Public health aspects of HTLV-1: A literature review

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EXECUTIVE SUMMARY

The human T-lymphotropic virus type 1 (HTLV-1) was discovered in the early 1980s. It causes adult T-cell leukaemia/lymphoma (ATL) and is strongly associated with HTLV-1 – associated myelopathy or tropical spastic paraparesis (HAM/TSP). The most recent global review estimated that between 5 and 10 million people have HTLV-1 infection, with endemic focal points in diverse and distinct geographic locations. Many populations have never been surveyed so the true number of infections may be substantially greater.

Descriptive epidemiology of HTLV-1 in Australia

The first case of HTLV-1 in Australia was detected in 1988. All published information on the prevalence of HTLV-1 in Australia has been based on the detection of HTLV-1 antibody through testing in the clinical setting or blood donor screening. Reported prevalences vary considerably. The available information indicates that Aboriginal people in Central Australia have prevalences of HTLV-1 infection 1000-10000 times higher than in blood donors. There is very little information available from Australian areas of high prevalence on occurrence in younger age groups, particular those under 20, and no published population based seroprevalence studies. In the absence of information about HTLV-1 prevalence by age and sex, it is not possible to infer the primary modes of transmission in the Australian setting.

Transmission of HTLV-1

The main transmission pathways of HTLV-1 are from mother to infant, and through sexual contact and blood contact. The transmission rate to infants born to women with HTLV-1 has been reported at rates between 3.9% and 32%. Studies have also shown higher infection rates among children who are breastfed compared with formula fed children although the differences in several studies were not statistically significant. Children breast fed for shorter durations of time had lower prevalence of infection than those breast fed for longer. Most of the studies were done retrospectively, potentially introducing recall bias and other forms of information and selection bias.

Diseases associated with HTLV-1

The causal role of HTLV-1 in ATL and HAM/TSP is well established through a number of sources of evidence. Both conditions have been rarely reported in Australia. There have been several investigations, all cross-sectional and mostly from Central Australia, of the relationship between bronchiectasis and HTLV-1. They show around a two-fold higher rate of bronchiectasis in those with HTLV-1 compared to those without. Infection with *S. Stercoralis,* which causes strongyloidiasis, is also associated with HTLV-1 on the basis of studies from several countries. For a number of other diseases, the relationship to HTLV-1 has been proposed largely on the basis of case reports and case series.

Prevention of HTLV-1 transmission

The main strategy that has been evaluated for population level control of HTLV-1 is avoidance of extended breast-feeding. There is reasonable evidence that limiting the duration of breastfeeding, either to 3 or 6 months, can substantially reduce the risk of transmission. Most studies have had small sample sizes, and ascertained feeding status retrospectively. Several studies have also demonstrated associations between HTLV-1 infection in adulthood, and history of sexually transmitted infections and the non-use of condoms.

INTRODUCTION AND PURPOSE OF THE REVIEW

The discovery of the first human retrovirus, now referred to as HTLV-1 (an abbreviation that has been used to stand for several variants of the full name “human T-cell lymphotropic virus type 1”), was reported in 1981, by a team from the National Cancer Institute laboratory of Robert Gallo. Animal retroviruses had already been shown to be causes of haematological cancers, and within a year, a particular type of leukaemia, designated adult T-cell leukaemia/lymphoma or ATL was shown to be strongly linked to infection with HTLV-1.[1] The virus was also found to be a major cause of a progressive myelopathy that became known as HTLV-1 –associated myelopathy or tropical spastic paraparesis (HAM/TSP). HTLV-2 is a closely related virus but infection is far less common globally, and while implicated in myelopathy, it has not been conclusively connected to other disease outcomes.[2]

The HTLV-1 virus has a single strand of RNA for its genome, and primarily targets the T-cells of the immune system. Phylogenetic analyses have led to the naming of four major types of HTLV-1, each with its own geographic focal areas: Cosmopolitan subtype A (endemic in Japan and found in the Caribbean, Central and South America, North and West Africa, as well as the Middle East); Central African subtype B; Australo-Melanesian subtype C; and Central African/Pygmies subtype D.[3] C is the most divergent of the four subtypes, likely reflecting the opportunity for evolution in geographically isolated areas of the Pacific.[3] Antibody tests developed to detect the immunological response to infection with HTLV-1 have been used to investigate the population distribution of infection, modes of transmission, and associations with other diseases. As with other human retroviruses, including most notably HIV, the presence of antibodies in a person is understood to be synonymous with infection, and is lifelong.

The first major global review of the occurrence of HTLV-1 estimated that there were 10-20 million people living with HTLV-1 globally, and that infection concentrated in specific geographic areas, particularly parts of Japan, the Caribbean, Latin America, Africa and Melanesia.[4] A recent update of this review put the global estimate of prevalence at about half this level, while pointing out that there were major populations that had never been surveyed for HTLV-1, so the level could well be substantially higher.[3] The geographic heterogeneity of prevalence has been attributed to “founder” effects, with infection being established in a small number of individuals and sustained in relatively isolated populations.

Prevalence surveys that collected information on risk factors also demonstrated that the key modes of HTLV-1 transmission were the same as those of HIV, namely blood contact, sex, and from mother to child. In endemic areas, maternal transmission, particularly via breast feeding, was determined to be of particular importance. Prevention programs were implemented in several countries based on altering patterns of breast feeding, and deemed to have had success in reducing transmission rates.

There has been an extensive body of research on the extent to which HTLV-1 may be a cause of human diseases other than ATL and HAM/TSP. The vast majority of this research is cross-sectional, with few longitudinal studies and no randomised trials of interventions aimed at reducing the occurrence of HTLV-1 infection rates or associated pathology.

The first case of HTLV-1 in Australia was detected in 1988 in an Aboriginal person from Central Australia, and was followed by investigations of prevalence that found high levels of

infection in some remote populations. In the context of numerous other major health issues, and uncertainty about the distribution and public health importance of HTLV-1 in these communities, there has been debate ever since then as to what, if any, action needed to be taken to control the infection and its complications in Australia. Blood donor screening for HTLV-1 became mandatory nationally in 1993, and the Northern Territory made the infection notifiable in 2001, but no other interventions have been recommended so far in Australia.

Over the past five years, there has been a resurgence of clinical and public health interest in HTLV-1 in Australia, and the first real research efforts aimed to establishing the role of infection in ill health in Central Australia. Improved estimates of local prevalence are indicated as a priority in the *Fourth National Aboriginal and Torres Strait Islander Blood-borne Viruses and Sexually Transmissible Infections Strategy 2014-2017*. A workshop was held in Alice Springs in 2012 to discuss the current state of knowledge.[5]

With further information emerging on clinical and epidemiological aspects of HTLV-1, the Northern Territory's Sexual Health Advisory Group proposed that a review be undertaken of the current state of knowledge, with a possible view to holding another workshop. The Kirby Institute undertook to facilitate this review, working with interested partners representing clinical, public health and laboratory expertise.

This document is the result, and focuses on Australian descriptive epidemiology, modes of transmission, disease associations and the impact of control strategies. Key issues related to HTLV-1 not addressed in this review include its perception and understanding by affected communities, and the possible social and medical implications of any strategy that might be implemented to reduce HTLV-1 transmission or mitigate its health consequences in affected communities.

