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Human T-cell Lymphotropic Virus/ Human Immunodeficiency Virus co-infection and inflammation

Impact of HTLV-1 co-infection on T-cells in patients with fully suppressed HIV infection: an open, single centre, cross-sectional study

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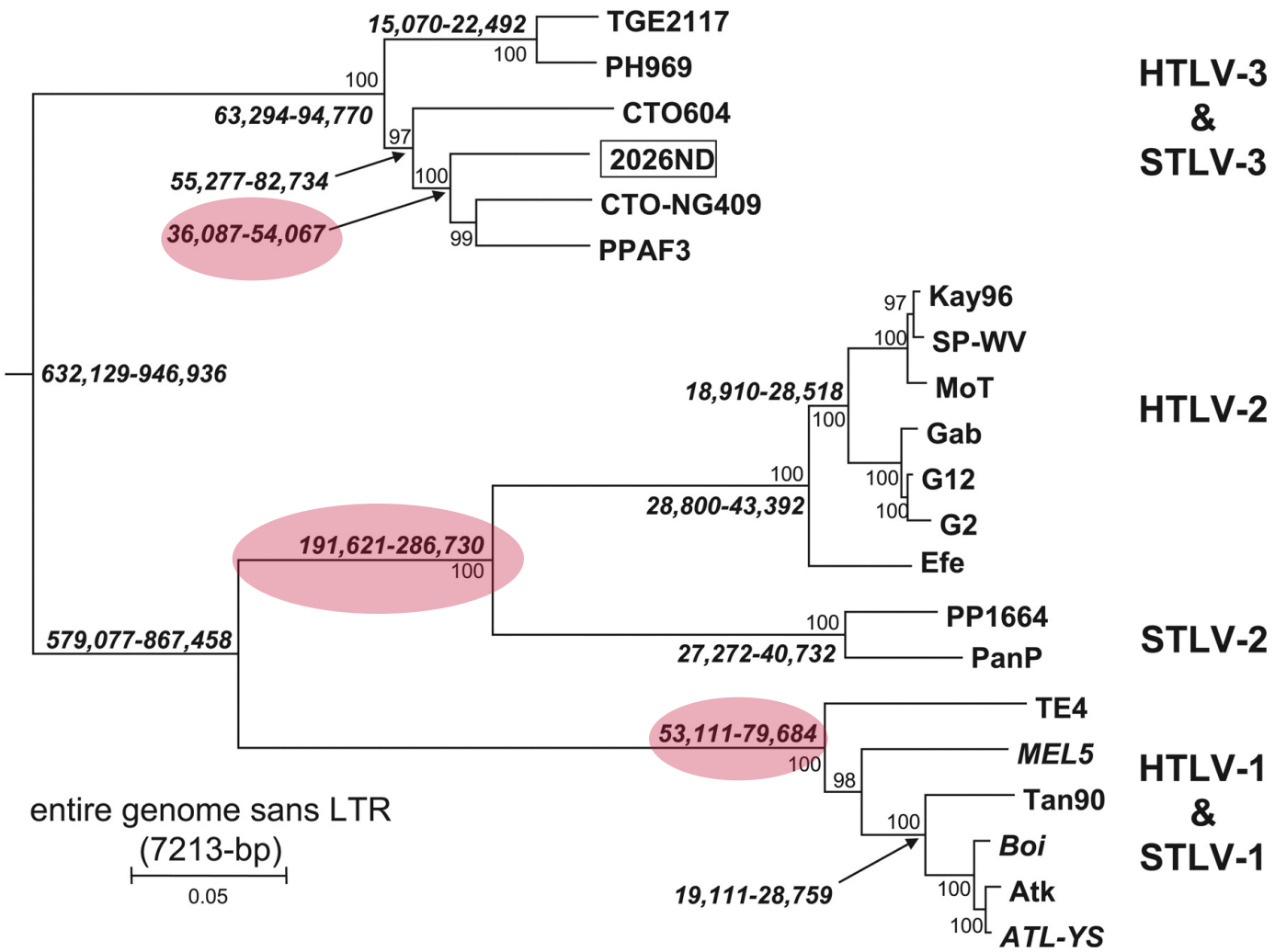
HTLV's diverged from PTLVs ~40,000 (HTLV-3) ~60,000 (HTLV-1), ~200,000 (HTLV-2) years ago



