays, especially when applied to screening large populations in areas with low prevalence. There is ongoing debate concerning the cost-benefit of blood donor screening for HTLV (325,326). Measures have been taken to improve the cost-effectiveness and include screening only new donors (Sweden) and pooling (Scotland and Wales) (326). Sensitivity comparisons have suggested that pooling up to five specimens is acceptable and ensures the feasibility of screening in areas with low prevalence (327). Saudi Arabia found no case of HTLV-1 among blood donors over 10 years and therefore proposed replacing universal HTLV testing with universal leukodepletion (328).

4. HEALTH EFFECTS OF HTLV-1 INFECTION

Most people with HTLV-1 infection do not develop conditions that can be directly linked to the infection. However, severe and potentially fatal complications can develop. Clinical entities corresponding to the serious diseases that became known as ATL and HAM/TSP had been recognized before HTLV-1 was discovered. Their strong association with HTLV-1 infection, following the discovery of the virus, led to them being defined as uniquely caused by HTLV-1. Subsequent clinical research sought to examine associations between HTLV-1 infection and several other clinical conditions. Subcategories of two other diseases, HTLV-1-associated uveitis (HAU) and infective dermatitis, have been added to the list of conditions uniquely related to HTLV-1, in the sense that the presence of HTLV-1 infection is a necessary diagnostic criterion. A recent surge of interest in the preventing and treating HTLV-1 infection and its complications has highlighted the need for robust information on the health effects of HTLV-1 infection (329).

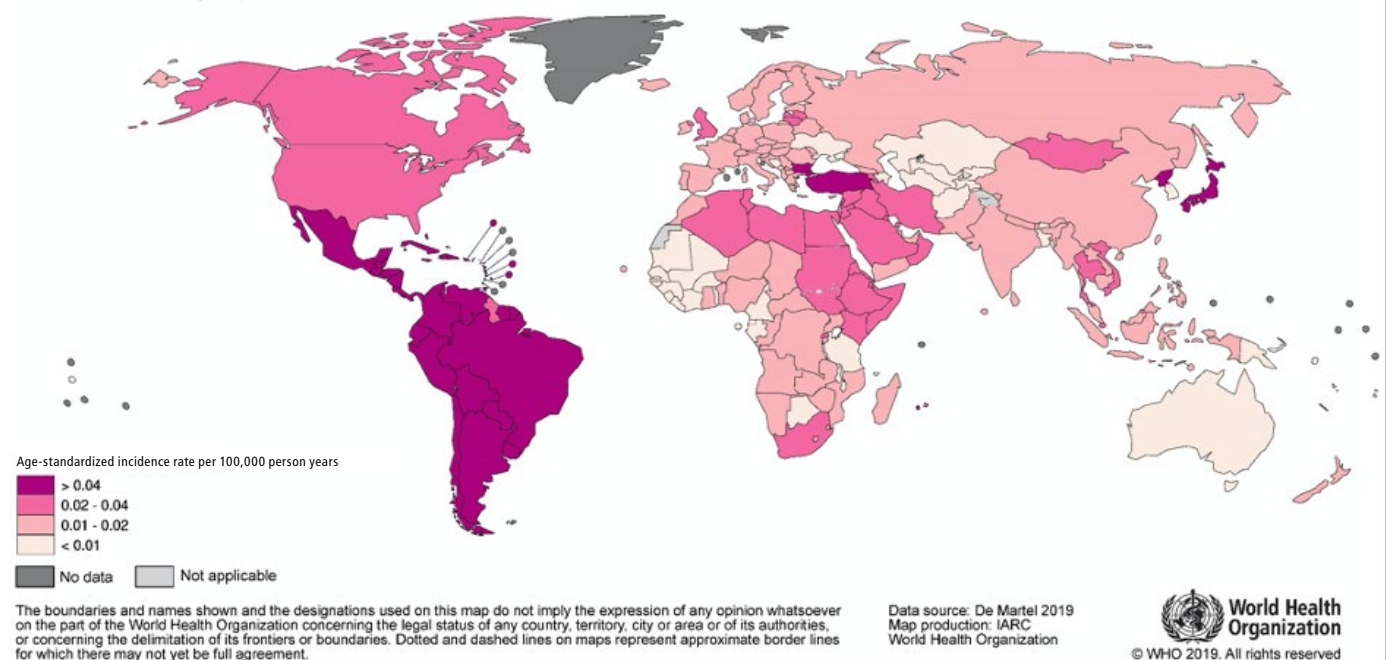
Adult T-cell Leukemia/Lymphoma

In 1979, the virus that became known as HTLV-1 was first isolated from a person with a cutaneous T-cell malignancy in the United States of America (2). Similarities with the clinical presentation and abnormal T-cell morphology led to the suggestion that HTLV-1 may be involved in the pathogenesis of ATL, which had been described in Japan a few years before (1). The causal association was soon established (330). In 1996, IARC concluded that HTLV-1 is carcinogenic to humans (331).

ATL has four clinical subtypes: acute, lymphomatous, chronic and smouldering, with the more aggressive subtypes (acute and lymphomatous) representing the majority of cases (332–334). Clinical presentation depends on the subtype. People may present with lymphadenopathy, hepatosplenomegaly, hypercalcaemia and involvement of the skin, lung, bones and other organs. Opportunistic infections may occur through immunosuppression related to dysfunctional HTLV-1-infected T cells. The median survival for people diagnosed with acute and lymphomatous ATL is less than 12 months (333,334).

Fig. 6. Country-specific age-standardized incidence rates of cancer attributable to HTLV-1, 2018

Human T-cell lymphomatic virus (n=3600)*



Adapted from de Martel et al. (335), GLOBOCAN 2019 (<http://gco.iarc.fr>).

* The estimated total number of cases of ATL in 2018, globally

Global overview of ATL

In 2018, IARC estimated that there were 3600 cases of ATL worldwide (335). This is likely to be a very conservative estimate, since ATL is underdiagnosed (and underreported) in many parts of the world. The age-standardized incidence varied substantially by country and region (Fig. 6), with the highest incidence and total number of reported cases in Japan. The incidence of ATL increased markedly with age (Fig. 7). Cases of ATL were divided roughly equally by gender (1900 men and 1700 women) (Fig. 7).

Incidence and risk of ATL among people with HTLV-1 infection

In cohort studies in Japan, the incidence of ATL among people with HTLV-1 infection ranged from 46 to 710 per 100 000 person-years (336–341), with higher incidence in HTLV-1 endemic regions (Fig. 8). In the studies that disaggregated by gender, the incidence was higher among men than women, in contrast to the global IARC estimates (Fig. 8). These results are consistent with a recent national population-based surveillance study, which found that the incidence of ATL among people with HTLV-1 was substantially higher in the known endemic region of Okinawa (218 per 100 000 population; 95% confidence interval (CI) 130–700) than in the rest of Japan (83 per 100 000 population; 95% CI 79–88) (342).

Estimates of the incidence of ATL among people with HTLV-1 outside Japan are sparse. In one clinic-based United Kingdom cohort including 92 people with asymptomatic HTLV-1 infection and 61 with HTLV-1-associated inflammatory disease, four cases of ATL were reported, for an incidence of aggressive ATL of 540 per 100 000 person-years (95% CI 83–1190) (343). Among blood donors screened in Israel, three cases of ATL were reported among 90 people diagnosed with HTLV-1 infection, for an incidence of 370 per 100 000 person (95% CI 130–1080) (344).

The lifetime risk of ATL among people with HTLV-1 infection is about 5%. In Japan, the estimated cumulative lifetime risk of ATL among people with HTLV-1 was estimated to be 4.8–5.2% (338,342). The risk was higher among men (6.6–7.3%) (342,345–347) than women (2.1–4.2%) (342,345–347). In Jamaica, the cumulative lifetime risk of ATL for people acquiring HTLV-1 infection before age 20 years was similar in men (4.0%) and women (4.2%) (348).

Two Japanese cohort studies of people with HTLV-1 infection reported crude mortality from ATL as 77 and 125 per 100 000, respectively (337,349). In studies with results disaggregated by gender, crude mortality was higher among men (68–191 per 100 000 person-years) than women (36–52 per 100 000 person years) (350).

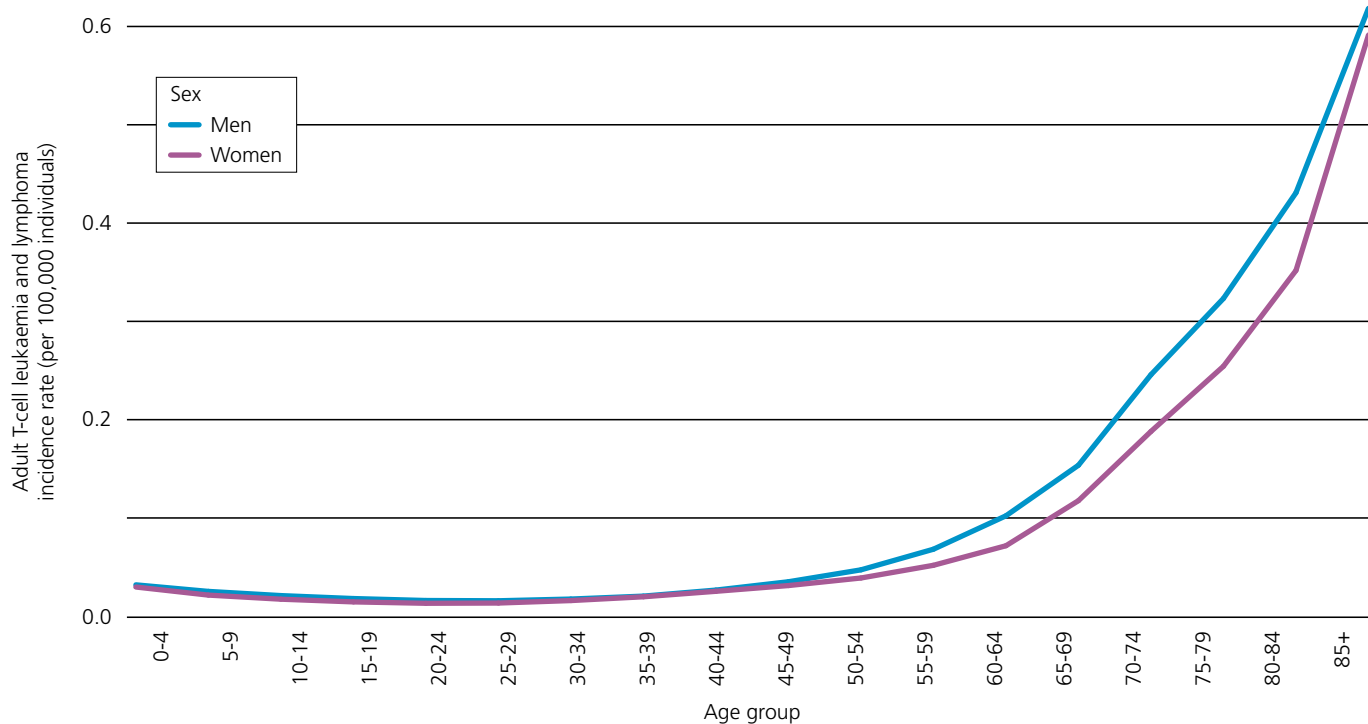
Factors associated with the development of ATL

