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HTLV: A Neglected Infection of Global Significance

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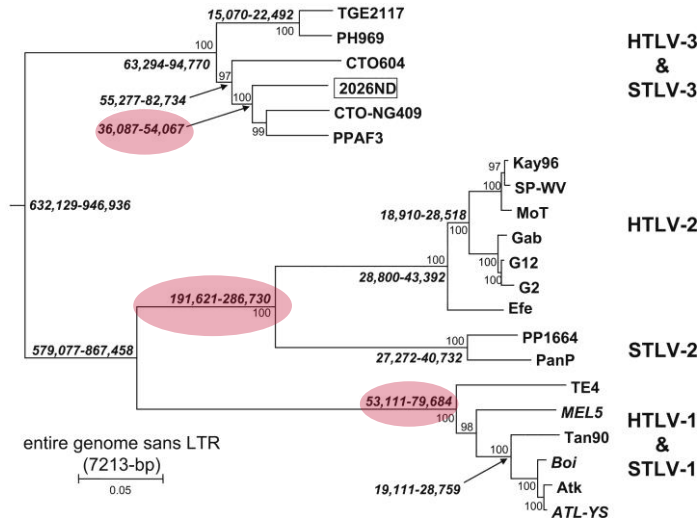
The next 30 minutes

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



Switzer W M *et al*. J. Virol. 2006;80:7427-7438

Journal of Virology

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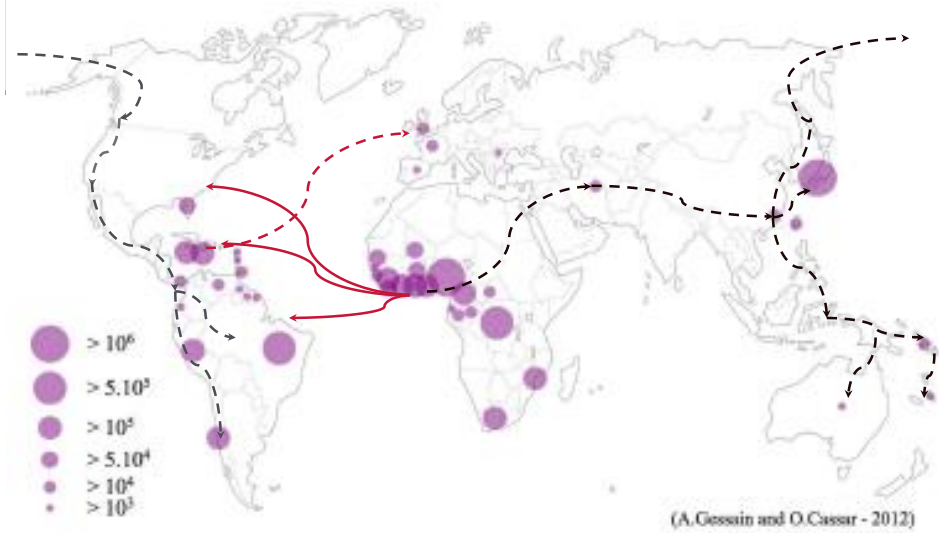


FIGURE 2 | Geographical distribution of the main foci of HTLV-1 infection. Estimates of the number of HTLV-1 infected carriers, based on approximately 1.5 billion of individuals from known endemic areas and reliable epidemiological data obtained from studies among pregnant women and/or blood donors and/or different adult populations. In few countries, HTLV-1 endemic areas are limited to residents of certain regions such as Mashad in Iran, The Fujian Province in China, Tumaco in Colombia and Central Australia.

