HTLV: A Neglected Infection of Global Significance

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The next 30 minutes

Origins
Epidemiology
Transmission & Prevention
Malignancy
Inflammatory Diseases
Asymptomatic Inflammation
HIV/HTLV Co-infection
HTLV’s diverged from PTLVs ~40,000 (HTLV-3) ~60,000 (HTLV-1), ~200,000 (HTLV-2) years ago.


Journal of Virology

Imperial College
High prevalence >1:100 general population

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Dragoslav Domanovic and produced by Antoine Gussain and Olivier Cassar (Institut Pasteur, Unité d'Epidémiologie et Physiopathologie des Virus Oncogènes, Département de Virologie, Paris, France).

2015
www.ecdc.europa.eu

S America & The Caribbean

High prevalence >1:10,000 first time blood donors

HTLV-1 Prevalence
- High
- Low prevalence or no HTLV-1 infection
- No data/concrete data
HTLV-1 prevalence in Africa

High prevalence >1:100 general population

HTLV-1 prevalence in Asia
HTLV-1 prevalence in North America

High prevalence >1:10,000 first time blood donors

HTLV-1 Prevalence in Europe
The highest reported prevalence of HTLV-1 is here

45%

5-10 million carriers worldwide is a conservative estimate

The next 24 minutes

Origins
Epidemiology
Transmission & Prevention
Malignancy
Inflammatory Diseases
Asymptomatic Inflammation
HIV/HTLV Co-infection
Transmission of HTLV-I/II

Mother-to-child
<33% with prolonged breastfeeding

Sexual intercourse
7% over 5 years between discordant couples

Blood transfusion
Cellular blood products ~ 30% transmission
Solid organ transplantation ~? 100%

Sharing of injecting paraphernalia

Sero-prevalence data from Bahia, Salvador, Brazil

Prevention of HTLV-1 transmission

Exclusive formula feeding reduces risk of transmission to 3%
- Ante-natal screening programme (except Japan √)
✓ Blood/Tissue donor screening
- Sexual health screening/advice
✓ Needle exchange programmes
✓ Wishful thinking
Adult T-cell Leukaemia/Lymphoma occurs in 5% of HTLV-1 carriers

Median age of onset 51.5 years
Males:Females - 1:2
Generalised lymphadenopathy
Hepatosplenomegaly
Skin lesions
Lytic bone lesions
Hypercalcaemia

Overall Survival ~8 months
Unchanged after 25 years

But better if treated with ‘anti-viral’ therapy

Hodson et al, J Clin Oncol 2011;29:4696-4701

ATLL is associated with high HTLV-1 viral load

~20% of carriers have Proviral loads >10%

1 in 100 PBMCs

High risk carriers can be identified

>4-10 in 100 PBMCs ~20% risk ATLL
ATLL is associated with infection in Infancy

LIFE COURSE OF ATLL

Birth 0 24% 58 58.7 63
ATL Presents
Death

Lifetime risk of 4%

ATLL can be prevented

Origins
Epidemiology
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Asymptomatic Inflammation
HIV/HTLV Co-infection
Lymphocytic infiltration
Initially CD4>CD8
Later CD8 predominate
Finally atrophy

Volume of distribution of $[^{11}C]PBR28$

Averaged Controls
Severe HAM
Moderate HAM
Mild HAM
Asymptomatic 1
Asymptomatic 2

Dimber et al
J Nuc Med
2016
jnumed.116.175083
Life time risk of HAM in HTLV-1 carrier

0.25% Japan

~3%

? Higher still in Brazil

activated T-cells and increased B2M in HAM

CD4 /CD8 ratio in HAM not different from other neurological disease
CD4 DR+ and CD8 DR+ increased

*Ijichi I et al J Neuroimmunol 1989;25:251-4*

*Kirk et al, Retrovirology 2011;8:81*
High levels of T-cell activation in patients with HAM/TSP

