

## HTLV-1 is rare in Far North Queensland despite a significant burden of classically associated diseases

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### Summary

Human T-lymphotropic virus type 1 (HTLV-1) is hyperendemic amongst Indigenous Australians living in Central Australia. The epidemiology of the disease is poorly defined in other parts of Australia, despite a high prevalence of classically associated conditions. All HTLV-1 serology tests requested through public health facilities in Far North Queensland (FNQ) from January 1999 to December 2016 were reviewed. The person's age, sex, ethnicity, location, rationale for testing and result were recorded. There were 444 tests performed in 409 people; 217 (53%) were male; 171 (42%) identified as Indigenous Australians. Testing increased over time and was performed throughout the region, suggesting increasing awareness of the disease. Testing occurred in patients with haematological, neurological, dermatological and respiratory complaints, but only four (1%) had proven infection. Three of these individuals were in the same family and two were asymptomatic. One of the two symptomatic seropositive individuals had recurrent scabies infection, the other T-cell lymphoma. HTLV-1 infection is extremely uncommon in FNQ. The high rates of bronchiectasis and other associated conditions that are seen in the region are more likely to be addressed by public health policies focusing on the socioeconomic determinants of health.

**Key words:** HTLV-1; Australia; indigenous health; bronchiectasis; social determinants of health.

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### INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1) is an oncogenic retrovirus endemic to Australia. The prevalence in Indigenous people living in central Australia is amongst the highest in the world,<sup>1</sup> which has led some authors to suggest that the clinical burden of HTLV-1 may be underestimated in Australia.<sup>2</sup> This has resulted in calls for increased testing for HTLV-1, to better characterise the epidemiology of the infection and to inform prevention strategies.<sup>3,4</sup>

Far North Queensland (FNQ) shares many similarities with central Australia. Approximately 42% of Indigenous

Australians in FNQ live in remote communities where there is reduced access to healthcare and significant socioeconomic disadvantage. The Australian Bureau of Statistics' Socio-Economic Indexes for Areas places 80% of the Torres Strait Islands and Cape York Peninsula population in the lowest two socioeconomic quintiles.<sup>5–7</sup>

The prevalence of HTLV-1 in FNQ has not been reported, but diseases that have an established connection to the virus—T-cell leukaemia/lymphoma, myelopathy and scabies—are all seen locally, with the burden of scabies particularly significant.<sup>8</sup> Other conditions that have been linked to HTLV-1 infection, including bronchiectasis, polymyositis and arthritis are also common.<sup>8,9</sup> This study was performed to determine the prevalence of HTLV-1 infection in FNQ, and the attributable burden of disease. Given recent calls to increase testing for HTLV-1, the study also aimed to assess local clinicians' awareness of the virus.

### METHODS

We reviewed all HTLV-1 serology tests requested in the public health system in FNQ between January 1999 and December 2016 using Queensland Health's laboratory electronic results database. For each test performed the person's demographics, the rationale for testing and the test's result were recorded. The population of FNQ has grown from 222,451 in 1999 to 279,354 people in 2016, 15% of whom identify as Indigenous Australians.<sup>6,7,10</sup> Over the study period, the following assays were used: HTLV1 Particle Agglutination assay (Serodia; Fujirebio, Japan) (1999–2009), HTLV 1+2 enzyme linked immunoassay (EIA) assay (Murex, France) (2009–June 2017) and Architect HTLV I/II Assay (Abbott, USA) (July 2017–present). Immunoblotting was performed at the National Reference Laboratory in Melbourne, Australia.

Data were analysed using statistical software (Stata version 14.0; Stata-Corp, USA); *p* for trend was calculated using an extension of the Wilcoxon rank-sum test.

The study was approved by the Far North Queensland Human Research Ethics Committee (HREC/17/QCH/33-1131QA).

