Epidemiological Aspects of HTLV-1 (Human T-Cell Leukemia virus type 1) with a Special Focus on Central Africa (the largest endemic HTLV-1 area)

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The First Human Onco-Retrovirus: HTLV-I

- **Discovery**: 1980 NIH USA, 1981 Japan
- **Retroviridae, Othoretrovirinae, Deltaretrovirus**
- **Several associated diseases** (hematological ATL, neurological TSP/HAM, dermatological ID, muscular Myositis, ...)
- **Peculiar epidemiology** (foci, high endemic areas, >5/10 millions of infected persons).
- **In vivo tropism**: mainly CD4+ and CD8 + lymphocytes
- **Cellular receptor complex**: HSPGs, GLUT-1 and NRP1

Extracellular Type C Retroviral particles produced by a T lymphoid cell line established from the culture of the PBMCs of a patient with a TSP/HAM. Gessain et al., 1989.

Isolation of HTLV-1
1980, USA

Description of ATL
1973-1977, Japan
# Diseases associated with HTLV-1 infection

## Diseases

<table>
<thead>
<tr>
<th>Adulthood</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult T-cell leukaemia/lymphoma (ATLL)</strong></td>
<td>++++</td>
</tr>
<tr>
<td><strong>Tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM)</strong></td>
<td>++++</td>
</tr>
<tr>
<td><strong>Infective dermatitis (very rare)</strong></td>
<td>++++</td>
</tr>
<tr>
<td><strong>Intermediate uveitis (Japan/Caribbean)</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Myositis (polymyositis and SIBM)</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Bronchiectasis (Central Australia)</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>HTLV-1 associated arthritis (Japan)</strong></td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infective dermatitis (Jamaica, Brazil, Africa)</strong></td>
<td>++++</td>
</tr>
<tr>
<td><strong>TSP/HAM (very rare)</strong></td>
<td>++++</td>
</tr>
<tr>
<td><strong>ATLL (very rare)</strong></td>
<td>++++</td>
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</tbody>
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The strength of association is based on epidemiological studies as well as molecular data, animal models and intervention trials. ++++: proven association, +++: probable association, ++: likely association.

The geographical location corresponds to the regions where these diseases were most commonly reported.

SIBM: Sporadic Inclusion Body Myositis.
1) What is the current real geographical distribution of HTLV-1 and how many individuals are infected worldwide?
Minimal estimation of 5-10 million HTLV-1 infected carriers based on available data for 1.5 billion persons originating from known endemic areas.

Current number is probably much higher.

World distribution major HTLV-1 endemic foci

Prevalence can reach >>20/30% in adults > 50 years in some areas

(A. Gessain and O. Cassar - 2012)
Asia & Australo-Melanesia

(>1.5 million)

<table>
<thead>
<tr>
<th>Continent / Country</th>
<th>Population⁰</th>
<th>HTLV-1 range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujian Province (China)</td>
<td>35 110 000</td>
<td>2 000</td>
</tr>
<tr>
<td>Japan*</td>
<td>127 368 088</td>
<td>1 080 000</td>
</tr>
<tr>
<td>Mashad area (Iran)</td>
<td>78 868 711</td>
<td>10 000</td>
</tr>
<tr>
<td>Taiwan</td>
<td>23 113 901</td>
<td>10 000</td>
</tr>
<tr>
<td>AUSTRALO-MELANESIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia (Aboriginal Australians)</td>
<td>463 900</td>
<td>2 500</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>584 578</td>
<td>3 000</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>227 574</td>
<td>250</td>
</tr>
</tbody>
</table>

For nearly 3 billion persons (China, India,…), no reliable epidemiological data, despite the presence of several small series or sporadic reported cases of ATLL and TSP/HAM
Africa (>2.5-5.5 millions)

No reliable estimation for the highly populated areas of North and East Africa, around half of the african population.

Need large epidemiological surveys in Africa (Nigeria, South Africa) and in Asia (India).

