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*Especial*

**HTLV-1:**  
una amenaza real para la Salud Pública

**HTLV-1:**  
A real Public Health threat

# HTLV-1: Screening, diagnosis and health consequences

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**Launch of HTLV-1 Technical Report  
Global HIV, Hepatitis, STI Programmes  
World Health Organization  
17 March 2021**



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# Outline

## HTLV-1 testing and diagnosis

- Testing methods
- Screening

## Health consequences of HTLV-1 infection

- HTLV-1 associated disease: Definite and possible
- All cause mortality



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# HTLV-1 testing and diagnosis

Testing methods

Screening



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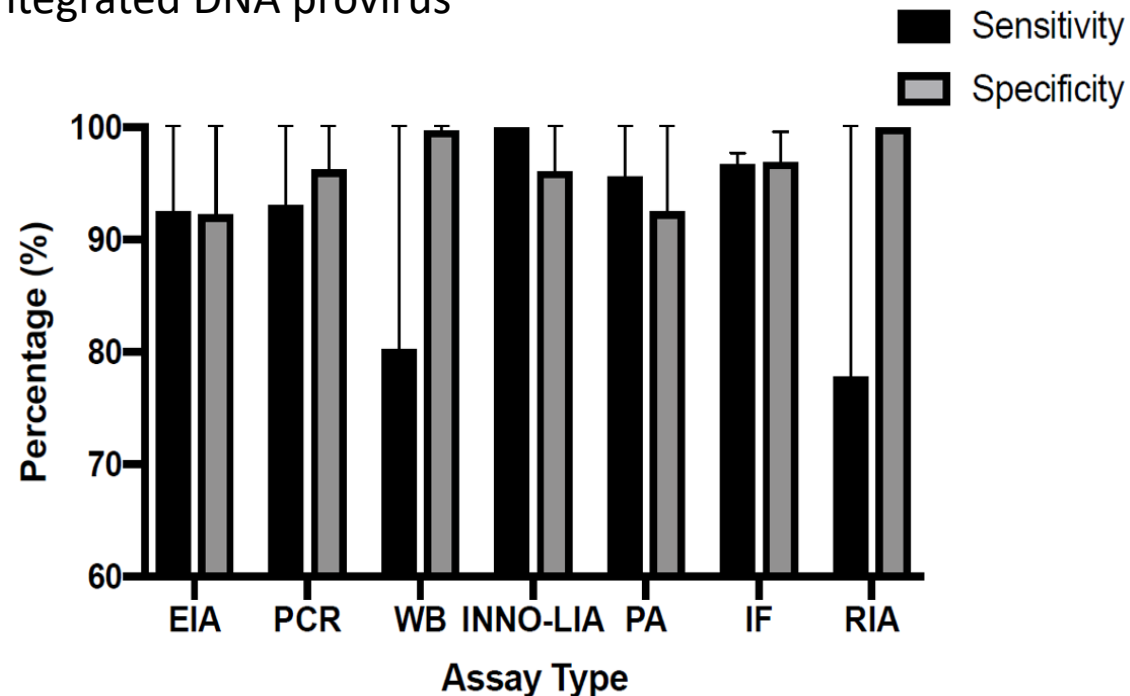
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# HTLV-1 testing and diagnosis

## HTLV-I serology and HTLV-I molecular testing

- Serology: Detect antibodies targeting multiple HTLV proteins
- NAT: Directed against integrated DNA provirus



Recent improvement in HTLV-I recombinant protein production has improved specificity  
(particularly for EIA)

Enzyme immunoassay (EIA), immunofluorescence assay (IFA), line immunoassay (INNO-LIA), nucleic acid testing (NAT), particle agglutination (PA), radioimmunoassay (RIA), western blot (WB).  
Slide courtesy of A/Prof R Bull



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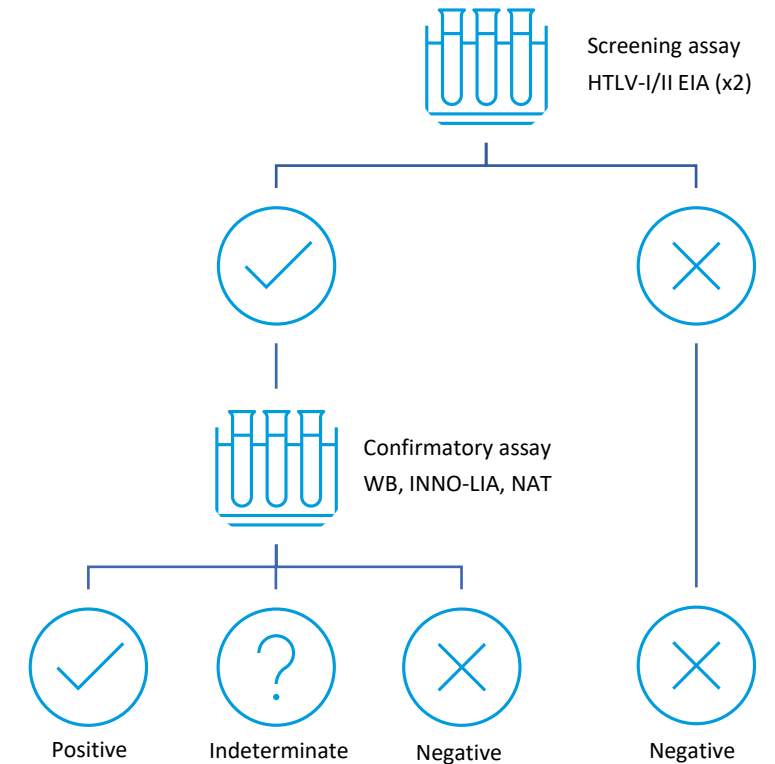
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# HTLV-1 testing and diagnosis

