Viral Infections in Aboriginal and Torres Strait Islander Australians

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ADVANCED TRAINEE
PAEDIATRIC INFECTIOUS DISEASES AND MICROBIOLOGY
VIRUSES IN MAY, KATOOMBA, BLUE MOUNTAINS 30 APRIL – 2 MAY 2015
Dedicated to
Dr Roland Davies
Outline

How and why are viral infections different in Aboriginal and Torres Strait Islander Australians?

HTLV-1 in Australia
  ◦ Epidemiology
  ◦ Clinical manifestations
  ◦ Public health interventions overseas and how we might implement them here
Viral Infections in Indigenous compared with non-Indigenous Australians
Viral infections in Indigenous Australians

High overall mortality rates and failure so far to address the 10 – 11 year gap in life expectancy

2.5 times more likely to be admitted to hospital

Indigenous people mainly die from non-communicable diseases, but are still 3 x more likely to die from communicable diseases than non-Indigenous counterparts

Between 2 and 30 times the notification rates for key bacterial, viral and parasitic infections, with highest rates of rheumatic fever / RHD, bronchiectasis and bloodstream infections in the world.

HIV notifications on par per capita, but more heterosexual and IVDU transmission and more females infected as a proportion.

- Barriers to accessing diagnosis and treatment
Viral Infections in Indigenous Australians

Very limited data on genetic / immunological differences in terms of infectious disease susceptibility – likely a minor player

- Increased NK cell numbers
- Increased prevalence of C4 null alleles
- Restricted polymorphisms for mannose binding lectin
- SNPs in pro-inflammatory cytokines with > 25 novel variants

Immune dysfunction secondary to burden of communicable and non-communicable disease states

Susceptibility to communicable diseases immediately upon colonisation due to population - immunological naivety

- European, Asian, American and African disease pools confluent due to colonisation, trade and slavery
- Geographical isolation

Major environmental and genetic changes since colonisation.
Social determinants of health
Geography, demography & health related infrastructure
Nation-wide indicators of Indigenous social disadvantage

Poorer educational participation & outcomes

Higher unemployment

Lower household income

High rates of psychosocial stressors
Figure 1  Area of residence, 2013, by Aboriginal and Torres Strait Islander status

Source: Australian Bureau of Statistics 2011
Human T-cell Lymphototropic Virus type 1
General Introduction & Virology
Human T-cell Lymphotrophic Virus Type 1 (HTLV-1)

First human retrovirus to be discovered

1979 – 1981, Poeisz & Gallo’s lab, France
- Essential technical preconditions for discovery, 1970s
- Bridging the knowledge gap from the animal studies
  - Bovine leukaemia virus
  - Observation of interspecies transmission of gibbon ape leukemia virus (GaLV) to a new world Wooly monkey

- Description of adult T-cell leukaemia, 1977 – 1983, Yodoi et al, Southern Japan
HTLV-1
HTLV-1 Replication strategy

Receptor is the ubiquitous GLUT-1 glucose transporter
Infection is not cytopathic to CD4 cells (unlike HIV)
Virus predominantly exists as integrated provirus

Early infection:
◦ Cell to cell spread through viral “synapse” – polyclonal

Later infection:
◦ Mitosis driven replication strategy - TAX
  ◦ ie, replication of CD-4 cells leads to replication of provirus without ever having to produce free virions
  ◦ → Genomic stability (using cellular DNA polymerase)
  ◦ → Immune evasion

Transmission is MUCH more efficient when there is cell to cell contact.
HTLV-1 transmission

1) Vertical – predominant mode
   - Breast feeding - 15-25% (cf bottle feeding 1-3%)
     - RFs:
       - Longer duration (32% > 12 months cf 9% < 12 months in one study)
       - Proviral load
       - HLA class I concordance
     - Transplacental – low efficiency; < 5%

2) Sexual - 0.9 per 100 person-years
   - Efficient: Male → female and male → male
   - Female → male less efficient.

