



Epidemiological aspects and world distribution of HTLV-1 infection

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The human T-cell leukemia virus type 1 (HTLV-1), identified as the first human oncogenic retrovirus 30 years ago, is not an ubiquitous virus. HTLV-1 is present throughout the world, with clusters of high endemicity located often nearby areas where the virus is nearly absent. The main HTLV-1 highly endemic regions are the Southwestern part of Japan, sub-Saharan Africa and South America, the Caribbean area, and foci in Middle East and Australo-Melanesia. The origin of this puzzling geographical or rather ethnic repartition is probably linked to a founder effect in some groups with the persistence of a high viral transmission rate. Despite different socio-economic and cultural environments, the HTLV-1 prevalence increases gradually with age, especially among women in all highly endemic areas. The three modes of HTLV-1 transmission are mother to child, sexual transmission, and transmission with contaminated blood products. Twenty years ago, de Thé and Bomford estimated the total number of HTLV-1 carriers to be 10–20 millions people. At that time, large regions had not been investigated, few population-based studies were available and the assays used for HTLV-1 serology were not enough specific. Despite the fact that there is still a lot of data lacking in large areas of the world and that most of the HTLV-1 studies concern only blood donors, pregnant women, or different selected patients or high-risk groups, we shall try based on the most recent data, to revisit the world distribution and the estimates of the number of HTLV-1 infected persons. Our best estimates range from 5–10 millions HTLV-1 infected individuals. However, these results were based on only approximately 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, thus, the current number of HTLV-1 carriers is very probably much higher.

Keywords: HTLV-1, HTLV-1 epidemiology, HTLV-1 world distribution, HTLV-1 in Europe, HTLV-1 in Africa, HTLV-1 in the Americas, HTLV-1 in Asia, HTLV-1 in Oceania

INTRODUCTION

Very rapidly after HTLV-1 discovery and its association with adult T-cell leukemia (ATL), several studies were initiated both by American and Japanese researchers, to get insights into the distribution, the transmission modes, as well as the origin of HTLV-1.

Thus, as soon as 1982–1984, important works demonstrated clearly that Japan was a high endemic area for HTLV-1. Interestingly, since the first studies, the geographic distribution of HTLV-1 carriers is quite uneven in Japan and the greatest prevalence is observed in Southwestern Japan (Kyushu island and the Okinawa archipelago). The origin of such a peculiar distribution is still the matter of several hypotheses (Ishida and Hinuma, 1986; Miura et al., 1994; Eguchi et al., 2009; Watanabe, 2011).

Nearly concomitantly to the initial papers by the Japanese groups, the US teams demonstrated that the Caribbean area was also endemic for HTLV-1. Soon after, ATL patients were reported in the Caribbean community living in the United Kingdom (Catovsky et al., 1982). Such data, together with some early epidemiological studies showing an HTLV-1 seroprevalence in

serum samples from inhabitants originating from different African countries, indicated then that such a retrovirus was also endemic in some areas of the African continent (Biggar et al., 1984; Hunsmann et al., 1984; Saxinger et al., 1984; de-The et al., 1985; de The and Gessain, 1986; Delaporte et al., 1989a,b, 1991; Ouattara et al., 1989; Verdier et al., 1989, 1994; Goubau et al., 1990; Dumas et al., 1991; Schrijvers et al., 1991).

The simian counterpart of HTLV-1 was also rapidly discovered, based on the findings of STLV-1 in several monkey species from Asia and Africa (Hunsmann et al., 1983; Guo et al., 1984; Hayami et al., 1984; Homma et al., 1984; Becker et al., 1985; Watanabe et al., 1985; Blakeslee et al., 1987; Korálnik et al., 1994).

The different transmission modes of HTLV-1 have been rapidly studied by the same groups (Kinoshita et al., 1984; Okochi et al., 1984; Hino et al., 1985; Kajiyama et al., 1986; Murphy et al., 1989; Takahashi et al., 1991; Hino, 2011). They are now rather well understood. This led to some efficient preventive measures in several countries (Ando et al., 1987; Hino et al., 1987; Inaba et al., 1989).

In contrast, the world distribution and the global and loco-regional estimation of the HTLV-1 prevalence remain yet poorly known. This lack of knowledge is mainly due to four different factors: (1) Several large regions/areas have not been investigated for HTLV-1 infection. Thus, the prevalence remains barely unknown in many areas of the world. This is evident in some highly populated regions of Asia or in East and North Africa. (2) The assays used for HTLV-1 serology exhibited some lack of specificity leading in the 1980s–1990s to an overestimated HTLV-1 prevalence. (3) Most of the works performed to appreciate the HTLV-1 prevalence are based on study of series of blood donors, pregnant women, or hospitalized patients. Population-based studies trying to estimate HTLV-1 prevalence in large areas, or even at a country level, remain very rare. (4) A very important last point is that, in most of the studied areas, HTLV-1 distribution is not homogeneous. HTLV-1 is indeed present mainly as relatively small foci or clusters with a high or very high prevalence of infection, with nearby quite low endemic areas. This has been very well exemplified in Southern Japan and in some areas of South America. Thus, to give a precise estimation of HTLV-1 prevalence in a specific country or area is relatively difficult and, in some cases, nearly impossible.

Very few studies have thus given an estimation of the HTLV-1 world prevalence. Japan and the African continent have been rapidly considered, as the two regions in which HTLV-1 infected persons were the most numerous. Then, South America has also been considered as a very important focus of HTLV-1 carriers and associated diseases (mainly ATL or tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM), a chronic severe neuromyelopathy). One of the most frequently quoted estimation number of infected persons is based on a paper, published in 1993 by G. de Thé and R. Bomford from our group in Pasteur (de Thé and Bomford, 1993). This study gave a rough estimation of 10–20 millions of HTLV-1 infected individuals worldwide. In most of the review published since then, this number is often taken as a fact (Proietti et al., 2005; Verdonck et al., 2007; Hlela et al., 2009; Watanabe, 2011).

By writing this paper, our main goal was to revisit the situation of HTLV-1 epidemiology, especially its world distribution, and its estimated prevalence. This will be based on the current data, available in 2012, thus around 30 years after the first published epidemiological studies and nearly 20 years after the last estimation of global HTLV-1 prevalence.

This ambitious work has been based on the analyses of: (1) most of the 1,100 papers referenced in PubMed on such a topic, (2) most of the available book chapters concerning HTLV-1 epidemiology but also (3) on all the abstracts (of the epidemiology sections) of the International Conference on HTLV and related viruses held since 1985.

This study was, of course, possible thanks to our expertise and experience in the field since 30 years for one of us and nearly 10 years for the other one.

After presenting the different methods used for the epidemiological studies of HTLV-1 infection, we shall describe briefly the major epidemiological determinants and the different transmission modes of this human retroviral infection. Then, a small chapter will report the major findings concerning the molecular

epidemiology of HTLV-1, which possesses an unusual great genetic stability for a retrovirus. Lastly, we shall try to present, with a table and a map, the HTLV-1 worldwide distribution and its prevalence estimates by continent and by country when possible.

METHODS FOR HTLV-1 EPIDEMIOLOGY

Most of the studies were performed on series of blood donors, pregnant women, or hospitalized patients. In few cases, population-based studies were done in some villages, towns, or even regions of a given country. The epidemiological and demographic characteristics of blood donors could be very different according to the countries: indeed, they can be quite representative of the middle-class population in some countries but in other areas, either they are mainly family members of hospitalized patients, or they originate from low socio-economic populations and are sometimes paid to give blood and, lastly, in several areas (especially in some African studies) they are mainly young men. HTLV-1 prevalence varies according to age, sex, and economic level in most of HTLV-1 endemic areas. Thus, the prevalence found in blood donors can be, of course, useful, but provides not always the best data to estimate precisely the HTLV-1 prevalence in a given country. The real prevalence is very probably higher than that found in blood donors in most of the cases. Thus, the data based on pregnant women are generally more useful to compare the situation between different areas or countries as first, it is quite representative of a given region and second, the mean age of pregnant women is generally comparable (about 22–26 years) in most of the countries. The studies in general populations, in or out-adult patients, can also be very useful to try to appreciate the HTLV-1 prevalence in a given area as, in the great majority, the tested patients do not suffer of the very rare diseases linked specifically to HTLV-1 infection.

Diagnostic methods used for the study of HTLV-1 infection include mainly serological assays searching for antibodies directed specifically against different HTLV-1 antigens. Screening tests are usually Enzyme-Linked Immunoabsorbent Assay (ELISA) or Particle Agglutination (PA). Confirmatory tests are immunofluorescence (IFA), but mostly Western Blot (WB), or Innogenetics line immunoassay (INNO-LIA). Moreover, research of integrated provirus, in the DNA from peripheral blood cells, could be done by qualitative and/or quantitative polymerase chain reaction (PCR). Despite some improvements in the WB assays specificity during the last two decades, indeterminate serological patterns remain frequent following WB analysis, and represent an important concern for routine screening in blood banks in Europe, the Americas, and some parts of Africa. It is also of course a major issue for comparative analyses between epidemiological studies performed in both low and high endemic areas, especially in intertropical areas (Mauclere et al., 1997; Filippone et al., 2012). The significance of these frequent indeterminate WB can be various but, in the majority of the cases, remains mostly unknown and a matter of debate reviewed in Filippone et al. (2012). Indeed, in rare cases, these patterns have been associated to (i) HTLV-1 but mostly HTLV-2 infection exhibiting an atypical HTLV-serology, (ii) HTLV-1 seroconversion, (iii) infection by a different retrovirus such as the recently discovered HTLV-3 or HTLV-4 (Mahieux and Gessain, 2009). Furthermore, some have been considered as the

results of cross-reactivity against other microbial agents, especially *Plasmodium falciparum* in Central Africa and Indonesia (Porter et al., 1995; Mahieux et al., 2000). In this review, we shall take into account, in the great majority, only the studies in which HTLV-1 infection has been confirmed by a specific test, mostly a WB.

