22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Workshop 3
HTLV epidemiology, phylogenetics, and diagnostics

Moderators: *Graham Taylor & Robert Harrod*

Thomas Jefferson University | Drexel University | Drexel Medicine

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Standardising molecular diagnosis of HTLV infections

Dr Philippa Hetzel,

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Co-Chair, IRVA's HTLV Testing Working group

SVI St Vincent's Institute MEDICAL RESEARCH | NRL Science of Quality

Conflicts of interest

- NRL conducts an Annual Australian Scientific Conference on Infectious Diseases for which we seek and receive sponsorship from a range of IVD manufacturers selling into Australia (e.g. in 2025 - DiaSorin, Roche, Cepheid, Abbott, Integrated Sciences, AusDiagnostics, Qiagen, Grifols, Abacus, SpeeDx, Genetic Signatures, BD, Diagnostic Technology and Hologic.)

- NRL is designated as a WHO Prequalification Evaluation Laboratory for the assessment of test kits / assays for use in low- and middle-income countries on behalf of WHO.

- NRL performs assessments of test kit performance on behalf of commercial IVD manufacturers under commercial arrangements and provides scientific services to enable IVD Manufacturer’s assays to achieve regulatory registration.

Overview

- Role of IRVA's International HTLV Testing Working Group
- How is molecular testing used in HTLV?
- What are the challenges with molecular testing for HTLV?
- Why standardize molecular testing for HTLV?
- How can we standardize this testing?
- How can we assure a high quality of molecular testing for HTLV?
- Summary

IRVA HTLV Testing Working Group

Since Q4 2023, IRVA's HTLV Testing Working Group (laboratory and clinician representatives from 8 countries) meet monthly to:

1. Provide a forum for discussion, knowledge sharing and provision of expert knowledge
2. Provide advice and support for establishing robust testing services, including to:
   - Improve the accuracy and reliability of testing globally incl distinguishing between HTLV-1 and HTLV-2.
   - Publish methods for molecular testing to improve access to nPCR and pro-viral load testing.
3. **Work towards the standardisation of assays** and support development of testing guidelines

Given there are no commercial molecular HTLV assays available globally → in-house (LDT) only

- Collation and publication of protocols from around the world
  - ➢ High quality and cost-effective testing solutions based on local infrastructure and funding
- Development of reagents/programs to improve the quality of molecular HTLV testing

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About HTLV molecular tests

1. Molecular tests for infectious diseases detect the infectious agent
2. Serology tests look for antibody against the infection = past exposure
3. **There is no commercial molecular assay available globally**

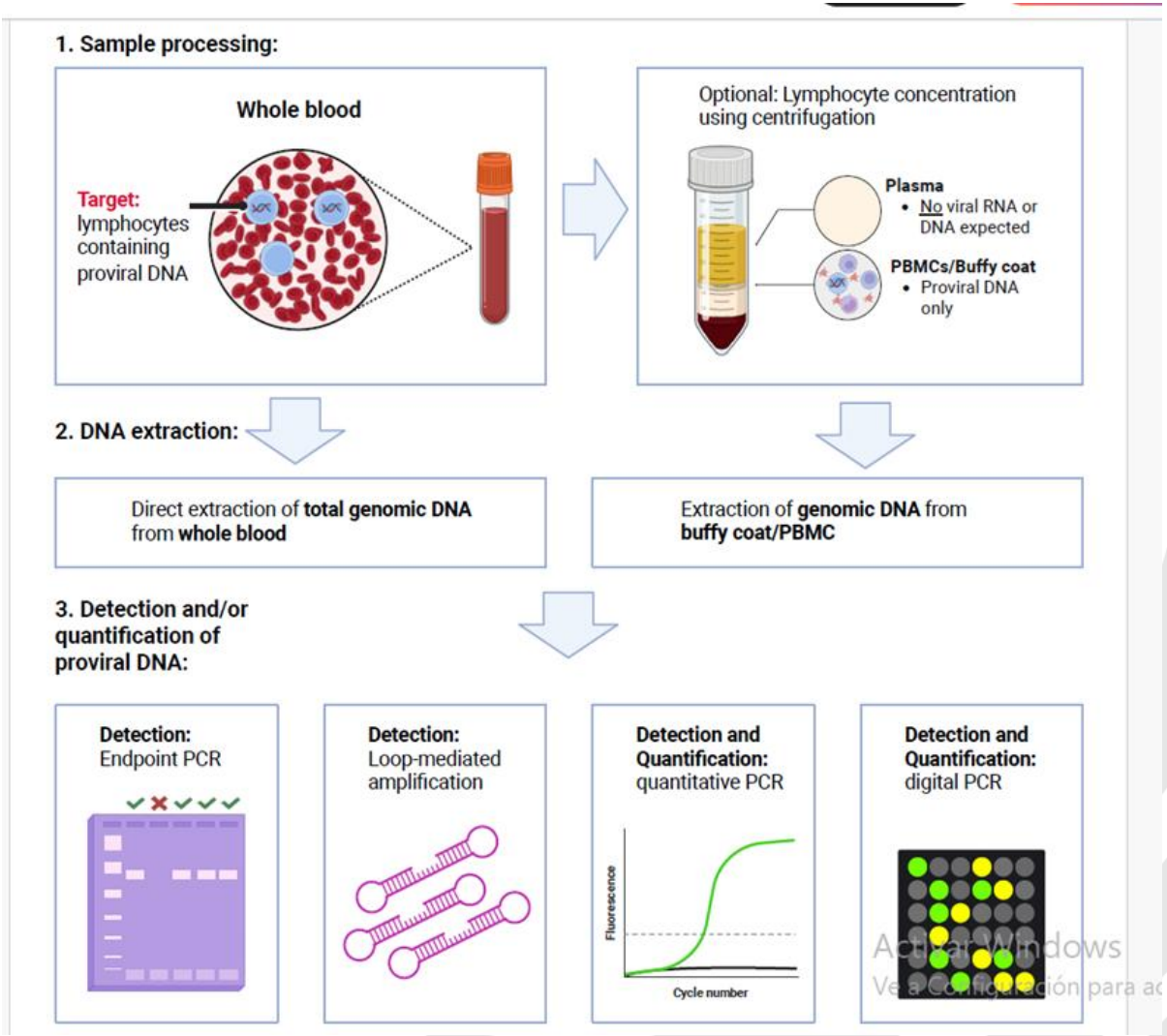
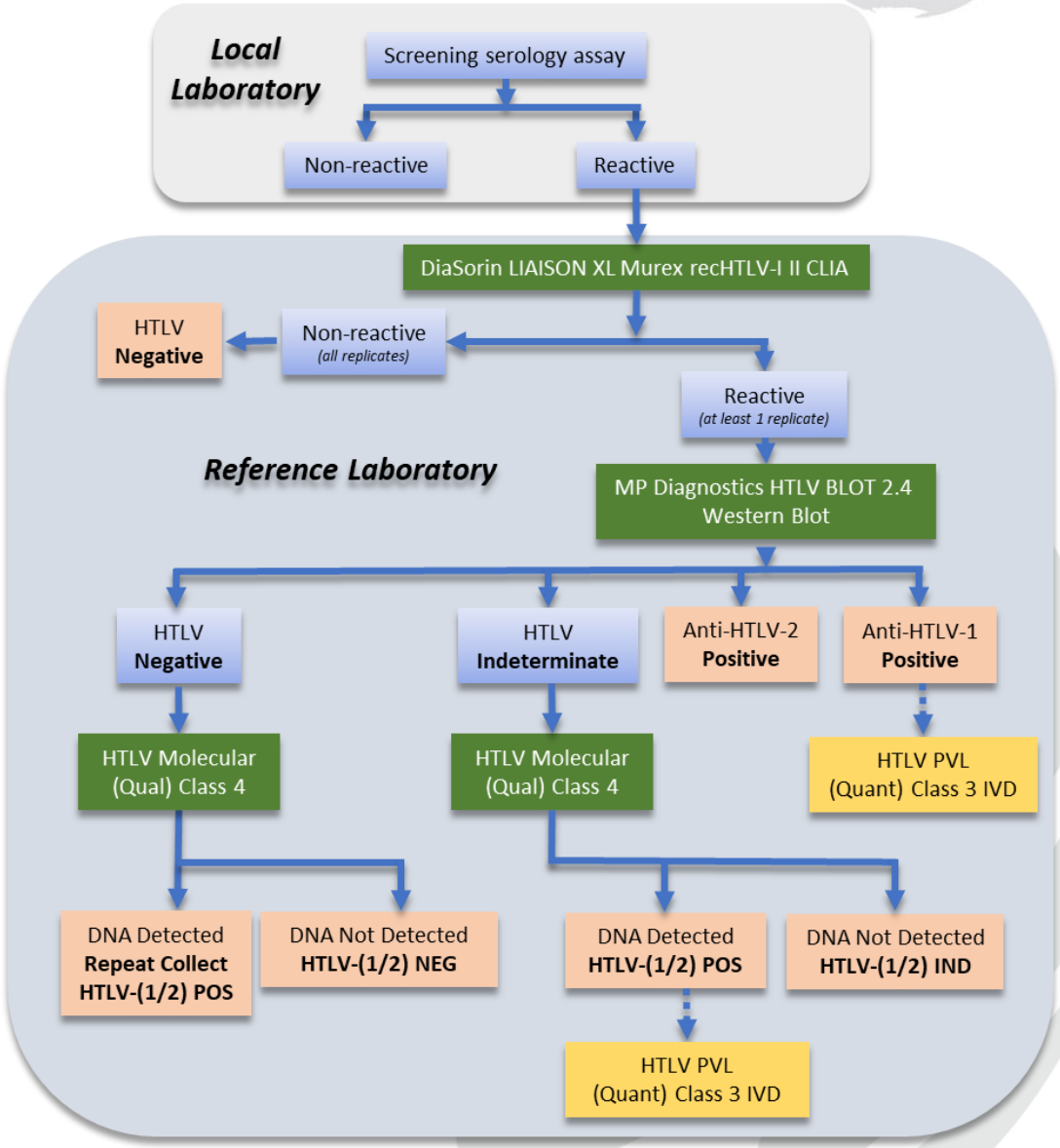


Figure: A Rowan ICL

Use-cases for Molecular Testing for HTLV

- **Diagnostic Algorithm**
  - Qualitative
  - Used as a confirmatory test to help resolve WB IND (approx. 10% → 3%) cases in Australia)
  - Confirm a WB Neg result

- **Monitoring test (Proviral load assay)**
  - Quantitative
  - Used as a prognostic marker in line with regional Clinical Guidelines
  - Used to inform risks to transmission (*e.g.*, MTCT in Australia)



Why standardize molecular diagnosis?

- Clinicians need laboratory test results to be reliable, accurate, sensitive and specific
- If different labs are performing the same test - the results must be comparable over time
- All new tests require validation/ verification to confirm that the test performance is acceptable – and especially when laboratories develop their own tests
- The process to validate a test uses a certified International Standard or Reference Material of known concentration and consistent performance.

There is no international certified HTLV reference material or standard to use

Use of a Certified Reference Material or International Standard

- Provides an independent reference to calibrate the Standard Curve for new HTLV molecular assays and existing in-house proviral load tests
- Ensures accuracy and consistency of proviral load testing between different laboratories / organisations
- A reference material can harmonise the assessment of HTLV-1 and HTLV-2 molecular assay sensitivity

NRL approached the Australian Government (Centre for Disease Control) and has received funding for the development of both HTLV 1 and HTLV 2 Certified Reference Materials and to develop an HTLV Molecular External Quality Assurance Scheme.

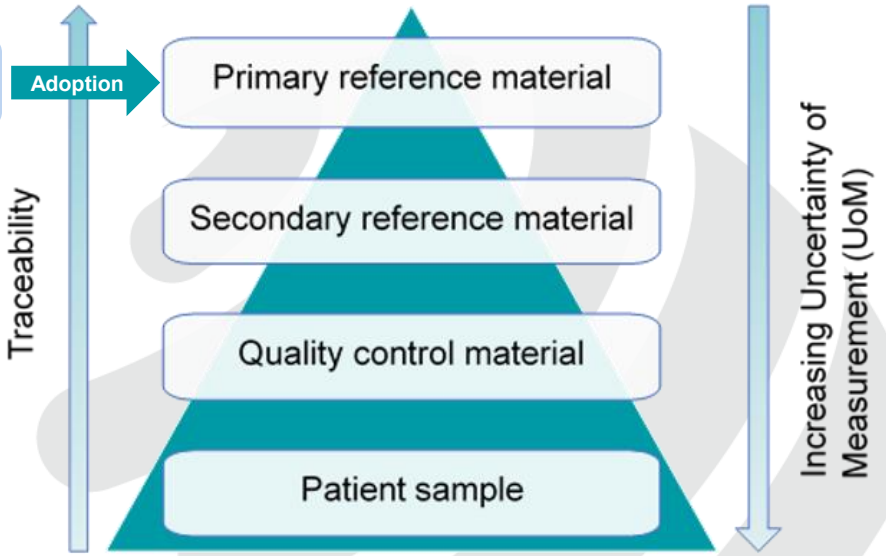
Certified Reference Material / International Standard

mission
TO PROMOTE THE QUALITY OF TESTS AND TESTING FOR INFECTIOUS DISEASES GLOBALLY

- Reference materials are vital to ensure that measurements performed on patient samples are comparable over time and between different laboratories.
- NRL has begun the process of developing Certified Reference Material / IS

Prototype reference material NMI-Australia → Feedback from labs IRVA → Production reference material NMI-Australia

- NIBSC established the International Working Group on the Standardisation of Genomic Amplification Techniques (SoGAT) in 1995 to help harmonise NAT-based tests
- NRL and NMI-A will work with SoGAT / WHO
  - ➢ HTLV Reference Materials will be adopted as CRM / IS



Reference: WHO Technical Report Series No. 932 2006
Recommendations for the preparation, characterization and establishment of international and other biological reference standards

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Certified Reference Material / International Standard

mission
TO PROMOTE THE QUALITY OF TESTS AND TESTING FOR INFECTIOUS DISEASES GLOBALLY

Three Reference Materials planned……

1. RM#1: HTLV-1 reference stock
   - TL-Om1 gDNA
2. RM#2: HTLV-1 dilution series
   - 5-member panel
   - TL-Om1 gDNA diluted through uninfected Jurkat E6-1 gDNA
3. RM#3: HTLV-2 dilution panel
   - 5-member panel
   - MoT gDNA diluted through uninfected Jurkat E6-1 gDNA

All RM's characterised by digital PCR for:

- HTLV-1/2 *tax* and *pol* copy number
- RNase P and Albumin copy number (single copy human genes in diploid human white blood cells)

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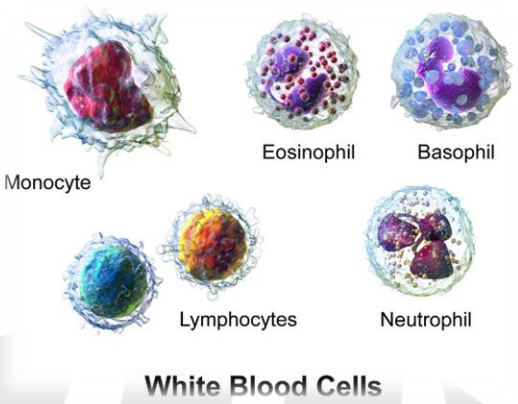
How to assure quality of Molecular HTLV Testing?

- No globally accessible External Quality Assessment Schemes (EQAS)
  - Local programs available in some jurisdictions
  - Laboratory exchange programs
  - No CRM / IS available to calibrate these programs
- No third-party External Quality Control (EQC) material available
  - Used in assay runs when performing assays in ISO/GMP environments
  - Trended over time (e.g., NRL offer EDCNet)
- Inconsistency in reporting methods / conventions
- Inconsistency in specimen types used to generate PVLs
  - PBMC vs PBL (Whole Blood, Buffy Coat, DBS)
  - **PVLs obtained from PBMC typically 1.5-2x higher than from PBL**



White Blood Cell (WBC) Type	Proportion Total WBC	PBL	PBMC	Note
Granulocytes				
Neutrophils	40-70%	✓	×	Not known reservoirs of HTLV Infection
Eosinophils	1-6%	✓	×	
Basophils	0.5-1%	✓	×	
Agranulocytes				
Lymphocytes	20-45%	✓	✓	Known reservoirs of HTLV Infection
Monocytes	2-10%	✓	✓	

Summary

- IRVA's HTLV Testing Working Group works towards improving access to and the quality of molecular testing for HTLV.
- There are no commercial molecular tests available globally.
- Working Group focus is on the standardisation of assays – working towards developing a Certified Reference Material and ultimately, International Standards for HTLV-1 and HTLV-2
- Work is beginning to develop an External Quality Assurance Scheme
- Review of reporting conventions and accommodation of starting materials is required

Acknowledgment:

CRM and EQAS work - funded by the Australian Government – Centre for Disease Control.

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Dr Madoka Kuramitsu

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Dr Leo Pinheiro

IRVA and the HTLV Testing Working Group

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Brazil	Tatione Assone	USP/ ITMSP
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Sweden	Kerstin Malm	OUH
United Kingdom	Graham Taylor Aileen Rowan Carolina Rosadas Lucy Cooke Daniel Bradshaw	ICL / ICH NHS Trust ICL ICL ICH NHS Trust UKHSA

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Diagnosis of HTLV infections in early life

Carolina Rosadas
Imperial College London, UK

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Diagnosis of HTLV-1 early life infection

Dr Carolina Rosadas

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Disclosure: More questions than answers!

* No conflict of interest

Paediatric diagnosis of HTLV-1

Part 1
Why?

Part 2
How?

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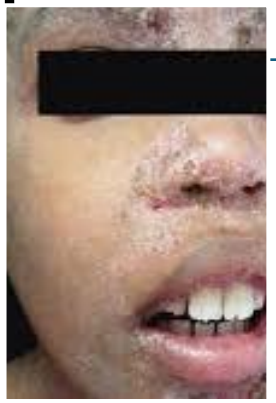
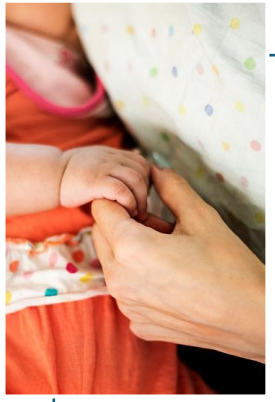
Why should we test for HTLV-1 infection in paediatric patients?

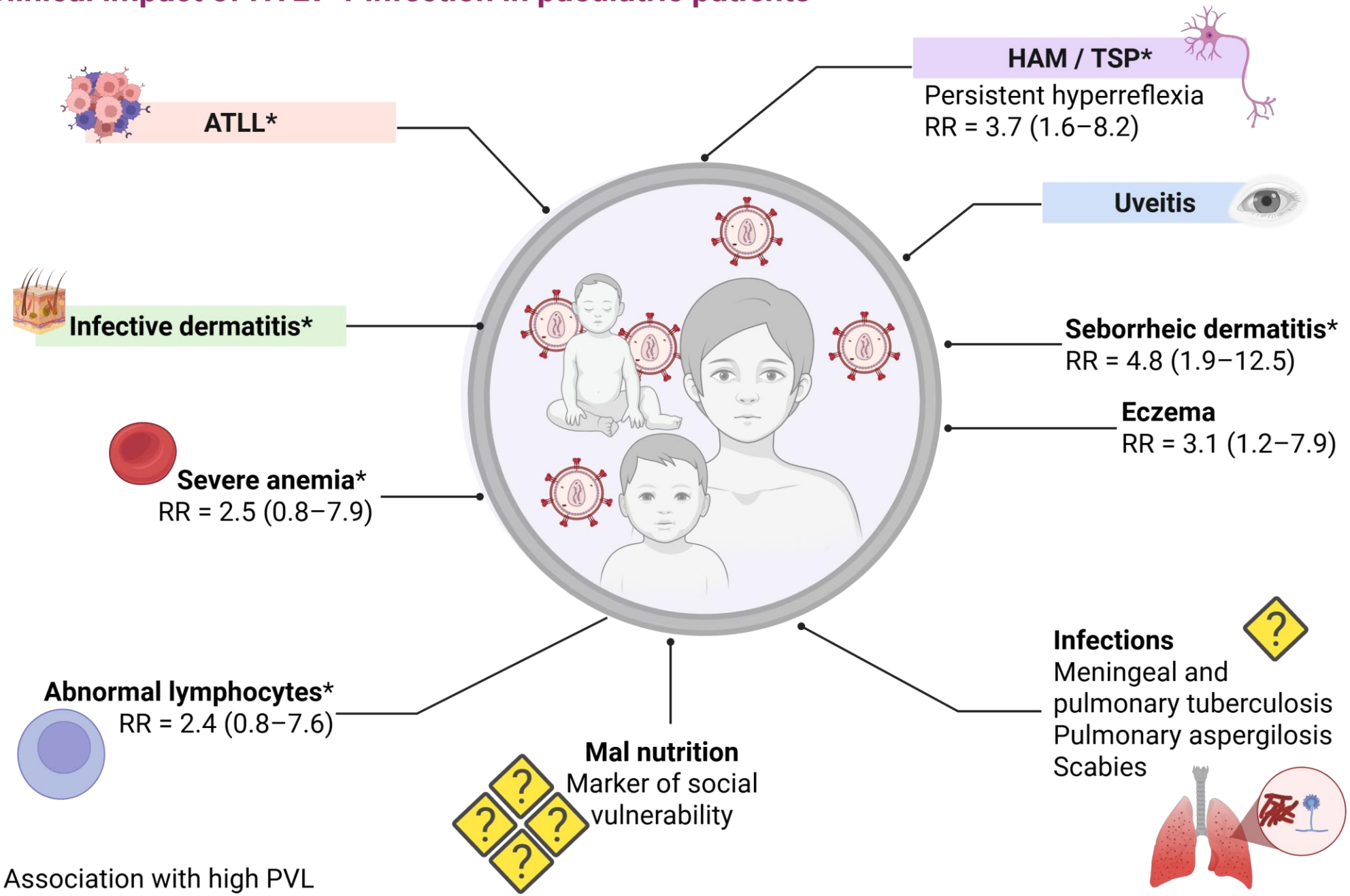


Symptomatic patients



Babies/Children exposed to the risk of HTLV-1 infection

Clinical impact of HTLV-1 infection in paediatric patients



* Association with high PVL

RR reported for 28 HTLV-1-infected and 280 uninfected children in Jamaica (Maloney et al 2004)

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ATLL in children and adolescents

1y: Vilmer et al 1985 (Sicilia)

2y: Pombo de Oliveira et al 1999 (Brazil)

Table 2. Published cases of adult T-cell leukemia/lymphoma (ATL) in childhood and puberty

