Clinical Associations of Human T-Lymphotrophic Virus Type 1 Infection in an Indigenous Australian Population

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Abstract

Introduction: In resource-poor areas, infectious diseases may be important causes of morbidity among individuals infected with the Human T-Lymphotrophic Virus type 1 (HTLV-1). We report the clinical associations of HTLV-1 infection among socially disadvantaged Indigenous adults in central Australia.

Methodology and Principal Findings: HTLV-1 serological results for Indigenous adults admitted 1st January 2000 to 31st December 2010 were obtained from the Alice Springs Hospital pathology database. Infections, comorbid conditions and HTLV-1 related diseases were identified using ICD-10 AM discharge morbidity codes. Relevant pathology and imaging results were reviewed. Disease associations, admission rates and risk factors for death were compared according to HTLV-1 serostatus. HTLV-1 western blots were positive for 531 (33.3%) of 1595 Indigenous adults tested. Clinical associations of HTLV-1 infection included bronchiectasis (adjusted Risk Ratio, 1.35; 95% CI, 1.14–1.60), blood stream infections (BSI) with enteric organisms (aRR, 1.36; 95% CI, 1.05–1.77) and admission with strongyloidiasis (aRR 1.38; 95% CI, 1.16–1.64). After adjusting for covariates, HTLV-1 infection remained associated with increased numbers of BSI episodes (adjusted negative binomial regression, coefficient, 0.21; 95% CI, 0.02–0.41) and increased admission numbers with strongyloidiasis (coefficient, 0.563; 95% CI, 0.17–0.95) and respiratory conditions including asthma (coefficient, 0.99; 95% CI, 0.27–1.7), lower respiratory tract infections (coefficient, 0.19; 95% CI, 0.04–0.34) and bronchectasis (coefficient, 0.60; 95% CI, 0.02–1.18). Two patients were admitted with adult T-cell Leukemia/Lymphoma, four with probable HTLV-1 associated myelopathy and another with infective dermatitis. Independent predictors of mortality included BSI with enteric organisms (aRR 1.78; 95% CI, 1.15–2.74) and bronchiectasis (aRR 2.07; 95% CI, 1.45–2.98).

Conclusion: HTLV-1 infection contributes to morbidity among socially disadvantaged Indigenous adults in central Australia. This is largely due to an increased risk of other infections and respiratory disease. The spectrum of HTLV-1 related diseases may vary according to the social circumstances of the affected population.

Introduction

The Human T Lymphotropic Virus type 1 (HTLV-1) is an oncogenic retrovirus that preferentially infects CD4+ T cells [1]. Worldwide, HTLV-1 infects at least 5–10 million people who predominantly dwell in areas of high endemicity in southern Japan, the Caribbean basin, parts of South America and tropical Africa. A smaller endemic focus is present in central Australia [2] and we have recently shown this to be due to infection with the HTLV-1c subtype [3]. Epidemiological and clinical associations have been best described for populations in the Caribbean basin, South America and Japan [1]. A minority of HTLV-1 carriers experience clinically significant sequelae, including a rapidly progressive hematological malignancy, Adult T cell Leukemia/Lymphoma (ATLL) [4,5], and inflammatory disorders, such as HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) [6]. A severe exudative eczema, infective dermatitis, predominantly affects children [7]. In Japan and the Caribbean, life-time risks range between 0.3–4% for HAM/TSP, 1–5% for ATL [1] and approach 10% for HTLV-1 associated malignancy or inflammatory diseases overall [1].

Infectious diseases also contribute to HTLV-1 related morbidity and mortality. Severe scabies [8], mycobacterial infections [9] and symptomatic infection with the nematode parasite Strongyloides stercoralis [10,11] are all more frequent among HTLV-1 carriers. In areas endemic for HTLV-1 and S.stercoralis, HTLV-1 infection is the major risk factor for complicated strongyloidiasis or ‘hyper-infection’, which is associated with pulmonary involvement [12] and life-threatening sepsis due to enteric bacterial pathogens [13]. Infection with S.stercoralis may also reduce the latent period...
required for the development of ATLL [14]. HTLV-1 infection reduces clearance rates of hepatitis C virus and increases the risk of liver disease and liver disease-related deaths [15]. Whether the risk of chronic hepatitis B virus (HBV) infection is similarly affected is unknown. Interactions between HTLV-1 related inflammatory diseases and infection have also been demonstrated. Infective dermatitis, for example, typically affects HTLV-1 carriers from lower socio-economic backgrounds and predisposes to skin infections with bacterial pathogens [7], which may progress to life-threatening invasive disease [16]. Recently, we reported high rates of HTLV-1 infection among socially disadvantaged Indigenous adults with bronchiectasis in central Australia [17]. Clinically significant pulmonary disease is not a feature of HTLV-1 infection in other developed countries [18–20], and we suggested that recurrent lower respiratory tract infections (LRTI) might contribute to this risk in our study population. The spectrum of HTLV-1 related clinical diseases may therefore differ according to social status and the risk of environmental exposure to other pathogens. However, demonstrating such an effect requires diagnostic capabilities that may not be available in developing countries in which a heavy burden of infectious diseases affects a population with a high prevalence of HTLV-1 infection.