MAJOR EPIDEMIOLOGICAL DETERMINANTS OF HTLV-1

HTLV-1 is not an ubiquitous virus. Indeed, it is present throughout the world, with clusters of high endemicity located often nearby areas where the virus is nearly absent. In these foci, the HTLV-1 seroprevalence in adults is estimated to be at least 1–2% but it can also reach 20–40% in persons older than 50 years in some specific clusters. The main very highly endemic areas are the Southwestern part of Japan, some parts of the Caribbean area, and its surroundings regions, foci in South America including especially parts of Colombia and French Guyana, some areas of intertropical Africa (such as South Gabon) and of the middle East (such as the Mashad region in Iran), and rare isolated clusters in Australo-Melanesia. In Europe, only Romania seems to represent an HTLV-1 endemic region. The origin of this puzzling geographical or rather ethnic repartition is not well understood but is probably linked to a founder effect in some groups, followed by the persistence of a high viral transmission rate.

Interestingly and despite different socio-economic and cultural environments, HTLV-1 seroprevalence increases gradually with age, especially in women, in all the highly endemic areas. The general increase with age may be related to a cohort effect, as well as demonstrated in Japan, while the increase in women might also be due to an accumulation of sexual exposures with age (Blattner et al., 1986; Chavance et al., 1989; Ueda et al., 1989; Mueller, 1991; Murphy et al., 1991).

Three modes of transmission have been demonstrated for HTLV-1. (1) Mother to child transmission, which is mainly linked to a prolonged breast-feeding after 6 months of age (Hino, 2011). Ten to 25% of the breast-fed children born from HTLV-1 infected mothers will become infected. High level of HTLV-1 proviral load in milk, in blood cells as well as high HTLV-1 antibody titers in the serum, and long duration of breast-feeding (at least >6 months) represent major risk factors for HTLV-1 transmission from mother to child (Takahashi et al., 1991; Hino et al., 1994; Ureta-Vidal et al., 1999; Li et al., 2004). (2) Sexual transmission, which mainly, but not exclusively, occurs from male to female, and is thought to be responsible for the increased seroprevalence with age in women (Murphy et al., 1989; Stuver et al., 1993; Takezaki et al., 1995; Kaplan et al., 1996; Roucoux et al., 2005). (3) Transmission with contaminated blood products (containing HTLV-1 infected lymphocytes), which is responsible for an acquired HTLV-1 infection among a high proportion (15–60%) of the blood recipients (Okochi et al., 1984; Inaba et al., 1989). HTLV-1 infection is also present among intravenous drug users but at a lesser extent than HTLV-2 (Murphy et al., 1999).

HTLV-1 MOLECULAR EPIDEMIOLOGY: PRESENCE OF GEOGRAPHICAL/ETHNIC RELATED SUBTYPES/GENOTYPES

On a molecular point of view, HTLV-1 possesses a remarkable genetic stability, an unusual feature for a retrovirus. Viral amplification via clonal expansion of infected cells, rather than by reverse

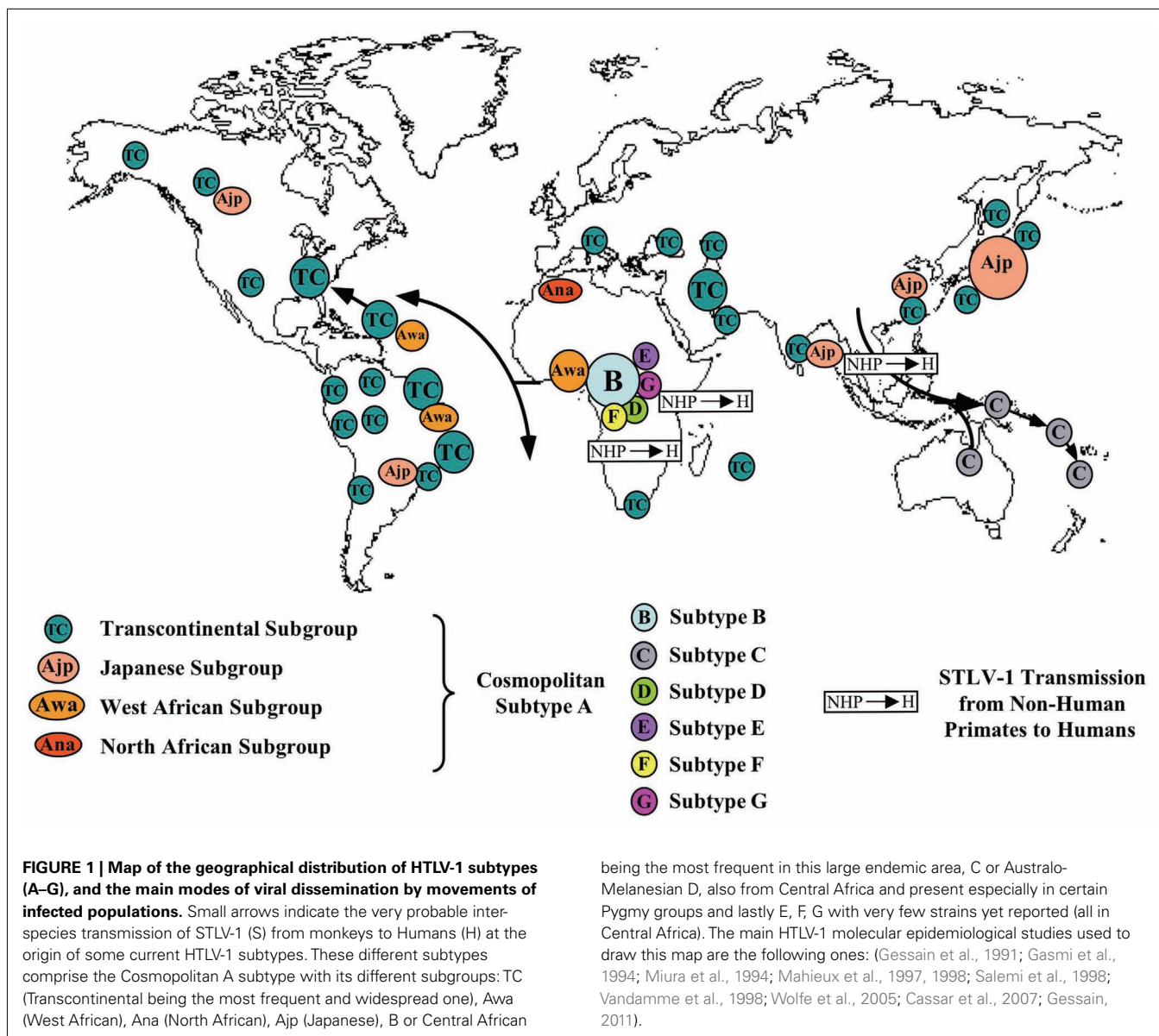
transcription is, very probably, the reason for this striking genetic stability. The low sequence variation of HTLV-1 can be used as a molecular tool to follow the migrations of infected populations in the recent or distant past and thus to gain new insights into the origin, evolution, and modes of dissemination of such retroviruses and of their hosts (Gessain et al., 1992b; Yanagihara, 1994). The few nucleotide substitutions observed among virus strains are indeed specific to the geographic origin of the patients rather than the pathology. Four major geographic subtypes (genotypes) have been reported. They include the Cosmopolitan subtype A, the Central African subtype B, the Central African/Pygmies subtype D, and the Australo-Melanesian subtype C. A limited number of strains found in Central Africa belong to other rare subtypes (E, F, G). The Cosmopolitan subtype A, which comprised several geographical subgroups (Japanese, West Africa, North African. . .) is the most widespread, being endemic in Japan, the Caribbean area, Central and South America, North and West Africa as well as part of the Middle East. The sequence variability within subtype A is very low. This is very likely to reflect a relatively recent dissemination (some centuries to few millenium) of this genotype from a common ancestor. The Australo-Melanesian subtype C is the most divergent. This result reflects a long period of evolution (at least several millenium) in isolated populations living in different islands of the Pacific area. The appearance of these HTLV-1 subtypes in humans was strongly suggested to be linked to interspecies transmission between STLV-1 infected monkeys and humans, followed by variable period of evolution in the human host (Salemi et al., 1998; Vandamme et al., 1998; Meertens et al., 2001; Nerrienet et al., 2001; Wolfe et al., 2005). Indeed, STLV-1, the simian counterpart of HTLV-1, infects several species of non-human primates (NHPs) of the Old World, ranging from chimpanzees, orangutans, and gorillas to mandrills, as well as several African small monkey species and a wide range of macaques, and other Asian monkeys. Interestingly, STLV-1 infection was also associated to the development of ATL in some NHPs.

A map of the different HTLV-1 molecular subtypes and places of possible interspecies transmissions from STLV-1 infected monkeys to humans is presented on **Figure 1**.

