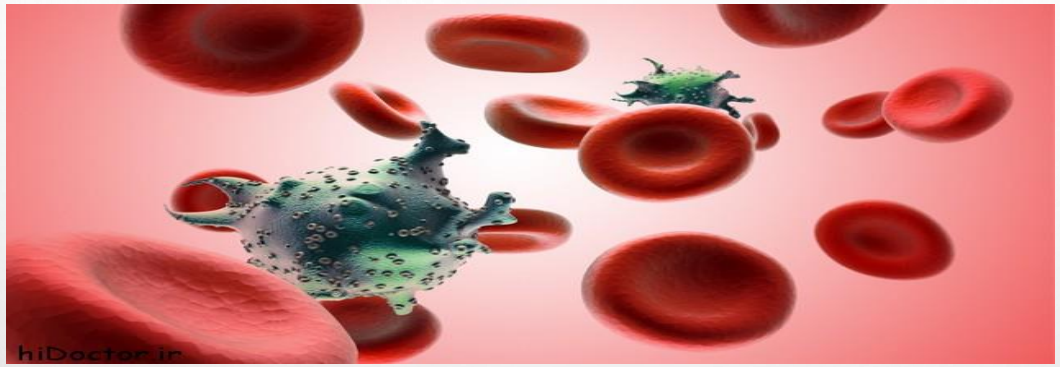
In The Name Of Allah

HTLV and Blood Diseases



By

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Faculty of Medicine

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Taxonomy2019 ICTV

Riboviria › Pararnavirae › Artverviricota › Revtraviricetes › Ortervirales › Retroviridae › Orthoretrovirinae › Deltaretrovirus

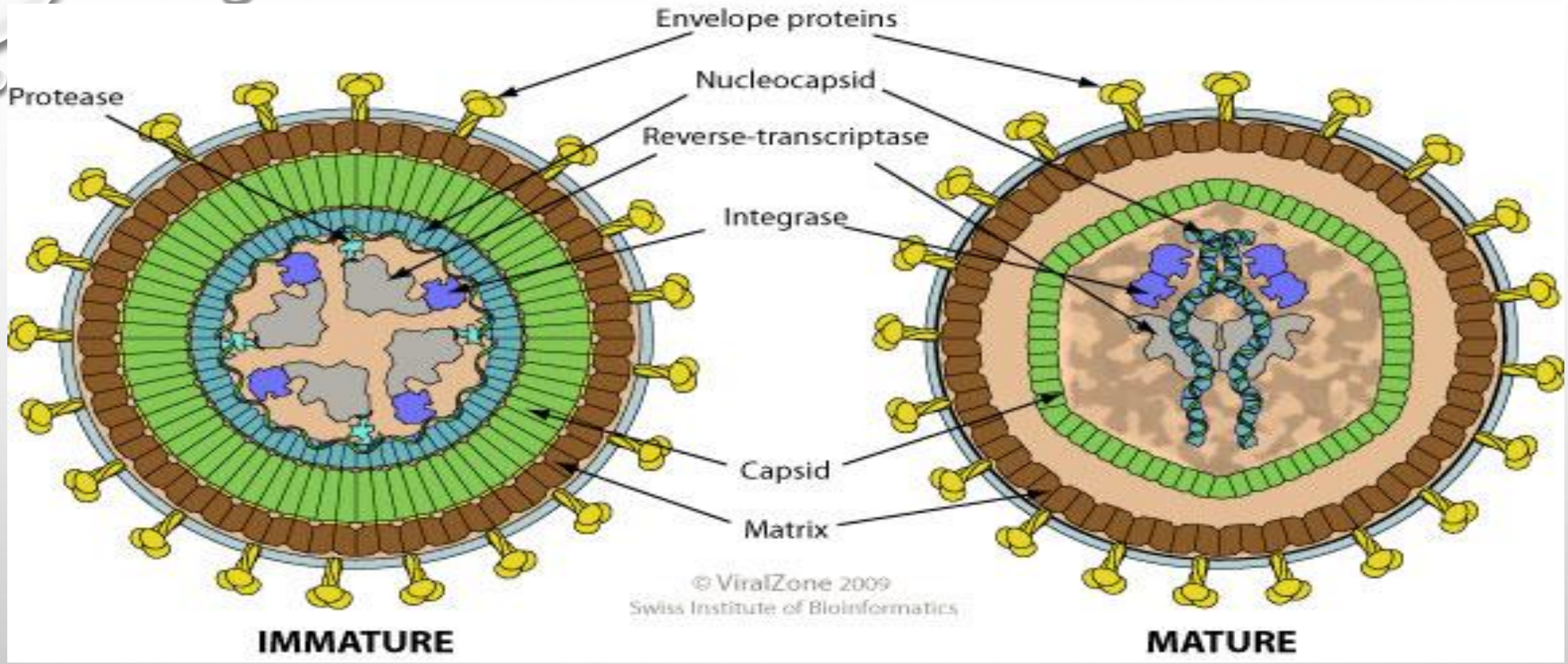
species:

Bovine leukemia virus

Primate T-lymphotropic virus 1

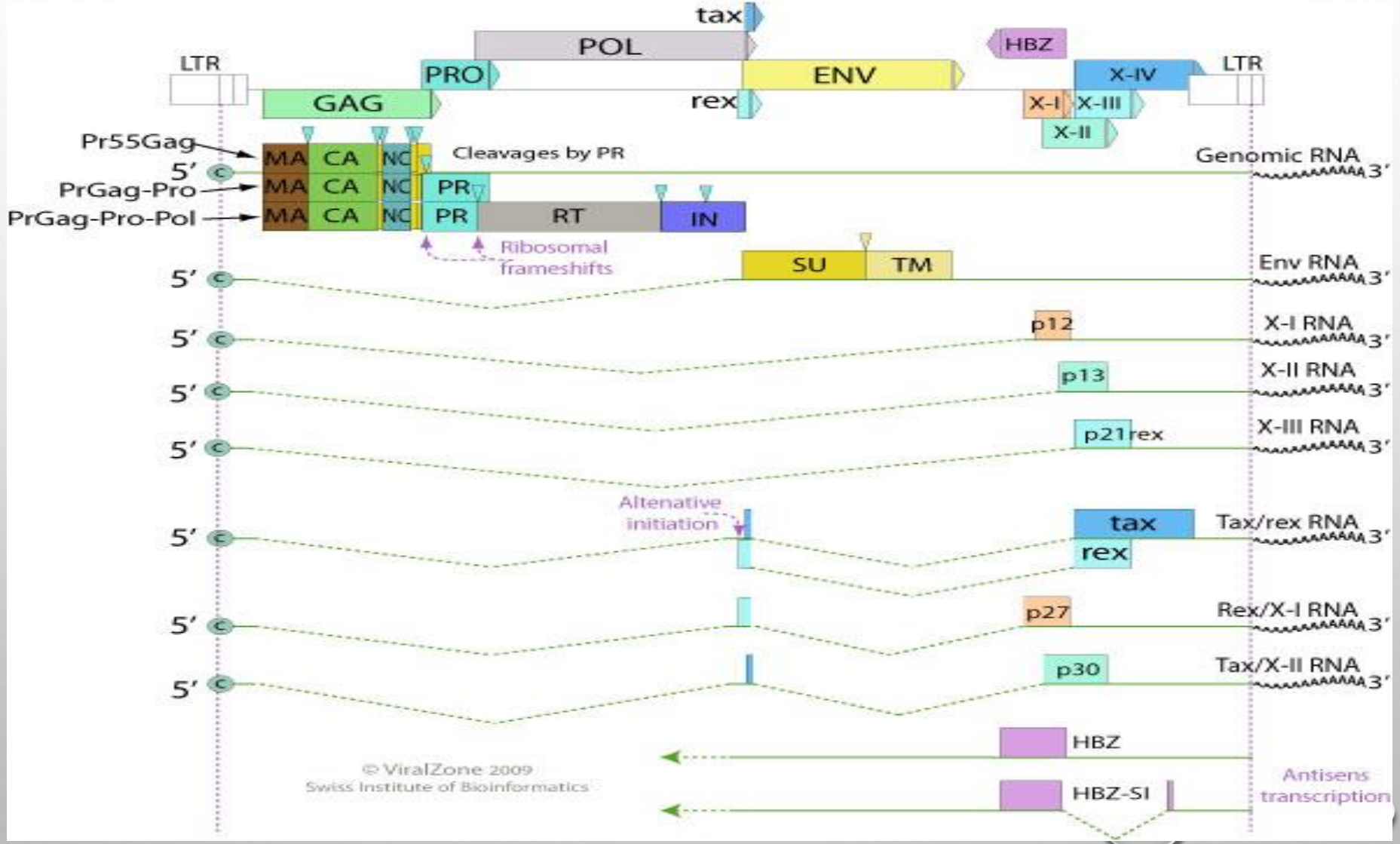
Primate T-lymphotropic virus 2

Primate T-lymphotropic virus 3



Enveloped. Spherical to pleomorphic, about 80-100 nm in diameter

Monopartite, linear, dimeric, ssRNA(+) genome of 8.4-9 kb, with a 5'-cap and a 3'poly-A tail.