<table>
<thead>
<tr>
<th>Median counts</th>
<th>Asymptomatic Carrier</th>
<th>HAM/TSP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>796</td>
<td>898</td>
<td>0.11</td>
</tr>
<tr>
<td>CD4%</td>
<td>49</td>
<td>47</td>
<td>0.22</td>
</tr>
<tr>
<td>CD8</td>
<td>352</td>
<td>538</td>
<td>0.0005</td>
</tr>
<tr>
<td>CD8%</td>
<td>23</td>
<td>24</td>
<td>0.01</td>
</tr>
<tr>
<td>CD4/CD25%</td>
<td>37</td>
<td>54</td>
<td>0.0000004</td>
</tr>
<tr>
<td>CD4/HLA DR%</td>
<td>13</td>
<td>28</td>
<td>0.000000004</td>
</tr>
<tr>
<td>CD8/CD25%</td>
<td>9</td>
<td>13</td>
<td>0.09</td>
</tr>
<tr>
<td>CD8/HLA DR%</td>
<td>30</td>
<td>46</td>
<td>0.000001</td>
</tr>
<tr>
<td>β2M</td>
<td>1.2</td>
<td>1.8</td>
<td>0.000003</td>
</tr>
</tbody>
</table>

HTLV-1 associated polymyositis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>β2M</td>
<td>4.3</td>
<td>0.9 - 2.3mg/L</td>
</tr>
<tr>
<td>HTLV-1 DNA /100 PBMCs</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>CD4+CD25+</td>
<td>58%</td>
<td>15.7 - 34.9</td>
</tr>
<tr>
<td>CD+HLA-DR+</td>
<td>28%</td>
<td>4.2 - 13.6</td>
</tr>
<tr>
<td>CD8+HLA-DR+</td>
<td>58%</td>
<td>5.7 - 38.2</td>
</tr>
</tbody>
</table>
**HTLV-1 associated uveitis**

HTLV-I uveitis: a distinct clinical entity caused by HTLV-I.

HTLV-1 Ab+ 35.4% idiopathic uveitis,
10.3% uveitis with a diagnosis of idiopathic uveitis.

Symptoms at presentation
- Sudden onset of floaters; Unilateral or bilateral foggy/blurred vision;
- Additional symptoms: Pain, burning, itching, sensation of foreign body.

Anatomical diagnosis of HU
- Intermediate degree of uveitis with moderate or heavy vitreous opacities
- Mild iris

@ NCHR, London

29/706 4% “idiopathic uveitis”

13/125 10.4% of patients with HAM

**HTLV-1-associated alveolitis**


**Lymphocyte alveolitis in HTLV-I-associated myelopathy.**

Sugimoto M, Nakashima H, Watanabe S, Uyama E, Tanaka F, Ando M, Araki S, Kawasaki S

**Eur Respir J.** 1993 Jul;6(7):938-43.

Pulmonary involvement in human T-cell lymphotropic virus type-I uveitis: T-lymphocytosis and high proviral DNA load in bronchoalveolar lavage fluid.


Table 2. Cell differentiation and proportion of T cell subsets in BALF, values are median (range)

<table>
<thead>
<tr>
<th>Volume recovered</th>
<th>Total cells (x 10^3/ml)</th>
<th>Macrophages, %</th>
<th>Lymphocytes, %</th>
<th>No. of lymphocytes (x 10^3/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>64.9 (50.0–76.7)</td>
<td>1.1 (0.5–1.5)</td>
<td>84.4 (71.0–95.8)</td>
<td>11.1 (8.2–20.6)</td>
</tr>
<tr>
<td>HTLV-I carriers</td>
<td>72.1 (64.0–90.0)</td>
<td>3.5 (1.2–5.7)</td>
<td>70.7 (53.3–96.3)</td>
<td>15.7 (5.7–58.6)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4⁺, %</th>
<th>CD8⁺, %</th>
<th>CD5⁺HLA-DR⁺, %</th>
<th>CD5⁺CD25⁺, %</th>
<th>CD4/CD8 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>82.7 (79.1–85.9)</td>
<td>39.3 (18.2–53.9)</td>
<td>49.9 (27.2–62.4)</td>
<td>41.4 (26.4–48.4)</td>
</tr>
<tr>
<td>HTLV-I carriers</td>
<td>90.7 (89.4–98.8)**</td>
<td>43.7 (10.0–71.5)</td>
<td>45.5 (15.2–63.5)</td>
<td>53.1 (67.7–87.5)*</td>
</tr>
</tbody>
</table>

*P < 0.01; **P < 0.05 compared with normal subjects (Mann–Whitney U-test); differences remained significant after Bonferroni correction.