TECHNICAL REPORT

Geographical distribution of areas with a high prevalence of HTLV-1 infection

High prevalence >1:100 general population

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

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

2015

www.ecdc.europa.eu

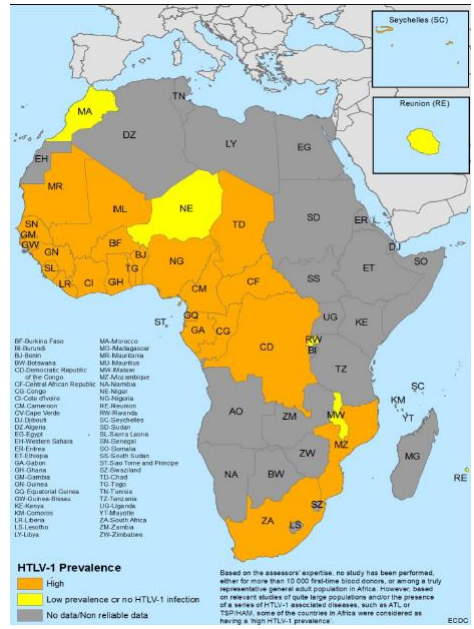
S America &

The Caribbean

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

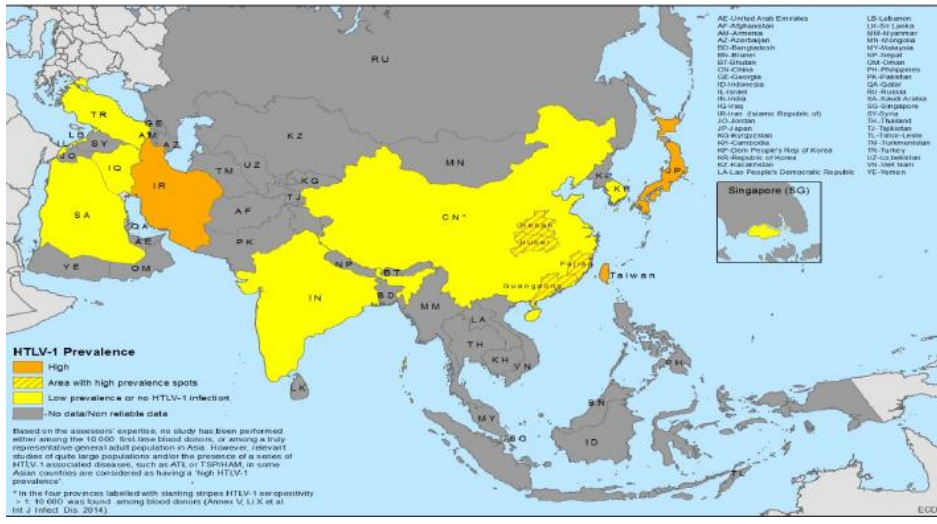
High prevalence >1:100 general population