In cohort and population-based surveillance studies, ATL incidence was associated with older age (338,346,347,351), male sex (345–347,351) and HTLV-1 proviral load (338,343). There was also evidence for an association with family history of ATL (338) and cigarette smoking (339). In cohort studies that examined HTLV-1 proviral load as a predictor of ATL, no cases of ATL were diagnosed among people with a baseline HTLV-1 proviral load of less than 40 copies per 1000 peripheral blood mononuclear cells (338,343).

Issues related to the epidemiology of ATL

A variety of risk factors and determinants for developing ATL among people with HTLV-1 infection have been reported. Much of this evidence is from Japan, so it may not be generalizable to other populations. Cohort studies provide evidence of associations with male sex, older age and higher HTLV-1 proviral load (≥ 40 copies per 1000 peripheral blood mononuclear cells). Population-based modelling studies suggest that longer duration of infection (> 20 years) and younger age at acquisition (in infancy or childhood) increases the risk of ATL. However, there is no definitive evidence that the route of transmission is associated with development of ATL. Cross-sectional and case-control studies have indicated other factors that may be associated with ATL, including HLA type, level of soluble interleukin-2 receptor, HTLV-1 antibody titre and *Strongyloides stercoralis* coinfection (352–356). Further research is required to accurately define the burden of disease and factors associated with the development of ATL.

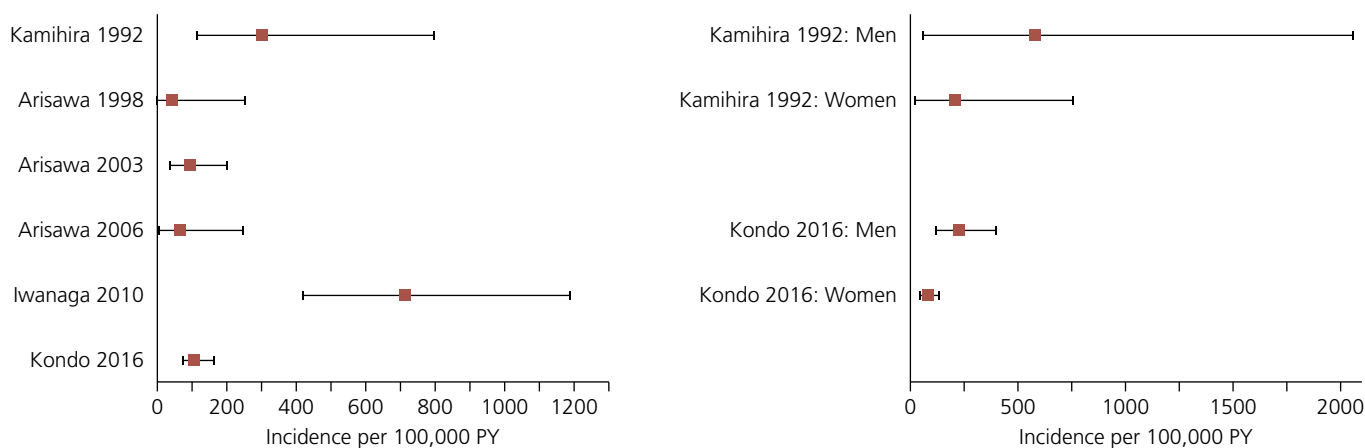
Fig. 7. Age and sex distribution of estimated age-standardized incidence rates of ATL worldwide, 2018



Adapted from de Martel et al. (335), GLOBOCAN 2018; <http://gco.iarc.fr>.

Fig. 8. Incidence of ATL among people with HTLV-1 infection in cohort studies in Japan

Panel A: Incidence of ATL among people with HTLV-1, overall. Panel B: Incidence of ATL among people with HTLV-1, disaggregated by gender. Ref: 336-341.



HTLV-1-associated myelopathy or tropical spastic paraparesis

In 1985, it was proposed that HTLV-1 was associated with a chronic progressive myelopathy of previously unknown causation referred to as TSP (357–359). A similar clinical entity was described in Japan in 1986 and was labelled HAM (360). After it was established that these were the same conditions, the disease was referred to as HAM/TSP, and WHO suggested the original diagnostic criteria in 1988 (361).

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 (361,362). Clinical findings can include muscle weakness, hyperreflexia and clonus in the lower limbs, along with extensor plantar responsive and a spastic gait. Cerebrospinal fluid (CSF) examination may show a mild pleocytosis, a mild to moderate increase in protein concentration and positive antibody and/or molecular tests for HTLV-1.

Incidence and risk of HAM/TSP among people with HTLV-1 infection

Three prospective cohort studies including 361 people with asymptomatic HTLV-1 infection documented 10 incident cases of HAM/TSP (total 2467 person-years of follow-up) (363–365). In the two larger cohorts of people with HTLV-1, HAM/TSP incidence was 530 per 100 000 person-years (95% CI 26–1090) in Brazil ($n = 181$) (365) and 184 per 100,000 person-years (95% CI 22–666) in the United States of America ($n = 139$) (364). Population-based surveillance studies reported lower incidence (366,367).

Estimates of the lifetime risk of HAM/TSP among people with HTLV-1 infection have ranged from 0.18% to 1.8%. In Jamaica and Trinidad, the cumulative lifetime risk of HAM/TSP among people with HTLV-1 was 1.3% among men and 1.8% among women (366). 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 women (0.26%) and a reduced risk with older age at HTLV-1 infection (367). Since the study in Japan involved passive case findings, these risk estimates are likely to be substantially lower than the true burden of disease.

Factors associated with development, progression and mortality

Development of HAM/TSP has been associated with higher HTLV-1 proviral load (364) and female sex (366,367). Orland et al. (364) demonstrated that HTLV-1 proviral load was significantly higher among people with HAM/TSP (29 per 1000 peripheral blood mononuclear cells) than those with asymptomatic HTLV-1 infection (2.8 per 1000 peripheral blood mononuclear cells). In population-based surveillance studies, the incidence and cumulative lifetime risk of HAM/TSP was higher among women than men (366,367).

Age (368), HTLV-1 proviral load (368) and markers of CSF inflammation (369,370) have been associated with progression of HAM/TSP. In two cohort studies evaluating factors associated with disease progression, the larger Martinique cohort found that higher HTLV-1 proviral load (>100 per 1000 peripheral blood mononuclear cells) was associated with shorter time from HAM/TSP onset to being wheelchair-dependent (368), and the second smaller United Kingdom cohort found no association (371). Markers of CSF inflammation, namely CXCL10 and neopterin, may also be useful for documenting disease activity, risk of nervous system disease progression and, potentially, response to treatment (369,370).

The direct impact of HAM/TSP on mortality is uncertain, with a lack of published data. Of 22 deaths in the Martinique cohort, the authors attributed 19 (86%) to HAM/TSP (368). The age of death among those who died related to HAM/TSP (mean age 63 years) did not differ from those who died from other causes (mean age 69 years). In a United Kingdom cohort (371), of five deaths (mortality rate 2.4 per 100 person-years), two were attributed to HAM/TSP and one was related to ATL. The median time from onset of HAM/TSP to death was 9.7 years (range 2.4–20.3).

Issues related to the epidemiology of HAM/TSP

Among people with HTLV-1 infection, the lifetime risk of HAM/TSP appears to be about 2%. Inconsistency and wide confidence intervals highlight the uncertainty of the reported incidence estimates, and different methods of case finding influence the results. In addition, underdiagnosis of HAM/TSP was likely in many settings.

Similar to ATL, HTLV-1 proviral load appears to be important in disease onset and progression. In addition to the evidence from the cohort studies included in this review, case–control studies have provided additional

supportive data, highlighting higher HTLV-1 proviral load among people with HAM/TSP compared with those with asymptomatic infection and higher proviral load among those with clinically defined “rapid” versus “slow” progression (372–377). The risk of HAM/TSP may also be moderated by the degree of HTLV-1-specific cytotoxic T-cell response (378) and HLA type (377,379), both of which may impact HTLV-1 proviral load.

HAM/TSP has been associated with substantial morbidity and disability. Further, nervous system disease (which does not fulfil the criteria for HAM) may be underrecognized among people with HTLV-1 infection, with a spectrum of (predominantly motor) abnormalities among people with HTLV-1 infection but without overt myelopathy (380,381). The mental health impact of HAM/TSP and HTLV-1 infection also requires evaluation. Unlike ATL, it is uncertain whether HAM/TSP directly contributes to mortality, since there is insufficient evidence to robustly assess the effect of HAM/TSP on life expectancy.