## Testing algorithms

- Current testing algorithms recommend stepwise testing process (multiple assays) to confirm HTLV positivity
- Common algorithm: Two screening serological tests (EIA), followed by confirmatory assay (WB, INNO-LIA, NAT)
- Challenges in standardising algorithm
  - Cost, laboratory requirements
  - No consensus on confirmatory test (WB definition)
  - Few FDA approved tests (2 EIA, 1 WB)





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# HTLV-1 testing and diagnosis

## Serology

- Primary assays used for diagnosis of HTLV-1 infection
- Available commercial assays have high sensitivity and specificity

## Qualitative and quantitative nucleic acid testing (NAT)

- Developed, but not produced commercially
- Limited access

## Uncertainty about optimal testing strategies and algorithms

### WHO Recommendations

*Develop guidance on testing approaches (including who to test) and strategies for HTLV-1 detection, appropriate to setting*



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# Health consequences of HTLV-1 infection

Adult T-cell leukaemia/lymphoma

HTLV-1 associated myelopathy / tropical spastic paraparesis

HTLV-1 associated uveitis

Infective dermatitis associated with HTLV-1





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# Health consequences of HTLV-1

- Most people living with HTLV-1 infection appear to remain asymptomatic
- Severe complications can develop
- HTLV-1 infection is necessary for the diagnosis of four diseases

Diseases defined as being caused by HTLV-1		Lifetime risk <sup>^</sup>
Cancer	Adult T-cell leukaemia-lymphoma	5%
	HTLV-1 associated myelopathy/tropical spastic paraparesis	2%
Inflammatory conditions	HTLV-1 associated uveitis	1%
	Infective dermatitis	Unknown



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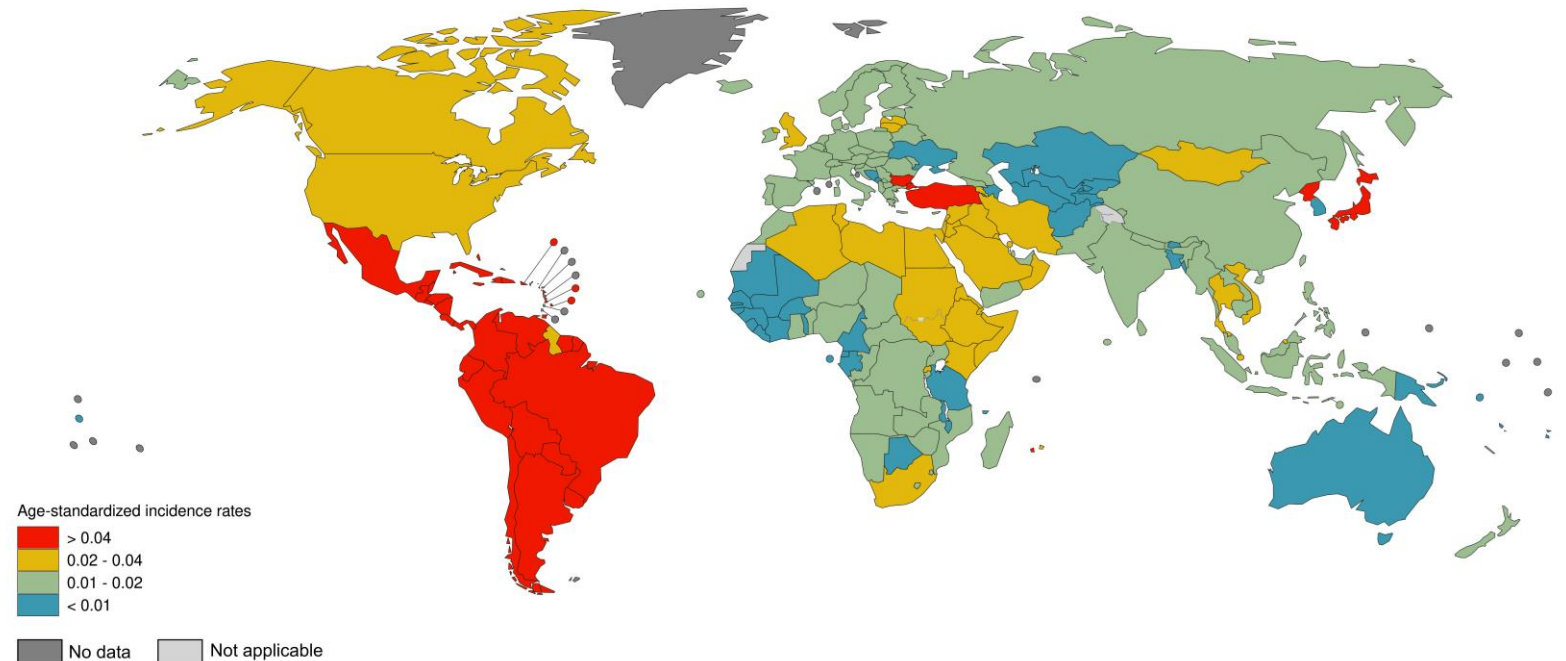
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# Health consequences of HTLV-1

## Adult T cell leukaemia / lymphoma

Estimated 3600 cases of ATL worldwide (2018)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: IARC 2019  
Map production: IARC  
World Health Organization



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## Incidence (age-standardised) of cancer attributable to HTLV-1

Adapted from de Martel et al. *Lancet Global Health*. 2020.