tax
POL
HBZ
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X-IV
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rex
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Pr55Gag
MA CA NC
Cleavages by PR
Genomic RNA
5′
PrGag-Pro
MA CA NC PR
PrGag-Pro-Pol
MA CA NC PR RT IN
Ribosomal frameshifts
SU TM
Env RNA
p12
X-I RNA
p13
X-II RNA
p21rex
X-III RNA
Altenative initiation
tax
rex
Tax/rex RNA
p27
Rex/X-I RNA
p30
Tax/X-II RNA
HBZ
HBZ-SI
Antisens transcription
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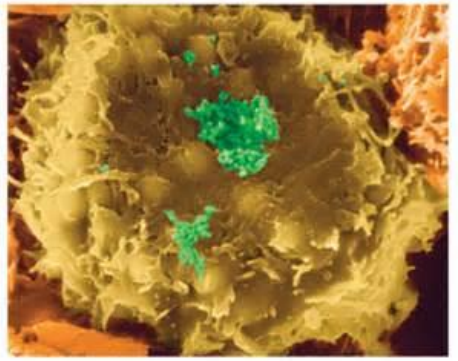
- Lymphoid malignancies are remarkable and heterogeneous group of neoplasm because of its difference in epidemiology and etiology in different areas around the world.
- Histopathologic subtypes of lymphoma are different in eastern and western countries and similar among Asian countries.
- The overall incidence of lymphoid malignancy in Asian countries is relatively low.

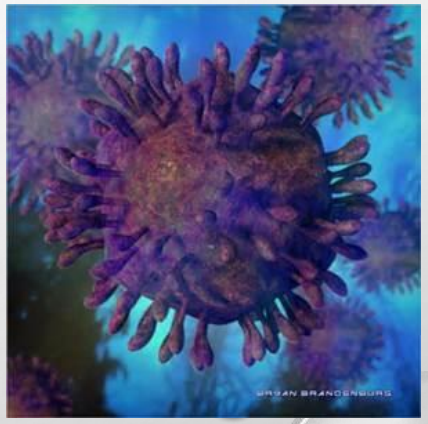
Table-1. Major subtype of T cell lymphoma by region

	PTCL %	AITL %	Anaplastic %	NKT CL%	ATLL %
NA	34.4	16	23.8	5.1	2
Europe	34.3	28.7	15.8	4.3	1
Asia	22.4	17.9	5.8	22.4	25

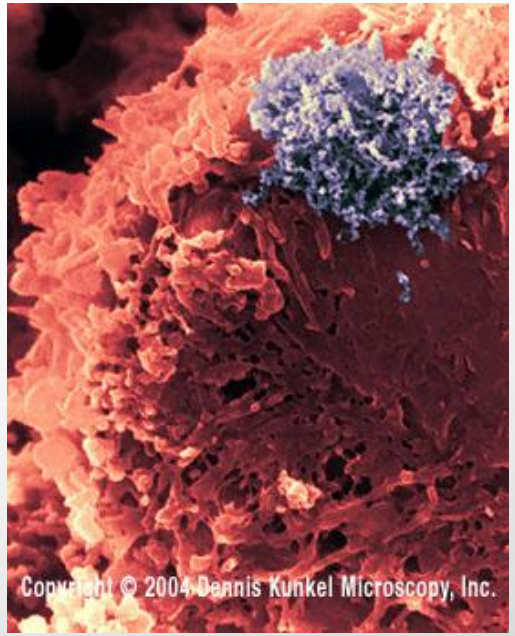
Abbreviations: **PTCL**: peripheral T cell lymphoma; **AITL**: Angioimmunoblastic T cell lymphoma; **NKT CL**: Natural Killer T cell lymphoma; **ATLL**: Adult T cell Lymphoma/ Leukemia; **NA**: North American (1).

- Bacterial and viral infections, which are relatively frequent especially in eastern area are human T-cell lymphotropic virus type1 (HTLV-1), Epstein–Barr virus (EBV), Helicobacter pylori infections and Hepatitis C Viruses (HCV) infection; They are responsible for different epidemiology of lymphoma.

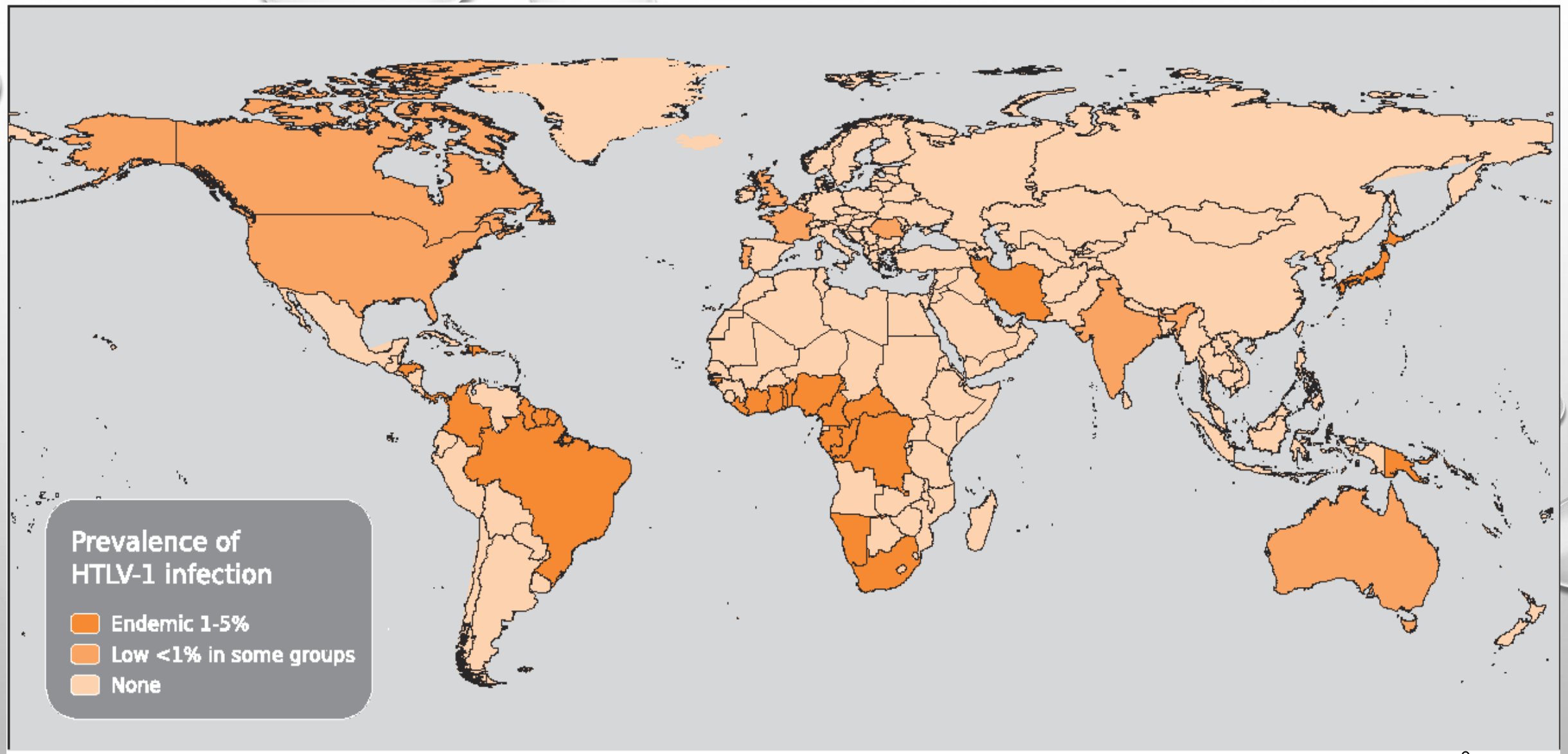




HUMAN T-LYMPHOTROPIC VIRUS-1



- **Human T-Lymphotrophic Virus-1 (HTLV-1) is a first human retrovirus to be discovered, and estimated to infect 10-20 million people worldwide.**
- **HTLV1 Infection is strongly related to adult T-cell leukemia/Lymphoma (ATLL), and HTLV1 associated Myelopathy.**



Adapted from and reprinted by permission from Macmillan Publishers Ltd: Oncogene, Proietti et al. (2005), http://www.nature.com/onc/index

Table-2. Prevalence of HTLV1 in different countries (1)

Country	Sample size	Prevalence of HTLV1	Group
Rural Miyazaki Southern Japan		Up to 30%	General population
Iran (Mashhad)	1653	2.1%	General population
Lebanon	3529	0.06	Blood donors
Taiwan	3700000	0.06	Blood donors
Korea	9281	0.13	Blood donors
Jamaica		3-6%	General population
Caribbean		6%	General population
Curacao	2524	1.92%	General population
Papua New Guinea	1221	0-14.6%	General population
Argentina	2082	1.9%	General population
U.S	1700000	0.01	Blood donors
Italy	14598	0.03	Blood donors
Germany	100852	0	Blood donors
U.K	570609	0.001	Blood donors

- **HTLV1 infection is endemic in southern Japan, the Caribbean, the Melanesian island, Papua New Guinea, the Middle East, central and South America, and southern Africa.**
- **In these endemic areas, seroprevalences range is different from about one (1-3%) percent in Mashhad in northeast Iran to 30% in rural Miyazaki in southern Japan.**
- **HTLV1 is primarily transmitted by blood transfusion, breast feeding, sexual transmission and sharing of needles. Vertical transmission results in clustering cases in familial or geographically discrete groups.**
- **Golestan**

Population-based seroprevalence of HTLV-I infection in Golestan province, South East of Caspian Sea, Iran. Kalavi, K. and Moradi, A. and Tabarraei, A. (2013)

Iranian Journal of Basic Medical Sciences, 16 (3). pp. 225-228.