N	Authors	Country	City/Region	Age[a]/ Gender	Ethnicity	Probable transmission	Disease duration (months)	Clinical type	Survival (years)
1	Barbosa *et al*, 1999[b] [25]	Brazil	Salvador	18/F	A. descent	. . .	2	Lymphoma	Deceased (1)
2	Barbosa, 1999[b] [25];Bittencourt *et al*, 2001 [26]; 2007[c] [27]	Brazil	Salvador	9[d]/M	A. descent	Vertical	2	Smoldering	Alive (15)
3	Bittencourt *et al*, 2001[b,e][26]	Brazil	Salvador	18/F	A. descent	Vertical	8	Chronic	Deceased (1.9)
4	Valle *et al*, 2001 [28]	Brazil	RJ	15/M	A. descent	Vertical	1	Acute	Deceased (0.4)
5	Pombo de Oliveira, 2002 [2]	Brazil	RJ	2/F	A. descent	Vertical	12	. . .	Deceased (2)
6	Pombo de Oliveira, 2002[c]	Brazil	RJ	18/M	Caucasian	Vertical	. . .	. . .	Deceased (0.6)
7	Pombo de Oliveira, 2002[c]	Brazil	RJ	11/M	A. descent	Vertical	120	. . .	Deceased (4)
8	Pombo de Oliveira, 2002[c]	Brazil	RJ	15/M	A. descent	Vertical	168	. . .	Deceased (0.2)
9	Pombo de Oliveira, 2002[c]	Brazil	RJ	14/M	A. descent	. . .	. . .	. . .	Deceased (0.5)
10	Pombo de Oliveira, 2002[c]	Brazil	RJ	16/F	Caucasian	. . .	. . .	. . .	Deceased (0.2)
11	Pombo de Oliveira, 2002[c]	Brazil	RJ	16/F	A. descent	Vertical	. . .	. . .	Deceased (0.2)
12	Pombo de Oliveira, 2002[c]	Brazil	RJ	7/M	A. descent	Vertical	72	. . .	Alive (3)
13	Farré *et al*,2008[b,c,e, f] [12]	Brazil	Salvador	16/F	A. descent	Vertical		Smoldering	Alive (10)
14	Lage *et al*, 2012[c] [29]	Brazil	São Paulo	17/F	. . .	. . .	12	Smoldering	Deceased
15	Oliveira *et al*,2013[c,e] [30]	Brazil	Salvador	19[g]/F	A. descent	. . .	0.5	Acute	Deceased (0.5)
16	Blank *et al*, 1993 [31]	Colombia	Cali	17/M	A. descent	Vertical	. . .	Lymphoma	Deceased (. . .)
17	Wilks *et al*,1993 [32]	Jamaica	Kingston	16/F	. . .	Vertical	5	. . .	Deceased (0.3)
18	Plumelle *et al*, 2015 [33]	Martinique	Fort-de-France	16/F	. . .	. . .	. . .	Chronic	Alive (12.5)
19	Foucar *et al*, 1985 [34]	USA	Iowa	16/F	Caucasian	. . .	0.5	Acute	Deceased (0.1)
20	Ratner *et al*, 1988 [35]	USA	Illinois	7/F	A. descent	Vertical	84	Acute	Deceased (. . .)
21	Fort *et al*, 1989[h] [36]	USA	Florida	16/M	A. descent	Vertical	. . .	. . .	Deceased (0.2)
22	Broniscer *et al*, 1996[c] [37]	USA	Memphis	16/F	A. descent	Transfusion[i]	0.25	Acute	Alive (2.1)
23	Zucker-Franklin*et al*, 1999 [38]	USA	New York	7/M	A. descent	Vertical	36	. . .	Alive (3.1)
24	Lewis *et al*, 2001[c] [39]	USA	Iowa	13/M	. . .	Transfusion[i]	10	. . .	Alive (. . .)
25	Lucas *et al*, 2008[f] [40]	USA	Birminghan city	16/F	A. descent	Transfusion[i]	36	Acute	Deceased (<0.2)
26	Williams *et al*, 1993 [41]	Nigeria	Ibadan	12/M	A. descent	Vertical	. . .	. . .	. . .

(Continued)

Oliveira et al 2017

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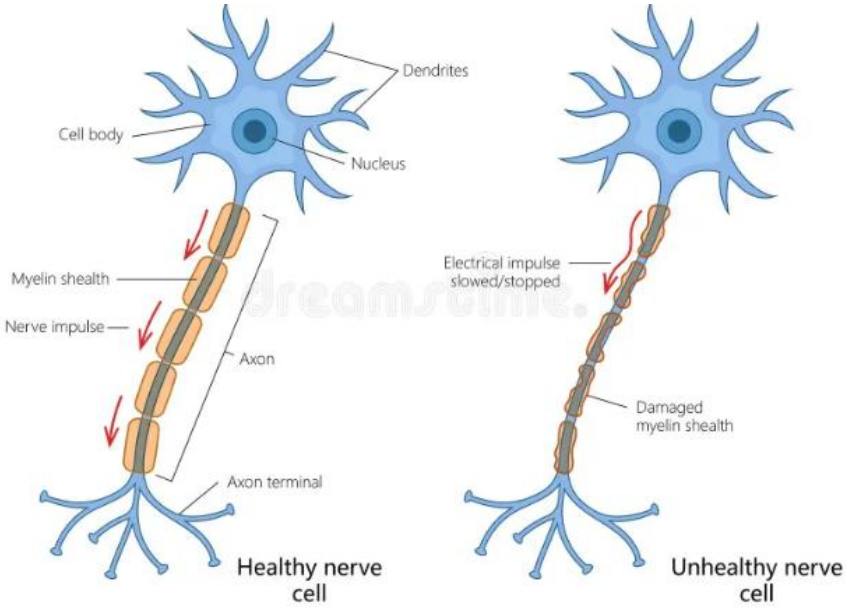
paedHAM/TSP: How early?

Peru: n=38	Brazil n=25
• Median age onset 14 years • **Early onset: 6 years** • Duration of symptoms prior to diagnosis: 6 years	• Median age onset 9 • **Early onset: 3 years** • Median age of HAM diagnosis 12,5

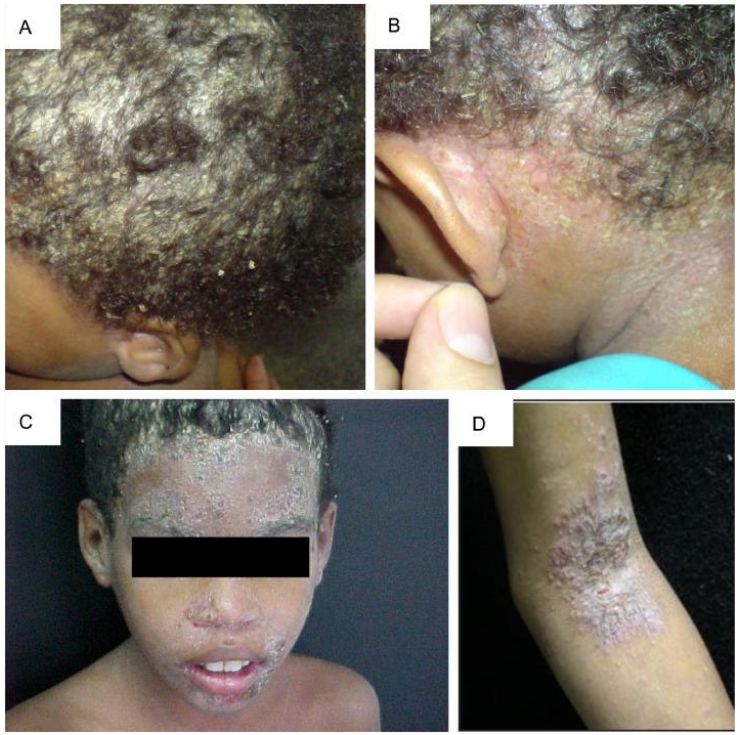
Years of neuronal damage that can not be undone



Schwalb et al 2020, Varandas et al 2020, Oliveira et al 2017

Infective dermatitis: How early?

Country	n	Age at diagnosis		Age at onset		Reference
		Median	Range	Median	Range	
Jamaica	50	6.9	1-32			La Grenade 1998
Peru	33	7	2-17			Puell et al 2004
Brazil*	20			2y	4m-9y	Varandas et al
Brazil*	20	8	4-14	2y		Primo et al 2005
Brazil*	42	8.9	2-18y	2.3y	2m-11y	De Oliveira 2012
Senegal	5		3-17y		7m-9y	Mahe et al 2004
South Africa	19	8	8m-15y			Hlela et al 2013
Argentina	1	11		5y		Benencio et al 2021
Brazil	1	7		18m		Garcia et al 2022
USA#	1	11		3y		Weiler et al 2019
Australia	1	2.3		13 m		Menz et al 2017
South Africa	1	7		1y		Webb et al 2013
French Guyana	1	8		2y		Clyti et al 2004
Jamaica	2		7.8-10.1y		NA-6 y	Miller et al 2001
Colombia	1	4				Blank et al 1995



Bittencourt et al 2024

* Probably overlapping cohorts

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Why to test symptomatic children?

- Diagnosis
- Treatment / Modify clinical management
- Counselling

Case Report: Relevance of an Accurate Diagnosis and Monitoring of Infective Dermatitis Associated With Human T-Lymphotropic Virus Type 1 in Childhood

Paula Benencio[1], Nicolás Ducasa[1], Lourdes Arruvito[1], Inés Irurzun[2], Laura Praino[3], Magdalena Lamberti[2], María Beraza[2], Carolina Berini[1†] and Mirna Biglione[1†]*

We need to increase knowledge among healthcare professionals!

International registry of paediatric patients

Please reach out if you are interested!

crosadas@ic.ac.uk

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Why to test children exposed to the risk of HTLV-1 infection?

- Aims:
  1. Confirm infection
  2. Rule out infection

- Perspectives:
  1. Mothers (family members)
  2. Children

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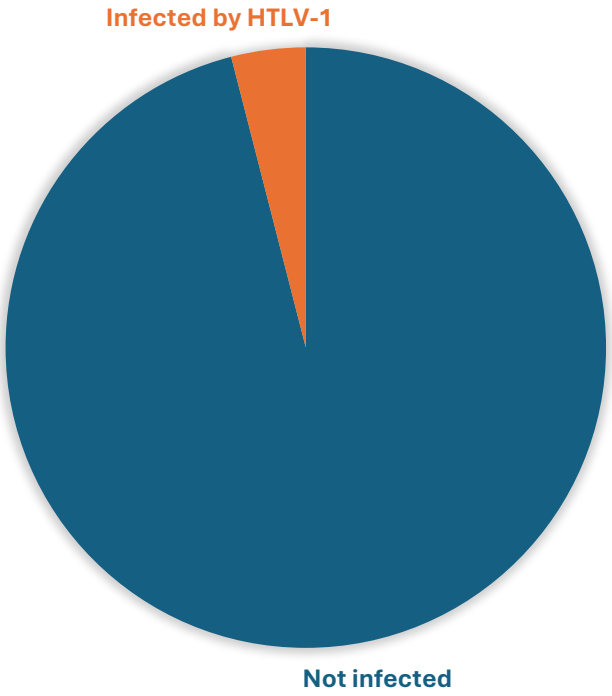
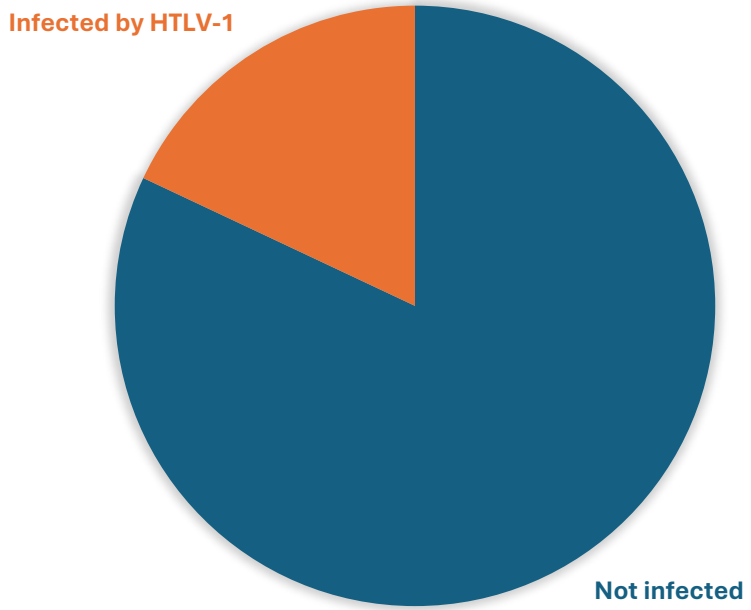
Why to test children exposed to the risk of HTLV-1 infection?

SUCCESSFUL PROGRAMME



End up anxiety for >95% of families and children

ABSCENCE OF POLICIES



End up anxiety for about 80% of families and children

Rosadas & Taylor 2022

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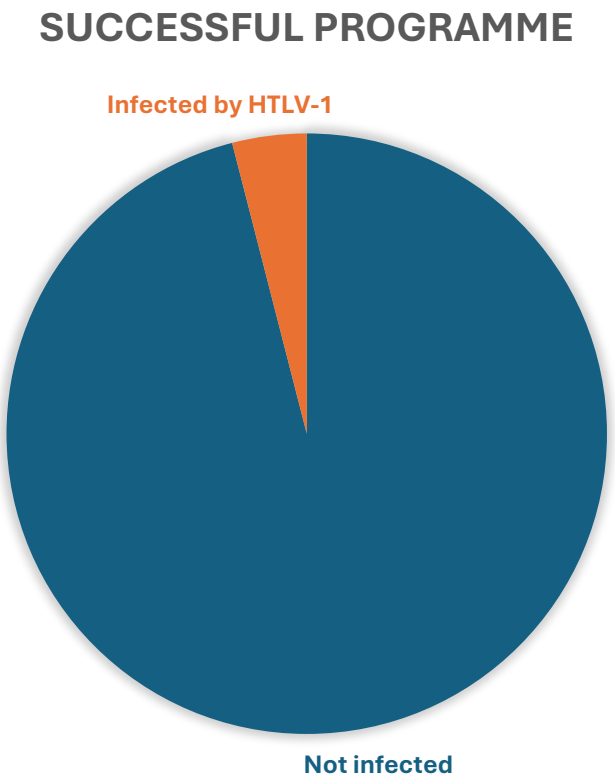
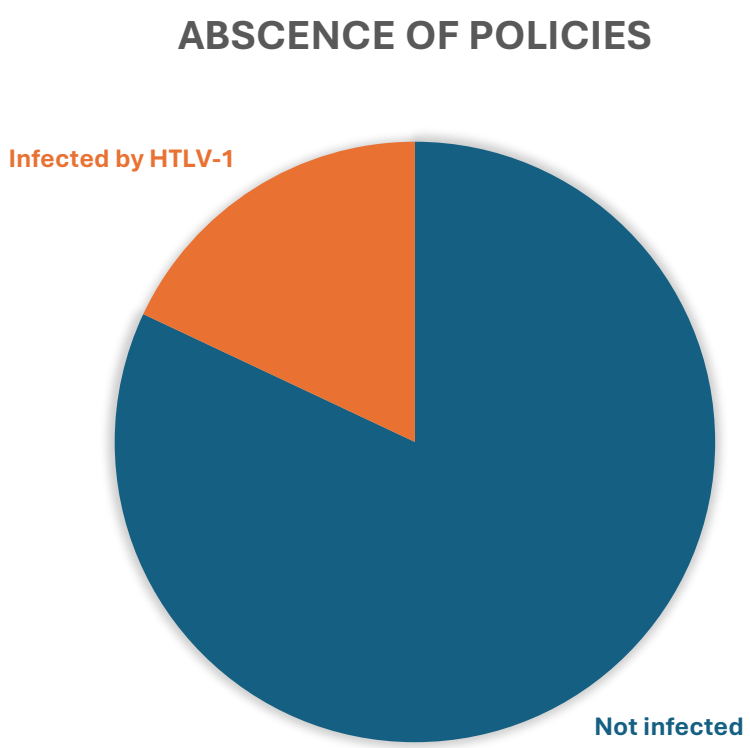
What about those cases when infection happened?





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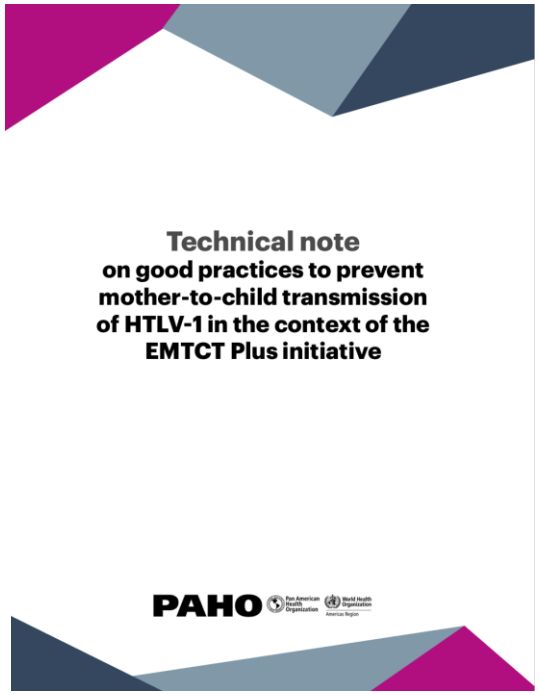
What about those cases when infection happened?

- Follow-up for early identification of disease
- Counselling (avoid transmission, early symptoms)

Public health perspective: + monitor programme

Test > 90% of children exposed to the risk of vertical transmission



Poster A92: Beatriz Luz, A080: Louine Morell

Paediatric diagnosis of HTLV-1

Part 1
Why?

Part 2
How?

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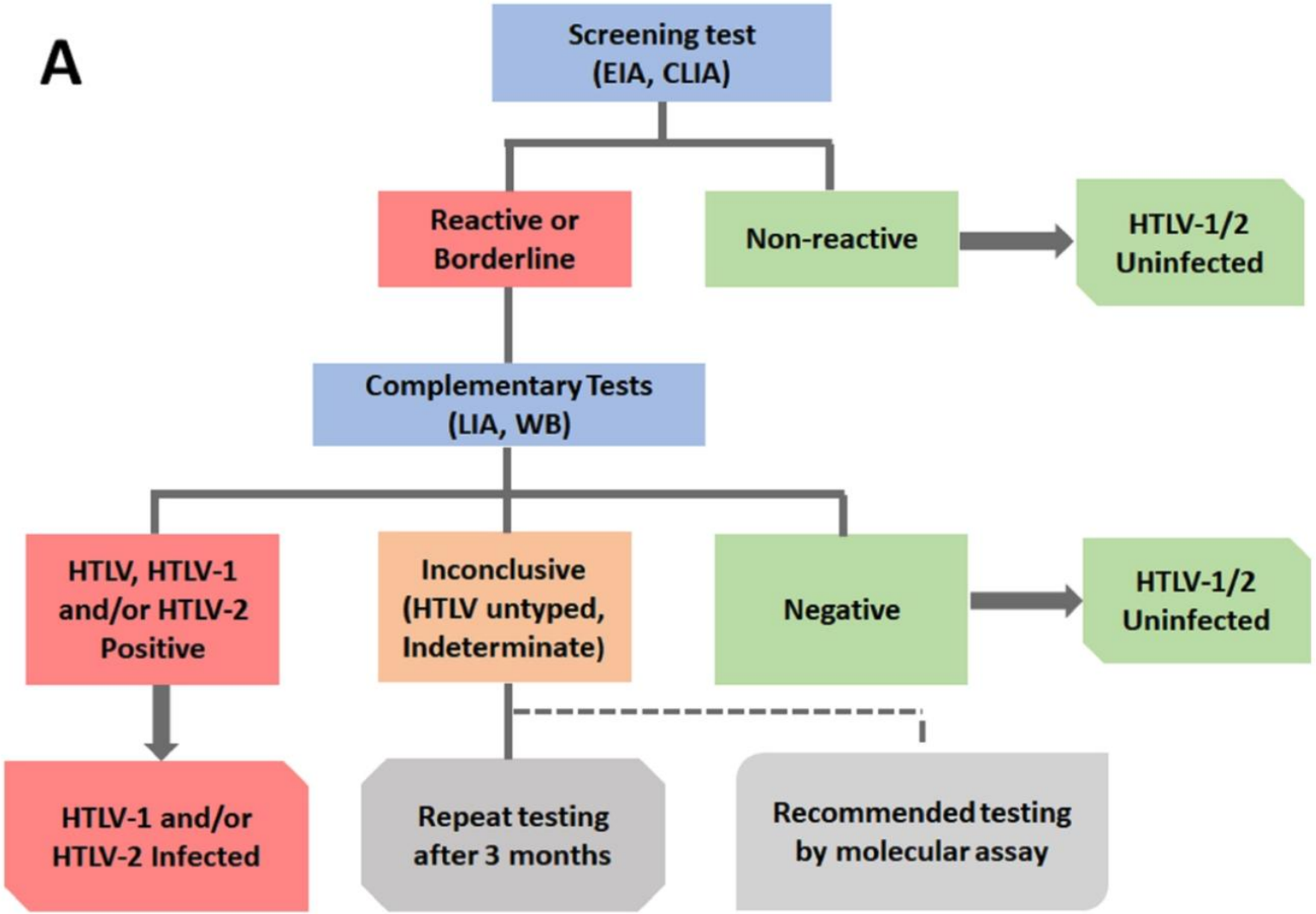
HTLV-1 diagnosis in adults



Caterino-de-Araujo et al 2021

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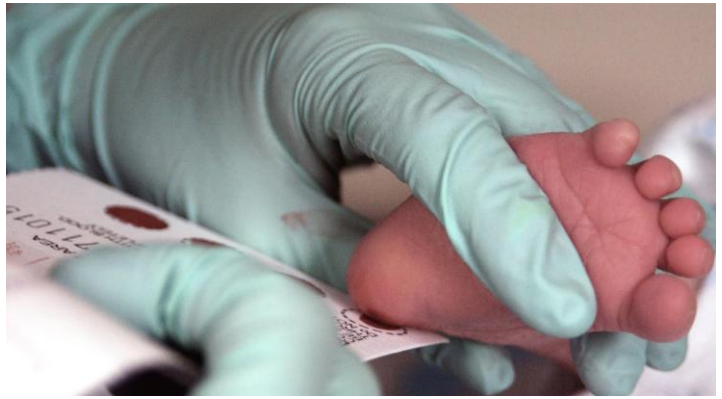
HTLV-1 diagnosis in paediatric patients

- Even more challenging!
  - Sampling
  - Passive transfer of maternal antibodies
  - Sensitivity/Specificity of molecular test is unknown
  - Time taken for seroconversion if infection happens