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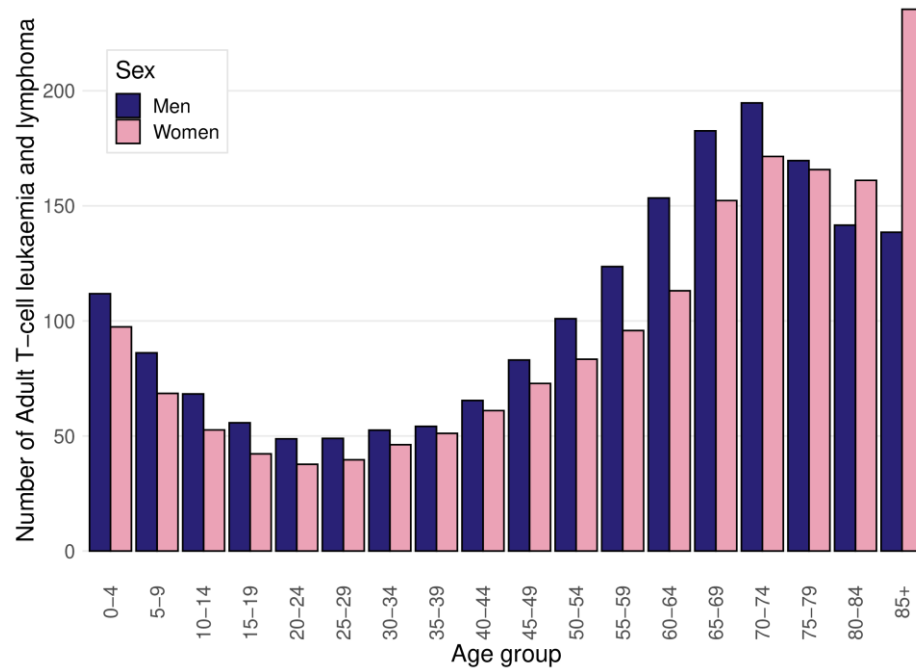
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# Health consequences of HTLV-1

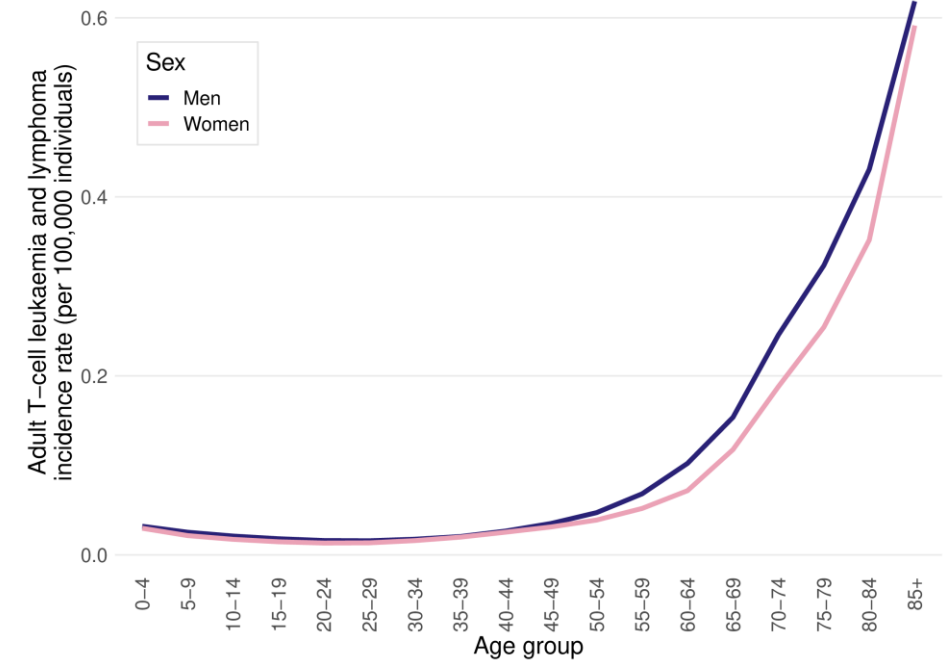
## Adult T cell leukaemia / lymphoma

Estimated 3600 cases of ATL worldwide (2018)



**ATL cases by age and sex**

Adapted from de Martel et al. *Lancet Global Health*. 2020.