There is so far no solid evidence that either a particular specific mutation or a genotype is associated with the development of a TSP/HAM or an ATL, in an asymptomatic carrier. Data concerning level of transmission or proviral load according to molecular subtypes need to be performed.

HTLV-1 WORLDWIDE DISTRIBUTION AND PREVALENCE ESTIMATES BY GEOGRAPHICAL AREA

To give a general overview of the HTLV-1 worldwide distribution was relatively easy for most of the regions. However, to try to provide an estimate, even rough, of the number of HTLV-1 infected persons in the different world areas, even in well-studied high HTLV-1 endemic regions was not at all an easy task. In all the cases, such estimates must be absolutely taken with cautious. Indeed, as said above, very few large population-based studies have been done and most of the analyzed studies concern mainly blood donors, pregnant women, or populations of different in or out-adult patients not really representative of the population of a given



area or country on an epidemiological point of view (Table 1 and Figure 2).

HTLV-1 IN EUROPE

Europe represents around 400 millions of persons. Numerous epidemiological studies have been performed in this continent, mainly in blood donors and in pregnant women (Courtois et al., 1990; Courouce et al., 1993; Nightingale et al., 1993; Zaaijer et al., 1994; Dalekos et al., 1995; Ferrante et al., 1997; Hale et al., 1997; Tuset et al., 1997; Poljak et al., 1998; Ades et al., 2000; Machuca et al., 2000; Tseliou et al., 2004, 2006; Vrieling and Reesink, 2004; Taylor et al., 2005; Davidson et al., 2006; Laperche et al., 2009; Brant et al., 2011). Furthermore, several large series of ATL and TSP/HAM have been reported (Gout et al., 1989; Rio et al., 1990; Plumelle et al., 1993; Martin et al., 2010; Ceesay et al., 2012). The most studied countries are the United Kingdom (UK), Metropolitan France, and Spain. Based on all these works, it is now clear that

most (at least more than 80%) of the persons infected by HTLV-1 living currently in Europe originate directly, or are children or descendents of immigrants, from a high endemic area, mostly West Indies and Africa. Thus, in UK, most of HTLV-1 carriers originate from the former British West Indies, especially Jamaica and also, at a lesser extent, Barbados, Trinidad, and Tobago (Catovsky et al., 1982; Payne et al., 2004; Dougan et al., 2005). More rarely, they originate from West Africa as Ghana or Sierra Leone. Concerning Metropolitan France, most of the persons originate from French West Indies as Martinique or Guadeloupe (Gout et al., 1989; Gessain et al., 1990c; Rio et al., 1990; Plumelle et al., 1993). They can also originate from West or Central Africa as Senegal, Mali, Guinea, Côte d'Ivoire, or Cameroon (Gessain et al., 1990b, 1992a; Rio et al., 1990; Mahe et al., 1994; Duval et al., 2010). It is important to note that in blood donors and, thus, very probably in the general population, a certain proportion of infected persons are women, of Caucasian background, that

Table 1 | HTLV-1 seroprevalence among pregnant women originating from HTLV-1 endemic countries in Africa, West Indies, North and South America, Asia, and Europe.

Region	Country	HTLV-1 seropositive women (%)	Reference
AFRICA	Guinea-Bissau	2.2 (27/1,231)	Andersson et al. (1997)
	Côte d'Ivoire	1.9 (10/513)	Verdier et al. (1989)
	Ghana	2.1 (20/960)	Armah et al. (2006)
	Burkina-Faso	1 (5/492)	Collenberg et al. (2006)
	Nigeria	5.5 (20/364)	Olaleye et al. (1995)
	Gabon	2.1 (19/907)	Etenna et al. (2008)
	Zaire	4.6 (19/414)	Goubau et al. (1993)
	Zaire	3.7 (43/1,166)	Delaporte et al. (1995)
	Congo	0.7 (14/2,070)	Tuppin et al. (1996)
	South Africa	0.2 (1/428)	Goubau et al. (1993)
WEST INDIES	Martinique	2.4 (17/716)	Denis et al. (1988)
	Martinique	1.9 (9/467)	Mansuy et al. (1999)
	Jamaica	3.5 (81/2,329)	Wiktor et al. (1993)
	Jamaica	3.8 (350/9,226)	Maloney et al. (2006)
	Haiti	2.2 (11/500)	Allain et al. (1992)
NORTH AMERICA	Haiti	4.2 (12/287)	Tortevoye et al. (2005)
ASIA	Mexico (Yucatan)	0 (0/590)	Gongora-Biachi et al. (1996)
ASIA	India (Vellore)	0 (0/201)	Ramalingam et al. (2001)
	Japan (Honshu)	0.6 (14/2,414)	Goto et al. (1997)
	Japan (Nagasaki and Kyushu)	3.7 (187/5,015)	Hino et al. (1985)
	Japan (whole Kyushu)	5.4 (885/16,283)	Oki et al. (1992)
	Japan (Kagoshima in Kyushu)	5.8 (138/2,374)	Umamoto et al. (1994)
	Japan (Okinawa)	3.9 (670/17,207)	Maehama (2004)
EUROPE	United Kingdom	0.04 (52/126,010)*	Ades et al. (2000)
	United Kingdom	0.03 (23/69,013) ^o	Ades et al. (2000)
	France	0.1 (12/10,398)	Courtois et al. (1990)
	Italy	0.02 (1/6,000)*	Taylor et al. (2005)
	Spain	0.01 (2/20,366)*	Machuca et al. (2000)
	Slovenia	0.01 (1/10,369)	Poljak et al. (1998)
	Greece	0 (0/2,016)	Tseliou et al. (2006)
	SOUTH AMERICA	French Guyana (Noir Marron population)	5.7 (70/1,225)
French Guyana (Noir Marron population)		4.2 (181/4,266)	Tortevoye et al. (2005)
Brazil (Mato Grosso)		0.2 (7/2,965)	Ydy et al. (2009)
Brazil (Mato Grosso South)		0.1 (37/32,512)	Figueiro-Filho et al. (2007)
Brazil (Salvador Bahia)		0.8 (57/6,754)	Bittencourt et al. (2001)
Brazil (Sao Paulo)		0.1 (1/913)	Olbrich Neto and Meira (2004)
Brazil (Sao Luis)		0.2 (4/2,044)	Guimaraes de Souza et al. (2012)
Peru (Andes, Coast, Jungle, Lima)		1.3 (32/2,492)	Alarcon et al. (2006)
Peru (Quechua population)		2.4 (5/211)	Zurita et al. (1997)
Argentina (Cordoba-Central)		0.1 (3/3,143)	Trenchi et al. (2007)

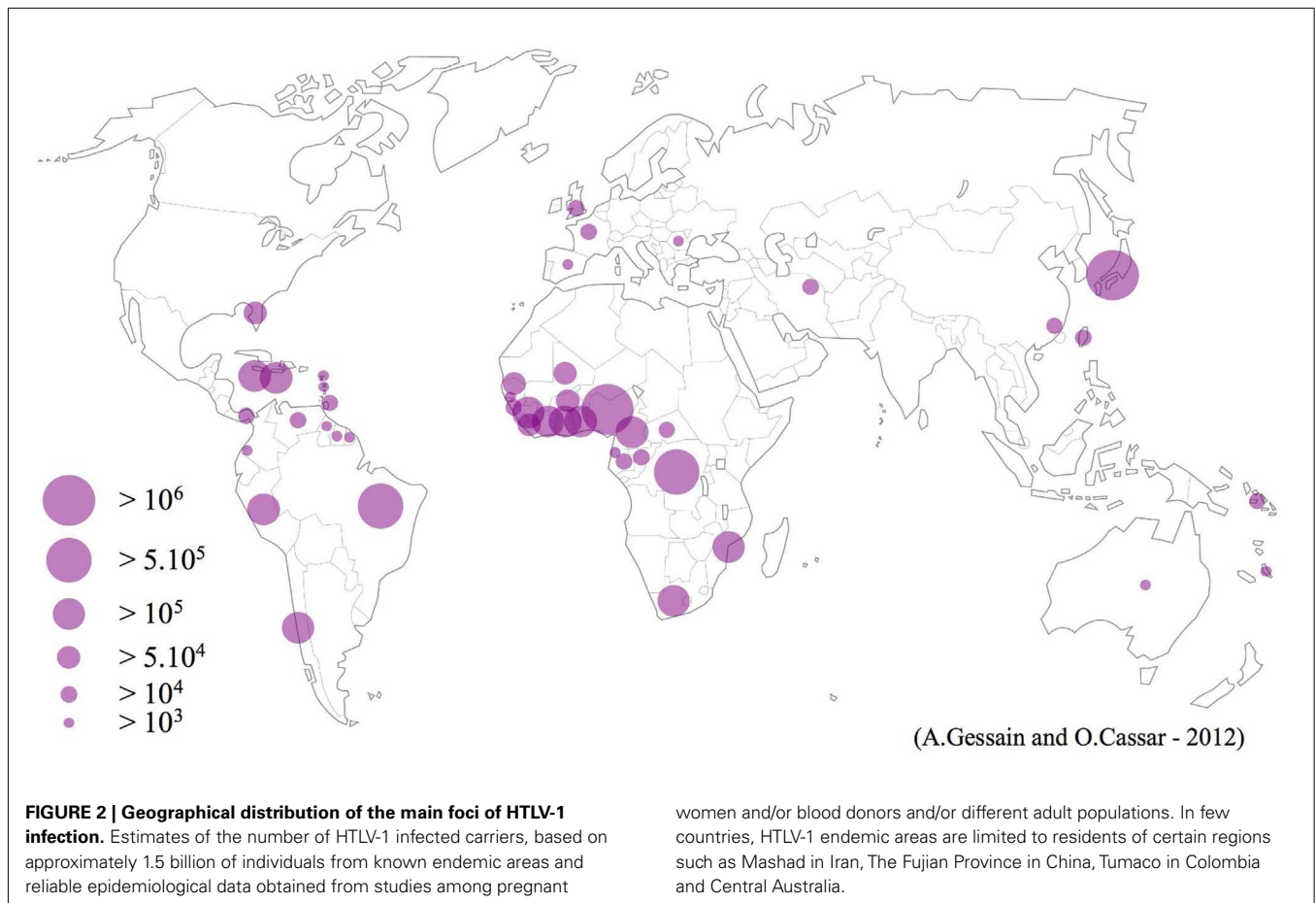
The quoted studies are, to our knowledge, among the most representative and reliable ones to date.