### RESULTS

During the study period, 444 tests were performed on 409 people who had a median age of 50 years (interquartile range 37–60 years, range 2–91 years); 217 (53%) were male; 171 (42%) identified as Indigenous Australians. The annual number of tests increased from one test in 1999 to 126 tests in 2016 (*p* for trend < 0.001) (Fig. 1). People from throughout FNQ, including people living in remote communities were tested (Fig. 2). HTLV-1 serological testing most commonly

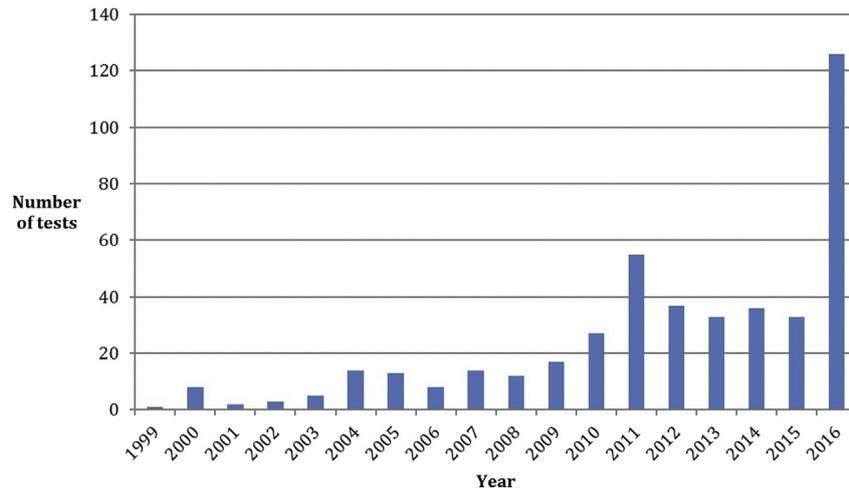


Fig. 1 Number of HTLV-1 serology tests performed per year in Far North Queensland between 1999 and 2016.