**ATL incidence by age and sex**



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# Health consequences of HTLV-1

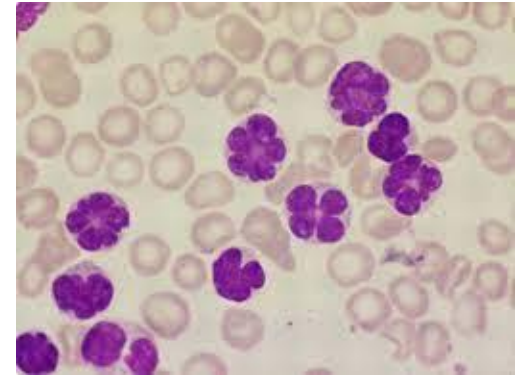
## Adult T cell leukaemia / lymphoma

### Factors associated with ATL among people with HTLV-1

- Older age  
(Male sex?)
- Family history of ATL
- Longer duration of HTLV-1 infection (>20 years)
- Younger age at HTLV-1 infection (infancy or childhood)
- Higher HTLV-1 proviral load

### Clinical presentation

- Skin lesions
- Lytic bone lesions
- Lymphadenopathy
- Hepatosplenomegaly
- Hypercalcaemia



Opportunistic infections

### Clinical subtypes

- Acute (50%)
- Lymphomatous (26%)
- Chronic (13%)
- Smoldering (11%)

Life expectancy  
<12 months

### Management



Interferon-based therapy



Chemotherapeutic and biologic agents



Allogeneic haematopoietic stem cell transplant

Expert opinion and international consensus; Cook et al *J Clin Onc* 2019



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# Health consequences of HTLV-1

## HTLV-1 associated myelopathy / tropical spastic paraparesis

### Diagnostic criteria for HAM/TSP

#### Clinical presentation

Non-remitting progressive spastic<sup>1</sup> paraparesis with sufficient impairment of gait to be noticed by the patient

#### HTLV-1 testing

Serology: Antibodies to HTLV-1 in blood and CSF  
Molecular: Positive molecular test (NAT) for HTLV-1 in blood and/or CSF

#### Other investigations

Spinal cord imaging (ie. CT, MRI) and other appropriate investigations to rule out alternate causes of progressive paraparesis

<sup>1</sup>Spasticity is a condition in which muscles stiffen or tighten, remain contracted and resist being stretched, preventing normal movement.



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# Health consequences of HTLV-1

## HTLV-1 associated myelopathy / tropical spastic paraparesis

### Factors associated with HAM among people with HTLV-1

Female sex  
Higher HTLV-1 proviral load

### Clinical presentation

Impaired (spastic) gait  
Muscle weakness (proximal > distal)  
Hyperreflexia, clonus in lower limbs, extensor plantar response  
Urinary incontinence or retention (early)  
Constipation (late)  
Sexual dysfunction (impotence or decreased libido)

### Clinical subtypes - proposed

Rapid  
Slow  
Very slow  
Non-progressing

Needs validation

### Management



Disease modifying therapy (ie. corticosteroids)



Symptomatic management

Expert opinion

<https://htlv.net/HAMpdf>



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# Health consequences of HTLV-1

## HTLV-1 associated uveitis

### Factors associated with HAU among people with HTLV-1

Unknown

Higher HTLV-1 proviral load?

### Clinical presentation

Visual disturbance - blurred vision, “floaters”

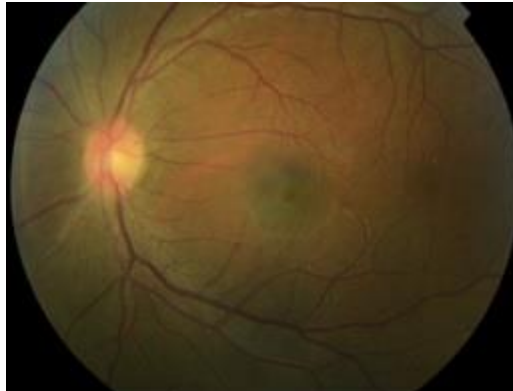
One or both eyes

Usually single episode; recurrence possible

Sight-threatening complications rare

### Clinical subtypes

Anterior or “intermediate”  
uveitis



### Management

 Topical corticosteroids

 Systemic corticosteroids

Expert opinion



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# Health consequences of HTLV-1

## Infective dermatitis associated with HTLV-1

### Major criteria required for the diagnosis of infective dermatitis associated with HTLV-1

**Erythematous, scaly, exudative, and crusted lesions on scalp, retro-auricular areas, neck, axillae, groin, paranasal and perioral skin, ears, thorax or abdomen, with evidence of  $\geq 3$  involved sites**

Crusting around the nostrils

**Chronic relapsing dermatitis with prompt response to appropriate therapy, but recurrence on discontinuation of antibiotics**

Diagnosis of **HTLV-1 infection** (by serological or molecular testing)

Text in **bold** is mandatory for the diagnosis  
Published by la Grenade et al and modified by de Oliveira et al





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# Health consequences of HTLV-1

## Infective dermatitis associated with HTLV-1

### Factors associated with IDH among people with HTLV-1

#### Younger age

Jamaica: Risk of IDH by four years of age - 2.0%  
(Maloney Paed Inf Dis 2000)

#### Higher HTLV-1 proviral load

Subsequent development of HAM, ATL

### Clinical presentation



### Management



Antibiotics

recurrence on treatment discontinuation



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# Health consequences of HTLV-1 infection