Additional work needs to be done to evaluate the epidemiology, burden of disease and factors associated with development and progression of HAM/TSP.

HTLV-1 associated Uveitis

HAU was the third clinical condition to be associated with HTLV-1. In 1989, case reports from Kyushu, in southern Japan, an HTLV-1 endemic region, suggested possible associations between HTLV-1 infection and a variety of ocular manifestations (382). Epidemiological, clinical and laboratory evidence for the causal role of HTLV-1 in HAU followed (383–388). The pathogenesis of HAU is thought to be related to lymphocyte-driven inflammation mediated by infected CD4⁺ T cells (386,387).

There is insufficient evidence to comment on the incidence of HAU among people with HTLV-1 infection or on predictors of disease development. A single case of HAU was documented in a United Kingdom cohort of 20 adults with HTLV-1 infection (mean follow-up 2.25 years) (363). HAU can occur as an isolated disorder or in association with other HTLV-1-related diseases. ATL and HAM/TSP have been reported both before and after the diagnosis of HAU (389–391). In the HAM-net cohort in Japan ($n = 434$), the incidence of HAU among people with HAM/TSP was 650 (95% CI 330–1270) per 100 000 person-years (392). Similar to other disease manifestations, HTLV-1 proviral load may be higher among those with HAU than those with asymptomatic HTLV-1 infection (393).

Issues related to the epidemiology of HAU

Although robust epidemiological data are limited, HAU appears to be uncommon. In cross-sectional studies, the prevalence of HAU among people with uveitis in Japan was 0.8–1.1% (394,395). Cross-sectional and retrospective cohort studies have documented the clinical features and visual outcomes of people diagnosed with HAU in Japan but have not systematically addressed the factors associated with disease development (390,391,396). Women may be more likely to be diagnosed with HAU than men, with cases documented among adults and children (age at diagnosis, range 7–83 years). HAU has predominantly been classified as intermediate uveitis, with unilateral or bilateral involvement. Blurred vision and floaters were common symptoms reported at initial presentation. Many people had a single episode of mild to moderate uveitis with resolution in weeks. Although prognosis was generally favourable, recurrence and vision-threatening complications were reported, including retinohoroidal degeneration, glaucoma and corticosteroid-induced cataracts (389–391). Additional work is required to evaluate the incidence, burden of disease and factors associated with the development of HAU.

Infective dermatitis

Infective dermatitis was the first syndrome reported among children in association with HTLV-1 infection (397). In 1966, Sweet (398) described a pattern of severe exudative eczema among 17 children in Jamaica that was characterized by crusting around the nostrils, ears and scalp followed by a generalized papular rash, which responded rapidly to antibiotics and topical steroids. This was the first description of the clinical syndrome labelled infective dermatitis. The association between HTLV-1 and infective dermatitis was proposed many years later (397,399). In 1996, the disease began to be referred to as infective dermatitis associated with HTLV-1, and in 1998, diagnostic criteria were proposed (399), with suggested revisions in 2012 (400). Essential features of the clinical presentation include chronic relapsing dermatitis (involving the scalp and retroauricular areas), with prompt response to therapy and recurrence on discontinuation. There are no distinctive histological features on skin biopsy. Differentiating infective dermatitis from other skin conditions, including atopic and seborrheic dermatitis, has relied on clinical assessment (401).

Little information is available on the incidence and burden of disease related to infective dermatitis among people with HTLV-1 or on factors that predict occurrence. A single case of infective dermatitis was documented in a cohort of 28 children with HTLV-1 infection in Jamaica followed for a median of 7.5 years (range, 1.4–9.0 years; 181 person-years) (402). The incidence of infective dermatitis among HTLV-1-infected children was 552 per 100 000 person-years (95% CI 14–3080), and the risk of developing infective dermatitis by four years of age was 2.0% (402).

Issues related to the epidemiology of infective dermatitis

Few case series (consisting of 50 people or less) have been published describing the characteristics of infective dermatitis associated with HTLV-1 (399–401). Similar to other HTLV-1 disease associations, there may be marked geographical variation. Cases of infectious dermatitis have been reported predominantly in tropical regions in which HTLV-1 is endemic, such as Brazil, Jamaica and Trinidad; few cases have been described in Japan.

Infective dermatitis may be associated with higher HTLV-1 proviral load (403) and the future development of other HTLV-1-related diseases (400,403–410). Similar to other inflammatory conditions associated with HTLV-1, infective dermatitis appears to be characterized by an exacerbated Th1 immune response (403). There are case reports of adults with ATL or HAM/TSP who have had a history of infective dermatitis in childhood (400,403–410). In a series of 42 people with infective dermatitis from Brazil, 20 (48%) were diagnosed with HAM/TSP in childhood or adolescence, and one was diagnosed with ATL as an adult (400,411). In addition, people with infective dermatitis may have an increased rate of infection of new clones and an increased number of existing HTLV-1-positive clones, which could contribute to a high HTLV-1 proviral load and contribute to the risk of ATL (412).

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

In addition to the diseases designated as “HTLV-1 associated”, several other diseases have been investigated for potential associations with HTLV-1 infection. 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.

The results presented in this subsection are drawn from a recently published systematic review and meta-analysis (413) (Table 4). See the original publication for details.

All-cause mortality

The strength of evidence for an association between HTLV-1 and all-cause mortality was strong. Nine cohort studies reported all-cause mortality (314,349,414–420). A meta-analysis of eight studies was performed; one study was excluded (415), since it was subsequently reported with longer follow-up (416). 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) (Table 4). Consistency between the results of individual studies was high across geographical 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 15–29 years old and 1.20 (95% CI 0.90–1.50) for those 60 years and older. The higher observed risk of death among younger people may result from fewer competing health risks and causes of death.

Conditions classified as inflammatory

Respiratory disease

HTLV-1 was associated with bronchiectasis, bronchitis and bronchiolitis (OR 2.90; 95% CI 2.00–4.30). Two case–control studies (412,422) both conducted within the same hospital population in Central Australia, with some participant overlap, found statistically significant associations between HTLV-1 and radiologically confirmed bronchiectasis, bronchitis and bronchiolitis. In contrast, two cohort studies in overlapping populations of blood donors in the United States of America did not find an association with bronchitis, ascertained by self-report (423,424). In a small cross-sectional study from Central Australia ($n = 27$), seven adults with HTLV-1 infection had “chronic lung disease” diagnosed by a physician blinded to HTLV-1 status, with no cases among those without HTLV-1 (422). Insufficient data were provided to adjust for age or other potential confounders. The strength of evidence for an association between HTLV-1 and bronchiectasis, bronchitis and bronchiolitis was limited.

TABLE 4. HTLV-1 INFECTION, ALL-CAUSE MORTALITY AND POSSIBLE DISEASE ASSOCIATIONS

Condition ^a	Summary estimate (95% CI)	Total number of studies	Studies used for summary estimate	Strength of association (GRADE) ^b
Mortality				
All-cause mortality	Relative risk (RR) 1.57 (1.37–1.80)	9	8	Strong
Inflammatory conditions				
Seborrhoeic dermatitis (adults)	Odds ratio (OR) 3.95 (1.99–7.81)	2	2	Limited
Seborrhoeic dermatitis (children)	RR 4.70 (1.70–13.20)	1	1	Limited
Eczema (children)	RR 3.10 (1.20–7.90)	1	1	Limited
Rheumatoid arthritis	OR 2.80 (1.80–4.60)	1	1	Very limited
Arthritis	RR 2.84 (1.51–5.33)	1	1	Very limited
Sjögren's syndrome	OR 3.25 (1.85–5.70)	2	2	Very limited
Fibromyalgia	OR 9.14 (2.42–34.52)	1	1	Very limited
Bronchiectasis, bronchitis, bronchiolitis ^c	OR 2.90 (2.00–4.30)	3	1	Limited
Asthma (males)	OR 3.40 (1.20–3.30)	1	1	Very limited
Cancer other than ATL				
Lymphoma other than ATL	OR 2.76 (1.36–5.62)	1	1	Limited
Liver cancer	RR 1.49 (0.97–2.30) OR 1.46 (0.85–2.51)	3 2	3 2	Limited
Gastric cancer	RR 0.45 (0.28–0.71)	3	3	Very limited
Cervical cancer	RR 8.30 (0.83–82.90) OR 3.59 (0.68–19.11)	1 1	1 1	Very limited
Infectious diseases				
Tuberculosis	RR 2.30 (1.60–4.10) OR 2.04 (1.36–3.06)	1 6	1 6	Moderate
Kidney and bladder infections	RR 2.32 (1.50–3.59) OR 1.80 (1.00–3.20)	2 1	1 1	Limited
Dermatophyte infection	OR 3.32 (1.5–7.35)	1	1	Very limited
Community-acquired pneumonia	OR 1.36 (1.00–1.85)	1	1	Very limited
<i>Strongyloides</i> hyperinfection syndrome	OR 120 (11.43–1259)	1	1	Very limited

Adapted from Schierhout et al. (413). Overall summary of meta-analysis of studies showing significant associations between disease or death and HTLV-1 infection.

^a 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 the effects are not shown here because fewer than five participants had these conditions.

^b Strength of association, based on modification of GRADE criteria.

^c As determined by the study authors. Reproduced with permission

A cross-sectional study conducted in Japan found that HTLV-1 infection was significantly associated with a self-reported diagnosis of asthma among men but not women. A cohort study of children reported no association between HTLV-1 and clinician-diagnosed asthma (425). Several of the studies evaluating respiratory disease did not adjust for smoking. The strength of evidence for an association between HTLV-1 and asthma was very limited.