*including black African and Afro-Caribbean women.

^oWomen born exclusively in the United Kingdom.

have acquired HTLV-1 through sexual contacts with a partner originating from an HTLV-1 endemic area. This situation can represent around 5–10% in different European countries including France or UK (Dougan et al., 2005). In Spain, the situation is slightly different as, due to historical reasons, most of the HTLV-1 infected persons are from South America (Toro et al., 2002; Padua et al., 2011; Trevino et al., 2012). However the prevalence

seems much lower than in UK or in Metropolitan France. In Portugal, this is about the same but, in some cases, the HTLV-1 infected persons can originate from ancient African colonies such as Mozambique and Angola (Padua et al., 2011). Intravenous drug users represent also a population relatively endemic for HTLV-1, specially in Spain, Italy, and Ireland even if HTLV-2 is always much more prevalent in such a specific population



(Gradilone et al., 1986; Calderon et al., 1995; Chironna et al., 1996).

The level of HTLV-1 infection in most of the other European countries is very low as demonstrated by an HTLV-1 prevalence in first-time blood donors of less than 0.4/10,000 and a great rarity of ATL or TSP/HAM reports (Laperche et al., 2009). The only exception seems to be Romania, which appears to be the only true HTLV-1 endemic area in Europe (Paun et al., 1994; Veelken et al., 1996). Indeed, a prevalence of 5.3/10,000 donations has been recently reported among first-time blood donors in this East European country (population of 22 millions; Laperche et al., 2009). HTLV-1 infection in polytransfused patients is also quite high ranging from 3 to 25%. Furthermore, series of cases of ATL or TSP/HAM have been reported in Romania. Lastly, sporadic cases have also been seen in immigrants from this country living in other European countries (Veelken et al., 1996; Manca et al., 1997). These data, taken together, demonstrate clearly a relatively high level of HTLV-1 infection in this country. The origin of such situation remains unknown and the matter of different hypotheses.

The estimation of the number of HTLV-1 infected persons in Europe is a very difficult exercise. Based on all data from UK and especially their numerous studies, the team of Graham Taylor suggests that 20,000–30,000 people have HTLV-1 infection in the UK (Ades et al., 2000). Concerning Metropolitan France, based on the study on prevalence in blood donors, pregnant women,

and the incidence of ATL cases, we can estimate that it is roughly equivalent with around 10,000–25,000 HTLV-1 infected persons. Importantly and, as in the UK, most of them are undiagnosed. Concerning Romania, this is more difficult, due to the few available studies. However, in a recent study, the prevalence in the first-time blood donors seems 10 times more in Romania than in UK and Metropolitan France (Laperche et al., 2009). A rough minimal estimation of few thousands with a wide range (3,000–15,000) can be proposed. However, we cannot rule out the presence of possible HTLV-1 clusters, or foci, in some specific areas or populations in such country.

HTLV-1 IN AFRICA

The total population of Africa is estimated at a little more than 1 billion in 2012. The African population has grown a lot over the past century. Indeed, the population doubled for the period 1982–2009 and quadrupled during the years 1955–2009. Thus, more than 40% of the population is below 15 years old in most sub-Saharan countries. Africa is probably the largest endemic area for HTLV-1. However, despite numerous epidemiological studies and reports of sporadic cases or even small series of ATL and TSP/HAM cases, the situation concerning the level of HTLV-1 infection, is not really known in several countries and regions of this large continent. Indeed, very few large studies on representative general population are available.

Here, we shall first briefly report the situation, based on the most solid studies (large populations of mainly blood donors, pregnant women, or adult hospitalized patients or control groups, and robust serological tests including mainly a WB for confirmation), according to five large geo-climatological areas: North Africa, West Africa, Central Africa, East Africa, and lastly South Africa. Then, we shall try to estimate the number of HTLV-1 infected persons in some specific countries for which reliable data are available.

North Africa/Maghreb

The very few studies concern mainly blood donors or multi-transfused patients from Egypt, Morocco, and Tunisia where the HTLV-1 seroprevalence appears to be very low or negative (Saxinger et al., 1984; de-The et al., 1985; de The and Gessain, 1986; El-ghazzawi et al., 1987; el-Farrash et al., 1988; van Doornum et al., 1990; Mojaat et al., 1999; Kawashti et al., 2005; Stienlauf et al., 2009). Very few cases of ATL or TSP/HAM have been reported in such countries, including at least Morocco and Egypt, either diagnosed locally or in immigrants, especially in France (Thyss et al., 1990; Gasmi et al., 1994; Gharibi et al., 2011). In summary, based on the scarce available data, Morocco seems to be, in North Africa, the only country that can be considered as HTLV-1 endemic, however at a low level and a reliable estimation of the number of HTLV-1 infected persons in North Africa is currently impossible.

West Africa

This large area comprises 16 countries: Benin, Burkina-Faso, Cape Verde, Côte d'Ivoire, Gambia, Ghana, Guinea and Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, and Togo. This represents more than 300 millions of inhabitants. Several large studies have been performed in Senegal, Guinea-Bissau, Côte d'Ivoire, Ghana, and Nigeria. Furthermore, ATL and/or TSP/HAM have been reported in most of these countries including especially Senegal, Mauritania, Mali, Côte d'Ivoire, Nigeria (Fleming et al., 1986; Gessain et al., 1990a,c; Williams et al., 1993, 1994; Mahe et al., 1994; Michel et al., 1996; Analo et al., 1998; Fouchard et al., 1998; Sene-Diouf et al., 2000). The HTLV-1 seroprevalence in blood donors ranged mainly from 0.2 to 3%. However, in most of these studies, blood donors are mainly young men. In Senegal, based on a study of 4,900 blood donors, HTLV-1 seroprevalence was of 0.16%, however most of the infected donors originated from the South of the country, where the prevalence reached 1% (Diop et al., 2006). In Guinea, it was of 1.2% (22/1,785; Gessain et al., 1993a), while in Côte d'Ivoire and Ghana it ranges from 0.5 to 2% depending on the studies (Ouattara et al., 1989; Verdier et al., 1989; Biggar et al., 1993; Sarkodie et al., 2001; Ampofo et al., 2002; Armah et al., 2006). In Nigeria, it varies from 0.7 to 3.7% according to geographical location (Fleming et al., 1986; Analo et al., 1998). Other studies were performed on pregnant women or representative general adult population or on different control groups. The HTLV-1 prevalence was around 1% in Guinea, with variations from 0.2 to 1.9% depending on the region (Jeannele et al., 1995), and ranged from 2.2 to 3.6% in Guinea-Bissau (Andersson et al., 1997; Larsen et al., 2000; da Silva et al., 2009). It was of 1.2% in Gambia (Del Mistro et al., 1994) and ranged from 0.2 to 1.2% in Senegal (Hunsmann et al., 1984). It was of 1% in

Burkina-Faso (Collenberg et al., 2006) and ranged from 1 to 1.6% in Liberia, Togo and Benin (Hunsmann et al., 1984; Dumas et al., 1991; Verdier et al., 1994; Houinato et al., 1996), and from 1 to 2.7% in Côte d'Ivoire and Ghana according to the type of studies (Ouattara et al., 1989; Verdier et al., 1989, 1994; Biggar et al., 1993; Goubau et al., 1993; Armah et al., 2006) and reached 5.5% in Nigeria (Olaleye et al., 1994, 1995). The estimates of the number of HTLV-1 infected persons in most of the West African countries are given in **Table 2**.