Central Australia is well placed to study the associations between poverty and infectious diseases [21]. HTLV-1 is endemic to this region and infects 7.2–15.9% [22,23] of socially disadvantaged Indigenous adults. There has been no attempt to control HTLV-1 transmission among the Indigenous residents of central Australia, most of whom reside in isolated remote communities in conditions of considerable socio-economic disadvantage [21]. Those who live in the major regional center of Alice Springs dwell in either overcrowded ‘town camps’, which have poor amenities and limited refuse disposal, or are integrated with the majority of the non-Indigenous population within the township’s suburbs [21]. Central Australia also has the highest reported blood stream infection (BSI) incidence rates [21] and the highest prevalence rate of adult bronchiectasis [17] worldwide. Prevalence rates of chronic HBV infection exceeded 20% in some communities prior to the introduction of vaccination [24]. Consequently, infection-related mortality rates approach those of some African countries prior to the current HIV pandemic [25]. A single well-resourced community-based hospital, Alice Springs Hospital (ASH), serves this region of 1,000,000 km² (Fig. 1). Critically ill patients are retrieved by air to tertiary referral centers 1,500 km away. Medical services are provided without charge and, notwithstanding the poor social circumstances of the resident population, sophisticated radiological, microbiological and other diagnostic facilities are readily available. The present study describes the spectrum of HTLV-1 associated diseases that affects socially disadvantaged Indigenous adults in central Australia.

Methods

Ethics statement

This study was approved by the Central Australian Human Research Ethics Committee, which is a regional committee supervised by the National Health and Medical Research Council of Australia.

Data collection

All adults (age ≥15 years) admitted to ASH between 1st January 2000 and 31st December 2010 who had an HTLV-1 screening test performed were identified from the hospital pathology data-base. HTLV-1 testing at ASH is performed where there are clinical suspicions of HTLV-1 related diseases, including malignancy, neurological disease, strongyloidiasis and bronchiectasis. Demographic data including ethnicity, dates of birth and death, Indigenous status and place of residence were obtained for all patients from the ASH patient management system. For each admission between 1st January 2005 and 31st December 2010 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10 AM) morbidity codes relating to non-communicable diseases, possible HTLV-1 related conditions and infectious diseases were also extracted (Table S1). Discharge morbidity codes for admissions prior to 2005 were not available and patients who died prior to this date were therefore excluded from statistical analysis. All data were de-identified prior to analysis. Infectious diseases were grouped according to ICD-10 AM codes; i) sepsis or bacterial infection for which a focus was not stated, ii) specified foci of infection and iii) strongyloidiasis (Table S1). HTLV-1 related conditions included ATLL, HAM/TSP, bronchiectasis and infective dermatitis. Cases of ATLL and HAM/TSP were also sought from specialist neurological and hematological units that provide tertiary level care to ASH patients. Case notes, microbiology, radiology and other relevant pathology results were reviewed for all patients with possible HTLV-1 related conditions including ATLL, neurological disorders, bronchiectasis and infective dermatitis.

Residence

Place of residence was categorized as i) remote (>80 km from Alice Springs), ii) Alice Springs town camp and iii) urban (resident in Alice Springs, but not in a town camp). Remote residence was further divided into quadrants (north, south, east and west) relative to Alice Springs.

Infections and definitions

Results for S.stercoralis serology, HBV serology and blood cultures were obtained from the ASH pathology data-base. During the study period, S.stercoralis serology was performed using
an in-house enzyme-linked immunosorbent assay based on antigen extracts of Strongyloides ratti, which is highly sensitive and specific. A blood culture from which a pathogen was isolated defined a ‘BSI episode’. Repeated culture of the same organism from blood culture was regarded as a separate ‘episode’ only if blood samples were drawn more than one month apart. Blood stream infections were drawn more than one month apart. Blood stream infections with bacteria included potential contaminants including coagulase negative staphylococci, bacillus spp., coryneforms and viridans streptococci unless grown from more than one BC in a 24 hour period and Acinetobacter spp in the absence of an identifiable focus. For statistical analysis, the major BSI pathogens were grouped according to their most likely origin: i) skin (Staphylococcus aureus and Streptococcus pyogenes), ii) respiratory (Streptococcus pneumoniae and Haemophilus influenzae), iii) urinary tract (Escherichia coli) and iv) gastrointestinal tract (Enterobacteriaceae other than E.coli). ‘Definite bronchiectasis’ was defined as an ICD-10 AM code for bronchiectasis that was confirmed by High Resolution Computed Tomography (HRCT) chest according to American College of Chest Physicians criteria. ‘Possible bronchiectasis’ was defined as an ICD-10 AM code for bronchiectasis in the absence of HRCT chest confirmation of this diagnosis. A diagnosis of ATLL [4] and HAM/TSP [26] was made using established criteria. Cases of HAM/TSP were categorized as ‘probable’ if the clinical presentation was consistent with HAM/TSP in the absence of confirmatory analysis of cerebrospinal fluid (CSF) [26].