Other potentially inflammatory conditions

HTLV-1 was associated with seborrhoeic dermatitis (pooled OR 3.95; 95% CI 1.99–7.81) (425–427) and Sjögren's syndrome (pooled OR 3.5; 95% CI 1.85–5.70) (428). Rheumatoid arthritis (429,430), fibromyalgia and ulcerative colitis (430) all showed significant associations with HTLV-1, with effect estimates adjusted for age. The strength of evidence for an association between HTLV-1 and seborrhoeic dermatitis, Sjögren's syndrome or rheumatoid arthritis was limited, and the association between fibromyalgia and ulcerative colitis was very limited.

Cancer

In five cohort studies, the association between HTLV-1 and cancer (excluding ATL) at any site (414,423,431) and the following specific sites was assessed: breast (431), bladder (431), cervix and uterus (414), colon and rectum (414,431), liver (414,431,432), lung (414,431), oropharynx (431), oesophagus (431), pancreas (431), prostate (431), stomach (414,431,433) and thyroid (431). In five case-control studies, the association between HTLV-1 and cancer (excluding ATL) at any site (434,435) and the following specific sites was assessed: biliary tract (434,435), cervix (436,437), colon and rectum (434,435), liver (434,435), lung (434,435), oesophagus (434,435,438), pancreas (434) and stomach (434,435). One cross-sectional study assessed the association between HTLV-1 and cancer (excluding ATL) at any site (439). The strength of evidence for an association between HTLV-1 and cancer other than ATL was limited to very limited.

One case-control study examined the association between HTLV-1 and lymphoma other than ATL (435). 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) compared with people who were HTLV-1 negative. The strength of evidence for an association between HTLV-1 and lymphoma other than ATL was limited.

People with HTLV-1 infection in Japan were less likely than those without HTLV-1 to develop gastric cancer (RR 0.45; 95% CI 0.28–0.71; three cohort studies) (414,431,433). Some of the studies examining the association between HTLV-1 infection and gastric cancer did not adjust for factors implicated in carcinogenesis, namely *Helicobacter pylori* infection, smoking and alcohol consumption; of note, participants with HTLV-1 infection were less likely to have concurrent *H. pylori* infection (414,431,433). The strength of evidence for an association between HTLV-1 and gastric cancer was very limited.

Infectious diseases

Tuberculosis

Seven studies found associations between HTLV-1 and tuberculosis (TB) (430,439–443), with a pooled odds of developing TB 2.25 times higher among people with HTLV-1 (OR 2.25, 95% CI 1.48–3.43) than their HTLV-1 negative counterparts, and a single cohort study reported a relative risk of developing TB of 2.30 (95% CI 1.60–4.10) (444). There were some concerns regarding lack of adjustment for confounding, including socioeconomic status.

Urinary tract infection

Evidence for an association between HTLV-1 and urinary tract infection derived from three studies based on the same cohort (439). At 4.3 years of follow-up, 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). The strength of evidence for an association between HTLV-1 and urinary tract infection was limited.

Strongyloides hyperinfection syndrome and symptomatic strongyloidiasis

Infection with *Strongyloides stercoralis* may influence HTLV-1-related disease progression (355), and as such, *Strongyloides* screening and treatment is routine in some centres caring for people with HTLV-1 infection.

An association between 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 (445). A small community cross-sectional study in Central Australia found two cases of symptomatic strongyloidiasis among the 22 people with HTLV-1 and no symptomatic strongyloidiasis among those without HTLV-1 (446).

Infectious skin conditions

Two cross-sectional studies suggested a weak association between HTLV-1 and dermatophyte infection (426,427).

Other infectious conditions

One cohort study each examined otitis media (425) and vulvovaginal candidiasis (423). A prospective cohort in Jamaica found no association between HTLV-1 and otitis media in children. A prospective cohort in the USA at 4.5 years of median follow-up found no association between HTLV-1 and vulvovaginal candidiasis among women. A cross-sectional study in Japan found no association between HTLV-1 infection and viral hepatitis (hepatitis B and C) (430).

Other conditions

“Chronic liver disease” was reported in a cohort study from Japan (432) and collected but not reported in a cross-sectional study (440). Two cross-sectional studies, both using self-report, reported 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 (432,439).

Issues related to the epidemiology of diseases not associated by definition with HTLV-1

HTLV-1 infection was associated with an increased risk of death (meta-analysis; pooled RR 1.57; 95% CI 1.37–1.80). The overall 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 has a high case-fatality rate but a low incidence. Although unmeasured confounding may be responsible for the mortality increment identified, this is unlikely given consistency across settings in diverse countries.

Evidence of limited to moderate quality suggests that people with HTLV-1 infection have increased odds of developing the following conditions: TB; seborrhoeic dermatitis; eczema; bronchitis, bronchiectasis and bronchiolitis; urinary tract infection; and lymphoma other than ATL. Evidence for an association between HTLV-1 and all other conditions studied was assessed to be very limited.

The burden of disease associated with HTLV-1 may be broader than generally recognized, and there are significant research gaps in the clinical conditions and health effects associated with HTLV-1 infection. HTLV-1-mediated chronic inflammation could contribute to the development of many of the possible disease associations. The systematic literature search did not identify any epidemiological studies elucidating the relationship between HTLV-1 and major global causes of morbidity and mortality, including cardiovascular, cerebrovascular and metabolic diseases.

A significant limitation of current epidemiological studies is the failure to further stratify risk by HTLV-1 proviral load, since such stratification enables clearer understanding of differing disease risk for subgroups of people with HTLV-1. For example, risk of a bronchiectasis-related death in a recent hospital-based study was only apparent among those with high HTLV-1 proviral load (421). Higher HTLV-1 proviral load also predicted death in a small study in Guinea-Bissau (417), and increased all-cause mortality was associated with higher HTLV-1 antibody titres (correlated with higher HTLV-1 proviral load) (447) in a cohort study in Japan (341).

Data about the extent and scope of morbidity associated with HTLV-1 infection are essential to inform guideline development and service delivery for surveillance, prevention, testing and treatment services for those affected along with guiding public health policies and allocation of health resources. Relatively few robust epidemiological studies of HTLV-1 disease associations were identified, with the studies that have been published being geographically restricted. Epidemiological studies are needed in this area but are challenging because of the range of possible outcomes associated with HTLV-1, difficulties ascertaining the time of acquisition and duration of infection, methodological constraints and the diversity of factors that may moderate the immune response to the virus. Many areas with endemic HTLV-1 are also areas of high public health disadvantage, creating difficulty in identifying any HTLV-1 contribution to an already high burden of illness and premature death in these contexts. International collaboration to overcome these challenges and to design and implement studies that can compare outcomes across settings and in different population groups is needed.

5. PREVENTING HTLV-1 TRANSMISSION

The available evidence on preventing HTLV-1 infection is limited to observational studies that investigated the implementation of specific preventive interventions. These studies focus on relatively limited series, and there is no published information on population-level effects. There are no reports related to preventing sexual transmission nor to prevention among people who inject drugs.

Cessation of breastfeeding

Based on observational studies of mother-to-child transmission, it was determined that shortening the duration of breastfeeding or even eliminating it altogether could enable women with HTLV-1 to limit the extent of exposure to their infants. A 20-year evaluation of ending breastfeeding in the Nagasaki prefecture in Japan showed that the prevalence of HTLV-1 infection among formula-fed children was significantly lower than among breastfed children. Among breastfed children, the prevalence was lower among children who were breastfed for less than six months than children breast fed six months or more. This long-term finding supported several earlier short-term evaluations of the strategy (182,183,195,197,449).

Breast-milk freeze-thaw method

The freeze-thaw method has been proposed as an alternative for preventing the transmission of HTLV-1 to allow infant consumption of breast-milk, because it effectively eliminates the cells in breast-milk that are infected with HTLV-1 and hence the source of transmission. A 1986 study (199) showed that the freeze-thawing process eliminated antigen-positive cells in vitro, and in 1989, a further study appeared from the same group (450). The results of a 12-month follow-up of 13 infants given frozen-thawed breast-milk found no HTLV-1 infection. Although this demonstrates the effectiveness of the freeze-thaw method, the authors noted that this strategy may not be practical in many situations, especially in low-resource settings where the required technology is unavailable.

Antibody screening among blood donors

Mandatory HTLV-1 antibody screening of all blood donations has been implemented in 23 countries (see Section 7 for further detail). Studies from Japan and the United States in the late 1980s and early 1990s reported on how universal antibody screening of blood donors affected the rate of HTLV-1 seroconversion among recipients (451–453).

Leukoreduction

A small study ($n = 113$) from the United Kingdom used a lookback method to review HTLV (both -1 and -2) seroconversion among people receiving blood products from HTLV-positive donors, with and without leukoreduction (454). This study demonstrated that leukoreduction effectively reduced the risk of HTLV infection, with the single case detected also reporting other HTLV risk factors. Several studies noted that, because HTLV-1 is almost always cell associated, leukoreduction may be as effective as blood donation screening (455).

Vaccine

Consistent with the public health approach for controlling infectious diseases, preventive vaccination has been proposed as the ideal strategy to reduce the burden of HTLV-1 infection and its associated diseases. Given the relatively low antigenic variability of HTLV-1, developing a vaccine has been considered feasible but far from straightforward. The necessary precursor preclinical studies are limited in part by the suitability of animal models for disease representative of HTLV-1 infection (456–459). Human trials would require recruiting and following up large numbers of people at risk of HTLV-1 infection, most likely through sexual exposure, and assessing outcomes over extended time frames.

Viral proteins have been tested as potential vaccine immunogens, but the most promising candidates were evaluated in small samples and have so far not provided definitive information about their protective potential (460). No candidate HTLV-1 vaccine has proceeded to a clinical trial with an efficacy endpoint.

6. PHARMACEUTICAL INTERVENTIONS IN MANAGING HTLV-1 INFECTION AND HTLV-1-ASSOCIATED DISEASE

Pharmaceutical interventions for asymptomatic HTLV-1 infection

HIV antiretroviral therapy

First-generation nucleoside analogue reverse-transcriptase inhibitors (NRTI) and integrase strand-transfer inhibitors (INSTI) developed as anti-HIV agents have showed in vitro activity against HTLV-1, but this has not been demonstrated in vivo (461–463). A pilot study of five people with HTLV-1 infection (including three with asymptomatic infection) did not show a substantial reduction in HTLV-1 proviral load after six months of treatment with raltegravir (464).

