UNIVERSIDAD PERUANA
CAYETANO HEREDIA
INSTITUTO DE MEDICINA TROPICAL
ALEXANDER VON HUMBOLDT

HTLV-1: overview of a neglected disease

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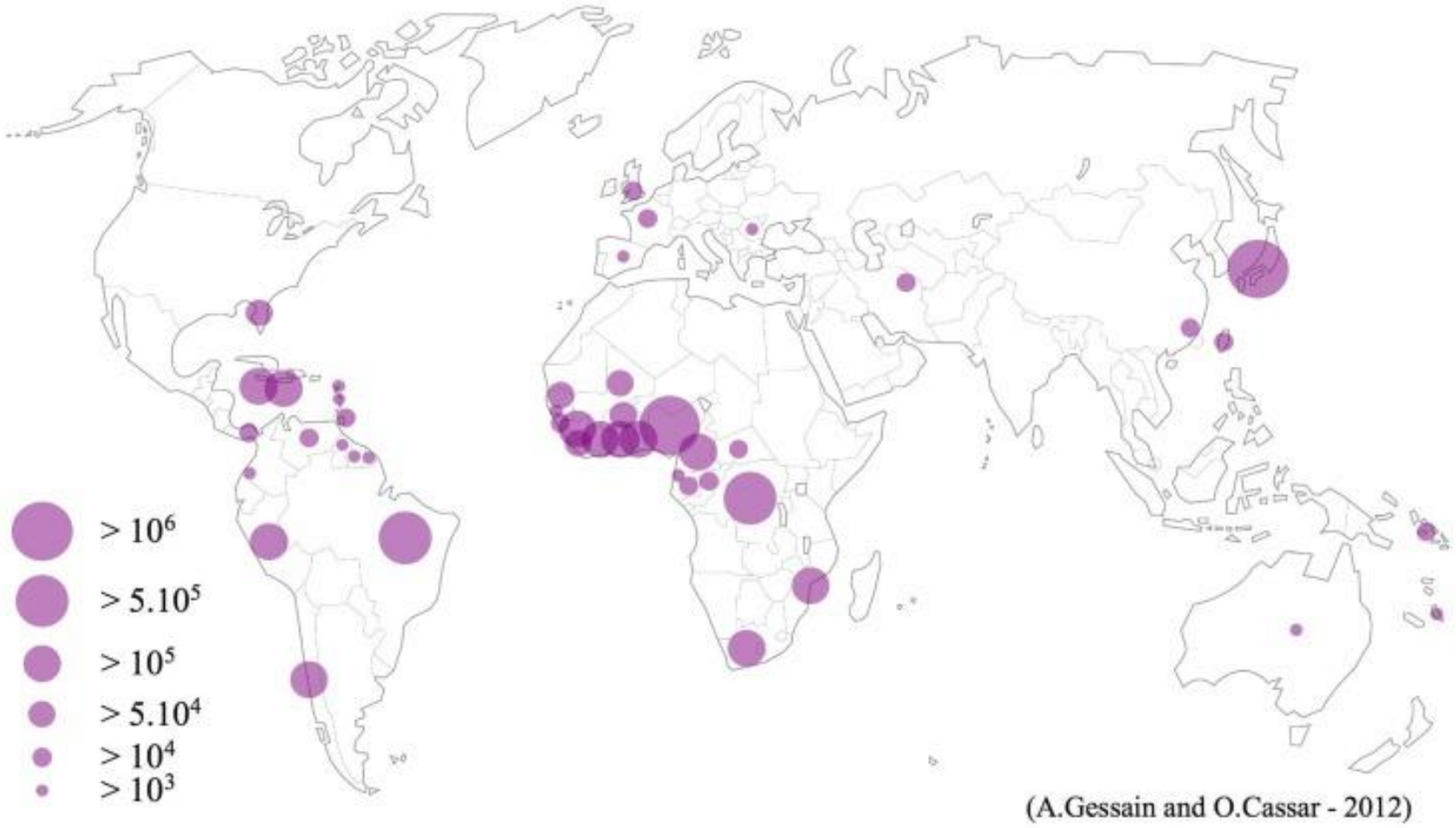
September 27th, 2025

We will review today:

- Epidemiology
- Biological cycle and transmission
- Diagnosis
- Clinical Outcomes or associated diseases:
  - Pro-inflammatory
  - Cell transformation
  - Immune deficiency

HTLV-1 worldwide prevalence: 5-10 million carriers globally?

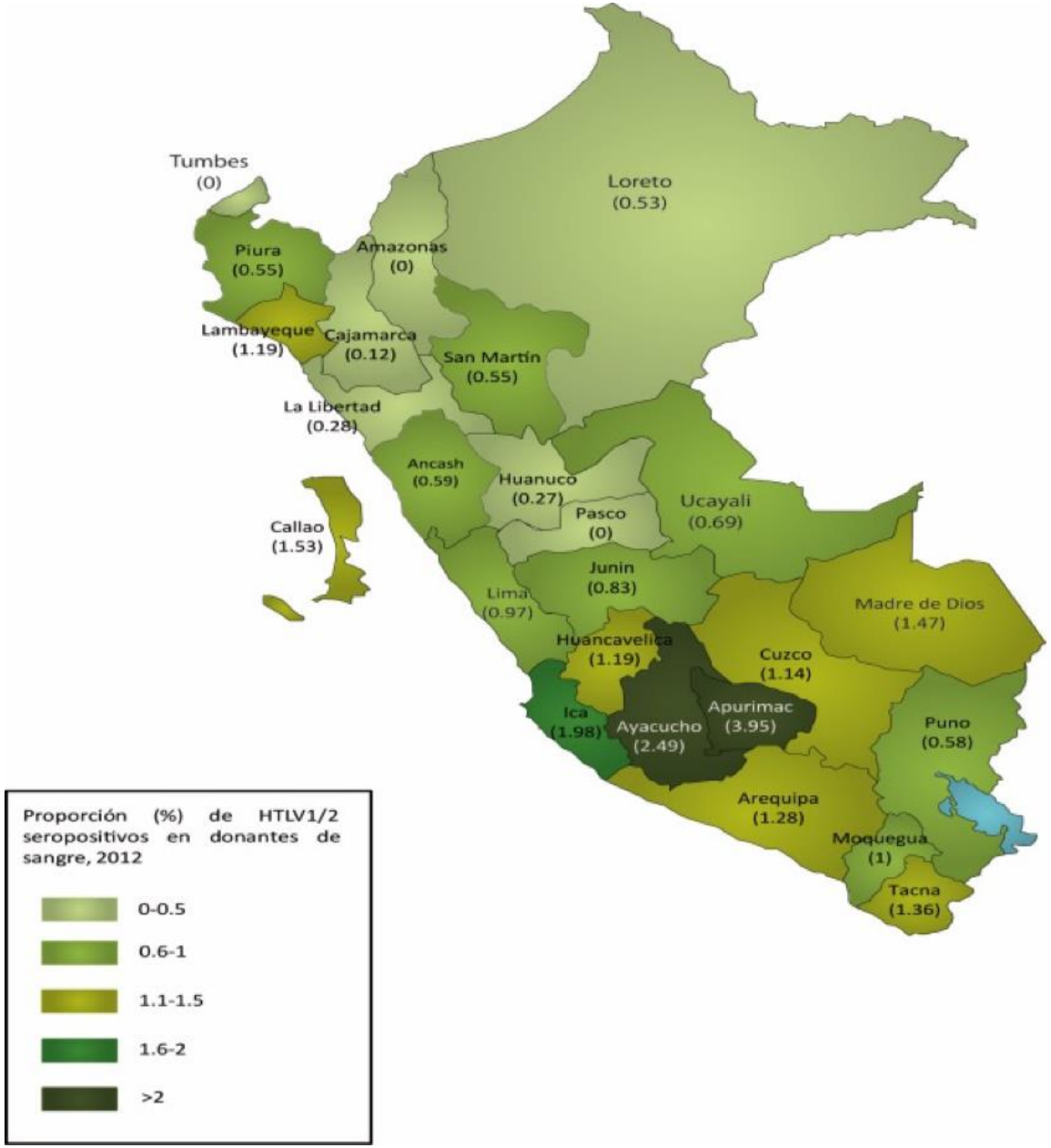


Limitations due to:

- Restricted studied populations
- Diagnostic methods
- Changing epidemiological trends

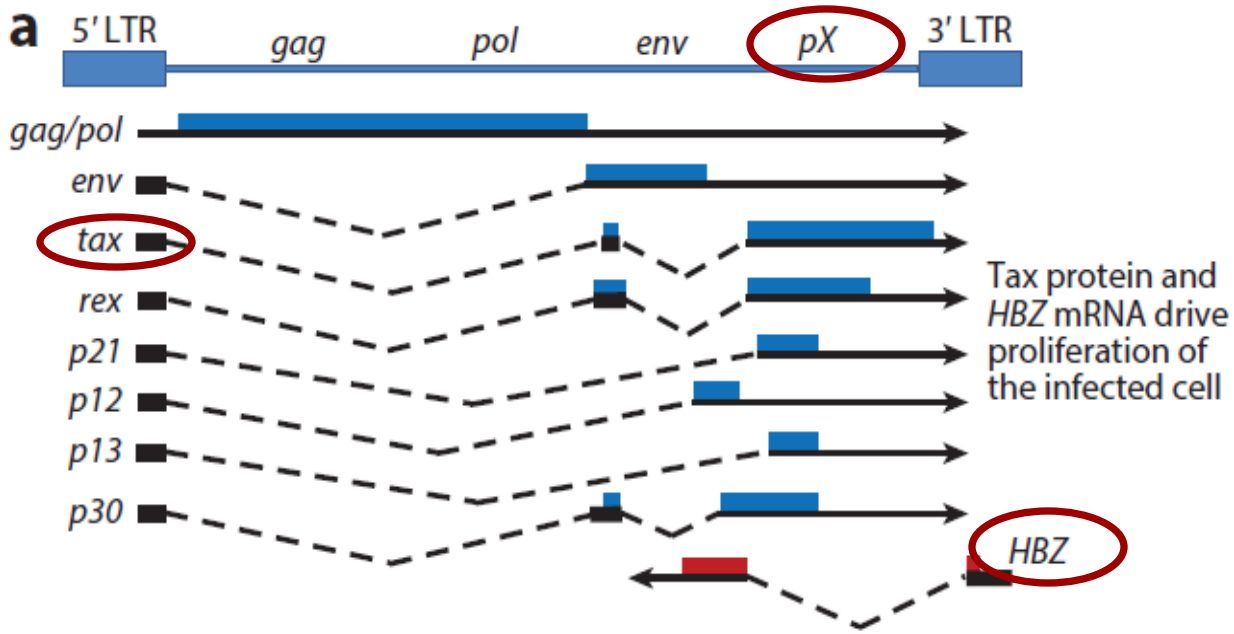
Trop Med Int Health. 2019;24(11):1277-1290.
Trop Med Int Health. 2019;24(8):934-953.
Front Microbiol. 2012;3:388.
Trop Med Int Health. 2015. doi: 10.1111/tmi.12659.
AIDS Rev. 2009;11(4):205-14.