Central Africa

This area comprises nine countries including, Angola, Cameroon, Central African Republic (CAR), Chad, Democratic Republic of the Congo (DRC) formerly Republic of Zaire, Equatorial Guinea, Gabon, Republic of the Congo, Sao-Tome-et-Principe. This represents around 130 millions of persons. Several important epidemiological studies have been performed in Cameroon and especially in Gabon. Cases of ATL and/or TSP/HAM have been reported mainly in Cameroon, Gabon and the DRC (Kayembe et al., 1990; Jeannele et al., 1993). HTLV-1 prevalence in adults living in Cameroon ranges globally from 0.5 to 2% depending on the geographical location, the studied population, and the ethnic group (Mauclere et al., 1997; Mauclère et al., 2011; Filippone et al., 2012). Indeed, the Pygmies groups, who live mainly in the Southern region of this country, have a much higher level of HTLV-1 prevalence (around of 2–10% in adults depending on age) than the Bantu groups (around 0.3–1.5%), who represent most of the population of this area (Mauclere et al., 1997; Mauclère et al., 2011; Filippone et al., 2012). In Gabon, several studies of different representative urban or rural populations have been performed (Delaporte et al., 1988, 1991; Bertherat et al., 1998). This is the best-studied country for Africa concerning the HTLV-1 infection. All the data indicated a global high HTLV-1 seroprevalence of around 5–10% in the adult populations (Delaporte et al., 1988, 1991; Bertherat et al., 1998). In pregnant women it ranged from 1 to 5% according to the geographical location (Schrijvers et al., 1991; Etenna et al., 2008). Based on several studies, it appears clearly that the Haut-Ogoué region (a Southeastern area of the country) is the highest endemic area of Gabon for HTLV-1 infection. Indeed, in some villages of this region, the HTLV-1 seroprevalence can reach more than 25% in elder adults, especially women (Delaporte et al., 1989b; Le Hésran et al., 1994). This area represents very probably the highest yet known HTLV-1 endemic area in the African continent. In CAR, HTLV-1 infection has been reported in Pygmies from the Southern region (Gessain et al., 1993b) and a seroprevalence of 7% has been recently shown in aged adults (>55 years old) of the same rain forest area (Pepin et al., 2010). In the Republic of the Congo and in DRC, HTLV-1 prevalence in pregnant women ranged from 0.7 to 3.7% depending on the studies (Delaporte et al., 1995; Tuppin et al., 1996). Furthermore, several other reports from DRC indicated that a relatively high HTLV-1 prevalence (5 to more than 20%) in different adult populations including hospitalized patients, prostitutes, leprosy patients (Kayembe et al., 1990; Wiktor et al., 1990; Delaporte et al., 1995; Lechat et al., 1997). Such results depended widely on the geographical areas of the tested persons with high prevalence region (as the Haut-Zaire/Equateur) and low prevalence ones (Goubau et al., 1993; Delaporte et al., 1995). The

Table 2 | Estimates of the number of HTLV-1 infected carriers, based on approximately 1.5 billion of individuals from known HTLV-1 endemic areas and reliable epidemiological data obtained from studies performed among pregnant women and/or blood donors and/or different adult populations.

Continent/ Country	Population!	HTLV-1 range	
AFRICA			
Senegal	12,969,606	30,000	105,000
Gambia	1,840,454	2,500	13,000
Guinea-Bissau	1,628,603	12,000	28,000
Guinea	10,884,958	75,000	150,000
Sierra Leone/ Liberia	5,485,998/3,887,886	50,000	100,000
Côte d'Ivoire	21,952,093	130,000	250,000
Ghana	25,241,998	125,000	375,000
Togo/Benin	6,961,049/9,598,787	80,000	160,000
Burkina Fasso	17,275,115	42,000	125,000
Mali	14,533,511	32,000	95,000
Nigeria	170,123,740	850,000	1,700,000
Cameroon	20,129,878	80,000	180,000
Eq. Guinea	685,991	1,500	4,500
Gabon	1,608,321	16,000	30,000
CAR	5,057,208	15,000	30,000
DRC	73,599,190	600,000	1,300,000
Republic of The Congo	4,366,266	12,000	36,000
Mozambique	23,515,934	120,000	360,000
South Africa	48,810,427	180,000	540,000
ASIA			
China (Fujian Province)	35,110,000	2,000	20,000
Japan*	127,368,088	1,080,000	1,300,000
Iran (Mashad area)	78,868,711	10,000	40,000
Taiwan	23,113,901	10,000	30,000
EUROPE			
United Kingdom**	63,047,162	20,000	30,000
France	65,630,692	15,000	25,000
Spain	47,042,984	1,000	8,000
Romania	21,848,504	3,000	15,000
CARIBBEAN REGION			
Haiti/Dominican Republic	9,801,664/10,088,598	150,000	350,000
Jamaica	2,889,187	100,000	140,000
Guadeloupe [#]	401,730	3,000	6,000
Martinique [#]	395,953	3,000	6,000
Trinidad and Tobago	1,226,383	9,000	18,000
NORTH AMERICA			
United States	313,847,465	90,000	100,000
CENTRAL AND SOUTH AMERICA			
Panama	3,510,045	3,500	25,000

(Continued)

Table 2 | Continued

Continent/ Country	Population!	HTLV-1 range	
Colombia (Tumaco area)	45,594 (est.1988)	1,000	1,500
Venezuela	28,047,938	14,000	70,000
Suriname	560,157	3,000	7,000
French Guyana	217,000	2,000	5,000
Guyana	741,908	2,000	5,000
Peru	29,549,517	150,000	450,000
Brazil	205,716,890	300,000	800,000
Chile	17,067,369	90,000	250,000
AUSTRALO-MELANESIA			
Australia (Aboriginal Australians)	463,900	2,500	5,000
Solomon Islands	584,578	3,000	6,000
Vanuatu	227,574	250	1,000
Total	1,567,570,505	4,520,250	9,295,000

The HTLV-1 ranges were estimated combining the prevalence rates deduced from the above studied populations and the global repartition of individuals by age and sex in each studied country. In some highly populated countries and regions, such as China, India, the Maghreb and East Africa, correct estimates are currently not possible. Thus, the current total number of HTLV-1 carriers in the world is very probably much higher. Eq. Guinea, Equatorial Guinea; CAR, Central African Republic.

!According to the CIA World Factbook 2012 estimations (www.cia.gov).

*According to Satake et al. (2012).

**According to Brant et al. (2011).

#According to the National Institute of Statistics and Economic Studies 2011 estimations (www.insee.fr).

prevalence of HTLV-1 in Chad seems quite lower (around 0.5–1% in adults in the Southern part). The situation in Angola is less known. The estimates of the number of HTLV-1 infected persons in Cameroon, Gabon, Equatorial Guinea, CAR, DRC and the Republic of The Congo are given in **Table 2**.

East Africa

This large area comprises 12 countries including: Burundi, Erythrea, Ethiopia, Kenya, Malawi, Mozambique, Rwanda, Somalia, Tanzania, Uganda, Zambia, and Zimbabwe. Relatively few studies on HTLV-1 infection (with the exception of Mozambique) have been performed in such a large and highly populated region (total of more than 330 millions of inhabitants). Moreover, only sporadic cases of ATL and/or TSP/HAM have been reported from East African countries. Lastly, this region appears globally much less endemic for HTLV-1 than West and Central Africa. The reasons of such a situation are unknown. Indeed, all the studies performed in the countries, North of Malawi, indicate a very low or an absence of HTLV-1 infection. As examples, a nationwide community-based survey performed in Rwanda on more than 2,500 samples indicated an HTLV-1 seroprevalence of 0.2% (Group, 1989), and in Zimbabwe, only one blood donor out of 931

(0.1%) was found HTLV-1 seropositive (Houston et al., 1994). The situation in Mozambique (a country of 24 millions) appears different. Indeed, a study on 2,019 blood donors from Maputo city reported an HTLV-1 seroprevalence of 0.9% (Gudo et al., 2009). Another study in blood donors found an HTLV-1 seroprevalence rate, among 15- to 49-year-old men and women respectively of 0.9 and 1.2% (Cunha et al., 2007). A study on 752 individuals attending public health centers from different areas of this country found a seroprevalence of 2.3% with geographical regional variation (Caterino-de-Araujo et al., 2010). Furthermore, some cases of TSP/HAM have been reported in Mozambique (Engelbrecht et al., 1999) and HTLV-1 infection has been seen at a rate of around 4% in HIV infected patients (Bhatt et al., 2009). The estimation of the number of HTLV-1 infected persons can be done only for Mozambique (Table 2).

South African region

This area comprises only three countries: Botswana, Namibia, and South Africa. Several studies have been performed but concern only South Africa, a country of 48 millions of inhabitants.

Indeed, several sporadic case or series of ATL, TSP/HAM, or infective dermatitis have been reported in South African patients (Bhigjee et al., 1990, 1993; Joubert et al., 1991; Jogessar et al., 1992). Indeed, as soon as 1999, around 200 black patients with a TSP/HAM have been seen in Durban. Furthermore, several studies performed in blood donors indicated an HTLV-1 seroprevalence ranging from 0 to 5% according to the type of tested population (black, white, young men, geographical location. . . ; Bhigjee et al., 1993). A community-based seroprevalence survey done in adults from Natal/KwaZulu found a seroprevalence of 2.6% (26/1,018; Bhigjee et al., 1993). Similar results (0.5–3%) have been found in adults in other districts of this state and other states of the country (Bhigjee et al., 1994; Taylor et al., 1996; van der Ryst et al., 1996). The estimate of the number of HTLV-1 carriers in South Africa is given on Table 2.

Concerning the islands of the Indian Ocean, very few data are available. The situation is barely unknown in Madagascar, Comoros, and Mauritius but, to our knowledge, no case of ATL or TSP/HAM has been reported from these countries. It is different for the Reunion Island (an overseas French department of approximately 800,000 inhabitants) and the Seychelles archipelago. Indeed, in the Reunion Island, despite that few cases of TSP/HAM and ATL have been reported (Cnudde et al., 1991; Mahieux et al., 1994), a study on 3,900 blood donors (mostly young adult males) indicated only one infected person (Mahieux et al., 1994). By contrast, in the Seychelles, a cluster of TSP/HAM cases has been described as well as an HTLV-1 seroprevalence of 3–5% in blood donors (Roman et al., 1987; Lavanchy et al., 1991).