Abstract

Objective(s): Human T-cell lymphotropic virus type-1 is an oncornavirus that causes adult T cell leukemia (ATL) HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Golestan province is located in North West of Khorasan province known as an endemic area for HTLV-I in Iran. This study aimed to evaluate seroprevalence of HTLV-I in Golestan province. Materials and Methods: In this cross-sectional descriptive study in 2007, blood samples were collected from **2034 healthy people** residing in different parts of Golestan province. Sera were assessed for **HTLV-I/II-specific antibodies by ELISA** method and reactive samples were confirmed by **Western blot**. Demographic and serologic data were entered in SPSS version 11.5 and statistical analysis was performed. Results: An overall HTLV-I/II prevalence of **0.7** was observed in 15 cases by ELISA. Six out of 15 were confirmed as HTLV-I by western blot. Regional variation in the prevalence of HTLV-I was observed; **0, 0, 0.1, 1.9, 0.3, 0, and 2.6** tested HTLV-I-positive from **west to east** of Golestan Province regions, respectively. Seropositivity increased with **age.** No association between HTLV-I infection and sex status was detected. Conclusion: Highest rate of HTLV-I seroprevalence was shown in east of this region located in neighborhood with Khorasan province, the only confirmed endemic area in Iran. It seems that eastern area of our province is endemic for HTLV-I. Further comprehensive detailed epidemiological and molecular studies are recommended.

- **HTLV-1 infected individuals is about 10 millions, these results were only based on nearly 1.5 billion of individuals originating from known HTLV-1 endemic areas with reliable available epidemiological data.**
- **Correct estimates in other highly populated regions, such as China, India, the Maghreb, and East Africa, is currently not possible.**
- **Therefore the real number of HTLV-1 carriers is probably very much higher.**

- **Population HTLV-I seroprevalence tends to increase with age and is twice as high in females.**
- **In Jamaica 4% of women over 70 and 1% of men over 70 were seropositive. In some area of Japan, HTLV-I seroprevalence in persons over 80 was 50% in females and 30% in males.**
- **This gender difference often emerges after 30 years of age and may be related to more efficient transmission of the virus from males to females in the years of sexual activity.**

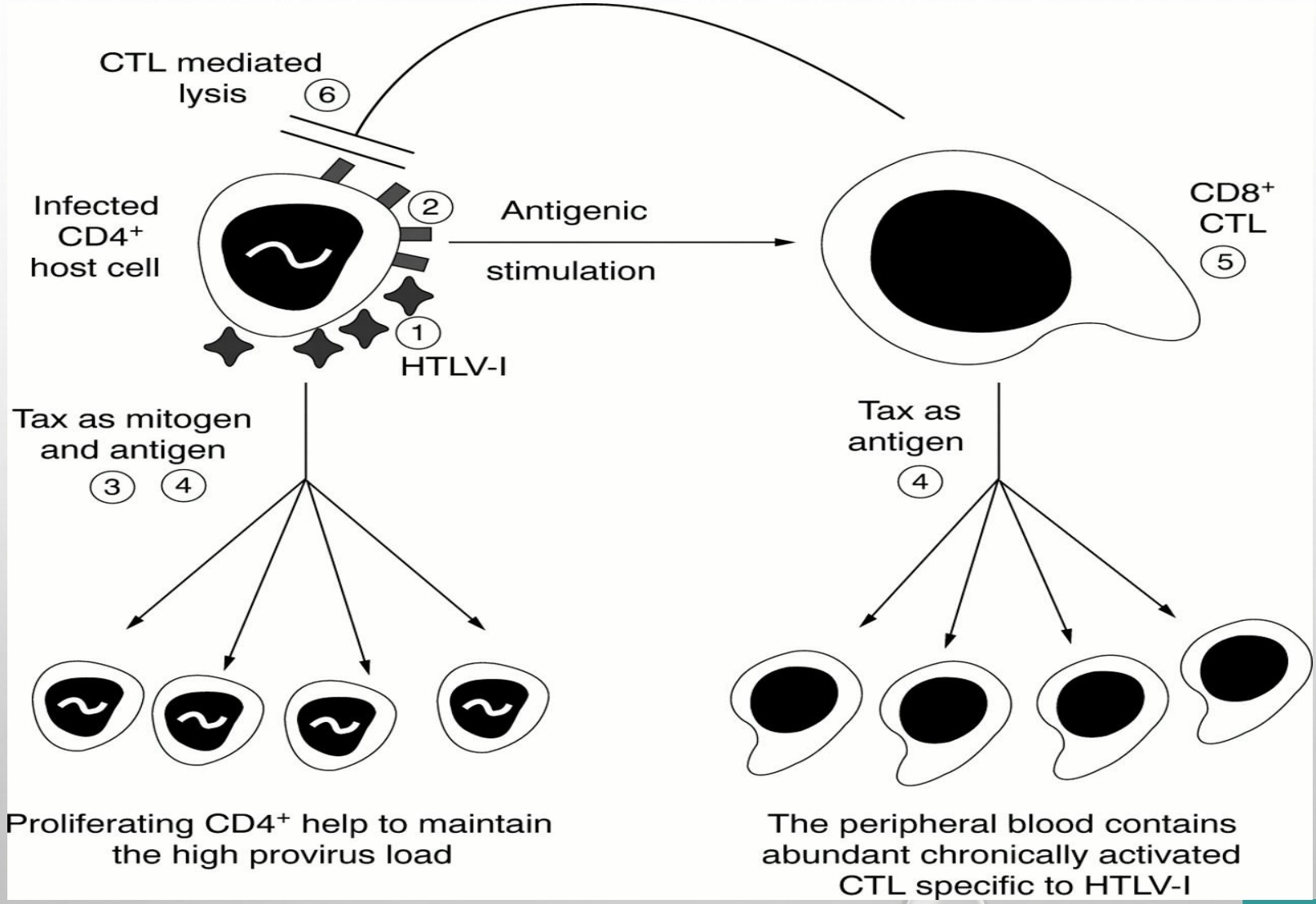
- **In mother to child transmission, 10 to 25% of the breast-fed children born from HTLV-1 infected mothers will become infected.**

- **Risk of infection is higher, about fourfold increase, in breast-fed infants than in those who are bottle fed, and a longer duration of breast feeding (more than 6 month) increase transmission risk. Provirus load is the other important risk factor in breast milk.**

- **Since there are no prospects of vaccines and screening of blood banks, and prenatal care settings are not available in all area, transmission is active in many areas such as some parts of Africa, South and Central America, Asia, the Caribbean region, and Melanesia.**