HTLV-1 prevalence in blood donors in Peru



HTLV-1: an ancient infection

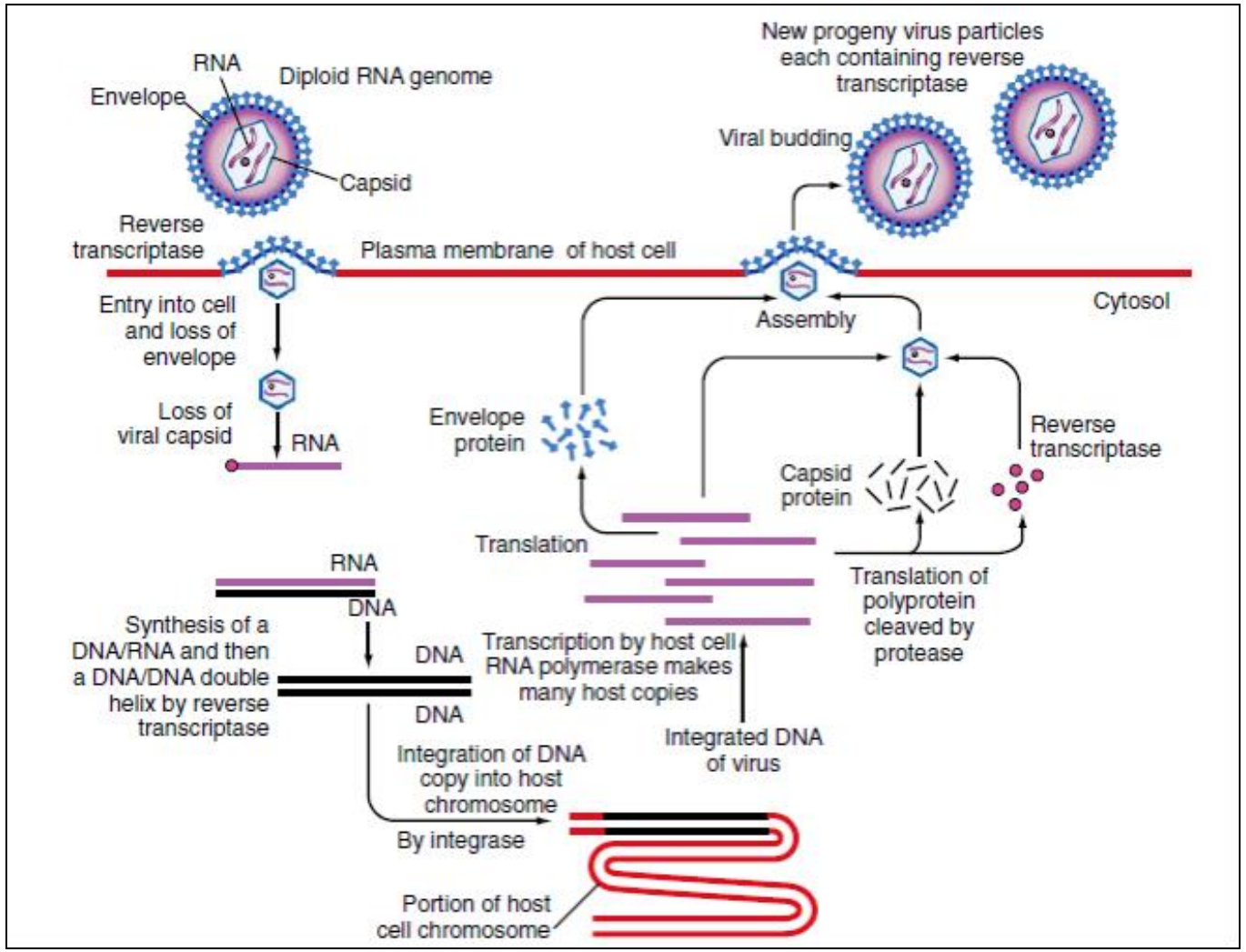
- Interspecies transmission from primates (STLV) > 5,000 years ago
- Main target: CD4+ T cells (also CD8+, B lymphs, fibroblasts, dendritic cells)
- Induces spontaneous proliferation of PBMC *in vitro*
- Persists as cell-associated provirus:
  lifelong infection

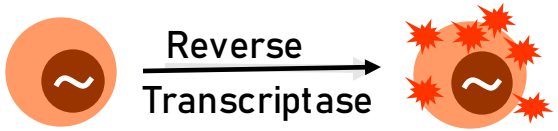


Philos Trans R Soc Lond B Biol Sci. 2017;372(1732).
Lancet Infect Dis 2007; 7: 266–81

Bull Soc Pathol Exot. 2011;104(3):167-80
Blood 2011;117(11):3113-22

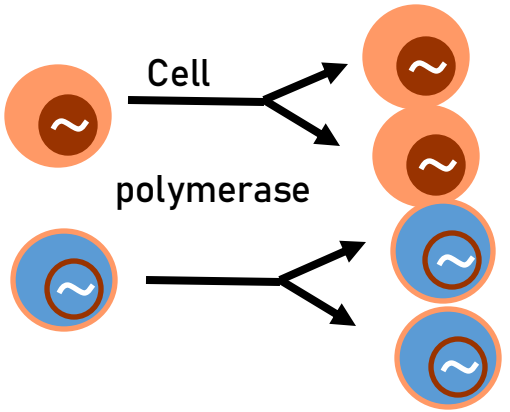
HTLV-1 in the host





Infectious (early) replication

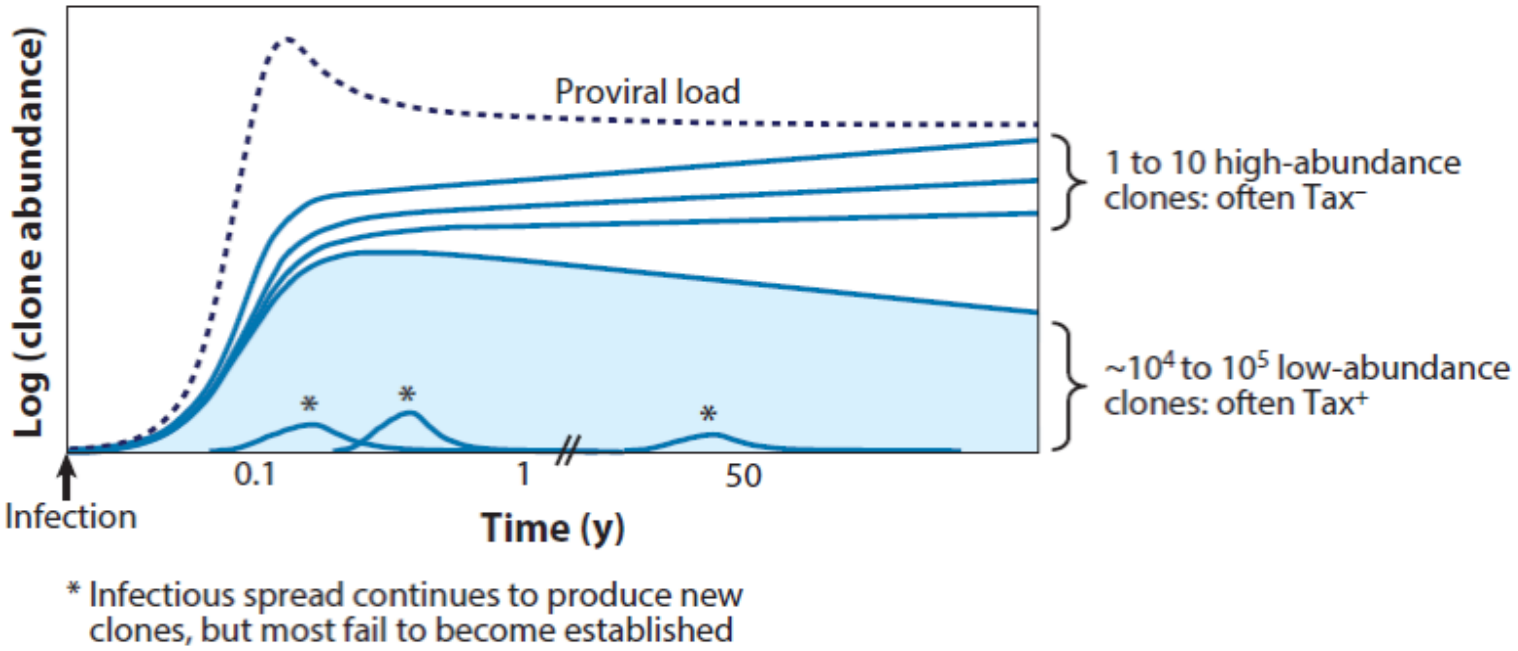
Mitotic (chronic) replication



PLoS Comput Biol. 2020 Sep 17;16(9):e1007470.
Annu. Rev. Immunol. 2018. 36:25–53; images kindly provided by Dr. C.Bangham

HTLV-1 proviral loal (PVL)

Surrogate of the number of HTLV-1-infected cells; in theory, of prognostic value



The PVL reaches a set point dependent on <u>the quality of the anti-HTLV-1 cytotoxic T lymphocyte (CTL) response</u>,

- ↑↑ in HAM/TSP or ATL cases
- Yet: "asymptomatic carriers" with high PVL

High interlaboratory variability and lack of gold standard limits technique's clinical use.