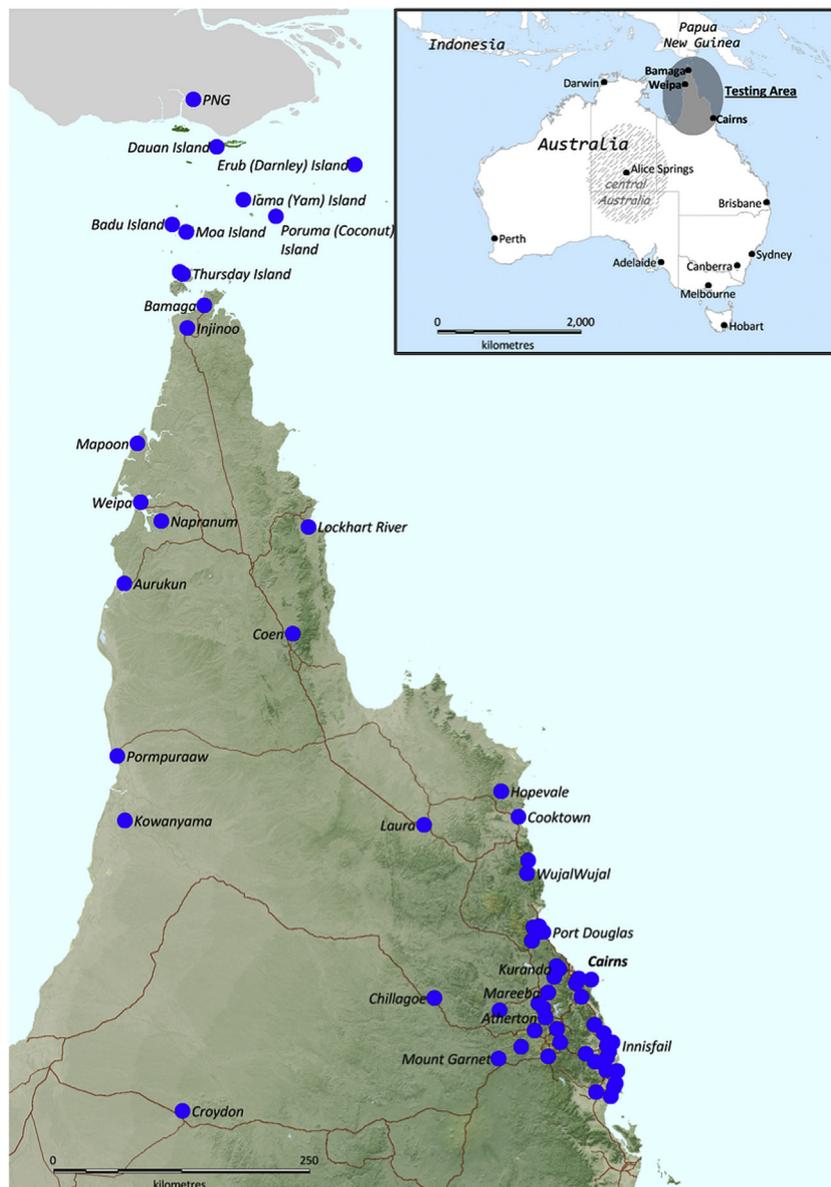


Fig. 2 Geographical location of people undergoing HTLV-1 serology testing.

occurred in the setting of a potentially associated disease (326/444, 73%). Sixty-three people (14%) were asymptomatic, 60 (95%) of whom underwent testing in 2016 as part of a younger person's health check in the eastern Cape York Peninsula. Testing was performed in a further 35 (8%) people with diseases that are not classically associated with HTLV-1 (Table 1). A screening antibody test was positive in seven tests; four were confirmed to be true positives by repeat testing and western blot analysis. Repeat serology and western blot testing were both negative when performed on the other three cases that were screening antibody positive. All confirmed positive cases occurred in Indigenous Australians but only two had clinical disease. The first, a 62-year-old female living in a remote community with recurrent scabies infection, was diagnosed in 2003. Her two adult sons were screened for the disease and while both returned a positive result, both were asymptomatic. The second was a 47-year-old female, diagnosed in 2012, who died from primary refractory, progressive T-cell lymphoma. She was also from a remote community and had no documented travel history.

## DISCUSSION

Diseases that have been associated with HTLV-1 are common in FNQ, but the infection itself is extremely rare. In the last 18 years, only four cases of HTLV-1 infection have been identified, three of which occurred in the same family, two of which were asymptomatic. This reported low prevalence does not appear to be explained by inadequate testing as the number of serology requests performed annually has increased significantly. It also does not appear to be explained by a lack of awareness, as testing—which has been targeted to those with potentially associated clinical presentations—has been performed by a variety of healthcare professionals including general practitioners, neurologists, haematologists, dermatologists and thoracic physicians across the region.

The conditions that are classically associated with HTLV-1, such as T-cell leukaemia/lymphoma, myelopathy and crusted scabies, are seen in FNQ; the high prevalence of scabies despite the apparent rarity of HTLV-1 is particularly notable in this context.<sup>11</sup> An association between HTLV-1 and bronchiectasis in Indigenous people living in central Australia has also been suggested, although the precise pathophysiology of any causal link is poorly defined. HTLV-1 associated bronchiectasis has been hypothesised to occur as a result of an inflammatory process triggered by HTLV-1 infected lymphocytic infiltration of bronchiole walls and