HTLV-1 studies

Initial screening tests were performed using the Serodia HTLV-I/II particle agglutination assay (Fujirebio, Japan) or Architect rHTLV-I/II assay at the Royal Darwin Hospital, Northern Territory of Australia, (1458) or the Institut Pasteur, Paris (156). Positive samples were again tested using both the Serodia HTLV-I particle agglutination assay and Murex HTLV-I+II test kit (Murex Diagnostics, Dartford, UK/National Serological Reference Laboratory, Melbourne) or an indirect immunofluorescence assay (IFA) using an HTLV-1-transformed human T cell line (MT2/Institut Pasteur). HTLV-1 serostatus was then confirmed by Western blot (HTLV Blot 2.4, MP Diagnostics) using stringent criteria for all samples for which screening tests were positive.

Statistics

Categorical variables were summarized using frequency and percentage and compared using a Chi-square test or, in the case of small numbers, a Fisher's Exact test. Multiple simultaneous comparisons were adjusted for using a Bonferroni correction. Continuous variables were assessed for significant departures from normality with normally distributed variables summarized using mean and standard deviation (SD) and compared using a t-test whilst skewed variables were summarized using median and inter-quartile range (IQR) and compared using a Wilcoxon rank-sum test. Predictors of HTLV-1 seropositivity were examined using Poisson regression with robust standard errors. Strongyloides admissions (identified by ICD-10 AM codes), rather than serology, were included in the multivariable model because these are more likely to reflect symptomatic strongyloidiasis [10,11,27]. Direct modeling of relative risk (RR) using Poisson was preferred over Odds Ratios (OR) from logistic regression to estimate RR due to the frequency of the outcome studied. A link test was used to assess the model for specification error whilst overall goodness of fit was assessed using both visual examination of residuals coupled with a likelihood-ratio test and a Pearson goodness-of-fit test.

Incidence rates of admission count by diagnostic group were expressed as a proportion of the total number of HTLV-1 seropositive and seronegative patients respectively. Predictors of admission counts for a range of diagnostic groups according to HTLV-1 seropositivity were examined using negative binomial regression and are presented with their negative binomial 95% confidence intervals. Negative binomial modeling was preferred over straight Poisson regression due to over-dispersion in admission count outcome variables. The model coefficients represent the estimated change in admission counts for a particular level of a predictor variable. The influence of HTLV-1 seropositivity on admission count was adjusted for demography and comorbidities. In the case of admissions with asthma, LRTI, pneumonia and chronic obstructive pulmonary disease, the model was adjusted for both definite and possible bronchiectasis and tobacco smoking. A link test was used to assess the model for specification error whilst overall goodness of fit was assessed using both visual examination of residuals coupled with a likelihood-ratio test and a Pearson goodness-of-fit test.

Predictors of hepatitis B surface antigen (HBsAg) positivity were analysed using logistic regression. In this case, a logistic approach was preferred secondary to the rarity of the outcome. Overall model fit was assessed using a Hosmer & Lemeshow goodness-of-fit test.

Predictors of time to mortality were examined using Cox Proportional Hazards Regression. Analysis of scaled Schoenfeld residuals were used to assess compliance with the proportional hazards assumption. For this analysis patients with possible bronchiectasis were assumed not to have the condition.

All reported p-values are two-tailed and for each analysis p< 0.05 was considered significant. All analyses were conducted using Stata version 12 (StataCorp, College Station, Texas).

Results

HTLV-1 screening tests were performed for 1614 Indigenous adults and these were positive for 624 (38.7%) cases. Samples from 605 patients were referred for confirmatory Western blot tests. These were indeterminate in 73 cases (4.6%) and confirmed HTLV-1 infection for 531 patients (33.3%). Patients whose western blot results were indeterminate were excluded from further analysis, as were 74 patients (HTLV-1 seropositive, 24; HTLV-1 seronegative, 50) who died prior to 2005. The subsequent analysis therefore included 1451 Indigenous adults (HTLV-1 seropositive, 507; HTLV-1 seronegative, 944) who were admitted 115,919 times (HTLV-1 seropositive 39,967; HTLV-1 seronegative 75,952) during the study period.

Demographics

HTLV-1 seropositivity rates among males increased significantly with age (<45 years, 106/329 (32.2%); ≥45 years, 133/319 (42.2%); p = 0.008). Rates were otherwise not significantly different between age groups or genders (Table 1). Seropositivity rates differed according to place and type of residence. Rates were lowest among residents of communities north of Alice Springs (14.6%) and
highest among those from communities to the south (64.3%) and west (37.5%) (Fig. 1) (Table 1). Seropositivity rates were higher among town camp residents (42.6%) and lowest among those living elsewhere in the township (27.0%). Demographic risk factors for HTLV-1 infection after multivariable analysis included age (adjusted RR, 1.01 per year; 95% CI, 1.01–1.02; p = 0.000) and residence in communities to the south (aRR 3.83; 95% CI, 2.64–5.57; p = 0.000) and west (aRR 2.77; 95% CI, 1.54–3.37; p = 0.001) of Alice Springs relative to those in the north (Table 2).