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

Journal of Virology

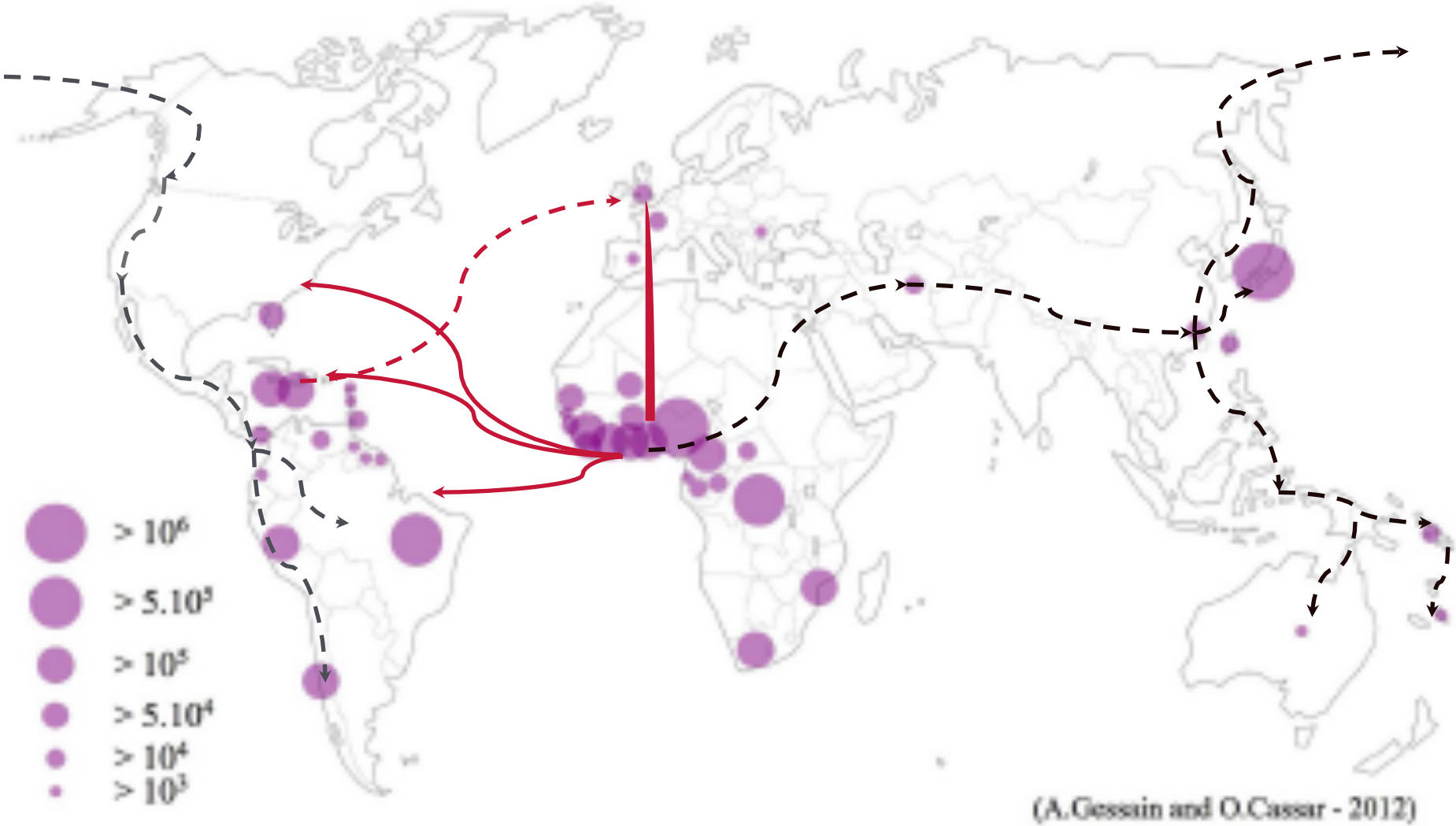


FIGURE 2 | Geographical distribution of the main foci of HTLV-1 infection. Estimates of the number of HTLV-1 infected carriers, based on approximately 1.5 billion of individuals from known endemic areas and reliable epidemiological data obtained from studies among pregnant women and/or blood donors and/or 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, Turnaco in Colombia and Central Australia.

HTLV-I prevalence in the UK

- 1993 N London Blood Donors n = 96,000
  – 1/20,000 Brennan et al BMJ 1993;307:1235-9
- 2000 N Thames Infant Heel Pricks n = 126,000
  - 1/2,000 Ades et al BMJ 2000;320:1497-1501
- Unpublished S London GU Clinic n =2,553
  - 1/330
- 2005 S London HIV+ patients n = 777
  - 1/130 Cooke et al J Med Virol 2005;76:143 - 5

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Adult T-cell Leukaemia/Lymphoma

Median age of onset 51.5 yrs

Life-time risk 4%

Mothers are carriers

Median survival 8 months

4%

HTLV-1-associated myelopathy/Tropical spastic paraparesis

3%

50% of patients become wheelchair dependent by 20 years

Gessain A et al Lancet 1985;2:407-10.
Osame M et al Lancet 1986;1:1031-2

Olindo et al

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Neuro-pathology – includes inflammation above the cord

The spinal cord loses volume

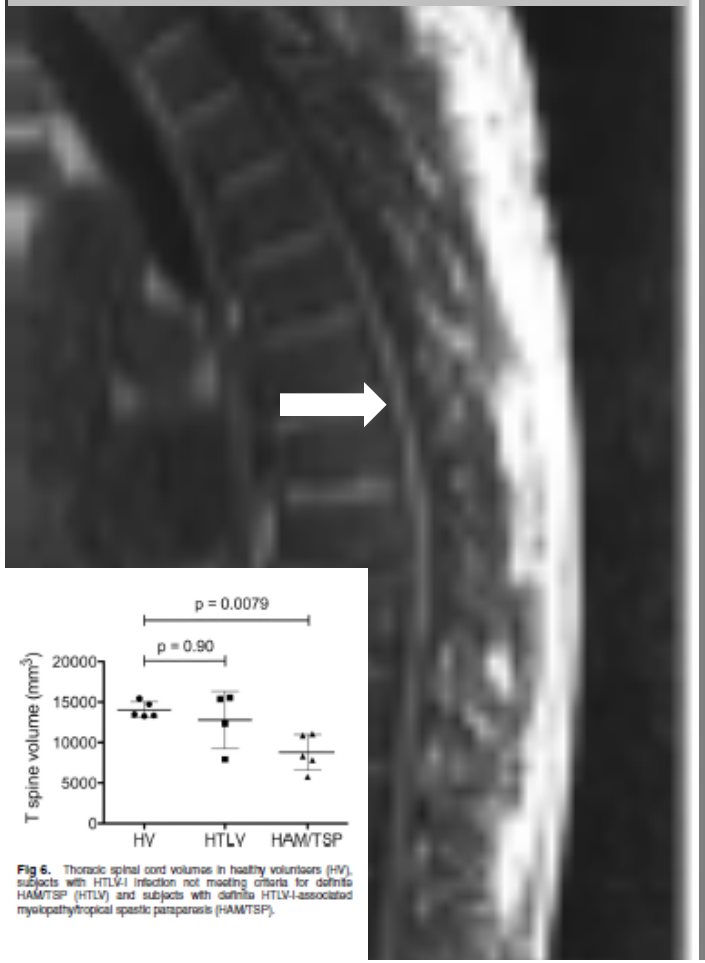


Fig 6. Thoracic spinal cord volumes in healthy volunteers (HV), subjects with HTLV-I infection not meeting criteria for definite HAM/TSP (HTLV) and subjects with definite HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