mucosal glands.<sup>12</sup> Recurrent bacterial and parasitic infections, which are seen more frequently in remote Indigenous communities, have been proposed to stimulate T-cell activation, which in turn increases HTLV-1 viral load levels resulting in more pulmonary inflammation.<sup>13</sup> While this hypothesis merits exploration, the significant burden of bronchiectasis in FNQ despite the low seroprevalence of HTLV-1<sup>8,14</sup> suggests that more prosaic explanations for recurrent lower respiratory tract infections—including smoking, overcrowding and poor access to healthcare—have a greater role in pathogenesis. Furthermore, although increased HTLV-1 proviral loads have been associated with an increased risk of bronchiectasis,<sup>9</sup> it is also possible that higher viral loads may simply be a marker of an intercurrent, unrelated illnesses, a phenomenon seen in human immunodeficiency virus (HIV) and other viral infections.<sup>15,16</sup> Most patients with HTLV-1 infection do not develop clinical disease, but it has been suggested that HTLV-1 contributes to the development of bronchiectasis in central Australia in up to 16.8% of patients with the condition.<sup>17</sup> The pathogenesis of adult T-cell leukaemia/lymphoma (ATL) and HTLV-1 associated myelopathy (HAM) is more clearly established and in studies from different locations around the world have repeatedly been reported to occur in 2–7% and up to 5% of carriers, respectively.<sup>18,19</sup> It is unclear why HTLV-1 would be responsible for so much lung disease in central Australia when more traditional aetiological factors are so common<sup>20,21</sup> and when the local incidence of ATL and HAM, diseases more typically associated with HTLV-1, is only 0.4% and 0.8%, respectively.<sup>17</sup>

Although this study found a very low prevalence of HTLV-1 in our population, our sample size was relatively small. Serological testing was not exhaustive and focal clusters of infected people may exist. The concept of focal clusters of high endemicity of HTLV-1 with absence of the infection in nearby areas is well described and is thought to represent a founder effect in some groups.<sup>22</sup> However, the number of people infected is likely to be small; HTLV-1 prevalence has recognised clinical associations and gradually increases with age.<sup>1</sup> In our study, almost 75% of the testing occurred in patients with a condition linked to HTLV-1 and their median age was 50, suggesting that thus far, serological testing has been focused on those most likely to carry the virus. For most of the study period, the public health system was the only available means of serology testing for people living in rural and remote FNQ. However, in more recent years there has been an increase in

**Table 1** Rationale for HTLV-1 serology testing in Far North Queensland

| Disease association       | Tests<br><i>n</i> = 444 (%) | Individuals tested<br><i>n</i> = 409 (%) | Indigenous Australians tested <i>n</i> (%) | Confirmed positive |
|---------------------------|-----------------------------|--|--|--------------------|
| Haematological malignancy | 211 (48%)                   | 185 (45%)                                | 29 (16%)                                   | 1                  |
| Neurological symptoms     | 51 (11%)                    | 47 (11%)                                 | 9 (19%)                                    | 0                  |
| Chronic lung disease      | 22 (5%)                     | 22 (5%)                                  | 18 (82%)                                   | 0                  |
| Organ donation            | 18 (4%)                     | 17 (4%)                                  | 2 (12%)                                    | 0                  |
| Skin disease              | 16 (4%)                     | 15 (4%)                                  | 7 (47%)                                    | 0                  |
| Scabies                   | 14 (3%)                     | 13 (3%)                                  | 13 (100%)                                  | 1                  |
| Rheumatological symptoms  | 11 (2%)                     | 11 (3%)                                  | 8 (73%)                                    | 0                  |
| Contact tracing           | 2 (<1%)                     | 2 (<1%)                                  | 2 (100%)                                   | 2                  |
| Strongyloidiasis          | 1 (<1%)                     | 1 (<1%)                                  | 0 (0%)                                     | 0                  |
| Asymptomatic screen       | 63 (14%)                    | 61 (15%)                                 | 55 (90%)                                   | 0                  |
| Other                     | 35 (8%)                     | 35 (9%)                                  | 28 (80%)                                   | 0                  |

private pathology service providers whose results were not included in our study.