REVIEW METHODS

The descriptive epidemiology section was based on a comprehensive literature search of all published studies of HTLV-1 prevalence in Australia. It was supplemented by unpublished information from laboratories and researchers. For other sections, the review was based on published studies that met inclusion criteria as outlined in each section.

DESCRIPTIVE EPIDEMIOLOGY OF HTLV-1 IN AUSTRALIA

Published studies

The first case of HTLV-1 infection in Australia was reported in 1988.[6] Since then, all published information on the occurrence of HTLV-1 has been based on detection of antibody positivity in clinical settings or through blood donor screening. There have been no published data based on surveys that specifically aimed to be population based. Some early reports were based on testing of blood specimens obtained for other purposes.[7, 8] Reports have come from a variety of clinical and geographic settings, mostly in Central Australia, within which some distinguished Aboriginality while others did not.

The studies (summarised in Table 1) have reported a wide range in prevalences, from 1.7% among Aboriginal adults in the Northern Territory to 51.7% among adults in the Anangu Pitjantjatjara Lands of South Australia.[9-11] A large retrospective study assessing results of serology tests for HTLV-1 across the Top End and Central Australia (mostly in adult Aboriginal in-patients and health care workers who had needle stick injuries) reported an overall prevalence of 10.4%, with substantially higher prevalences in tests reported from Central Australia (17.1%, 51.7% and 50% for tests from the Northern Territory, South Australia and Western Australia respectively).[12] The prevalence reported for the Top End was substantially lower, at 0.8%.[12] Positivity was associated with Indigenous status, with 99.7% of cases detected as positive being in Aboriginal people.[12] In a retrospective study among patients receiving haemodialysis in the Top End of the Northern Territory the prevalence of HTLV-1 was 2.2%.[11] A recent study among Aboriginal adults admitted to Alice Springs Hospital who had a HTLV-1 test found a prevalence of 33.3%, with particularly higher rates reported in people from communities to the south of Alice Springs.[10]

Published studies have provided some limited information on prevalence by age and sex. Bastian et al[9] found that HTLV-1 prevalence increased with age, from 0% (95% CI 0-2.9%) in 0-14 year olds to 3.2% (1.3-7.4%) in those aged older than 45. The same study found no difference in prevalence between men and women. Results from a study in Alice Springs Hospital found that seropositivity increased with age in males, with a prevalence of 32.2% in patients aged <45, and 42.2% in patients aged ≥45 years.[10] No other significant differences were found by age or sex. Analysis of HTLV-1 serology requests to the Northern Territory Government Pathology Service found no difference in positivity between males and females.[12]

The Annual Surveillance Report on Transfusion-Transmissible Infections in Australia summarised the testing of blood donations, including trends in HTLV-1 prevalence and incidence. While HTLV-1 prevalence has remained very low in blood donors since testing began over 20 years ago, an unusually high number of positive donations was recorded in 2013, with nine donors tested positive to HTLV-1, representing a rate of 8.9 per 100,000 donations compared to 1.7 per 100,000 in 2012, a more typical year[13] Overall there has been a slight, non-significant increase in HTLV-1 prevalence in the period 2005-2013.[13] The cases in 2013 were detected in blood donors in NSW/ACT, Queensland, and Victoria and there were no obvious demographic patterns.

A new diagnosis of HTLV-1 has been a notifiable condition in the Northern Territory since 2001, reportable by laboratories to the NT CDC. Between 2001 and 2013 there were 864

new diagnoses of HTLV-1 reported, with the majority from Alice Springs (91%, Figure 1) [14]. There is considerable overlap between these notified cases and cases that have been reported in the peer reviewed prevalence/positivity studies summarised above.

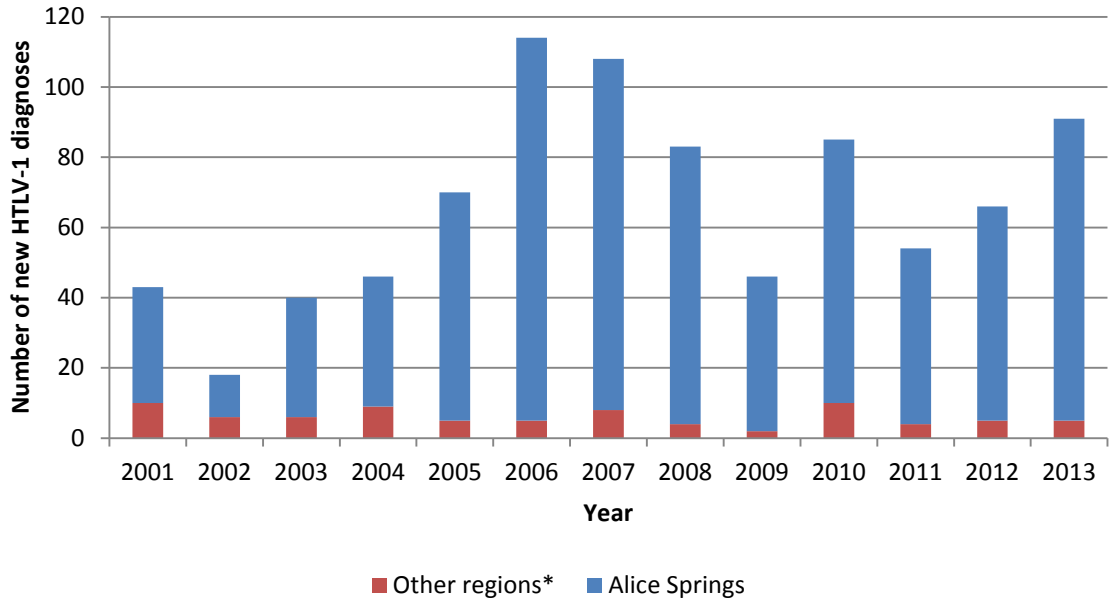

Figure 1: HTLV-1 notifications to the Northern Territory Centre for Disease Control, by year (2001 - 2013) and region**

* Other regions are: Barkly, Darwin, East Arnhem, Katherine. Regions combined due to small number of notifications in each region.
**Source: The Northern Territory Disease Control Bulletin

Table 1: Published studies of HTLV-1 prevalence in Australia

Reference	Year study conducted	Study population	Aboriginality	Age of population	Sex	Region	HTLV-1 prevalence
Bastian et al[9]	1988	Serum samples collected from Indigenous Australians for HBV and syphilis screening or blood cross-matching. Serum obtained from Royal Darwin Hospital Pathology Department.	All Aboriginal	Primarily adult. Eight percent of sample <15 years old.		Northern Territory (overall)	1.7% (28/1897); 95% CI: 1.2%-2.3%
						Barkly	4.7% (19/466); 95% CI: 3.1%-7.1%
						Alice Springs	13.9% (5/36); 95% CI 6.0%-28.9%
Bastian et al[7]	1991-1992	Blood donors in the Northern Territory	Not specified for all donors, HTLV-1 positive specimen from an Aboriginal donor	Predominantly adult, mean age 38.7. 1.5% (84) <20	50% (2863) male 50% (2810) female	Northern Territory	0.009% (1/11121)
Einsiedel et al[10]	2000-2010	Adults admitted to Alice Springs Hospital who had a HTLV-1 serological test	All Aboriginal	Adults (≥15 years old)	648 (45%) males 803 (55%) females	Residence was categorised by remote region (in 4 “quadrants”), town camp, rural, nursing home	33.3% (531/1614); 95% CI: 31.0%-35.6%
						Central Australia	38.5% (308/800); 95% CI: 35.1% – 42.0%
Davies et al[11]	2000-2009	Patients receiving haemodialysis for at least 3 months	371 (84.3%) Indigenous 53 (12.1%) non-Indigenous 16 (36%) Other	Primarily adult, range 5-78 years, <5% aged 19 or younger	196 (44.6%) male, 244 (55.4%) female	Top End of the Northern Territory (TENT)	2.3% (10/440) CI: 1.1% - 4.1%
Grivas et al[12]	2008-2011	All HTLV serology requests	2205 (62%)	Adults, mean	1706 (48%)	All	10.4%