Green tea extract

A preclinical study suggested that green tea polyphenols could inhibit the growth of T cells from people with ATL and asymptomatic HTLV-1 infection by suppressing HTLV-1 *pX* gene expression (465). In a subsequent randomized (1:1) control trial among people with asymptomatic HTLV-1 infection, HTLV-1 proviral load did not change substantially among the 37 people receiving a fixed amount of green tea extract powder (equivalent to 10 cups of regular green tea) compared with the 46 controls.

Issues related to managing asymptomatic HTLV-1 infection

WHO has not produced any guidelines or recommendations on managing HTLV-1 infection or HTLV-1-associated conditions. More broadly, no treatment is currently recommended for people with asymptomatic HTLV-1 infection. Recommendations managing people with HTLV-1 infection include longitudinal assessment for manifestations of HTLV-1-associated diseases, namely ATL and HAM/TSP, and screening for comorbidities and coinfection (including *Strongyloides stercoralis*). Currently, no single biological marker or clinical feature accurately predicts the development of or quantifies the risk of HTLV-1-associated disease. Improvements in risk prediction would assist in clinical management (to appropriately risk stratify and counsel people with HTLV-1 infection) and in research design (to determine appropriate and clinically meaningful endpoints).

Pharmaceutical interventions for ATL

WHO has not produced guidelines or recommendations on ATL treatment. More broadly, treatment strategies for ATL include “antiviral” regimens (with interferon-based therapy) and multi-agent chemotherapy, with the more recent addition of biological agents (Table 5). Recommendations for managing ATL were originally published in 2009 following international consensus meetings (466) and were updated in 2019 (467). Given the paucity of data, these recommendations are largely based on expert opinion and suggest that people with ATL should be considered for enrolment in a clinical trial, if available.

TABLE 5. SUMMARY OF INTERVENTIONS EVALUATED IN CLINICAL TRIALS AMONG PEOPLE WITH ATL^a

Pharmaceutical intervention	Clinical trial phase	Recommended for clinical use	References
Interferon-based therapy			
Interferon-alpha + zidovudine	II	Yes	(468–470)
Interferon-alpha + arsenic	II	No (toxicity)	(471)
Interferon + zidovudine + arsenic	II	No (toxicity)	(472)
Chemotherapy			
Chemotherapy – various regimens	II–III	Yes Regimen specific	(473–482)
Chemotherapy (followed by interferon-alpha + zidovudine + lamivudine)	II	No	(483)
Biological agents			
Alemtuzumab	II	Insufficient evidence	(484)
Daclizumab	II	Insufficient evidence	(485)
Lenalidomide	II	Yes	(486)
Mogamulizumab	II	Yes	(487)
Mogamulizumab + chemotherapy	II	Yes	(488, 489)

^a Allogeneic hematopoietic stem cell transplant has not been evaluated in clinical trials among people with ATL, but it is a recommended management strategy in the appropriate clinical context.

Interferon-based therapy for ATL

“Antiviral” therapy (with interferon in combination with zidovudine) has been reported to induce remission and improve survival in cases of acute, chronic and smouldering ATL, although the mechanism of action remains unclear. Clinical trial evidence for the efficacy of interferon-based therapy is limited (468–470,490). Given the small sample size in individual studies and lack of a randomized control trial, retrospective cohort studies have been performed (491,492). In the largest cohort to date, Bazarbachi et al. assessed 254 people with ATL treated between 1995 and 2008 with one of the following regimens: (1) antiviral therapy (interferon-alpha plus zidovudine and/or other HIV antiretroviral therapy), (2) chemotherapy and (3) chemotherapy followed by antiviral therapy (491). Among people with acute, chronic and smouldering subtypes, those who received first-line antiviral therapy had improved five-year survival, whereas people with lymphoma subtype appeared to have better outcomes with chemotherapy. For those with acute ATL, achieving complete remission with antiviral therapy resulted in 82% five-year survival. Antiviral therapy in chronic and smouldering ATL resulted in 100% five-year survival. Although these retrospective analyses suggest benefit, selection bias cannot be excluded.

International consensus recommendations have suggested that interferon-alpha and zidovudine can be considered as first-line therapy for people with symptomatic smouldering ATL, favourable or unfavourable chronic ATL and acute ATL (467). A Phase III clinical trial comparing interferon-alpha and zidovudine with “watchful waiting” among people with indolent ATL (JCOG1111C) is underway in Japan. Trials comparing “antiviral therapy” (interferon plus zidovudine) with chemotherapy among people with acute ATL could also be considered.

Using combination chemotherapy for ATL treatment

International consensus recommendations have suggested that intensive chemotherapy be considered as first-line therapy for people with lymphoma-type ATL (467). One Phase III multicentre open-label randomized trial (JCOG9801) was conducted among people with untreated aggressive ATL in Japan, comparing the efficacy of two multi-agent chemotherapy regimens, vincristine, cyclophosphamide, doxorubicin, prednisolone-doxorubicin, ranimustine, prednisolone-vindesine, etoposide, carboplatin, prednisolone (VCAP-AMP-VECP; dose-intensified modified LSG15 protocol) and

biweekly cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) (480). Superior efficacy was demonstrated with VCAP-AMP-VECP (complete response, 40%) compared with biweekly CHOP (complete response, 25%). However, the median survival was only 13 months. A subsequent propensity score analysis of transplant-eligible patients with ATL who received only VCAP-AMP-VECP ($n = 947$) or CHOP ($n = 513$) suggested that the VCAP-AMP-VECP regimen was preferable first-line therapy for people with aggressive ATL in intermediate- and high-risk groups (493). 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.

Expert consensus has recommended chemotherapy regimens for use (467). In Japan, recommended chemotherapy regimens include: VCAP-AMP-VECP (modified LSG15) and etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin (EPOCH). Outside Japan, recommended chemotherapy regimens include: CHOP; cyclophosphamide, vincristine, doxorubicin, etoposide and prednisolone (CHOEP); dose-adjusted EPOCH; and cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high-dose methotrexate and cytarabine (hyper-CVAD).

Using biological agents for ATL treatment

ATL is characterized by the proliferation of malignant CD4⁺ CD25⁺ T cells in the peripheral blood, lymph nodes and other tissues. In addition, most ATL cells are CD52⁺ and almost all ($\geq 90\%$) overexpress C-C chemokine receptor 4 (CCR4). These immunophenotypic markers are useful for targeted therapeutic intervention.

Mogamulizumab

Mogamulizumab, a first-in-class humanized anti-CCR4 monoclonal antibody, was approved in Japan for the treatment of people with relapsed or refractory ATL in 2012 and subsequently for chemotherapy-naïve CCR4-positive ATL. In a Phase II open-label single-arm trial of mogamulizumab among people with relapsed aggressive CCR4-positive ATL in Japan, complete and overall response were 31% and 50%, respectively (487). 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 chemotherapy (modified LSG15) plus mogamulizumab (arm A) or chemotherapy alone (modified LSG15; arm B) (488). Complete response in arms A and B

was 52% and 33%, respectively. Overall response in arms A and B was 86% and 75%, respectively. One-year overall survival was 65% in arm A and 80% in arm B. Outside Japan, mogamulizumab is approved for treatment of T cell malignancies by the FDA and European Medicines Agency. Phillips et al. (489) 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 in the United States of America, Europe and Latin America. The overall response rate was 11% in the mogamulizumab arm and 0% in the chemotherapy arm. In contrast to the results obtained in Japan, relapsed or refractory ATL had a very poor prognosis, regardless of treatment regimen.

Lenalidomide

In Japan, lenalidomide is licensed for use in relapsed or refractory aggressive ATL. One Phase II study evaluated the efficacy and safety of lenalidomide monotherapy among people with relapsed or recurrent ATL (n=26) (494). The overall response rate was 42%. The median progression-free survival and overall survival were 3.8 and 20.3 months, respectively. The efficacy and safety profile would suggest that further evaluation of lenalidomide in managing ATL should be considered.

Allogenic haematopoietic stem cell transplantation for ATL

No prospective randomized trials support the use of allogenic haematopoietic stem cell transplantation in ATL. Case series and retrospective cohort studies of allogenic haematopoietic stem cell transplantation after chemotherapy for aggressive ATL suggested improvements in overall survival but with substantial transplantation-related morbidity and mortality (495–502). Fuji et al. (500) conducted a retrospective analysis of clinical outcomes among 2553 people diagnosed with aggressive ATL in Japan between 2000 and 2013, of whom 996 (39%) received allogenic haematopoietic stem cell transplantation. The probabilities of two-year overall survival after diagnosis were 45% (95% CI 42–48) among those who underwent allogenic haematopoietic stem cell transplantation and 20% (95% CI 18–23) among those who did not. Younger age and complete response at the time of transplant were associated with improved survival. Risk stratification and development of a prognostic index would guide clinicians in identifying the people who may benefit from early allogenic haematopoietic stem cell transplantation.

Issues related to ATL treatment

Despite advances in pathophysiology and therapeutics (including the use of intensive chemotherapy regimens), aggressive ATL subtypes continue to have 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. Although the overall response rates exceed 50% for many of the therapeutic strategies, the 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, hypercalcaemia and high serum lactate dehydrogenase (466). 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. More recent therapeutic strategies involving biological agents and intensive multi-agent chemotherapy may signal better outcomes. Given the uncertainties about treatment options, everyone with ATL should be considered for enrolment in a clinical trial, if available.