Medical conditions previously associated with HTLV-1 infection

i) Respiratory diseases. A bronchiectasis-related discharge morbidity code was recorded for 170 patients. Bronchiectasis was confirmed radiologically in 142 patients of whom 81 (57.0%) were HTLV-1 seropositive. Radiologically confirmed bronchiectasis was an independent predictor of HTLV-1 infection in a multivariable analysis that included age (adjusted RR, 1.01 per year; 95% CI, 1.01–1.02; p = 0.000) and place of residence (aRR 3.83; 95% CI, 2.64–5.57; p = 0.000) and west (aRR 2.77; 95% CI, 1.54–3.37; p = 0.001) of Alice Springs relative to those in the north (Table 2).

Table 1. Patient characteristics for 1451 Indigenous Adults admitted 2005–2010.

| HTLV-1 WB result | Level | Positive (n = 507) | Negative (n = 944) | p-value |
|------------------|-------|-------------------|--------------------|---------|
| Sex n (% of level) | Male/Female | 241 (45.4)/266 (50.1) | 407 (41.0)/537 (54.0) | 0.106 |
| Age, median years (IQR) | 47.1 (38.7, 57.4) | 43.5 (32.9,55.3) | <0.001 |
| <45 years | Male/Female | 106 (32.2)/116 (29.9) | 223 (67.7)/272 (70.1) | 0.503 |
| ≥45 years | Male/Female | 135 (42.2)/149 (36.1) | 184 (57.8)/264 (63.9) | 0.086 |
| Residence n (% of level) | Town Camp | 107 (42.6) | 144 (57.4) | 0.001 |
| | Remote | 308 (38.5) | 493 (61.6) | |
| | Nursing Home | 18 (34.6) | 34 (65.4) | |
| | Urban | 57 (27.0) | 154 (73.0) | |
| Quadrant n (% of level) | North | 49 (14.6) | 286 (85.4) | <0.001 |
| | East | 12 (17.4) | 57 (82.6) | |
| | South | 155 (64.3) | 86 (35.7) | |
| | West | 115 (37.5) | 192 (62.5) | |
| Death n (%) | 120 (23.7) | 218 (23.1) | 0.805 |
| Age, median years (IQR) | 56.9 (46.2,63.9) | 53.2 (44.4,62.5) | 0.235 |

*Excluding patients with an indeterminate western blot and those who died prior to 2005.
*Analyzed according to gender within each group.
*Excluding 134 patients who resided outside central Australia and 2 patients whose place of residence was unknown. Data are expressed as proportion of total patients tested for each place of residence.
*Residents of remote communities relative to the regional center of Alice Springs and excluding 498 Alice Springs residents. Data are expressed as proportion of total patients tested for each quadrant.
* Died during observation period.
*All pair-wise quadrant comparisons were p < 0.001 (Bonferroni-corrected), except the North vs East comparison.
*Pair-wise comparisons of urban-residence compared with all other residences were p < 0.001 (Bonferroni-corrected).

Medical conditions previously associated with HTLV-1 infection

ii) Strongyloidiasis. Strongyloides serology was performed for 1126 (77.6%) patients of whom 269 (23.9%) were Strongyloides seropositive (Table 6). Although HTLV-1 carriers were more likely to record a Strongyloides serology result (Table 6), Strongyloides seropositivity rates were not significantly higher in this group (HTLV-1 seropositive, 27.1%; HTLV-1 seronegative, 22.0% (p = 0.063) (Table 6). Routine stool microscopy was performed in only 47 cases at the time of diagnosis with strongyloidiasis and stool was cultured for strongyloides in only eight of these cases. Larvae were identified in 19 cases (HTLV-1 seronegative, 7; HTLV-1 seropositive, 12). The numbers of admissions with strongyloidiasis were significantly higher among HTLV-1 carriers (Table 4) and the likelihood of admission with strongyloidiasis remained increased in a multivariable model (aRR 1.38; 95% CI, 1.16–1.64; p = 0.000) (Table 2).