PLoS Comput Biol. 2020 Sep 17;16(9):e1007470.
Annu. Rev. Immunol. 2018. 36:25–53

J Neurovirol 2022 Jan 13.
Cancer Sci 2010; 101: 2361–67

Transmission of HTLV-1 is cell-associated

HTLV-1 transmission

Mode	Parenteral	Mother-child	Sexual
Through	Transfusion of cells, IVDU, **Solid organ transplant**	Breastfeeding, related with duration (> 3 months)	Sexual intercourse
Frequency amongst exposed	**14-47% for blood transfusion** ↓ with storage	9-32%	1 per 100 person-years
Comment	High risk for HAM/TSP	Rare before and during childbirth	Male to female > female to male?
Prevention	Screening in blood banks & organ donors	Screening / no breastfeeding <u>if secure alternatives in place</u>	Condom use

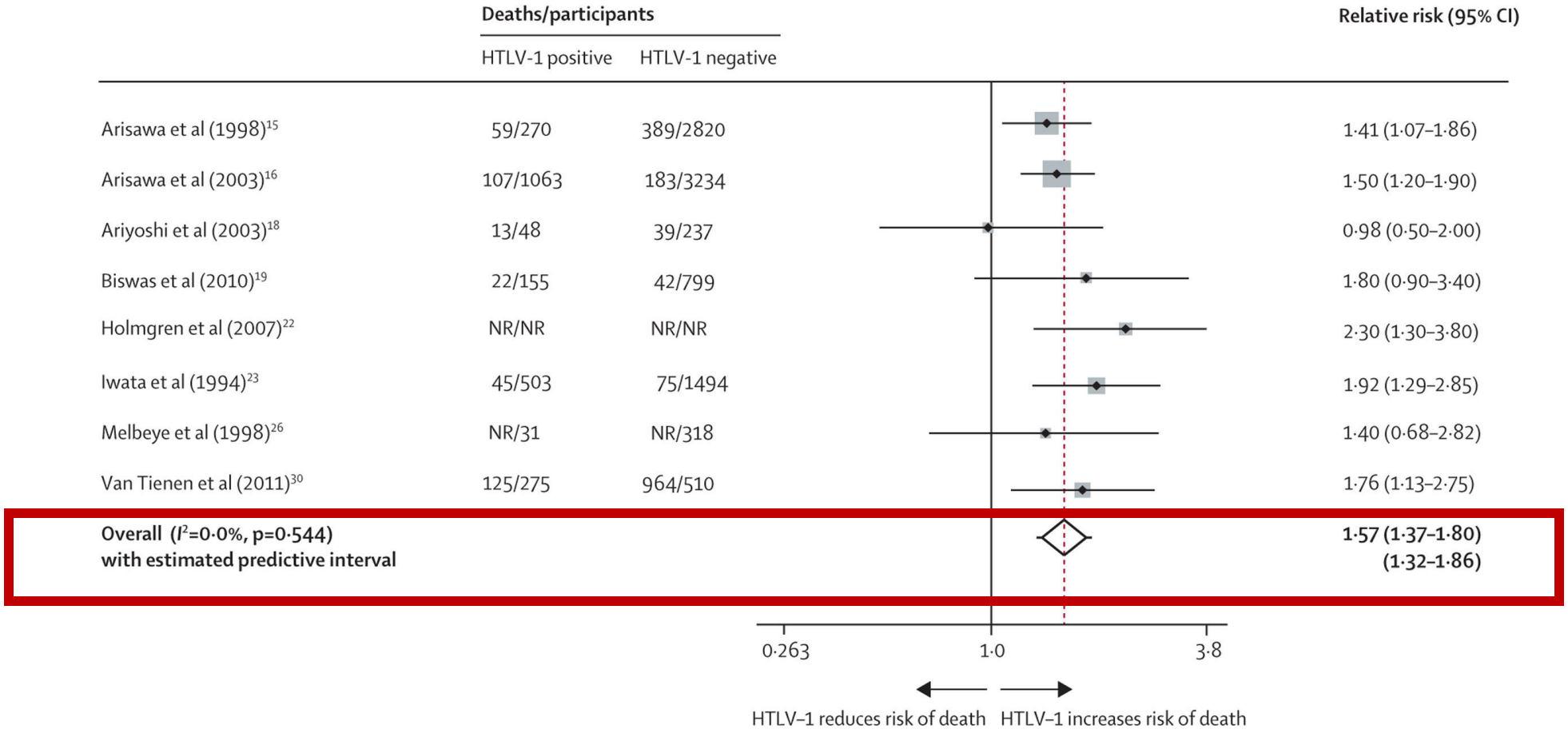
HTLV infections - Diagnostic Strategies

Method	Screening	Confirmation	Disadvantage	Observations
Recombinant enzyme immunoassay (EIA – 3rd generation)	+++	+	Requires confirmation	Do not discriminate HTLV-1 vs. HTLV-2
Western blot	±	+++	“Expensive”	Repeat at 3 months if indeterminate and “high-risk”
Qualitative PCR	+	++	Non-commercial techniques Requires PCR facilities	Consider in children < 2 years
Quantitative PCR	+	++		Also for proviral load (PVL) determination

Front Microbiol. 2020 Jun 3;11:1151. doi: 10.3389/fmicb.2020.01151
J Cell Physiol. 2019 Jan 11. doi: 10.1002/jcp.28087.
J Med Virol. 2010;82(10):1746-53.

What are the health consequences for people living with HTLV-1 infection?

Meta-analysis of HTLV-1 and deaths from all causes (2019)



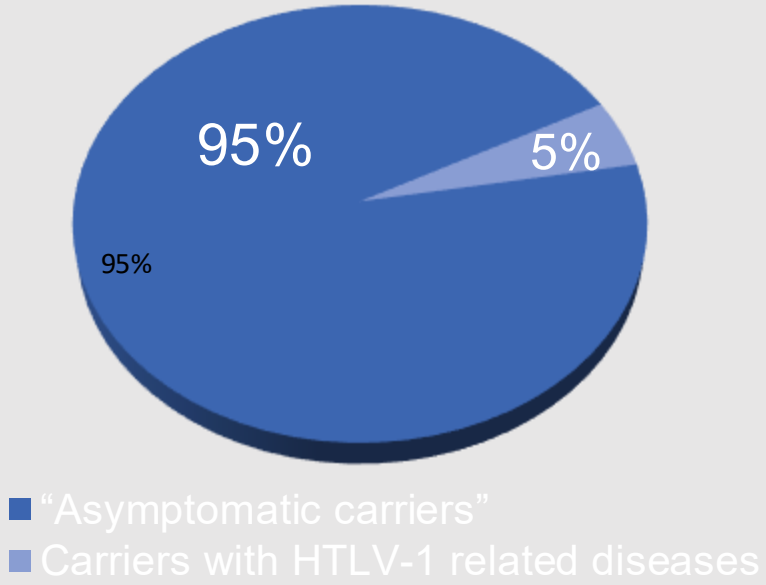
↑ adjusted risk of death by any cause in people with HTLV-1 vs. HTLV-1-negative.

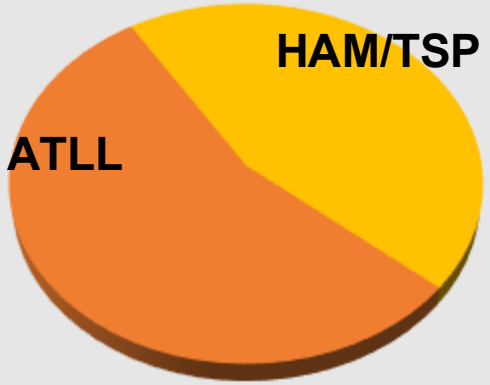
strong association with risk of <u>premature</u> death: RR 3.80 (95% CI 1·7–8.3) ages15-29

Lancet Infect Dis. 2020;20(1):133-143. doi: 10.1016/S1473-3099(19)30402-5.

The HTLV-1 paradox

People living with HTLV-1

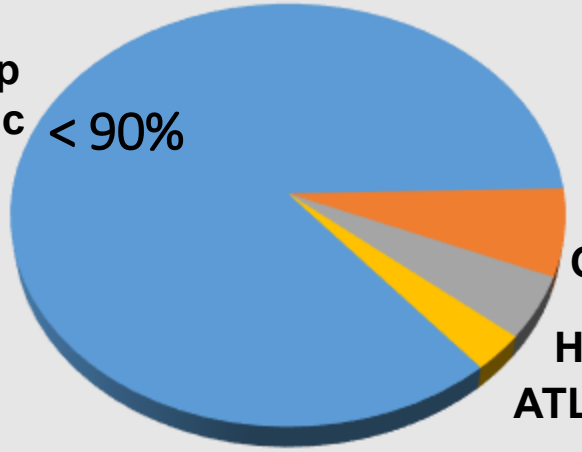




HAM/TSP: severe motor disability (5y): ~45%

ATLL: low survival rates (4y): < 25%

Asymptomatic



Infective dermatitis
Opportunistic infections
Polyneuropathy
↑ risk cervical cancer
…..

HTLV-1 clinical outcomes: three key messages

1. Despite predominance over one organ or system, HTLV-1 infection has systemic effects

2. Three groups of complications/outcomes:
   - Inflammatory/Autoimmune disorders
   - Immune deficiency
   - Cell transformation/cancer

3. HTLV-1 as a “family infection” (genetic background)

HTLV-1 Associated Diseases: Inflammatory/Autoimmune

Infective *dermatitis* (ID)

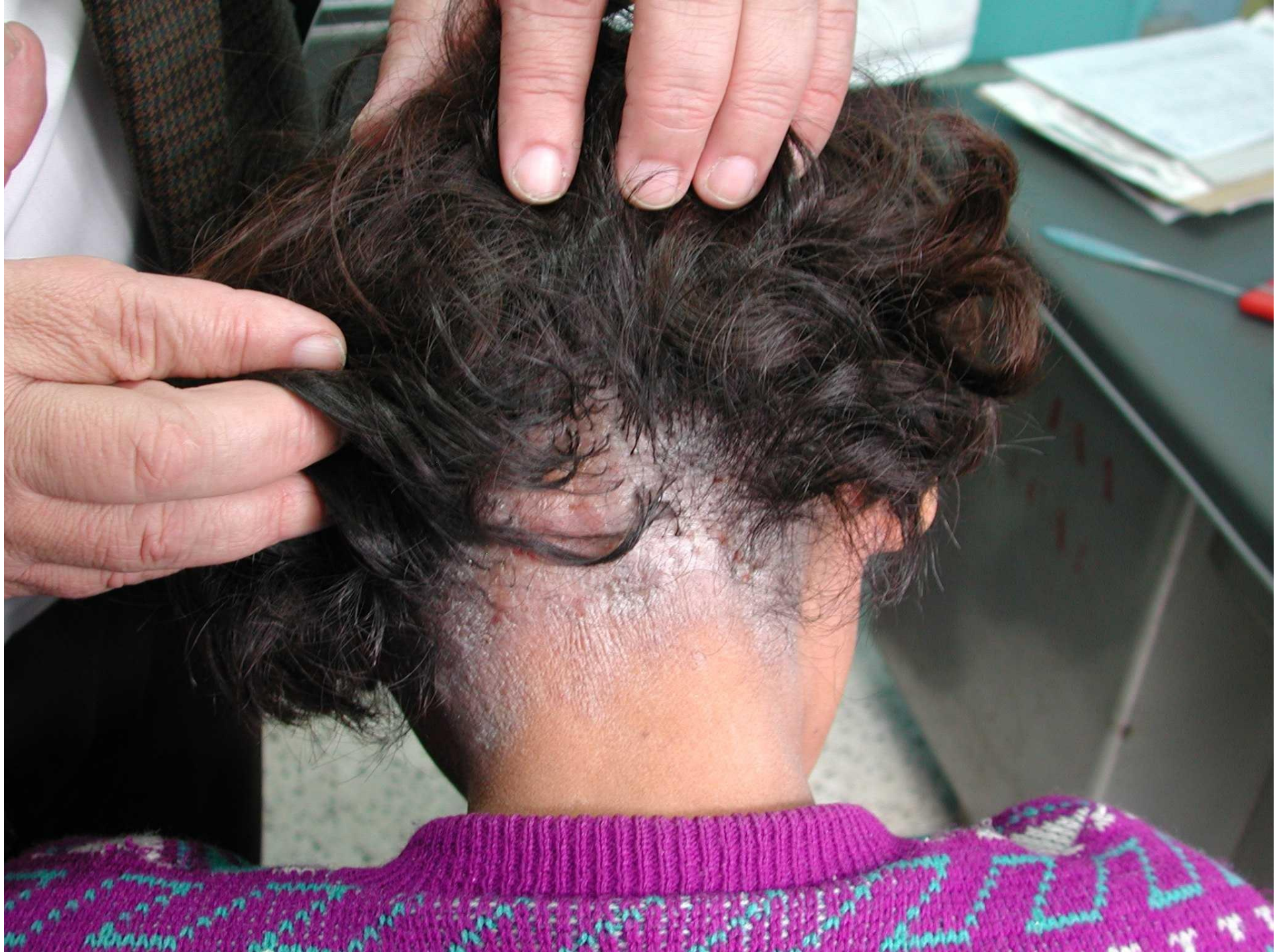
- Chronic, relapsing syndrome observed in tropical regions
- Onset at ~ 3 y-o; usually ceases by age 15.