HTLV-1 prevalence in Africa

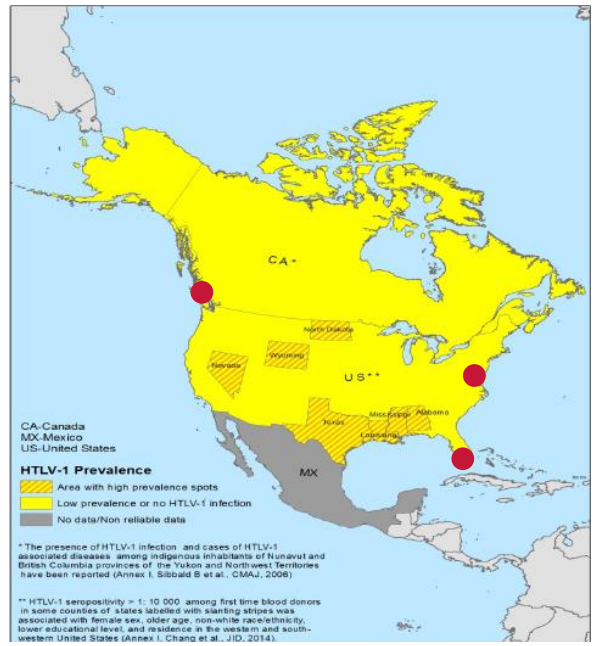


High prevalence >1:100 general population

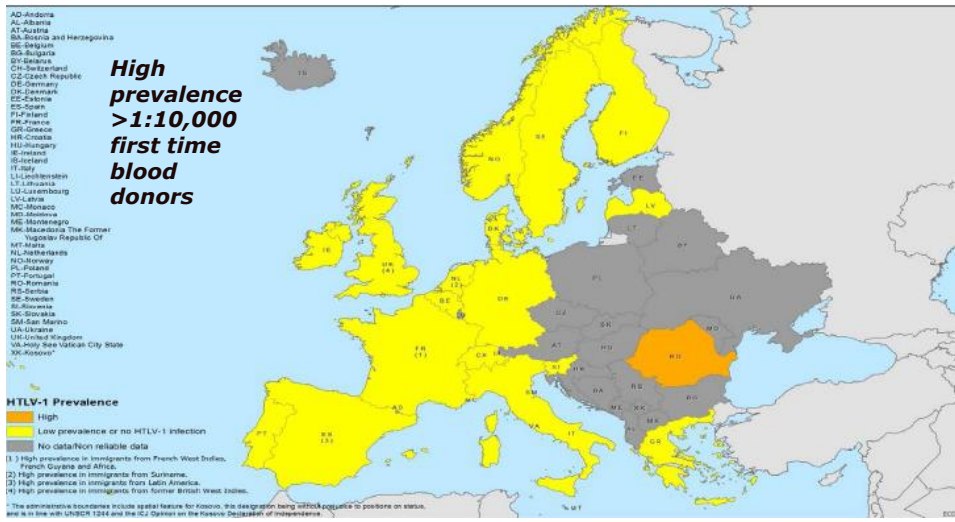
HTLV-1 prevalence in Asia



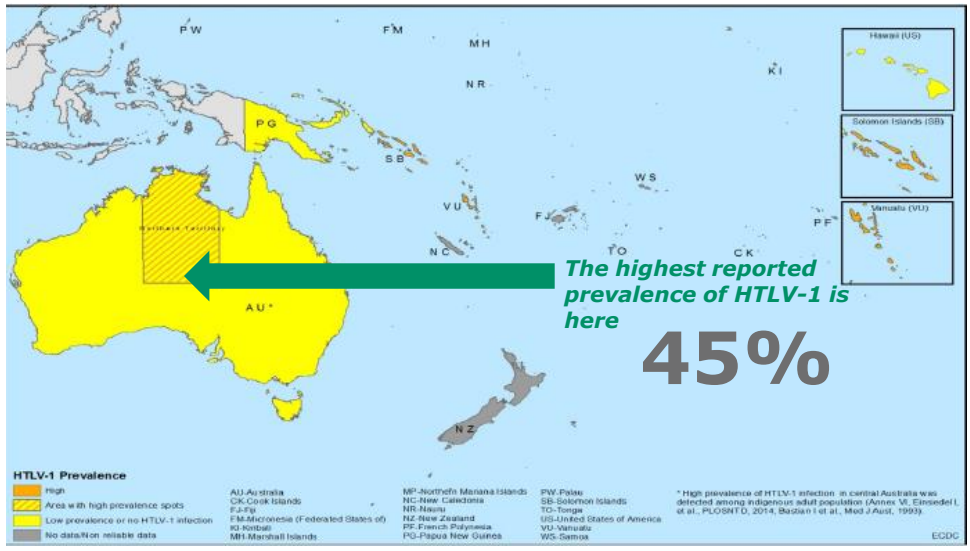
HTLV-1 prevalence in North America



HTLV-1 Prevalence in Europe



HTLV-1 prevalence in South west Pacific



5-10 million carriers worldwide is a conservative estimate

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The next 24 minutes

Origins

Epidemiology

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Inflammatory Diseases

Asymptomatic Inflammation

HIV/HTLV Co-infection

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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

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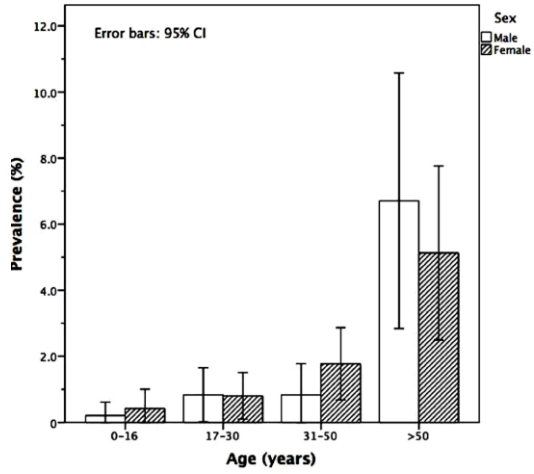
Sero-prevalence data from Bahia, Salvador, Brazil



Nunes et al PLoS ONE 12(2): e0171303.

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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

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Origins

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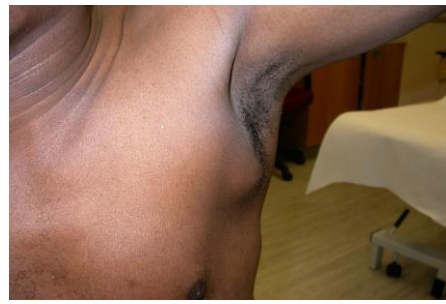
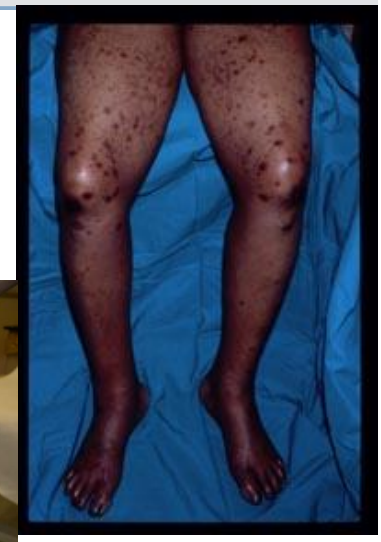
Adult T-cell Leukaemia/Lymphoma occurs in 5% of HTLV-1 carriers

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





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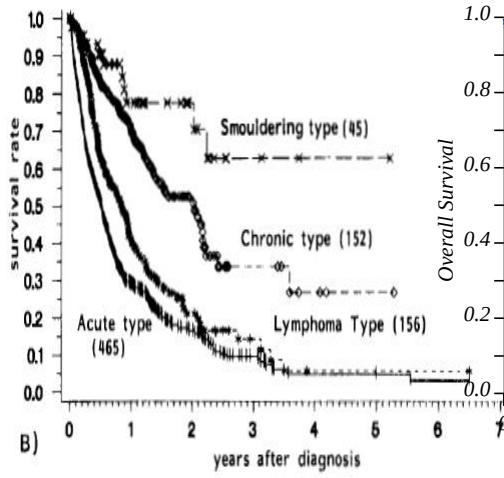
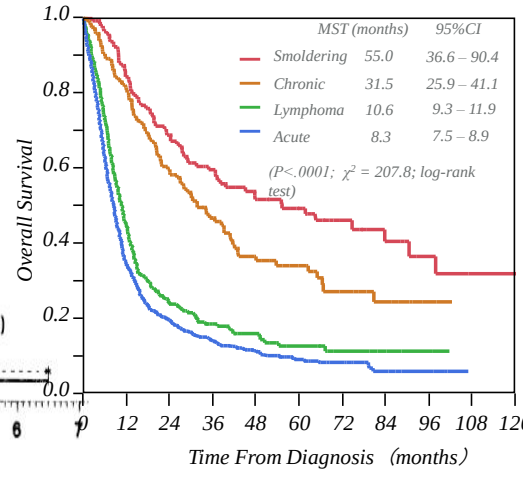
Adult T-cell Leukaemia/Lymphoma

Overall Survival ~8 months Unchanged after 25 years





Shimoyama M, Br J Haematol 1991;79:428-437 Katsuya H, et al, Blood 2015;126:2570-7