HTLV-1 IN THE AMERICAS

North America

Most of the available studies on HTLV-1 prevalence in the United States, concern blood donors and intravenous drug users. In one of the first large study, nearly 40,000 blood donors in eight geographically diverse areas were screened for HTLV-1. Only 10 of them (0.025%) showed evidence of HTLV-1 infection (Williams et al., 1988). Seroprevalence rates ranged from 0 to 0.1% at the

locations sampled, with HTLV-1 antibodies found predominantly in donors from the Southeastern and Southwestern United States. The Retrovirus Epidemiology Donor Study group (REDS) evaluated, during 1991–1995, the HTLV-1 prevalence among 1.7 million donors from five REDS blood centers to 0.009% (Schreiber et al., 1997). In 2001, another study reported that the HTLV-1 seroprevalence rate among 21,000 individuals representing various patient populations including blood donors was 0.02% (Poiesz et al., 2001). HTLV-1, but mostly HTLV-2, infections are highly endemic among intravenous drug users in certain urban areas of the country (e.g., New Jersey), with seroprevalence rates reaching nearly 20% (Freeman et al., 1995). Among them, African-Americans were significantly more likely than Hispanics and other racial groups to be HTLV-1 positive (Lee et al., 1990; Cantor et al., 1991). The first patient with ATL, initially thought to have a Sezary's syndrome and from whom HTLV-1 was first isolated, was described in 1980 in the United States (USI Poiesz et al., 1980). Typical ATL cases were detected among US native-born patients (Blayney et al., 1983; Dosik et al., 1988) and the first description of ATL in members of a single family from the US occurred in 1988 (Denic et al., 1988). Concerning TSP/HAM, small series of cases were published since 1988 (Bhagavati et al., 1988; Janssen et al., 1991). Later, larger series of ATL and TSP/HAM cases have been described in the US and most of the cases were identified in African-American individuals from the Southeastern states such as Florida (Harrington et al., 1995). A study estimates the number of HTLV-1 and 2 infected persons at around 260,000 and that they are likely more than 3,600 people in the United States with unrecognized TSP/HAM (Orland et al., 2003). It remains difficult to provide a solid estimate for HTLV-1 in the USA (Table 2).

HTLV-1 seems to be rare in Canada and the number of HTLV-1 cases is unknown. Nevertheless, the HTLV-1 prevalence observed among 168,668 blood donors in the Toronto region was 0.02 and 2.3% among regional individuals and people of Caribbean origin respectively (Chiavetta et al., 1992). HTLV-1 infection was also described in Amerindians from the coastal regions of British Columbia (Dekaban et al., 1994; Picard et al., 1995; Peters et al., 2000). Furthermore, some associated diseases (ATL and TSP/HAM) were reported in coastal British Columbia Indians (Power et al., 1989; Oger et al., 1993; Dekaban et al., 1994; Gascoyne et al., 1996).

In Mexico, there is little information on HTLV-1 prevalence in the general population despite the large population size of this country which counts nearly 115 millions inhabitants. The few studies are mainly conducted in the Yucatan peninsula or some different states (Nuevo Leon in Northeast Mexico) and show the absence of HTLV-1 infection among healthy women as well as in blood donors (Gongora-Biachi et al., 1996, 1997; Trejo-Avila et al., 1996).

Central America

Central America consists of seven states (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama). In 2012, its estimated population is 42.6 millions. Despite the fact that some of these countries have strong commercial and cultural ties with the highly HTLV-1 endemic Caribbean Islands, relatively few studies concerning the HTLV-1 infection and the associated diseases

have been performed except in the Honduras, Panama and, to a lesser extent, in Costa Rica. In these countries, the HTLV-1 seroprevalence is rather low but with significant differences between the populations tested. Thus, the HTLV-1 prevalence is significantly higher in non-Mestizo population, especially individuals living in the coastal cities of Honduras, than in the Mestizo ethnic groups (8.1 versus 0.5% respectively; de Rivera et al., 1995). Additional studies showed an overall HTLV-1 prevalence of 0.3% in the general Honduran population who live in central and North-western part of the country (Segurado et al., 1997) and a higher HTLV-1 prevalence in black natives individuals, without known risk factors, but originating from cities located on the Atlantic coast (Vallejo et al., 1996). In Panama, HTLV-1 seroprevalence varied from 0.2 to 2% in the general adult population throughout the country (Reeves et al., 1990). Few ATL or TSP/HAM cases have been reported from Honduran native-born individuals (Temple et al., 1986) and in the Panamanian population (Levine et al., 1989; Gracia et al., 1990).

The situation regarding HTLV-1 in Nicaragua and Costa Rica is poorly known but rare studies revealed similar relatively low HTLV-1 prevalence rates (0.2–0.7%), among the Nicaraguan and Costa Rican adult populations (Khabbaz et al., 1990; Qiu et al., 2008). In Belize, Guatemala and El Salvador, no HTLV-1 record about the prevalence of the HTLV-1 infection has been published to our knowledge.

South America

This area comprises 13 countries including Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guyana (an overseas region of France), Guyana, Paraguay, Peru, Surinam, Uruguay, and Venezuela. This represents around 400 millions of persons. Numerous studies on HTLV-1 prevalence have been performed in many of these countries, especially in Brazil, Peru, Columbia, Chile, Argentina, and French Guyana. This vast continent represents, as a whole, a major endemic area for HTLV-1 infection and associated diseases. Even more than in other world regions, it is very difficult to appreciate the general HTLV-1 prevalence in a given country, as specific high endemic foci have been frequently reported in several South American countries. This is exemplified in Peru, in some of the Quechua population groups, and also in Columbia (Tumaco area) or in French Guyana (Noir-Marron population), where some specific groups of African origin are highly endemic for HTLV-1 infection and associated diseases.

In Peru, a real multiethnic country mainly inhabited by Mestizos and Amerindians, HTLV-1 prevalence in blood donors ranges from 1.2 to 1.7% depending on the region (Quispe et al., 2009) and from 1.3 to 3.8% in pregnant women or in the adult general population (Zurita et al., 1997; Sanchez-Palacios et al., 2003; Alarcon et al., 2006). Furthermore several large series of TSP/HAM and ATL have been reported (Gotuzzo et al., 2004; Beltran et al., 2011). However, as noted above, several studies have clearly demonstrated that persons of Amerindians origin (Quechua speaking groups), often living in isolated areas, are highly HTLV-1 endemic (Fujiyoshi et al., 1999; Einsiedel et al., 2010).

In Chile, mainly populated by persons of Spanish ancestry mixed with various Amerindian groups, the situation appears, by certain aspects, roughly similar than in Peru. Indeed, HTLV-1

seems more endemic among indigenous people from isolated Amerindians groups, living in the Andes, or in the most Southern region of the country, than in the general population. Studies indicated an HTLV-1 seroprevalence ranging from 0.7 to 1.9% in blood donors (Vasquez et al., 1991). Large series of TSP/HAM (more than 200 cases seen before 1991) have been reported in Chilean patients (Cartier et al., 1989, 1992) while ATL were more rarely described (Cabrera et al., 1991).

In Columbia, several studies were focused on Tumaco, a densely populated island of the Pacific lowland recognized as having a very high prevalence of TSP/HAM (Arango et al., 1988; Zaninovic et al., 1988). In the general population of this specific focus (mostly inhabited by persons of African ancestry), the overall prevalence rate of HTLV-1 was 2.8% and reached 5.3% in the adults (Trujillo et al., 1992). Other reports indicated the presence of some foci of HTLV-1 infection in different isolated Indian populations (Zaninovic et al., 1994). Several ATL cases have also been described in patients from Columbia (Blank et al., 1993).

In Venezuela, based on the few available data, the HTLV-1 seroprevalence seems quite low. Indeed, it was of 0.2% in a large series of blood donors from Caracas (Leon et al., 2003). Furthermore, only rare cases of TSP/HAM have been reported (Zabaleta et al., 1994).

In Paraguay, HTLV-1 is rare and seems absent among the Paraguayan general healthy population (Zoulek et al., 1992). In Uruguay, the seroprevalence reached 0.75% among the Urugayan blood donors (Muchinik et al., 1992).

French Guiana has been extensively studied for HTLV-1 infection (Kazanji and Gessain, 2003). In this French overseas region, HTLV-1 is mainly found in the Noir-Marron population, an ethnic group of African ancestry, also present currently in Surinam (Tortevoye et al., 2000, 2005). Indeed, this population is highly endemic for HTLV-1 (Plancoulaine et al., 1998; Carles et al., 2004) and several ATL cases have been reported in this ethnic group (Gerard et al., 1995). HTLV-1 infection and few associated diseases have also been reported in Guyana, and Surinam mainly in the persons of African ancestry (Pouliquen et al., 2004).

The numerous studies performed on blood donors and pregnant women from different areas of Argentina have revealed globally a low or very HTLV-1 seroprevalence, ranging roughly from 0.01 to 0.2% depending on the type and geographical location of the tested populations (Gastaldello et al., 2004; Trenchi et al., 2007; Berini et al., 2010). Some regions are thus considered as non-endemic (as the central areas) in contrast to the Northeastern provinces of the country (Biglione et al., 2005). In the same line, relatively few cases of TSP/HAM and ATL have been reported in this country (Biglione et al., 2003) ATL cases seems to be only described in individuals of Caucasian origin (Gioseffi et al., 1995; Marin et al., 2002).