- Generalized papular rash
- Exudates and crusting on different areas
- Lymphadenopathy
- Failure to thrive

Pediatr Dermatol. 2019;36(1):e12-e16.

J Pediatr (Rio J). 2006;82(6):411-20.

J Acquir Immune Defic Syndr Hum Retrovirol. 1996;13 Suppl 1:S46-9.



A NEUROPATHIC SYNDROME OF UNCERTAIN ORIGIN

REVIEW OF 100 CASES

E. K. CRUICKSHANK

A neuropathic syndrome with features which do not conform to any recognised disease pattern has been known to occur in the West Indies for some years. It was first recorded by Strachan in 1888, and there have been other brief accounts since. The most detailed comes from Scott (1918) who called the condition a "Central Neuritis". A similar syndrome has been reported from North and West Africa, Trinidad, Malaya, India, Java, Hong Kong and Spain during the Spanish Civil War (Spillane and Scott, 1945; Stannus, 1911; Moore, 1946; Money and Scott Smith, 1955; Metevier, 1947; Pallister, 1940; Nichols, 1935; Hobbs and Forbes, 1946; Crawford and Reid, 1947; Peraita, 1942). Dietary deficiency or imbalance is regarded as the main causative factor.

The clinical features of 100 cases investigated at the University College Hospital of the West Indies since 1953 are to be presented and the aetiology

West Indian Med J. 1956;5(3):147-58.

HTLV-1-associated ***myelopathy*** / Tropical spastic paraparesis (HAM)

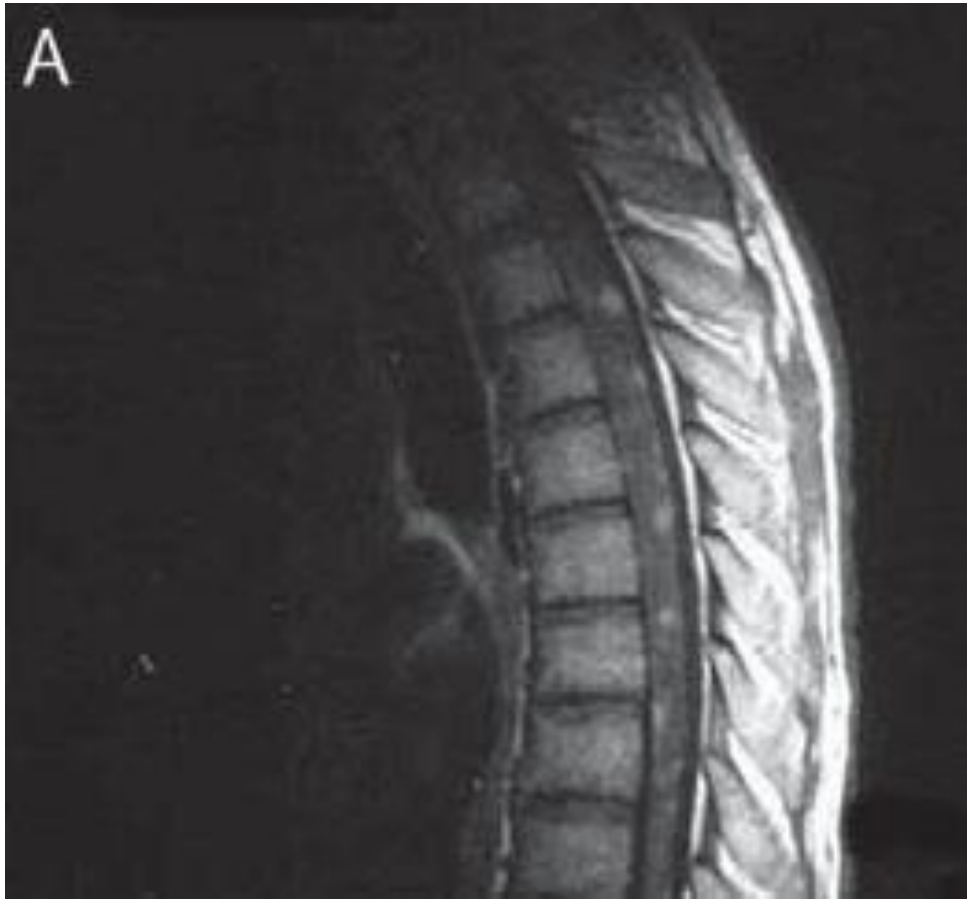
- Women >> men
  - Incidence (Brazil): 5.3 cases per 1,000 HTLV-1-seropositive cases per year (95% IC: 2.6-10.9)
  - Japan: history of blood transfusion ↑in HAM vs general sample cases (20% vs 3%; OR = 7.7)
  - In ± 30% of HAM, HTLV-1 infection through their mothers
- Chronic inflammation of white and grey matter of lower thoracic spinal cord (infiltration of T cells – bystander effect / auto-antibodies) followed by atrophy
  - Candidate biomarkers for prognosis/ treatment response: Inflammatory mediators (CXCL10 and neopterin) in the cerebrospinal fluid
- Clinical translation: Gradually appearing, usually slowly progressive symmetrical paraparesis of lower limbs, sphincter dysfunction, and mild sensory disturbance in the lower extremities.
- Lumbar pain, bladder disorders and repeated falls due to “clumsy legs” are early signs

Lancet Neurol 2006;5(12):1068-76.
Pharmacol Ther. 2021;218:107669
AIDS Res Hum Retroviruses. 2013;29(9):1199-202
J Neurovirol. 2020;26(5):652-663.

HAM/TSP – cont

- Diagnosis considers a “typical clinical presentation”
    + HTLV-1 infection
    + Ruling out other causes

- *Challenge for care*: could early treatment, before fulfillment of diagnostic criteria, reverse neurological damage?



Lancet Neurol 2006;5(12):1068-76
AIDS Rev 2009;11(2):71-8

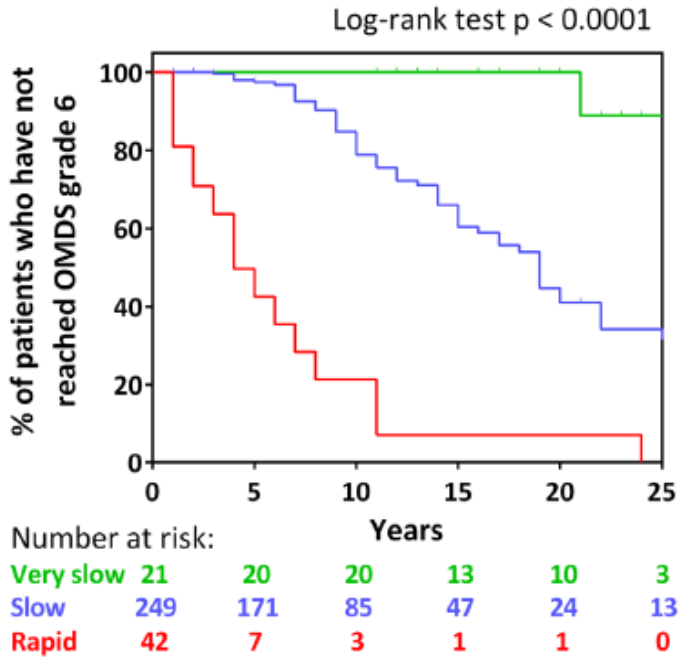
Handb Clin Neurol. 2014;123:507-30

HAM: “rapid” vs. “slow” progressors

“Rapid progressors”, under different definitions, have been reported in most cohorts

- Peru: unable to walk without two canes within 2 years of disease onset: 34 of 158 patients (21.5%)

Disease activity	Description – based on Osame Motor Disability Score (OMDS)	CSF neopterin (pmol/L)	CSF CXCL 10 (pg/mL)
High	Rapid progressor: OMDS > 5 within 2 years	≥ 44	≥ 4400
Moderate	Slow progressor	6-43	320-4399
Low	Very slow progressor: OMDS < 3 10 years after onset	≤ 5	≤ 320



Osame motor disability score (OMDS)

Score	Description
0	No walking abnormalities
3	Unable to run
6	Bilateral support to walk
9	Does not walk, but crawls
12	Cannot turn over in bed

Orphanet J Rare Dis. 2019;14(1):227. Front Microbiol. 2018;9:1651.

HAM: treatment options?

- Limited evidence.
- Outside clinical trials, balance the potential responsiveness to therapy and treatment risks.
  - “Patients with rapidly progressing disease should be treated immediately”
  - Mandatory screening/treatment for HIV, hepatitis B and C, syphilis, *Strongyloides stercoralis* and tuberculosis before use of corticosteroids
- For progressive disease: high-dose pulsed methyl prednisolone for induction and low-dose (5 mg) oral prednisolone as maintenance therapy for progressive disease.
- No role for antiretroviral therapy or interferon α
- Supportive therapy: Symptomatic (baclofen, benzodiazepines)
- **Rehabilitation (motor, vesical)**
- **Control of pain**

Neurol Clin Pract. 2021;11(1):49-56.
Rev Neurol (Paris). 2012;168(3):257-69

Annu. Rev. Immunol. 2018. 36:25–53
Viruses 2022;14(1):136.