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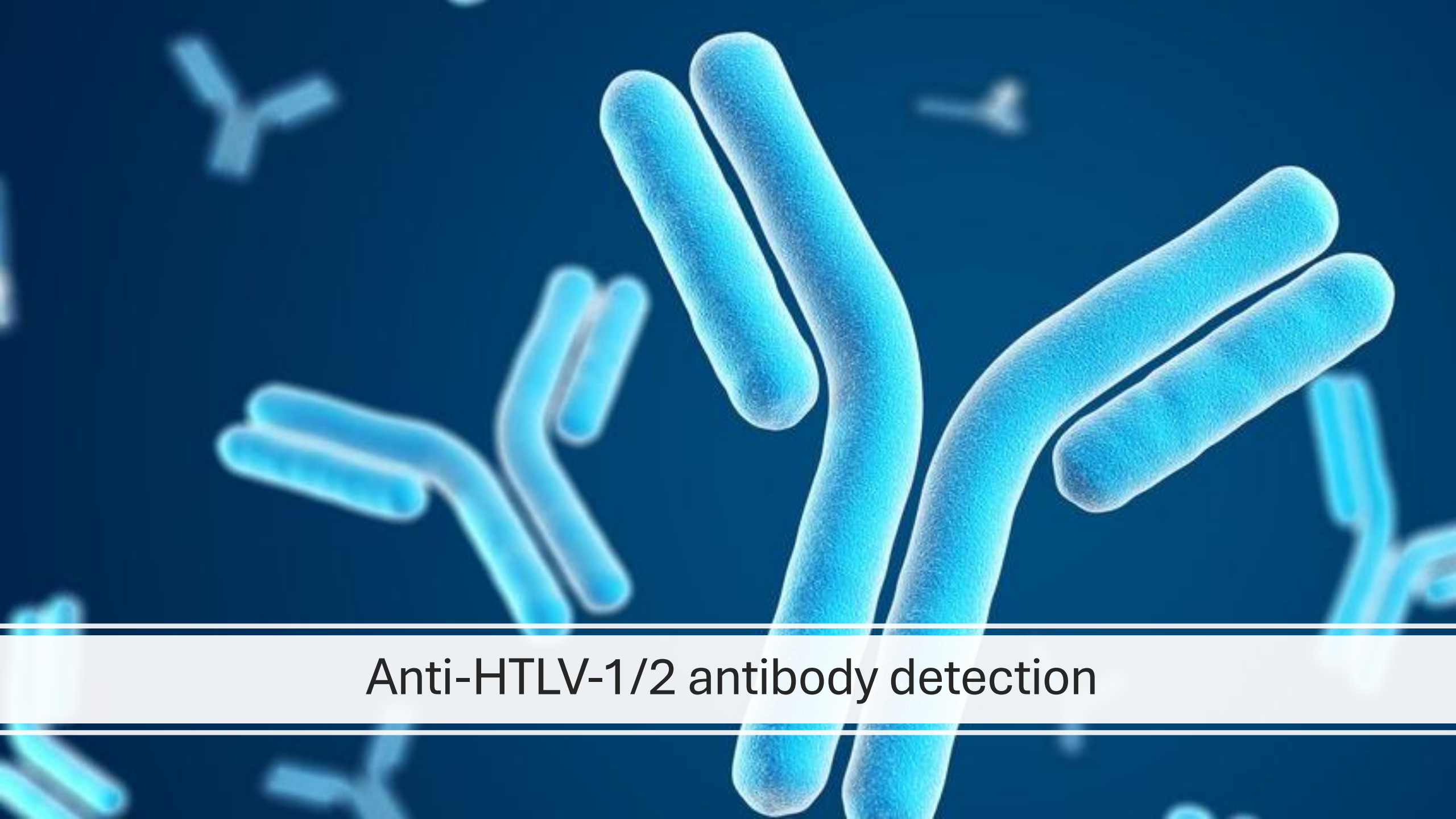
HTLV-1 diagnosis in paediatric patients

- Current practices:
  - Antibody detection
    - 15 months, 18 months, 3 years
  - Other strategies
    - Serial testing for Ab + PCR
    - Serial PCR testing



Anti-HTLV-1/2 antibody detection

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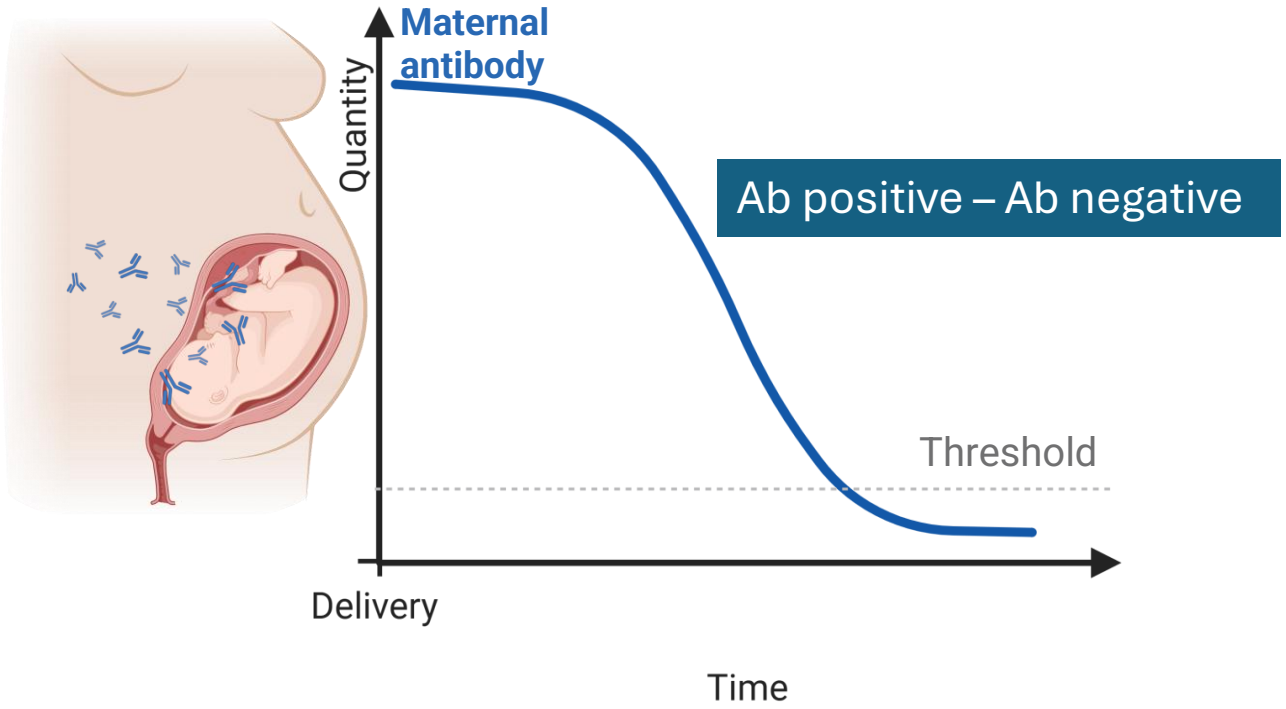
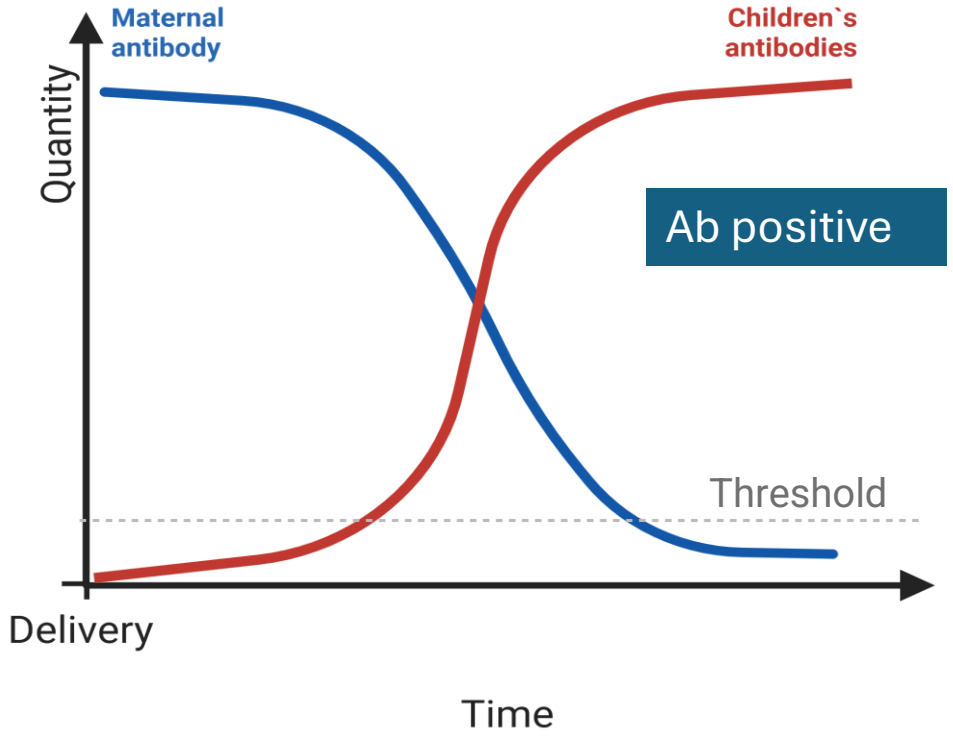
Children born to women living with HTLV-1

Not infected



Infected



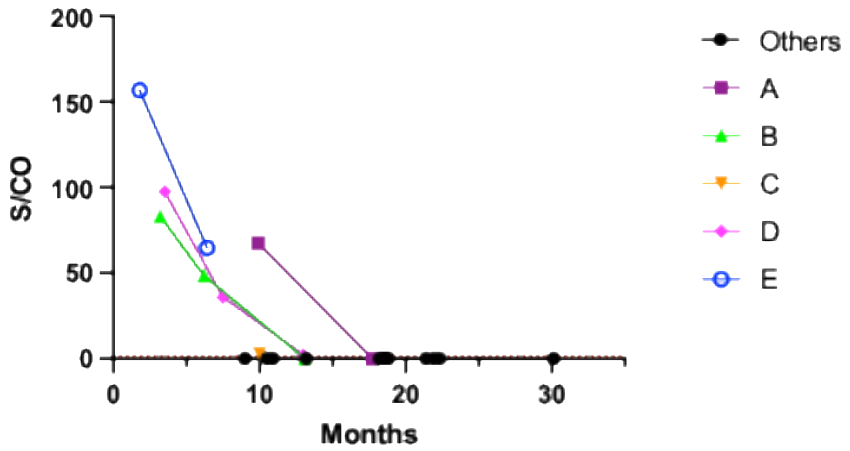
- Antibody testing at delivery or early testing – not useful!
- Seroreversion to rule out infection?
- How long maternal antibody lasts?

Children born to women living with HTLV-1

Not infected

Quick review of the literature:

- After six months, half were already seronegative, increasing to 90% at 9 months.

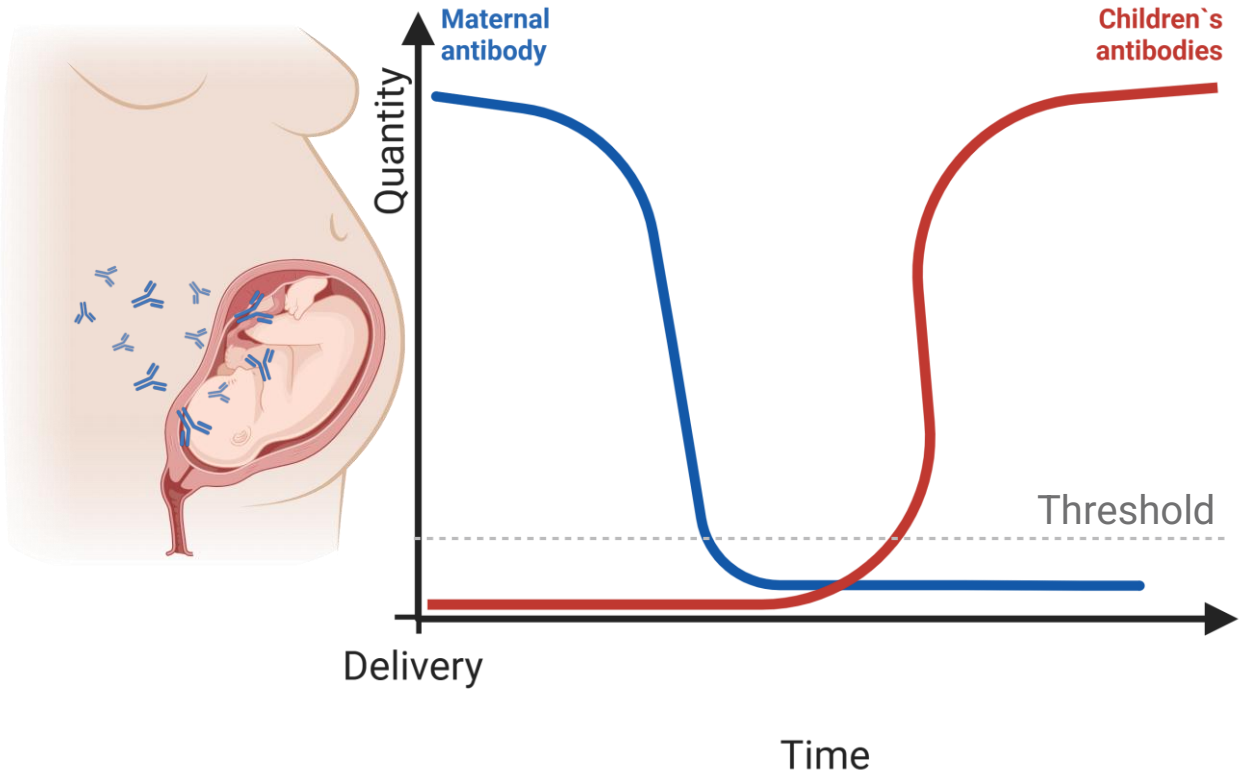


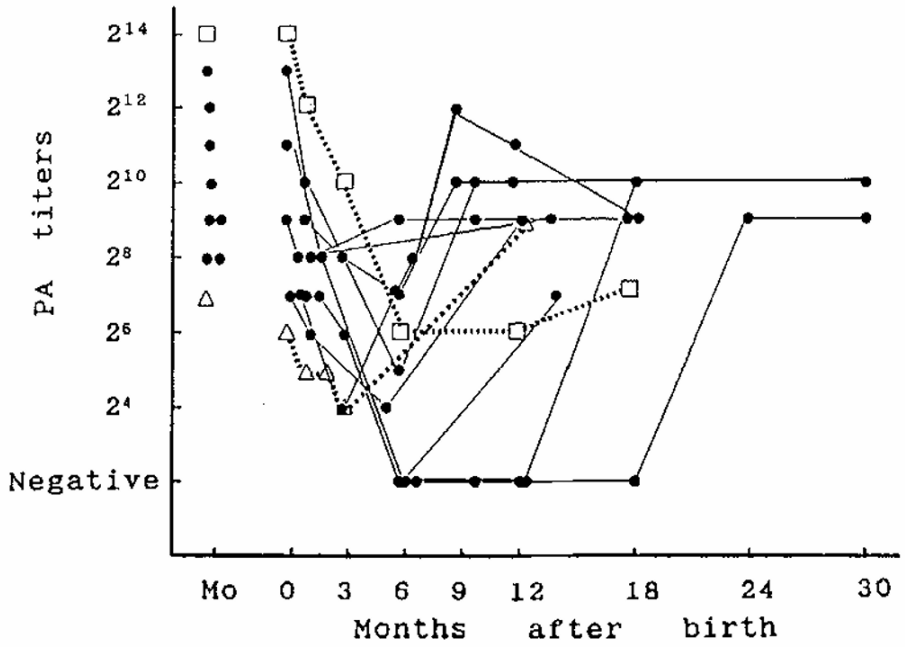
UK Cohort: those who had a positive anti-HTLV-1 antibody test had become negative by 18 months, **last positive maternal antibody detected at 10 months**

Penner et al submitted manuscript

Children born to women living with HTLV-1 and infected

Ab positive – Ab negative – Ab positive





Takahashi, et al 1991

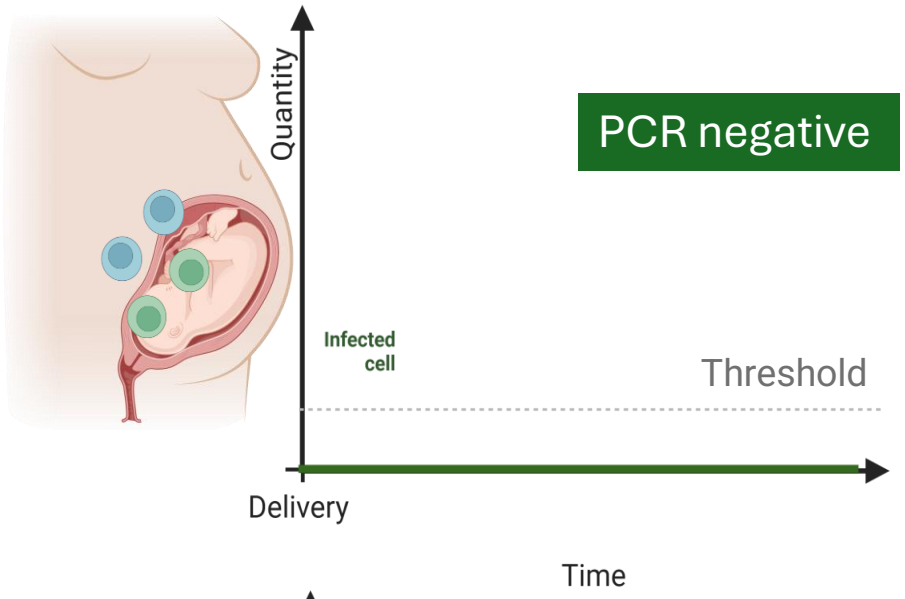
This may happen in breastfed children

Reports in exclusive formula fed children

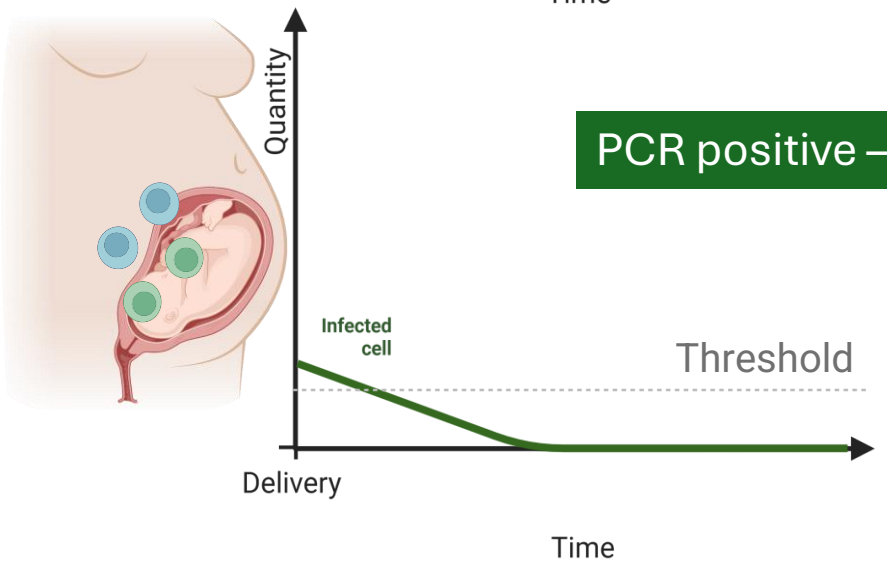
Seroconversion after 2 years occurred only in breastfed babies.

Detection of HTLV-1/2 proviral DNA

Children born to women living with HTLV-1 and not infected



PCR negative

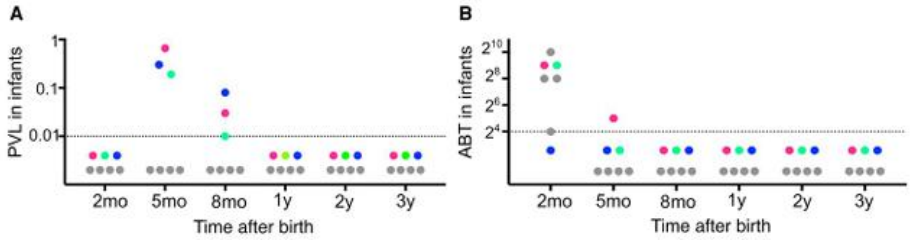


PCR positive – PCR negative?