Pharmaceutical interventions for HAM/TSP

HAM/TSP can result in substantial morbidity. However, the evidence base for managing people living with HAM/TSP is extremely limited. Pharmaceutical therapies assessed in clinical trials among people with HAM/TSP include corticosteroids, HIV antiretroviral therapy and interferon, but no agent has demonstrated lasting benefit (Table 6). The International Retrovirology Association published guidelines for managing HAM/TSP in 2018, with most of the recommendations limited to expert opinion (503). Prednisolone is the mainstay of therapy, although clinical trials are lacking. WHO has produced no guidelines or recommendations on managing HAM/TSP.

TABLE 6. SUMMARY OF INTERVENTIONS EVALUATED IN CLINICAL TRIALS AMONG PEOPLE WITH HAM/TSP^a

Pharmaceutical intervention	Clinical trial phase	Recommended for clinical use (503)	References
Agents postulated to alter disease course			
Corticosteroids Methylprednisolone (IV)	Pilot, IV	Yes	(504,505)
Cyclosporin	Pilot	Possible	(506)
Heparin	Pilot	No	(507)
HIV antiretroviral therapy Zidovudine + lamivudine	II	No	(508)
Raltegravir	Pilot	No	(464)
Tenofovir disoproxil fumarate	Pilot	No	(509)
Interferon-alpha and interferon-beta	Pilot, II, III	Consider as second-line therapy	(510–515)
Monoclonal antibody against interleukin-2 receptor (anti-Tac)	Pilot	No	(516)
Mogamulizumab	II	Insufficient evidence Ongoing evaluation	(517)
Sodium valproate	Pilot	No	(518)
Agents postulated to provide symptomatic benefit			
Danazol	II	No	(519)
<i>Lactobacillus casei</i>	Pilot	No	(520)
Pentosan polysulfate	Pilot	No	(521)
Pentoxifylline	Pilot	No	(522)
Prosultiamine	Pilot	No	(523)
Vitamin C	Pilot	No	(524)

^a Other immunosuppressive or immunomodulatory agents that are used in clinical practice but have not been evaluated in clinical trials include prednisolone, methotrexate and azathioprine.

Agents postulated to alter the disease course of HAM/TSP

Corticosteroids

Although corticosteroids are commonly used in clinical practice and recommended in an international consensus statement (503), no placebo-controlled study has been conducted to evaluate efficacy in managing HAM/TSP; a study is open to recruitment in Japan (503). Many of the data on the use of corticosteroids stem from case series and cohort studies (504,525–527). Although 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 United Kingdom (504,505). Current evidence on the 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 (525,527,528). The available data would suggest that any benefit of pulsed methylprednisolone is transient and limited to pain and spasticity.

Prednisolone

No prospective clinical trials have evaluated the efficacy and safety of prednisolone in the management of HAM/TSP. Retrospective observational studies have been published and are used to support a role for corticosteroids in managing people with HAM/TSP, despite their limitations and risk of bias (526).

Corticosteroids have been the mainstay of therapy, but available evidence for their use in HAM/TSP is limited. Clinical trials to address the efficacy and safety of corticosteroids in this population should be considered. Recent International Retrovirology Association guidelines refer to an ongoing 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) (503).

Cyclosporin

Cyclosporin is a calcineurin antagonist, which blocks the action of calcineurin in activated T cells, preventing production of interleukin-2 and other cytokines that 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 ($n = 7$) (506). Five patients showed evidence of clinical improvement, but four met criteria for clinical failure by 48 weeks.

Heparin

Investigators hypothesized that heparin would affect activated T-cell trafficking into the central nervous system and inhibit inflammation among people with HAM. In a small uncontrolled open-label trial involving 10 people with different disease durations and motor disability, all reported subjective improvement (decreased spasticity) and motor function appeared to improve among those who were ambulatory (reduction in timed walk test; 6 of 7) (507).

HIV antiretroviral drugs

Similar to asymptomatic HTLV-1 infection, *in vitro* data or case reports of clinical improvement or reduction in HTLV-1 proviral load ignited interest in the effectiveness of HIV antiretroviral therapy among people with HAM/TSP. One small randomized double-blind placebo-controlled study evaluated the impact of zidovudine + lamivudine for six months among 16 people with HAM/TSP (508). There was no evidence of clinical response and no difference in proviral load or T-cell activation and proliferation. In a small open-label study ($n = 6$), people with HAM/TSP were prescribed tenofovir disoproxil fumarate, with no change noted in HTLV-1 proviral load, timed walk test or visual

analogue pain score (509). A pilot study of five people with HTLV-1 infection (including two with HAM/TSP) did not show a substantial reduction in HTLV-1 proviral load after six months of treatment with raltegravir (464).

Interferon-alpha and interferon-beta

Six clinical trials evaluating the efficacy and safety of interferon (five interferon-alpha and one interferon-beta) among people with HAM/TSP were identified, including one double-blind randomized trial (514). The randomized trial ($n = 48$) noted a dose-dependent response (512). Post-marketing surveillance was performed to investigate the safety and efficacy of interferon-alpha for HAM/TSP ($n = 167$) (529). Efficacy at four weeks, defined as "modest to markedly improved" and "mildly improved" symptoms, was reported for 66%. Sustained improvement of Osame's motor disability scores for at least five months after cessation was seen in 11 of 30 evaluable patients. Factors associated with efficacy were Osame's motor disability scores at baseline, duration of illness and stage of illness.

Methotrexate

Although methotrexate is used in clinical practice, no clinical trials and no published peer-reviewed literature were found evaluating the use of methotrexate in HAM/TSP. A retrospective cohort study (published in abstract form) reported on the use of methotrexate among 13 people with HAM and suggested that treatment improved the 10-metre walk test and reduced pain (530).

Monoclonal antibodies specific for interleukin2 receptor (anti-Tac)

The potential mechanism of action of anti-Tac monoclonal antibodies in HAM/TSP is thought to be related to the selective downregulation of activated T cells and a decrease in the HTLV1 proviral load in peripheral blood lymphocytes. However, the results from one small open-label pilot study ($n = 9$) demonstrated no significant clinical response (516).

Mogamulizumab

In one uncontrolled Phase I/IIa trial ($n = 21$), Sato et al. (517) examined the safety and efficacy of mogamulizumab, a humanized anti-CCR4 monoclonal antibody, among people with glucocorticoid-refractory HAM/TSP. All participants were maintained on less than 10 mg of prednisolone per day. The Phase I dose-escalation study found dose-dependent reductions in the frequency of CCR4+ cells, HTLV-1 proviral load and inflammatory markers in the CSF (CXCL10 and neopterin). The reductions 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% and the mean reduction in CSF neopterin concentration was 45%. Clinical measures

improved and were sustained through week 24, including mean global-assessment scores, Modified Ashworth Scale score and Osame's motor disability scores; improvements in motor function were more likely for those with shorter duration of disease (<10 years) and mild disability (Osame's motor disability scores <5). Long-term follow-up for these study participants is ongoing (UMIN000019942). Further clinical trials are required to determine the utility of mogamulizumab in managing HAM/TSP. A randomized placebo-controlled clinical trial could be considered to evaluate efficacy.

Sodium valproate (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 (518). 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 for three people, which was attributed to adverse drug effects, including drowsiness and tremor; this was reversible after stopping treatment. Side-effects were common.

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 neural deficit is unclear (531). One published placebo-controlled trial evaluated the efficacy of danazol ($n = 38$) or placebo ($n = 33$) for 24 weeks among people with HAM/TSP in the Islamic Republic of Iran (519). Although the investigators reported that danazol was beneficial, insufficient data were presented to substantiate their claims.

Lactobacillus

One single-arm open-label pilot study evaluated *Lactobacillus casei* strain Shirota from fermented milk (twice daily for four weeks; $n = 10$) (520). Improvements in spasticity (modified Ashworth Scale scores) and urinary symptoms were reported after receiving *Lactobacillus casei*.

Pentosan polysulfate

A small open-label single-arm trial ($n = 12$) assessed the efficacy of pentosan polysulfate among people with HAM/TSP with a duration of disease ranging between 3 and 52 years (521). Three received concomitant therapy, including interferon-alpha and prednisolone. Improvements in lower-extremity motor function were reported.

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 (522). Motor disability, especially spasticity, reportedly improved in 13 patients.

Prosultiamine

The thiamine derivative, prosultiamine, may improve motor function among 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 (532). Most reportedly had reduced spasticity and improved walk time and urodynamic parameters. The HTLV-1 proviral load in peripheral blood decreased by 15% compared with pre-treatment levels.

Vitamin C

One open-label pilot study ($n = 7$) examined the efficacy of intermittent high-dose oral vitamin C, 35–40 mg per kg per day (524). Six patients improved in disability score by 2 or more grades, and the overall mean disability score decreased.

Issues related to HAM/TSP treatment

No high-quality evidence supports the use of any pharmaceutical intervention in managing HAM/TSP. Available clinical trial data regarding the use of most of the agents listed above among people with HAM/TSP are very limited, subject to bias and insufficient to evaluate the impact of this intervention in this population.

The low incidence of the disease and the occurrence of cases in resource-limited settings pose challenges in developing a robust evidence base. Guidelines published by the International Retrovirology Association in 2018 (503) highlight the need for high-quality data to guide management and a validated clinical classification system to assist health-care providers in making management decisions, improving prognostication and standardizing clinical trial assessment and reporting. The expert panel recommended that people with HAM/TSP be classified by the speed of disease progression into "rapid progressors", "slow progressors" and "very slow progressors" (503). The definitions and suggested criteria are largely subjective. These definitions require validation before being adopted. However, these subclassifications 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 differences are not accounted for. Given the uncertainties about treatment options, everyone with HAM/TSP should be considered for enrolment in a clinical trial, if available, regardless of the severity and duration of disease.

7. POLICIES AND GUIDELINES FOR PREVENTING HTLV-1 TRANSMISSION AND TREATING PEOPLE WITH HTLV-1-ASSOCIATED DISEASES

HTLV-1 prevention policies and guidelines

Information was obtained from 69 countries on the status of policies on HTLV-1. Of these countries, the available information for 14 indicated no specific policy, and 55 had a policy on at least one HTLV-1 preventive intervention. For all other countries, no specific information was available on the presence or absence of HTLV-1-related policy.