	received by the Northern Territory Pathology Service between 2008 and 2011	Indigenous 1348 (37.9%) non-Indigenous 2 (0.1%) not specified	age 41.6 (±17.6)	male, 1849 (52%) female		(368/3555) CI: 9.4% - 11.4%
					Top End	0.8% (14/1716) CI: 0.4% - 1.4%
					Central Australia	17.1% (264/1541) CI: 15.2% - 19.1%
					SA	51.7% (61/118) CI: 42.3% - 61.0%
					WA	50.0% (22/44) CI: 34.6% - 65.4%
					Other	5.1% (7/136) CI: 2.1% - 10.3%

Unpublished data on HTLV-1 prevalence

Demographic data for 1889 Aboriginal people admitted to Alice Springs Hospital and had a test for HTLV-1 shows that seropositivity increases with age and is higher in men. Adult prevalence of seropositivity was 17.3% among those aged 15-29 years, 36.2% in 30-49 year olds and 41.7% in those aged 50-64 years. In a logistic regression analysis of the odds of positivity, age (odds ratio, OR per year = 1.04; 95% CI, 1.03-1.04), male gender (OR = 1.41; 95% CI, 1.08-1.85), residence in the south (OR = 10.7; 95% CI, 7.4-15.6) or west (OR = 4.4; 95% CI, 3.1-6.3) of Central Australia and history of a previous sexually transmitted infections (OR, 1.42; 95% CI, 1.04-1.95) were associated with HTLV-1 infection. There were also 3 seroconversions among 351 adults who were tested more than once during the study period, giving an incidence per 100 person years of 0.85 (CI 0.18-2.48). Among 77 children tested one three year old (1.3%) was positive for HTLV-1. Most children tested were not from communities with the highest seropositivity rates in adult patients.

In addition to peer-reviewed publications, data have been collected by public health laboratories on positivity rates among those tested for HTLV-1. PathWest Laboratory Medicine, Western Australia's primary public referral pathology laboratory reported that it had carried out 17280 HTLV-1 antibody tests in the period March 2006 to July 2014, including 16938 for which sex was recorded on the request. Roughly equal numbers of males and females were tested overall and the number of tests increased with age, with more females testing in the 20-29, 30-39 and 70+ year old age groups and more males being tested in all other age groups. The smallest numbers of tests were reported in those under 20.

The overall HTLV-1 positivity rate among those tested with gender specified was 1.97% (2.8% if all specimens included). Overall positivity was slightly higher for females tested than males (2.31 vs 1.63%), but male prevalence was higher in the age group 10-19 and 20-29. HTLV-1 positivity in samples tested was less than 3% in all years with the exception of 2009 and 2010 when it reached 6.2% and 4.1% respectively. The highest overall positivity of over 5% was found in 40-49 year old females. A major limitation to this data set is the absence of information on Aboriginality, place of residence and reason for test. The records include regional location but refer to where the specimen was collected, not necessarily residence. Of the specimens tested, 1129 (7%) were recorded as having been collected in remote or regional locations. Compared to specimens collected in metropolitan locations, positivity was 7.1 vs 2.6%.

Pathology requests to the Royal Darwin Hospital laboratory in 2011 (n=1637) indicate an HTLV-1 positivity of 9.8%. Virtually all of the testing is done on specimens from either Alice Springs or Royal Darwin hospitals, with a much higher positivity in Alice Springs (21.1%) compared to Darwin (1.9%) and lower for the other locations combined (0.6%).

TRANSMISSION OF HTLV-1

Three modes of transmission have been demonstrated for HTLV-1: vertical (mother to child) transmission, sexual transmission, and through blood contact, either in a medical setting or as a result of injection of illicit drugs. The universal screening of blood and tissue for HTLV-1 and the widespread effectiveness of infection control for procedures involving risk of blood contact in Australia has eliminated this mode of transmission, and will not be covered in this review. Other modes of blood contact, for example through the re-use of contaminated injecting equipment used for administration of illicit drugs, are recognised as a highly effective means of transmission of all blood borne viral agents including HTLV-1. Australian policy for HIV and hepatitis C prevention has ensured the wide availability of clean injecting equipment through needle and syringe distribution sites including pharmacies. The remainder of this section will focus on mother to child transmission and sexual transmission, based on international research. There have been no studies of HTLV-1 transmission reported from Australia.

Vertical (mother to child) transmission

There have been several reviews on the extent and risk factors of HTLV-1 transmission from mother to child in endemic populations.[15] Early studies detected HTLV-1 infected cells in breast milk from HTLV-1 positive mothers.[16, 17] HTLV-1 infection has been transmitted to marmosets via an oral inoculation of fresh milk from lactating women with HTLV-1.[18] Depending on duration of breast feeding, estimates of the transmission rate to infants born to women with HTLV-1 have ranged from 3.9% and 32%.[15]

Studies have also demonstrated a generally higher prevalence of HTLV-1 infection among breastfed children of women with HTLV-1 compared with formula fed children[19-23] (Table 2). However, the majority of risk ratios calculated in these studies are not statistically significant at the 0.05 level, possibly due to small sample sizes and the limited duration of breast feeding. It is also possible that factors other than infant feeding practices differed between the comparison groups and may have acted as confounders. The majority of studies prospectively or retrospectively followed up women with HTLV-1 infection and categorised them according to whether they had elected to breast feed or formula feed their infants.

Table 2: *Studies comparing HTLV-1 prevalence between people who as infants were* exclusively breast-fed versus formula fed.

Reference	Age at time of study	Prevalence of HTLV-1		Odds ratio (95% CI), p value
		Breast-fed	Formula	
Tsuji et al (1990) Japan[21]	1-13 years old	17/44 (39%)	0/10 (0%)	Unable to calculate
Takahashi et al (1991) Japan[22]	1-25 years old*	24/229 (10.0%)	9/158 (5.7%)	2.0 (0.9-5.1), p=0.07
Hirata et al (1992) Japan[19]	0-19 years old (mean, 5.5)	18/97 (18.6%)	10/78 (12.8%)	1.5 (0.6-4.0), p=0.3
Takezaki et al (1997) Japan[20]	0-3 years old	15/115 (13.0%)	4/162 (2.5%)	5.9 (1.8-25.1), p=0.0006
Hino et al (2011) Japan[23]	Not known	89/567 (15.7%)	29/1152 (2.5%)	7.2 (4.6-11.5), p<0.001

* 1-5 years old (prospective study); 11-25 years old (retrospective study)

As shown in Table 2, HTLV-1 was detected in children whose feeding was reported as exclusively formula. Based on the prevalences in these children, it can be estimated that the risk of intrauterine and peripartum transmission of HTLV-1 is around 5%.[24-26]

Table 3 summarises comparisons of the rates of HTLV-1 infection between those who as infants were formula fed, breast fed for a shorter duration (<6 months) and breast fed for a longer duration. All of the studies demonstrated a significantly lower HTLV-1 prevalence among those who were breastfed for a shorter duration versus those breastfed for longer.

