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The Epidemiology and Clinical Impact of HTLV Infections in Europe

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Abstract

The adoption of a single common algorithm for the detection and confirmation of HTLV-I and HTLV-II infections by participants in a European concerted action and the generalised use of improved screening and confirmatory assays has resulted in seroprevalence data in Europe which are comparable across time and space. HTLV-I remains present among blood donors at a low but uniform rate (2-12/100,000); seroconversions among existing blood donors are rare and screening all current donors and new donors once seems an appropriate use of resources. HTLV-I and -II infections are 10-100 times more common among pregnant women than among blood donors. Although perinatal transmission is preventable, no studies of transmission rates in Europe have yet been conducted. The highest rates of HTLV-II infection appear to be among IDU in Eire and Norway but rates are increasing in Spain, particularly among prisoners. There is a paucity of data on HTLV-I/II infection in patients attending sexual health clinics. The majority of cases of ATLL and HAM/TSP have been reported in France and the UK but rare cases have been reported in most other EU member states. The lifetime risk of HAM/TSP among carriers in the UK is high compared with Japan but consistent with Caribbean data. Life expectancy for acute ATLL in Europe is five months despite therapy.

Key words

HTLV-I. HTLV-II. Europe. Epidemiology. Disease. Adult T-cell. Leukaemia/Lymphoma. HTLV-I-associated myelopathy.

Introduction

The human T-cell leukaemia/lymphoma viruses types I and II (HTLV-I and HTLV-II) and their simian relatives are ancient viruses which have migrated with their hosts between Africa, Asia, Austronesia and the Americas. Phylogenetic analyses suggest that HTLV-II infection crossed the Bering Strait with its human host 10 - 35,000 years ago, whilst the Melanesian HTLV-I subtype, HTLV-Ic, was probably transmitted from Indonesian macaques to humans 50,000 years ago[1]. In the last few centuries enforced migration from Africa has taken HTLV-I to the Caribbean and the Americas[2]. HTLV-II appeared to be even more geographically restricted as initial reports of endemicity were restricted to isolated native American Indian populations[3]. Thus, HTLV-I was considered to be of the Old World and HTLV-II of the New World. Subsequent evidence of HTLV-II infection amongst African pygmies[4] and in the Horn of Africa[5] and of the Asian origin of HTLV-Ic has lead to new hypotheses of the origin and ancient migration of these infection. The recognised endemic areas for HTLV-I are Japan, Africa, Melanesia, South America, the Caribbean and the Southern States of the USA (reviewed in[6]). Conversely, HTLV-I is uncommon among native Europeans; in-

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deed case reports of HTLV-I infection in European Caucasians are noted because they are rare[7,8].

However, during the last fifty years there has been extensive immigration to Europe from Africa and the Caribbean, particularly between countries with strong historical links; thus in 1991 484,000 persons of Afro-Caribbean and 289,000 of Black African origin were resident in the UK[9]. During the same period, HTLV-II has spread among injecting drug users (IDU) and appears to have preceded HIV to Europe[10]. The two main HTLV-II subtypes (A and B) are estimated to have entered the networks of IDU circa 1955 and 1975 respectively[11]. Transmission of HTLV-I and -II is from mother-to-child[12] and between adults through sexual intercourse[13]. In modern times HTLV-I and -II have been transmitted through blood-to-blood contact, either iatrogenically, especially through whole blood transfusion[14], or through needle sharing[15].