Other HTLV-1 associated inflammatory/autoimmune disorders:

Eyes

HTLV-1-Associated Uveitis

Skin

Eczcema and seborrheic dermatitis

Respiratory system

Bronchiectasis

Interstitial pneumonitis

Endocrine system

Calcium disorders

Thyroiditis

Osteoarticular system

Artropathy

Polymyositis,

HTLV-1 Associated Diseases: Adult T-cell leukemia/lymphoma

Malignancy associated with oncogenic microorganisms

Infectious organism	Global burden (% in population)	Lifetime risk of malignancy
H. pylori	5.5	3%
HPV	5.2	0.29
HBV + HVC	4.9	< 3%
HHV-8	25	Minimally oncogenic by itself
EBV	> 90	0.3 ~0.4%
HTLV-1	**0.3**	**5 -10%**
MCV	0.06	??

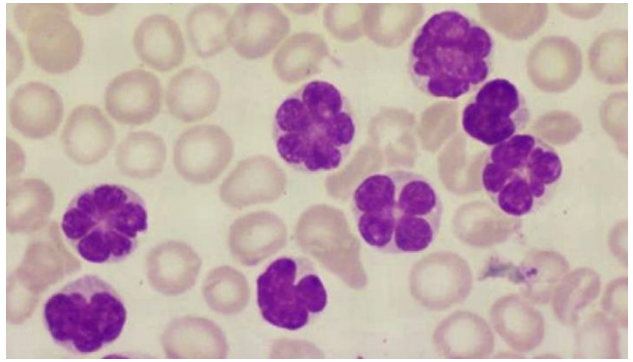
Up to date, HTLV-1 is the most oncogenic virus through effects of viral gene products interacting with host proteins.

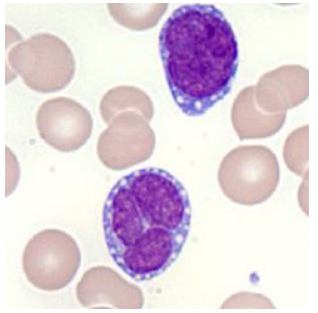
Front Microbiol. 2017;8:1425. doi: 10.3389/fmicb.2017.01425.

Adult T-cell leukemia/lymphoma (ATL)

- Peripheral mature CD4 T cell neoplasm with monoclonal integration of HTLV-1
- Tax protein induces abnormal cell growth; sustained by HBZ

- Male/female 1.5:1
- Almost limited to people with HTLV-1 since early childhood; role of genomic events & co-infections?
- Usually in fifth decade, earlier onset in the Caribbean and South America
- Clinical subtypes (with overlaps) based on presence and degree of leukemic T cells, additional sites of infiltration, lactate dehydrogenase level (LDH), and hypercalcemia





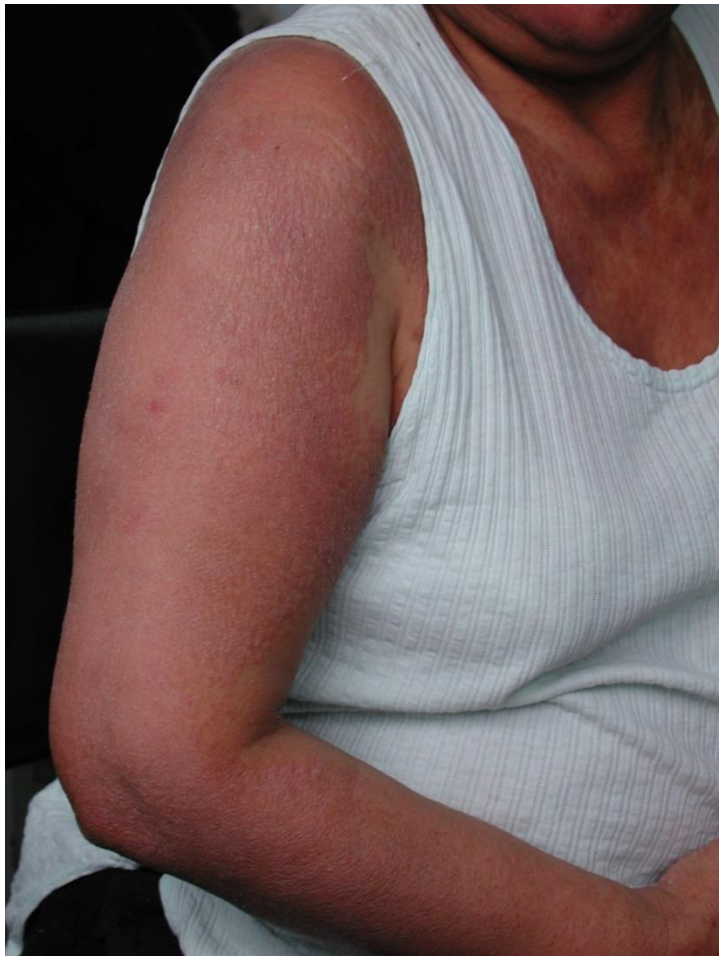
Flower cells

Cancer Sci. 2020 Dec;111(12):4567-4580. Front Microbiol. 2020;11:1124. Hematol Oncol Clin North Am. 2017 ;31(2):25 Br J Haematol. 2017 ;177(4):507. Lancet Oncol. 2014;15(11):e517-26.

ATL: marked diversity in clinical presentation

- Skin lesions of various presentations
- Lymphadenopathy
- Hepatosplenomegaly
- Involvement of lung, gastro-intestinal tract, CNS
- Hypercalcemia (presenting feature in up to 70%)
- Susceptibility to opportunistic infections

- Predilection for extranodal sites of disease; full skin exam and skeletal survey for select patients with bone symptoms, fractures, or an unexplained elevation in alkaline phosphatase



Curr Hematol Malig Rep. 2018;13(4):300-307.

Bull Soc Pathol Exot. 2011;104(3):167-80

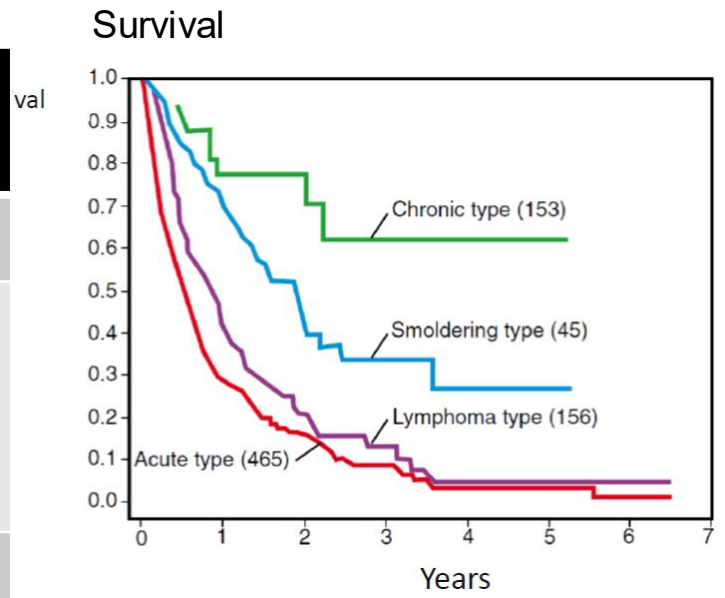
ATL: requirements for diagnosis

- HTLV-1 seropositivity
- Histologically or cytologic proved lymphoid malignancy with T-cell surface antigens present(CD3, CD4, and CD25, CD7-; in ~ 10–15%of cases, cells express both CD4 and CD8
- CCR4 is expressed in more than 90% of cases, and is associated with poor outcome
- Abnormal T lymphocytes (“flower cells”) consistently present in peripheral blood
- “*Demonstration of clonality of proviral DNA as well as clonal integration of proviral DNA*” (which is rarely available at clinical services in endemic areas)

Lancet Oncol. 2014;15(11):e517-26.

ATL subtypes

Subtype	Sites of infiltration	% leukemic cells	↑Ca	LDH
Acute (60%)	Organomegaly, lymph nodes, víscera, other extra-nodal sites	Yes	Yes	↑
Lymphoma (20%)		No (≤ 1%)	Yes	↑
Chronic (15%)	Skin, liver, spleen, lung, LN	Occasionally	No	< 2N
Smoldering (5%)	Skin, lung	Occasionally (> 5%)	No	< 1.5 N

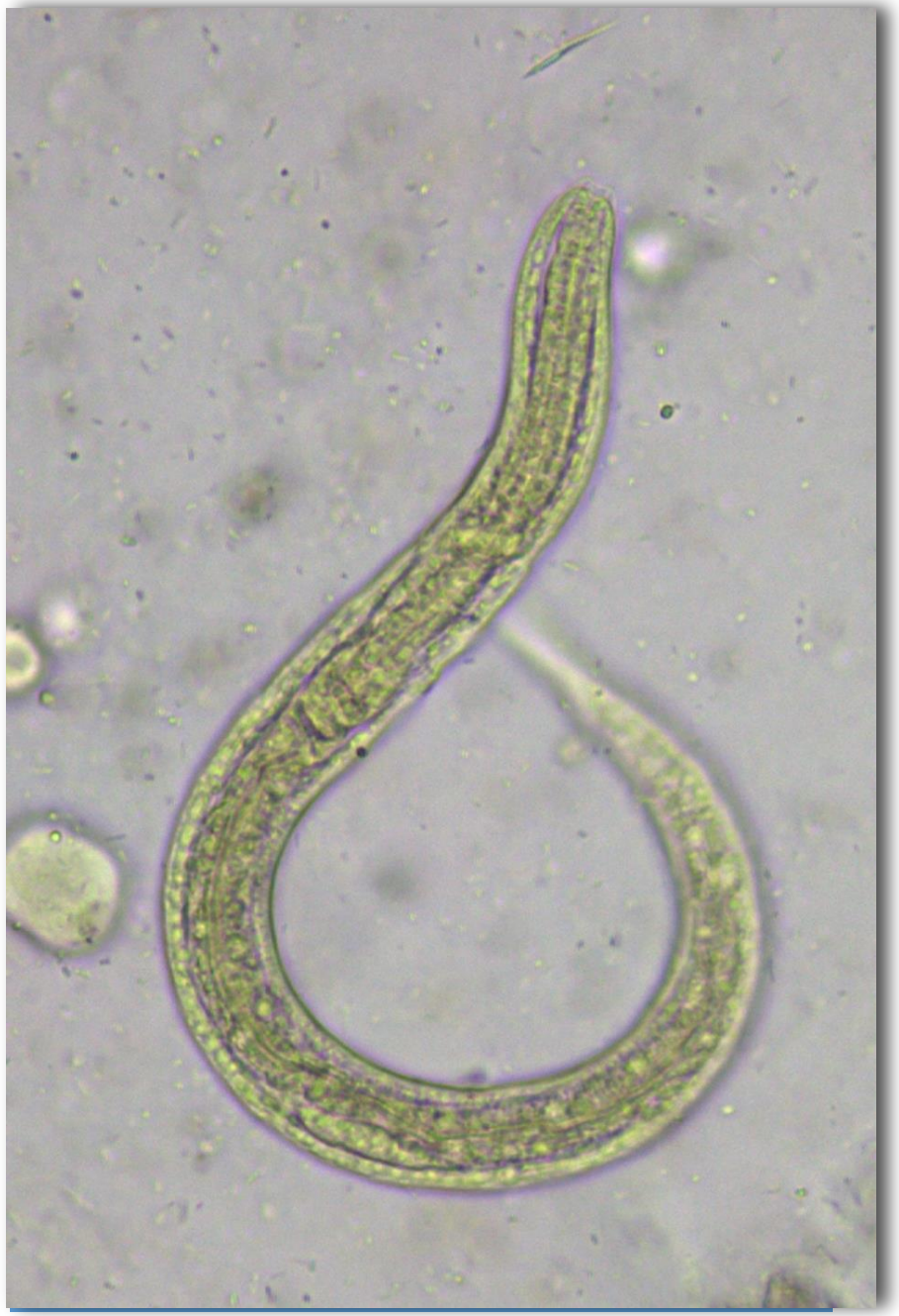


Differentiation of ATL subtypes impacts on prognosis and is crucial for treatment

Curr Hematol Malig Rep. 2018;13(4):300-307.