Epidémiologie et Physiopathologie des Virus Oncogènes
2) Concerning Europe, what is the origin of HTLV-1 in Romania and what is its real extend and importance?
Europe (UK, France, Spain,..) Individuals originating from high HTLV-1 endemic areas (Caribbean area, South America and Africa,..), except Romania.

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</thead>
<tbody>
<tr>
<td>EUROPE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United kingdom**</td>
<td>63,047,162</td>
<td>20,000</td>
</tr>
<tr>
<td>France</td>
<td>65,630,692</td>
<td>15,000</td>
</tr>
<tr>
<td>Spain</td>
<td>47,042,984</td>
<td>1,000</td>
</tr>
<tr>
<td>Romania</td>
<td>21,848,504</td>
<td>3,000</td>
</tr>
</tbody>
</table>

Epidémiologie et Physiopathologie des Virus Oncogènes
In 2012, the EU Commission requested ECDC to construct a map indicating all the HTLV-1 high prevalence areas in the world. EPVO unit was asked to respond to a request for offer entitled: “Systematic Review of Scientific Evidence on the Prevalence of HTLV-1 Infection”

By analysing more than 1000 papers and hundreds of abstracts, we provided the first complete epidemiological data (maps and tables) for the 203 world’s countries.

Ongoing collaborative studies (EPVO/Necker/Romania) combining:
1) Epidemiology
2) Genotyping of HTLV-1 strains (complete sequences)
3) Populations genetics to try to decipher the origin of these strains and this HTLV-1 focus.
3) What is the situation in Australian Natives from Central Australia?

Epidemiology and Genotype

The Guardian

'People are scared': the fight against a deadly virus no one has heard of

HTLV-1 is endemic across central Australia. But testing takes six months and is not freely available

A call to arms against the other retrovirus

HTLV-1, discovered just before HIV but almost forgotten, infects millions and causes cancer

Correspondence

Time to eradicate HTLV-1: an open letter to WHO

*Fabiola Martin, Yutaka Tagaya, Robert Gallo
fabiola.martin@uq.edu.au
www.thelancet.com Vol 391 May 12, 2018

Doctors raise alarm about ancient HTLV-1 virus: 'Prevalence is off the charts' in Australia

World experts call for Australia to act on devastating HTLV-1 virus

UK clinician says central Australia’s ‘shocking’ 45% infection rate demands action
A) Indigenous Australians have one of the highest HTLV-1 prevalence in the world

(long-term collaboration with Lloyd Einsiedel from Alice Springs)
Such high prevalences have been already reported in some very high endemic areas for at least 20 to 40 years....

Villagers in South Japan

Noir-Marron (population of African Origin) in French Guyana
The origin of this puzzling geographical or often ethnic repartition, associated with a high prevalence is not well explained but is very probably linked to a founder effect in some groups, with a persistence of a high level of viral transmission rate.

These modes of transmission could be different according to the situation.

Pygmies, Indigenous Australians, South Japan, Noir-Marron, Mashhad, Tumaco, Haut-Ogoué,....
B) HTLV-1c Genetic Variant is endemic in Indigenous people from Australo-Melanesia (PNG, Solomon Islands, Vanuatu, Australia, …).
Human T Lymphotropic Virus Type 1 Subtype C Melanesian Genetic Variants of the Vanuatu Archipelago and Solomon Islands Share a Common Ancestor

Olivier Cassar,1,2 Corinne Capurro,1 Sylviane Basset,3 Françoise Charavay,1 Renan Duprez,2 Philippe V. Afonso,3 Myriam Abid,1 Helene Weiler,4 Wohaka Mere, Paul M. V. Martin,1 Etienne Choungue,4 and Antoine Cassar1

1Laboratoire d’Épidémiologie Moléculaire, Institut Pasteur de Nouvelle-Calédonie, Nouméa, and 2Unité d’Épidémiologie et Physiopathologie des Virus Oncogènes, Département de Virologie, Institut Pasteur, Paris, France, 3World Health Organization, 4Ministry of Health of the Republic of Vanuatu, and 5Vanuatu Family Health Association, Port Vila, Vanuatu

At least two different strains quite ancient >10,000 years

Epidémiologie et Physiopathologie des Virus Oncogènes
4) What is the Simian Origin (STLV-1) of the Most Commonly World-Wide Spread Genotype (a Cosmopolitan) of HTLV-1?
HTLVs originate from STLVs found in Apes and Monkeys through interspecies transmission

PTLV = Primate T-lymphotropic viruses

1) Some of the infected monkeys develop a typical ATL with clonal integration of STLV-1 provirus in the tumor cells.