HTLV-1 infection, all-cause mortality, and other possible disease associations



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# Health consequences of HTLV-1

Diseases with evidence of an association with HTLV-1		
<b>Cancer</b>	Lymphoma other than ATL	Limited evidence
<b>Inflammatory conditions</b>	Lung: Bronchitis, bronchiectasis and bronchiolitis	Limited evidence
	Rheumatological: Arthritis, fibromyalgia, rheumatoid arthritis, Sjogren's syndrome	Very limited evidence
	Skin: Seborrheic dermatitis (adults and children), eczema (children)	Limited evidence
<b>Infectious diseases</b>	Tuberculosis	Moderate evidence
	Urinary tract infection	Limited evidence
	Dermatophyte infection	Very limited evidence
	Community acquired pneumonia	Very limited evidence
	<i>Strongyloides</i> hyperinfection syndrome	Very limited evidence



Adapted Schierhout et al *Lancet Inf Dis* 2020



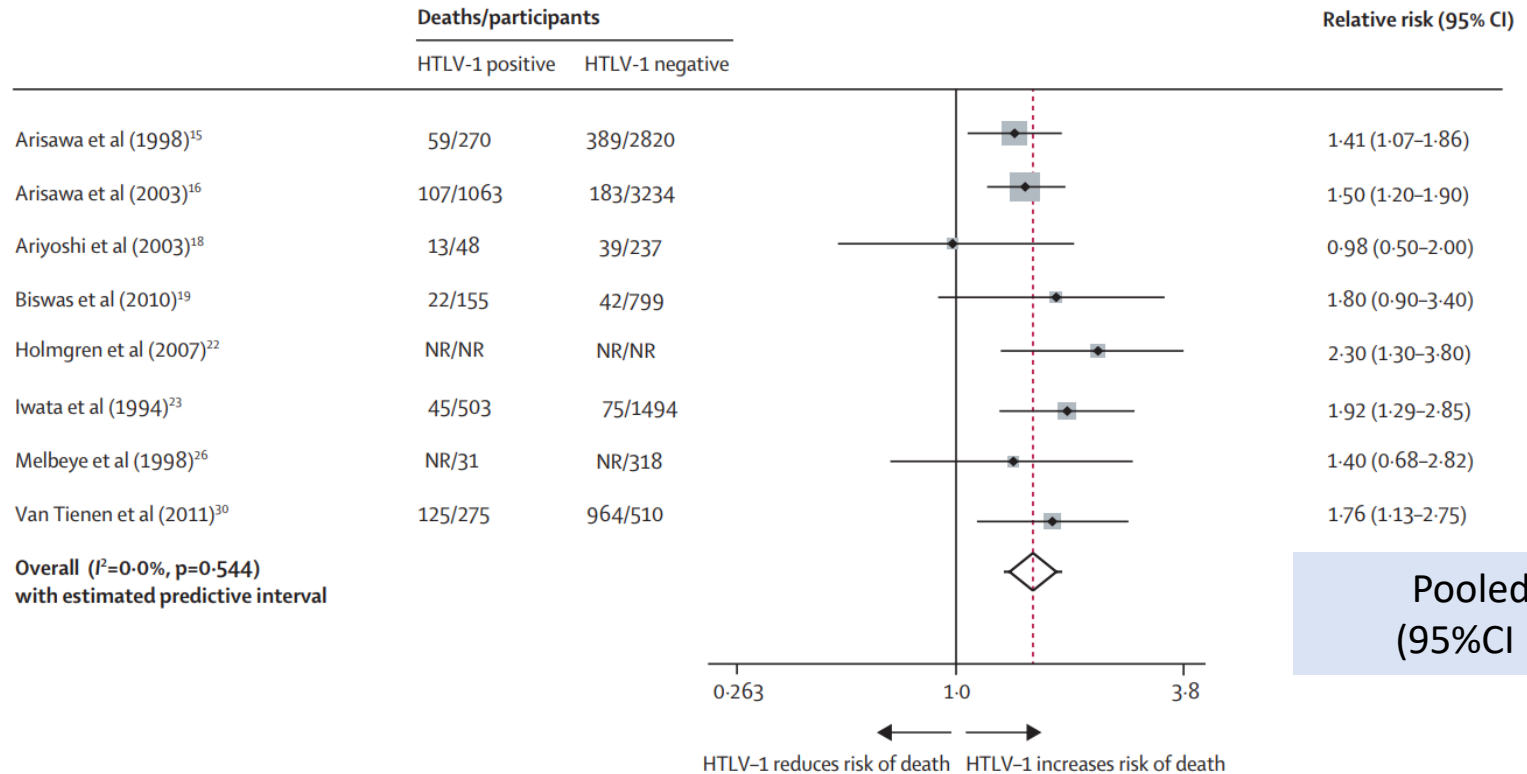
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# Health consequences of HTLV-1

## HTLV-1 and all cause mortality



Meta-analysis of the association between HTLV-1 and death from all causes: multivariate adjusted RR from eight cohort studies

Strength of evidence for an association between HTLV-1 and all-cause mortality: **STRONG (GRADE 4)**



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# Health consequences of HTLV-1

- Major recognised health consequences: **ATL** and **HAM/TSP**
- **Excess mortality >50%** among people with HTLV-1 infection
- Disease burden highly variable across affected populations
- Other consequences that have been under-recognised?
- **Lack of guidance on clinical management** for people with HTLV-1 infection

Knowledge gaps...