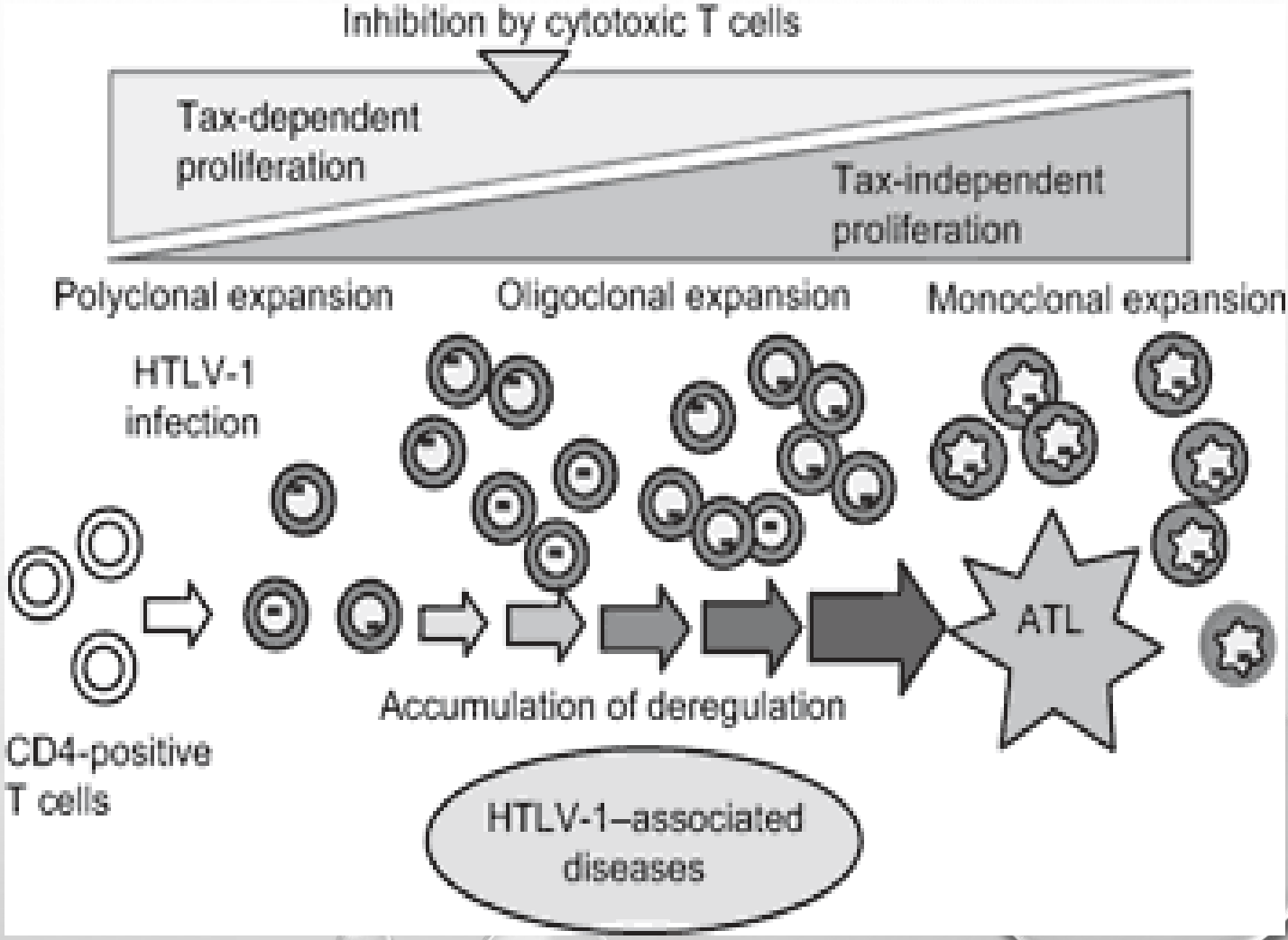
- **The infection is usually asymptomatic in the beginning and the disease typically manifests later in life, because of long latent period; therefore silent transmission occurs.**

Human T lymphotropic virus type 1 (HTLV-1) infection establishes a dynamic equilibrium between virus replication and immune destruction.

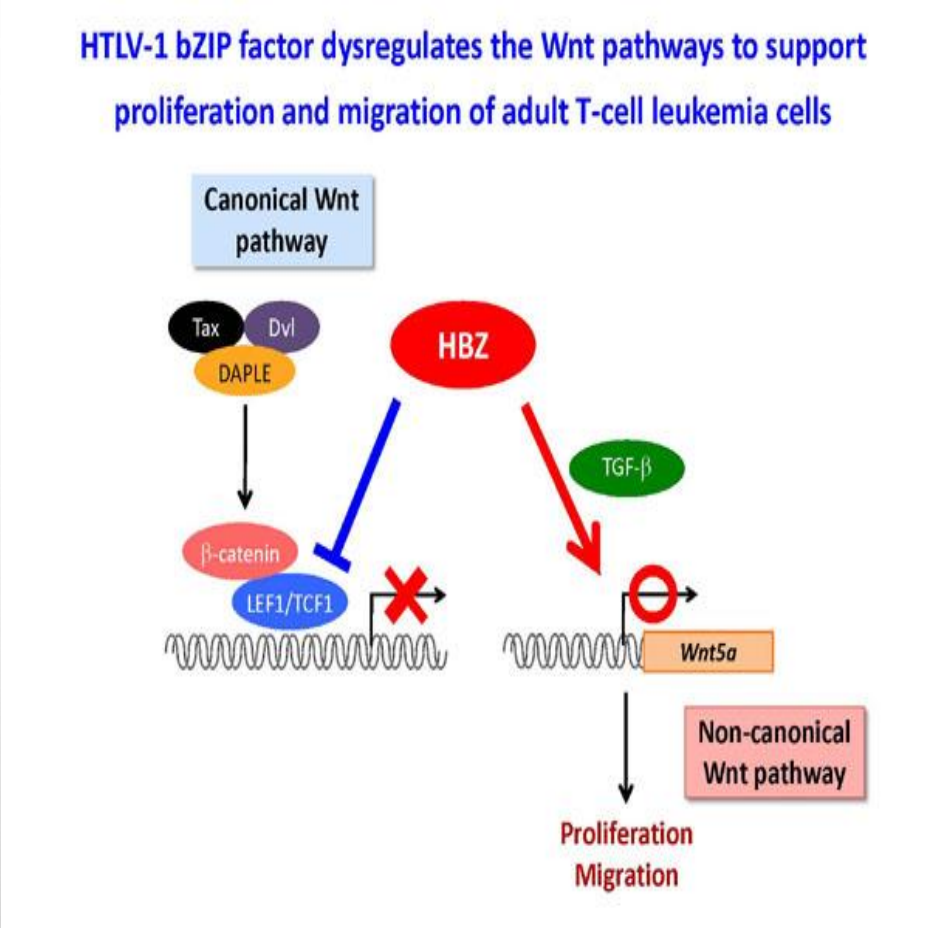


Charles R M Bangham J Clin Pathol 2000;53:581-586

In ATL, the tax gene plays a central role in the proliferation and transformation of HTLV-1-infected cells in vivo.



- Another gene recently described, the HTLV-1 bZIP factor (HBZ), uniformly expressed in ATL cells, seems to have a more important functional role in cellular transformation and leukemogenesis than does tax. HBZ transcription seems to be correlated with provirus load and also with the severity of HAM/TSP.



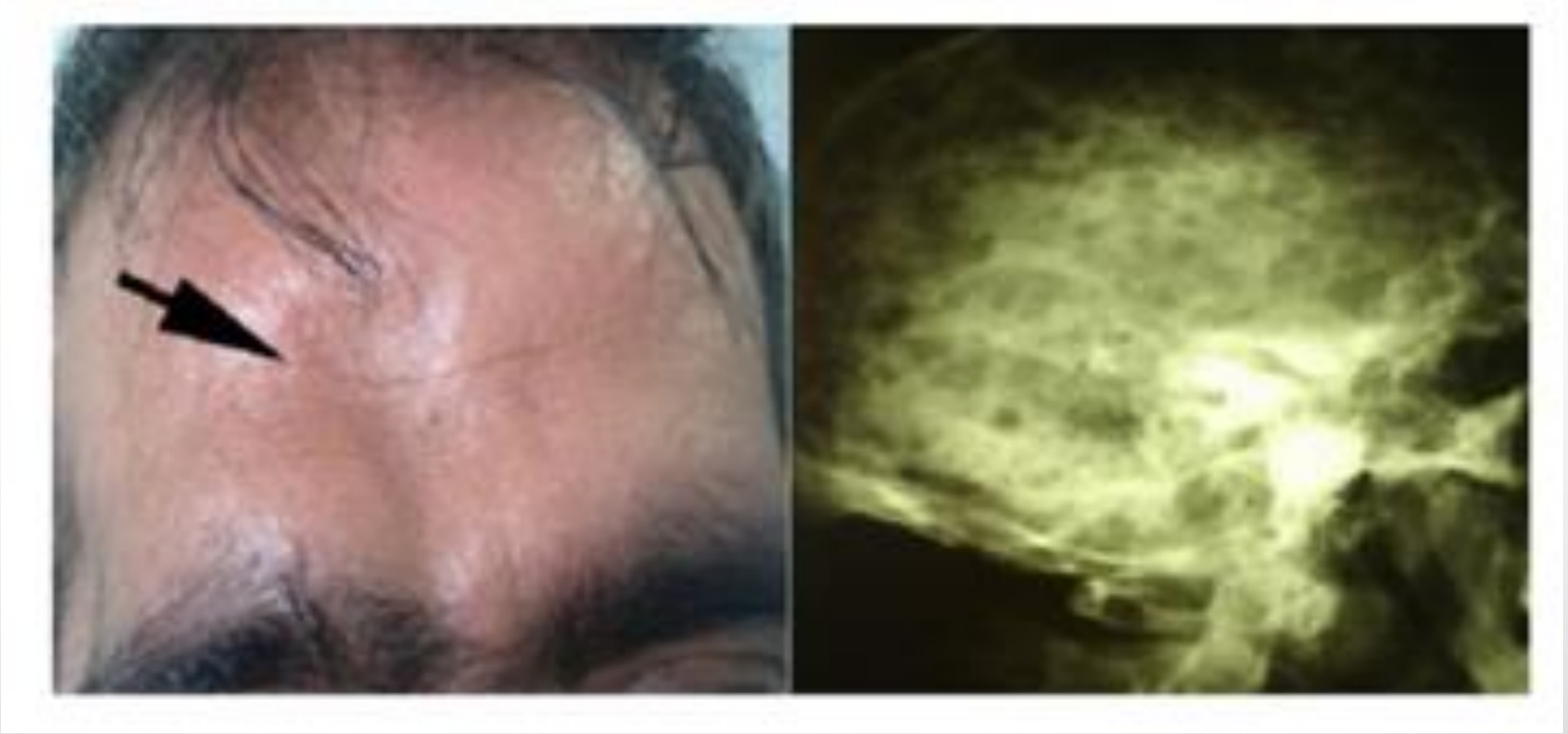
ADULT T-CELL LYMPHOMA LEUKEMIA

- Adult T-cell lymphoma leukemia (ATL) is a lymphoproliferative malignancy, with short survival in its acute form, and with an incidence of less than 5% in HTLV-1 infected people. The cumulative incidence of ATL among Japanese HTLV1 carrier is about 3-5% in male and 1-2% in female (average 2.5%).
- ATL occurs at least 20 to 30 years after onset of HTLV-1 infection, and is more common in men, although women are more infected with HTLV1.
- ATL was at first described in Japan and later in the South America and Caribbean region.