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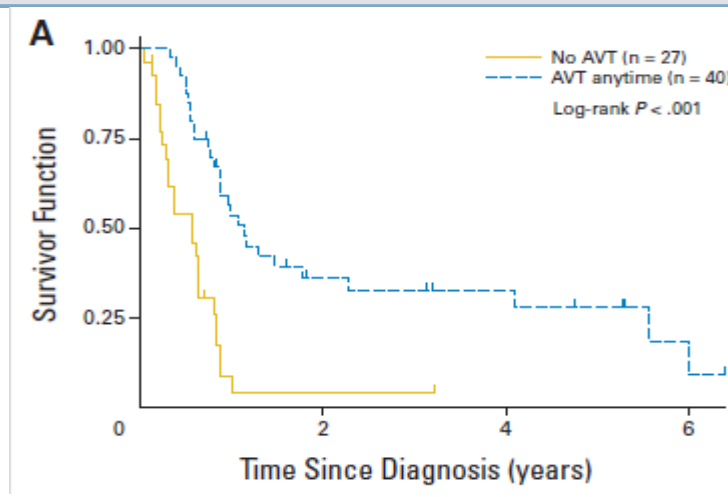
But better if treated with 'anti-viral' therapy



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

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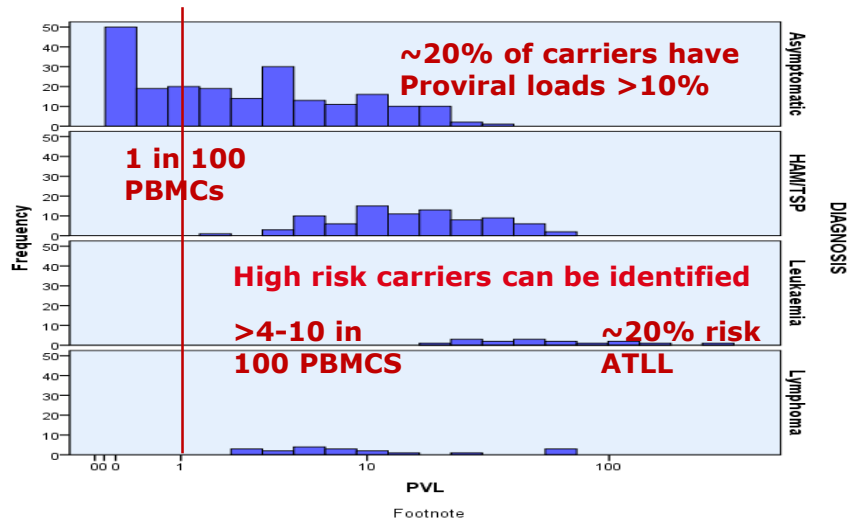
ATLL is associated with high HTLV-1 viral load



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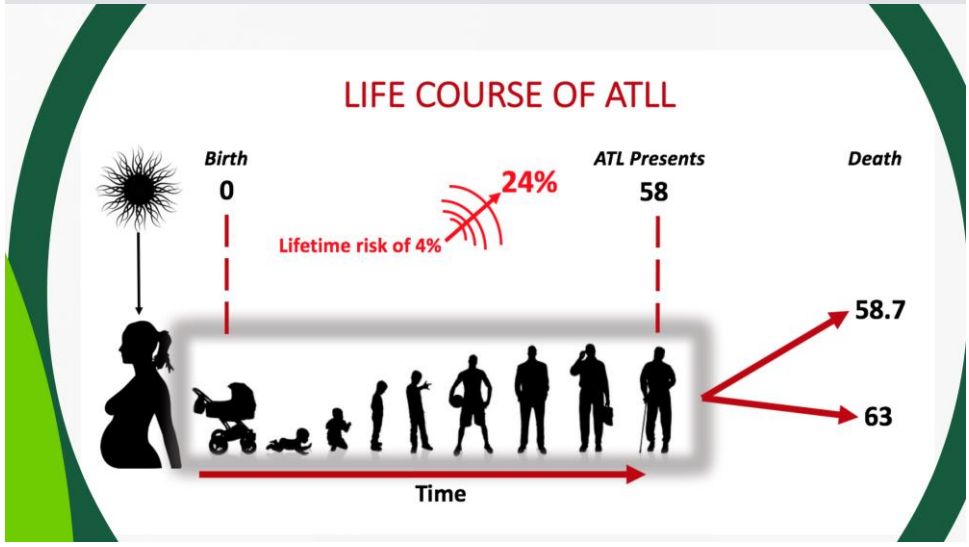
ATLL is associated with infection in Infancy