3) Blood exposure
   - Traditional practices
   - IVDU, needlestick
   - Contaminated cellular blood products 40%
Global epidemiology & disease associations HTLV-1
Global Epidemiology of HTLV-1

Widely quoted global prevalence:
10-20 million infected individuals (de The & Bomford 1993)

Revised estimate (2012):
5 – 10 million infected individuals
- Results based only on 1.5 billion people in known endemic countries with available epidemiological data
- Probably an underestimate
Global Epidemiology of HTLV-1

Problems with the epidemiology:

Representativeness of data
Pregnant women, blood donors, hospitalised patients

Diagnostic methods used
Screening: ELISA, Particle agglutination
Confirmation: Western Blot, Innogenetics line immunoassay, qual/quant proviral PCR

Widely quoted global prevalence: 10–20 million infected individuals (de The & Bomford 1993)

Revised estimate (2012): 5–10 million infected individuals

Results based only on 1.5 billion people in known endemic countries with available epidemiological data

Probably an underestimate
Figure 1 | Map of the geographical distribution of HTLV-1 subtypes (A–G), and the main modes of viral dissemination by movements of infected populations. Small arrows indicate the very probable interspecies transmission of STLV-1 (S) from monkeys to Humans (H) at the origin of some current HTLV-1 subtypes. These different subtypes comprise the Cosmopolitan A subtype with its different subgroups: TC (Transcontinental being the most frequent and widespread one), Awa (West African), Ana (North African), Aip (Japanese), B or Central African being the most frequent in this large endemic area, C or Australo-Melanesian D, also from Central Africa and present especially in certain Pygmy groups and lastly E, F, G with very few strains yet reported fall in Central Africa. The main HTLV-1 molecular epidemiological studies used to draw this map are the following ones: (Gessain et al., 1991; Gasmii et al., 1994; Miura et al., 1994; Maheux et al., 1997, 1998; Salemi et al., 1998; Vandamme et al., 1998; Wolfe et al., 2005; Cassar et al., 2007; Gessain, 2011).
### Table 2: Diseases reported in association with HTLV-1 and basis for this association

<table>
<thead>
<tr>
<th>Inflammatory syndromes</th>
<th>Case reports or series</th>
<th>Case control studies</th>
<th>Cohort studies</th>
<th>Biological evidence</th>
</tr>
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<tbody>
<tr>
<td>HAM/TSP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Uveitis</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Arthropathy</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Sjögren’s syndrome</td>
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<td>Polymyositis</td>
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<td>Thyroiditis</td>
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<td>Pneumopathy</td>
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<td>T lymphocyte alveolitis</td>
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<tr>
<td>Malignant diseases</td>
<td></td>
<td></td>
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<tr>
<td>ATL</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Cutaneous T-cell lymphoma</td>
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<tr>
<td>Infectious complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>Crusted scabies</td>
<td>Yes</td>
<td>...</td>
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<td>...</td>
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<tr>
<td>Infective dermatitis</td>
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<td>Tuberculosis</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Leprosy</td>
<td>Yes</td>
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</table>

HAM/TSP = HTLV-1-associated myelopathy/tropical spastic paraparesis. ATL = adult T-cell leukaemia/lymphoma.

### Lifetime risk:

- **HAM/TSP** 0.3 – 4%
- **ATL** 1 – 5%

- Assoc with acquiring infection early in life
- Acute form median survival 6 mo.
- **Any inflammatory / malignant disease** 10%

### HIV

- HTLV-1 in 10% of HIV infected people in co-endemic areas
- HIV disease progression
- ‘False’ rise in CD4+
- ?? to ART earlier or not
HTLV-1 in Australia: Recognition and Epidemiology
Recognition of HTLV-1 in Australian Aboriginal people

1988: Antibodies to HTLV-1 found in stored sera (1956-1975) from populations in the south-western Pacific (Asher, Goudsmit et al. 1988)
  ◦ Cape York Peninsula 2/156 (1.3%)

Early 1990s
  ◦ Antibodies found in NT Aboriginal people with Western Blot confirmation (May, Stent et al. 1990; Bastian, Gardner et al. 1993; Bastian, Hinuma et al. 1993)
  ◦ First published report of HTLV-1 virus isolation from cell culture from a seropositive NT Aboriginal person (Bastian 1993)
  ◦ Sequencing suggests existence of highly divergent Australo-Melanesian subtype (Gessain 1993, Nerurkar 1993 J Infect Dis)
  ◦ Case reports ATLL, HAM/TSP in Aust Aboriginal people
  ◦ Small cohort study linking HTLV-1 seropositivity with crusted scabies, skin sores and bronchiectasis.
Current understanding of Australian epidemiology of HTLV-1

Non-Indigenous Australians (blood donor serosurveys etc) 0.001 – 0.032%

Summary estimate as part of global survey (2012):
- Population: 463,900 Aboriginal and Torres Strait Islander people
- Number infected people: 2500 – 5000 people, (0.54 – 1.08%)
- Not evenly distributed