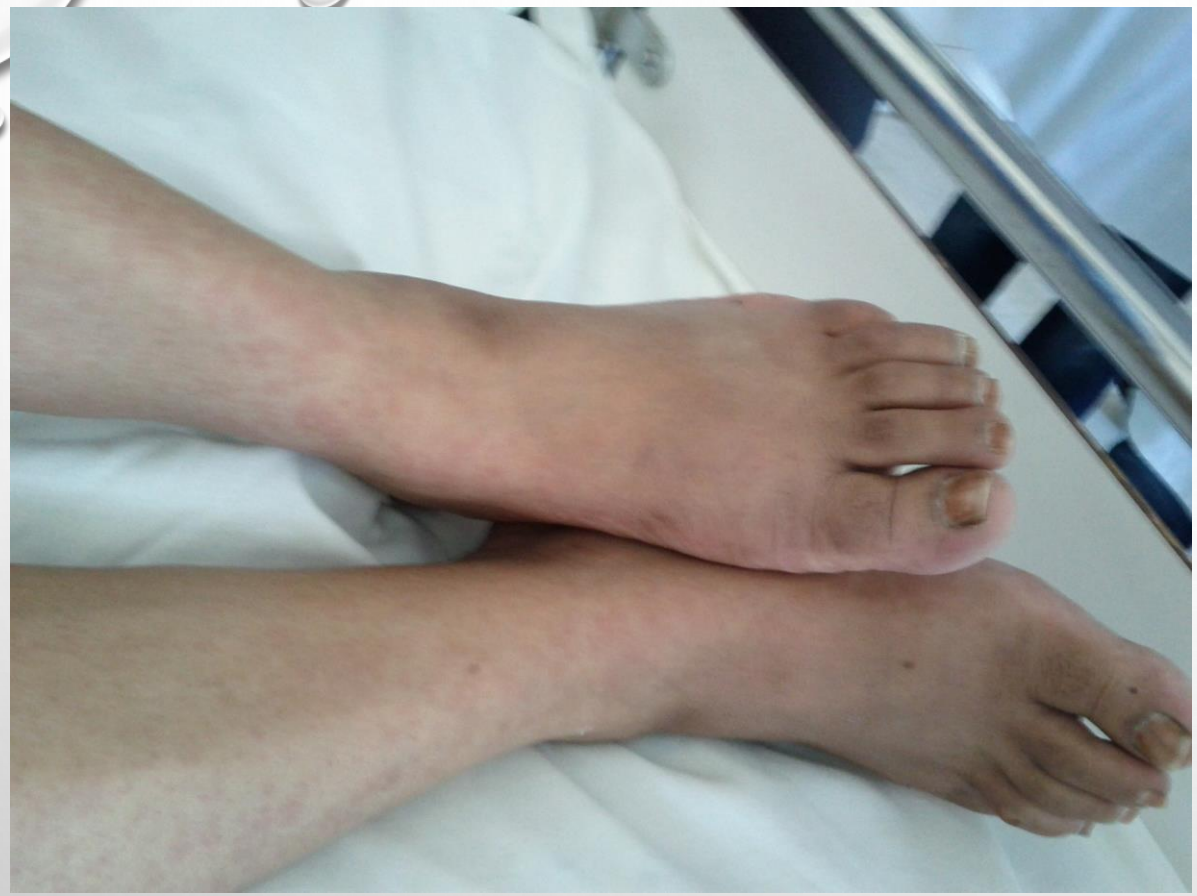
- In the United States and Europe, ATL was diagnosed in immigrants from the endemic regions.
- Individuals infected in childhood may be at a higher risk of developing ATL in comparison to people who infected in adult age.
- Local factors may play a role in disease pathogenesis, because the occurrence of ATL in the fourth decade predominates in Brazil and in Jamaica, but in Japan, the fifth decade of life is predominant for the occurrence of ATL.

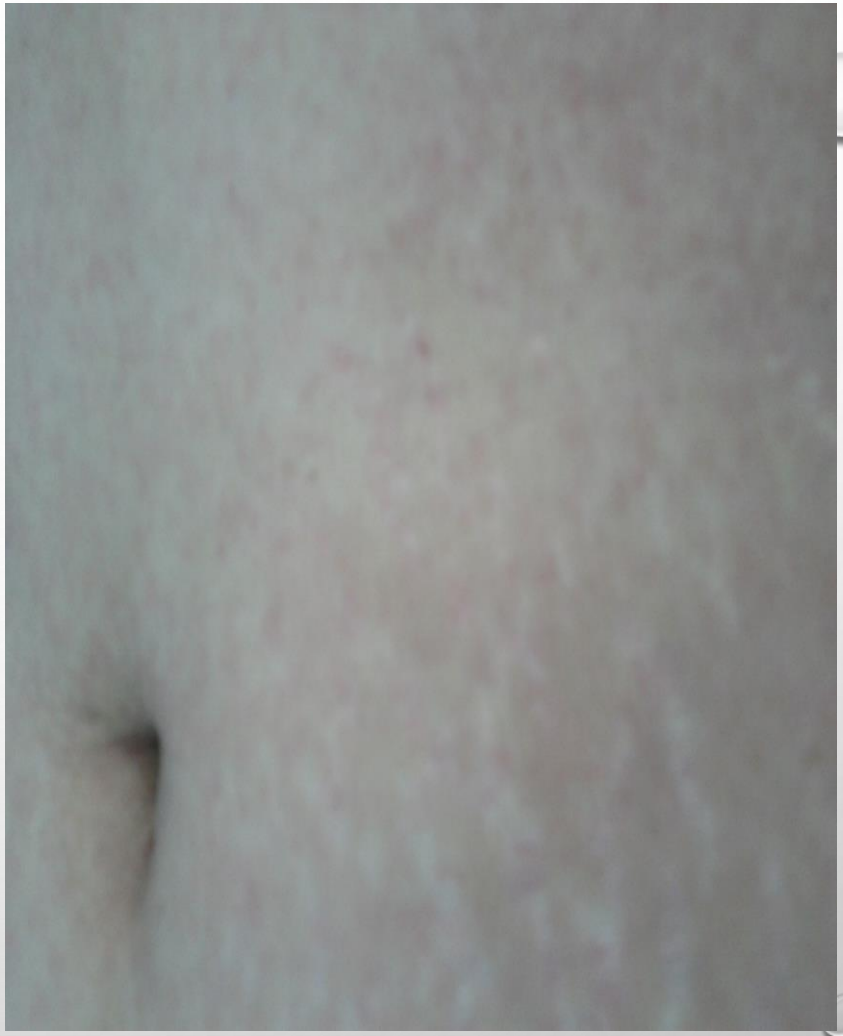
HTLV-1-associated lymphomas include

- 1- Acute ATL, account for 47% to 57% of cases with median survival of 6 month.
- clinical features include:
- Skin rash, bone pain, and lymphadenopathy,
- hypercalcaemia may also be present which can cause confusion, and severe constipation, raised level of LDH
- lytic bone lesions
- lymphoma cells appear in the blood,

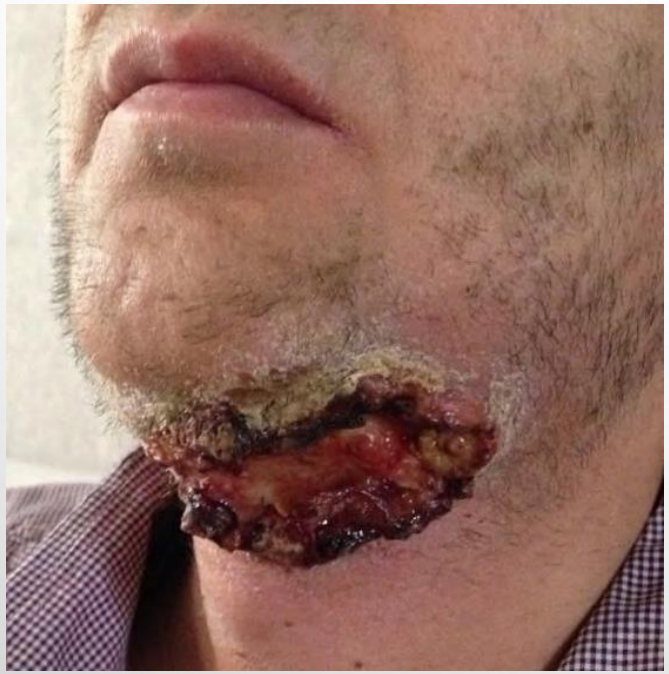


Bone lesion in adult T cell lymphoma leukemia





Skin rash in ATL



Skin mass in T cell lymphoma with HTLV1 positive.