Both HTLV-I and HTLV-II cause lifelong infection. HTLV-I was first isolated from a patient with a cutaneous T-cell lymphoma[16] and the association with adult T-cell leukaemia/lymphoma (ATLL) was rapidly established. Two - four percent of HTLV-I carriers develop ATLL[17] and, whilst incidence rates seem similar around the globe, the mean age at onset is older in Japan than in South America. A high seroprevalence of anti-HTLV-I antibodies was observed in patients with Tropical Spastic Paraparesis (TSP) in Martinique in 1985[18], where this condition occurs frequently in carriers[19]. A similar neurological association, HTLV-I-associated myelopathy (HAM), was described in Japan in 1986[20] and the condition is now known as HAM/TSP. However, the lifetime risk of HAM/TSP in Japanese carriers is only 0.25%. Other conditions characterised by lymphocytic infiltration have been reported in patients with HTLV-I: uveitis[21,22], polymyositis[23], alveolitis[24], arthritis[25] and infective dermatitis[26]. Evidence that HTLV-II is also associated with a chronic myelopathy is now accumulating[3,27]. Studies of the disease associations of HTLV-II have been difficult, particularly in industrialised countries, because of frequent co-infections with hepatitis B, hepatitis C and HIV-1, but in the later patients predominantly sensory peripheral neuropathy is more common[28]. In a prospective study HTLV-II infected blood donors in North America were more likely to develop respiratory and urinary tract infections than matched controls[29].

In the context of this continuing global spread of HTLVs, a background of incomplete knowledge of the prevalence of HTLV-I/II infection and the absence of a reporting system for HTLV-associated disease, a concerted action, the HTLV European Research Network (HERN) was established in 1994 to better understand the epidemiology of these infections within the member states of the European Union (EU). The initial findings were that HTLV-I and -II infections were present among blood donors at low but uniform rates, whilst levels 100 - 1000 times higher were found among women attending antenatal clinics, among men and women attending clinics for sexually transmitted infections and among IDU. However, with the exception of the screening of blood donors, surveys were few, of small sample size and, particularly for the earliest studies, hampered by the poor sensitivity and specificity of the available assays[30]. In this paper we review new data from a workshop in October 1997 which further clarify the sero-epidemiology of HTLV-I and -II in 12 European Countries (the participants are listed in the Appendix). As all the samples have been tested according to a common algorithm, the data are directly comparable and allow, for the first time, an assessment of trends in the epidemiology of HTLV-I and -II in Europe. Secondly, the incidence of HTLV-I/II associated diseases in Europe is reviewed and new data from the HERN ATLL Register are presented.

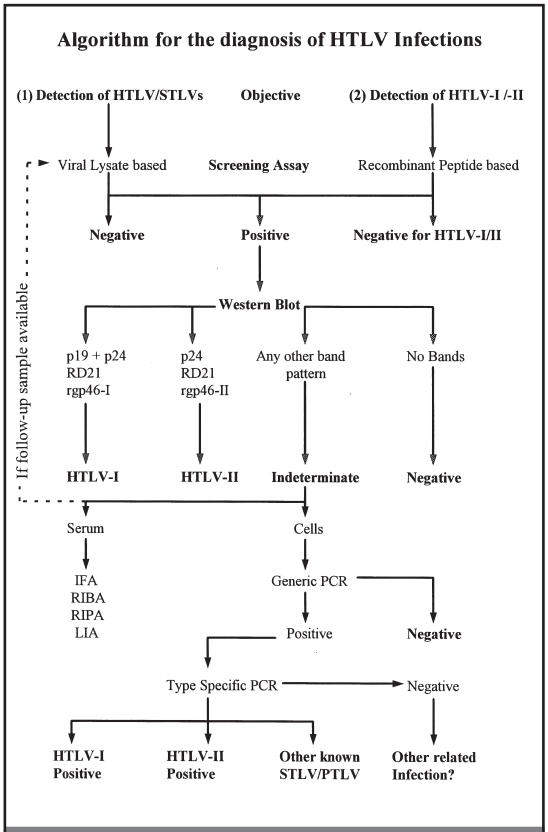


Fig. 1. *1997 HERN algorithm for the diagnosis of HTLV-I and HTLV-II infections in seroprevalence studies.*

HTLV-I/II serology

The 1994 HERN algorithm for the diagnosis of HTLV-I and HTLV-II infection suitable for seroepidemiology[30] was reviewed. The Western Blot criteria for confirmation of a positive result were confirmed. The algorithm was extended to include further investigation of indeterminate WB antibody patterns (Fig. 1). It was noted that the increased specificity of the latest screening assays, particularly those including recombinant peptides, may not allow the detection of related, known or as yet unidentified viruses. The workshop concluded that if the purpose of a screening programme is to specifically detect HTLV-I and HTLV-II, assays with high specificity, usually based on recombinant proteins, are recommended. However, to detect infection with re-