The studies that did not detect associations with duration were generally smaller with information on breastfeeding duration collected retrospectively. A recent, large study from Japan concurred with previous studies in demonstrating that the incidence of HTLV-1 infection in formula fed children was significantly lower than in children breast fed for greater than 6 months, and that HTLV-1 incidence in children breastfed for less than 6 months was lower than in children breastfed for greater than 6 months.[23] However, in contrast to previous Japanese studies, this one found a significantly higher prevalence of HTLV-1 among children breast fed for less than 6 months than in formula fed children.[23] Given the small sample sizes of the other studies, it is likely that previous analyses were underpowered to detect this difference as significant.

In addition to duration of breastfeeding, the risk of HTLV-1 infection in children of seropositive mothers was predicted by the provirus load in breast milk, concordance of HLA class I type between mother and child and prolonged duration of ruptured membranes during childbirth.[27-29] Analyses by Li et al found that after adjustment for other known risk factors

provirus load remained a significant predictor of transmission (RR=2.34 per quartile; 95% CI, 1.37-4.01).[28] The hazard ratio for children with 3 matched HLA class I types compared to children with 5 or 6 matched types, was 3 (95% CI, 1.0-9.5).[29]

Table 3: The effect of duration of breastfeeding on HTLV-1 prevalence

Reference	Type of study	Duration of breastfeeding (Group 1)	Duration of breastfeeding (Group 2)	Formula	Group1 vs Group2 OR (95% CI), p value	Formula vs Group1 OR (95% CI), p value
		0-6 months	**>6 months**			
Takahashi et al (1991)[22] Japan	Retrospective cohort (210) Prospective cohort (177)	4/90 (4.4%)	20/139 (14.4%)	9/158 (5.7%)	0.27 (0.07-0.87), p=0.016)	1.3 (0.35-5.9), p=0.67
Hirata et al (1992)[19] Japan	Retrospective cohort (159) Prospective cohort (16)	7/61 (11.5%)	11/36 (30.6%)	10/78 (12.8%)	0.4 (0.2-0.9), p=0.002	1.3 (0.4-3.8), p=0.59
Takezaki et al (1997)[20] Japan	Prospective cohort	2/51 (3.9%)	13/64 (20.3%)	4/162 (2.5%)	0.2 (0.05-0.8), p=0.01	0.6 (0.09-7.1), p=0.6
Hino et al (2011)[23] Japan	Retrospective cohort	15/202 (7.4%)	74/365 (20%)	29/1152 (2.5%)	0.3 (0.2-0.6), p=0.001	0.3 (0.2-0.7), p<0.001
		0-12 months	**>12 months**			
Wiktor et al (1997)[27] Jamaica	Prospective cohort	8/86 (9%)	19/60 (32%)		0.2 (0.08-0.6), p=0.006)	No formula group

Sexual transmission

HTLV-1 has been detected in cervical secretions[30, 31] and seminal fluid[32] of people with infection. One study compared serum, saliva and cervicovaginal secretions from 17 women with HTLV-1 in Central Africa in regard to IgG antibodies to HTLV-1.[31] Results from this study showed that the titre of HTLV-1 IgG antibodies was over 450 times lower in cervicovaginal secretions and 1800 times lower in saliva, compared to serum.

Cross sectional serosurveys have identified that sexual activity is a risk factor for HTLV-1, based on higher prevalences in populations such as sex workers,[33, 34] men who have sex with men,[34] and sexual partners of people who are HTLV-1 positive.[35] Table 4 summarises a selection of cross sectional surveys conducted among sex workers. While most found higher seroprevalences of HTLV-1 among sex workers compared to the general population,[36, 37] one study from the Democratic Republic of the Congo found HTLV-1 prevalence to be similar among sex workers and pregnant women.[38] A number of sexual behaviours have been identified as risk factors for HTLV-1 infection in cross-sectional studies including history of unprotected sex,[39] number of partners,[40, 41] and a history or coinfection with other STIs.[34, 37, 38, 41, 42]

A recent systematic review evaluated the evidence for sexual transmission of HTLV-1 and found that the rate of HTLV-1 transmission from males to females is higher than transmission from females to males, and transmission risk is associated with co-infection with ulcerative or inflammatory sexually transmitted infections.[43] They also found associations between higher transmission risk and the presence of antibodies to the HTLV-1 protein Tax, higher proviral load in peripheral blood lymphocytes, and higher levels of HTLV-1 in cervicovaginal or seminal secretions.[43]

A summary of key transmission studies is provided in Table 5. An early Japanese couples study estimated the rates of HTLV-1 transmission over a 10 year period to be 60.8% from husband to wife and 0.4% from wife to husband.[44] A more recent prospective study of 85 serodiscordant couples found a combined HTLV-1 and HTLV-2 transmission rate of 0.9 transmission per 100 person years with the male to female rate higher than female to male (1.2 vs 0.4 transmissions/100 person years).[35]

Table 4: Selection of cross sectional HTLV-1 serosurveys of sex workers and factors associated with HTLV-1 positivity

Reference	Country	Population	Key findings	Significant association with HTLV-1
Khabbaz et al[45]	United States	Sex workers (n=1305)	HTLV-1/2 seroprevalence rates between 0%-25.4% (6.7% overall)	Race Intravenous drug use Hepatitis B seropositity Area of recruitment Years of sexual activity
Verdier et al 1989[36]	Ivory Coast	Sex workers (n=390) and general population groups (n=1291)	HTLV-1 seroprevalence 7.4% in sex workers compared to 1.8% seroprevalence in other subgroups representative of the general population ($p<0.001$)	No factors assessed
Delaporte et al[38]	Democratic Republic of the Congo	Sex workers (n=1183) and pregnant women (n=1166)	In two regions, there was no significance difference in the HTLV-1 seroprevalence of sexworkers (4.3%) and pregnant women from the same region (3.5%).	Increasing age Active syphilis HIV infection [increasing number of years in sex work, number of clients per day, and condom use – NO association]
Gotuzzo et al[39]	Peru	Sex workers (n=400)	7% HTLV-1 seropositivity	Length of sex work Lack of condom use Presence of antibodies to HSV-2 Prior Chlamydia infections
Berini et al 2007[37]	Argentina	High risk groups (n=2055)	Overall HTLV-1 seroprevalence was 1.3% in the high risk groups (IDU, female sex workers, MSM, patients with TB, patients attending clinics with STIs).	No factors assessed

Table 5: Studies of sexual transmission of HTLV-1

Reference	Country	Type of study	Population	Key findings
Murphy et al 1989[46]			2050 consecutive patients with new episode of STI	In women, risk factors were: >10 lifetime sexual partners and a current diagnosis of syphilis. In men, a history of penile sores or ulcers and a current diagnosis of syphilis.
Kajiyama et al 1986[44]	Japan	Cross sectional		Male to female 60.8% over a 10 year period Female to male 0.4% over a 10 year period.
Roucoux et al 2005[35]	US	Prospective	30 HTLV-1 positive blood donors and partners.	The male to female 1.2 /100 person years. The female to male 0.4 transmissions/ 100 person years.
Stuver et al 1993[47]	Japan	Prospective	Couples followed for 5 years; 95 concordant positive, 97 discordant, 342 concordant negative	6 transmissions among 80 at-risk subjects 1 among 549 subjects married to people without HTLV-1 2.5 transmissions / 100 person years.