Japan was the only country for which an overall national policy on HTLV-1 prevention (including a mother-to-child programme since 2011) could be identified (448,533,534). In England, the National Health Service England provides guidance for diagnosing and managing HTLV-1 infection and services in HTLV-1-specific specialist centres in three hospitals. Overall, there are policies on interventions aimed at preventing HTLV-1 transmission: (1) screening blood donations; (2) screening breast-milk donations; (3) antenatal screening; and (4) screening donor tissue and cells. This review found no evidence of policies or guidelines in any country on interventions to prevent sexual or injecting drug use transmission that were specific to HTLV-1. Many countries have policies related to preventing sexually transmitted and bloodborne infections, but the review could not find evidence of any that specifically addressed the potential of these policies to reduce HTLV-1 risk.

Preventing mother-to-child transmission

Strategies to prevent mother-to-child transmission are based on detecting HTLV-1 in the mother during pregnancy followed by avoiding or minimizing breast-milk exposure among those found to be positive. Table 7 presents a summary for countries for which information was available on mother-to-child transmission policies. Japan is the only country that has implemented a nationwide HTLV-1 mother-to-child prevention and control programme (448,533,534). The mother-to-child transmission programme recommends that all women be offered HTLV-1 screening in pregnancy and that those found to have HTLV-1 infection either formula feed their child; breastfeed for a short term (up to three months); or feed with thawed frozen milk. Antenatal HTLV-1 screening is recommended clinical practice in some regions in Brazil (such as the state of Bahia) but is neither mandatory nor implemented (535,536).

Blood donor screening

Blood donor screening policies relate to: testing donations for the presence of HTLV-1; deferring or excluding people as donors if there is evidence that they are at higher risk of HTLV-1; or using technologies that remove infectious organisms from blood products.

TABLE 7. COUNTRIES WITH POLICIES OR GUIDELINES ON PREVENTING THE MOTHER-TO-CHILD TRANSMISSION OF HTLV-1, 2021

WHO region	Antenatal screening	Breast-milk donation screening
African Region	No information	
Eastern Mediterranean Region	No information	
European Region ^a	France (screening of people from endemic regions recommended) (537) ^b	France (screening of breast-milk donors from endemic regions recommended) (537) ^b
Region of the Americas	Brazil (some regions recommended), Chile (recommended) (536,538)	United Kingdom (539)
Western Pacific Region	Japan (nationwide policy since 2011) (448,533)	
South-East Asia Region	No information	No information

^a The Milk Bank Association for the establishment and operation of human milk banks in Europe states that donors of breast-milk may be screened for HTLV according to local evaluation (540).

^b Endemic regions of the Caribbean, Africa, Japan and South-East Asia.

There is evidence that 23 countries have implemented mandatory screening of all donated blood for HTLV-1 antibodies (Table 8). In 1988, Japan became the first country to implement mandatory screening of blood donations (541). The United States of America and Canada began mandatory screening of blood donations in 1988 and 1989, respectively. In Canada, a licensed or registered establishment must perform a lookback procedure on previous donations from an allogeneic blood donor whose blood or blood components have evidence of confirmed infection (542).

Caribbean nations (Dominican Republic, Haiti and Jamaica) and French territories in the Americas (French Guiana, Guadeloupe and Martinique) also introduced universal blood screening policies in 1989, as did Cuba, although it appears that this is not enforced uniformly.

Mandatory screening of all blood donations in Australia, Brazil, France, Greece, Ireland, Netherlands, Portugal, Romania and Taiwan, China began in the 1990s. In 2018, the Australian Red Cross received regulatory approval to test only first-time donors plus donations intended for manufacturing leukocyte components (563) but has not yet implemented this policy (563). Mandatory screening

was initiated in Khorasan province of the Islamic Republic of Iran in 1993. Mandatory screening was introduced in the United Kingdom and Colombia in 2002 and 2014, respectively. Currently, Denmark, France, Guadeloupe, Martinique, Portugal and Sweden routinely screen first-time donors only. In Norway, first-time donor screening was initiated in 2000 but then ceased in 2007 because there were no HTLV-1 cases (545). Finland screens first-time donors only and repeat donors who did not donate for more than three years, but screening is not mandatory. Gabon is the only country in the African Region that reports screening blood donations for HTLV-1 at its National Center for Blood Transfusion; however, a formal policy does not exist.

From 1997 to 2000, PAHO performed an external quality control programme in serology for infectious diseases, including HTLV, with 16 countries participating and 21 public institutions in Latin America. Due to the diversity of population in different geographic areas, migration and displacement, it is timely to apply regular tests in blood donations to complement and update the epidemiological scenario of the risk of HTLV-1 transmission through blood transfusions in this region (564)

TABLE 8. COUNTRIES AND TERRITORIES WITH POLICIES OR GUIDELINES ON SCREENING BLOOD DONATIONS FOR HTLV-1, 2021

WHO region	All donations	First-time donors only	Specific areas	Leukoreduction ^a
African Region	Gabon (only at the National Centre for Blood Transfusion – no national formal policy)			
Eastern Mediterranean Region	Saudi Arabia (543)		Islamic Republic of Iran (Khorasan) (544)	
European Region ^b	French Guiana, Greece, Ireland, Israel, Netherlands, Romania and United Kingdom (545–547)	Denmark, Finland, France, Guadeloupe, Martinique, Portugal and Sweden (109,545,548,549)		Austria, Belgium, Czechia, Finland, France, Germany, Greece, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Spain (545–547,549–551)
Region of the Americas	Brazil, Canada, Chile, Colombia, Dominican Republic, Haiti, Jamaica, Peru, United States of America and Uruguay (111,536,538,542,552–559)		Argentina and Bolivarian Republic of Venezuela (536,560)	
Western Pacific Region	Australia, Japan, New Zealand and Taiwan, China (147,541,546,561,562)		China (546,562)	
South-East Asia Region	No information			

^a All blood or cellular components or on medical request.

^b Includes French territories in the Americas: French Guiana, Guadeloupe and Martinique.

Organ donor screening

Very few policies and guidelines for HTLV-1 screening of organ donations exist. Mandatory screening of deceased organ donors was eliminated in the United States of America in 2009 because of the presumed very high false-positive rates of HTLV-1 screening tests in a low-prevalence setting, which were leading to high levels of organ donor wastage (557, 565). Current guidance nevertheless recognizes that potential health issues are associated with HTLV-1 in organ donation.⁵⁶⁴

In 2012, the European Commission adopted directive 2012/39/EU, which requires HTLV-1 antibody testing for donors living in, or originating from, high-prevalence areas or with sexual partners originating from these areas or if the donor's parents originate from these areas for both donors of non-reproductive tissues and cells and reproductive cells (566).

Although the transplant of organs from people with HTLV-1 is permitted in Japan, in 2014, Japan's Ministry of Health, Labor and Welfare began working towards implementing HTLV-1 screening of all kidney donations (567). The United Kingdom Human Tissue Authority issued new transplant guidance stating that all donors of tissues and cells (or stored for personal use, including cord blood) for human application are tested for HTLV-1 at the time of donation (567). In Spain, HTLV-1 screening is recommended for organ and tissue donors from endemic regions and sex partners or parents from such regions.

National or regional surveillance programmes

Surveillance for HTLV-1 may be based on routine reporting of new diagnoses of HTLV-1 or associated diseases or prevalence surveys. There are limited examples of national surveillance initiatives directed specifically at HTLV-1. In the United Kingdom, Public Health England introduced surveillance of HTLV-1 in 1987, with laboratories reporting all newly diagnosed cases of HTLV-1 (547). In 2002, enhanced surveillance began with notifications of new HTLV-1 diagnoses received from laboratories and clinicians in England and Wales (568).

In Australia, new diagnoses of HTLV-1 and associated diseases (ATL) are notifiable in the Northern Territory (561). HTLV-1 infection has been identified as a priority area for research and policy development in the National Aboriginal and Torres Strait Islander Blood Borne Viruses and Sexually Transmissible Infections Strategy 2018–2022 (569).

Many countries have cancer registries, but their coding systems do not enable the routine analysis of ATL as a distinct entity. Japan has ATL-specific coding in its national cancer registry and HAM-specific coding in another national registry.

International guidance and recommendations

In 1992, a WHO report (570) recommended HTLV-1 preventive measures, including breastfeeding restrictions, blood safety with needles and syringes among injecting drug users and safe sexual practices. In 2010, WHO recommended blood donor screening for HTLV-1 (571). However, the WHO global database on blood safety does not include the status of HTLV testing among its data collected from countries worldwide (554). In 2012, the Pan American Health Organization released the Caribbean Regional Standards for Blood Banks and Transfusion Services (555). The recommendations included procedures to screen for HTLV-1, with donors indefinitely deferred for HTLV-1 positivity and records of donors subsequently confirmed to have HTLV-1 retained for a minimum of 15 years (555).

HTLV-1 testing: who to test and when

Guidelines and strategies on who to test and when are very limited. In an advocacy letter to WHO in 2018, a group of clinicians, researchers and advocates recommended that the following populations be offered HTLV-1 testing, monitoring and counselling services (329): (1) sexually active populations attending sexual health clinics; (2) donors and recipients of blood, blood products or tissue; (3) pregnant women and children born to and partners of HTLV-1-positive mothers; and (4) people who inject drugs. The letter did not specify whether these populations should be tested universally or in specific countries.

Summary of country-specific HTLV-1 testing guidelines

Testing health-care workers exposed to HTLV-1

- **Northern Territory, Australia.** The policy for occupational exposure includes testing the source patient for baseline HTLV-1 infection and follow-up serology on the recipient for six months to monitor for seroconversion (572). Post-exposure prophylaxis with HIV antiretroviral therapy has reportedly been considered on an individual case basis; however, its efficacy in preventing the occupational transmission of HTLV-1 remains unknown.