Table 1. *1994-1997 seroprevalence data by country and risk group for HTLV-I and HTLV-II infections showing number of positive tests per number of subjects tested, seroprevalence rates per 100,000 blood donors, 10,000 pregnant women and 100 IDU. 95% confidence intervals calculated from Poisson distribution tables.*

Country	Assay	Blood Donors			Pregnant Women			Special Risk Groups			
		No. positive	Seroprevalence /100,000		No. positive	Seroprevalence /10,000		No. positive	Seroprevalence /100		Patients
		No. tested	Rate	95% CI	No. tested	Rate	95% CI	No. tested	Rate	95% CI	
DENMARK	a, f	8/260,000	3	1-6				2/900	0,22		IDU
EIRE	a	1/170,000	0,6	0.015-3.2				14/103	13,6	7.6-22.8	IDU
FRANCE	Many	75/892,000	7								
FINLAND	c, e	5/250,000	2	0.26-2.9							
GERMANY	e				2/30,000	0,7		0/6,000	0	0 - 0.06	IDU
Bavaria	f	4/370,000	1,1	0.3-3.1							
Hamburg		1/9,700	10	0.26-57.4							
Mintz		1/11,000	9	0.22 - 50.6							
Heschia		0/100,000	0	0 - 3.7							
Frankfurt	e	0/100733	0	0 - 3.7							
GREECE	a,f,e	5/60.071	8,3	2.7 - 19.5				2/707	0,3	0.03 - 1.0	IDU
								5/357	1,4	0.45 - 3.3	Thalassemia
								1/198	0,5	0.01 - 2.8	Haemophilia
ITALY	a, d, e							36/2015	1,8		IDU
	d							0/309	0		non-Hodgkin's
PORTUGAL	a,b,e	12/160,000	7,5	3.9 - 13	0/2100	0	0 - 17.6	0/519	0	0 - 0.7	IDU
SPAIN					3/5885	5	1 - 14.9	32/393	8,1	5.6 - 11.5	IDU
UK	Select	7/1100	640	254 - 1309							
	e,a				5/10135	5	1.6 - 11.5				
	e,a							4/201	2	0.55 - 5.1	HIV-1

lated but divergent primate viruses, screening with a viral lysate-based assay is recommended.

The sensitivity and specificity of the screening assays used for the diagnosis of HTLV-I and HTLV-II infection by the participants in this workshop is summarised in Table 1. Serological confirmation was by Western Blot using Genelabs HTLV WB 2.3 / 2.4 or Cambridge Biotech HTLV WB. However, severely immunosuppressed HIV-1 infected patients co-infected with HTLV-II frequently show lack of reactivity to viral lysate antigens which gives rise to 'Indeterminate' western blot patterns [V. Soriano personal communication] .

Inter-laboratory variation

Inter-laboratory variation among thirteen participating centres was determined with a panel collected in Europe. The panel comprised 8 anti-HTLV-I positive, 6 anti-HTLV-II positive, 2 anti-HTLV-I positive but no MTA-1 (rgp46-I) band on Genelabs HTLV 2.3 Western Blot, 1 HTLV-I PCR confirmed Western Blot indeterminate, 7 PCR negative Western Blot indeterminate samples, 2 series of anti-HTLV-I positive and 2 series of anti-HTLV-II positive dilutions and a negative control. Participants analysed these samples in blinded fashion prior to the workshop. For HTLV-I positive samples 12/13 (92%) were faultless and one laboratory identified one serum as HTLV-indeterminate. For HTLV-II positive samples 11/13 (85%) gave fully correct answers with one false negative and one laboratory identifying 5 sera as indeterminate. The anti-HTLV-I/II negative sera were correctly identified, but the false-positive anti-HTLV-I samples caused some difficulty with only those laboratories which screened with the Murex HTLV-I/II EIA (Murex Biotech Ltd., Dartford, UK) and/or Serodia HTLV particle agglutination (Fujirebio, Tokyo, Japan) correctly discerning the results.