after treatment with radiation therapy

- **2. Lymphomatous ATL, occurs in approximately 20-25% of cases, with median survival of 2 years.**
- **Which presents with lymphadenopathy, hepatosplenomegaly, skin rash and hypercalsemia, without leukemic involvement.**

- **3- Chronic ATL, account for approximately 25% of cases, with median survival of 2 years.**

- **Its characterized by skin lesions, leukemic, nodal, and visceral disease without hypercalcemia, gastrointestinal involvement, bone, or central nervous system disease.**

- **4- Smoldering ATL, is the least common type (5%), with median survival more than 5 years.**
- **which is characterized by small numbers of circulating leukemia cells**
- **without nodal involvement, and hypercalsemia.**

- **Patients with the chronic or smoldering types of ATLL can progress to the acute form of disease in about 25% of cases.**

Human T-lymphotropic virus (HTLV) testing is used to detect an infection by HTLV-I or HTLV-II

- **THE BODY'S IMMUNE SYSTEM RESPONDS BY PRODUCING ANTIBODIES THAT TARGET THE VIRUS**
- HTLV TESTING MAY BE USED IN A FEW DIFFERENT WAYS:

1. **IN PEOPLE WITH RISK FACTORS FOR HTLV (SUCH AS LIVING IN PARTS OF THE WORLD WHERE HTLV INFECTION IS MORE COMMON, HAVING A SEXUAL PARTNER WHO CAME FROM ONE OF THESE AREAS, HAVING MULTIPLE SEX PARTNERS, BEING AN IV DRUG USER, BEING A NATIVE AMERICAN INDIAN, OR HAVING A HISTORY OF BLOOD TRANSFUSIONS), TESTING MAY BE USED TO FOLLOW-UP ABNORMAL FINDINGS FROM A COMPLETE BLOOD COUNT (CBC) AND WBC DIFFERENTIAL, SUCH AS AN INCREASED NUMBER OF IMMATURE AND/OR ABNORMAL LYMPHOCYTES.**
2. **TO DIAGNOSE THE CAUSE OF A T-CELL-RELATED DISORDER IF A PERSON HAS SYMPTOMS CONSISTENT WITH HTLV-I–ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS (HAM/TSP), ESPECIALLY IF THE PERSON HAS RISK FACTORS ASSOCIATED WITH THIS CONDITION; IN SOME CASES, CEREBROSPINAL FLUID (CSF) MAY BE TESTED FOR HTLV.**
3. **TO DETERMINE THE SOURCE OF AN AFFECTED INDIVIDUAL'S INFECTION; SINCE HTLV CAN BE PASSED FROM MOTHER TO BABY DURING PREGNANCY, THE MOTHER OF AN AFFECTED CHILD MAY BE TESTED FOR HTLV-I OR HTLV-II TO DETERMINE IF SHE IS THE LIKELY SOURCE OF THE CHILD'S INFECTION. LIKEWISE, THE SEXUAL PARTNER OF AN AFFECTED PERSON MAY BE TESTED.**

- **TWO TYPES OF HTLV TESTING ARE AVAILABLE, ANTIBODY AND MOLECULAR TESTING:**
- **ANTIBODY.** EIA (ENZYME IMMUNOASSAY) AND WESTERN BLOT
- **PCR**

- **IN THE U.S., ALL DONATED BLOOD IS SCREENED FOR HTLV. IF A PERSON WHO HAS DONATED BLOOD TESTS POSITIVE FOR HTLV-I/II, THEN CONFIRMATORY TESTING MAY BE PERFORMED TO DETERMINE IF THE INITIAL SCREENING RESULT IS A FALSE POSITIVE OR IF THE PERSON WHO DONATED THE BLOOD HAS AN HTLV-I/II INFECTION.**

- **IN IRAN ,HTLV TEST IS PERFORMED IN SOME ENDEMIC AREA FOR BLOOD DONORS**

ADULT T-CELL LYMPHOCYTIC LEUKEMIA OR LYMPHOMA

- FEVER
- NIGHT SWEATS
- FATIGUE
- INCREASED NUMBER AND ABNORMAL IMMATURE LYMPHOCYTES
- ENLARGED LYMPH NODES

HTLV-I–ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

- WEAKNESS IN THE LOWER LIMBS
- MUSCLE SPASMS AND CONTRACTIONS
- LOWER BACK PAIN
- MUSCLE STIFFNESS
- URINARY, BOWEL, AND SEXUAL DYSFUNCTION

TESTING MAY BE PERFORMED ON:

- A MOTHER WHEN HER CHILD HAS BEEN DIAGNOSED WITH AN HTLV INFECTION
- THE SEXUAL PARTNER(S) OF A PERSON WHEN THAT PERSON HAS BEEN DIAGNOSED WITH AN HTLV INFECTION
- A PERSON WHEN HE OR SHE HAS BEEN TOLD THAT THE BLOOD THAT THE PERSON DONATED WAS POSITIVE FOR HTLV-I/II
- A PERSON WHEN HE OR SHE HAS RISK FACTORS AND SYMPTOMS THAT THE HEALTHCARE PRACTITIONER SUSPECTS MAY BE LINKED TO AN HTLV INFECTION, SUCH AS UVEITIS, DERMATITIS, OR ARTHRITIS

Initial Antibody Testing (HTLV I/II)	Confirmatory Testing (Western blot)	Additional Testing	Likely Interpretation
Negative	N/A	N/A	No infection
Positive	Negative	Repeat Western blot negative	False positive on initial test
Positive	Positive HTLV-I	N/A	HTLV-I infection
Positive	Positive HTLV-II	N/A	HTLV-II infection
Positive	Indeterminate	Molecular test (PCR) positive or repeat Western blot positive for HTLV-I or HTLV-II	HTLV-I or HTLV-II infection
Positive	Indeterminate	Molecular test (PCR) negative or indeterminate and repeat Western blot negative or still indeterminate	Likely false positive on initial antibody testing

Should everyone be tested for HTLV-I/II?

No. The incidence of HTLV-I/II is low in the iran and most people who are infected do not ever become ill, so it is not considered necessary. However, since the viruses can be passed from one person to another through blood transfusions and organ transplants, all donated blood and all relevant donated organs in endemic area are tested for HTLV-I/II.

Western blotting		PCR (*tax*/*pol*)			Real-time PCR (*pol*)		
Results[a]	*n*	HTLV-1	HTLV-2	Negative	HTLV-1	HTLV-2	Negative
HTLV-1	24	20	–	**4**	20	–	**4**
HTLV-2	21	–	15	**6**	–	15	**6**
HTLV	3	1	1	**1**	1	1	**1**
Indeterminate	16	**1**	**3**	12	**1**	**4**	11
Negative	9	–	–	9	–	–	9
Total	73	22	19	32	22	20	31
Positive samples	48 (63.8%)		41 (56.2%)			42 (57.5%)	

Test algorithm for screening and confirmation of HTLV-1/2 infection in low-endemic areas