Identification of Natural Remission of Mother-to-Child Retroviral Transmission

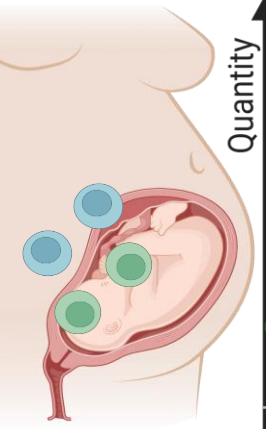
Poonam Grover,[1] Megumi Murata,[1] Maureen Kidiga,[1,6] Sakura Hayashi,[1,6] Hirotaka Ode,[2,6] Yasumasa Iwatani,[2,6] Mayumi Morimoto,[1] Takayoshi Natsume,[1] Akihisa Kaneko,[1] Jun-ichirou Yasunaga,[3,6] Masao Matsuoka,[3] Madoka Kuramitsu,[4,6] Yohei Seki,[4] Takuo Mizukami,[4,6] and Hirofumi Akari[1,6]

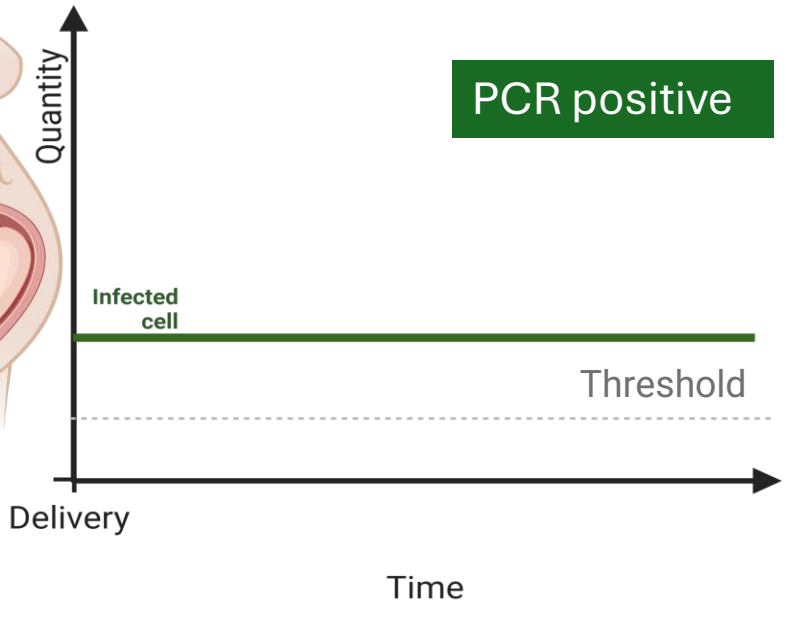
[1]Center for Evolutionary Origins of Human Behavior, Kyoto University, Inuyama, Japan; [2]Clinical Research Center, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [3]Department of Hematology, Rheumatology, and Infectious Disease, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; and [4]Research Center for Biological Products in the Next Generation, National Institute of Infectious Diseases, Tokyo, Japan

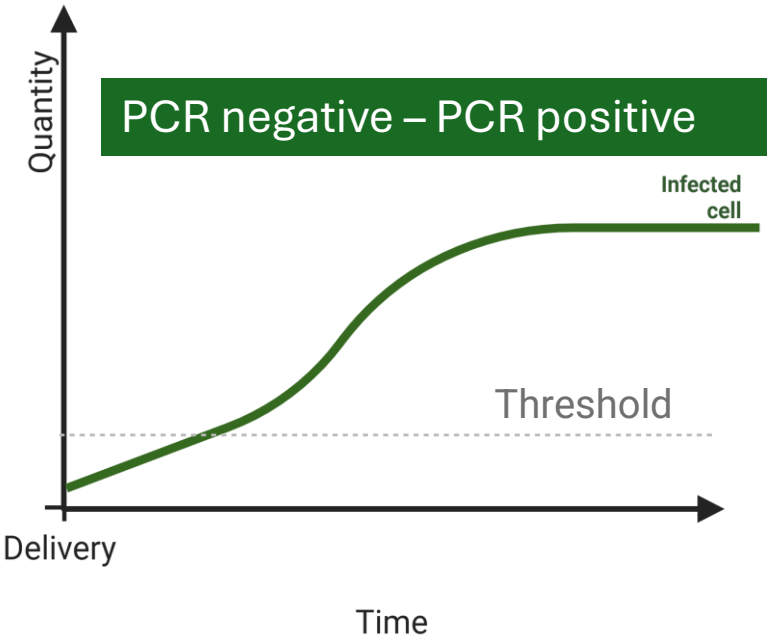


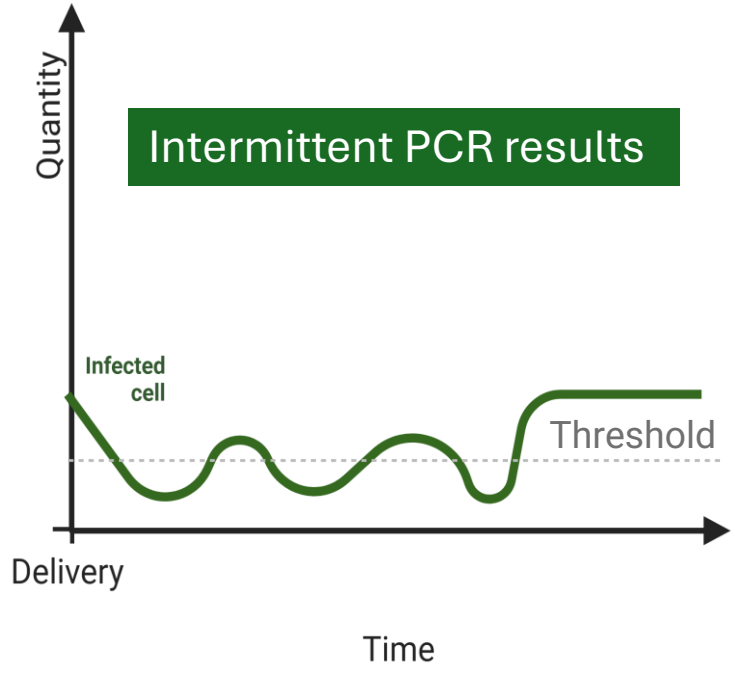
Reported in animal model

Children born to women living with HTLV-1 and infected









When to test?

What is the sensitivity of PCR in early life infection?

Summary

- Paediatric patients may have HTLV-1 associated diseases, but **we need to increase our knowledge** on the impact of early life infection
- Paediatric diagnosis **allow counselling and monitoring**, providing opportunity to prevent transmission and facilitating early diagnosis of disease
- **Testing for antibodies at birth / early testing is not useful**
- **We need more studies** to improve testing strategies for paediatric patients
- **International registry** will be important to acquire meaningful data

IMPERIAL

Thank you!

People living with HTLV-1

Adijeane Oliveira

Marcia Brandao

Fatumata Djalo

Erika Archanjo

Imperial

Graham Taylor

Claire Greiller

NHS

Prof Hermione Lyall

Dr Justin Penner

PAHO

Leandro Sereno

Monica Alonso

Aranai Guarabira

WHO

Cheryl Johnson

Magdalena Barr-Dichiara

Brazilian HTLV Network

Maria Fernanda Rios Grassi

Ana Rita Coimbra

Tatiana Assone

Jorge Casseb

Aline Carralas

Denise Peluso

NCHR

Health managers from state secretariat in Brazil

Beatriz Luz (SES-DF)

International registry of paediatric patients

Drexel UNIVERSITY | Drexel MEDICINE

22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Pathogenesis of HAM/TSP and Its Implications for Drug Discovery

Yoshi Yamano
St. Marianna University School of Medicine, Japan

Pathogenesis of HAM/TSP and Its Implications for Drug Discovery

Yoshihisa Yamano

Department of Neurology
Department of Rare Diseases Research
St. Marianna University School of Medicine

Conflict of Interest Disclosure

Presenter：Yoshihisa Yamano

I have no actual or potential conflict of interest in relation to this presentation.

HTLV-1 Infection Outcomes

Lifetime risk
0.3%

Lifetime risk
5 %

HAM/TSP –
HTLV-1-Associated Myelopathy /Tropical Spastic Paraparesis

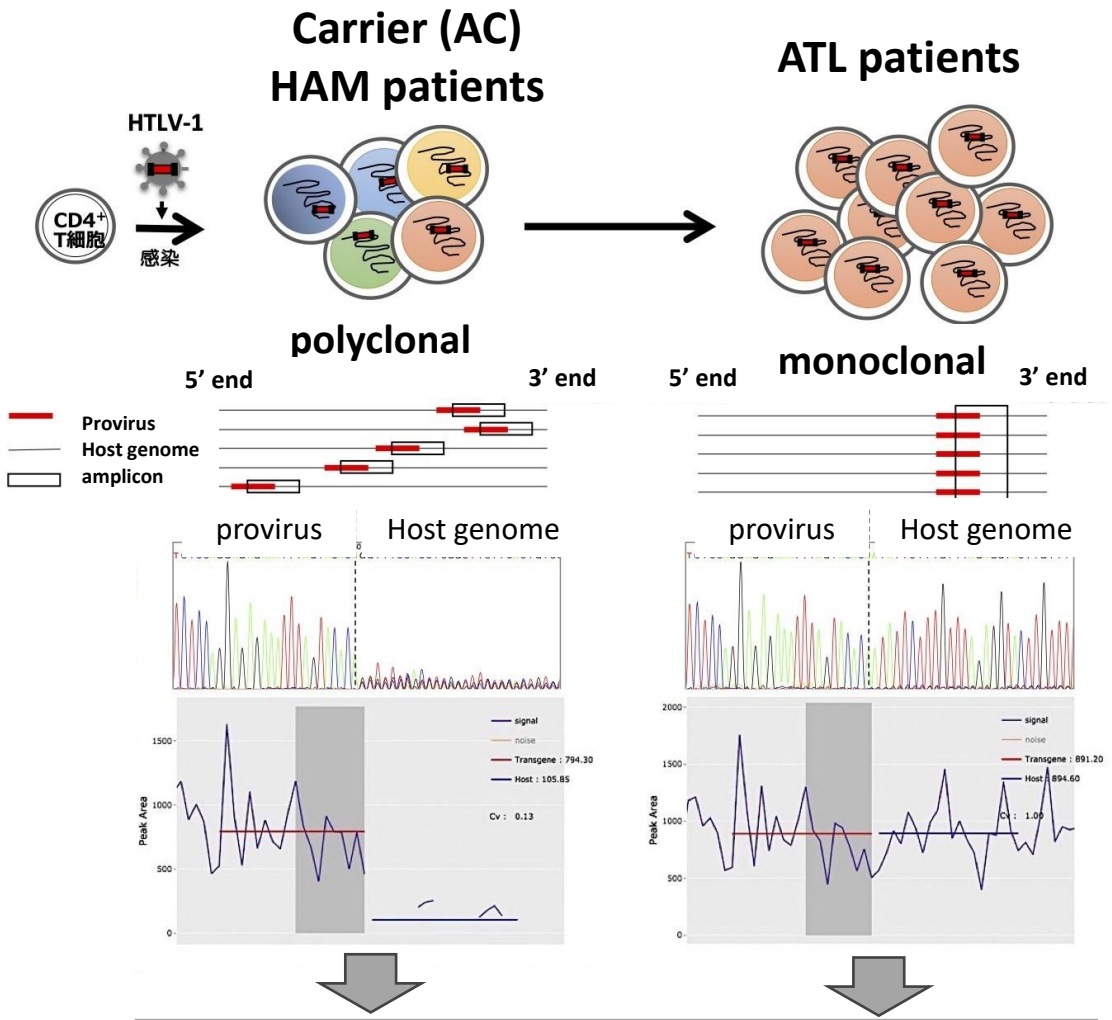
ATL –
Adult T Cell Leukemia /Lymphoma

ATL incidence in HAM/TSP patients: 3.81 per 1,000 person-years

(Nagasaka M et al, Proc Natl Acad Sci U S A. 2020)

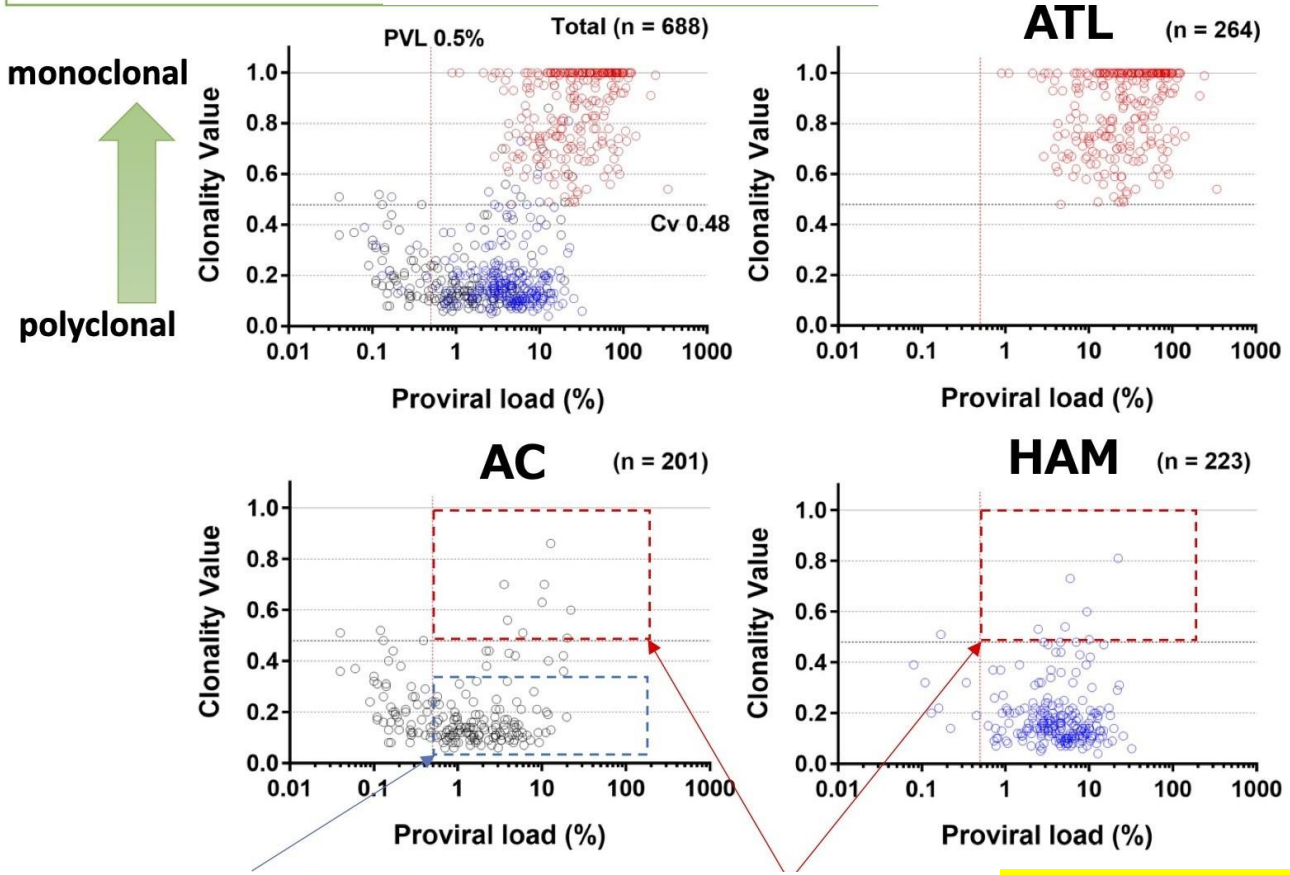
which kind of carriers and HAM patients go on to develop ATL?

The quantitative clonality analysis of HTLV-1–infected cells in AC, HAM and ATL



Quantification of the degree of clonality of HTLV-1–infected cells, expressed as the Cv (Clonality Value)

Cv (Clonality Value) Values closer to 1 indicate more monoclonal expansion



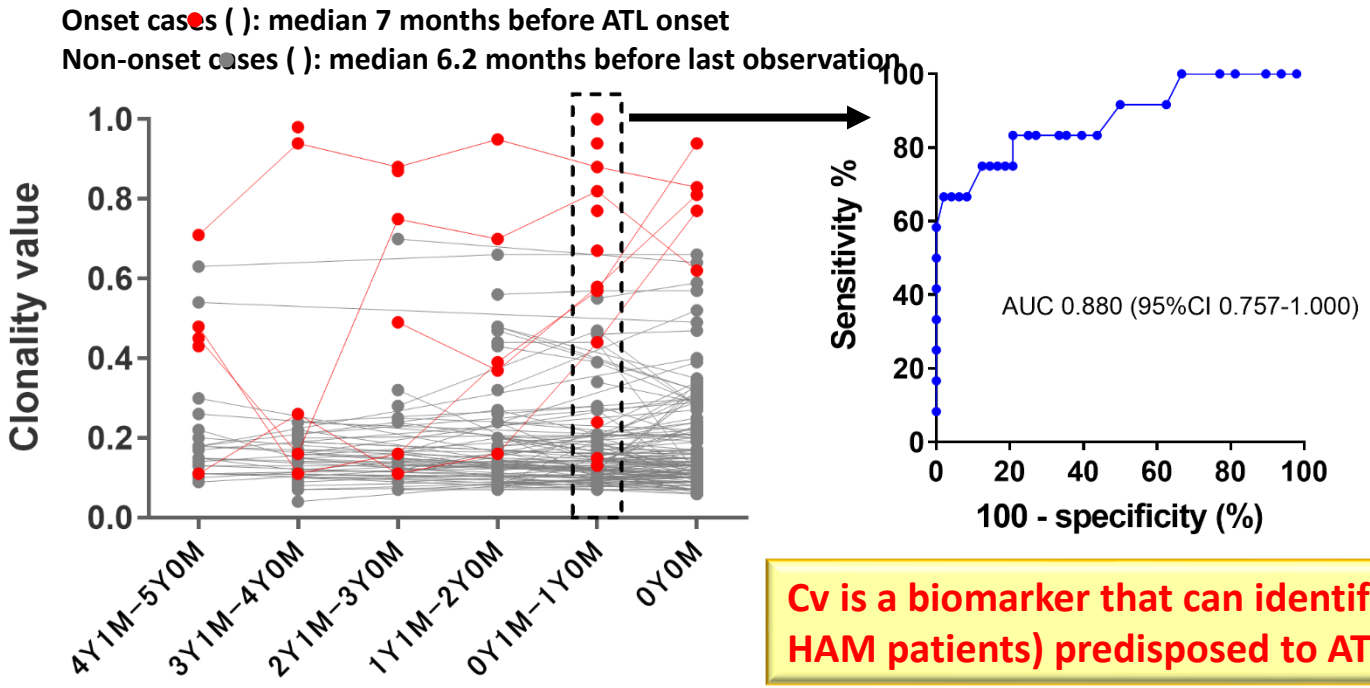
HAM high-risk group (polyclonal expansion)

ATL high-risk group (monoclonal expansion)

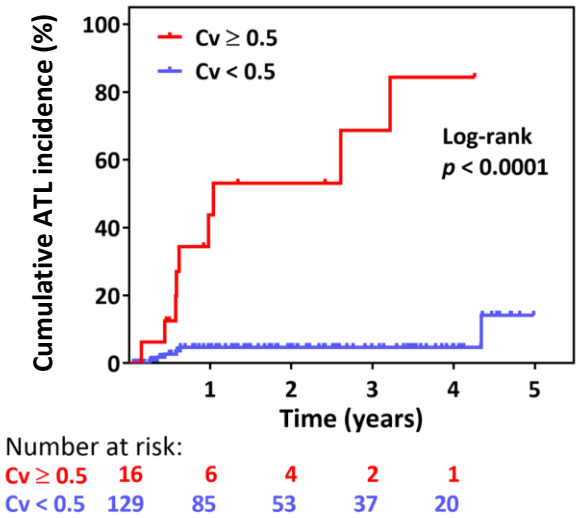
4% of HAM and HTLV-1 carriers

Wada Y and Saito M et al, Commun Biol 2022

Clonal proliferation of HTLV-1–infected cells confers a high risk of ATL onset



	AUC
Cv	0.880
PVL	0.738
sIL-2R	0.782



Cv is a biomarker that can identify carriers (including HAM patients) predisposed to ATL progression

Within the ATL high-risk group with Cv ≥ 0.5, the time for the proportion of people who developed ATL to reach 50% is 380 days

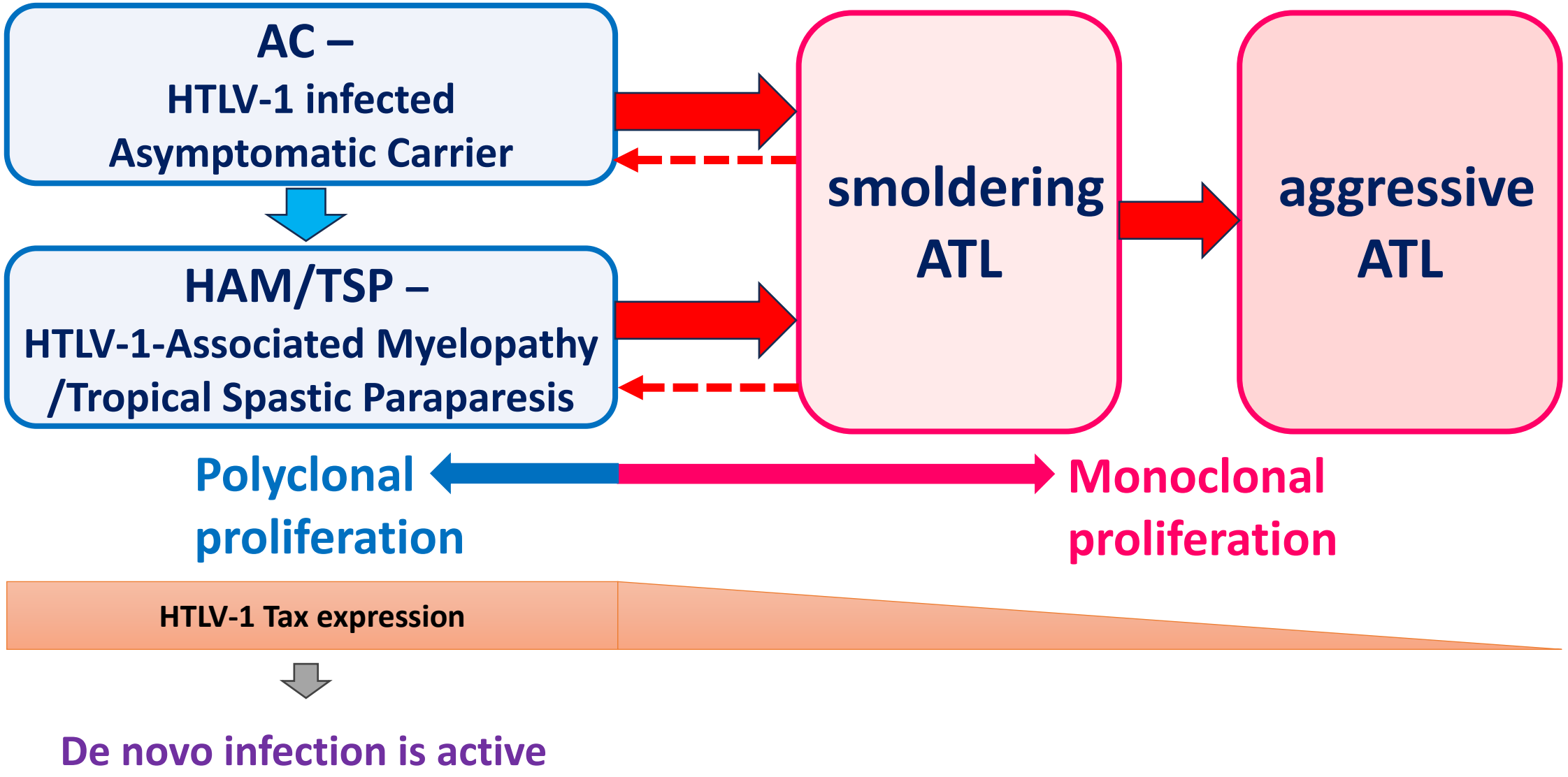
Reference criteria for classifying ATL onset risk (cut-off Cv value)

	Cv	PVL	sIL-2R		Cv	PVL	sIL-2R
Cut-off value separating the high-risk group	0.50	13.5	1260	Cut-off value separating the low-risk group	0.24	5.0	479
Sensitivity (%)	66.7	50.0	33.3	Sensitivity (%)	83.3	83.3	83.3
Specificity (%)	95.8	95.8	95.6	Specificity (%)	79.2	43.8	51.1

Carriers and HAM patients in whom HTLV-1–infected cells proliferate monoclonally have a high risk of ATL onset

(Wada Y and Saito M et al., Commun Biol 2022)