Seroepidemiology of HTLV-I and HTLV-II infection in the EU

Data collected from 1994-1997 are presented by country and by risk group in Table 2.

Blood donors

Since 1994, no new data were available from Austria, Belgium, Spain and Sweden. An additional 160,000 blood donors had been screened in Denmark with three HTLV infected new donors identified. The overall seroprevalence in Danish blood donors is therefore reduced to 3/100,000. Screening was introduced in Eire in 1996 with one HTLV-I seropositive donor found among the first 170,000 donors tested, a rate of 0.6/100,000. France has continued to test all donations. Between the introduction of screening in 1991 and the end of 1997 approximately 17 million donations have been assayed for HTLV-I/II antibodies in Metropolitan France, with 303 HTLV-I and seven HTLV-II infections confirmed. The seropositive rate of 7/100,000 new donors in 1995 and 1996 is unchanged from earlier years. Six seroconversions have been observed in repeated donors since screening was introduced [*Reseau National de Santé Publique*]. Following a pilot study in Southern Finland in which two HTLV-I positives were identified among 25,470 blood donors, screening was introduced nationally in 1995. By August 1997 five HTLV-I infections among approximately 250,000 donors (926,147 donations) had been detected. Routine screening of blood donors has not been introduced in Germany, but a number of regional studies have been conducted by the transfusion services. Seroprevalence rates vary between 0/100,000 and 10/100,000. A study of 60,071 donors in Greece during 1997 identified four HTLV-I and one HTLV-II infections, an overall rate of 8.3/100,000 and routine screening has commenced. Compulsory blood donor screening commenced in Portugal in February 1996 and 12 donors of 160,000 tested have been found to be HTLV-I positive (7.5/100,000). During a campaign to increase the number of U-negative donors in the UK donor pool, 1100 donors of Afro-Caribbean origin were screened resulting in six confirmed HTLV-I and one confirmed HTLV-II infections (6.4/1000) [P. Hewitt Personal Communication].

Pregnant women

In 1994 attention was drawn to the HTLV-I/II seroprevalence rates in pregnant women in France and the UK which were up to 100-fold higher than

Table 2. *Sensitivity and specificity of the screening assays used by the workshop participants based on 127 HTLV-I and 62 HTLV-II sera from Sweden and Guinea-Bissau and 400-500 (seronegative) Swedish blood donors.*

Assay	Sensitivity		Specificity
	HTLV-I	HTLV-II	
Murex HTLV-I/II EIA GE80/81	100	100	98,4
Roche Cobas Core	100	100	99,8
Genelabs	100	96,8	99,8
Fujirebio Serodia	100	100	100
Abbott HTLV-I/II	100	96,8	99,8
Orthoprism HTLV-I/II	100	100	99,4

among blood donors. Between 1994 and 1997 new studies among women attending ante-natal clinics were conducted in Germany, Portugal, Spain and the UK. Among 5885 women in Spain, two were infected with HTLV-II and one with HTLV-I, a seroprevalence rate equivalent to 5/10,000. In Germany, 30,000 Guthrie cards from neonates were screened with two HTLV-I infections identified (7/100,000). A small study in Portugal did not identify any positive cases. A pilot study using dried blood spots from 10,135 infants in London detected five HTLV-I infections.

High risk groups

A study of intravenous drug users (IDU) in Eire found 14/103 (13.6%) to be infected with HTLV-II. In Copenhagen, 900 IDU were tested for HTLV-I/II antibodies *post mortem*, with only 2 HTLV-II infections identified. No HTLV infections were found among 6000 IDU in Germany or 519 IDU in Portugal. This contrasts with the experience from Madrid, where in 1995 the seroprevalence of HTLV-II was 32/393 (8.1%), 5-fold higher than that found seven years earlier[31]. 1.8% of 2015 IDU in Northern Italy were HTLV-II, (predominantly IIb) infected with a higher rate found in HIV-1 infected (4.5%) than in uninfected (0.8%) subjects. Among 201 HIV-1 positive patients routinely screened at a London hospital 2% were positive - 2 HTLV-I, (Caucasian homosexual males) and 2 HTLV-II (one male and one female IDU). In Portugal 22 patients are known to be co-infected with HIV-1/2 and HTLV-I/II. Epidemiologically, the majority are linked to West Africa with 15 HIV-2/HTLV co-infections, including one subject infected with HIV-2 and HTLV-II. In Greece 5/357 (1.4%) of poly-transfused patients and 2/707 (0.3%) IDU were HTLV-I seropositive.