Medical conditions previously associated with HTLV-1 infection

iii) Scabies. HTLV-1 carriers were more likely to record a discharge morbidity code for scabies (Table 3) and had higher admission rates for this condition (Table 4); however, this association was lost in an adjusted model (Table 5). Severity of scabies could not be determined from ICD-10 AM codes and skin scrapings were performed for few patients.

iv) Malignancy, HAM/TSP and infective dermatitis. The risk of non-hematological malignancies was significantly reduced among HTLV-1 carriers (Table 2). Six patients were admitted with hematological malignancies including two who were diagnosed with ATLL after referral to a tertiary hospital. The clinical presentation of four HTLV-1 seropositive patients was consistent with HAM/TSP; however, in no case were HTLV-1 specific investigations applied to CSF. A single patient with HTLV-1 related infective dermatitis was identified.
Table 2. Adjusted Poisson modeling of predictors of HTLV-1 infection.

| Residence                  | Relative Risk | 95% CI      | p-value |
|----------------------------|---------------|-------------|---------|
| Male Gender                | 1.00          | 0.88–1.15   | 0.968   |
| Residence                  |               |             |         |
| Remote                     | 0.90          | 0.57–1.55   | 0.809   |
| Town Camp                  | 0.711         | 0.42–1.21   | 0.211   |
| Urban                      |               |             |         |

Mortality

Among 338 deaths that occurred during 5,739 years of follow-up, 120 (33.7%) were HTLV-1 seropositive and 218 (23.1%) were HTLV-1 seronegative. There was no difference between HTLV-1 seropositive and seronegative patients in median age of death (HTLV-1 seropositive, 56.9 years; IQR, 46.2, 63.9; HTLV-1 seronegative, 53.2 years; IQR, 44.4, 62.5) (Table 1). Demographic risk factors for death included male gender and increasing age (Table 7).

Bronchiectasis (HR, 2.07; 95% CI, 1.45–2.98; p = 0.000) and BSI with Enterobacteriaceae other than E. coli (HR 1.78; 95% CI, 1.15–2.74; 0.009) remained significant predictors of death after multivariable analysis (Table 7). Other risk factors for death were S. pneumoniae BSI (HR, 1.70; 95% CI, 1.09–2.64; p = 0.018) and non-communicable diseases (chronic liver disease, diabetes and malignancy) (Table 7).

Discussion

In a hospitalized cohort of Indigenous Australian adults, we found an HTLV-1 seropositivity rate (33.3%) that was approximately three times the estimated background rate in central Australia (7.2–13.9%) [22, 23]. This suggests that HTLV-1 associated morbidity in our study population may substantially exceed that resulting from the occasional cases of ATL and HAM/TSP that are reported here. Consistent with its global epidemiology [2], HTLV-1 carriers were more likely to live in poverty in town camps or remote communities and more often had a history of harmful alcohol consumption. HTLV-1 infection was associated with strongyloidiasis and blood stream infections with enteric pathogens; however, respiratory diseases contributed most to HTLV-1 related morbidity in this socially disadvantaged Indigenous population. After adjusting for covariates, HTLV-1 infection was associated with bronchiectasis and with increased admission numbers for all respiratory conditions studied with the exception of chronic obstructive pulmonary disease.

Pulmonary involvement is common among HTLV-1 carriers elsewhere. Radiological abnormalities, for example, have been reported in 50% of Japanese patients with HAM/TSP and 30% of asymptomatic HTLV-1 carriers who were examined by chest X-ray [28] and chest CT [29], respectively. Airway involvement is frequent in this population; chest CT reveals bronchiolitis or bronchitis in 19% [30] and bronchiectasis in 18–26% [29, 30] of cases. Lymphocyte infiltration of bronchioles [31] and partial bronchiolar obstruction [31, 32] are the histopathological correlates of these radiological findings. Lymphocytes obtained from HTLV-1 carriers by bronchoalveolar lavage (BAL) have high HTLV-1 proviral loads [33, 34] and these are correlated with those of peripheral blood [31]. An inflammatory response to the HTLV-1 infection was associated with bronchiectasis and with increased admission numbers for all respiratory conditions studied with the exception of chronic obstructive pulmonary disease.
antigen load derived from infected lymphocytes is thought to be the major determinant of other HTLV-1 related inflammatory diseases [35]. Airway inflammation in response to HTLV-1 antigens, such as the immuno-dominant regulatory protein, Tax [30], may therefore provide the pathological basis for clinical associations with asthma and LRTI other than pneumonia in our Indigenous cohort and for the increased incidence of self-reported asthma among HTLV-1 carriers in the USA [20].

Nevertheless, clinically significant pulmonary disease is an uncommon feature of HTLV-1 infection in developed countries [18–20]. In contrast, HTLV-1 infection contributes to bronchiectasis prevalence rates among Indigenous adults in central Australia that are the highest reported worldwide [17]. In the present study, 142 cases of bronchiectasis were confirmed by HRCT and nearly 60% of these patients were HTLV-1 infected. Consistent with our previous study [17], bronchiectasis was associated with a very high early mortality. Previously we have shown that HTLV-1 infection is associated with more extensive bronchiectasis, more frequent right heart failure and with bronchiectasis-related deaths [17]. In a recent case-control study the mean HTLV-1 proviral load in peripheral blood lymphocytes was significantly higher among HTLV-1 infected patients with bronchiectasis [36]. An HTLV-1 mediated inflammatory process [35] may therefore underlie HTLV-1 associated pulmonary disease in our study population. Disease progression to multifocal bronchiectasis might then follow further pulmonary injury resulting from recurrent LRTI, which were more common among HTLV-1 carriers in the present study.