DISEASES ASSOCIATED WITH HTLV-1

Overview of disease associations

HTLV-1 is now clearly recognised as being the primary causal agent for adult T-cell leukemia (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Reviews of the pathogenesis of these two conditions, and the role played by HTLV-1, have been published. People with HTLV-1 have been estimated to have a lifetime risk of 3-5% and 0.25-3% of developing these two diseases, respectively. However, there is considerable geographic variability in the extent to which they are reported in people with HTLV-1,[48] which may reflect differences in reporting and surveillance systems and in the presence of other causes of morbidity and mortality. Assuming a population of 10,000 people with 20% prevalence of HTLV-1 and 3% lifetime risk of ATL at a median life expectancy of 60 years, there would be around 1 case of ATL expected per year.

In the Northern Territory, since ATL and HAM/TSP were designated as notifiable conditions, there has been 1 case of ATL and no HAM/TSP reported to public health authorities. However, there have been additional cases from Central Australia of both conditions written up in medical publications.[49,50, 51]. Among adults admitted to Alice Spring Hospital who had a test for HTLV-1 there were 4 cases of probable HAM/TSP (confirmatory cerebrospinal fluid tests were not done for clinical reasons) and 2 cases of ATL (unpublished data, Einsiedel). It is possible that cases were not reported if patients were transferred to medical centres outside the Northern Territory for care, prior to the confirmation of diagnosis.

The diseases that have been proposed as being linked to HTLV-1 can be categorised as malignancies, inflammatory syndromes, infectious diseases and dermatological syndromes. Examples of diseases within each of these categories are given in Table 6. There is very substantial variation across these diseases in regard to the type of evidence available to determine whether the association is causal. It ranges from case reports or series (weakest evidence) to case control studies to cohort studies (strongest evidence of association). Biological evidence for associations with a few of the diseases (primarily ATL) includes the presence of HTLV-1 in lesions, associations between risk of disease and HTLV-1 proviral load and the development of disease in an animal model.

All of these diseases are present in Central Australia, with some at occurring that rates that are extreme by Australian and even international standards. The co-occurrence of two conditions at high levels in the one population does not of course prove a causal association. In the following sections, we consider in detail the epidemiological evidence available for two diseases of importance in Central Australia, that have been proposed as being linked to HTLV-1. In considering the role of HTLV-1 in the causation of a specific disease, a distinction can be made between HTLV-1 leading to increased susceptibility to the disease on one hand, as compared to HTLV-1 as a worsening factor, which increases the rapidity or severity of disease manifestations, or reduces the efficacy of treatment. Both types of association are important. The literature on the relationship between HTLV-1 and specific diseases addresses them to a degree which varies by disease.

Table 6: Examples of diseases reported in association with HTLV-1 and basis of this association.*

	Epidemiological evidence			Biological evidence	
	Case reports or series	**Case control studies**	**Cohort studies**	**HTLV-1 detected in lesions**	**Animal model**
Inflammatory syndromes					
HAM/TSP	Yes[52, 53]	Yes[54]	Yes[55, 56]	Yes[57, 58]	Yes[59, 60]
Bronchiectasis	Yes[61-65]	Yes[66]		Yes[67]	Yes[68]
Uveitis	Yes[69, 70]	Yes[71, 72]		Yes[73, 74]	Yes[75]
Arthropathy	Yes[76, 77]		Yes[78]	Yes[79]	Yes[80, 81]
Sjogren's syndrome	Yes[82, 83]			Yes[84]	Yes[80, 85]
Polymyositis	Yes[86, 87]				Yes[75]
Thyroiditis	Yes[88, 89]			Yes[90, 91]	
Malignant diseases					
ATL	Yes[92, 93]	Yes[94]	Yes[95, 96]	Yes[97]	Yes[98]
Cutaneous T-cell lymphoma	Yes[99, 100]			Yes[101]	
Infectious diseases					
Strongyloides stercoralis	Yes[102-104]	Yes[105,106,107]			
Crusted scabies	Yes[108, 109]				
Tuberculosis	Yes[110-112]	Yes[113]			
Dermatological syndromes					
Infective dermatitis (infective skin lesions)	Yes[114, 115]				
Autoimmune skin disorders	Yes[116]				

*** Table modified from Verdonck et al.[48]**

Bronchiectasis

A broad spectrum of lung disease has been reported, primarily via case series, in people with lung conditions found to have HTLV-1. Published case reports describe people with HTLV-1 who have bronchiolitis,[117] diffuse panbronchiolitis,[117-119] pneumonia.[120] A study from Central Australian has reported on HTLV-1 in association with a range of pulmonary diseases.[10]

Bronchiectasis is defined as a permanent abnormal dilation of one or more bronchi and typically represents an advanced stage of persistent airway inflammation. Clinically, bronchiectasis is characterised by a chronic cough, excessive sputum production, bacterial colonisation, and recurrent bacterial infections. Diagnosis is made radiologically. The primary cause of bronchiectasis is considered to be childhood respiratory infections, pertussis, measles and tuberculosis. However, inflammation due to autoimmune conditions such as rheumatoid arthritis and systemic sclerosis are also associated with bronchiectasis. HTLV-1 has been proposed as playing a causal role through the release of pro-inflammatory cytokines from HTLV-1 infected cells in the pulmonary parenchyma, triggering an inflammatory response and resultant injury.[121-124]

Aboriginal people in Central Australia have among the highest reported prevalences of bronchiectasis worldwide (1%), with cases occurring at a young age and frequently severe.[61] The condition is associated with significant morbidity due to pulmonary hypertension, cor pulmonale and respiratory failure, and high mortality rates with 34% of patients followed up at Alice Springs Hospital dying during 7 years of observation, at a median age of 42.5 years. People with bronchiectasis who also had HTLV-1 had a worse course of illness than those without HTLV-1.

Among the diseases that have been investigated as associated with HTLV-1 apart from ATL and HAM/TSP, bronchiectasis (and its related spectrum of pulmonary conditions) stands out, because of its severity and the limited therapeutic options for advanced disease. There has been no published systematic review of the relationship between HTLV-1 and bronchiectasis. We therefore conducted a systematic review to determine the extent and level of evidence for the association between HTLV-1 and bronchiectasis. Published literature was searched using the MEDLINE database (to April 2015) for studies that examined the relationship between HTLV-1 and bronchiectasis. The search terms used were: [HTLV-1 or human T-cell lymphotrophic virus] AND [bronchiectasis or pulmonary or lung or pneumopathy]. The computerized search was supplemented with manual searches of reference lists additional studies. Studies were categorised by study design (case series or reports, case control studies, and cohort studies) and place of research (international studies and Australian studies). The study selection process is shown in Figure 2.