Concerning Brazil, the situation is quite different and based on a large amount of solid publications, we can consider without any doubt that this country of more than 200 millions of inhabitants represents one of the largest endemic area for HTLV-1 and associated diseases. Indeed, several hundreds of cases of TSP/HAM, ATL, as well as large series of infective dermatitis cases have been reported in Brazilian patients (de Oliveira et al., 1990; Pombo De Oliveira, 1996; Araujo et al., 1998; Bittencourt et al., 2009).

Furthermore, several studies performed on large populations of blood donors have found an heterogeneous HTLV-1 seroprevalence ranging from 0.04 to 1% depending on the geographical location. The prevalence was higher in the North and Northeast than in the South (Catalan-Soares et al., 2005). Another more recent and large study show Brazilian blood donors prevalence of HTLV-1 on the order of one per 1,000 with regional differences probably due to the ethnic origin of the underlying population with indeed a higher prevalence in donors with black skin color (2.14/1,000) versus mixed (1.58/1,000) or white (0.79/1,000; Carneiro-Proietti et al., 2012). Similarly, HTLV-1 prevalence in pregnant women ranges from 0.1 to 0.8% depending on the tested area (Bittencourt et al., 2001; Olbrich Neto and Meira, 2004; Figueiro-Filho et al., 2007; Ydy et al., 2009; Guimaraes de Souza et al., 2012). Interestingly, Salvador de Bahia, a large city of the eastern part of the country, with a majority of inhabitants of African ancestry, is considered as the Brazilian city with the highest global HTLV-1 prevalence (around 1.3% of blood donors, and 1.8% in the general population; Galvao-Castro et al., 1997; Dourado et al., 2003).

HTLV-1 IN THE CARIBBEAN REGION

This region comprises more than 7,000 islands organized into 30 territories including sovereign states (e.g., Cuba, Jamaica, Haiti and Dominican Republic), overseas departments (e.g., Martinique, Guadeloupe) and dependencies (e.g., Bermuda, Caiman Islands), totalizing around 40 millions of inhabitants. The majority of these islands have a relatively small population (few thousands to half million persons). Only Cuba, Haiti/Dominican Republic, and Jamaica have a population of more than two millions. All the islands, which are mainly peopled with persons of African ancestry, represent a high endemic region for HTLV-1 infection and associated diseases.

Jamaica has been extensively studied concerning HTLV-1 infection (Clark et al., 1985; Murphy et al., 1991). Large series of ATL, TSP/HAM, and infective dermatitis have been reported in this island and in immigrants from Jamaica living, especially, in the United Kingdom (Gibbs et al., 1984; Rodgers-Johnson et al., 1988; Mowbray et al., 1989; La Grenade et al., 1990). In a large cohort of 13,260 Jamaicans from all parts of the island, HTLV-1 seroprevalence was high (mean 6.1%) ranging from 1.7 to 17.4%, depending on sex and age (Murphy et al., 1991). In pregnant women and in blood donors, it was of around 2–3.8% (Wiktor et al., 1993; Dowe et al., 1998; Brady-West and Buchner, 2000; Maloney et al., 2006). The situation is less known but could be quite similar in Haiti and the Dominican Republic. HTLV-1 seroprevalence in pregnant women is around 2.2–4.2% (Allain et al., 1992; Tortevoeye et al., 2005) and it is around of 3.8–4.3% in rural Haitian populations (Schill et al., 1989; Grant et al., 1992). Furthermore, some series of ATL and TSP/HAM have been reported mainly in immigrants from this island living in France and the US (Vernant et al., 1987; Bhagavati et al., 1988; Gout et al., 1989; Gessain et al., 1990a; Besson et al., 2001). In the French West Indies (FWI: Martinique and Guadeloupe), HTLV-1 seroprevalence in blood donors is around 0.3–0.4% (Cesaire et al., 1999; Rouet et al., 1999a,b) and in pregnant women from Martinique it is of around 2% (Denis et al., 1988; Mansuy et al., 1999). Furthermore, few hundreds of TSP/HAM and of ATL have been reported during the last 25 years

in these islands (Vernant et al., 1987; Plumelle et al., 1993) and in immigrants in Metropolitan France (Gout et al., 1989; Gessain et al., 1990a,c; Besson et al., 2001). HTLV-1 is also endemic at a similar level in Trinidad and Tobago (Blattner et al., 1990; Daisley et al., 1991) as well as in Barbados (Riedel et al., 1989).

In contrast, the studies performed in Cuba indicated that HTLV-1 seroprevalence is very low in this island (Hernandez Ramirez et al., 1991; Silva Cabrera et al., 1997) with also only very few ATL or TSP/HAM cases reported (Estrada et al., 1995). This is very probably linked, partly, to the different ethnic background of the islands with relatively few persons of African ancestry in Cuba as compared to Jamaica, Haiti, or the French West Indies. The estimates of the number of HTLV-1 infected persons for some islands in the Caribbean are given in **Table 2**.

HTLV-1 IN ASIA

Asia is the world's largest and most populous continent with nearly 3.9 billion people (60% of the world's current human population). Here we arbitrarily defined four subregions: (1) East Asia (China, Japan, North and South Korea, Mongolia, and Taiwan), (2) North (Siberia), Central (Afghanistan, Iran, Kazakhstan, Kyrgyzstan, Turkmenistan, and Uzbekistan,) and Southwest Asia (Arabian Peninsula, Armenia, Georgia, Israel, Jordan, Lebanon, Syria, and Turkey), (3) South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka,) and (4) Southeast Asia (Brunei, Burma, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, East Timor, and Vietnam). Except for some very important endemic foci including mainly Japan and Iran, the prevalence of HTLV-1 and associated diseases in Asia seems very low. However, in most of the areas, due to the lack of large and representative studies, the situation remains still poorly known.

East Asia

East Asia comprises more than 1.4 billion people (about 20% of the world population). In Mainland China, no general population-based study has been performed to our knowledge regarding HTLV-1 prevalence. However, a large-scale study concerning 145,293 blood donors representative of 13 provinces revealed a very low global prevalence (0.013%; Wang et al., 2005). Interestingly, all HTLV-1 seropositive individuals originate from the Fujian province in the Southeast and the prevalence rate in this peculiar province reached 0.055%. This confirmed the prevalence rate (0.06%) previously found in the same province among healthy individuals (Wang et al., 2004). Concerning the HTLV-1 related diseases, while very few cases of TSP/HAM have been reported (Seyfert et al., 2004), some series of ATL cases were found in Chinese patients (Zhuo et al., 1995; Au and Lo, 2005). These ATL cases were mainly distributed in patients from the coastal provinces and the Southeast China especially in the Fujian province.

In Japan, HTLV-1 infection has been extensively studied for more than 30 years. Japan is one of the most important foci of HTLV-1 infection and associated diseases (Watanabe, 2011). Indeed, around 1,000 of ATL cases are diagnosed each year (Tajima, 1990) and several hundreds of TSP/HAM have been reported (Osame et al., 1990), as well as large series of other HTLV-1 associated diseases including uveitis (Mochizuki et al., 1992). The minimal global prevalence of HTLV-1 infection in Japan as determined

by screening of blood donors is estimated to be at least 1.08 million in 2006 (Satake et al., 2012). Based on a previous nationwide survey, performed also among blood donors, the number of HTLV-1 infected individuals was around 1.2 million (Tajima, 1990). For several reasons, the prevalence calculated from blood donors survey is very probably lower than the actual value (Satake et al., 2012). Thus, Japan comprises very probably the largest HTLV-1 carriers number in the world. Since the first studies, the repartition of HTLV-1 carriers in Japan is quite uneven with prevalence rates among blood donors varying from 1% in Hokkaido to more than 6% in Kyushu and Okinawa Islands in the Southern part of the archipelago (Hinuma et al., 1982; Maeda et al., 1984; Tajima, 1990). Several studies in pregnant women also revealed such a heterogeneous situation, which origin remains to be determined, with an HTLV-1 prevalence ranging from 0.5% (in North/central Japan) to 5.8% (Southern part of the country; Oki et al., 1992; Umemoto et al., 1994; Goto et al., 1997; Maehama, 2004). In some villages or towns of highly endemic areas, HTLV-1 prevalence can reach 30–40% in adults, aged more than 50 years old (Kohakura et al., 1986; Tajima et al., 1987). Several programs aimed to prevent HTLV-1 transmission from mother to child, by refraining HTLV-1 infected mothers to breast-feed their children, have been implemented with great success (Hino, 2011). Although the HTLV-1 prevalence in Japan is very high, it is not clear why neighboring regions such as East China or Korea have a low prevalence. Indeed, the studies among Korean blood donors from various districts of Korea revealed very low HTLV-1 seropositive rates (0.007–0.25%; Lee et al., 1986; Kim et al., 1999; Kwon et al., 2008). Furthermore, very few cases of ATL and TSP/HAM have been reported in Korean patients (Park et al., 1991; Saito et al., 1993; Jeon et al., 2000).

In Taiwan, slightly more data are available and the prevalence of HTLV-1 infection seems higher. HTLV-1 screening in six blood centers revealed indeed an HTLV-1 seropositivity rate of 0.058% (Lu et al., 2001). Furthermore, in the Taiwanese adult population, aged more than 30 years, the HTLV-1 prevalence varies from 0.82 to 1.63% according to the districts investigated (Chen et al., 1999). Lastly, series of ATL cases have been diagnosed in Taipei (Lee et al., 2010).