Consistent with the results of other studies [27,37], HTLV-1 carriers in central Australia were not at increased risk of serologically defined strongyloidiasis. Nevertheless, HTLV-1 infection in other populations is associated with a higher larval burden and with increased risks of symptomatic, recurrent and complicated strongyloidiasis [10,11,27]. Our study design and the use of serological tests to diagnose strongyloidiasis preclude any

Table 3. Comparison of clinical conditions identified by International Classification of Diseases-10 (Australian Modification) morbidity codes according to HTLV-1 serostatus among 1451 Indigenous adults admitted 2005–2010a.

|                      | HTLV-1 Positive (n = 507) n (%) | HTLV-1 Negative (n = 944) n (%) | p-value |
|----------------------|--------------------------------|--------------------------------|---------|
| **Non-Communicable Diseases** |                                |                                |         |
| Smoking              | 316 (62.3)                     | 538 (57.0)                     | 0.049   |
| Alcohol              | 275 (54.2)                     | 380 (40.3)                     | <0.001  |
| Diabetes             | 252 (49.7)                     | 467 (49.5)                     | 0.932   |
| CKD                  | 164 (32.3)                     | 297 (31.5)                     | 0.730   |
| HD                   | 107 (21.1)                     | 214 (22.7)                     | 0.600   |
| CCF                  | 94 (18.5)                      | 144 (15.3)                     | 0.107   |
| CLD                  | 68 (13.4)                      | 88 (9.3)                       | 0.016   |
| Malignancyb           | 12 (2.4)                       | 49 (5.2)                       | 0.011   |
| **Infections**       |                                |                                |         |
| Sepsis/No focus      | 391 (77.1)                     | 621 (65.8)                     | <0.001  |
| Pneumonia            | 316 (62.3)                     | 477 (50.5)                     | <0.001  |
| LRTIc                | 227 (47.2)                     | 342 (40.0)                     | 0.002   |
| Skin                 | 207 (40.8)                     | 349 (37.0)                     | 0.159   |
| Scabies              | 72 (14.2)                      | 80 (8.5)                       | 0.001   |
| Bone/Joint           | 51 (10.1)                      | 92 (9.8)                       | 0.849   |
| **Respiratory Diseases** |                                |                                |         |
| Bronchiectasisd      | 81 (16.8)                      | 61 (7.1)                       | <0.001  |
| COPD                 | 78 (15.4)                      | 82 (8.7)                       | <0.001  |
| Asthma               | 34 (7.1)                       | 54 (6.3)                       | 0.46    |
| **HTLV-1 associated conditions** |                                |                                |         |
| Strongyloides stercoralis | 111 (23.1)                  | 157 (18.3)                     | 0.039   |
| HAM/TSPf             | 4 (0.8)                        | 0                               | **      |
| ATLL                 | 2 (0.4)                        | 0                               | **      |
| Infective dermatitis | 1 (0.2)                        | 0                               | **      |

Data derived from 115,919 admissions (HTLV-1 seropositive 39,967; HTLV-1 seronegative, 75,952) among 481 HTLV-1 seropositive and 856 HTLV-1 seronegative Indigenous adults.

aExcluding patients with an indeterminate western blot and those who died prior to 2005.

bNon-hematological malignancies.

1LRTI other than pneumonia.

2Bronchiectasis confirmed by chest high resolution computed tomography.

3Identified by ICD-10 AM coding.

4Probable HAM/TSP. Confirmatory tests not applied to cerebrospinal fluid.

**no p-value provided due to small numbers recorded.

Abbreviations: ATLL, adult T cell leukemia/lymphoma; CCF, congestive cardiac failure; CKD, chronic kidney disease; CLD, chronic liver disease; HAM/TSP, HTLV-1 associated myelopathy/tropical spastic paraparesis; HD, hemodialysis; LRTI, lower respiratory tract infection; WB, Western blot.

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Excluding patients who died prior to 2005 and those residing outside central Australia for whom admission data was incomplete.

Admission rates for 1317 adult Indigenous residents of central Australia 2005–2010 admitted to Alice Springs Hospital with respiratory conditions and infections.

HTLV-1 serostatus.

that is associated with the presence of the predictor variable according to HTLV-1 serological status rather than HTLV-1 proviral load, which is closely associated with HTLV-1 related morbidity were increased among HTLV-1 carriers in the absence of an increased risk of death. However, an effect of HTLV-1 infection on mortality may be obscured by analysis comparing groups of patients with different serological status. Certainly, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related morbidity were increased among HTLV-1 carriers in the absence of an increased risk of death. However, an effect of HTLV-1 infection on mortality may be obscured by analysis comparing groups of patients with different serological status. Certainly, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related morbidity were increased among HTLV-1 carriers in the absence of an increased risk of death. However, an effect of HTLV-1 infection on mortality may be obscured by analysis comparing groups of patients with different serological status.