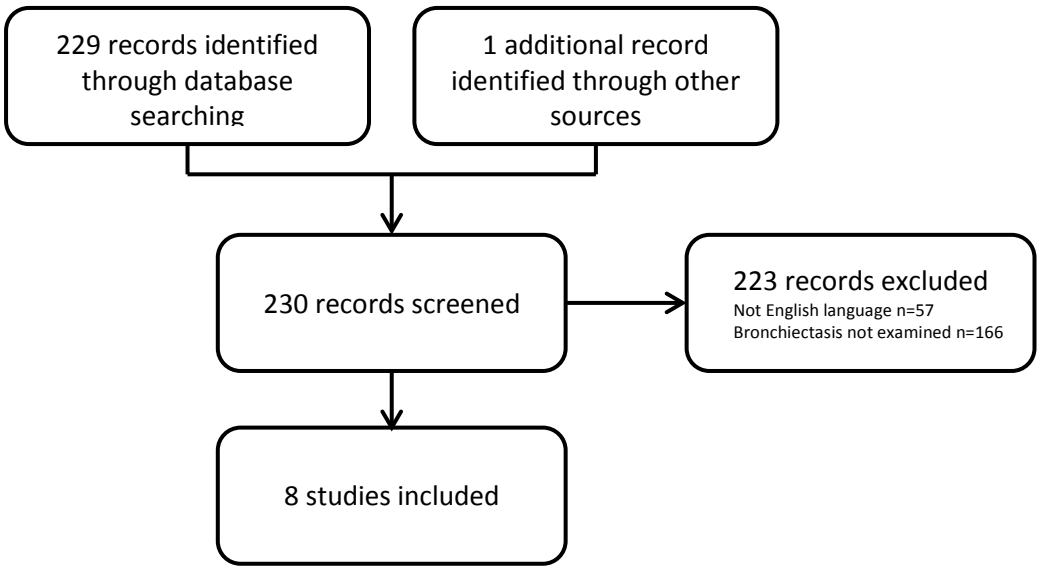

Figure 2: Flow diagram of the identification of studies that examine the association between HTLV-1 and bronchiectasis.

Eight publications were identified as being relevant and are included in Table 7. We were unable to identify studies from outside Australia that have compared rates of bronchiectasis in people with and without HTLV-1, or compared HTLV-1 rates in people with and without bronchiectasis. In one study, from the UK, people with "known" HTLV-1 related diseases were 15 times more likely to have bronchiectasis than those who had asymptomatic HTLV-1 infection.[125] Two further studies examined the pulmonary findings of HTLV-1 patients but did not include a comparison group of people without HTLV-1.[64, 126] Results of these radiological studies showed that pulmonary abnormalities were found in 30.1% (98/320)[64] and 61.3% (65/106)[126] of HTLV-1 patients. Bronchiectasis was found in 15.6% (50/320)[64] and 26.4% (28/106)[126] of the HTLV-1 positive patients.

In Australia, there have been five published studies of the association between HTLV-1 and bronchiectasis (Table 7). Three of the reports were of case series, and there has been one cross-sectional study and one case control study. In the cross-sectional study, bronchiectasis was detected 2.4 times more frequently in people with HTLV-1 than in those without.[10] In the case control study, HTLV-1 infection was more common among people with bronchiectasis than those without bronchiectasis and HTLV-1 infection was associated with bronchiectasis in a multivariate analysis (odds ratio 1.8, Table 7)[66] that adjusted for possible confounders including other infectious conditions and alcohol consumption. In a case series of people admitted to hospital with bronchiectasis, those positive for HTLV-1 were more likely to have scabies (15/52, 29% vs 4/37, 11%; p=0.041) and have been admitted for treatment of skin infection (8/52, 15% vs 0/37, p=0.019).[61] Consistent with the possible aetiological role of a diffuse inflammatory process, bronchiectasis in those with HTLV-1 was more often multifocal than for those who were HTLV-1 negative.[61]

On the basis of this literature review, it appears that the two Australian studies are the only ones to directly measure the association between HTLV-1 and bronchiectasis. They find an approximately doubling of risk of bronchiectasis in relation to HTLV-1. The two-fold increase found in the Central Australian case-control study has been confirmed in a much larger study in the same population, comparing 80 radiologically confirmed cases (representing 90% of all eligible cases admitted to Alice Springs Hospital during the study period) with 160

matched controls. (unadjusted OR, 2.28; 95% CI, 1.32-3.95, Einsiedel unpublished data). With a small number of studies essentially in the one population and limited adjustment for confounding, the evidence for HTLV-1's role in the causation of bronchiectasis remains solid but not overwhelming. Nevertheless it has recently been highlighted in the American Public Health Association's recognition of bronchiectasis as HTLV-1 related in the most recent edition of its Infectious Disease Handbook

Table 7: Studies included in the systematic review that examined the relationship between HTLV-1 and bronchiectasis.

Reference	Study design	Country /Region	Year study conducted	Study population	Conclusions	Comments on study
International studies						
Honarbakhsh and Taylor (2015)[125]	Case series	UK	1993-2012	Two groups of patients: HTLV-1 symptomatic patients (ATL, HAM/TSP, polymyostitis and strongyloidiasis) and asymptomatic HTLV-1 patients.	• Bronchiectasis was identified in 1/246 of those with asymptomatic HTLV-1 (0.4%) and 13/167 (7.8%) symptomatic patients.	No HTLV-1 negative comparison group.
Yamashiro et al (2012)[126]	Case series	Japan	Not defined	106 patients with HTLV-1 who had undergone chest CT scans	• Chest CT scans revealed abnormalities in 65 (61.3%) of 106 HTLV-1 patients. • 28 (26.4%) of 106 HTLV-1 patients found to have bronchiectasis.	Study population all had CT scans indicating possible bias as they may have been symptomatic for lung conditions.
Okada et al (2006)[64]	Case series	Japan	1996-2004	320 patients with HTLV-1 who had undergone chest CT scans at three institutions.	• Chest CT scans revealed abnormalities in 98 (30.1%) of 320 HTLV-1 patients. • 50 (15.6%) of 320 HTLV-1 patients found to have bronchiectasis.	Study population all had CT scans indicating possible bias as they may have been symptomatic for lung conditions. Radiologists not blinded to HTLV-1 status.
Australian studies						
Einsiedel et al (2014)[10]	Cross-sectional survey	Central Australia	2000-2010	Adults admitted to Alice Springs Hospital (ASH) who had a HTLV-1 screening test.	• Bronchiectasis prevalence was 16.8% (81/507) among HTLV-1 positive patients and 7.1% (61/944) among HTLV-1 negative patients. Crude relative risk is 2.4 (p=0.001).	Bronchiectasis was identified using ICD-10 codes and confirmed by chest high resolution computed tomography.
Mollison et al[63]	Case series	Central Australia	1992-1993	Adults admitted to ASH who had a HTLV-1 screening test and who had diseases associated with HTLV-1.	• Bronchiectasis was present in 25% (4/16) HTLV-1 positive patients and 3% (1/33) HTLV-1 negative patients (p=0.003).	
Einsiedel et al (2012)[61]	Case series	Central Australia	2000-2006	Adults admitted to ASH with bronchiectasis.	• 52/89 (58.4%) indigenous patients admitted with bronchiectasis were positive for HTLV-1.	No comparison group without bronchiectasis
Steinfort et al (2008)[65]	Case series	Central Australia	2004-2005	Adults discharged from ASH with a primary diagnosis of bronchiectasis.	• 61 patients identified and 25 had HTLV-1 serology performed. • 18/25 (72%) were HTLV-1 positive.	No comparison group without bronchiectasis
Einsiedel et al (2014)[66]	Case control	Central Australia	2008-2009	36 Indigenous adults admitted with bronchiectasis matched (by	• HTLV-1 infection was more common in cases (25/36; 69.4%) than controls	Patients were more likely to have more severe

	study	sex, age, ethno-geographic region) to 36 controls.	(15/36; 41.7%); p=0.018. • HTLV-1 infection was associated with bronchiectasis in a multivariate model (aRR 1.8; 95% CI 1.2-2.8).	bronchiectasis than those in the community potentially biasing results. Multivariate model controlled for a number of factors (see text).