Global epidemiology and burden of disease

Factors associated with disease development and progression

Reason for increase in mortality? Relationship with other major causes of mortality?

HTLV-1 and chronic inflammation?

## WHO Recommendations

*Collaborative cohort studies - geographic differences in disease manifestations and progression rates*

*Burden of disease calculations*



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Additional slides



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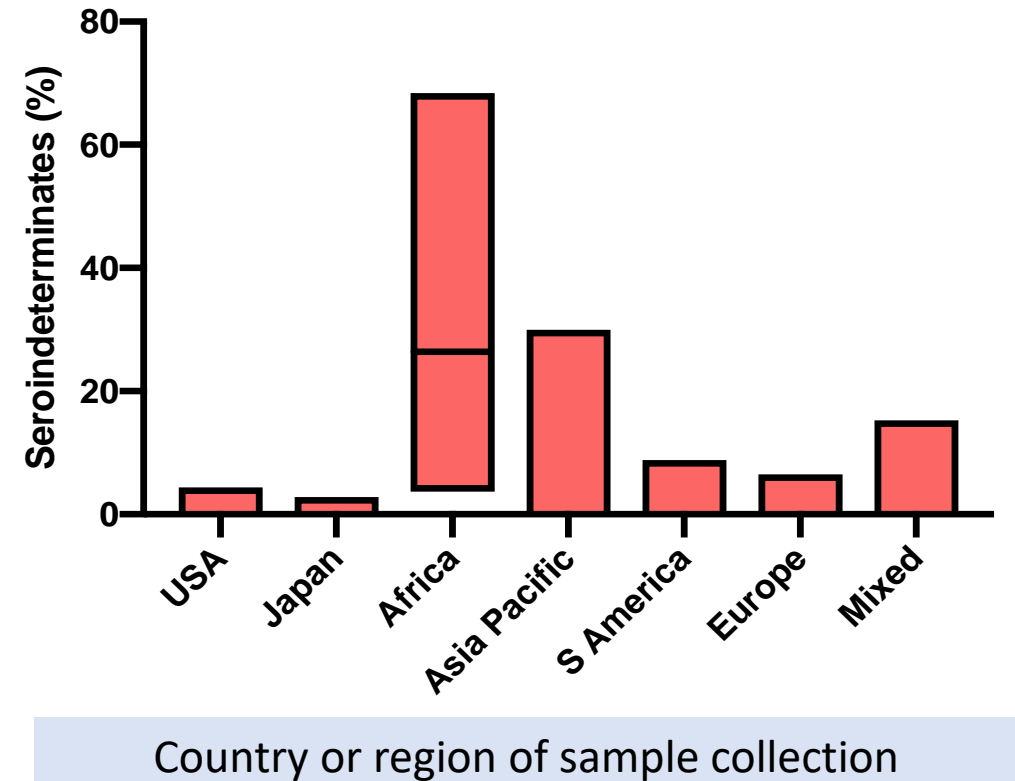
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# HTLV-1 testing and diagnosis

## False positive results

Causes of 'false' reactivity, include:

1. Cross-reactivity with other HTLV types II, IV
2. Cross-reactivity with *Plasmodium falciparum*, in particular the gp21 protein
3. Non-specific cross reactivity with other pathogens or self







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Assay type	Advantages	Disadvantages
Western blot	<ul style="list-style-type: none"><li>• FDA approved</li><li>• Differentiate between HTLV-I and II</li></ul>	<ul style="list-style-type: none"><li>• Definition of positive varies</li></ul>
Nucleic acid	<ul style="list-style-type: none"><li>• Quantitation - proviral load (prognosis?)</li><li>• Detection in seroindeterminate (and seronegative)</li></ul>	<ul style="list-style-type: none"><li>• Requires PBMCs</li><li>• No FDA approved test</li><li>• Requires careful selection of target</li><li>• Lower limit of detection?</li></ul>
Inno-LIA	<ul style="list-style-type: none"><li>• High sensitivity and specificity (limited studies)</li></ul>	<ul style="list-style-type: none"><li>• Another serology test</li></ul>



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# HTLV-1 testing and diagnosis

## Screening and prevention policies



**69** countries with information on HTLV-1 policies

**56** had at least one HTLV-I policy

**13** countries indicated no specific policy

**All other countries**, no specific information on presence or absence of policy



Prevention policies

1. Screening of blood donations
2. Antenatal and milk donation screening
3. Screening of donor tissue and cells



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# HTLV-1 testing and diagnosis

## Screening of blood donations

Region	All donations	First-time donors only	Specific areas	Leucoreduction**
African	Gabon			
Eastern Mediterranean	Saudi Arabia		Iran (Khorasan)	
European †	<b>French Guiana</b> , Greece, Ireland, Israel, Netherlands, Romania, UK,	Denmark, Finland, France, <b>Guadelupe, Martinique</b> , Portugal, Sweden		Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain
Americas	<b>Brazil</b> , Canada, <b>Chile</b> , <b>Colombia</b> , <b>Dominican Republic</b> , <b>Haiti</b> , <b>Jamaica</b> , <b>Peru</b> , US, <b>Uruguay</b>		<b>Argentina</b> , <b>Venezuela</b>	
Western Pacific	Australia, China (Taiwan), Japan, NZ		China	