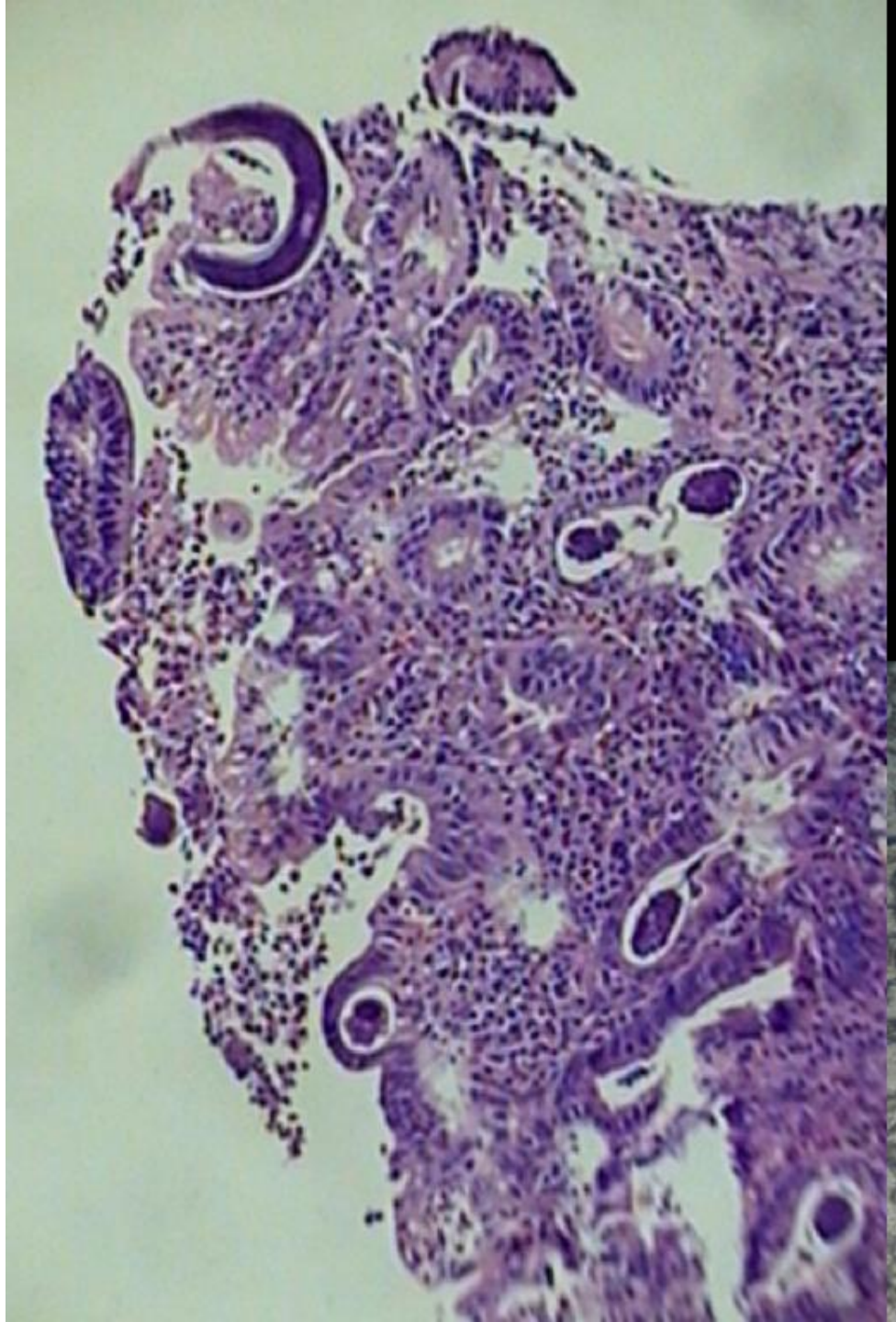
Hematol Oncol Clin North Am. 2017 ;31(2):255-272.

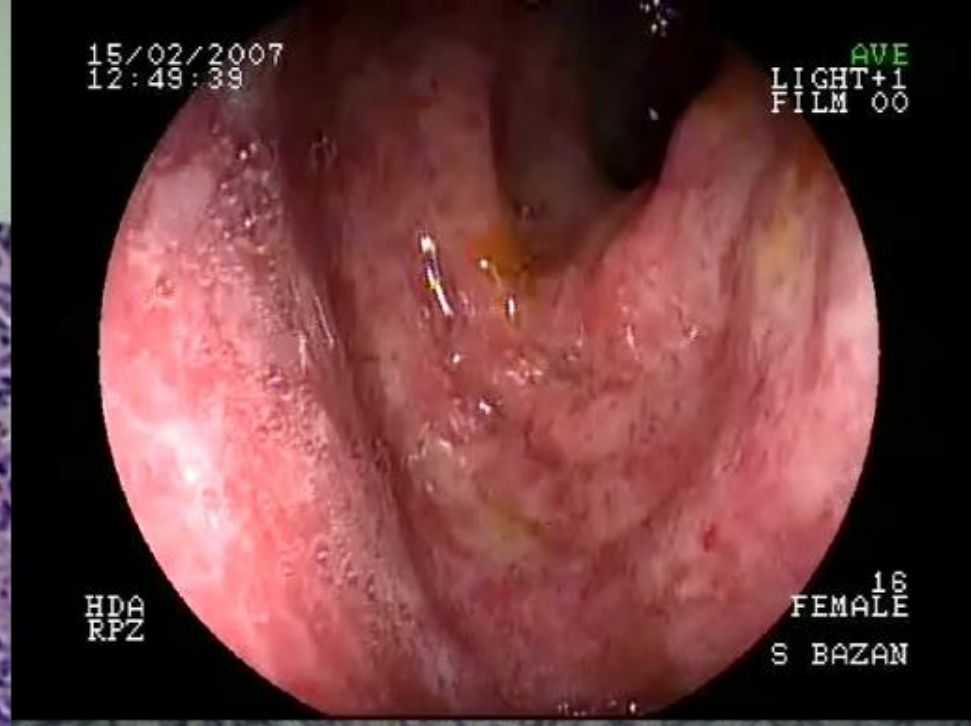
HTLV-1 Associated Diseases: immune deficiencies



Strongyloides stercoralis

- 30-100 million people infected with Strongyloides in moist tropical and sub-tropical climates (Bethony J, 2006).
- Unique soil transmitted helminth:
  Complete life cycle within the host.
- Most cases are asymptomatic
- Clinical diagnosis is difficult:
  - clinical suspicion
  - intermittent excretion of rhabditoid larvae in stools
- Some patients may develop severe manifestations due to immune dysfunction.

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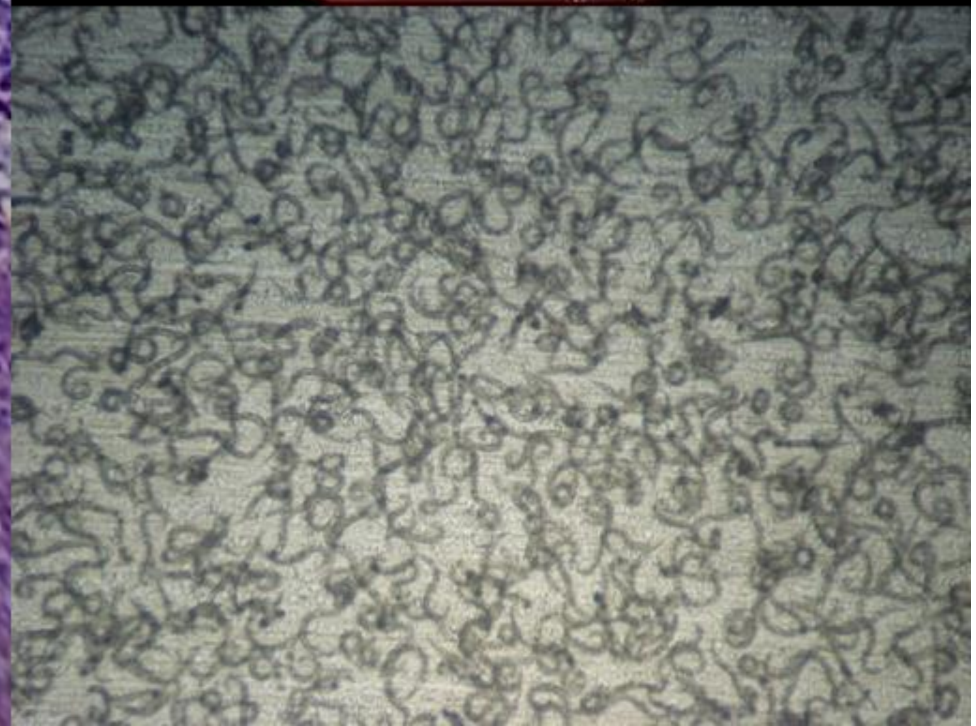


Strongyloidiasis: treatment

Intestinal Strongyloidiasis &HTLV-1: cure rates of two regimens of ivermectin

	Ivermectin 110 µg/kg dose		Ivermectin 200 µg/kg dose	
	4 weeks after treatment	4-12 months after treatment	4 weeks after treatment	4-12 months after treatment
HTLV-1 (-)	98%	93%	100%	100%
HTLV-1 (+)	90%	50%	97%	90%