Table 4. Admission rates for respiratory conditions and other infections according to HTLV-1 serostatus.

| Category                | HTLV-1 positive (n = 490) | HTLV-1 negative (n = 827) | p-value |
|-------------------------|---------------------------|---------------------------|---------|
|                         | (admissions/patient)      | (admissions/patient)      |         |
| Respiratory Diseasesa   |                           |                           |         |
| Asthma                  | 0.67                      | 0.19                      | <0.0001 |
| LRTIb                   | 1.33                      | 0.86                      | <0.0001 |
| Pneumonia               | 2.05                      | 1.32                      | <0.0001 |
| Bronchiectasis          | 1.95                      | 0.87                      | <0.0001 |
| COPD                    | 0.48                      | 0.43                      | 0.1872  |
| Infectionsa             |                           |                           |         |
| Sepsis                  | 3.98                      | 3.07                      | <0.0001 |
| BSI episodesd           | 0.58                      | 0.42                      | 0.0001  |
| Strongyloides           | 0.23                      | 0.11                      | <0.0001 |
| Scabies                 | 0.19                      | 0.14                      | 0.0385  |

Admission rates for 1317 adult Indigenous residents of central Australia 2005–2010 admitted to Alice Springs Hospital with respiratory conditions and infections. Excluding patients who died prior to 2005 and those residing outside central Australia for whom admission data was incomplete.

Identified by ICD-10 AM code. Bronchiectasis was confirmed by chest high resolution computed tomography.

LRTI other than pneumonia.

The number of blood cultures that yielded a significant pathogen as defined in methods.

Identified by ICD-10 AM code with the exception of BSI episodes.

The association between respiratory conditions and infections according to HTLV-1 serostatus.

Table 5. Adjusted negative binomial regression of predictors for number of admissionsa with respiratory conditions and other infections according to HTLV-1 serostatus.

| Category                | Coefficientb | 95% CIl  | p-value |
|-------------------------|--------------|----------|---------|
| Respiratory Diseasesa   |              |          |         |
| Asthma                  | 0.986        | 0.271, 1.701 | 0.007   |
| LRTIb                   | 0.254        | 0.067, 0.441 | 0.008   |
| Pneumonia               | 0.189        | 0.039, 0.340 | 0.014   |
| Bronchiectasis          | 0.598        | 0.015, 1.180 | 0.044   |
| COPD                    | 0.214        | −0.257, 0.685 | 0.374   |
| Infectionsa             |              |          |         |
| Sepsis                  | 0.123        | −0.017, 0.264 | 0.085   |
| BSI episodesd           | 0.210        | 0.016, 0.405 | 0.034   |
| Strongyloides           | 0.563        | 0.174, 0.953 | 0.005   |
| Scabies                 | 0.358        | −0.011, 0.726 | 0.057   |

Adjusted negative binomial modelling of predictors for admission to Alice Springs Hospital among 1317 adult Indigenous residents of central Australia, 2005–2010. Excluding patients who died prior to 2005 and those residing outside central Australia for whom admission data was incomplete.

Adjusted for comorbidities (harmful alcohol consumption, diabetes, chronic liver disease, chronic kidney disease, hemodialysis), age, gender and place of residence. Respiratory conditions were also adjusted for smoking and, in the case of asthma, LRTI and pneumonia, for definite or possible bronchiectasis.

The coefficient represents the average change in the number of admissions that is associated with the presence of the predictor variable according to HTLV-1 serostatus.

Identified by ICD-10 AM code. Bronchiectasis was confirmed by high resolution computed tomography chest.

LRTI other than pneumonia.

Identified by ICD-10 AM code with the exception of BSI episodes.

The number of blood cultures that yielded a significant pathogen as defined in methods.

Abbreviations: BSI, blood stream infection; COPD, chronic obstructive pulmonary disease; LRTI, lower respiratory tract infection.

In our Indigenous Australian cohort, respiratory and infection-related morbidity were increased among HTLV-1 carriers in the absence of an increased risk of death. However, an effect of HTLV-1 infection on mortality may be obscured by analysis comparing groups of patients with different serological status. Certainly, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related diseases [1]. In addition, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related diseases [1]. In addition, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related diseases [1]. In addition, the recent finding of higher HTLV-1 proviral load, which is closely associated with HTLV-1 related diseases [1].
### Table 6. Results of microbiological tests for 1451 Indigenous Adults admitted 2005–2010a.

| HTLV-1 WB result | Positive (n = 507) n (%) | Negative (n = 944) n (%) | p-value |
|------------------|-------------------------|--------------------------|---------|
| Blood Stream Infections | 181 (35.7) | 254 (26.9) | <0.001 |
| Strongyloides serology | | | |
| Tested | 409 (80.7) | 717 (76.0) | 0.040 |
| Positive | 111 (27.1) | 158 (22.0) | 0.063a |
| Borderline | 61 (14.9) | 115 (16.0) | |
| Negative | 237 (58.0) | 444 (61.9) | |
| Hepatitis B Virus serology | | | |
| Tested | 337 (66.5) | 651 (69.0) | 0.290 |
| Anti-HBc | 201 (59.6) | 338 (51.9) | 0.021 |
| HBsAg | 65 (32.3) | 62 (18.3) | <0.001 |
| HBeAg | 5 (7.7) | 11 (17.7) | 0.077 |

*aPair-wise comparisons of Strongyloides serological results were Bonferroni-corrected.