\*South-East Asia Region: no information; \*\*all blood or cellular components, or on medical request; †Includes overseas departments of France: French Guiana, Guadelupe, Martinique



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# HTLV-1 testing and diagnosis

## Prevention of mother-to-child transmission

Region	Antenatal screening for HTLV-1	Breast milk donation screening for HTLV-1
African Region		
Eastern Mediterranean Region		
European Region	France (screening of people from endemic regions recommended)	UK
Region of the Americas	<b>Brazil</b> (some regions – recommended) <b>Chile</b> (recommended)	
Western Pacific Region	Japan (national policy - 2011)	



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# HTLV-1 testing and diagnosis

## Donor tissue and cell screening

- Very few policies found
- Mandatory deceased organ donor screening removed in the US in 2009
- 2012 European Commission directive for screening of donors (or donors with sexual partners or parents) from high prevalence countries
- Japan working towards screening all kidney donations



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# HTLV-1 testing and diagnosis

## Screening: Who to test and when?

**Guidance and strategies are very limited**

### Pregnant women

- Japan: Comprehensive nationwide HTLV-I mother-to-child transmission policy

### Children born to HTLV-I positive mothers

- Brazil
- Chile
- Japan – no consensus

### Healthcare workers exposed to HTLV-I

- Australia (Northern Territory only)

No guidelines on testing strategies to prevent transmission related to sexual exposure or injecting drug use

- Brazil: Recommendation to offer testing to sexual partners, PWID, sex workers
- Chile: Recommendation to test PWID, sex workers, people with HIV

People who inject drugs (PWID)



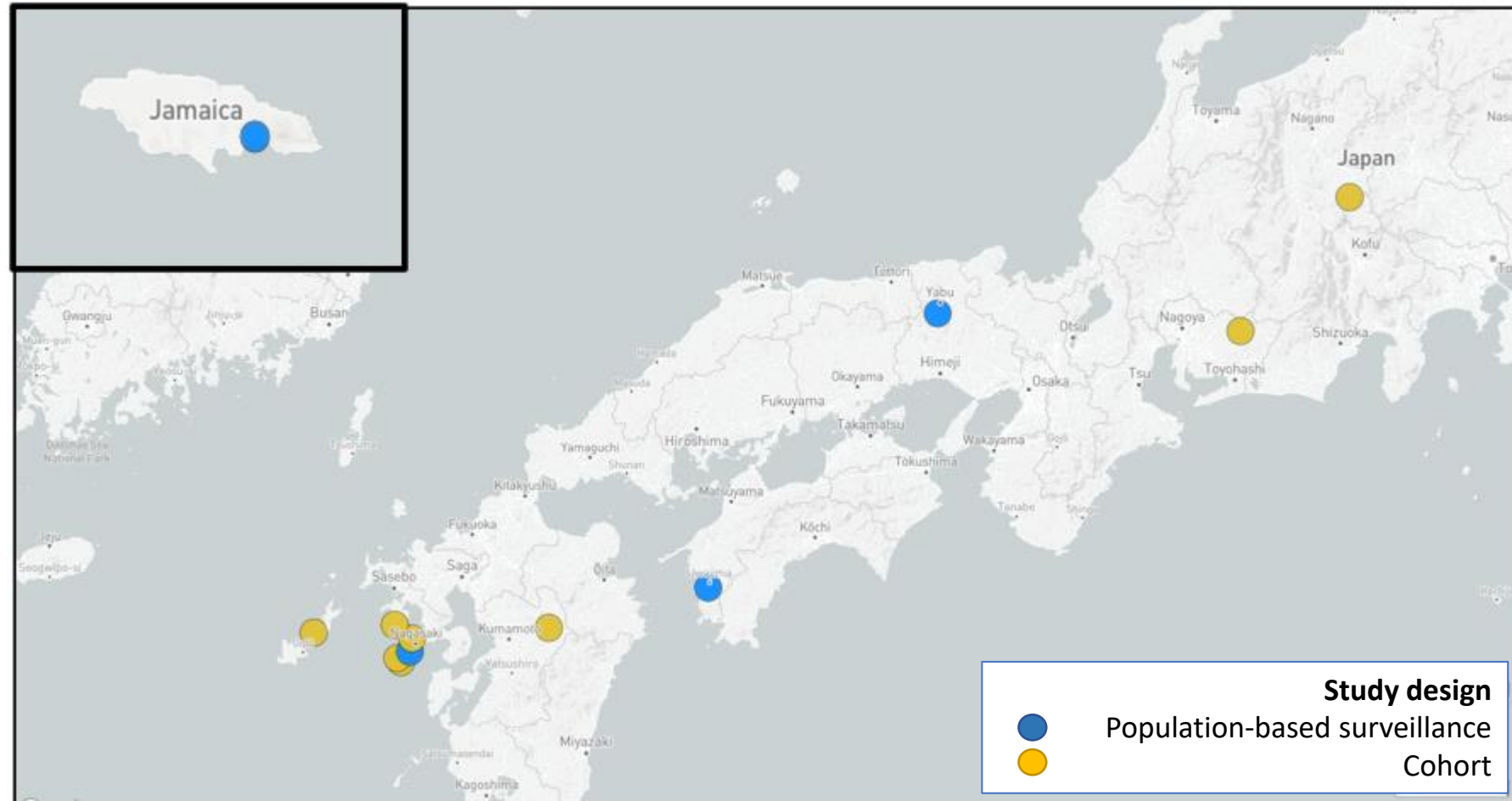
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# Health consequences of HTLV-1