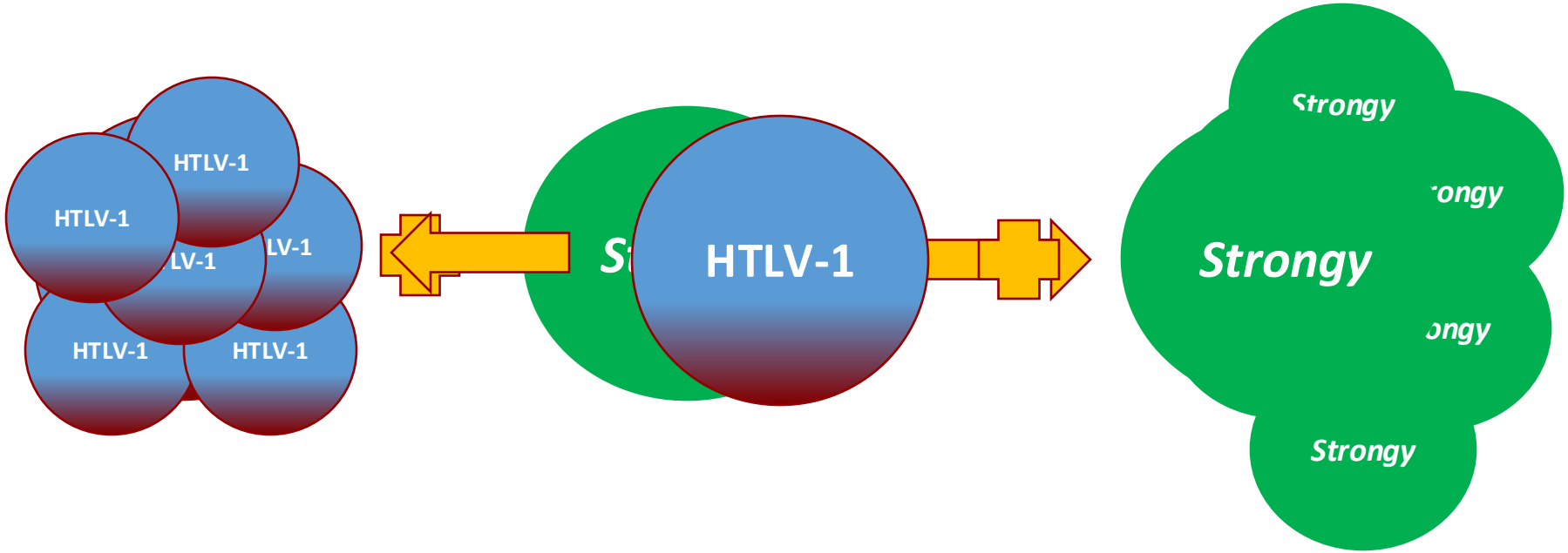
Do check for erradication after treatment completion

PLoS Negl Trop Dis. 2013 ;7(7):e2288.
Rev Chilena Infectol. 2017 ;34(1):47-53.

Ann Pharmacother. 2007;41(12):1992-2001.
Clin Chemoth 2004;10:348

Strongyloides/HTLV-1 Co-infection

- Effect of co-infection on the host response
  - HTLV-1 predisposes to *Strongyloides* hyperinfection syndrome (Gotuzzo, 1999)
  - Ss may increased the risk of HTLV-1 neoplasia (ATLL) (Satoh, 2002)



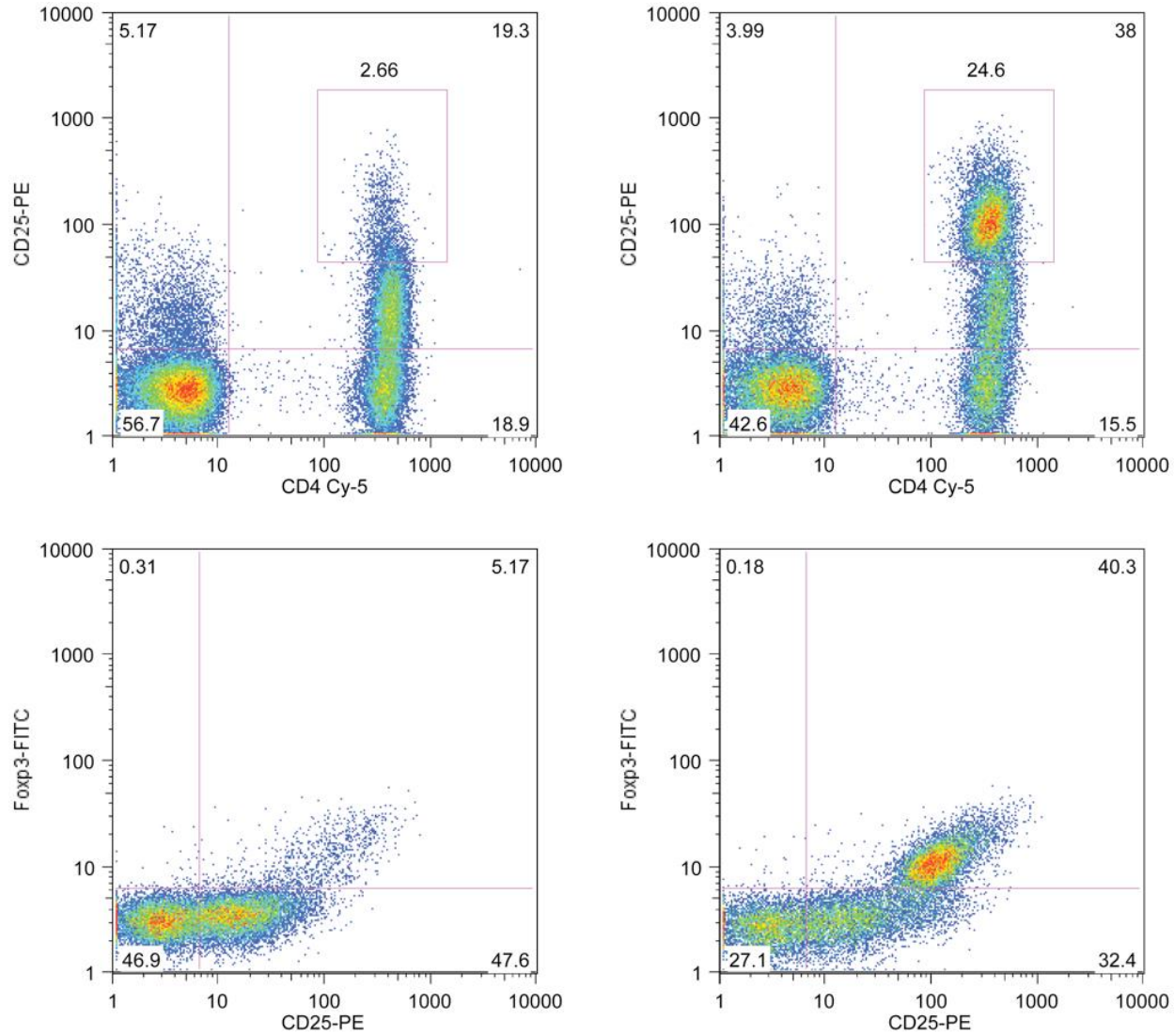
OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Regulatory T Cell Expansion in HTLV-1 and Strongyloidiasis Co-infection Is Associated with Reduced IL-5 Responses to *Strongyloides stercoralis* Antigen

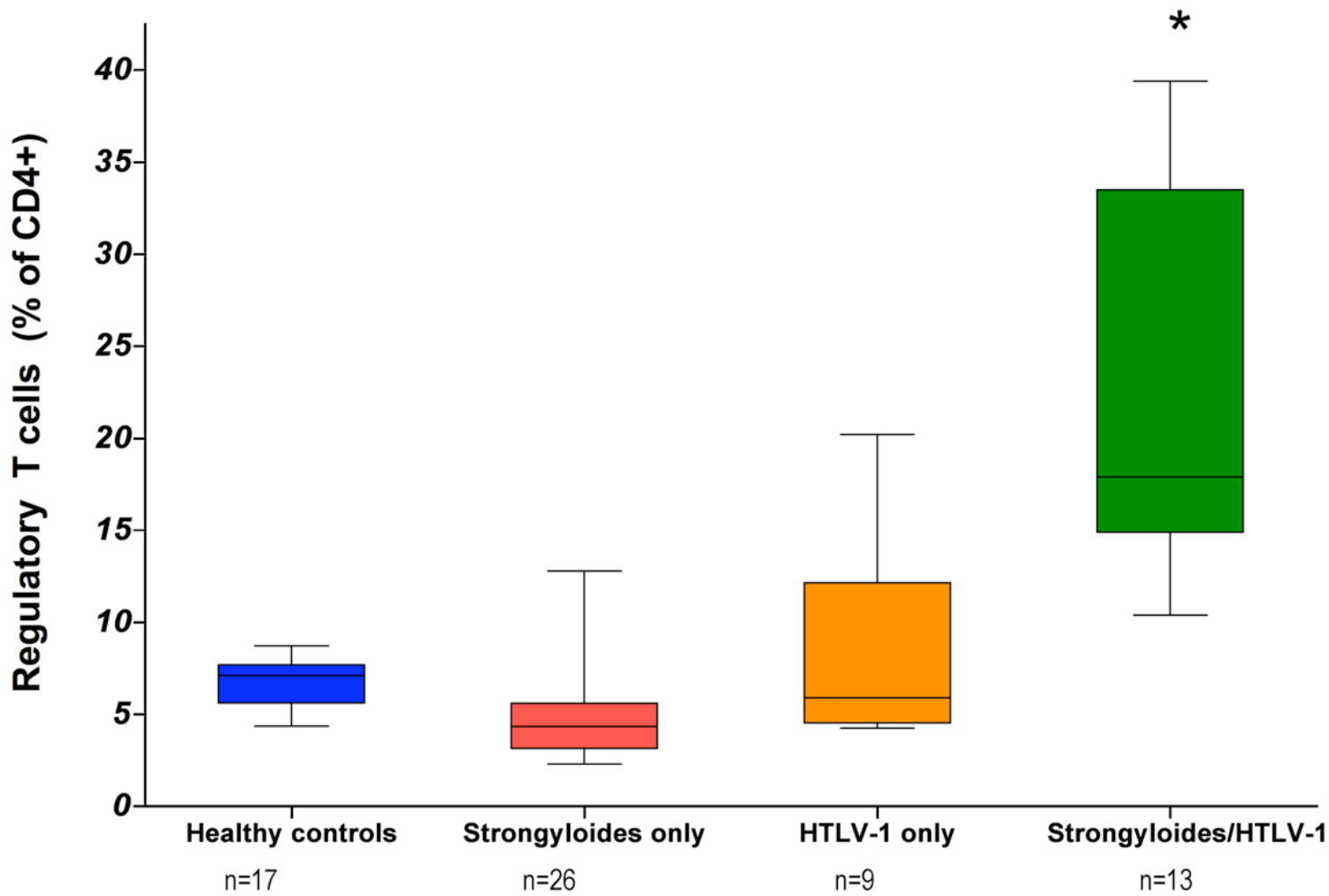
Martin Montes[1,2]*, Cesar Sanchez[1], Kristien Verdonck[1,2], Jordan E. Lake[3], Elsa Gonzalez[1], Giovanni Lopez[1], Angelica Terashima[1], Thomas Nolan[4], Dorothy E. Lewis[5], Eduardo Gotuzzo[1], A. Clinton White Jr.[5]