J Neuroimaging 2014;24:74-78.
DOI: 10.1111/j.1552-6569.2011.00648.x

Averaged Controls

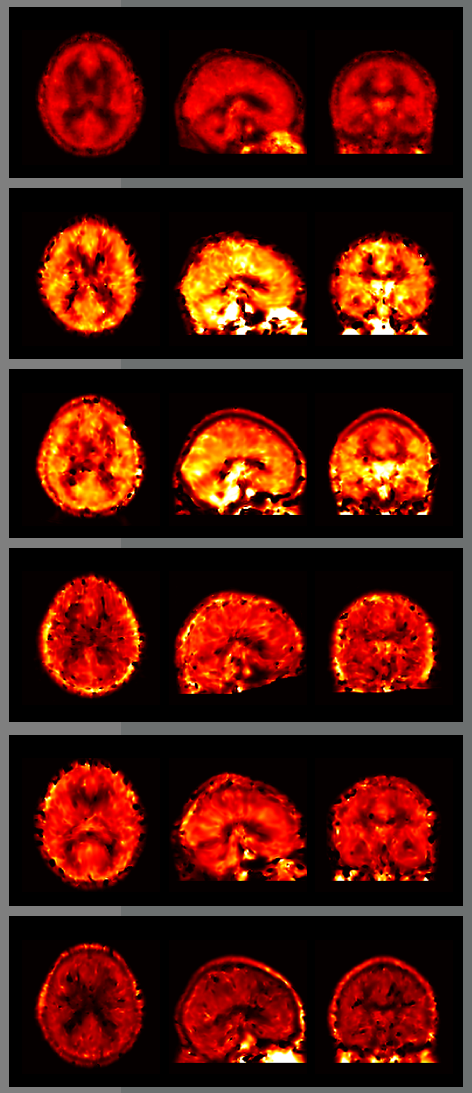
Severe HAM

Moderate HAM

Mild HAM

Asymptomatic 1

Asymptomatic 2



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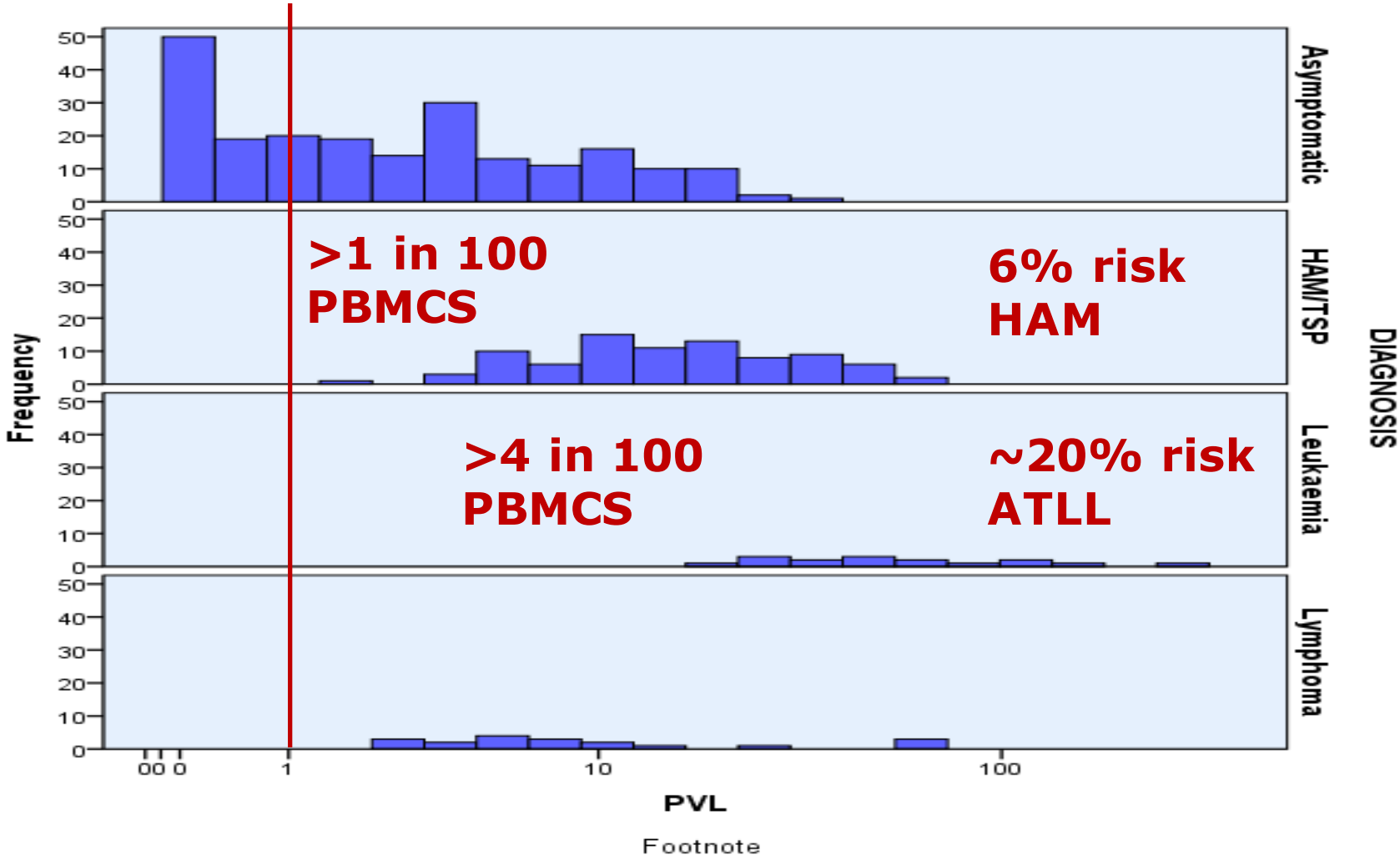
HAM and ATLL are associated with high HTLV-1 proviral load (>1% PBMCs infected)