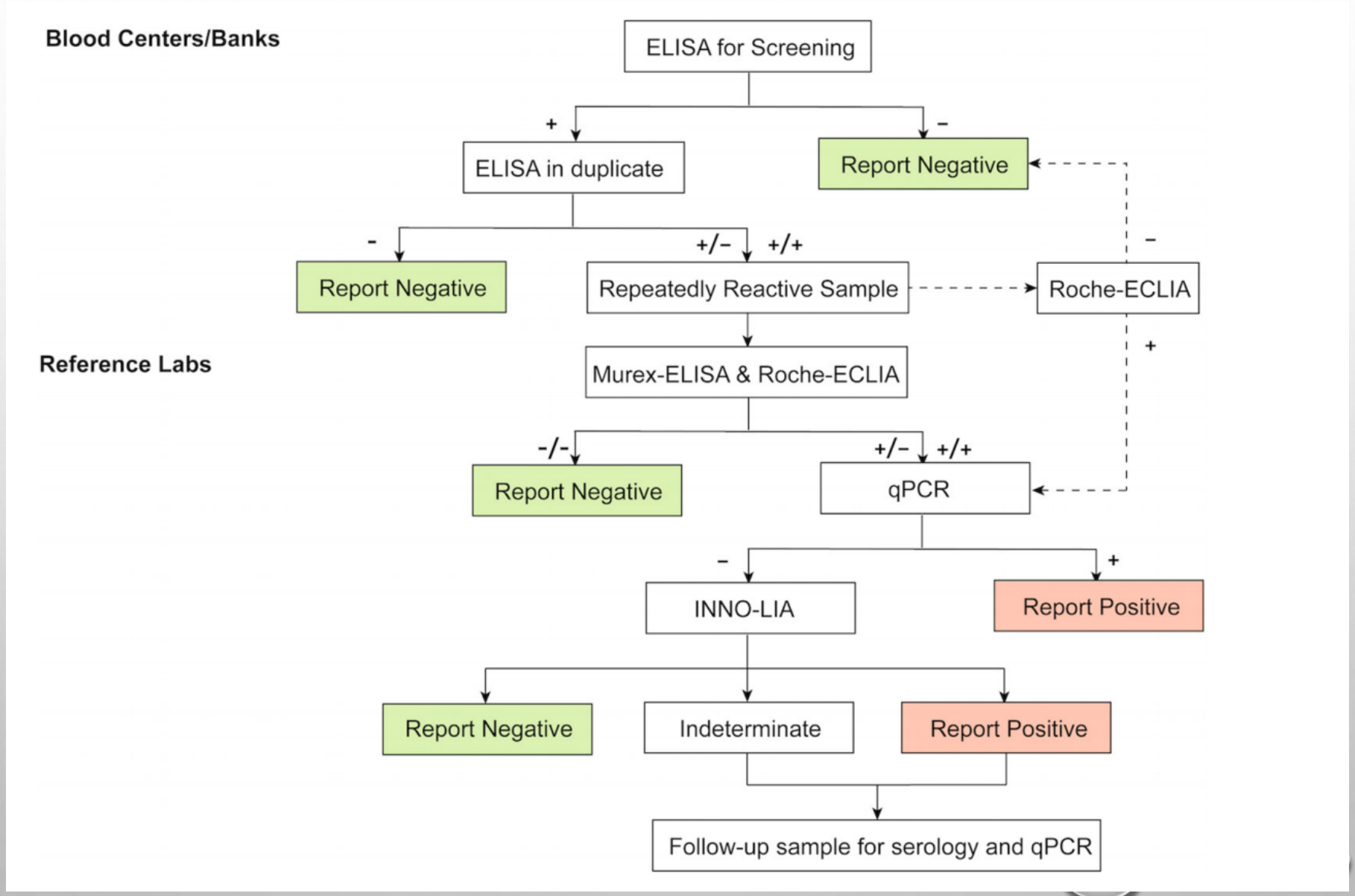


TABLE 1 | Technical features of evaluated assays and confirmatory assays used in the study.

Assay name	Manufacturer	Assay type	Detection antigens	Testing time
Elecsys HTLV-I/II	Roche diagnostics	One-step double-antigen sandwich chemiluminescent immunoassay	Viral recombinant antigens gp21 and p24	18 min
Lumipulse G HTLV-I/II	Fujirebio	Two-step sandwich chemiluminescent immunoassay	Recombinant antigens p19 I/II, p24 I/II, gp46 I/II, gp21 I	4 min
Avioq HTLV-I/II Microelisa System	Avioq	ELISA	Viral antigens (purified viral lysate) and recombinant HTLV-1 p21E antigen	150 min
Murex HTLV-I/II	Diasorin	ELISA	HTLV-1 and HTLV-2 antigens	90 min
INNO-LIA HTLV I/II score	Fujirebio	A line immunoassay	Recombinant antigens p19 I/II, p24 I/II, gp46 I/II, gp21 I/II	18 h
MP HTLV Blot 2.4	MP Biomedicals	Western Blot assay	Recombinant HTLV-1/2 antigens and HTLV-1 viral lysate	150 min

ELISA, enzyme-linked immunosorbent assay.

- **The diagnosis of ATL is based upon a combination of:**
- **specific clinical featurs,**
- **the morphology ”Flower cell”**

- **immunophenotype of the malignant cells “analysis of CD3, CD4, CD7, CD8, and CD25 for an immunophenotypic diagnosis is required”**

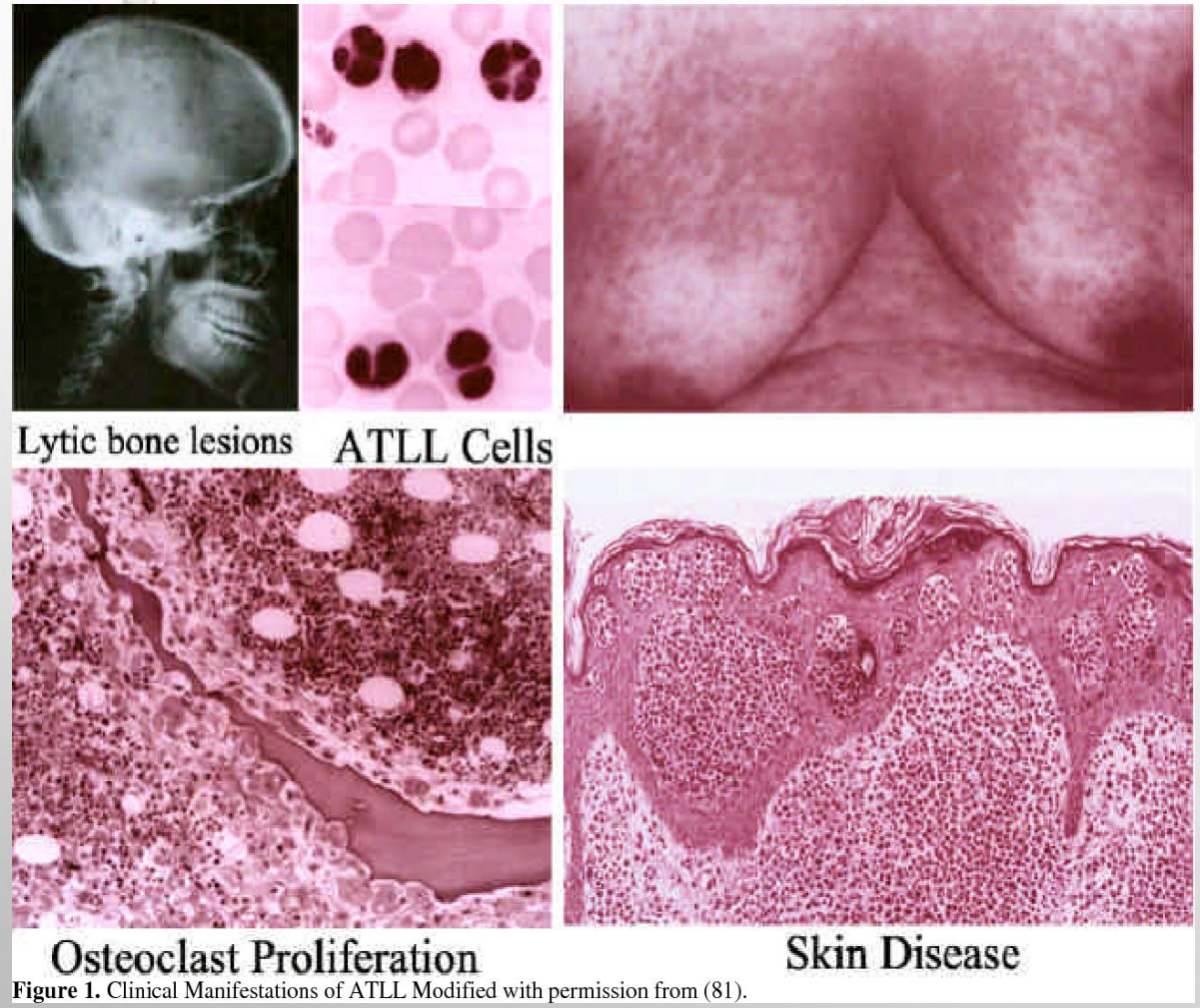
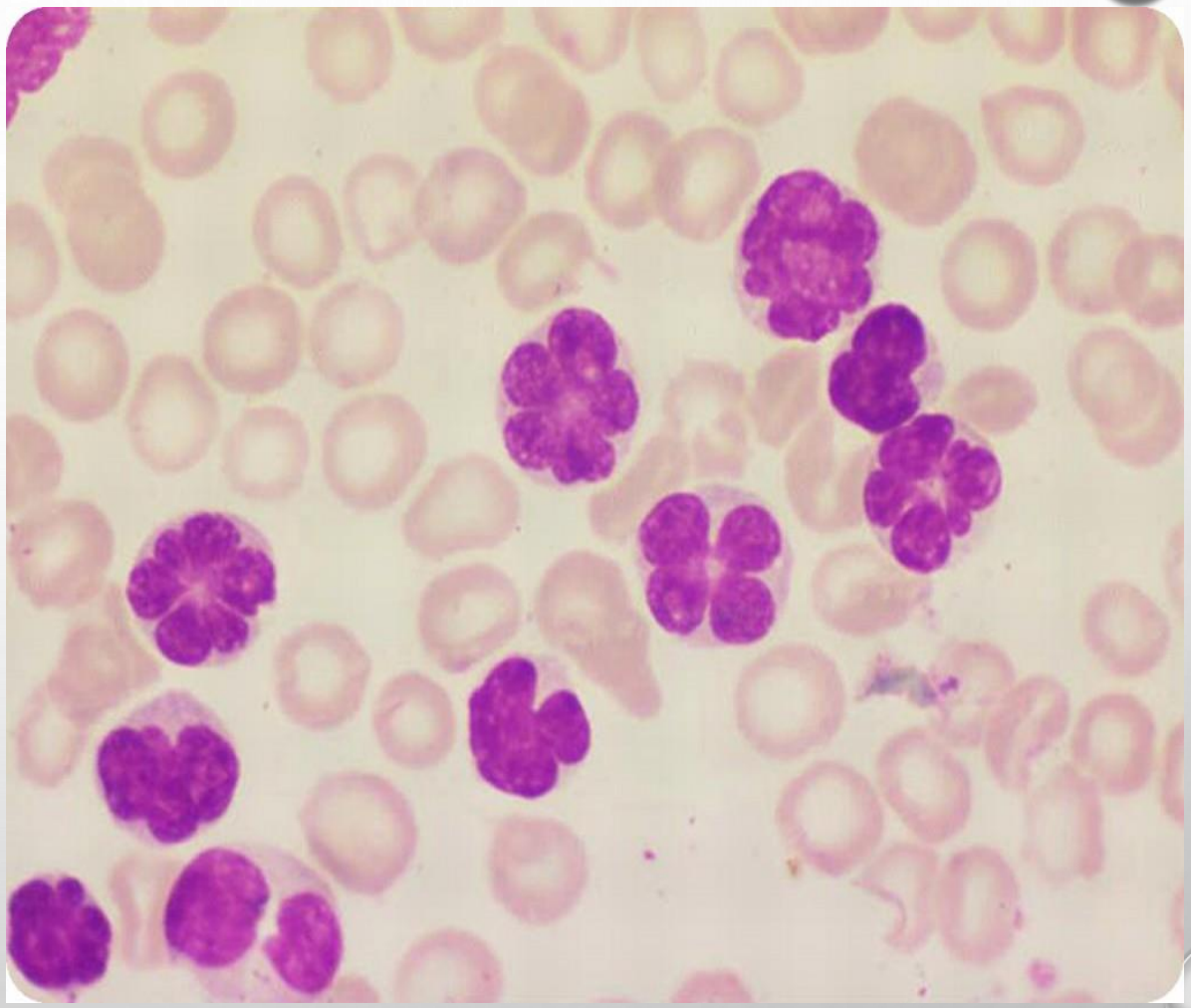