2) STLV-1 infection is widespread in Old World monkey and ape species (chimpanzee, gorilla, mandrill, AGM, macaques, Orang-utan).

If found in NHP = STLV
If found in Human = HTLV

(A. Gessain and O. Cassar - 2012)
Map of the geographical distribution of HTLV-1 subtypes (A–G), and the main modes of viral dissemination by movements of infected populations.
Quid about interspecies transmission from STLV-1 monkeys to Human in Asia?

4) Several monkeys species are infected by STLV-1 in Asia (macaques ++), however there is no known human populations infected by such strains? This contrast with the situation in Central Africa where spill-over is still ongoing and also does not fit with the fact that other simian retroviruses, as the SFV, are still being transmitted from monkeys to humans in several Asian countries.
5) Are the different modes of transmission/acquisition of HTLV-1 similar on a quantitative point of view in the main high endemic areas?

Such data are crucial for public health actions aimed to decrease HTLV-1 infection.
MTCT has been often considered as the most important mode of transmission in high endemic areas but solid data on such topic remain scarce. A recent paper in Japan demonstrated that sexual transmission between young adults is important with around 4,000 new infections/year.

The modes of acquisition of HTLV-1 in Central Africa, which is the largest HTLV-1 endemic area in the world

In Central Africa, at least five different modes of acquisition/transmission can occur:

- Mother to child
- Sexual
- Transfusion
- Scarification
- Contact with fluids from NHPs

The relative contribution of each of the different transmission routes for HTLV-1/STLV-1 (between the different inter-humans modes and inter-humans vs inter-species/NHP-Humans) remains unknown.

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The first study was performed in Cameroon focused on the origin and interspecies transmission of different retroviruses from NHPs living in the wild.

More than 5000 plasmas and buffy-coats of adults (mean age 50 years) were tested in a retrospective study in general rural population including Pygmees or Bantus living close to NHPs habitats and a prospective study focused on more than 300 individuals who reported direct contacts (bites, wounds,...) with animals, especially NHPs mainly during hunting activities.

Calattini et al., EID, 2007
STLV-3/HTLV-3

**Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa**
Sara Calattini¹, Sébastien Alain Chevalier¹, Renan Duprez¹, Sylviane Bassot¹, Alain Froment², Renaud Mahieux¹, and Antoine Gessayin*¹

**New Strain of Human T Lymphotropic Virus (HTLV) Type 3 in a Pygmy from Cameroon with Peculiar HTLV Serologic Results**
Sara Calattini, Edouard Betsem, Sylviane Bassot, Sébastien Alain Chevalier, Renaud Mahieux, Alain Froment, and Antoine Gessayin

STLV-4/HTLV-4

**Zoonotic Transmission of Two New Strains of Human T-lymphotropic Virus Type 4 in Hunters Bitten by a Gorilla in Central Africa**
Léa Richard, Augustin Mounia-ondème, Edouard Betsem, Claudia Filippone, Eric Nerrienet, Mirsad Kazanji, and Antoine Gessayin

Clinical Infectious Diseases Advance Access published April 1, 2015

**A Severe Bite From a Nonhuman Primate is a Major Risk Factor for HTLV-1 Infection in Hunters From Central Africa**
Claudia Filippone, Edouard Betsem, Patricia Tortevoye, Olivier Cassar, Sylviane Bassot, Alain Froment, Arnaud Fontanet, and Antoine Gessayin