HTLV-I/II associated disease in Europe

Malignancy

Prior to the establishing of an ATLL Register in 1996 the clinical impact of HTLV- I/II in Europe can only be estimated from published reports. HTLV-I associated disease in Europe was first reported in 1982 by Catovsky *et al* whose description of 6 patients from the United Kingdom with ATLL included a patient who presented in 1977[32]. Gessain *et al* reported 17 cases of ATLL in France between 1986 and 1988[33] -all these patients originated from Africa or the Caribbean-. Conversely, in Italy and Spain rare examples of ATLL in European natives have been reported[34-36]. Since the introduction of blood donor screening, an increased number of patients with HTLV-associated diseases, including seven cases of ATLL presenting with lymphoma, have been reported in Portugal [F. Avillez, personal communication]. This may be due to increased awareness among medical staff of the possibility of HTLV-I infection and associated diseases. In England and Wales it has been possible to identify patients with HTLV-associated disease by reviewing HTLV-I/II serology requests, since the majority of confirmatory requests are handled by two reference laboratories. Between 1986 and 1997 more than 400 HTLV infections have been diagnosed[37,38]. Of these, the clinical details were consistent with Adult T-cell Leukaemia in 91, an average of 8.5 cases per annum. Five cases of ATLL have been diagnosed in Germany, three of the patients originated from Central Europe [G. Pauli, personal communication].

To date 66 cases have been reported to the ATLL register. As expected, the majority of cases have been reported from France (33%) and the UK (55%) with four cases from the Netherlands and solitary cases from each of Sweden, Denmark and Italy. Whilst most patients were born in the Caribbean basin, eleven were from Africa, mostly West Africa and three from the Middle East (Iran, Iraq and Kuwait), a recently recognised HTLV-I endemic area. Two further important observations can be made from the ATLL Register: the age at presentation (mean 42 years) is much younger than in Japan (mean 57.5 years)[39] and life expectancy following diagnosis is short, 5 months, for acute ATLL, despite access to chemotherapy and antiviral therapy. Prolonged survival (mean 5.9 years) is common in patients with chronic or smouldering ATLL with conservative management.

Inflammatory Diseases

Like ATLL, the majority of patients with HAM/TSP have been seen in France and the UK with single cases reported in Germany[40], Switzerland[41] Sweden, Italy and Portugal [unpublished data]. Gessain *et al* reported 21 cases diagnosed in France between 1986 and 1988[33]. Through serology requests, 159 cases have been identified in England and Wales since 1986[37,38]. During the first seven years which immediately followed the initial description of the association of HTLV-I with myelopathy, an average of 14 cases were diagnosed per annum. This figure is likely to include many prevalent cases with onset of symptoms prior to 1985. However, during the second survey period, 12 new diagnoses of HAM/TSP were still being made each year. Based on an estimated population of 22,000 HTLV-I carriers, the calculated lifetime risk of HAM/TSP in carriers in the UK was 3%[38] which, whilst 12 times higher than in Japan, is consistent with Caribbean and US data[19,42].

Other inflammatory diseases were uncommon with only polymyositis[38] and uveitis[43,44] cases reported in France and the UK, but in the UK it was apparent that such presentations rarely prompted requests for HTLV-I serology. Whilst infective dermatitis has been mostly observed in the Caribbean[26], the condition may persist in a temperate climate, as has been reported in France[45].