Testing pregnant women

- **Japan.** The mother-to-child transmission programme recommends that pregnant women undergo serological HTLV-1 testing from early to mid-gestation (up to 30 weeks of gestation) (533). If a pregnant woman tests negative, she is determined to be uninfected. If positive, confirmatory testing by western blot or PCR is recommended.

Testing infants born to HTLV-1-positive mothers

- **Brazil.** The recommendation is to offer serological testing to children born to HTLV-1-positive mothers, but information on the circumstances and timing of testing could not be found (552,573).
- **Chile.** The recommendation is to offer serological and PCR testing to infants born to HTLV-1-positive mothers within the first 15 days of the newborn's life (538). If the first serological test conducted within 15 days of birth is positive, then PCR testing should be performed within 2–3 months. Otherwise, PCR testing at one year and three years of age is recommended.
- **Japan.** There is no consensus on antibody testing of infants in Japan. Follow-up of infants born to HTLV-1-positive mothers is based on the agreed method of infant nutrition and includes: at one month ensuring adherence to the agreed method of milk nutrition; for mothers whose chose short-term breastfeeding, a three-month follow-up is recommended to counsel on breastfeeding interruption (533). At three years of age, serological HTLV-1 testing is offered and confirmatory testing by western blot is performed for those testing positive.
- The 2005 WHO Caribbean HIV guidelines recommend that HIV-infected or exposed infants should have blood samples drawn at six weeks to two months of age for hepatitis B surface antigen and HTLV-1 serology testing, as appropriate (574), but current implementation is uncertain.

Testing strategies to prevent sexual or injecting drug use transmission of HTLV-1

- No specific policies or guidelines were found.
- **Brazil.** There is a recommendation to offering serological testing to the sexual partners of known HTLV-1-positive people, people with a history of injecting drug use and sex workers (552).
- **Chile.** Chile's management guidelines state that target populations include people who inject drugs, sex workers, sexual partners and immunocompromised people, including transplant recipients and people living with HIV (538).

ATL and HAM/TSP treatment guidelines

ATL is not curable with current treatment options, and there is no optimal standard treatment given the limited evidence from clinical trials (467). Although several publications of country treatment guidelines (Brazil (552), Chile (538), Japan, United Kingdom (575) and United States of America (576)) were identified, the ATL international consensus meeting report published in 2009 (and updated in 2019) has become the reference for both clinical trials and guide for clinically managing ATL (467, 577, 578). The international consensus report recommendations are based on expert opinion for best practice approach. Recommendations on treatment strategies are also based on the licensing of therapeutic agents in countries. In addition, all patients should be considered for enrolment in clinical trials.

There is currently no cure for HAM/TSP, and international guidelines were compiled on behalf of the International Retrovirology Association for managing people with HAM/TSP, with a focus on providing the evidence base for disease-modifying therapies (503). Consensus includes strong recommendations that clinical studies of therapy for HAM predefine patients into progression of disease categories. It also recommends that all everyone with HAM/TSP be considered for clinical trials of disease-modifying agents regardless of the severity and duration of disease. Overall, there was weak or insufficient evidence to support the use of currently available treatment options. In 2019, Japan has released Japan's clinical management guidelines on HAM/TSP.

Conclusion

Japan appears to be the only country to have implemented a nationwide policy to prevent the transmission of HTLV-1 up to 2020. Several countries are screening all or some blood donations for HTLV-1. There is no consensus on testing children born to HTLV-1-positive mothers. Given limited evidence from clinical trials, international guidelines for managing ATL and HAM/TSP are largely based on expert opinion for good practice. There are limited examples of any other HTLV-1-related health policies and, where policies exist, little or no evidence on their implementation or uptake.

CONCLUSIONS AND RECOMMENDATIONS OF THE WHO GLOBAL CONSULTATION ON HTLV-1

The initial draft of this report was prepared as background material for the first WHO Global Consultation on HTLV-1. The Consultation was held in Tokyo, Japan on 13–15 November 2019. The aim was to review the evidence synthesized in the report, assess the global situation of HTLV-1 from a public health perspective and provide recommendations for future research and implementable public health measures. The technical report was updated and revised following contributions from Consultation participants.

The WHO Consultation gave rise to the following conclusions and recommendations, reproduced here from the formal report of the Consultation.

Geographical distribution and surveillance

Based on available prevalence data, the geographical distribution of HTLV-1 infection continues to be highly focal, with known areas of high prevalence in Japan and several countries in central and western Africa, the Caribbean, Europe, Latin America, Oceania and the Middle East. Whereas migration has contributed to increased detection of HTLV-1 cases in some low-prevalence countries, there is little evidence of ongoing expansion beyond known endemic areas. There remain large populations for which the prevalence of HTLV-1 is unknown, such as countries in South and South-East Asia and northern and eastern Africa. In addition, reports of ATL and HAM/TSP in populous countries (such as India) with little HTLV-1 prevalence data currently available show the need for larger-scale studies. There are also gaps in information on the variation of prevalence within endemic countries and about prevalence in subpopulations that might be at higher risk, such as people who inject drugs and men who have sex with men. No country has yet adopted systematic approaches to the surveillance of HTLV-1.

Recommendation 1. *Guidance should be developed on HTLV-1 surveillance methods, to cover infections, its complications and public health responses.*

Recommendation 2. *Guidance should be developed on rapid assessment methods to determine HTLV-1 prevalence and the country and endemic context, to generate key data to inform national policies, priorities and investments.*

Testing strategies for HTLV-1 infection

The assays primarily used for diagnosing HTLV-1 infection are immunoassays that detect antibodies in serum and plasma (serology assays). Currently available commercial assays have high sensitivity and specificity and have been combined sequentially in testing strategies for diagnosis. Qualitative and quantitative NAT technologies for HTLV-1 DNA have also been developed but are not produced commercially. Outside high-income settings, there is a lack of access to NAT technology and uncertainty about what testing strategies and algorithms should be used.

Recommendation 3. *Guidance should be developed for low-resource settings on testing approaches and strategies for HTLV-1 detection that are appropriate to the setting and the purpose.*

Recommendation 4. *Guidance should be developed on HTLV-1 testing approaches, including guidance on who should be offered testing for HTLV-1, accompanied by strategies for communicating test outcomes to individuals and to communities.*

HTLV-1 transmission and prevention

The major modes of HTLV-1 transmission are well established by research. Mother-to-infant transmission occurs primarily through breastfeeding, at an average rate of about 20%, with shorter durations of breastfeeding associated with lower rates of transmission. Sexual transmission is more frequent from men to women than from women to men. There are limited data on transmission between same-sex couples. Transfusion of cellular blood products from a person living with HTLV-1 carries a very high risk of transmission (up to 60%), as does solid organ transplant. However, transfusion of cell-free plasma carries a low or no risk of transmission. The risk of nosocomial transmission or transmission associated with injecting drug use is unknown. It is well established that higher HTLV-1 proviral load is a risk factor for transmission, but the risk associated with very low or undetectable levels remains unknown. Prevention strategies explicitly targeting HTLV-1 transmission remain limited to screening of blood donations, and in a limited number of settings (Japan and some Latin American countries) the screening of pregnant

women and support to limit breastfeeding for those found to have infection. It is likely that existing strategies for the prevention of other sexually transmitted and bloodborne viral infections, such as condom programming, infection prevention and control and harm-reduction interventions for people who use drugs, may also contribute to preventing HTLV-1 transmission. Future research priorities may consider developing new biomedical prevention interventions, such as an HTLV-1 vaccine.

Recommendation 5. *Available data should be further analysed to better define the risk of HTLV-1 transmission associated with specific durations of breastfeeding, balanced with the risks of other adverse health outcomes that may result from reduced breastfeeding.*

Recommendation 6. *Available data should be further analysed to determine whether there is a level of proviral load below which transmission risk is negligible.*

Recommendation 7. *Consideration should be given to the opportunities (and risks) of integrating HTLV-1 control with other prevention strategies, such as condom promotion in high-risk sexual settings; partner notification strategies; universal precautions for infection control in health-care settings; and harm-reduction for people who inject drugs.*

Health effects, burden of disease and treatment

ATL and HAM/TSP are recognized as the major health effects of HTLV-1 infection, with the lifetime risk of each disease among people living with HTLV-1 estimated at 5% and 2%, respectively. The disease burden appears to be highly variable across the affected populations. HTLV-1 infection may have other effects that have been underrecognized, as suggested by an excess mortality of greater than 50% among people living with HTLV-1. The Consultation discussed other possible disease associations where evidence is not as strong, including uveitis and dermatitis.

Whereas there have been efforts to develop treatment guidelines for ATL and HAM/TSP, there is a lack of more general guidance on clinical management for people living with HTLV-1. The Consultation participants highlighted the need for further investments in clinical and therapeutic research and vaccine development.

Recommendation 8. *Collaborative cohort studies of people with HTLV-1 should be established to provide insight into geographical differences in disease manifestations and progression rates.*

Recommendation 9. *The burden of disease should be calculated to provide countries an indication of the impact of HTLV-1 infection.*

Recommendation 10. *WHO should consider incorporating HTLV-1 testing, diagnosis, management and care interventions into relevant clinical, service delivery and programmatic guidance and policies, such as those for sexually transmitted infections and preventing mother-to-child infection.*

General

Even in endemic countries, there is not wide awareness of HTLV-1, its modes of transmission, its disease course, its effects and strategies for controlling it. An international perspective will assist countries, communities and individuals affected by HTLV-1.

Recommendation 11. *WHO should develop a fact sheet on HTLV-1 for its website that would provide relevant information for people with HTLV-1, their families and caregivers and health-care workers caring for people with and at risk of acquiring HTLV-1. A key element of developing this fact sheet will be identifying the appropriate use of language relating to HTLV-1.*

Recommendation 12. *WHO should produce a technical report on HTLV-1, consolidating the three background papers and input from the Consultation.*

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