Strongyloides stercoralis

Strongyloides stercoralis is an intestinal nematode that is able to complete a life cycle and multiply within its host, establishing a chronic infection. *S. stercoralis* is distributed worldwide, predominantly in tropical and sub-tropical regions and infects between 50-100 million people globally. While the majority of *S. stercoralis* infections are asymptomatic for extended periods, many people develop a wide range of debilitating symptoms, primarily dermatological, pulmonary and gastrointestinal, collectively referred to as strongyloidiasis. Pharmaceutical treatment is available and generally highly effective. A severe, life-threatening form of the disease can occur following dissemination of the parasite particularly in people who are immunocompromised. Stool examination is the gold standard test for the diagnosis of *S. Stercoralis.* Serological tests have high cross reactivity with several other helminthic infections. We conducted a systematic review of the association between HTLV-1 and *S. Stercoralis* infection.[48, 127]. Published literature was searched using the MEDLINE database (to April 2015). The search terms used were: [HTLV-1 or human T-cell lymphotropic virus] AND [strongyloides]. The computerized search was supplemented with manual searches of reference lists additional studies. Studies were categorised by study design (case series or reports, case control studies, and cohort studies). The study selection process is shown in Figure 3.

Forty studies were identified as being relevant with the majority of these being case reports or series (n=37). Three case control studies and no cohort studies were identified. A summary of the case control studies is presented in Table 8. Two of the three case control studies found an association between HTLV-1 and infection with *S. stercoralis*. A study from French West Indies compared strongyloides prevalence between HTLV-1 positive (cases) and negative (controls) blood donors and found a significant association (OR = 3.6, CI 1.8-7.3).[107] A Peruvian report of 21 cases and controls presented higher HTLV-1 seropositivity rates among patients with hyperinfections compared with the matched controls (86% vs 4.7%; p=0.001).[106] A case control study from Jamaica found the prevalence of infection with *S. stercoralis* was similar between cases and controls (12.7% vs 11.7%; p=0.79).[105]

A number of case series have reported on HTLV-1 and infection with *S. stercoralis*.[103, 104, 127] Concurrent infection with HTLV-1 has also been associated with dissemination of the parasite and severe strongyloidiasis.[106, 128,129] Data have been published showing a reduced efficacy of chemotherapy with thiabendazole among patients in Japan with *S. stercoralis* HTLV-1 infection.[130]

In Central Australia, a hospital based cohort found a 24% prevalence of infection with *S. stercoralis* among 1126 Aboriginal adults.[10] The reported number of hospital admissions per patient for strongyloidiasis was more than twice as high among those who were also positive for HTLV-1 compared with those negative.[10]

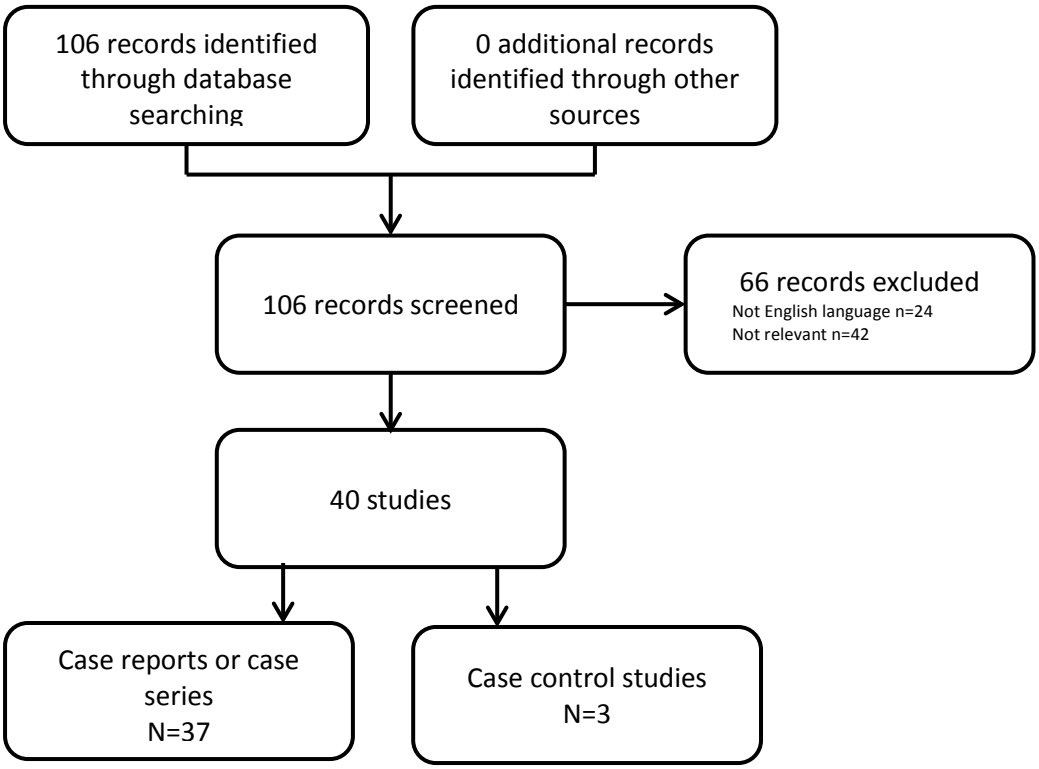

Figure 3. Flow diagram of the identification of studies that examine the association between HTLV-1 and *Strongyloides*.

Table 8. Case control studies included in the systematic review that examined the relationship between HTLV-1 and *S. stercoralis*.

Study	Country	Study type	Cases	Controls	Matched by	Strongyloides detection method	Results
Chaturvedi et al[105]	Jamaica	Case control	HTLV-1 positive blood donors (n=482)	HTLV-1 negative blood donors (n=355)	Frequency matched by age (±5 years), sex, date of blood donation (±3 months)	Antibody assay	Prevalence of *S. stercoralis* was similar between cases and controls (12.7% vs 11.7%; p=0.79)
Gotuzzo et al[106]	Peru	Case control	Patients presenting to hospital with *S. stercoralis* hyperinfection (n=21)	Healthy patients with no Stronglyoides enrolled at the same hospital (n=21)	Age and sex matched	Stool detection	HTLV-1 seropositivity rates (18/21; 85.7%) among patients with *Strongyloides* hyperinfections were significantly higher than the rates (1/21; 4.7%) for the matched control subjects (p=0.001).
Courouble et al[107]	French West Indies	Case control	HTLV-1 positive blood donors (n=85)	HTLV-1 negative blood donors (n=255)	Age (± 5years), 1:3 ratio	Antibody assay	*S. stercoralis* infection was independently associated with HTLV-1 seropositivity (OR = 3.6, CI 1.8-7.3).