ATLL can be prevented

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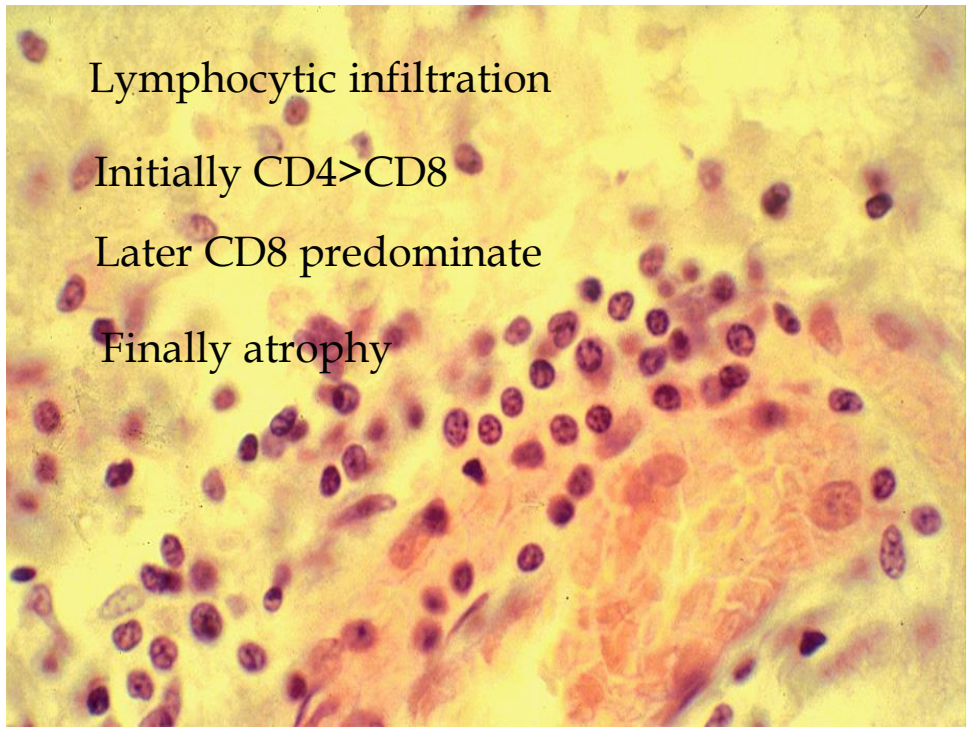

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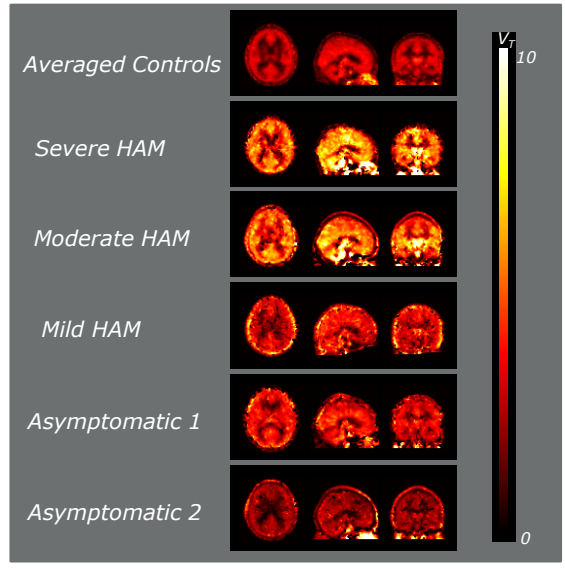
Volume of distribution of [^{11}C]PBR28



Dimber *et al* J Nuc Med 2016 *jnumed.116.175083*

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Life time risk of HAM in HTLV-1 carrier

0.25% Japan

~3%

? Higher still in Brazil

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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

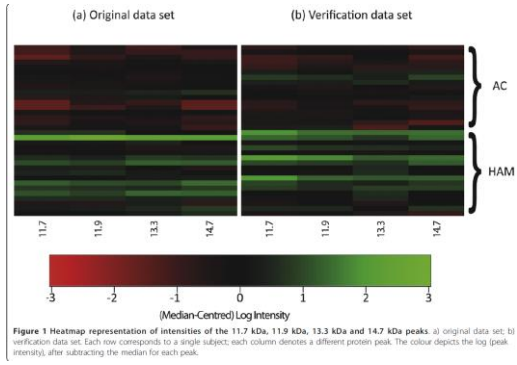

Figure 1 Heatmap representation of intensities of the 11.7 kDa, 11.9 kDa, 13.3 kDa and 14.7 kDa peaks. a) original data set; b) verification data set. Each row corresponds to a single subject; each column denotes a different protein peak. The colour depicts the log (peak intensity), after subtracting the median for each peak.

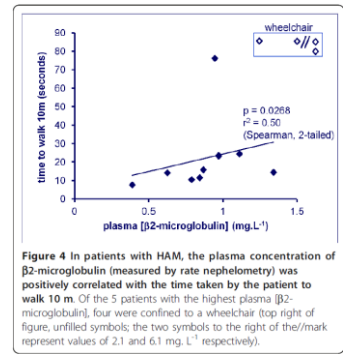

Figure 4 In patients with HAM, the plasma concentration of β2-microglobulin (measured by rate nephelometry) was positively correlated with the time taken by the patient to walk 10 m. Of the 5 patients with the highest plasma [β2-microglobulin], four were confined to a wheelchair (top right of figure, unfilled symbols; the two symbols to the right of the//mark represent values of 2.1 and 6.1 mg. L^{-1} respectively).

Kirk et al, Retrovirology 2011;8:81

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High levels of T-cell activation in patients with HAM/TSP

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

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HTLV-1 associated polymyositis

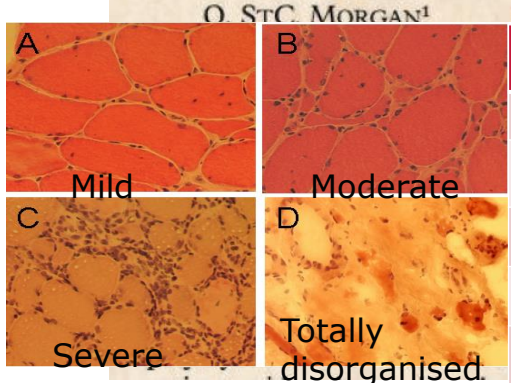
7/706 patients attending National Centre for Human Retrovirology 1995 - 2017