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

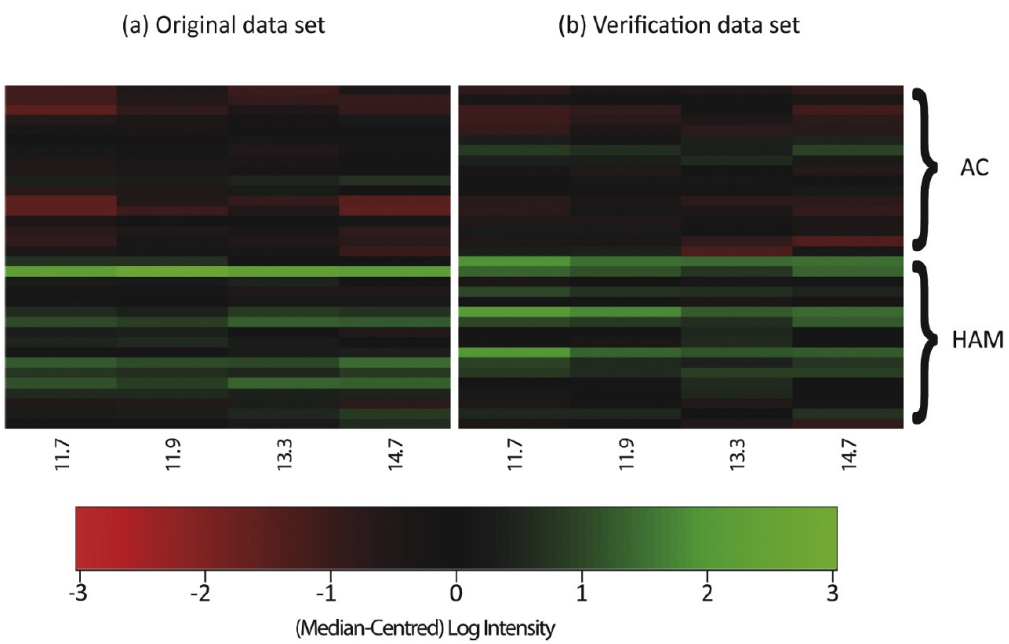


Figure 1 Heatmap representation of intensities of the 11.7 kDa, 11.9 kDa, 13.3 kDa and 14.7 kDa peaks. a) original data set; b) verification data set. Each row corresponds to a single subject; each column denotes a different protein peak. The colour depicts the log (peak intensity), after subtracting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

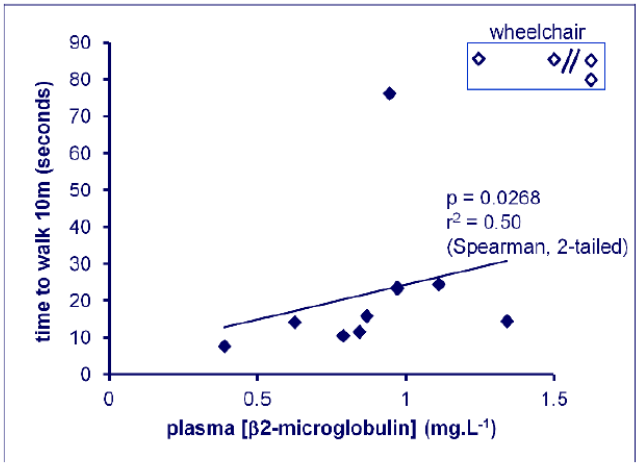


Figure 4 In patients with HAM, the plasma concentration of β2-microglobulin (measured by rate nephelometry) was positively correlated with the time taken by the patient to walk 10 m. Of the 5 patients with the highest plasma [β2-microglobulin], four were confined to a wheelchair (top right of figure, 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

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

Medians	Asymptomatic Carriers	HAM/TSP	p
CD4/μL	796	898	0.11
CD4%	49	47	0.22
CD8/μL	**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 μg/ml	**1.2**	**1.8**	**0.000003**