To fully define the prevalence of HTLV-1 in Australia, universal screening of both symptomatic and asymptomatic people considered at risk would be required. Widespread screening must be balanced with the lower positive predictive value of the test in low prevalence settings and the resulting anxiety generated by false positive results. In our study, three of seven (42%) of the positive EIAs were false positives, and rates of indeterminate serology have been reported to be much higher.<sup>23</sup> The prioritisation of determining HTLV-1 seroprevalence also has to be considered in the context of the delivery of care to Indigenous Australians who are frequently not receiving care for hepatitis B and other blood borne viruses for which treatment options are available, and which are highly prevalent in the region.<sup>24</sup> A contemporary sero-survey may be reasonable if performed alongside testing for other blood borne viruses.

The disparity between the high seroprevalence of HTLV-1 in central Australia and FNQ is striking. FNQ is in close proximity to Papua New Guinea where HTLV-1 is also endemic.<sup>25</sup> Low rates of transmission to FNQ residents may relate to strongly defined sexual networks; visitors from highly-endemic areas may travel to FNQ, but due to assortative partnering may not have any new sexual partners. Little is known about the sexual networks involving Traditional Inhabitants of the Papua New Guinea Treaty Villages and the Torres Strait Islander population. Furthermore, sexual transmission of HTLV-1 may not be very efficient. A prospective study of 30 HTLV-1 positive blood donors and their stable ( $\geq 6$  months) heterosexual partners followed over 10 years found only two transmissions during that time, giving an incidence rate of 0.9/100 person-years (95% confidence interval 0.1–3.3).<sup>26</sup> An increased length of relationship may be a risk factor for HTLV-1 acquisition, perhaps as a result of accumulated exposure to an infected partner. It is possible that if sexual relationships in the border region are predominantly casual, sexual transmission of the virus may be uncommon. Meanwhile, intravenous drug use has been rare in the region.

## CONCLUSIONS

In summary, while there is a significant burden of bronchiectasis and skin disease in FNQ, this appears to be unrelated to HTLV-1 infection, which is extremely rare in the region. Despite targeted testing of patients with haematological malignancies and myelopathy, only a single case has been identified in patients with these two conditions in the last 18 years. Local clinicians appear to be aware of the disease and are testing and contact tracing appropriately. A greater focus on blood borne viruses with available therapies and public health policies that address the socioeconomic determinants of health are more likely to improve the health outcomes of the Indigenous people in the region.