Virological differences in HTLV-1–infected cells between AC, HAM and ATL



Virological differences in HTLV-1–infected cells between AC, HAM and ATL

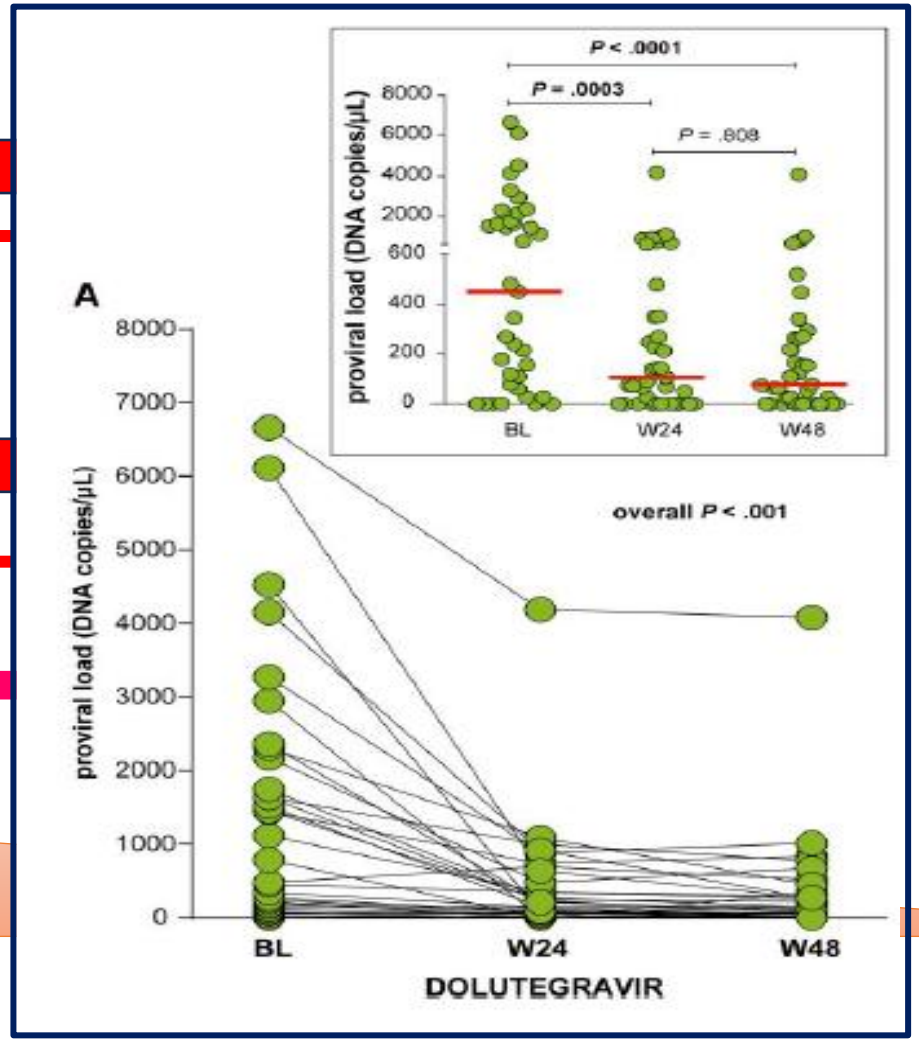
AC –
HTLV-1 infected
Asymptomatic Carrier

HAM/TSP –
HTLV-1-Associated Myelopathy
/Tropical Spastic Paraparesis

Polyclonal proliferation

HTLV-1 Tax expression

De novo infection is active

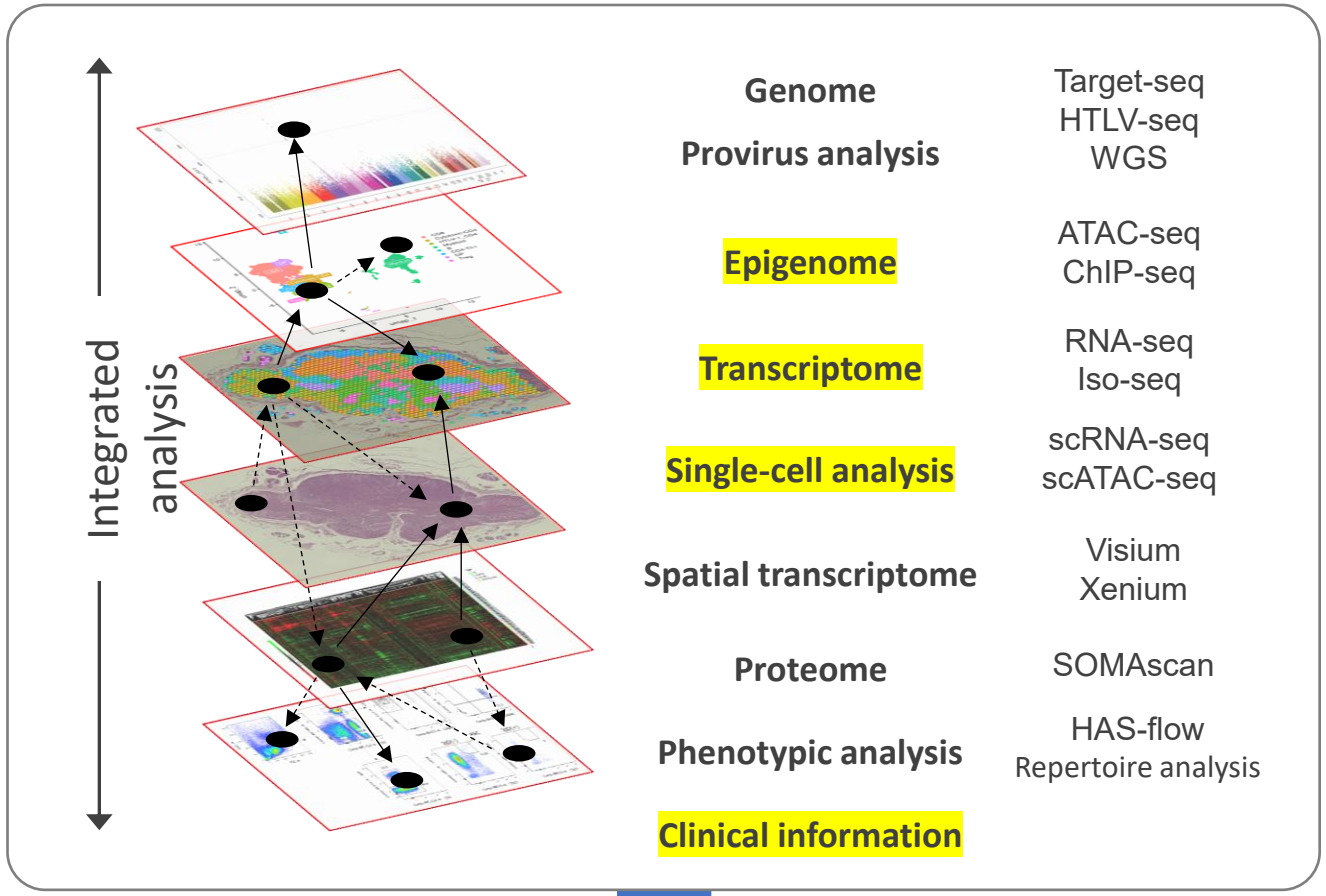


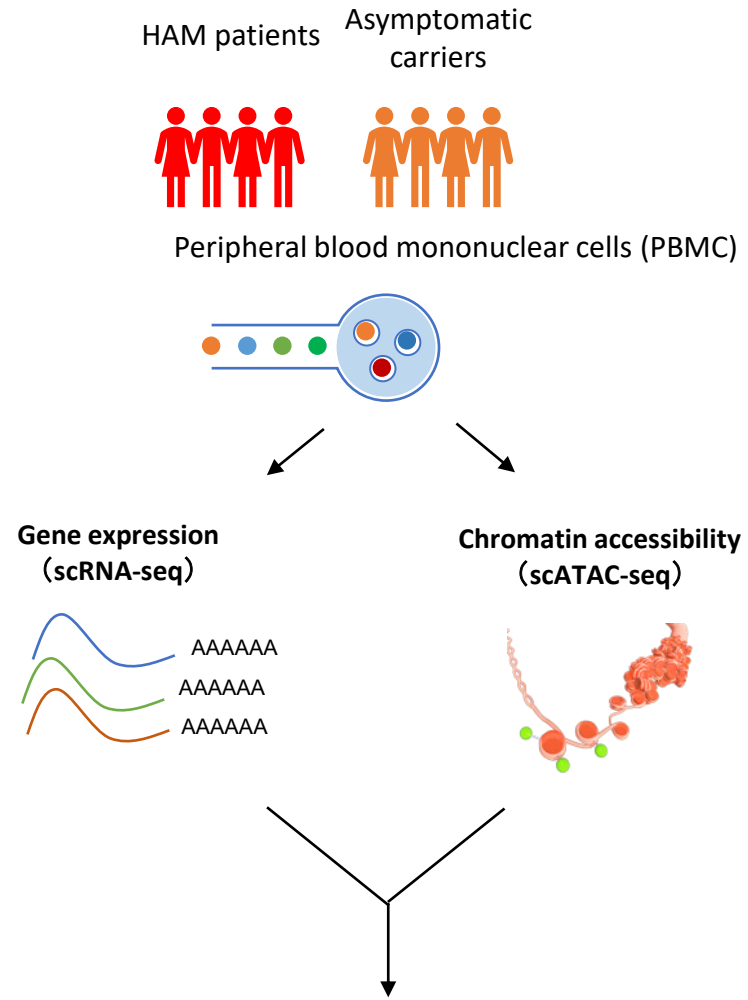
Dolutegravir reduced Proviral Load in HAM/TSP patients

(C Brites et al. Clinical Infectious Diseases, 2026)

Elucidation of pathogenesis and development of novel therapies through multi-omics analysis

HTLV-1–associated myelopathy (HAM)

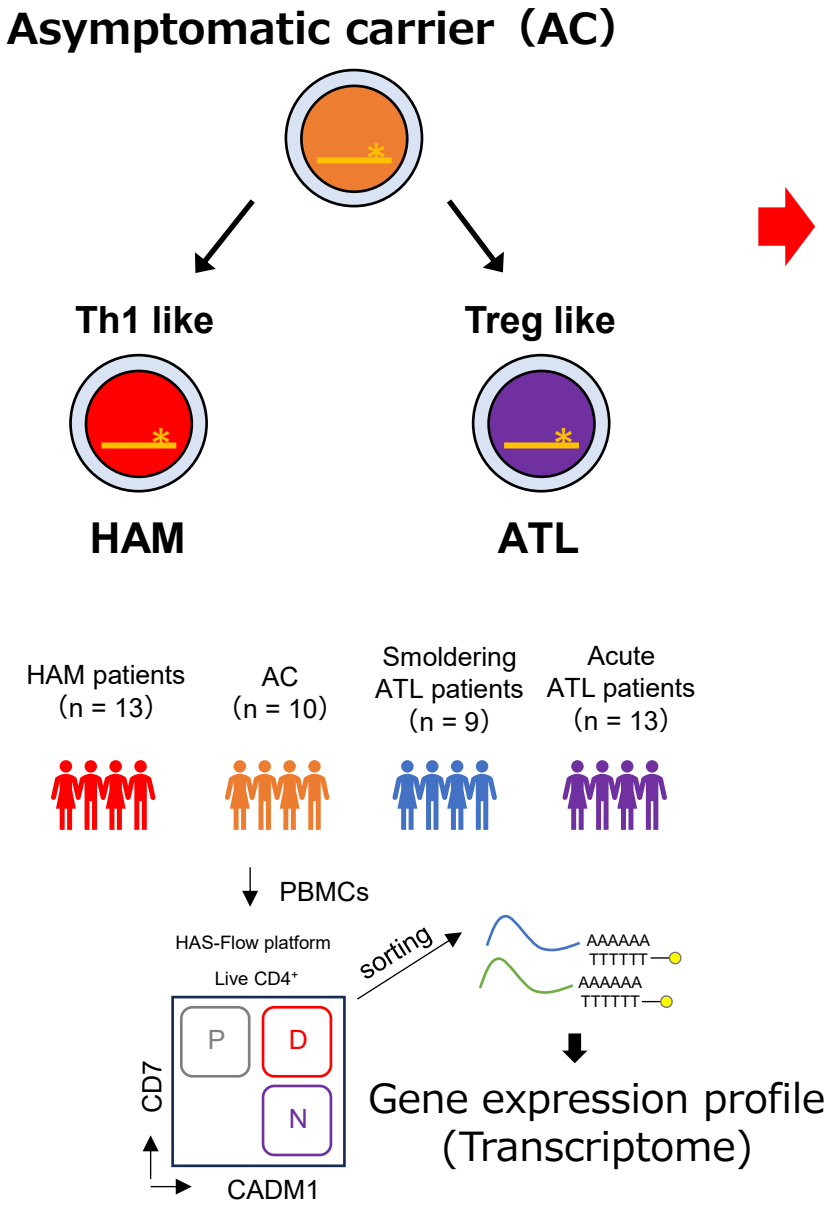


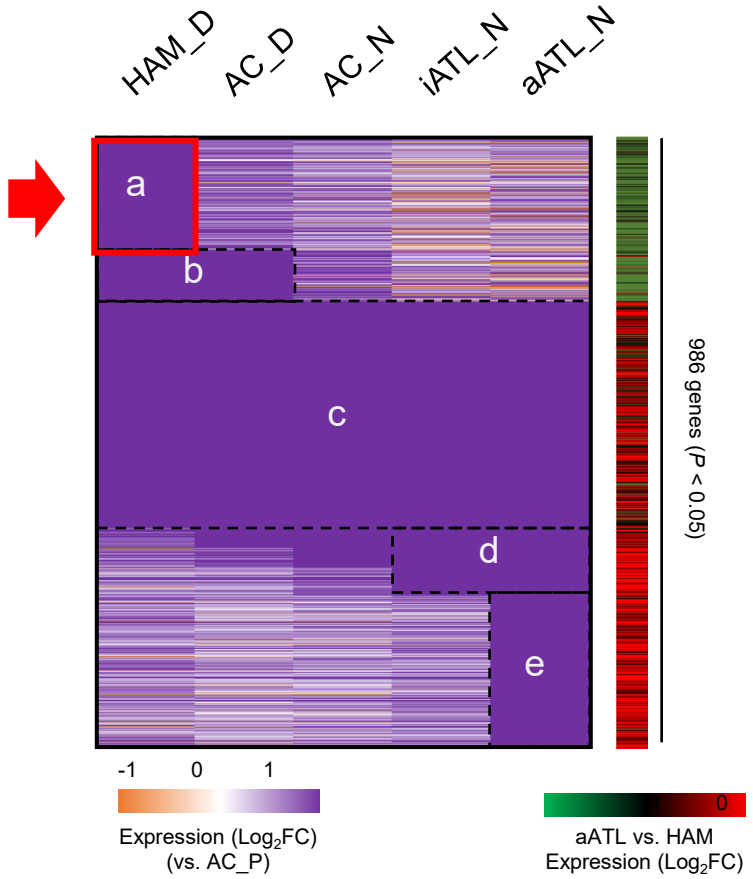


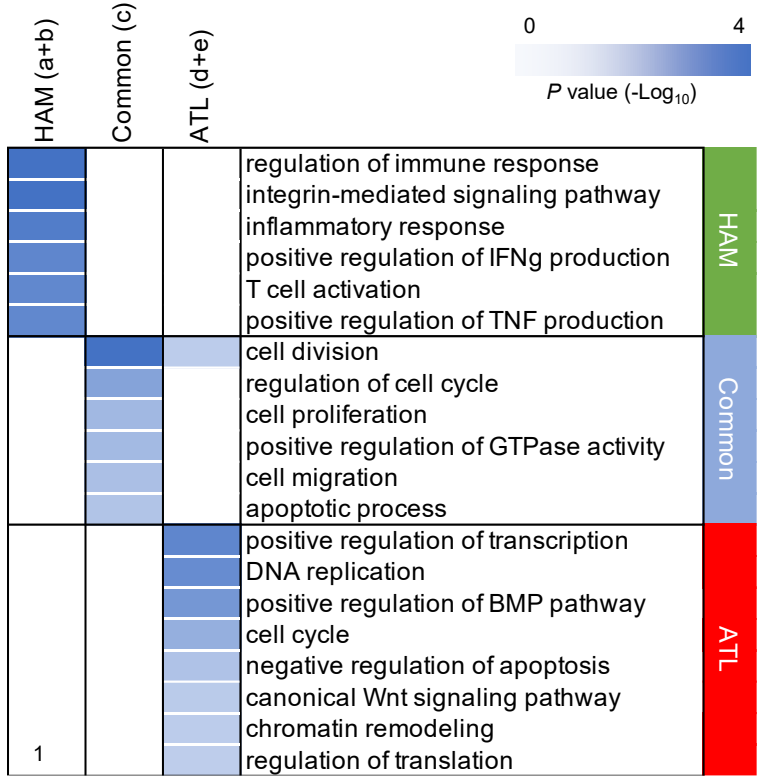
Single-cell multiome analysis
(scRNA-seq+scATAC-seq)

Development of novel therapies targeting causative genes

HAM-Specific Gene Expression Profile



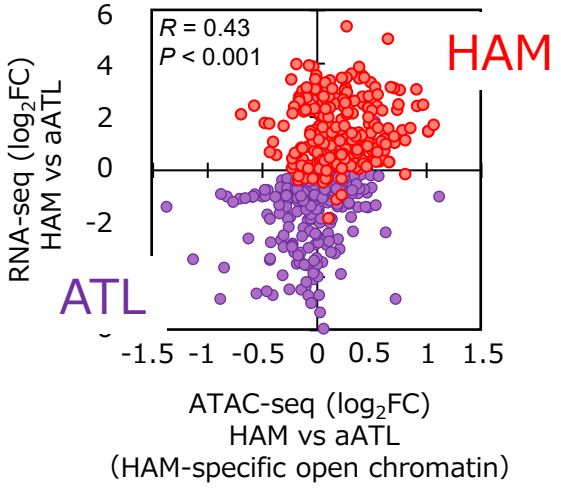


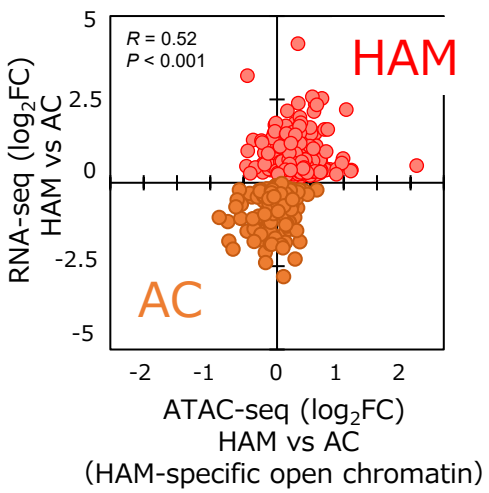


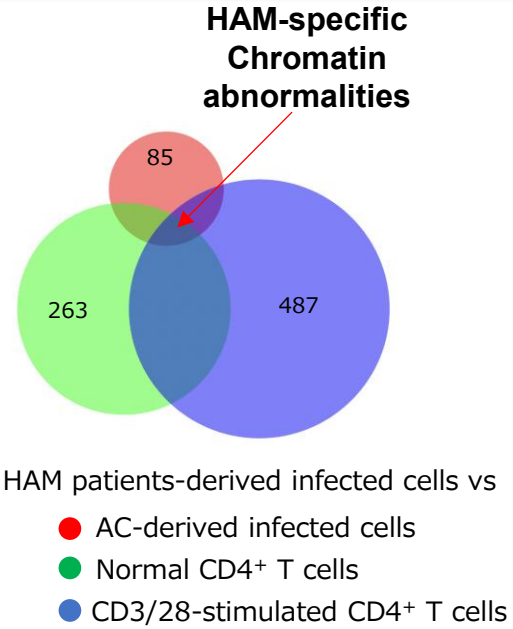
Among the genes specifically overexpressed in infected cells from HAM patients, it is considered that important genes defining the inflammatory pathology are included.

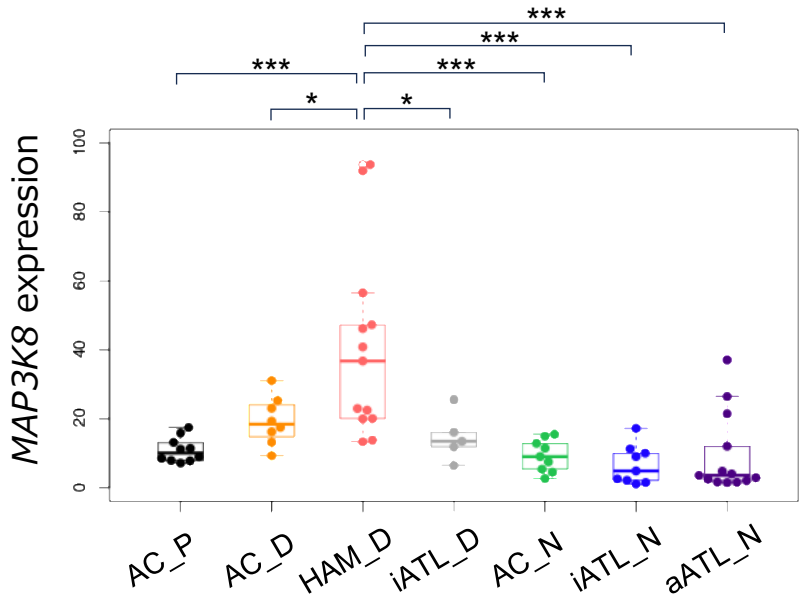
Nakashima M et al., Nat Commun 2025.