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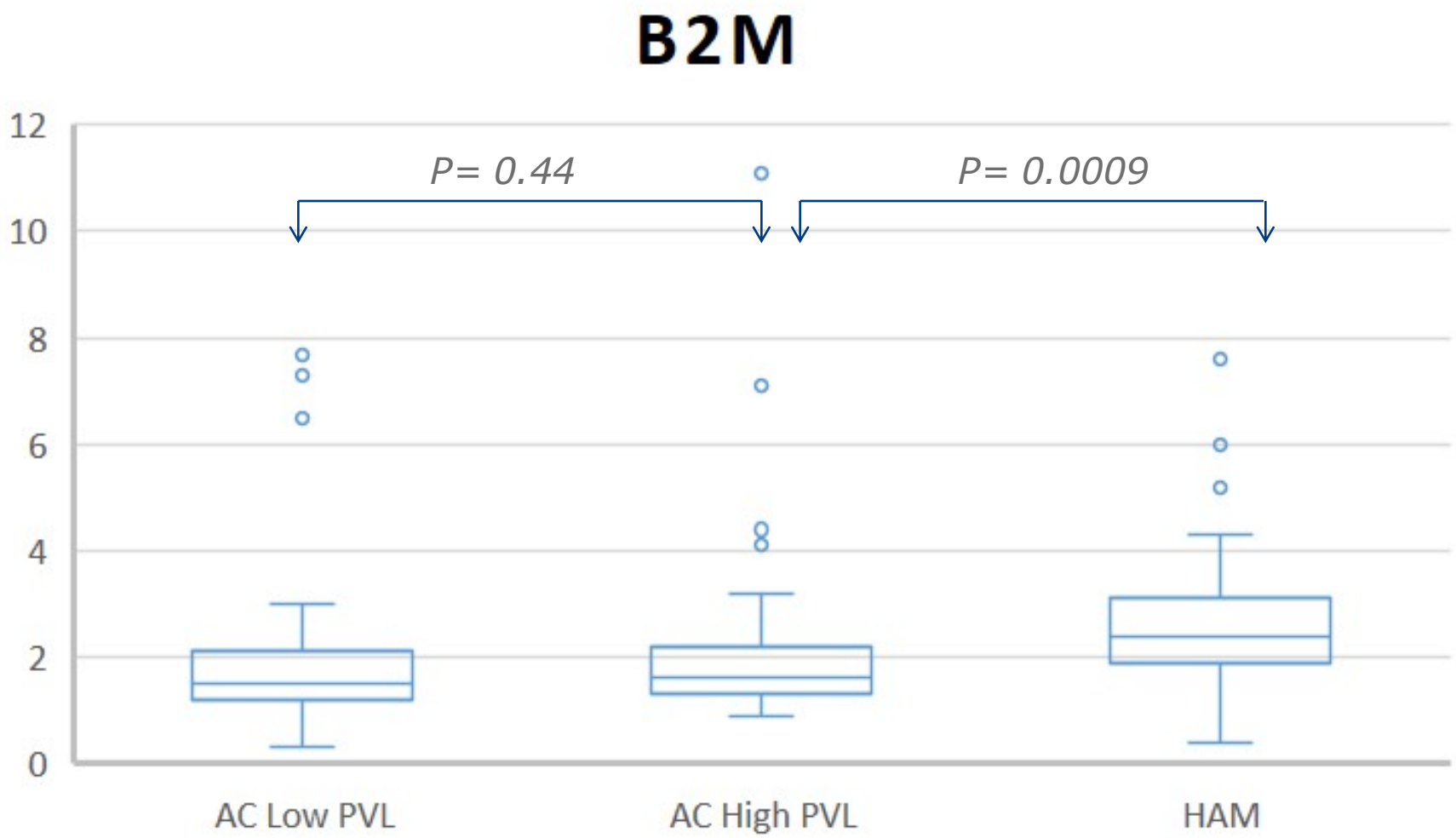
B2M and HTLV-1 associated inflammation