1993 Serosurvey in Darwin ~1900 Aboriginal adults from NT
- 1.7% seroprevalence (WB confirmed)
- 4.7% “cattle country” between Katherine and Alice Springs
- 13.9% Alice Springs
Current understanding of Australian epidemiology of HTLV-1


Retrospective study

All adults ≥ 15 years admitted to ASH 1/1/2000 – 31/12/2010 who had an HTLV-1 screening test for clinical reasons (neurological disease, malignancy, strongyloidiasis, bronchiectasis)

1614 adults tested
- 624 (38.7%) positive
- 605 referred for Western Blot confirmation
  - 531 confirmed
  - 4.6% indeterminate

33.3% seropositivity in a symptomatic inpatient population in Central Australia
Current understanding of Australian epidemiology of HTLV-1

NT pathology HTLV-1 serology requests 2008-2011
5527 requests (1972 repeats); 3555 patients, 2205 Indigenous One seroconversion among the repeats

Fig. 1 Geographical distribution of positive HTLV-1 serology requests. Percent positivity, no. of positive HTLV-1 requests/no. of total HTLV-1 requests.
Quick note on HTLV-1 diagnosis

Western Blot Criteria differ:
- WHO: gp46 or gp62/68 plus either p19, p24 or p53
- HTLV European Research Network: p19 and p24 bands plus rgp21 and rgp46-I.
- NRL, Australia: Both rgp21 and rgp46-I, and/or envelope gp46, plus at least three other viral specific proteins of the gag and pol series.

Table 1  Comparison of HTLV reactivity in sera from Northern Territory hospital patients screened with Serodia or Abbott Architect assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Positive screening assay n/N (%) (95% CI)</th>
<th>Western blot n (%) (95% CI)</th>
<th>Positive</th>
<th>Indeterminate</th>
<th>Negative</th>
<th>Not tested</th>
<th>Specificity (95% CI)</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 Particle agglutination (n = 955)</td>
<td>123/955 (12.9) (10.9–15.1)</td>
<td></td>
<td>112 (91.1) (84.7–94.9)</td>
<td>7 (5.7) (2.8–11.3)</td>
<td>1 (0.8)</td>
<td>3 (2.4)</td>
<td>98.7% (97.7–99.3)</td>
<td>91.06%</td>
</tr>
<tr>
<td>2009–2012 Abbott Architect* (n = 2600)</td>
<td>343/2600 (13.2) (11.9–14.5)</td>
<td></td>
<td>256 (74.6) (69.8–78.9)</td>
<td>62 (18.1) (14.4–22.5)</td>
<td>5 (1.5)</td>
<td>20 (5.8)</td>
<td>96.3% (95.4–97)</td>
<td>74.64%</td>
</tr>
</tbody>
</table>

* n = 123 for particle agglutination (comprising 119 screening positive and 4 indeterminate particle agglutination results); and 343 initial positive for Abbott Architect results referred for confirmatory western blot testing. 95% CI, 95% confidence interval.
Clinical associations of HTLV-1 in Australia
Clinical correlates

- **HAM/TSP**: 4 clinical cases
  - None had CSF molecular confirmation

- **ATLL**: 2 cases

- Higher risk of admission with strongyloidiasis

- Radiologically confirmed bronchiectasis was an independent predictor of HTLV-1 seropositivity

- Seropositive patients were more likely to be admitted with pneumonia and other lower respiratory tract infections except COPD

- More admissions with sepsis syndrome and proven BSI
  - BSI from likely GIT source remained significantly higher after adjusting for covariates

**Mortality:**
- 23.7 seropositive
- 23.1 seronegative

3rd case of ATLL reported since All 3 died of sepsis within 6 wks of diagnosis
More on the bronchiectasis story


61 patients adm to ASH with radiologically confirmed bronchiectasis July 2004-June 2005
- 70% recurrent childhood respiratory infections
- Few had Ix for underlying cause
- 25 pts had HTLV-1 serology; 18 (72%) were positive

- Retrospective cohort study: adults with bronchiectasis & known HTLV-1 status admitted to ASH 2000 – 2006
  - 58.4% of 89 patients were seropositive
  - Increased number of bronchiectatic lobes (OR 1.51; 95% CI 1.03–2.20; p=0.033) and ground glass change on HRCT (OR, 8.54; 95% CI, 1.04–70.03; p=0.046) predicted HTLV-1 seropositivity
  - Cor pulmonale (HTLV-1–positive group, 10/52; HTLV-1–negative group, 1/37; p=0.023 and disease-specific mortality (OR 5.78; 95% CI, 1.17–26.75; p=0.028) higher in seropositive group
  - Overall 34.2% mortality; median age of death 42.5 yrs
Case control study 36 adults adm ASH with bronchiectasis 2008-2009