HAM-Specific Overexpression of *MAP3K8* and Chromatin Abnormalities



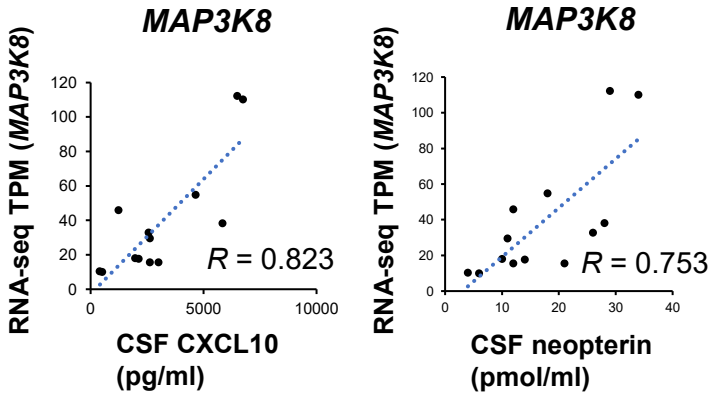




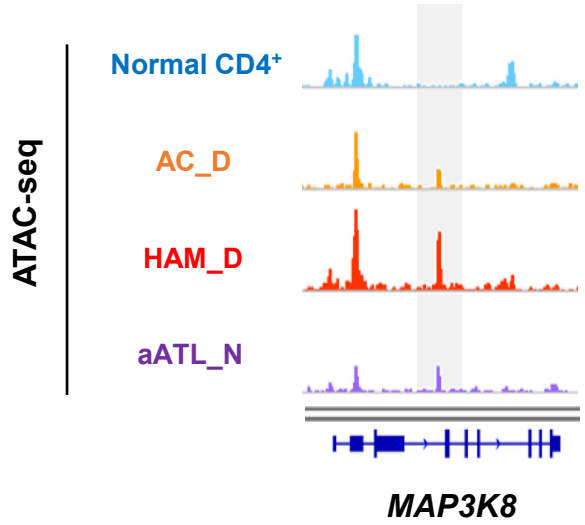


	CXCL10	Neopterin
MAP3K8	0.823	0.753
ENSA	0.823	0.753
CCDC97	0.707	0.552
GMPR	0.689	0.486
GNA15	0.498	0.550
ABCG1	0.437	0.387
SLC7A5	0.266	0.115
NUGGC	-0.296	-0.034

−1 1
Correlation efficient



HAM-specific open chromatin



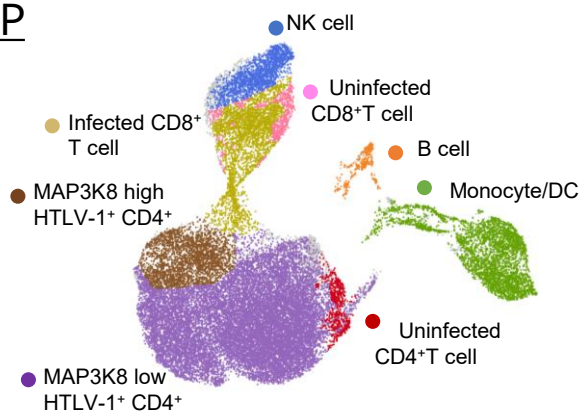
➢ The expression of *MAP3K8* is associated with inflammatory pathology of HAM

Nakashima M et al., Nat Commun *2025*

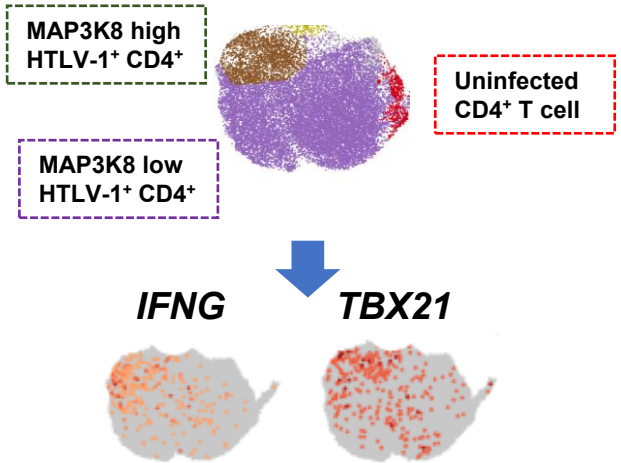
Characteristics of *MAP3K8*-high-Expressing Infected Cells

Single-cell GEX + ATAC analysis
(31,633 cells)
(HAM patients PBMC + infected cells)

UMAP



CD4⁺ T cells

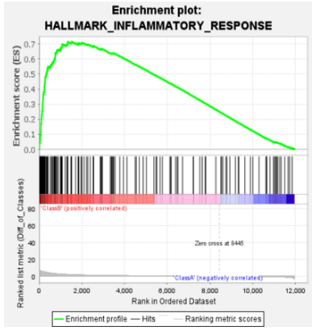


GSEA (*MAP3K8* high vs low)

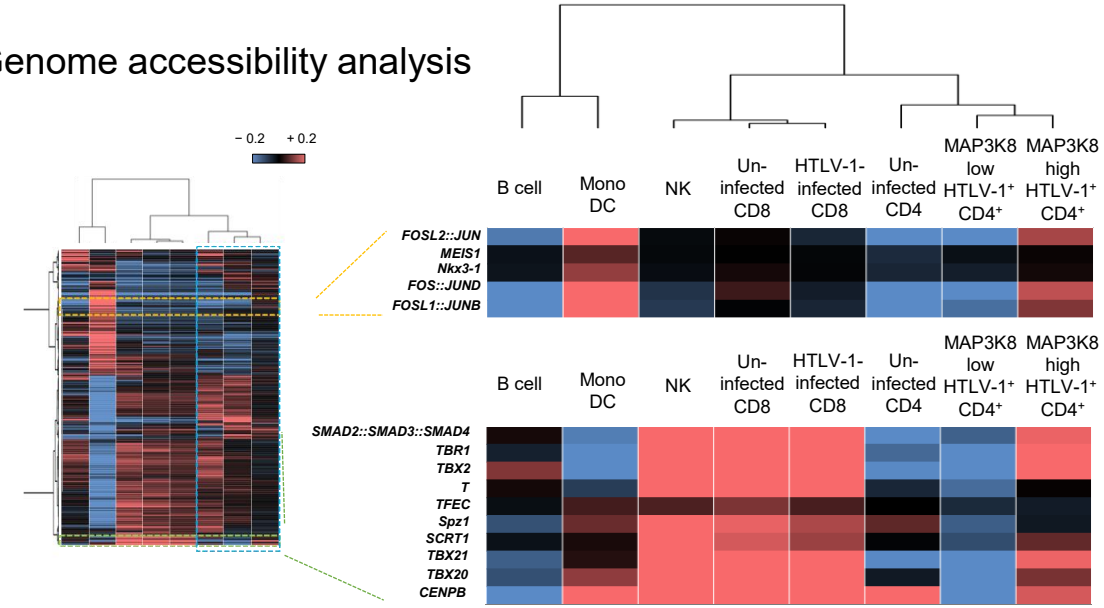
Inflammatory response

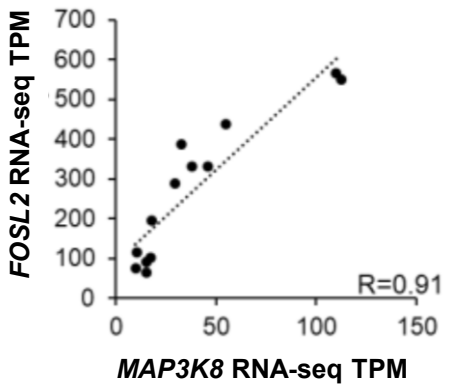
(Nominal $p < 0.05$)

NAME	NES
HALLMARK_INFLAMMATORY_RESPONSE	1.677
HALLMARK_IL6_JAK_STAT3_SIGNALING	1.600
HALLMARK_TNFA_SIGNALING_VIA_NFKB	1.590
HALLMARK_COMPLEMENT	1.550
HALLMARK_KRAS_SIGNALING_UP	1.548
HALLMARK_ANGIOGENESIS	1.535



Genome accessibility analysis





Fosl2

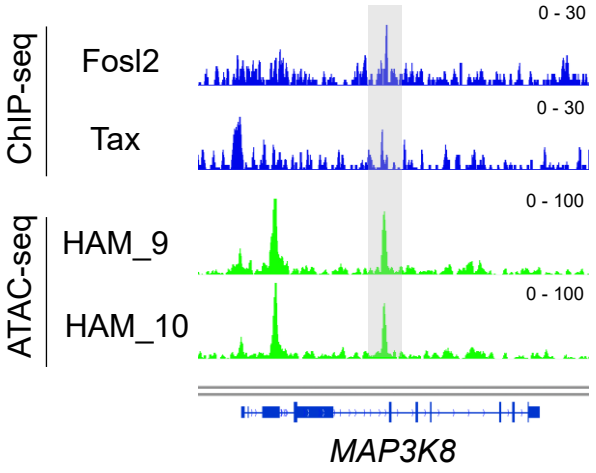
Fosl2 : a transcription factor
Forms heterodimers and functions as AP-1.

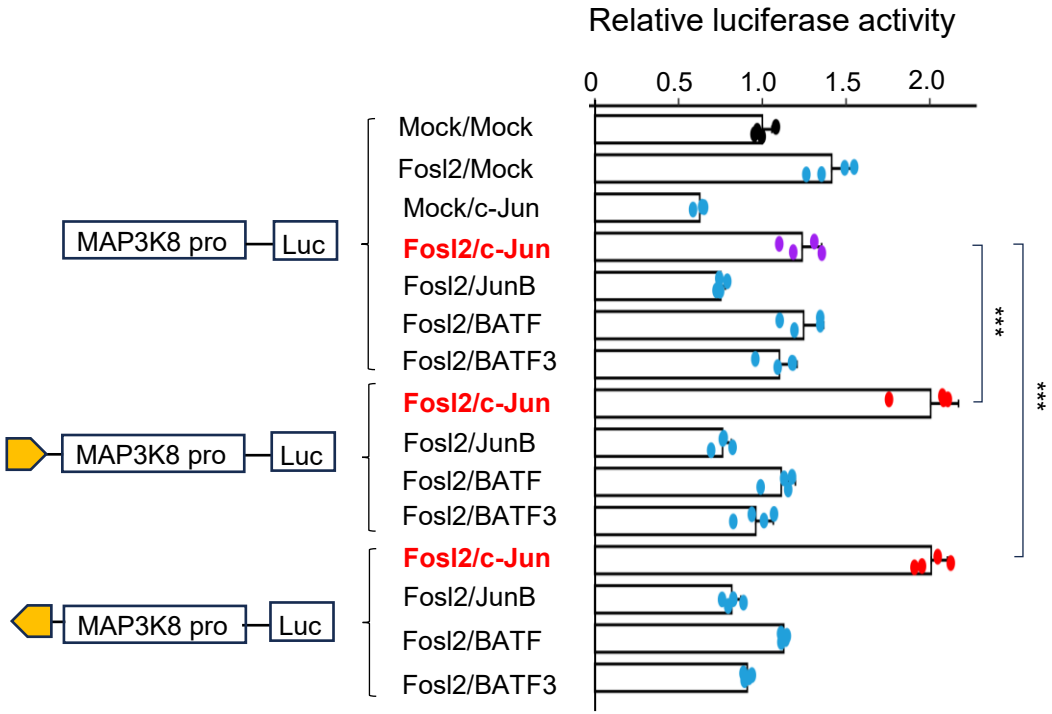
The expression of *MAP3K8* may be regulated by The transcription factor Fosl2.

Nakashima M et al., Nat Commun *2025*

Chromatin Remodeling at the *MAP3K8* Locus Specific to HAM

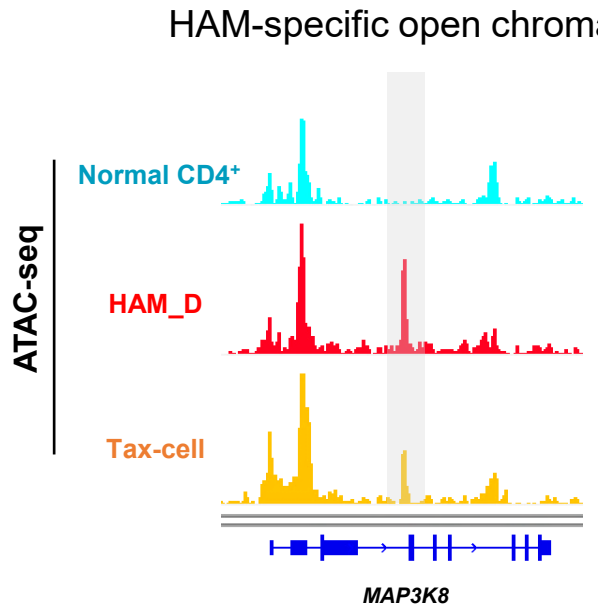
HAM-specific open chromatin



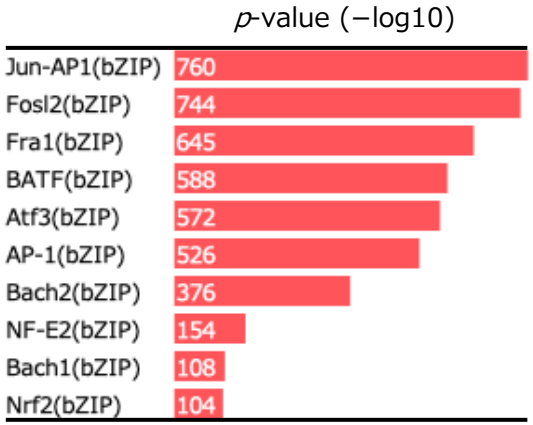


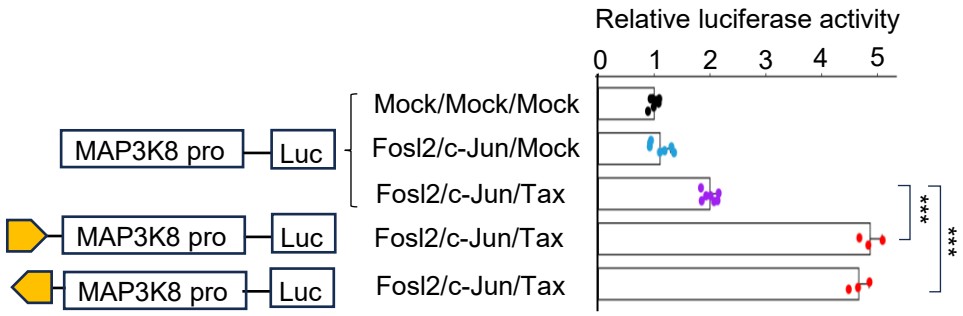
CD4⁺ T cells + Lentiviral vector

(Tax transduction : Tax-cell)



Fosl2 ChIP-seq (motif analysis)



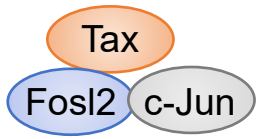


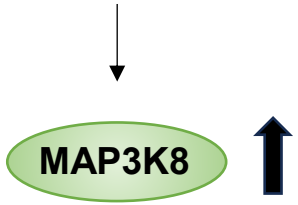
Chromatin remodeling of the HAM-specific enhancer region by Tax

: HAM-specific open chromatin region (457 bp)

Nakashima M et al., Nat Commun *2025*

Suppression of HTLV-1–infected Cell Proliferation by MEK inhibitors

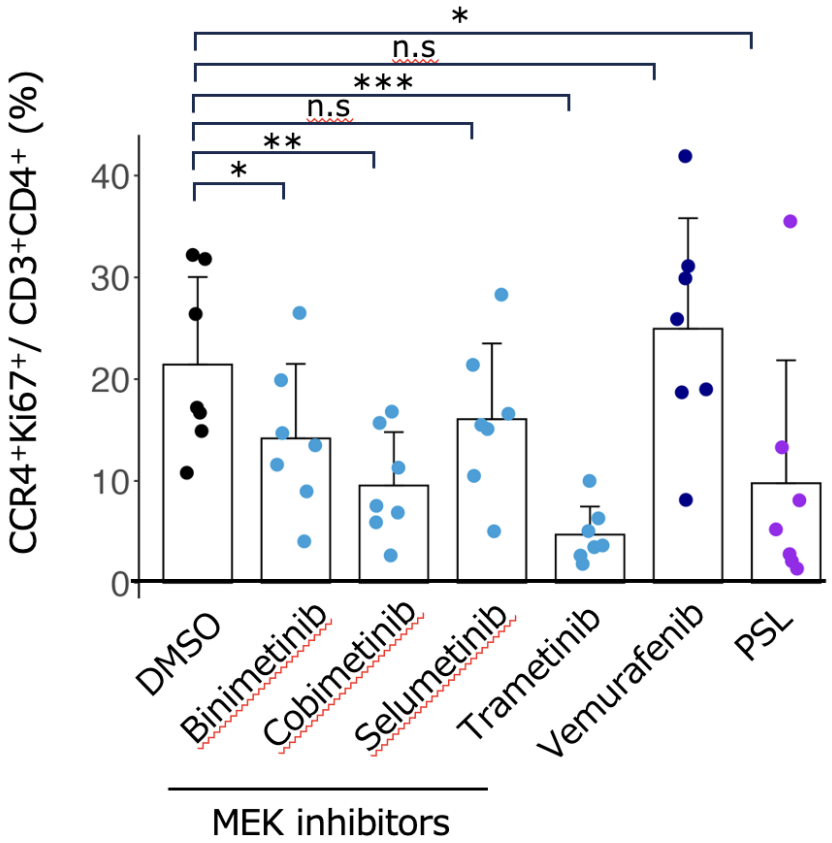


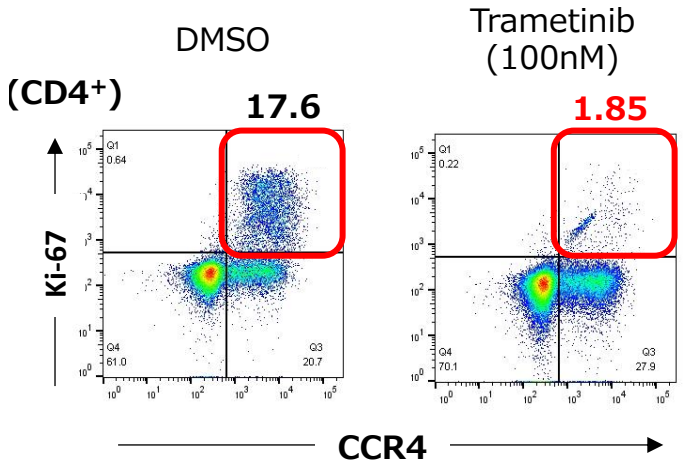


MEK inhibitors
- Trametinib
- Binimetinib
- Cobimetinib
- Selumetinib

- **Th1 differentiation induction**
- **Upregulation of inflammation-related gene**
- **Excessive IFN-γ production**

HAM patient PBMC
***ex vivo* culture model**

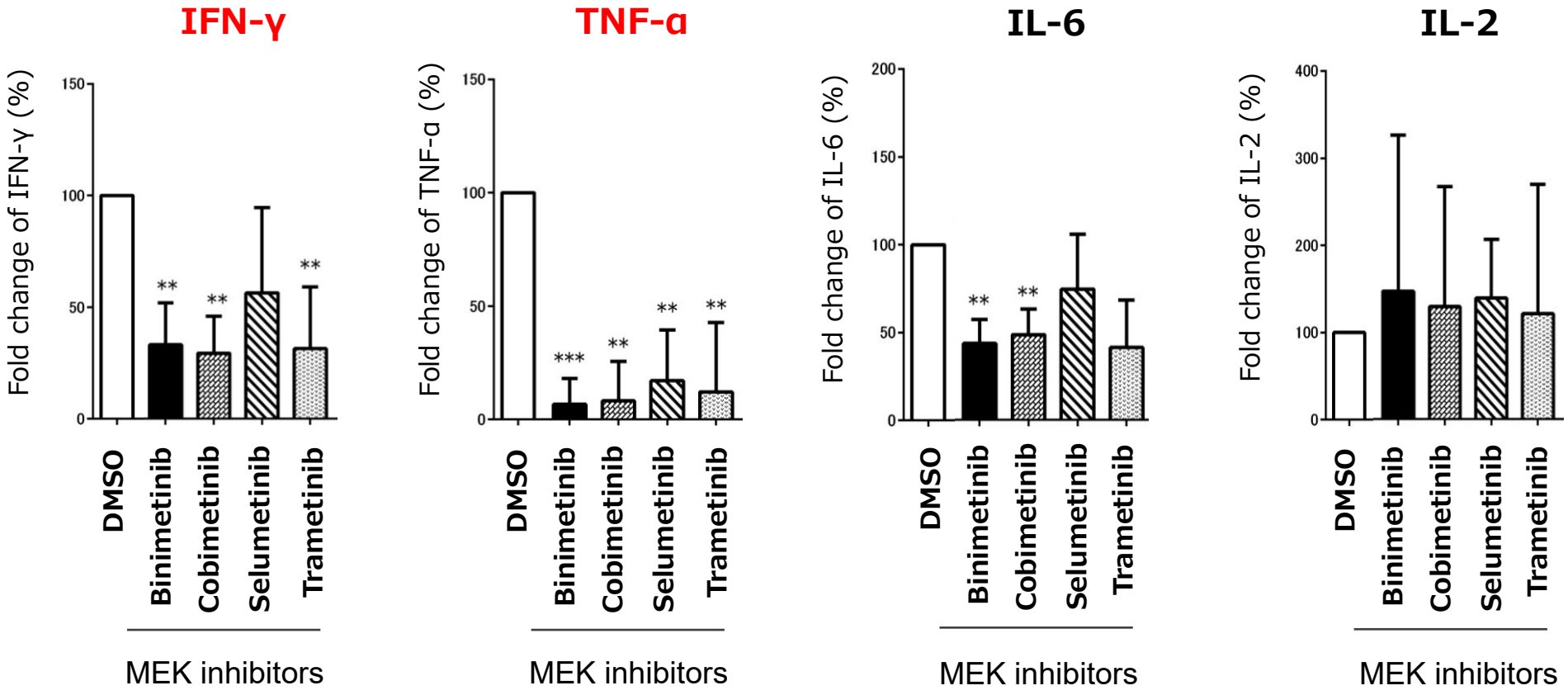




Nakashima M et al., Nat Commun *2025*

Inhibitory Effects of MEK Inhibitors on the Production of Inflammatory Cytokines

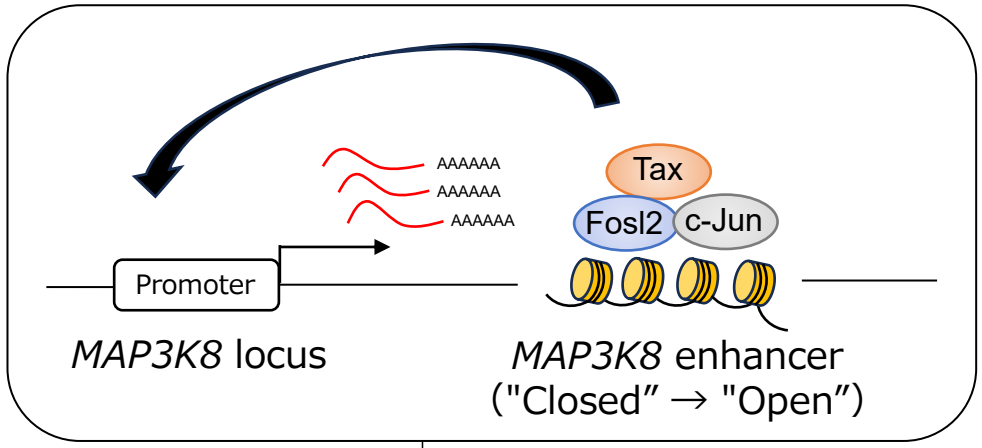
HAM patient PBMC
***ex vivo* culture model**
supernatant



*P < 0.05, **P < 0.01

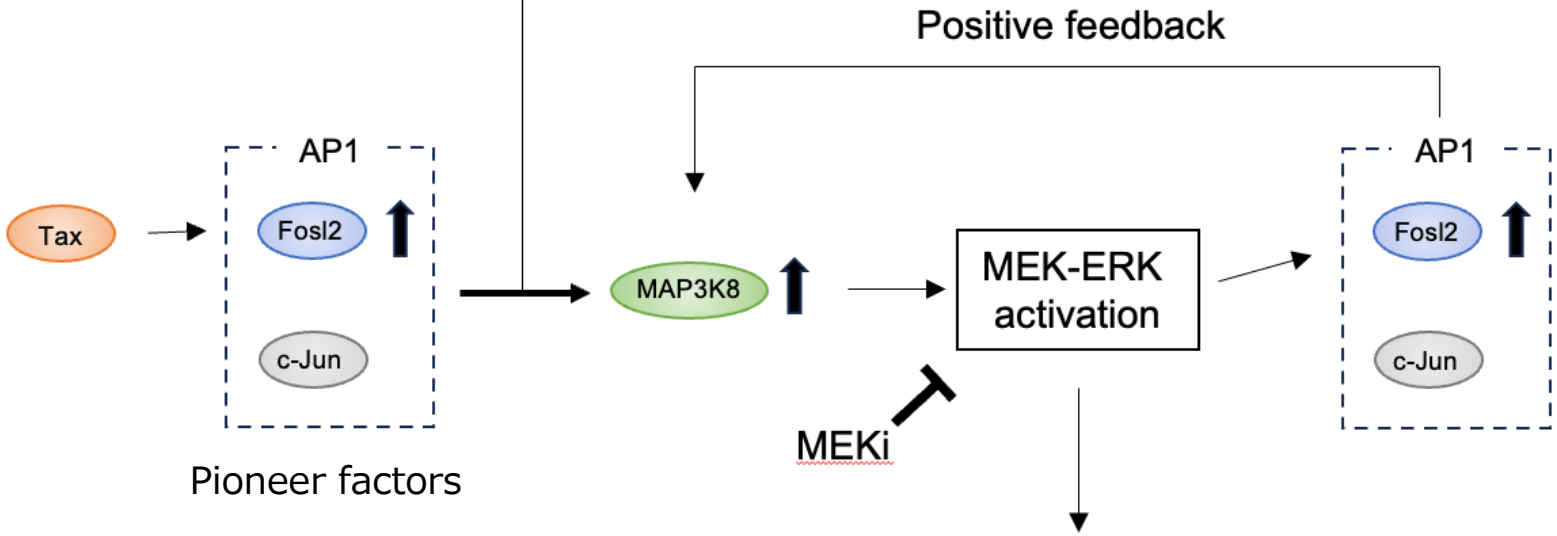
Nakashima M et al., Nat Commun *2025*

HAM-Specific Mechanism of *MAP3K8* Overexpression Mediated by HTLV-1 Tax



➢ Through the cooperative interaction between viral and host factors, disease-specific chromatin remodeling occurs, leading to the aberrant overexpression of pro-inflammatory genes

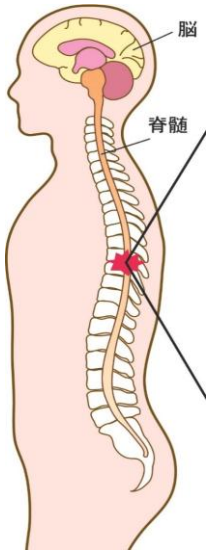
➢ Based on the molecular basis of HAM, MEK inhibitors identified in this study are expected to contribute to the development of innovative therapeutic strategies.