Daniel Harding et al P-E-10 Tokyo 2017



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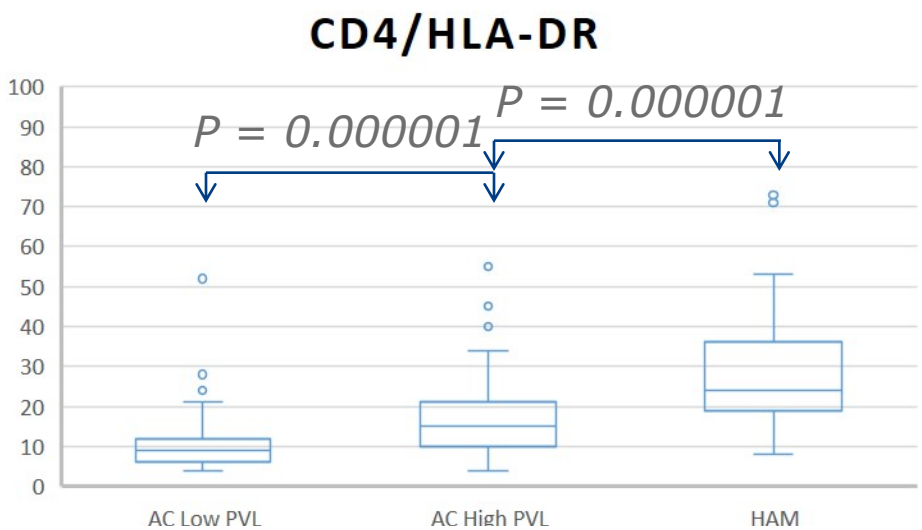
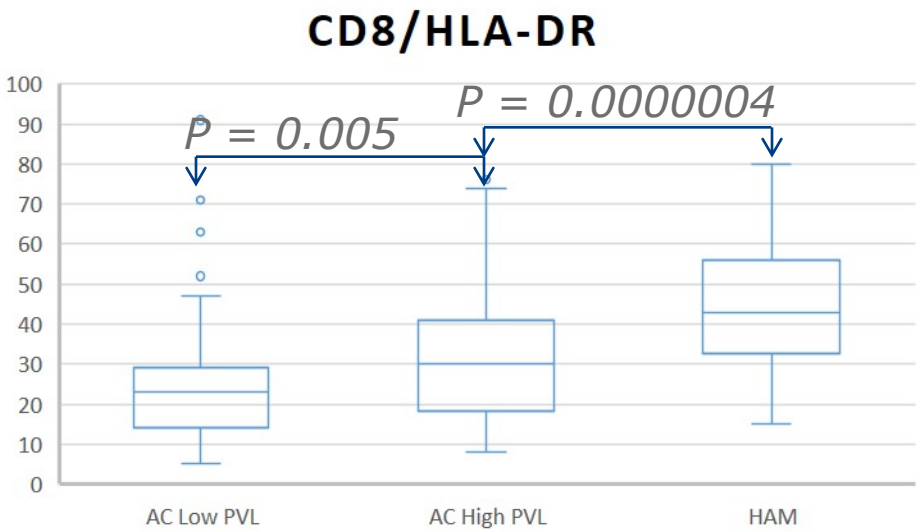
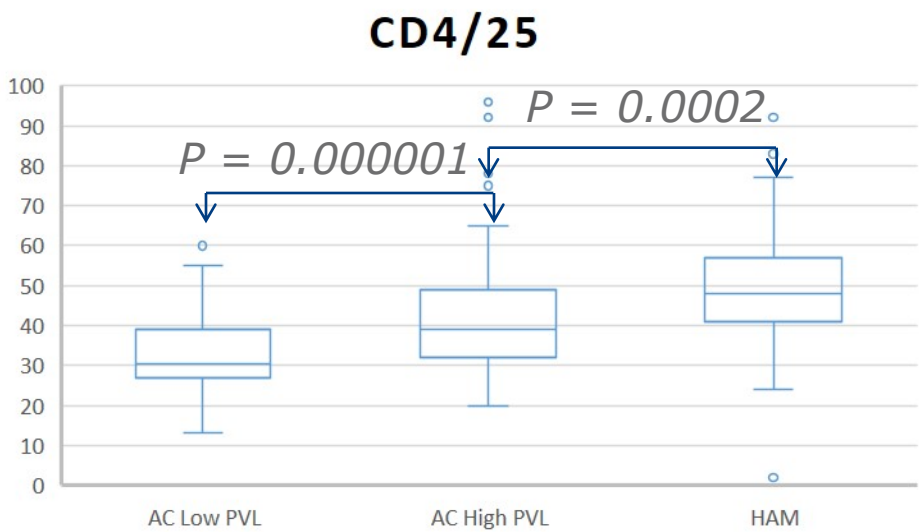
T-cell activation in AC and patients with HAM

Daniel Harding et al P-E-10 Tokyo 2017







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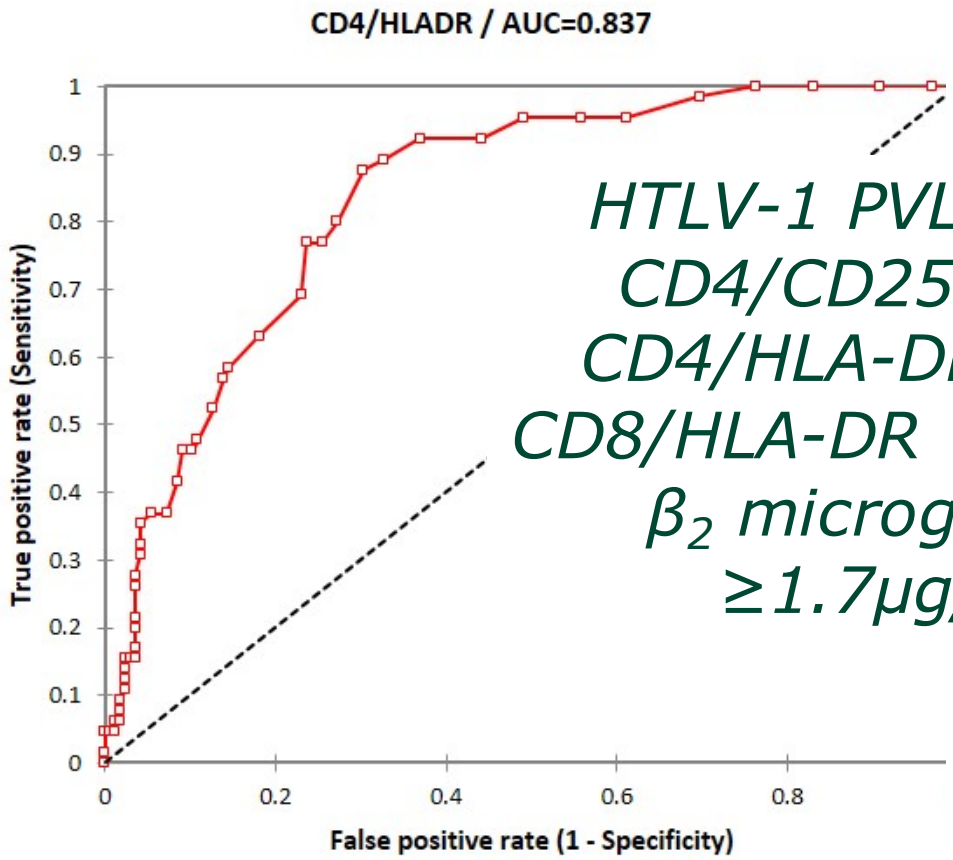
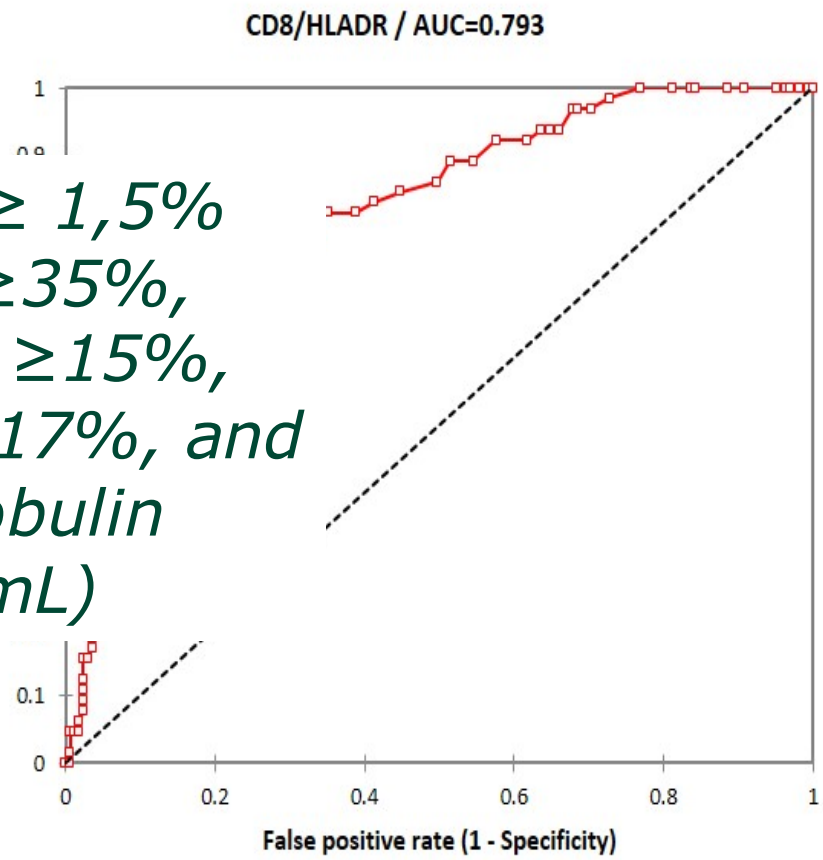
Identifying HAM