Inclusion Body Myositis
Lymphocytic myositis

THE LANCET, NOVEMBER 18, 1989

HTLV-1 AND POLYMYOSITIS IN JAMAICA

O. STC. MORGAN[1] P. RODGERS-JOHNSON[2]



Parameter	Median	Normal Range
β2M	4.3	0.9 - 2.3mg/L
HTLV-1 DNA /100 PBMCs	11.7	
CD4+CD25+	58%	15.7 - 34.9
CD+HLA-DR+	28%	4.2 - 13.6
CD8+HLA-DR+	58%	5.7 - 38.2

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HTLV-1 associated uveitis

Jpn J Cancer Res. 1992;83(3):236-9.
HTLV-I uveitis: a distinct clinical entity caused by HTLV-I.
Mochizuki M[1], Watanabe T, Yamaguchi K, Takatsuki K, Yoshimura K, Shirao M, Nakashima S, Mori S, Araki S, Miyata N.

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

@ NCHR, London
29/706 4% "idiopathic uveitis"
13/125 10.4% of patients with HAM

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 iritis

Parameter	Median	Normal Range
b2M	2.0	0.9 - 2.3mg/L
HTLV-1 DNA /100 PBMCs	7.5	
CD4+CD25+	45%	15.7 - 34.9
CD+HLA-DR+	19%	4.2 - 13.6
CD8+HLA-DR+	37%	5.7 - 38.2

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HTLV-1-associated alveolitis

Lancet. 1987;2(8569):1220.
T-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.
Sugimoto M[1], Mita S, Tokunaga M, Yamaguchi K, Cho I, Matsumoto M, Mochizuki M, Araki S, Takatsuki K, Ando M.

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

	Volume recovered	Total cells ($\times 10^5$/ml)	Macrophages, %	Lymphocytes, %	No. of lymphocytes ($\times 10^5$/ml)
Normal subjects ($n = 10$)	64·9 (50·0–76·7)	1·1 (0·5–1·5)	84·4 (71·0–95·8)	11·4 (4·2–20·6)	0·1 (0·05–0·3)
HTLV-1 carriers ($n = 13$)	72·1 (48·0–99·0)	3·5 (1·2–5·7)**	70·7 (7·3–96·3)	25·7 (5·7–68·0)*	1·0 (0·1–3·9)**

	$CD3^+$, %	$CD4^+$, %	$CD8^+$, %	$CD3^+HLA\text{-}DR^+$, %	$CD3^+CD25^+$, %	CD4/CD8 ratio
Normal subjects ($n = 10$)	82·7 (79·1–85·9)	39·3 (18·2–53·9)	40·9 (27·2–62·4)	41·4 (26·8–48·4)	3·5 (1·4–10·8)	1·1 (0·3–1·9)
HTLV-1 carriers ($n = 13$)	90·7 (69·4–98·8)**	43·7 (16·0–71·5)	43·5 (15·2–63·5)	53·1 (9·7–87·9)*	20·3 (8·7–51·3)**	1·1 (0·2–2·5)

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

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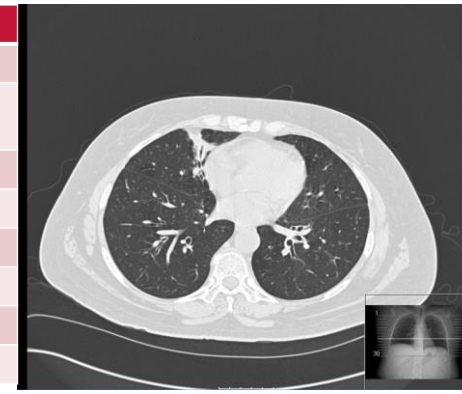
Pulmonary disease in HTLV-1 infection

Radiology. 2006 Aug;240(2):559-64.
Pulmonary CT findings in 320 carriers of human T-lymphotropic virus type 1.
Okada F[1], Ando Y, Yoshitake S, Yotsumoto S, Matsumoto S, Wakisaka M, Maeda T, Mori H

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

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



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Bronchiectasis

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

Einsiedel L, CID 2012;54:43-50.

Einsiedel L, PLoS Negl Trop Dis. 2014;8, e2643.

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

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HTLV-associated inflammatory diseases

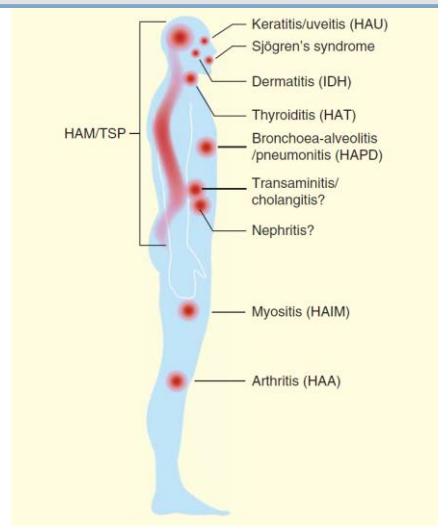

Figure 2. Distribution of human T lymphotropic virus type 1-associated inflammatory diseases by body sites.