- Controls matched by age, sex, ethno-geographic origin
- HTLV-1 infection was the main predictor of bronchiectasis (multivariate)
  - adjusted risk ratio [aRR], 1.84; 95% confidence interval [CI], 1.19–2.84; P = .006
- Median HTLV-1c PVL in cases was > 100 fold that of controls
  - cases, 0.319 [0.007, 0.749]; controls, 0.003 [0.000, 0.051] per 100 peripheral blood lymphocytes; P = .007
- HTLV-1c PVL closely correlated with radiologically determined pulmonary injury scores (Spearman’s rho = 0.7457; P = .0000).
- Other predictors of bronchiectasis were:
  - positive Strongyloides serology (aRR, 1.69; 95% CI, 1.13–2.53)
  - childhood skin infections (aRR, 1.62; 95% CI, 1.07–2.44).
- Bronchiectasis was the major predictor of death
  - aRR, 2.71; 95% CI, 1.36–5.39; P = .004.
Infective dermatitis

- 39 yo man p/w recurrent MRSA bacteraemia
- Extensive rash: scalp, face, neck, axillae, cubital fossae, groin
- Intractable; 12 admissions
- Undiagnosed for 2 decades
- Steroids for “seborrhoeic dermatitis”
- Ivermectin for scabies, *Strongyloides*.
- Biopsies: spongiosis & acanthosis c/w eczema; perivascular lymphocytic infiltrate
- HTLV-1 confirmed Western blot, high PVL
- Long term cotrimoxazole
Infective Dermatitis

- Typically affects children
- Jamaican cohort 1990s
- Low socioeconomic status; bacterial co-pathogenesis
- Exaggerated Th1 immune response, high HTLV-1 viral load
- Generalised chronic dermatitis
  - Scalp, axillae, groin, external ears, retroauricular and paranasal areas.

Diagnostic criteria
- Typical distribution
- Chronic nasal discharge
- Prompt response to antibiotics with relapse when ceased
- Onset in childhood
- HTLV-1 seropositivity

30% develop HAM/TSP
Seroprevalence in Central Australia largely unknown
  ◦ Up to 35% in some communities

Hyperinfection associated with up to 90% mortality

Case series of 18 patients at ASH 2000 – 2006 with complicated strongyloidiasis
  ◦ 7 / 11 patient tested were HTLV-1 seropositive

*Strongyloides stercoralis* and HTLV-1 are a potentially lethal duo
Strongyloides stercoralis and HTLV-1 coinfection

A. HTLV-1 clone abundance distribution in the blood

- Infective dermatitis (IDH)
- Strongyloides stercoralis (St)

<table>
<thead>
<tr>
<th></th>
<th>IDH</th>
<th>St</th>
<th>St</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoclonality index</td>
<td>0.48</td>
<td>0.39</td>
<td>0.76</td>
</tr>
<tr>
<td>Number of unique insertion sites detected</td>
<td>1,285</td>
<td>1,864</td>
<td>626</td>
</tr>
<tr>
<td>Proviral load (copies per 10^6 PBMCs)</td>
<td>9.9×10^4</td>
<td>1.9×10^5</td>
<td>1.4×10^5</td>
</tr>
</tbody>
</table>

GILLET 2013 PLOS PATHOGENS 9(4):E1003263
Figure 1. HTLV-1 clonal structure in the blood of subjects with HTLV-1 infection alone and those with co-infections.


http://127.0.0.1:8081/plospathogens/article?id=info:doi/10.1371/journal.ppat.1003263
Management of HTLV-1 in Australia
Prevention of vertical transmission - Japan

1987 Nagasaki Prefecture universal screening in 3<sup>rd</sup> trimester

Seropositive women (~1% in 1987) counselled against BF

Infant testing at 6, 12, 24, 36 months of age

MTCT 20% in BF, 2.5% in non-BF
  ◦ < 6 mo 7.4%
  ◦ > 6 mo 20.3%

Nationwide antenatal screening implemented 2010
PMTCT - Jamaica

Jamaica Breastfeeding Intervention Study
Primary data not yet published
1996–2000

Mothers were counselled and encouraged not to breast feed for longer than six months
PMTCT- Brazil

PCR based screening 55,293 newborns

Maternal AB screening, confirmation, PVL testing

42 Seropositive mothers counselled to stop BF at 7 days of life
  ◦ Infant formula provided for a minimum of 6 months
  ◦ Actual breast feeding duration reported 0 – 60 days, mean 27

EIA, WB and PCR repeated at 12 months (87.5% followed up)
  ◦ 1 tested positive (2.8%)
  ◦ 34 tested negative (97.2%)

Strategy deemed effective and safe
Any role for ART?