1 Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru, **2** Division of Infectious Diseases, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, United States of America, **3** Virology Unit, Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium, **4** Department of Medicine, Division of Infectious Diseases, University of California at Los Angeles, Los Angeles, California, United States of America, **5** Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, United States of America



Strongyloides only

Strongyloides/HTLV-1


Regulatory T cells (% of CD4+)
40
35
30
25
20
15
10
5
0
*
Healthy controls
n=17
Strongyloides only
n=26
HTLV-1 only
n=9
Strongyloides/HTLV-1
n=13

A case of ATL

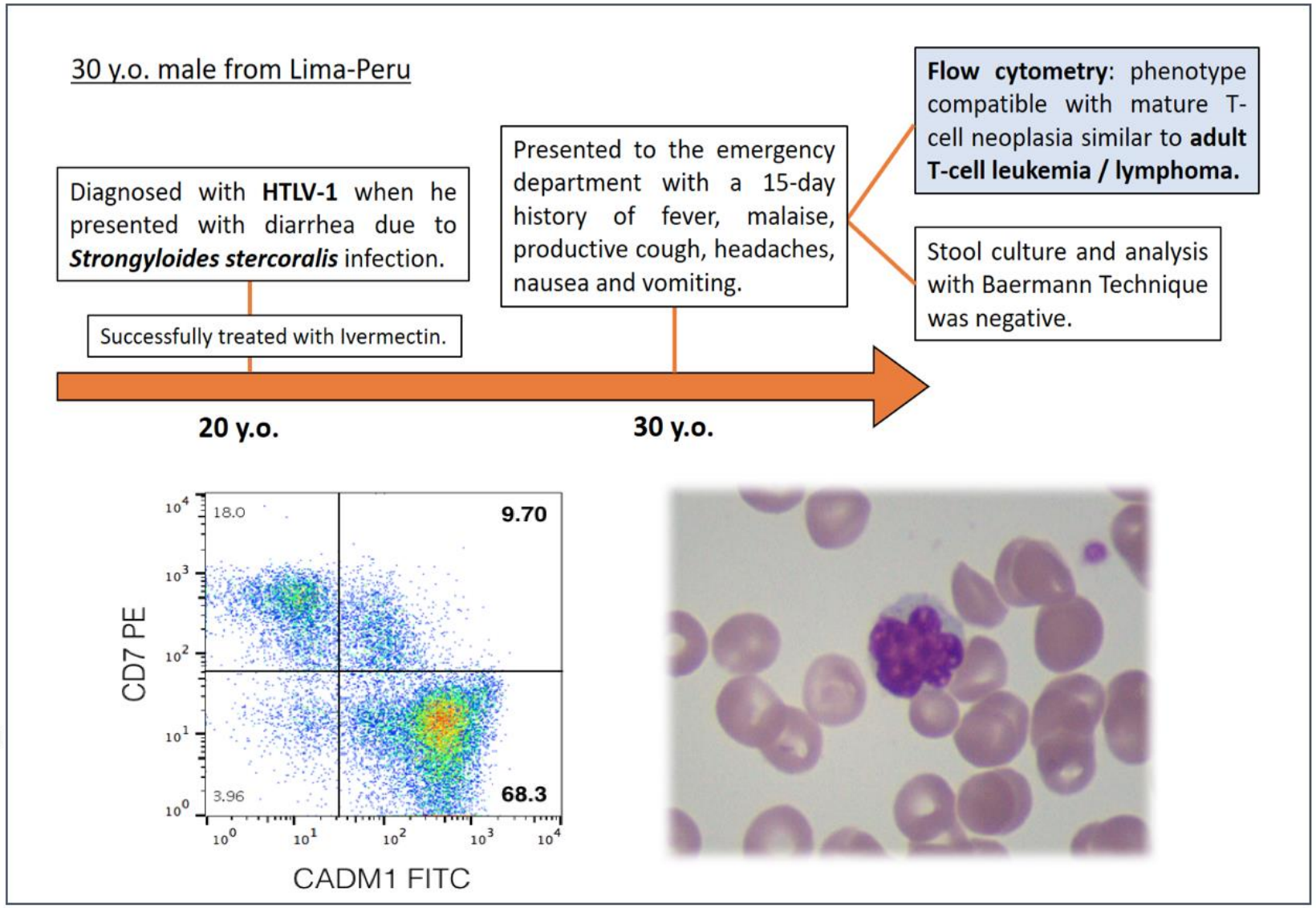


Figure 3. 30 y.o. patient with newly diagnosed ATL, 10 years after being diagnosed with HTLV-1/SS co-infection.

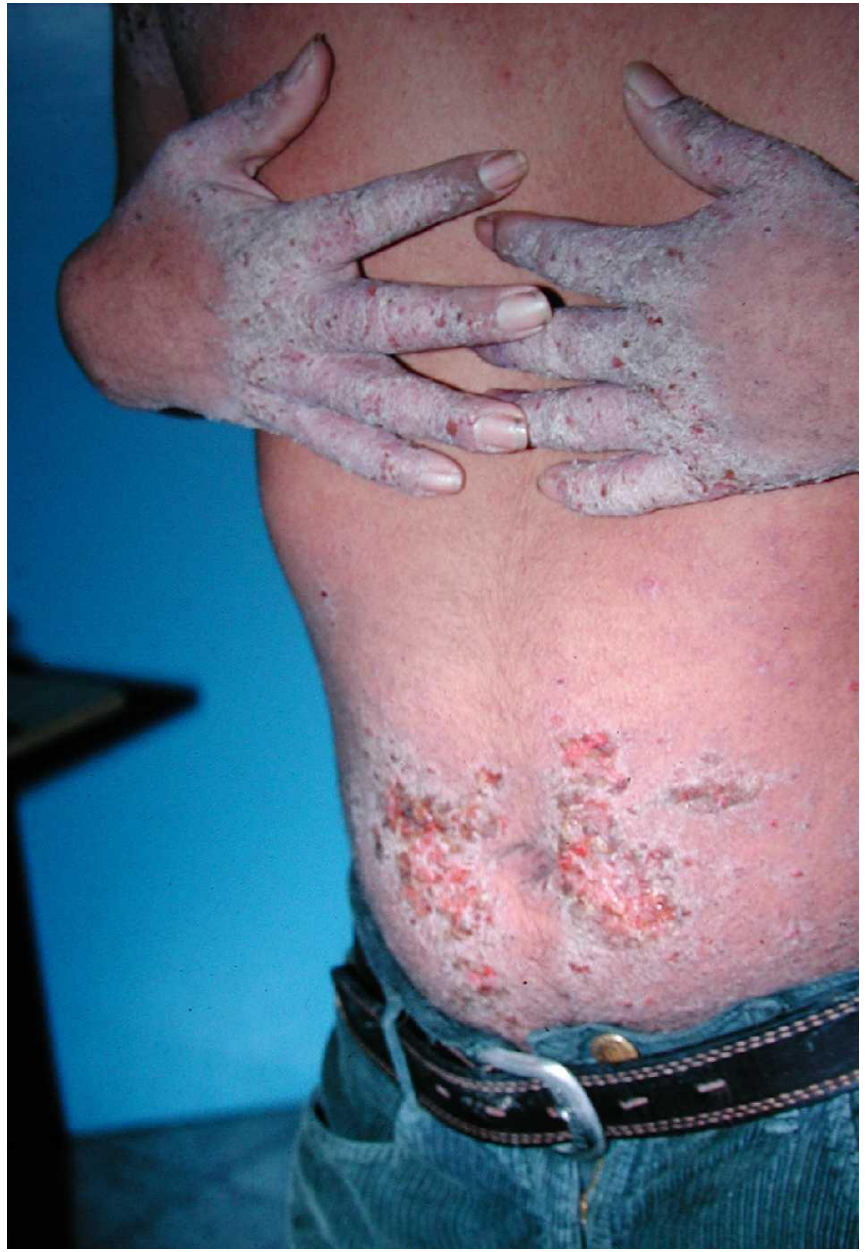
Crusted scabies

Study of 91 cases of scabies in Brazil

- Crusted scabies strongly associated with HTLV-1; in lesser degree with HIV.
- Co-infected patients had a higher risk of death.

Study of 23 cases of crusted scabies in Peru

HTLV-1 in 16 (70%).



Front Med (Lausanne) 2022;9:812016.
AIDS. 2002;16(9):1292-3.

Am J Trop Med Hyg. 2005;72(6):855-7.

Take home messages

- HTLV-1 is a lifelong infection, leads to complex and severe health outcomes in selected populations.
- Clinical outcomes are varied, more research on pathophysiology needed in endemic countries regarding opportunistic infections.
- HTLV-1 as family infection secondary to “silent” transmission
  - “Clustering” of diseases
- Control, based on preventing transmission, impacts on prevention of cancer and disability

Suggested recent reviews

General overview

- F1000Res. 2019;8. pii: F1000 Faculty Rev-228. PMID: 30854194
- Clin Microbiol Rev. 2022 Feb 23:e0007821. PMID: 35195446

HAM/TSP

- Management (Systematic Review and Consensus-based Recommendations): Neurol Clin Pract. 2021;11(1):49-56. PMID: 33968472
- Update on clinical and laboratory biomarkers: Pharmacol Ther. 2021;218:107669. PMID: 32835825.

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Diagnostic Approaches and Established Treatments. Front Microbiol. 2020;11:1207. PMID: 32636814.

HTLV-1 & *Strongyloides* coinfection

Front Med (Lausanne). 2022 Feb 14;9:832430. doi: 10.3389/fmed.2022.832430. eCollection 2022.

HTLV-1 & coinfections

Front Med (Lausanne). 2022 Feb 3;9:812016.

HTLV-1 in Ophthalmology.

Front Microbiol. 2020;11:388. PMID: 32218778

HTLV-1 Associated Neurological Complex.

AIDS Rev. 2019;21(4):211-217.