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)

9% of AC in London have a 'HAM-like' phenotype

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

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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

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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

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?

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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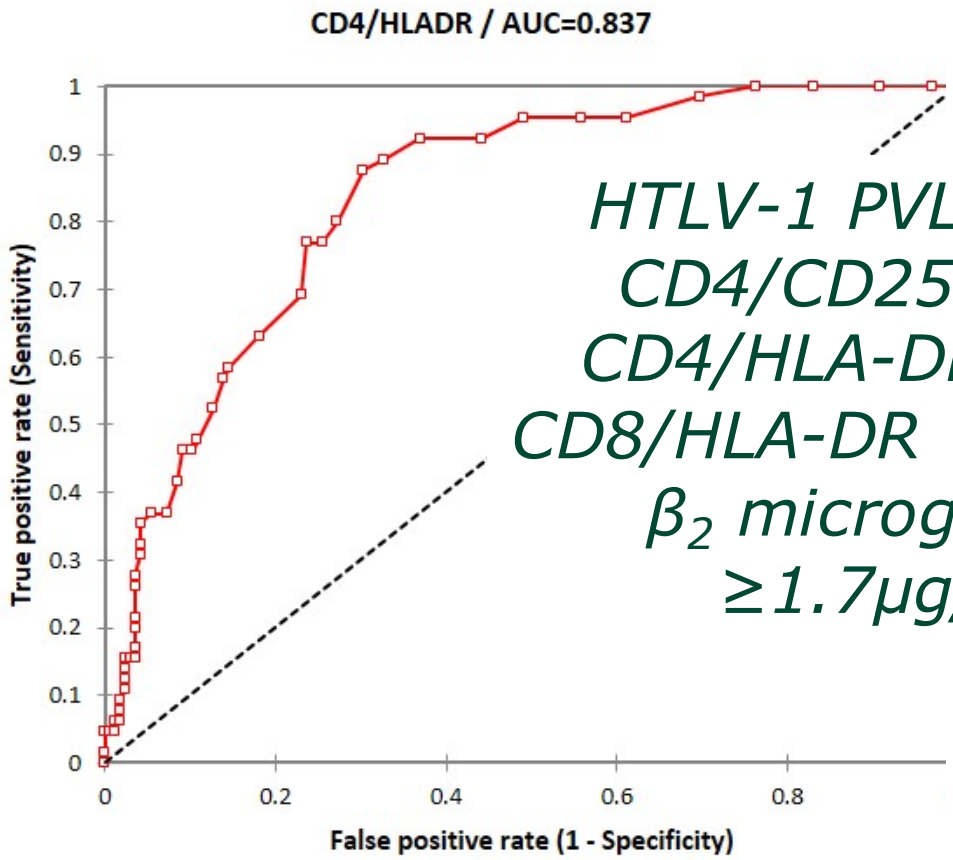
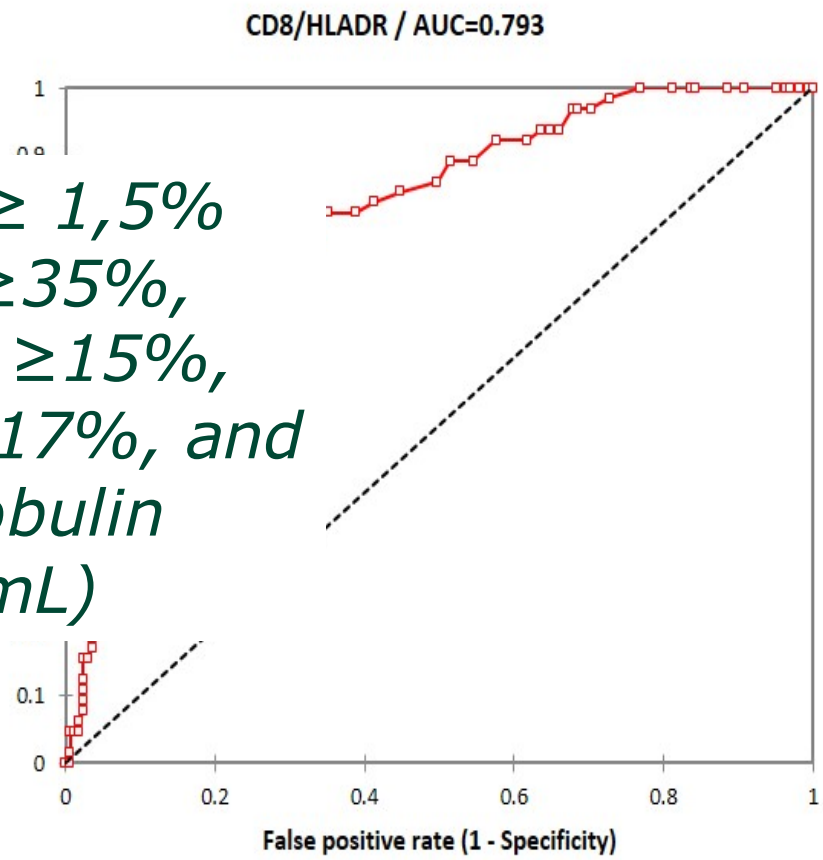
Identifying risk of retrovirus related inflammation