**HTLV-1 infection was associated to the severity of the bite**
Case-control Study
Indicates the Presence of
Some Biological Differences
In Hunters Infected with SFV from Gorilla

Clinical Signs and Blood Test Results Among Humans Infected With Zoonotic Simian Foamy Virus: A Case-Control Study
The second projet is currently developped in Gabon

We will try to quantify each of the different modes of transmission by conducting studies in specific populations including at least 12 000 persons:

1) **General population of rural areas** with a specific questionnaire for heterosexual transmission within couples, transfusion, hospitalisation, contact with monkeys, especially bites, and scarifications and other suspected risk factors. 2000 persons are already included. We plan to study 4 000 (both Bantus ++ and Pygmies).

2) **Pregnant women** (3000) and **children** (1500) to get insights into MTCT. Children in such high endemic area can also be infected by transfusion.

3) **Blood donors** from the Libreville National Transfusion Centre. 3000 persons are already included.

**Risk factors** associated with HTLV-1 infection and corresponding attributable fractions will be identified using logistic regression models.
Preliminary data

2060 individuals from six different provinces were included 1205 men and 855 women (mean age 49 years)

WB and PCR demonstrated that the prevalence rate is of 8.7%

Increase with age and higher in women and in Pygmies

D. D. Djuicy, PNTD 2018
The distribution of HTLV-1 infection is heterogeneous across the country.

The overall prevalence (8.7%) appears to be higher than in neighboring countries (Cameroon CAR, ..) for similar populations.
Risk factors for HTLV-1 infection

According to crude OR, HTLV-1 infection is associated with sex (women>> men), increased age, Pygmy groups, scarification, history of blood transfusion, multiple hospitalisations.

In the final multivariable analysis model, we found an increased independent risk of HTLV-1 in women, the elderly, persons having a history of multiple hospitalisations (more than 5 times) and Pygmies. In addition, a NHP bite appears to be marginally associated with a higher risk of HTLV-1.

D. D. Djuicy, PNTD 2018
Molecular Epidemiology of HTLV-1 in Central Africa

A total of 178 strains were partially characterized env and/or LTR.

The majority of the strains belong to the Central African molecular b-subtype (90.%). However, there was a certain genetic diversity: 10 viral strains belong to the Cosmopolitan a subtype (TC subgroup) (3.8%), 6 strains to the d subtype (5.3%), while 3 strains are of the f-subtype (1.5%) and a single strain from Cameroon belongs to the rare g-subtype (0.6%).
First complete sequences of African HTLV-1 b, d and f genotypes

- 2 HTLV-1b
- 2 HTLV-1d
- 1 HTLV-1f
Take-Home Messages

1) The current real geographical distribution of HTLV-1 and the number of HTLV-1 infected individuals remain unknown: Need large epidemiological surveys in Africa and in Asia

2) In Africa, the largest HTLV-1 endemic area, the relative contribution of each of the different transmission routes remains unknown

3) Gabon is a very high HTLV-1 endemic foci and HTLV-1 can be acquired by different means: sexual, mother to child, during hospitalization, and through contact with NHPs.

4) In Central Africa there is some genetic diversity of HTLV-1 (b, d, e, f, g,) with subtype b being highly predominant.
What is the world burden of HTLV-1 associated diseases?

Except in Japan where the situation is quite well known at least for:

- ATLL (around 800-1000 cases/year) and TSP/HAM (at least 50 cases a year).

Situation in most of the other endemic areas in the world is not really known. This is linked to several factors:

- HTLV-1 and the associated diseases are not well known from the clinicians who thus do not diagnosed them.

- Tests for HTLV-1 infection are rarely available in many areas and countries.

- Hematologists and neurologists are rare in many countries endemic for HTLV-1 (Africa).

- No specific studies on large scale for a given country.

This leads to a huge under-reporting of such diseases and new studies are absolutely necessary.
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Epidémiologie et Physiopathologie des Virus Oncogènes

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Epidémiologie des maladies émergentes
Arnaud Fontanet