Biological plausibility – similar enzymes to HIV

Some in vitro activity
- NRTI
- Raltegravir

No benefit on PVL or clinically in HAM/TSP

Zidovudine effective as part of ATL chemotherapy regimens

Impact of replication strategy

Offered as part of occupational PEP
Current knowledge about HTLV-1 in Central Australia: Proceedings from the first workshop on HTLV-1 in Central Australia

Claire L. Gordon and Saliya Hewagama - Infectious Disease Physicians

Response “requires ongoing consideration” - follow up workshops are proposed.

Gaps in knowledge identified:
- the need for better estimates of local seroprevalence
- better understanding of the potential clinical associations of HTLV-1, particularly infective;
- the risk/benefit of continuing breast-feeding beyond 6 months; and
- the awareness/acceptance Indigenous people have of this infection and any potential future interventions.

Major concerns about early weaning
- Feasibility
- Culturally acceptability
- Safety given the nutritional and anti-infective benefits and lack of alternatives
- Logistical / resource requirements for education and implementation of early weaning
HTLV1 is increasingly being recognised as an important concern in some Aboriginal and Torres Strait Islander communities.

There would be benefit in applying principles emerging from the public health management of HTLV1 in international settings, such as Brazil and Japan, where it is prevalent.

- no specific treatment and no vaccine;
- testing and preventing transmission is the public health focus.
- combination of antenatal testing to identify at-risk mothers and breastfeeding interventions to reduce the risk of transmission to children born to HTLV1-positive mothers.

The related work conducted over the last few years in central Australia should be built on in the Australian context.
Other confidential deliberations

2nd HTLV-1 symposium in Darwin 2013
ASHM
NT Government
Whatever we do it will need to include (my 2 cents):

Disclosure to the affected communities

Community consultation and engagement

Collection of further seroprevalence data \(\rightarrow\) ethical implications of collection without intervention / community benefit

Ongoing elucidation of the clinical manifestations and their interactions with other infective and non infective disease processes

Best practice treatment of “facilitator” diseases such as strongyloidsis

Long term vision - addressing social determinants of health

And possibly:

- Antenatal screening and risk stratification by PVL
- Early postnatal interventions – counselling, informed choice ?ART ?early weaning
Acknowledgements:
Dr Lloyd Einsiedel
Research team at Flinders University Alice Springs Campus
Department of Paediatrics Alice Springs Hospital
Central Australian Remote Health Service, Alice Springs & Remote Clinics
Patients and Communities Alice Springs Hospital and Central Australia
Transmission – Breast feeding

Late 1980s, early 1990s in Japan

- HTLV-1 by PCR rarely detected in cord blood of neonates but commonly found in breast milk
- Human breast milk infectious to primates when given by mouth
- Small cohorts of no breast feeding – few transmissions

1991 Takahashi Int J Cancer - large non-randomised mixed prospective / retrospective MTCT study (780 babies)
- apparent ‘seroconversions’ 3-24 mo after disappearance of maternal antibodies

**Neonatal cord blood lymphocytes + infected breast milk + seronegative plasma → infection (antigen production)**

**Neonatal cord blood lymphocytes + infected breast milk + seropositive plasma → no infection**

Maternal antibodies protective

**TABLE 1 – HTLIV-1 SEROCONVERSION IN CHILDREN BORN TO HTLIV-1-CARRIER MOTHERS**

<table>
<thead>
<tr>
<th>Study group</th>
<th>HTLV-1 seropositive/total</th>
<th>Seroconversion rate (%)</th>
</tr>
</thead>
</table>
| Prospective
  study
  Breast-fed
  ≤ 6 months   | 1/23                       | 4.3                     |
  > 6 months   | 1/3                        | 33.3                    |
  Bottle-fed   | 9/151                      | 6.0                     |
| Retrospective study
  Breast-fed
  ≤ 6 months   | 3/67                       | 4.5                     |
  > 7 months   | 19/136                     | 14.0                    |
  Bottle-fed   | 0/7                        | 0.0                     |
| Total        |                           |                         |
  Breast-fed   | 4/90                       | 4.4                     |
  > 7 months   | 20/139                     | 14.4                    |
  Bottle-fed   | 9/158                      | 5.7                     |

Prospectively studied children were more than 12 months old and retrospectively studied children were more than 24 months old.