HTLV-II associated disease

A single patient with HTLV-II (HIV-1/2 negative) and myelopathy has been reported in the UK dur-

ing the last 14 years. However, in Italy mixed motor and sensory polyneuropathy was found to be more common in HIV-1 patients co-infected with HTLV-II than in patients with HIV-1 infection only. Given the neurotoxicity of a number of the nucleoside analogues currently prescribed long term for HIV-1/2 infection, the screening of HIV-1 patients for HTLV-II co-infection may become increasingly important to appropriately diagnose peripheral neuropathy and perhaps to consider less neurotoxic compounds for patients co-infected with HTLV-II or HTLV-I.

Discussion

The adoption of a common algorithm, improvement in the sensitivity and specificity of commercial assays and the almost universal usage of a HTLV Western Blot with type specific recombinant peptides to confirm HTLV seropositivity ensure that the data from Europe since 1994 are highly comparable. This was confirmed by the inter-laboratory quality control study.

The recent isolation of new members of the HTLV/STLV family among non-human primates[46,47] gives rise to concern that the increased specificity for HTLV-I and HTLV-II of the assays based on recombinant peptides may allow more divergent viruses to escape detection. With this theoretical risk in mind, the workshop revised the algorithm for the diagnosis and confirmation of HTLV infections. Since these new viruses have been identified by detection of sero-reactivity in assays based viral lysates, it is suggested that, where the identification of all possible members of the HTLV/STLV family is a concern, the initial screen should be with a lysate based assay. However, in many other circumstances, e.g. screening of blood donors, the increased number of false positives that this would generate would not be welcome and therefore the use of assays which reliably detect HTLV-I and HTLV-II with high specificity is recommended. The antibody bands required to confirm a HTLV-I or HTLV-II seropositive status remain unchanged from the 1994 algorithm. Whilst a number of studies indicate that certain 'Indeterminate' Western Blot patterns are extremely unlikely to represent true infection[48-50], the further investigation of these subjects is recommended, by repeat or different serology, testing follow-up samples and, where cells are available, by PCR using generic and type specific primers[51].

New and continued screening of blood donors confirms the findings of the 1994 workshop (Fig. 2a); the prevalence of HTLV-I/II infection among blood donors across Europe is low, but uniform, with no country having a rate much above 1/10,000 donors. Data from France, which has the most extensive experience, indicate that seroconversions among existing donors are very rare events occurring approximately once per year. These data vindicate the position of those transfusion services which have elected to screen all existing and new donors once. The number of countries now routinely screening blood donors within the EC has steadily risen to nine. France, Holland and Luxembourg were the first European countries to introduce universal blood donor screening. Of the Scandinavian countries, Denmark, Sweden and Finland have introduced screening and, following a pilot study, Norway[52] is now considering its approach. Screening has recently been introduced in Eire, Greece and Portugal. Of those countries, which do not currently screen donors, Belgium and Germany have the lowest reported European blood donor seroprevalence rates, but Italy and the UK[53] have rates similar to or higher than in those countries, which have already elected to screen. Infection among blood donors is usually with HTLV-I, which suggests that recognition of risk factors for other transfusion transmitted infections exclude HTLV-II but not HTLV-I infected subjects from donor panels.

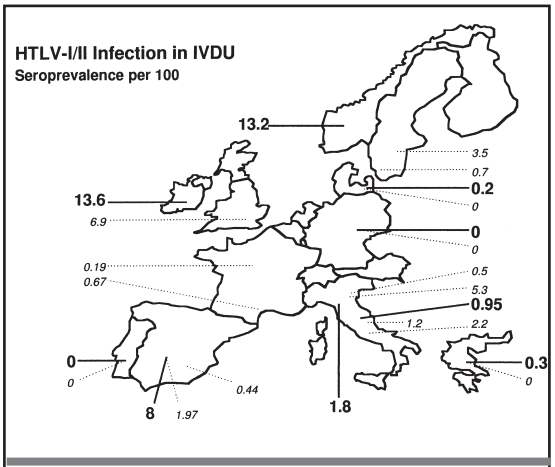
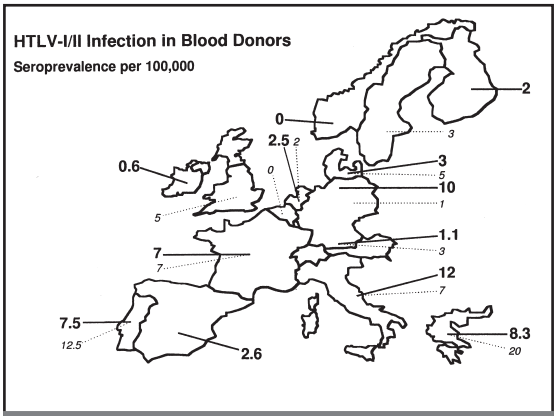