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15
Pulmonary disease in HTLV-1 infection

Pulmonary CT findings in 320 carriers of human T-lymphotropic virus type 1.
Okada F, Ando Y, Yoshitake S, Yotsumoto S, Matsumoto S, Wakisaka M, Nasut T, Mori H

Retrospective review of Pulm CT from 320 HTLV-1+ patients
98 (30.1%) were abnormal

<table>
<thead>
<tr>
<th>CT Finding</th>
<th>N/98 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrilobular nodules</td>
<td>95 (97)</td>
</tr>
<tr>
<td>Thickening bronchovascular bundles</td>
<td>55 (56)</td>
</tr>
<tr>
<td>Ground glass opacity</td>
<td>51 (52)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>50 (51)</td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Lymph Node enlargement</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Australian aborigines;
RR for HTLV by no. bronchiectatic lobes 1.5 (1.03 – 2.2; p=0.03)
More extensive disease
More deaths
Associated with high HTLV-1 proviral load

London - 0.1% general population have bronchiectasis
14/413 subjects attending clinic have diagnosed (3.4%)
Associated with HAM
1/246 asymptomatic carriers
10/95 patients with HAM
1/54 patients with ATL
RR for bronchiectasis if had HTLV-1-associated inflammatory disease = 8.4
(2.7 - 26.1. p<0.001
Honarbakhsh & Taylor BMC Inf Dis 2015;15:258
HTLV-associated inflammatory diseases

HAM and other inflammatory diseases are associated with high HTLV-1 viral load

Figure 2. Distribution of human T lymphotropic virus type 1-associated inflammatory diseases by body sites.

>1 in 100 PBMCS

>6% risk HTLV associated inflammation
B2M and HTLV-1 associated inflammation

Daniel Harding et al. P-E-10 Tokyo 2017

**B2M**

![Box plot showing B2M levels in AC Low PVL, AC High PVL, and HAM with p-values](image)

- P = 0.44
- P = 0.0009

**T-cell activation in AC and patients with HAM**

Daniel Harding et al. P-E-10 Tokyo 2017

**CD4/HLA-DR**

- P = 0.000001
- P = 0.000001

- P = 0.005
- P = 0.0000004

**CD4/25**

- P = 0.00002

**CD8/HLA-DR**

- P = 0.005
- P = 0.0000004
Identifying HAM

Daniel Harding et al P-E-10 Tokyo 2017

HTLV-1 PVL ≥ 1.5%, CD4/CD25 ≥35%, CD4/HLA-DR ≥15%, CD8/HLA-DR ≥17%, and β2 microglobulin ≥1.7µg/mL)

~10% of AC in London have a ‘HAM-like’ phenotype

HTLV-I causes a range of Inflammatory Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelopathy</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Myositis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Alveolitis</td>
<td>? sub-clinical</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Common esp HAM</td>
</tr>
<tr>
<td>Sicca Syndrome</td>
<td>Common esp HAM</td>
</tr>
<tr>
<td>Arthritis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Uveitis</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>&lt;4%</td>
</tr>
<tr>
<td>Infective dermatitis</td>
<td>Tropics only</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>? %</td>
</tr>
</tbody>
</table>

~10% AC have an “inflammatory” phenotype
What is the impact of HIV-1 infection on inflammation in HTLV-1 infection

HIV-1/HTLV-1 co-infected patients matched to HTLV-1 mono-infected patients

All HIV co-infected patients taking ART >12 months and fully suppressed

<table>
<thead>
<tr>
<th>HTLV-1</th>
<th>HTLV-1/HIV-1</th>
</tr>
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<tbody>
<tr>
<td>Median age 46 years</td>
<td>Median age 47 years</td>
</tr>
<tr>
<td>65% female</td>
<td>63% female</td>
</tr>
<tr>
<td>93% Black</td>
<td>93% Black</td>
</tr>
<tr>
<td></td>
<td>ART 59 months</td>
</tr>
</tbody>
</table>
Expected difference in CD4 and CD8 counts