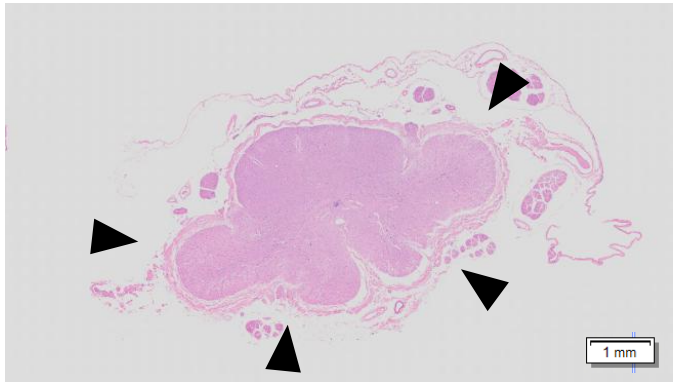
➢ Induction of Th1 differentiation
➢ Upregulation of inflammation-related genes
➢ Excessive IFN-γ production

Nakashima M et al., Nat Commun *2025*

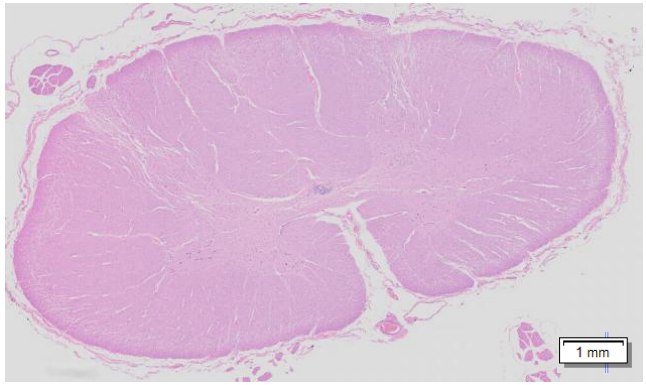
Analysis of HAM Spinal Cord Reveals the Core of the Pathophysiology



HAM : Spinal Cord lesion



Healthy Donor : Spinal Cord



Pathological findings to Date

- ➢ Inflammatory cell infiltration around small vessels
- ➢ HTLV-1 infection in infiltrating T cells
- ➢ No evidence of HTLV-1 infection in spinal cord tissue
- ➢ Tax-specific CTLs are detected in HAM spinal cord lesions

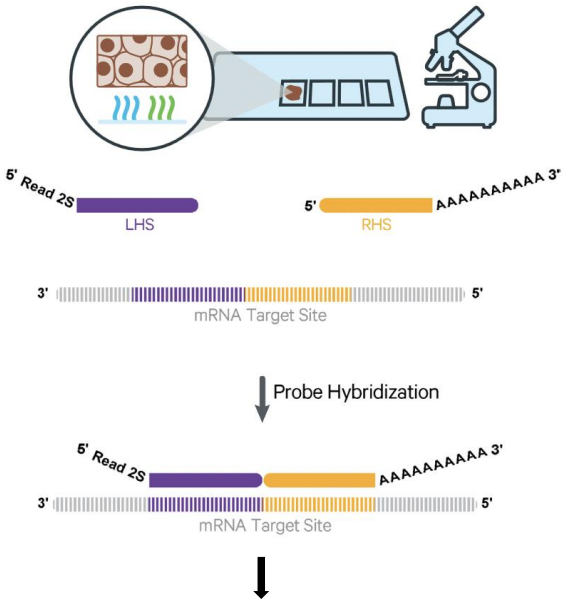
} Increased cellular immunity contributes to spinal cord inflammation.

- ➢ In the chronic phase, gliosis progresses and regression of the thoracic spinal cord (anterior and lateral cords) is predominant

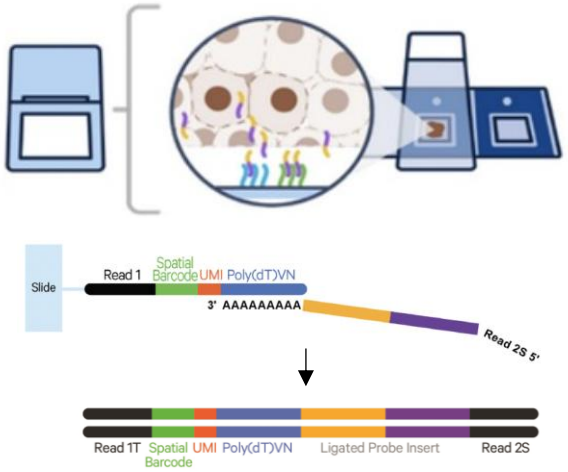
Limitation:
Comprehensive gene expression analysis of spinal cord lesions had been difficult.
The molecular basis of inflammatory lesions is unknown, making it difficult to develop therapeutic strategies.

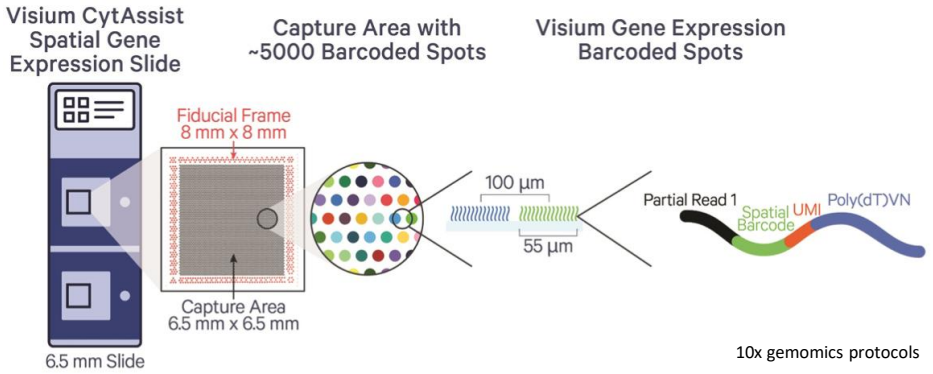
Spatial transcriptome analysis（Visium CytAssist）

The platform by Visium CytAssist



Probe ligation/mRNA digestion





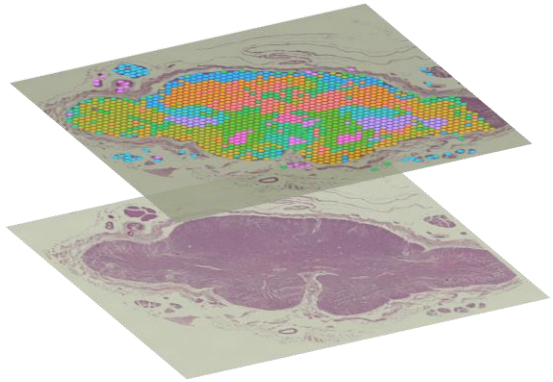
1. Spot: Poly dT with molecular barcode is placed. The position information on the slice is added to the probe.
2. The spots are 55 µm in diameter, so the resolution averages 5 to 10 cells per Spot.
3. By sequencing with NGS, total gene expression data can be obtained per each Spot.

HAM patients

(N=3, 5 regions)

Healthy donor

(N=1, a region)



Gene expression profiles were obtained for the entire sectioned region of the spinal cord.

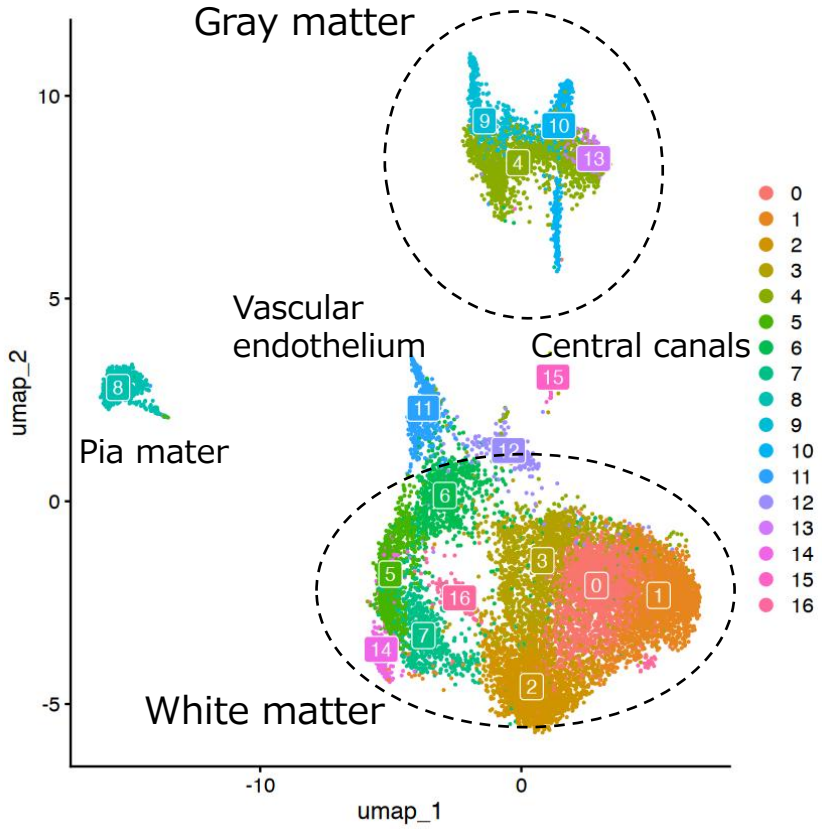
Spatial transcriptome analysis of HAM spinal cord lesions

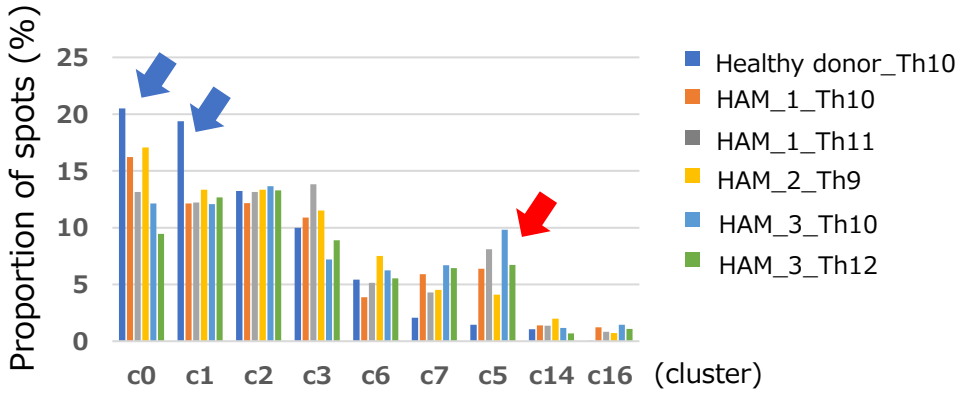
UMAP clustering

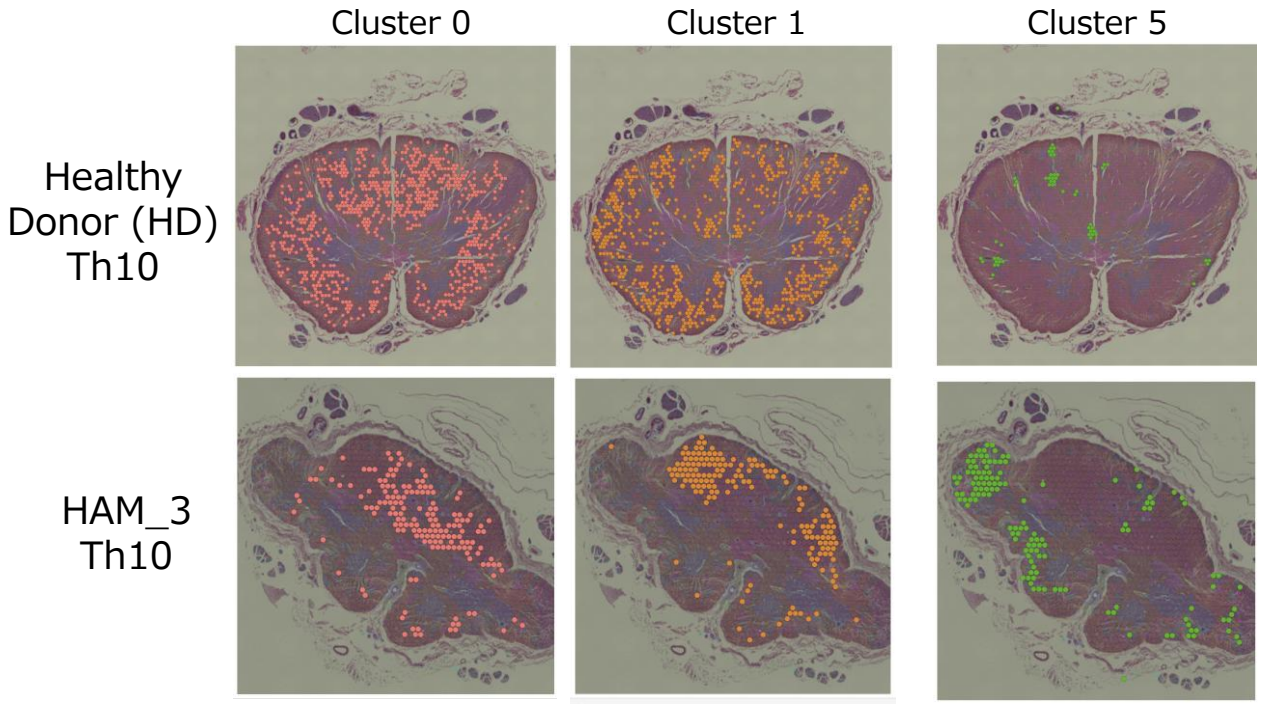
⬇

Classify each cluster based on spatial distribution information

HAM patients (5 regions) and one healthy donor (one regions)
: 15484 spots



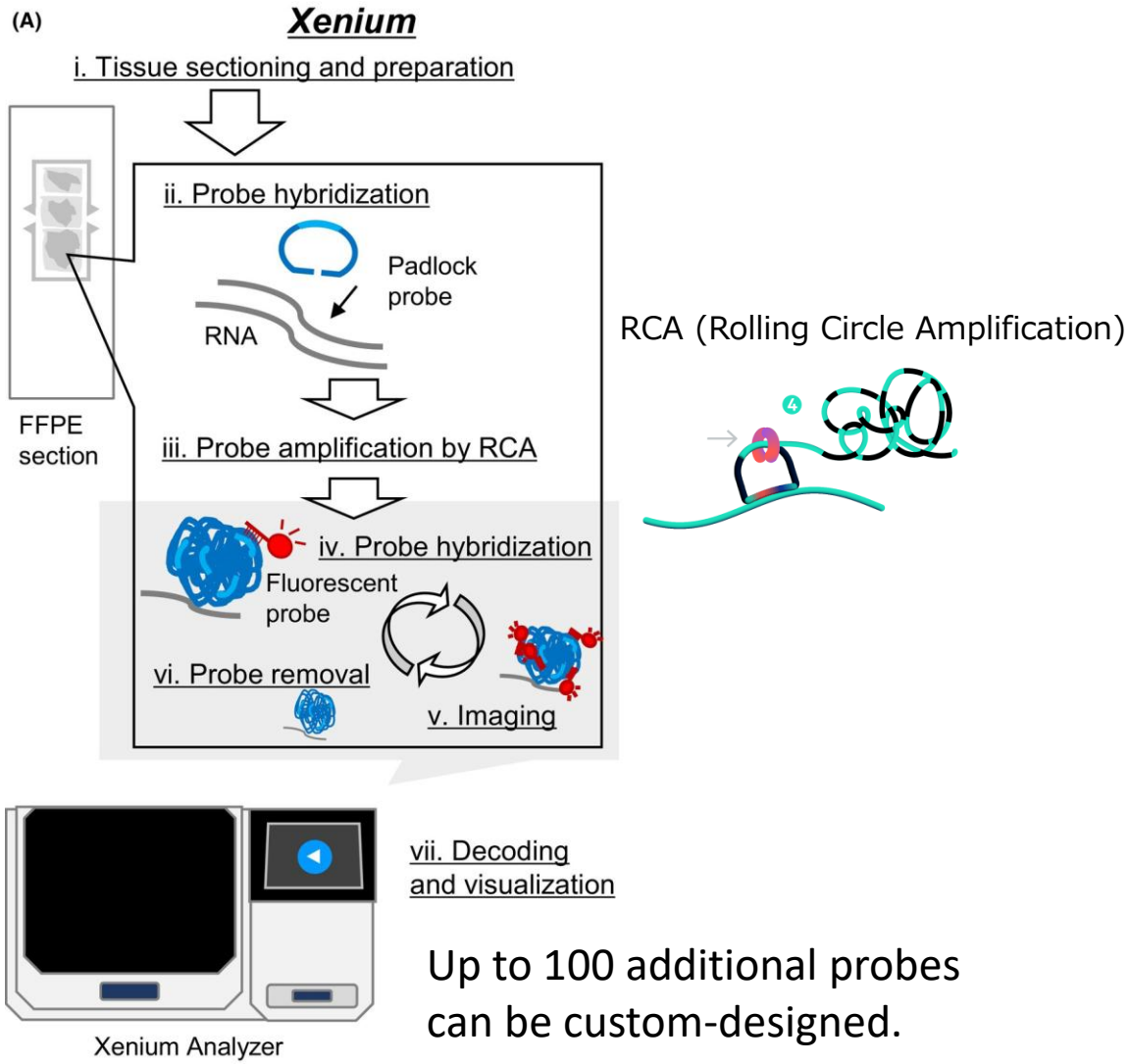




➢ **Clusters 0 and 1 distributed throughout the white matter in HD**
Cluster 5 predominates in the anterior and lateral cords of HAM patients

Single-cell spatial transcriptomic analysis (Xenium)

Xenium platform (in situ hybridization with 5,000 probes)

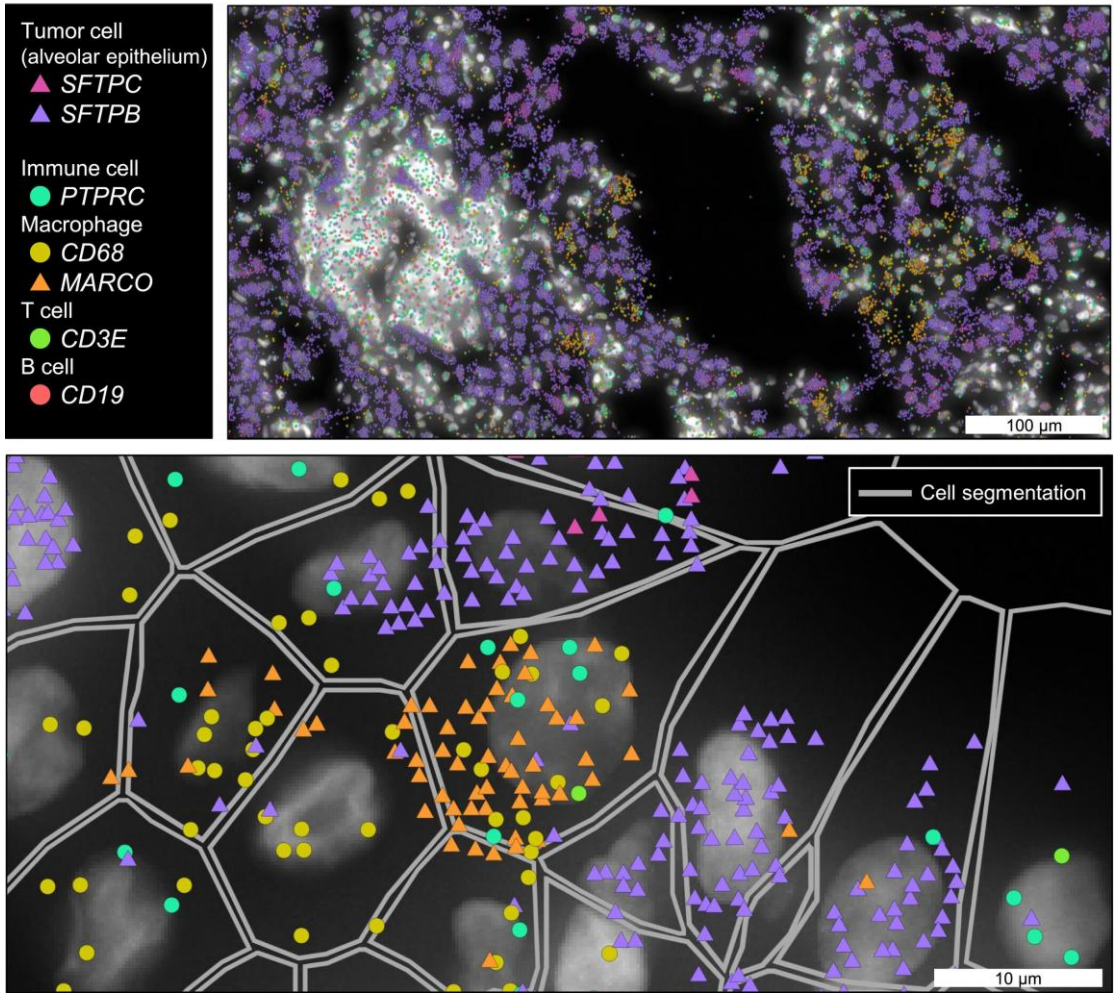


RCA (Rolling Circle Amplification)

Up to 100 additional probes can be custom-designed.