Fig. 2. *HTLV-I seroprevalence rates in Europe indicating changes since 1994. Data published since the 1994 workshop are included. 1997 figures in bold, 1994 figures in italics. A) Blood Donors: More than four million blood donors have been tested since 1991.*
French and Dutch blood donor rates refer to new donors only. Norwegian blood donor data[67].

Eight new studies of ante-natal clinic attenders have been completed since 1994 (Fig. 2b). In Marseille[54] (Feb '92- Nov '92) 0.32% and in single centre studies in London 0.2% (1990-1992)[55] and 0.4% (1994)[56] of pregnant women were infected with HTLVs usually HTLV-I. Data from these centres support the 1994 observation that HTLV infection is up

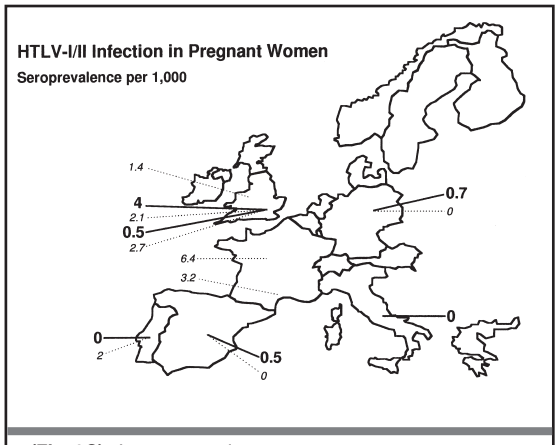


(Fig. 2B): *Pregnant women.*

to 100-times more common in the ante-natal population than among blood donors. However, such studies are usually conducted because the centres serve communities with large ethnic minority populations. In an ante-natal study designed to reduced this bias, dried blood spots from 10,135 neonates from multiple hospitals in Greater London were tested, with 5 HTLV-I infections identified[57]. The 5/10,000 seroprevalence rate remains 10-fold higher than among local blood donors, but is less than in the single centre studies. Although HTLV infection has not been found in the ante-natal populations of Italy[58] and Portugal (Table 2), these were small studies with broad confidence intervals which overlap with the higher rates documented elsewhere. This is exemplified in Spain, where a rate similar to that seen in London has been reported in 1997 (Table 2), whereas in much smaller studies reported in 1994 no mothers were been found to be HTLV positive[30]. In both Spain and Germany the ANC rate of infection is 10-fold higher than among blood donors.

These ante-natal data are important because pregnant women are more representative of the general population than blood donors and because the majority of mother-to-child transmission can be prevented by avoidance of breast-feeding[12]. Although the rate of transmission is generally less for mother-to-child transmission than for blood transfusion transmitted infection, the rate of acquisition by infants breast fed longer than 6 months is 20-25%. Since the life expectancy of a baby born to an HTLV-infected mother is many decades, whilst approximately 1/3 of all blood is given to recipients who die within 24 months, the risk of developing HTLV-I/II related disease may be higher following mother-to-child transmission than following transfusion transmitted infection. Whilst HAM/TSP is associated, in some cases, with a history of blood transfusion[59], family studies suggest that Adult T-cell leukaemia/lymphoma develops in adults who acquired HTLV-I infection in early life[17] and there are few reports associating transfusion acquired infection with subsequent ATLL[60]. Confirmation of the high seroprevalence of HTLV-I/II infection in this population would have important implications for the maternal services. However, the mother-to-child transmission rate of HTLV-I (or HTLV-II) has not been determined in Europe and it has been suggested from family studies that transmission occurs less frequently in Europe than in the Caribbean[61]. A multi-centre European study to determine the seroprevalence of HTLV-I/II infections among 250,000 women attending ante-natal clinics in Belgium, France, Germany, Italy, Portugal, Spain, Sweden and the UK is due to report in AD 2000.