Abbreviations: HBV, hepatitis B virus; anti-HBc, hepatitis B core antibody positive; HBeAg, hepatitis B e antigen positive; HBsAg, hepatitis B surface antigen positive; WB, Western blot.

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### Table 7. Adjusted Cox proportional hazards modeling of predictors of deatha.

| | Hazard Ratio | 95% Confidence Interval | p-value |
|------------------|--------------|--------------------------|---------|
| Ageb | 1.03 | 1.02–1.04 | 0.000 |
| Male Gender | 1.34 | 1.07–1.68 | 0.011 |
| Residencec | | | |
| Type | | | |
| Remote | Reference | | |
| Town Camp | 1.11 | 0.82–1.51 | 0.506 |
| Urban | 1.03 | 0.58–1.83 | 0.914 |
| Comorbiditiesd | | | |
| Bronchiectasisc | 2.07 | 1.45–2.98 | 0.000 |
| Diabetes | 1.45 | 1.08–1.95 | 0.013 |
| Chronic Liver Disease | 1.91 | 1.43–2.56 | 0.000 |
| Chronic Kidney Disease | 1.19 | 0.88–1.62 | 0.264 |
| Malignancy | 1.81 | 1.21–2.69 | 0.004 |
| Cardiac Failure | 1.29 | 0.98–1.69 | 0.070 |
| Infection | | | |
| HTLV-1 | 0.80 | 0.62–1.03 | 0.085 |
| Strongyloidesd | 1.11 | 0.96–1.28 | 0.169 |
| Blood Stream Infectionsg | | | |
| Enterobacteriaceae | 1.78 | 1.15–2.74 | 0.009 |
| Klebsiella pneumoniae | 1.06 | 0.57–1.96 | 0.849 |
| Staphylococcus aureus | 0.77 | 0.28–2.14 | 0.620 |
| Streptococcus pneumoniae | 1.70 | 1.09–2.64 | 0.018 |
| HBsAg positive | 1.10 | 0.76–1.61 | 0.605 |

*aIncluding 338 deaths that occurred after 1st January 2005.
*bRisk of death for each 5 years increase in age.
*cExcluding 134 patients who resided outside central Australia and 2 patients whose place of residence was unknown.
*dIdentified by ICD-10 AM coding.
*eDefinite bronchiectasis identified by ICD-10 AM code and confirmed by High Resolution Computed Tomography.
*fStrongyloides identified by ICD-10 AM code.
*gBlood stream infections identified from blood cultures.
*hExcluding Escherichia coli.

Abbreviations: HBsAg, hepatitis B surface antigen; HTLV-1, Human T-Lymphotropic Virus type 1.

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In a setting of overcrowded housing, inadequate health hardware and poor community hygiene [43,46], HTLV-I infection substantially increases respiratory and infection-related morbidity. Socially disadvantaged HTLV-I carriers in our Indigenous Australian cohort experienced more BSI episodes and were more often admitted with respiratory conditions including LRTI and bronchiectasis, which was the major independent risk factor for death. In contrast to other developed countries [1], infection-related complications were more common than either ATL or HAM/TSP. The spectrum of HTLV-I related diseases is therefore likely to vary according to the social circumstances of the affected population. These findings have not been reported previously; however, access to the medical facilities required to confirm these diagnoses is limited in developing countries in which populations with a similar burden of disease exists. Clearly, the benefits accrued by controlling the vertical transmission of HTLV-I in a resource poor setting must be considered relative to the capacity of the health care system to ensure the safety of alternative sources of infant nutrition. However, our data provides strong support for public health interventions, such as improvements to housing and community hygiene, that limit the exposure of HTLV-I carriers to other pathogens.

Supporting Information

Table S1  Disease categories and their ICD-10 AM codes recorded 2005–2010. International classification of diseases 10th revision, Australian modification, codes recorded for 1337 Indigenous adults admitted to Alice Springs Hospital, 2005–2010. These codes formed the basis for subsequent analysis according to the categories listed. Abbreviations: COPD, chronic obstructive pulmonary disease; LRTI, lower respiratory tract infection; ICD-10 AM, international classification of diseases 10 Australian Modification.

Author Contributions

Conceived and designed the experiments: LE. Performed the experiments: LE. EG, MA. Analyzed the data: LE. TS. Contributed reagents/materials/analysis tools: OC AG. Wrote the paper: LE TS AG.

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