Figure 1. Clinical Manifestations of ATLL Modified with permission from (81).



- The ATLL treatment strategies are vary between different countries for example;
- In Japanese patients demonstrated higher CRR with more aggressive regimen instead CHOP(40% versus 25%), but OS was similar.
- AZT/IFN-α therapy has not been extensively investigated in Japan and very few experiences are available.
- By contrast, AZT/IFN-α therapy has been the treatment of choice in practical settings in the USA, England, France, Brazil and IRAN.
- Allogenic stem cell transplantation has been reported to benefit some patients already in remission.

The major prognostic factors are advanced performance status, high calcium and LDH levels, age of more than 40 years, and more than three involved lesions. Bone marrow involvement is an independent poor prognostic factor for ATL

The rate of survival varies depending on the **subtype:**

4 to 6 months for the **acute type,**

9 to 10 months for the **lymphomatous type,**

17 to 24 months for the **chronic type,**

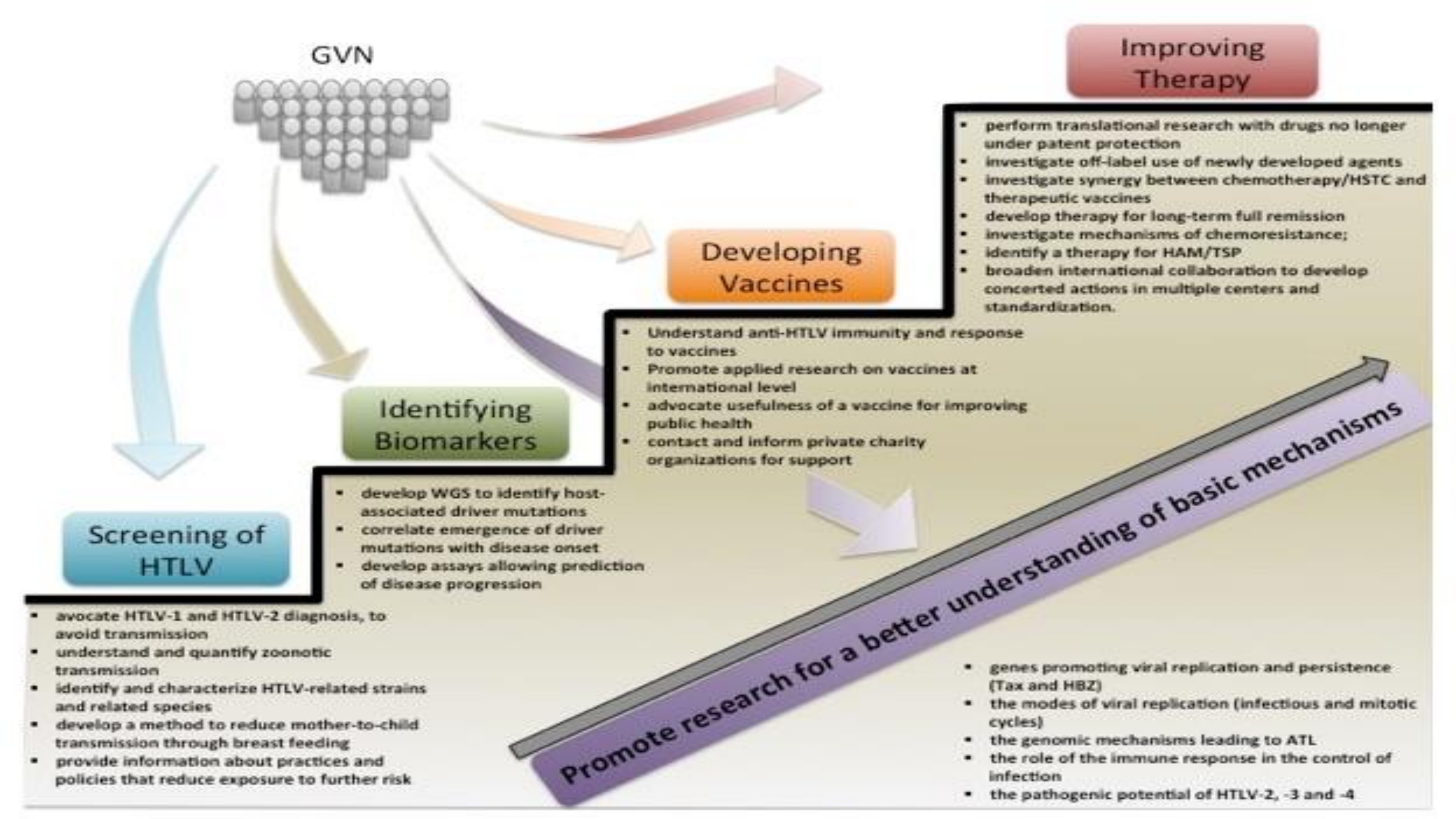
34 months to more than 5 years for the **smoldering type**

CONCLUSION 1

- **Future epidemiological research on T cell lymphoma will be enhanced by analyses of its sub-types, improved reliability and validity of exposure assessment tools to evaluate environmental and personal exposure and evaluation of susceptible subgroups of individuals whose risk of T cell lymphoma may differ from that of the general population, especially in some specific area**

CONCLUSION 2

- Although the incidence of ATL is found to be relatively low among individuals with HTLV-1 infection, because the diseases are generally severe and progressively incapacitating, the prevention of virus transmission is advantageous not only at the individual level but also in the public health setting as well.
- HTLV-1 should be added to the list of diseases that are preventable with safe sexual behavior. The development of an effective and safe vaccine as well as preventive measures in blood banks and prenatal care settings in areas of endemicity should be emphasized.
- Treatment strategies should be based on ATL sub-classification and prognostic factors at onset.


GVN
Improving Therapy
perform translational research with drugs no longer under patent protection
investigate off-label use of newly developed agents
investigate synergy between chemotherapy/HSTC and therapeutic vaccines
develop therapy for long-term full remission
investigate mechanisms of chemoresistance;
identify a therapy for HAM/TSP
broaden international collaboration to develop concerted actions in multiple centers and standardization.
Developing Vaccines
Understand anti-HTLV immunity and response to vaccines
Promote applied research on vaccines at international level
advocate usefulness of a vaccine for improving public health
contact and inform private charity organizations for support
Identifying Biomarkers
develop WGS to identify host-associated driver mutations
correlate emergence of driver mutations with disease onset
develop assays allowing prediction of disease progression
Screening of HTLV
avocate HTLV-1 and HTLV-2 diagnosis, to avoid transmission
understand and quantify zoonotic transmission
identify and characterize HTLV-related strains and related species
develop a method to reduce mother-to-child transmission through breast feeding
provide information about practices and policies that reduce exposure to further risk
Promote research for a better understanding of basic mechanisms
genes promoting viral replication and persistence (Tax and HBZ)
the modes of viral replication (infectious and mitotic cycles)
the genomic mechanisms leading to ATL
the role of the immune response in the control of infection
the pathogenic potential of HTLV-2, -3 and -4