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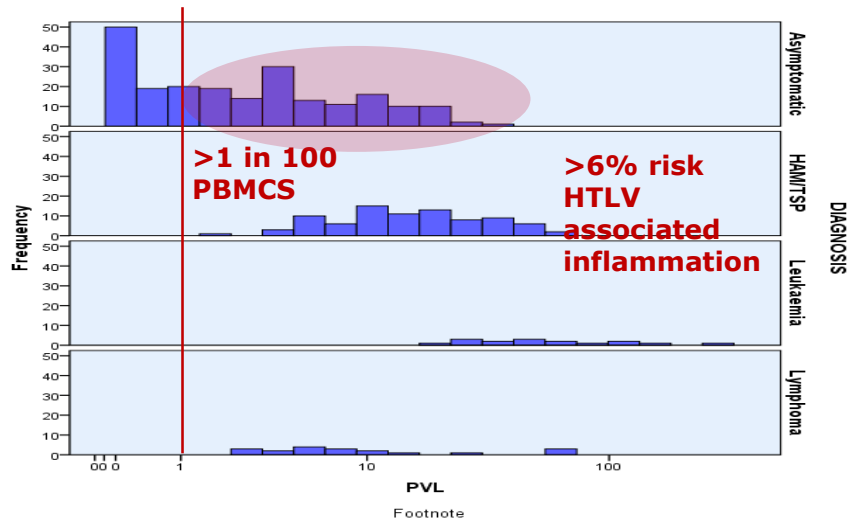
HAM and other inflammatory diseases are associated with high HTLV-1 viral load



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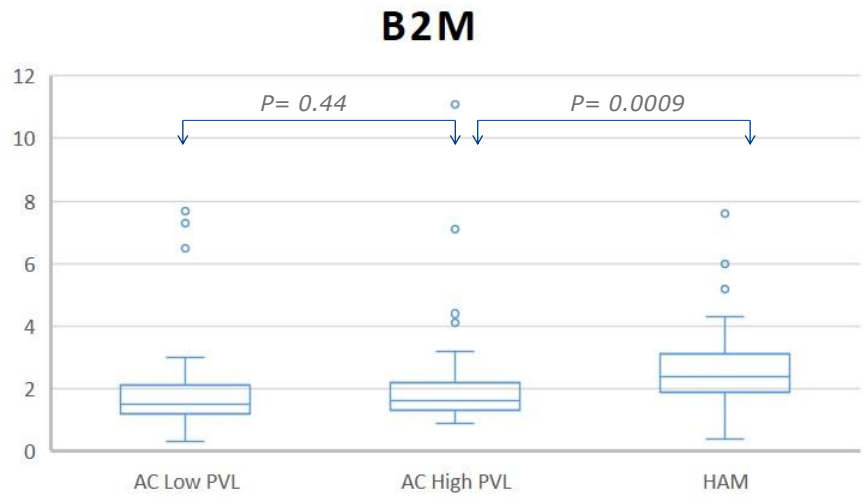
B2M and HTLV-1 associated inflammation

Daniel Harding et al P-E-10 Tokyo 2017



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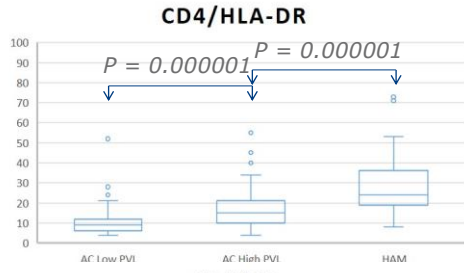
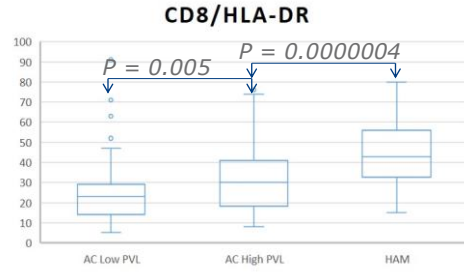
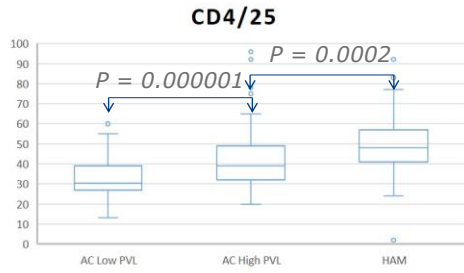
T-cell activation in AC and patients with HAM

Daniel Harding et al P-E-10 Tokyo 2017







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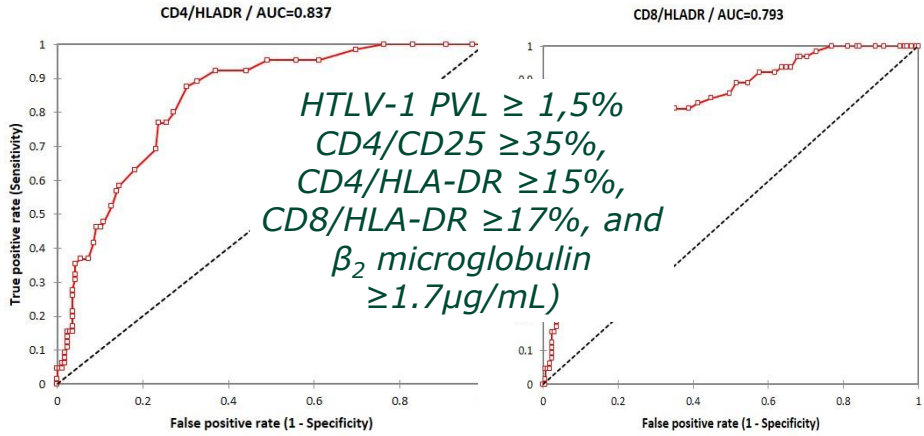
Identifying HAM