North, Central, and Southwest Asia

Sporadic HTLV-1 infection cases have been detected in various small ethnic populations of Northern and Eastern Siberia, especially among individuals from the Nivikhi group (Seniuta et al., 1990; Gessain and de The, 1996). These data suggest the possible existence of HTLV-1 foci, which makes impossible a global estimation of the HTLV-1 prevalence in these vast regions. In Central Asia, Iran is by far the most studied country, especially the area of Mashad in the Northeast of the country. According to the type of studies and of tested populations, HTLV-1 prevalence is estimated to range from 0.77 to 3% in adults (Safai et al., 1996; Abbaszadegan et al., 2003; Rafatpanah et al., 2011). A more recent study indicates an HTLV-1 prevalence of 1.66% in adults from the city of Sabzevar located in the Southeast of Mashad and confirmed that HTLV-1 is highly endemic in this region (Azarpazhooh et al., 2012). Furthermore, relatively large series of ATL as well as TSP/HAM cases originating from the Mashad region are reported in Iran (Sidi et al., 1990; Kchour et al., 2009) but also in Iranian immigrants

living in European countries, the United States, or Israël (Sidi et al., 1990; Gabarre et al., 1993; Miller et al., 1998). No data are available from other areas of central Asia except scarce findings from Turkmenistan where the HTLV-1 seroprevalence rate among blood donors reached 0.2% (3/1,510; Senyuta et al., 1998).

In Southwest Asia, the HTLV-1 infection appeared to be non-endemic. In Saudi Arabia, there is no case of HTLV-1 infection or extremely low HTLV-1 seroprevalence rates (0.002–0.0052%) reported among blood donors (Bernvil et al., 1997; Arif and Ramia, 1998; El-Hazmi, 2004). The situation is quite comparable in other Persian Gulf countries such as Kuwait where the HTLV-1 seroprevalence observed among blood donors reached 0.009% (Al-Mufti et al., 1997). Nevertheless, few symptomatic HTLV-1 cases have been described in this latter country (Voevodin et al., 1995) and Iraq (Denic et al., 1990).

In Israel, an immigration state, studies indicated that most of infected persons originated from highly endemic countries (Iran, Romania, and Africa). Thus, the HTLV-1 prevalence must be appreciated according to the donors' countries of origin. However, the HTLV-1 prevalence in blood donors born in Israel reached 0.001% (Stienlauf et al., 2009). Furthermore, some ATL and TSP/HAM cases have been described mainly among immigrants of Romanian or Iranian origin (Sidi et al., 1990; Shtalrid et al., 2005).

In Lebanon, none of 1,900 blood donors screened was seropositive for HTLV-1 (Naman et al., 2002) although one ATL case of Lebanese origin has been described (Bitar et al., 2009). Quite comparable situation is observed in Turkey where none among 10,000 Healthy blood donors was HTLV-1 seroreactive (Sertoz et al., 2010). No data are available, to our knowledge, concerning the HTLV-1 situation in Jordan, Syria, and Armenia.

South Asia

India is with China, the second most populated country in the world with 1.2 billion inhabitants. If we consider neighboring countries such as Pakistan, Bangladesh, Sri Lanka, and Nepal plus Bhutan and Maldives territories, the South Asian population reached 1.6 billion (a quarter of the world population). In this region, the studies concerning HTLV-1 prevalence are scarce and the most recent one among Indian blood donors revealed a 0.14% prevalence rate (Kumar and Gupta, 2006). Other study demonstrated no serological evidence of HTLV-1 infection among the pregnant women tested (Ramalingam et al., 2001). Despite the low HTLV-1 prevalence rate, some ATL, and TSP/HAM cases have been regularly reported especially in Southern India (Andhra Pradesh, Kerala, and Tamil Nadu; Chandy et al., 1991; Babu et al., 1993; Jain et al., 2008; Ahmed et al., 2012) and Western India (Singhal et al., 1993). Thus, the prevalence of HTLV-1 carriers in India seems rare but taken into account the huge population size, large-scale studies are necessary to assess the global prevalence rate before to conclude that this infection is a minor public health hazard and to estimate a reliable HTLV-1 prevalence rate.

In Bangladesh, despite the large population size, no HTLV-1 prevalence study has been performed. A sporadic occurrence of HTLV-1 infection (0.9%) was found among patients with motor neuron disease called neurolathyrism (Haque et al., 1994). In Pakistan, who shares with Bangladesh the same population size, no

data concerning HTLV-1 prevalence is available. This situation is quite the same in others South Asian territories such as Nepal, Sri Lanka, Bhutan, and Maldives archipelago where HTLV-1 infection has never been investigated to our knowledge.

Southeast Asia

The Southeast Asian region comprises more than half a billion individuals. However, the situation regarding the HTLV-1 prevalence in the most populated countries has been poorly described. In Indonesia, the few studies revealed no HTLV-1 carrier among the blood donors tested (Tanggo et al., 2000). In Philippines, anecdotal, and ancient study suggested that the infection is present in the general population (Ishida et al., 1988). In the neighboring countries such as Malaysia, Vietnam, Cambodia, Laos, and Burma, no reliable information is available concerning the HTLV-1 global epidemiology. Moreover, no evidence of HTLV-1 infection among Hmong individuals from Northern Thailand was reported (Louisirirotchanakul et al., 2000) and a study performed on Hmong refugees living in French Guyana confirmed this data (Tortevoye et al., 2000). The situation seems quite different in the eastern part of New Guinea Island called Irian Jaya, where sporadic cases of HTLV-1 infection have been reported in some small isolated tribes (Re et al., 1989). Despite the lack of population-based studies in the Southeast Asian populations, the HTLV-1 prevalence rate seems to be low.

HTLV-1 IN OCEANIA

Oceania is a vast zone between continental Asia and the Americas comprising mostly coral atolls and volcanic islands. It is divided into three subregions, Micronesia (Kiribati, Marshall Islands, and Nauru), Australo-Melanesia (Australia, Fiji Islands, New Caledonia, Papua New Guinea, Solomon Islands, and Vanuatu), and Polynesia (American Samoa, Cook Islands, Easter Island, French Polynesia, Hawaii, New Zealand, Samoa, Tonga, Tuvalu, Wallis, and Futuna). The population is around 35 millions individuals with two third of Australian origin.

Australo-Melanesia

Only few population-based-study using solid serological confirmation criteria have been performed regarding HTLV-1 prevalence in the Australo-Melanesian region. Interestingly, few studies, conducted among Papuan aboriginal populations, demonstrated that some remote tribes as the Hagahai population living in the highlands (Madang province), exhibited higher HTLV-1 prevalence rate than population groups originating from different Papuan provinces such as the Sepik province (Yanagihara et al., 1990; Sanders et al., 1993; Yamaguchi et al., 1993; Takao et al., 2000). In the Solomon Islands, the HTLV-1 seroprevalence rate range from 1.2 to 3% according to the populations (hospitalized individuals, blood donors) and the islands investigated (Yanagihara et al., 1991; Nicholson et al., 1992; Furusyo et al., 1999). In Vanuatu archipelago, a large-scale population-based-study (4,247 individuals mostly adults) showed that the HTLV-1 prevalence rate was of 0.62% (Cassar et al., 2007). In Fiji and New Caledonia archipelagoes, no HTLV-1 infection was brought out by the very few studies performed among the native-born populations tested (Louis et al., 1990; Nicholson et al., 1992; Chungue et al., 1993).

In Australia, the situation for HTLV-1 is quite different as we considered Aboriginal populations from Central Australia or blood donors comprising mainly white non-Aboriginal individuals living in coastal areas. Thus, the studies conducted among blood donors from main Australian cities (Adelaide, Brisbane, Melbourne, Perth, and Sydney) revealed that HTLV-1 prevalence rate is very low, comprised between 0.001 and 0.032% (Whyte, 1997; Polizzotto et al., 2008). In contrast, several studies indicated that the Aboriginal groups of inland Australian regions represent a high HTLV-1 endemic population (May et al., 1988; Einsiedel et al., 2010, 2012). Moreover, HTLV-1 related cases, ATL and/or TSP/HAM, have been described among the Aboriginal communities of central Australia (Kirkland et al., 1991; Rajabalendran et al., 1993), Papua New Guinea (Yanagihara et al., 1990), and the Solomon Islands (Ajdukiewicz et al., 1989).

Polynesia/Micronesia

The few reliable studies performed in Polynesia/Micronesia regarding the HTLV-1 prevalence among native-born Polynesian individuals, indicated that the infection is absent or very rare (Nicholson et al., 1992; Chungue et al., 1993; Ohkura et al., 1999). In the Hawaiian archipelago, the virus is present but the studies suggested that HTLV-1 was introduced with the Japanese immigration (Kimata et al., 1989). Indeed, ATL and TSP/HAM cases were observed among immigrants from Southern Japan and their descendants (Yim et al., 1986; Yanagihara et al., 1989; Dixon et al., 1990). Few other studies have described the HTLV-1 situation in the Cook Islands, Kiribati, New Zealand, the Samoa and Wallis, and Futuna, but no HTLV-1 seropositive case has been documented to date (Reddy et al., 1987; Louis et al., 1990; Nicholson et al., 1992; Chungue et al., 1993).

CONCLUSION

Our best estimates range approximately from 5 to 10 millions HTLV-1 infected individuals. However, 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. The real number of HTLV-1 carriers is thus very probably much higher.

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