HTLV-1 PVL ≥ 1,5%
CD4/CD25 ≥35%,
CD4/HLA-DR ≥15%,
CD8/HLA-DR ≥17%, and
β_2 microglobulin
≥1.7μg/mL)

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

HTLV-1/HIV-1 co-infection – what was known

Risk of (HTLV-1-associated) myelopathy increased (x4)

ATLL occurs in co-infection

Immunosuppression is poorly predicted by CD4 counts
OIs occur at high CD4 counts

Current ART does not impact HTLV-1 proviral load in established infection

Co-infection occurs in ~ 1% of UK HIV-1 infected patients

Largely undiagnosed

HTLV-1/HIV-1 co-infection – what is new?

T-cell activation high in co-infection resembling HAM

despite fully suppressive therapy >12 months

is not due to HIV alone

long-term implications uncertain

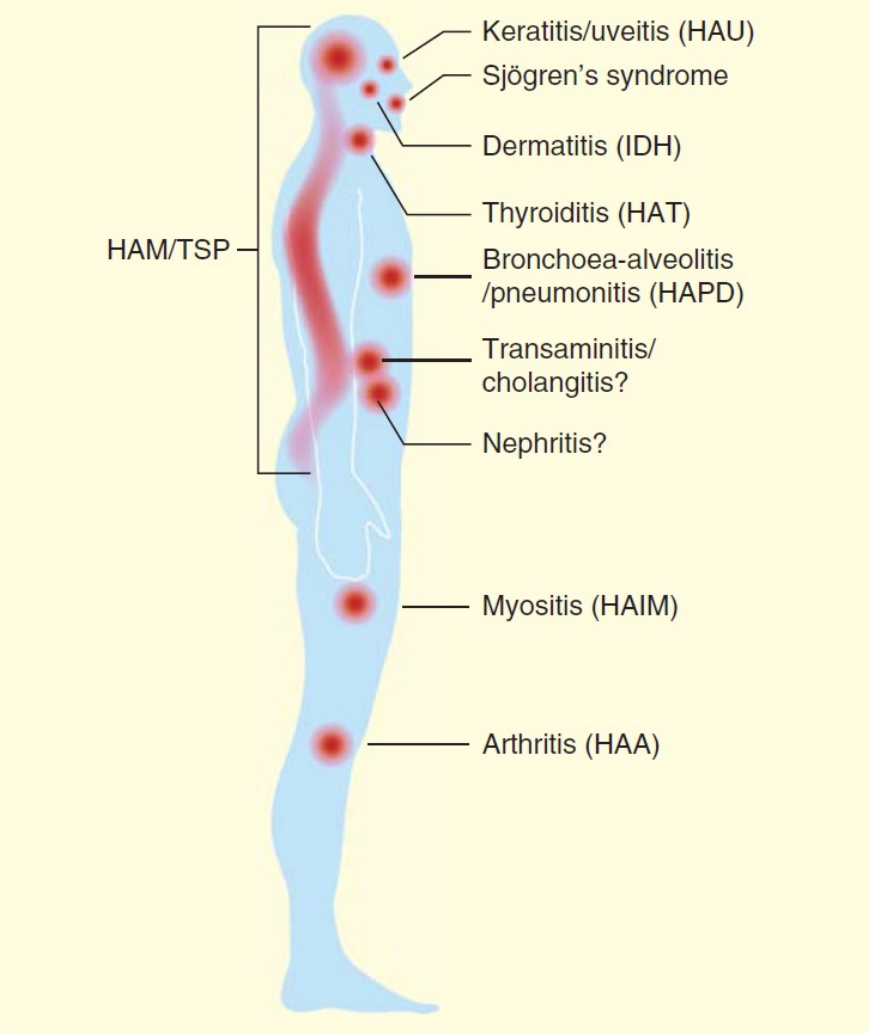


Figure 2. Distribution of human T lymphotropic virus type 1-associated inflammatory diseases by body sites.

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Thanks to:

Patients

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