Xenium analysis: lung adenocarcinoma

Lung adenocarcinoma (Noguchi type B; Adenocarcinoma *in situ*)



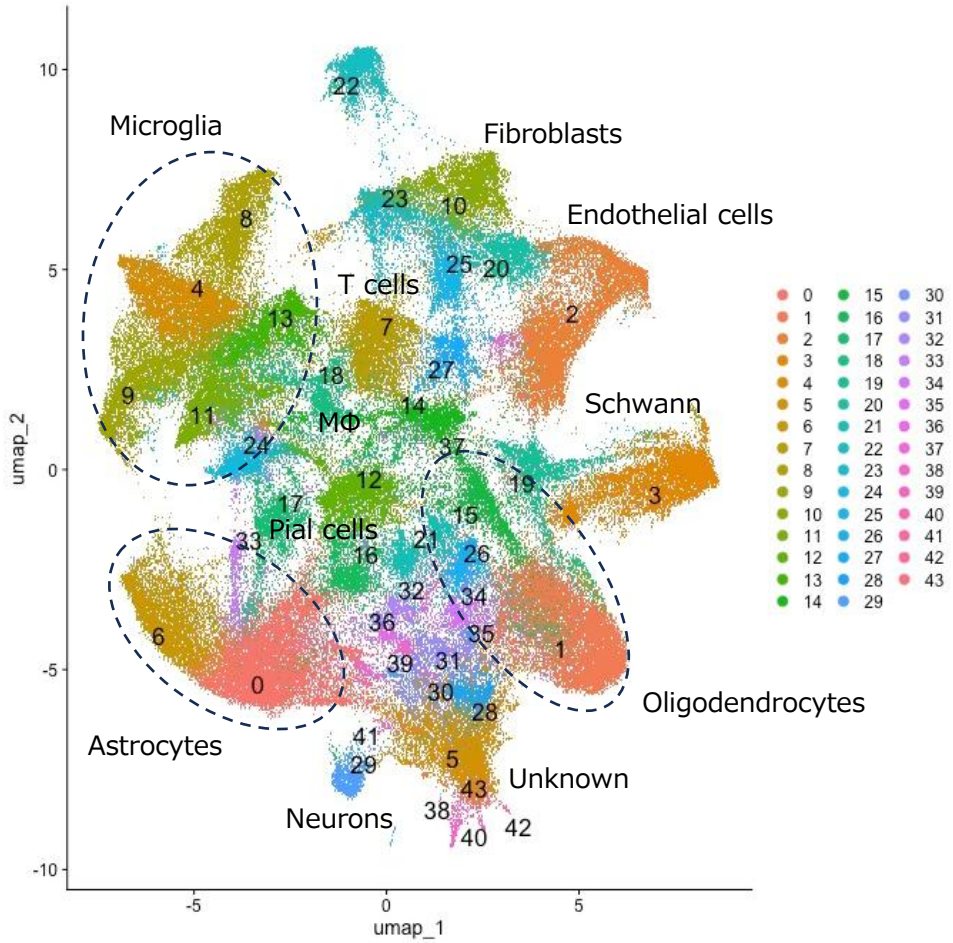
Visualization of the spatial distribution and abundance of mRNA at the single-cell level

Nagasawa S et al., Cancer Sci 2024

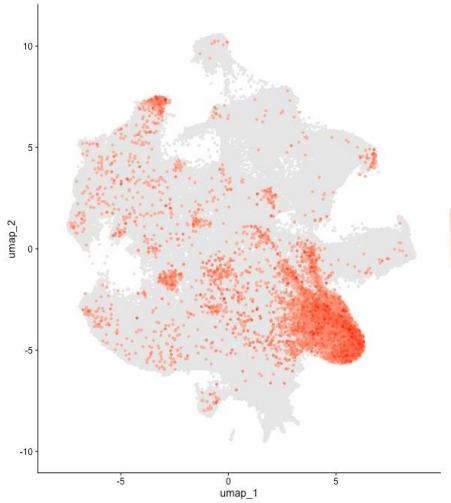
Clustering by UMAP (Xenium)

Three HAM cases and one healthy control

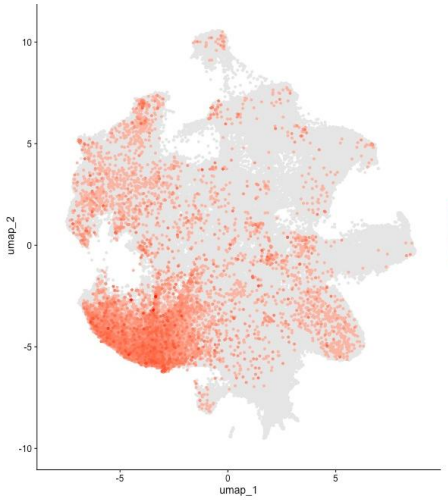
Integrated analysis（162,499 cells）



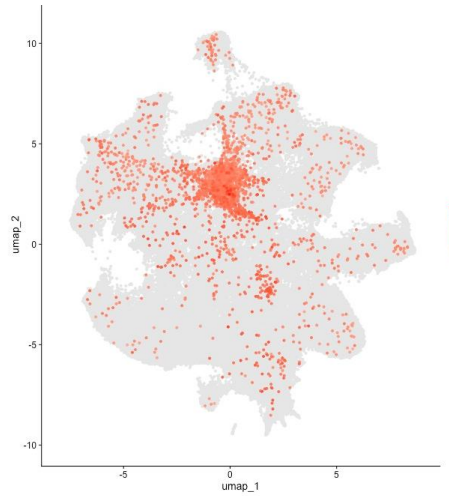
***MOG* (Oligodendrocyte)**



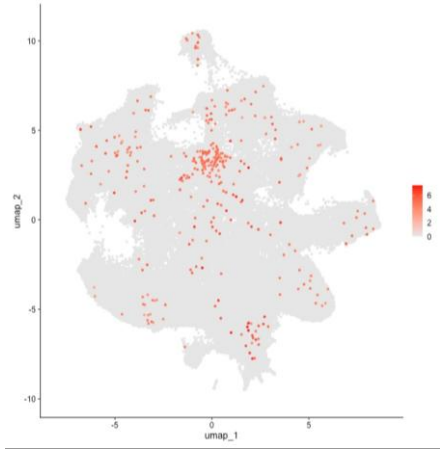
***AQP4* (Astrocyte)**



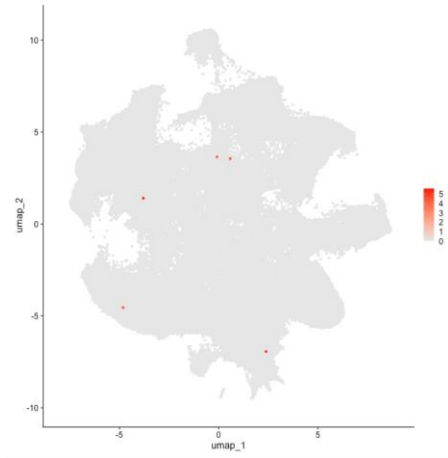
***CD3E* (T cell)**



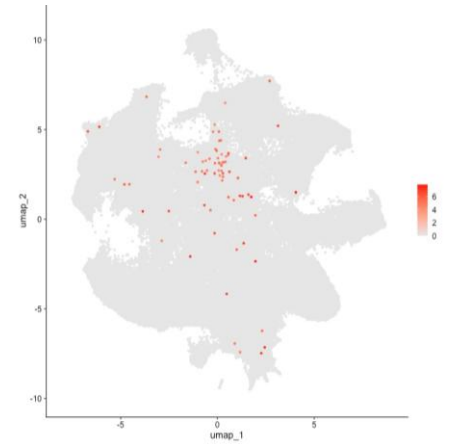
CCR4



tax 701-900

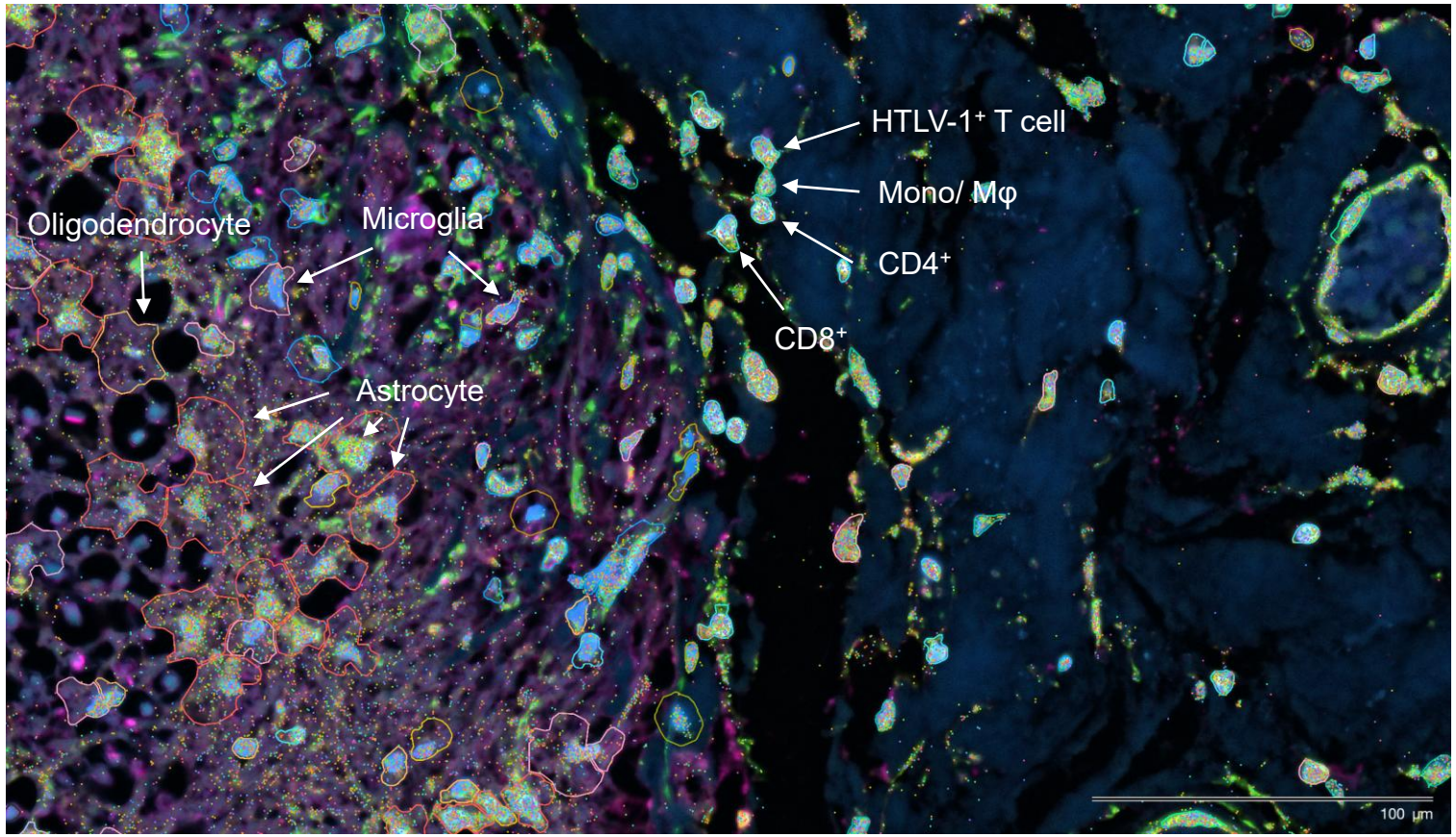


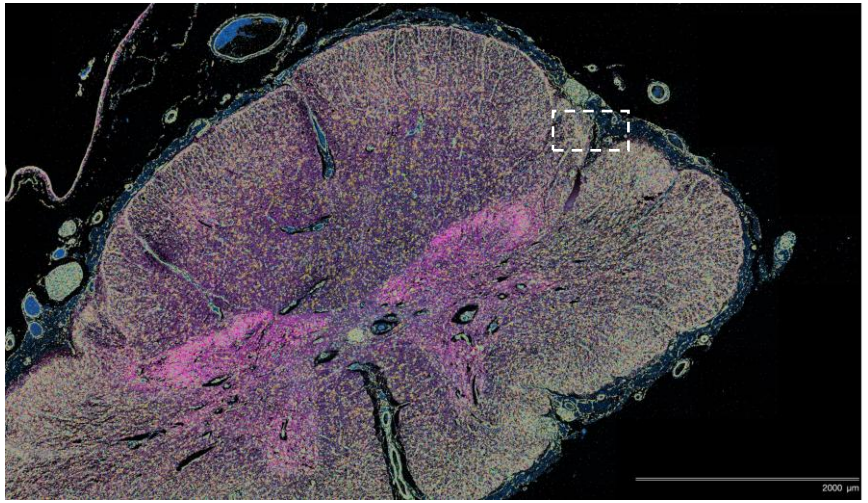
hbz 1372-1571



Spatial Distribution of Various Cell Types in HAM Spinal Cord Lesions

HAM patients: Thoracic spinal cord, lateral column regions, and subpial areas





Take home message

- In HAM patients, HTLV-1–infected cells are characterized by polyclonal proliferation and Tax expression, suggesting the presence of de novo infection.
- The reduction in PVL by dolutegravir in HAM patients demonstrated that de novo infection is active.
- In HTLV-1–infected cells of HAM patients, Tax induces characteristic chromatin abnormalities, and the upregulation of MAP3K8 confers a pro-inflammatory function.
- Therapeutics targeting MAP3K8 and its downstream pathway are suggested to improve the inflammatory pathology of HAM.
- Spatial transcriptomic analysis of HAM spinal cord lesions is expected to provide new insights into the disease pathogenesis.

22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Molecular epidemiology of HTLV-1/2 in the Americas

Ricardo Ishak
Federal Do Para, Brazil

- Pre record to add

Thomas Jefferson University | Drexel University | Drexel Medicine

22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Revision of the Japanese clinical practice guidelines for HTLV-1–Associated Myelopathy

Tomoo Sato and Yoshihisa Yamano

St. Marianna University School of Medicine, Kawasaki, JAPAN

Conflict of Interest Disclosure

Presenter：Tomoo Sato

I have no actual or potential conflict of interest in relation to this presentation.

Today's Outline

1. Brief review of the previous 2019 edition
2. Background of the 2025 revision
3. Structure of the new guideline
4. Comparison with the international guideline
5. Updated treatment algorithm

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Japanese HAM Clinical Practice Guidelines (CPG) 2019

Key Points of the 2019 Edition

- ✓ **Four Clinical Questions (CQs) and recommendations for HAM treatment:** developed using the GRADE approach. No recommendation was issued for steroid pulse therapy due to insufficient evidence.
- ✓ **Diagnostic algorithm for HAM**
- ✓ **Disease activity classification and HAM treatment algorithm:** patients are stratified into high, moderate, and low activity, with treatment intensity tailored to each group to avoid the risks of under- or over-treatment.

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Key Developments Since the 2019 HAM Guidelines

2022

- **HTLV-1 Mother-to-Child Infection Prevention Manual (2nd edition) published**
- **RAISING method developed; clonality of HTLV-1-infected cells shown to be important for ATL onset risk in HAM** (Saito et al., *Commun Biol* 2022)
- **Results of a randomized controlled trial of corticosteroid treatment in HAM patients reported** (Yamauchi et al., *Viruses* 2022)

2023

- **Obstetrics and Gynecology Clinical Practice Guidelines, Obstetrics Edition 2023 published**
- **HAL (Hybrid Assistive Limb) approved for HAM indication and covered by national health insurance**

2024

- **HTLV-1 Carrier Clinical Practice Guidelines 2024 published**
- **Diagnostic Recommendations for HTLV-1 Infection (3rd edition) published**
- **PA method, the primary HTLV-1 screening assay, discontinued and no longer available**
- **Report on diagnostic accuracy of non-PA assays for CSF anti-HTLV-1 antibody titers and cutoff values for HAM diagnosis** (Sato et al., *Viruses* 2024)
- **Report on clinical performance testing of the CXCL10 ELISA kit** (Ko et al., *CENI* 2024)
- **CXCL10 ELISA kit received regulatory approval as an in vitro diagnostic**

Japanese HAM Clinical Practice Guidelines (CPG) 2025

Revised in October 2025

HAM CPG 2025
(PDF)

With NotebookLM, you can explore the guidelines in various languages.

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2025 HAM Guidelines : Table of Contents

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Comparison of Japanese and International Guidelines

	Therapy	Japanese Guideline (2025)	International Guideline (2019) *Neurol Clin Pract*. 2021;11(1):49-56
CQ1	**Oral Corticosteroids (Prednisolone)**	**Conditional (Weak) Recommendation** Certainty of Evidence: Very Low	**Weak (2) Recommendation** Strength of Evidence: Weak (C)
CQ2	**Steroid Pulse Therapy (Methylprednisolone)**	**Conditional (Weak) Recommendation** Certainty of Evidence: Very Low	**Strong (1) for rapid progression** Strength of Evidence: Low (C) **Weak (2) for slow progression** Strength of Evidence: Very Low (D)
CQ3	**Interferon-α (IFN-α)**	**Conditional (Weak) Recommendation** Certainty of Evidence: Very Low	**Strong (1) Against as first-line therapy** Strength of Evidence: Weak (C)
CQ4	**Antiretroviral Drugs (Reverse transcriptase inhibitors)**	**Strongly Recommended Against** Certainty of Evidence: Low	**Strong (1) Against** Strength of Evidence: Moderate (B)

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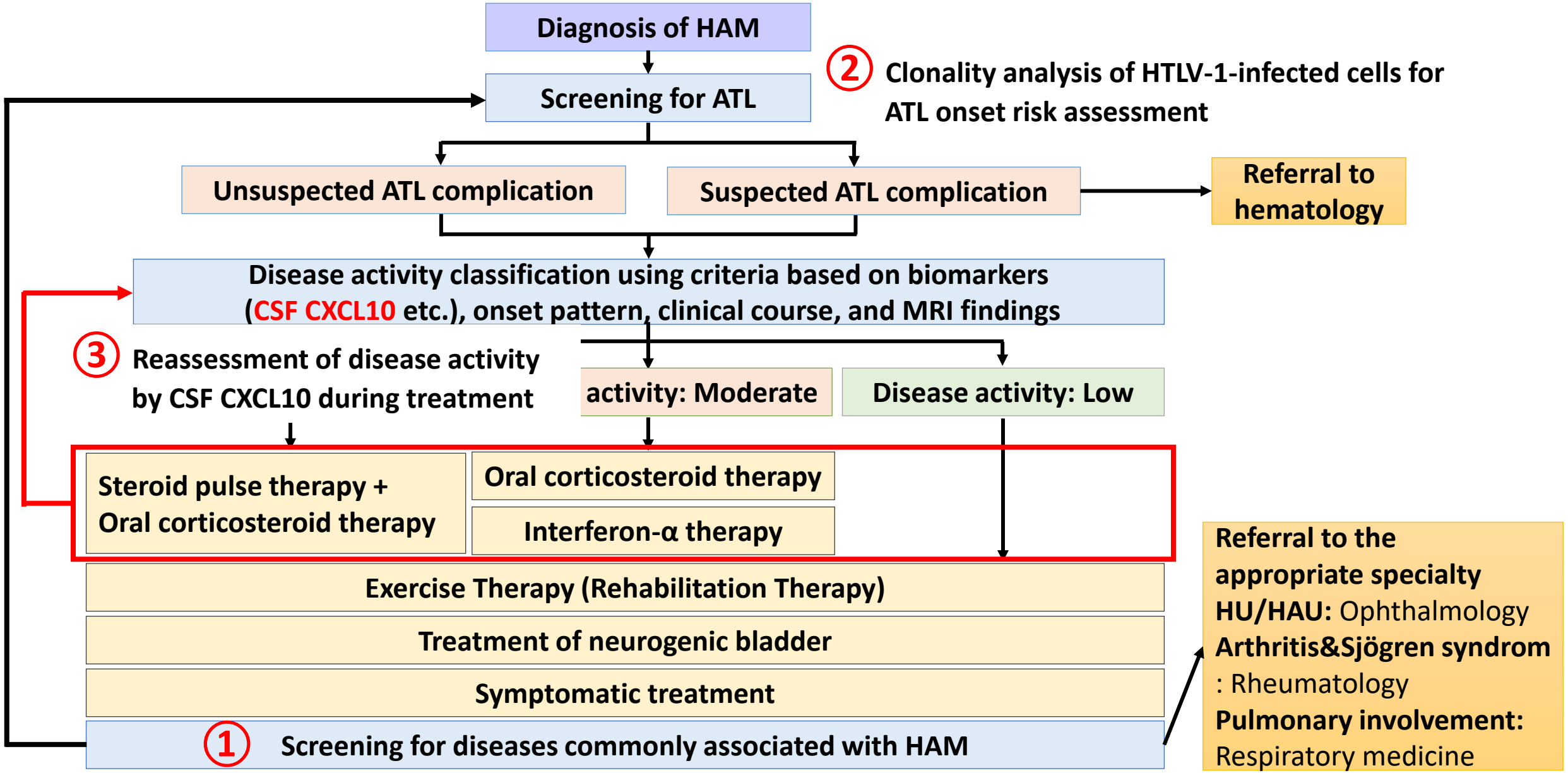
Treatment algorithm for HAM



Take home message

- The **Japanese HAM Clinical Practice Guidelines were revised in October 2025**, the first update in six years.
- A new chapter on **shared decision-making** was added, incorporating the voices of patients alongside the existing CQ-based recommendations.
- The updated treatment algorithm introduces **three key revisions**: screening for HAM-associated comorbidities, clonality analysis of HTLV-1-infected cells, and CSF CXCL10-based reassessment during treatment.
- The Japanese and international guidelines **largely agree** on corticosteroid use, while differing on interferon alpha; emerging data on dolutegravir may reshape future recommendations.