## Adult T cell leukaemia / lymphoma





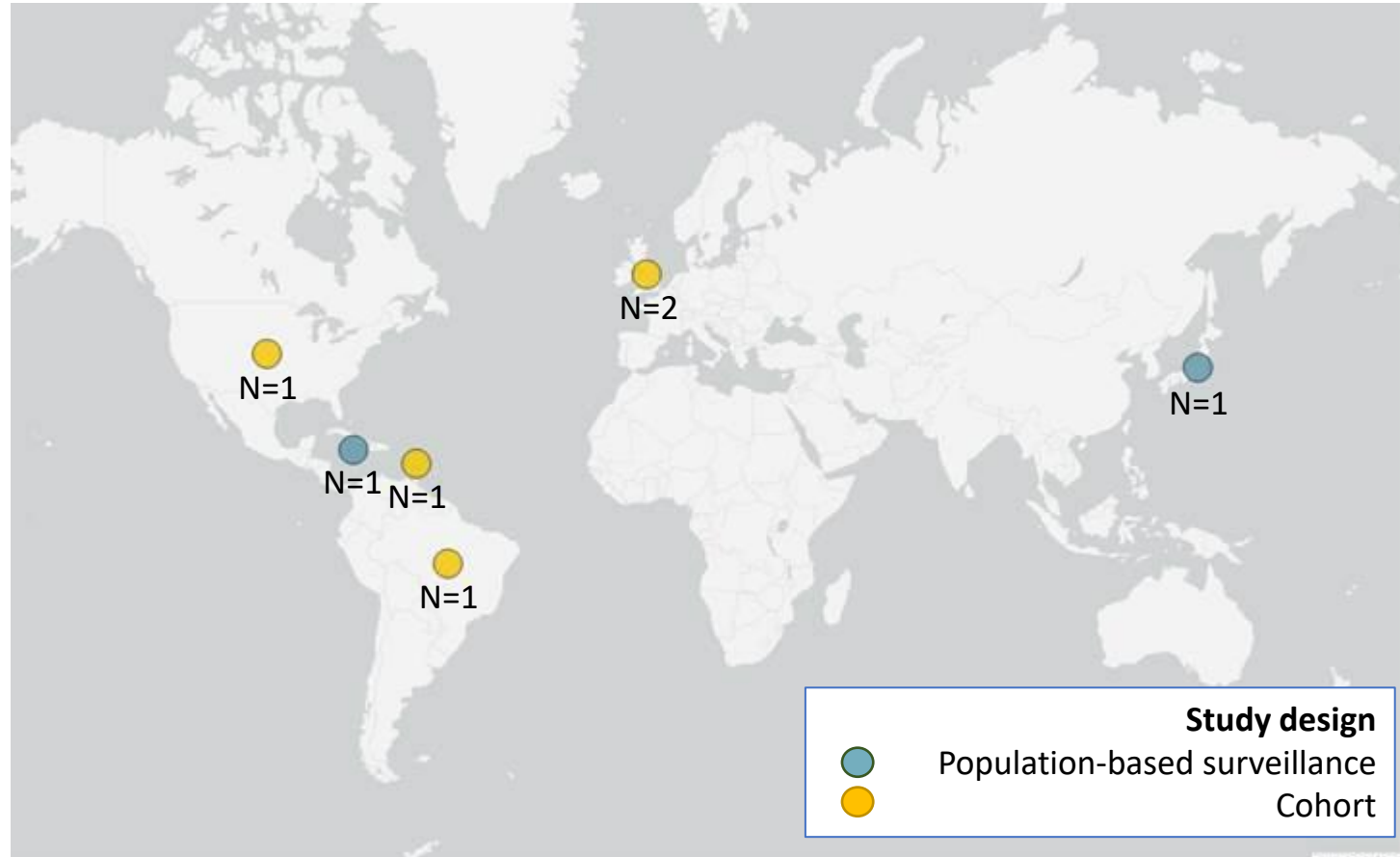
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# Health consequences of HTLV-1

## HTLV-1 associated myelopathy / tropical spastic paraparesis







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# Health consequences of HTLV-1

## All cause mortality and other possible disease associations

- Strong evidence for association: **All-cause mortality**
- Limited to moderate quality evidence: Tuberculosis; seborrheic dermatitis; eczema; bronchitis, bronchiectasis and bronchiolitis; urinary tract infection; lymphoma (not ATL)
- Limitations of available data
  - Unable to estimate contribution of HTLV-1 to total burden of condition studied
  - Geographical restriction
  - Limited assessment of or adjustment for confounders
  - Representativeness and generalizability, publication bias?
  - Impact of HTLV-1 proviral load: stratification of risk