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## References

- Einsiedel LJ, Pham H, Woodman RJ, *et al.* The prevalence and clinical associations of HTLV-1 infection in a remote Indigenous community. *Med J Aust* 2016; 205: 305–9.
- Einsiedel L, Woodman RJ, Flynn M, *et al.* Human T-Lymphotropic Virus type 1 infection in an Indigenous Australian population: epidemiological insights from a hospital-based cohort study. *BMC Public Health* 2016; 16: 787.
- Martin F, Tagaya Y, Gallo R. Time to eradicate HTLV-1: an open letter to WHO. *Lancet* 2018; 391: 1893–4.
- Einsiedel L, Purcell D, Schinke S, *et al.* Highlights from the HTLV-1 symposium at the 2017 Australasian HIV and AIDS Conference held jointly with the 2017 Australasian sexual health Conference, November 2017, Canberra, Australia. *J Virus Erad* 2018; 4: 48–50.
- Northern Queensland Primary Health Network. *Health needs assessment: June 2016*; Cited Jul 2018. <http://www.primaryhealth.com.au/wp-content/uploads/2016/06/NQPHN-Health-Needs-Assessment-June-2016.pdf>
- Australian Bureau of Statistics. *2016 census QuickStats*. Cairns. Cited Jul 2018. [http://www.censusdata.abs.gov.au/census\\_services/getproduct/census/2016/quickstat/306?opendocument](http://www.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/306?opendocument)
- Australian Bureau of Statistics. *2016 census QuickStats*. Far North. Cited Jul 2018. [http://www.censusdata.abs.gov.au/census\\_services/getproduct/census/2016/quickstat/31501?opendocument](http://www.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/31501?opendocument)
- Queensland Health. *Indigenous Health Indicators: North Queensland 2011*. Cairns: Tropical Regional Services, 2011. [https://www.health.qld.gov.au/\\_data/assets/pdf\\_file/0027/433782/indigenous-indicators.pdf](https://www.health.qld.gov.au/_data/assets/pdf_file/0027/433782/indigenous-indicators.pdf)
- Einsiedel L, Cassar O, Goeman E, *et al.* Higher human T-lymphotropic virus type 1 subtype C proviral loads are associated with bronchiectasis in indigenous Australians: results of a case-control study. *Open Forum Infect Dis* 2014; 1: ofu023.
- Queensland Health Statistical Services Branch. Population – census counts. 2018; Cited Jul 2018. <https://qheps.health.qld.gov.au/hsu/infobank/infobank-demography-estimated>
- Valery PC, Wenitong M, Clements V, *et al.* Skin infections among Indigenous Australians in an urban setting in far North Queensland. *Epidemiol Infect* 2008; 136: 1103–8.
- Sugisaki K, Tsuda T, Kumamoto T, *et al.* Clinicopathologic characteristics of the lungs of patients with human T cell lymphotropic virus type 1-associated myelopathy. *Am J Trop Med Hyg* 1998; 58: 721–5.
- Einsiedel L, Fernandes L, Spelman T, *et al.* Bronchiectasis is associated with human T-lymphotropic virus 1 infection in an Indigenous Australian population. *Clin Infect Dis* 2012; 54: 43–50.
- O'Grady KF, Revell A, Maguire G, *et al.* *Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland*. Brisbane: Queensland Health, 2010.
- Ekwaru JP, Campbell J, Malamba S, *et al.* The effect of opportunistic illness on HIV RNA viral load and CD4+ T cell count among HIV-positive adults taking antiretroviral therapy. *J Int AIDS Soc* 2013; 16: 17355.
- Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. *Crit Care* 2009; 13: R68.
- Einsiedel L, Spelman T, Goeman E, *et al.* Clinical associations of Human T-Lymphotropic Virus type 1 infection in an indigenous Australian population. *PLoS Negl Trop Dis* 2014; 8: e2643.
- Iwanaga M, Watanabe T, Yamaguchi K. Adult T-cell leukemia: a review of epidemiological evidence. *Front Microbiol* 2012; 3: 322.
- Bangham CR, Araujo A, Yamano Y, *et al.* HTLV-1-associated myelopathy/tropical spastic paraparesis. *Nat Rev Dis Prim* 2015; 1: 15012.
- Hudson L, White A, Roseby R. Tobacco smoke exposure in hospitalised Aboriginal children in Central Australia. *J Paediatr Child Health* 2009; 45: 224–7.
- Australian Institute of Health and Welfare (AIHW). *Housing Circumstances of Indigenous Households: Tenure and Overcrowding*. Cat. No. IHW 132. Canberra: AIHW, 2014.
- Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol* 2012; 3: 388.
- Grivas R, Freeman K, Baird R. Human T-lymphotropic virus-1 serology in the Northern Territory: 2008–2011. *Pathology* 2014; 46: 644–8.
- MacLachlan JH, Cowie BC. *Hepatitis B Mapping Project: Estimates of Chronic Hepatitis B Prevalence, Diagnosis, Monitoring and Treatment by Primary Health Network*. National Report 2014/15. Melbourne: Australasian Society for HIV Medicine and Victorian Infectious Diseases Reference Laboratory, 2016.
- Takao S, Ishida T, Bhatia KK, *et al.* Seroprevalence of human T-lymphotropic virus type 1 in Papua New Guinea and Irian Jaya measured using different western blot criteria. *J Clin Virol* 2000; 16: 129–33.
- Roucoux DF, Wang B, Smith D, *et al.* A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. *J Infect Dis* 2005; 191: 1490–7.