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
β_2 microglobulin
≥1.7µg/mL)

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

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HTLV-I causes a range of Inflammatory Diseases

Myelopathy	<4%
Myositis	?<1%
Alveolitis	? sub-clinical
Bronchiectasis	Common esp HAM
Sicca Syndrome	Common esp HAM
Arthritis	<1%
Uveitis	<4%
Thyroiditis	? <4%
Infective dermatitis	Tropics only
Hepatitis	? %

~10% AC have an "inflammatory" phenotype

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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

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

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

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Expected difference in CD4 and CD8 counts

Medians	HTLV-1 mono-infection	HTLV-1/HIV-1 co-infection	p
CD4/μL	879	489	0.003
CD4%	46	28	0.000001
CD8/μL	349	751	0.003
CD8%	24	42	0.000001
CD4/CD8 Ratio	2.0	0.6	0.0000004

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

Medians	HTLV-1 mono-infection	HTLV-1/HIV-1 co-infection	p
CD4/μL	879	489	0.003
CD4%	46	28	0.000001
CD8/μL	349	751	0.003
CD8%	24	42	0.000001
CD4/CD8 Ratio	2.0	0.6	0.0000004
CD4/CD25%	31	44	0.002
CD4/HLA DR%	10	31	0.0001
CD8/CD25%	6	10	0.05
CD8/HLA DR%	18	58	0.000001
β2M μg/ml	1.2	1.8	NS

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Levels of T-cell activation in patients with HTLV-1/HIV co-infection resemble those of patients with HAM/TSP

Medians	HTLV-1/HIV-1 co-infection	HAM/TSP
CD4/CD25%	**44**	**54**
CD4/HLA DR%	**31**	**28**
CD8/CD25%	**10**	13
CD8/HLA DR%	**58**	**46**
β2M μg/ml	1.8	**1.8**

Is this the effect on HIV-1 alone?

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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

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High levels of T-cell activation in patients with HTLV-1/HIV-1 co-infection may not be due to HIV-1 infection

Medians	HTLV-1 mono-infection	HTLV-1/HIV-1 co-infection	HIV-1 mono-infection	HIV-1 v Co-infect p
CD4/μL	**879**	**489**	**682**	**0.04**
CD4%	**46**	**28**	**39**	**0.003**
CD8/μL	349	751	794	NS
CD8%	24	42	40	NS
CD4/CD8 Ratio	**2.0**	**0.6**	**1.0**	**0.04**
CD4/CD25%	**31**	**44**	**20**	**0.001**
CD4/HLA DR%	**10**	**31**	**7**	**0.00002**
CD8/CD25%	**6**	**10**	**6**	**0.03**
CD8/HLA DR%	**18**	**58**	**19**	**0.000002**
β2M μg/ml	1.2	1.8	2.2	NS

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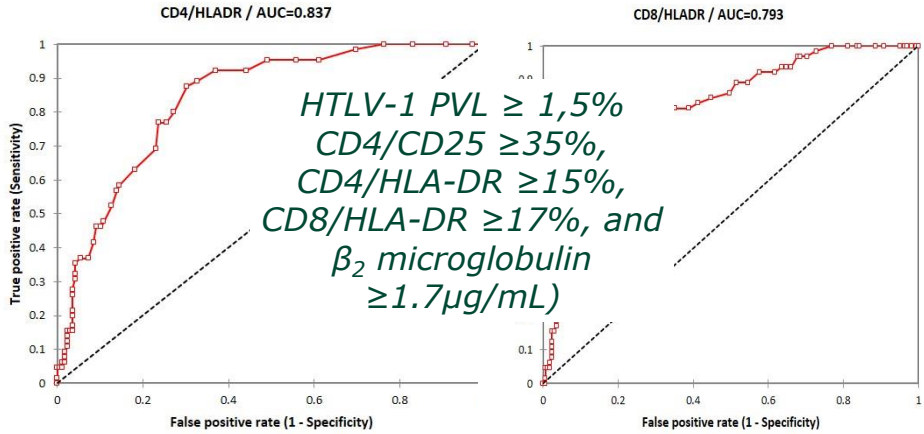
Identifying risk of retrovirus related inflammation



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

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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

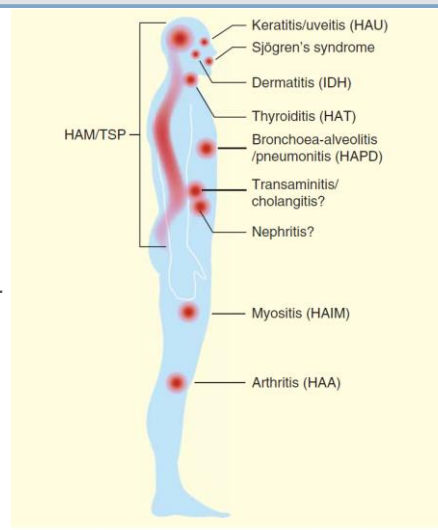

Figure 2. Distribution of human T lymphotropic virus type 1-associated inflammatory diseases by body sites.

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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

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Improving the health and wealth of the nation through research

NHS National Institute for Health Research

Bloodwise
Beating blood cancer since 1960

wellcome trust