HTLV-1 PROVIRAL LOAD

HTLV-I is not usually found as cell-free virus so the viral load is quantified as the proportion of peripheral blood mononuclear cells (PBMCs) carrying integrated HTLV-I provirus. This is referred to as proviral load (pVL). A commercial kit for the measurement of HTLV-1 pVL is not available and therefore, several in-house quantitative real-time PCR assays have been developed.[131-134]

HTLV-1 pVL varies 1000-fold between people with the infection,[135] but is relatively stable within an individual over time.[136] There have been a number of studies that have assessed the relationship between HTLV-1 pVL and either risk of transmission[34, 46, 71] or the occurrence of HTLV-1 related disease. High HTLV-1 pVL has been associated with an increased risk of HAM/TSP,[137] ATL,[138] uveitis,[67] dermatitis[139] and bronchiectasis,[66] with median proviral load 100 fold higher among bronchiectasis cases with HTLV-1 than controls, and an association between the extent of radiologically defined pulmonary injury and the proviral load. Higher HTLV-1 pVL has also been demonstrated in people with HTLV-1 related disease compared to those with HTLV-1 but no symptoms.[137, 140] Finally, studies have shown that infection with *Strongyloides stercoralis* might increase circulating HTLV-1 proviral loads.[138, 141]

POSSIBLE STRATEGIES FOR PREVENTION OF TRANSMISSION

There are no systematic reviews available on the prevention of HTLV-1 transmission. However there are several literature reviews that have dedicated sections to reviewing strategies for the prevention of HTLV-1 transmission.[15, 21, 43, 142, 143] A brief summary will be provided below.

Prevention of vertical HTLV-1 transmission

Preventing the vertical transmission of HTLV-1 has been promoted as the key measure for control of infection in Japanese communities where infection is endemic, because mother to child transmission is believed to be the primary route of transmission. In addition, it may also help reduce the incidence of ATL because acquisition of HTLV-1 maternally has been identified as a major risk factor for the development of this condition.[144] There have been no randomised trials of interventions to prevent infant exposure to HTLV-1, but several observational studies have been reported, generally using ecological designs.

1. *Exclusive formula feeding in place of breastfeeding*

   In Japanese communities with endemic HTLV-1 infection, recommendations for women with HTLV-1 to exclusively formula feed their babies were introduced in order to reduce HTLV-1 vertical transmission. Kashiwagi et al (2004) observed a reduction in the prevalence of HTLV-1 infection in Okinawa, Japan (from 20-25% to 4%) and attributed it largely to a decrease in the number and duration of mothers breastfeeding.[145] This conclusion must be considered with caution however as the age-specific rates fell in age-groups too old to be affected by the breastfeeding policy. Furthermore, the relative

risk reduction in HTLV1 over time was the same regardless of breastfeeding status of infants. This suggests that other factors had a role in the fall of HTLV1 prevalence[20,23].

A small study in Brazil reported that newborns were screened for HTLV-1 using a neonatal screening program and breastfeeding interruption was recommended for those whose mothers were confirmed HTLV-1 positive. The rate of vertical transmission following interrupted breastfeeding was 2.8% (1/35; 95% CI 0.1%-14.9%), similar to rates reported in other studies where breastfeeding was substituted with formula after 6 months.[20]

2. *Limit the duration of breastfeeding*

Studies have shown that a shorter duration of breastfeeding (<6 months) has resulted in lower transmission HTLV-1 rates between mother and child. See the section on Vertical Transmission for more detailed data.

3. *Freeze-thaw method*

The infectivity of HTLV-1 in breast milk of seropositive mothers was shown to be lost during the freezing and thawing processes. Freeze-thawing destroys HTLV-1 infected cells in breastmilk *in vitro* and small field studies demonstrated a reduction in the mother to child transmission of HTLV-1.[146]

Prevention of sexual transmission of HTLV-1

There have been no published studies of the impact of any strategies for reducing the sexual transmission of HTLV-1 infection. The possible options that might be considered are those that have been used, and shown effective to varying degrees, for other sexually transmitted infection. These strategies are formally in place nationally in Australia, with various modifications to account for differences in the epidemiology and health service context. HIV is probably the most relevant comparison to HTLV-1 in regard to sexual transmission. Prevention of HIV until relatively recently was primarily based on the promotion of safe sex. In some settings, safe sex relates specifically to condom use, whereas in other settings, reduction in partner numbers is included. The strategy of reducing the occurrence of other sexually transmitted infection to reduce the risk of HIV infection has also been adopted, but for HIV prevention has not been found to be effective in most studies. In the last half-decade, HIV prevention has strongly emphasised testing with early treatment for those with infection, to reduce viral load and hence infectiousness. In the absence of an effective therapeutic strategy, this approach is not available for HTLV-1 prevention, but counselling to reduce sexual risk behaviour specifically in those with infection, or those with high proviral loads, is an option that could be considered, as it was in an earlier era of HIV prevention.

The extent to which safe sex promotion can reduce the risk of HTLV-1 transmission, and ultimately the prevalence and long-term consequences in communities will be dependent on the relative roles of vertical and sexual transmission, and possibly other modes such as blood contact. For Central Australia and other HTLV-1 endemic regions, a key gap in knowledge is the extent to which prevalence increases in adolescence and early adulthood. A large increase would suggest that sexual transmission plays an important role in the transmission of HTLV-1, whereas if the rates are high in young children and do not increase

substantially thereafter, breastfeeding or other early childhood exposures will be most relevant.

CONCLUDING COMMENTS

The majority of published HTLV-1 prevalence studies in Australia have been based on specimens obtained from hospital based testing for HTLV-1. These surveys demonstrate the presence of HTLV-1 in Central Australia at levels that are substantially higher, by at least three orders of magnitude, than prevalence found among blood donors nationally. None of the studies reviewed were representative prevalence surveys, limiting interpretation about population level prevalence

Children and adolescents have been underrepresented in these studies. The absence of epidemiological data relating to infection among these age groups limits our ability to draw conclusions about the primary mode of transmission in . Gender differences in prevalence observed in hospital based studies also need further exploration, to see if they apply at the community level and if so what they may be due to.

Further information is also needed about disease associations in central Australia, and particularly the role of HTLV-1 proviral load, which may increase the risk of disease complications, but may also be increased by the presence of infectious, inflammatory or malignant disease.

This review has focussed on public health aspects of HTLV-1, and not attempted a comprehensive coverage of clinical aspects of HTLV-1 and related disease entities. Also, the review did not address the broader context of health service delivery that will need to be considered in regard to any initiative aimed at reducing the burden of HTLV-1 and its complication in central Australia. For example, strategies aimed at reducing transmission through breast feeding will need to take account of the potential adverse consequences of both identifying women with HTLV-1, and discouraging breast feeding for their infants.

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