<table>
<thead>
<tr>
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<td>CD4/µL</td>
<td>879</td>
<td>489</td>
<td>0.003</td>
</tr>
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<td>CD4%</td>
<td>46</td>
<td>28</td>
<td>0.000001</td>
</tr>
<tr>
<td>CD8/µL</td>
<td>349</td>
<td>751</td>
<td>0.003</td>
</tr>
<tr>
<td>CD8%</td>
<td>24</td>
<td>42</td>
<td>0.000001</td>
</tr>
<tr>
<td>CD4/CD8 Ratio</td>
<td>2.0</td>
<td>0.6</td>
<td>0.0000004</td>
</tr>
</tbody>
</table>

High levels of T-cell activation in patients with HTLV-1/HIV-1 co-infection despite HIV viral suppression

<table>
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<tr>
<td>CD4/CD25%</td>
<td>31</td>
<td>44</td>
<td>0.002</td>
</tr>
<tr>
<td>CD4/HLA DR%</td>
<td>10</td>
<td>31</td>
<td>0.0001</td>
</tr>
<tr>
<td>CD8/CD25%</td>
<td>6</td>
<td>10</td>
<td>0.05</td>
</tr>
<tr>
<td>CD8/HLA DR%</td>
<td>18</td>
<td>58</td>
<td>0.000001</td>
</tr>
<tr>
<td>β2M µg/ml</td>
<td>1.2</td>
<td>1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
Levels of T-cell activation in patients with HTLV-1/HIV co-infection resemble those of patients with HAM/TSP

<table>
<thead>
<tr>
<th>Medians</th>
<th>HTLV-1/HIV-1 co-infection</th>
<th>HAM/TSP</th>
</tr>
</thead>
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<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Is this the effect on HIV-1 alone?

What is the impact of HIV-1 infection on inflammation in HTLV-1 infection

Matched 16 HIV-1/HTLV-1 co-infected patients to 14 HTLV-1 mono-infected patients

All HIV co-infected patients taking ART >12 months and fully suppressed

HTLV-1
Median age 46 years
65% female
93% Black

HTLV-1/HIV-1
Median age 47 years
63% female
93% Black
Median months on ART 59

All HIV mono-infected patients taking ART >12 months and fully suppressed

H1V-1
Median age 37 years
36% female
45% Black
Median months on ART 78
High levels of T-cell activation in patients with HTLV-1/HIV-1 co-infection may not be due to HIV-1 infection

<table>
<thead>
<tr>
<th>Medians</th>
<th>HTLV-1 mono-infection</th>
<th>HTLV-1/HIV-1 co-infection</th>
<th>HIV-1 mono-infection</th>
<th>HIV-1 v Co-infect p</th>
</tr>
</thead>
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<tr>
<td>CD4/μL</td>
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<td>682</td>
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<td>CD4/HLA DR%</td>
<td>10</td>
<td>31</td>
<td>7</td>
<td>0.00002</td>
</tr>
<tr>
<td>CD8/CD25%</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>CD8/HLA DR%</td>
<td>18</td>
<td>58</td>
<td>19</td>
<td>0.000002</td>
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</tr>
</tbody>
</table>

Identifying risk of retrovirus related inflammation

>50% of HTLV-1/HIV-1 co-infected patients had a 'HAM-like' phenotype
HTLV-1/HIV-1 co-infection

T-cell activation high in co-infection resembling HAM
despite fully suppressive cART >12 months
is due to co-infection not HIV *per se*
long-term implications uncertain

HTLV-1: A neglected STI of global significance

10 million infections globally – mostly in LMIC
80% acquired sexually
5% develop a preventable, aggressive, T-cell malignancy
3% develop spastic paraparesis with >20 years of morbidity
?% develop other inflammatory conditions
Full spectrum of HTLV-1-associated diseases not described
Paradoxically HTLV/HIV co-infection becomes more important with fully suppressive HIV therapy
Patients at National Centre for Human Retrovirology

Clinical Staff

Staff and Students at Retrovirology Theme at Imperial College
Australasian Society of HIV, HTLV, viral Hepatitis and Sexual Health Medicine