The highest HTLV-II infection rates in Europe, confirmed by highly specific assays (Table 1), are to be found among IDU in Eire and Spain (Table 2) with similar rates reported from Norway[62] and Sweden[10]. Infection remains sporadic among IDU, suggesting that networks of injecting drug users are relatively localised. The rate of HTLV-II infection in Denmark remains low despite the prevalence of



(Fig. 2C): *Intravenous drug users.*

HTLV-II infection in other Scandinavian countries. No IDU native to Germany has tested positive, although expatriate ex-IDU infected with HTLV-II have been found among Germany's blood donors. Similarly, HTLV-II remains relatively rare in France and Portugal (where it has not yet been detected in native IDU), yet common in Northern Spain and Northern Italy (Fig. 2c). The importance of local networks is emphasised by the increasing prevalence of HTLV-II among the residents of Spanish prisons (Table 2)[63]. Like HTLV-II isolates from Scandinavia[64] and the UK[65], the Irish HTLV-II isolates were all subtype IIa. This supports the concept of at least two separate introductions of HTLV-II into Europe with HTLV-IIb commonly found in the south and HTLV-IIa almost exclusively in Northern Europe. Although HTLV-I has rarely been reported among IDU in Europe, the first HTLV-positive IDU found in Greece were infected with HTLV-I. Among 2015 Italian IDU, the prevalence of HTLV-II was 1.8%, but 4.5% in HIV-1 infected IDU, compared with 0.8% among HIV-1 uninfected IDU. This rate is similar to that found by Icardi *et al*, who had examined sera from more than 10,000 IDU in a multicentre study[58].

Few studies among other high risk groups were conducted or reported during 1994-7, although the data from London suggest little change in the prevalence of HTLV infections amongst HIV infected subjects since 1984[66]. HTLV-I was found in Caucasian homosexual males and HTLV-II in Caucasian IDU whereas in Portugal, HTLV/HIV co-infections were linked to West Africa. The evidence of HTLV-I among thalassaemia patients in Greece, the recipients of multiple transfusions, confirms the presence of HTLV-I in the Greek blood donor pool.

HTLV-associated diseases are most commonly diagnosed in France and the UK in patients from the recognised endemic areas. Despite the previous absence of centralised reporting, the number of cases of ATLL described in France and the UK is consistent with the estimated number of HTLV-I carriers, which suggests good awareness amongst haematologists and oncologists. Similarly, neurologists appear to have a low threshold for requesting HTLV-I serology in patients with myelopathy. Conversely, other inflammatory conditions associated with HTLV-I are rarely reported which may be due to

a low prevalence or under diagnosis. Evidence is increasing that HTLV-II may be associated with myelopathy, but as yet few cases have been reported in Europe. This diagnosis may be difficult because HTLV-II is commonly a co-infection with HIV-1. However, with combination antiretroviral therapy HIV-1 replication can be suppressed to very low levels for prolonged periods. Paradoxically, this could result in an increase in the diagnosis of HTLV-II associated disease, although these are still likely to occur in only a small minority of patients unless the faster evolution of HTLV-II in European IDU[11] results in a change in the behaviour and pathogenicity of HTLV-II.

Conclusions

Highly specific and sensitive assays used according to a common algorithm allow changes in HTLV-I/II seroprevalence in Europe to be determined. The majority of current EU member states screen blood donors among whom the prevalence of HTLV-I infection is very low. The higher rates of HTLV-I/II infection confirmed among pregnant women suggest that routine ante-natal screening should be considered in 'high risk' areas. HTLV-II is common among IDU with evidence of increasing prevalence in Spain. Priority should now be given to studies to determine the prevalence of HTLV-I/II infections among sexually active men and (non-pregnant) women, to improve the collation of data on the incidence of HTLV-associated diseases in Europe, which at present are mainly found in minority groups, and to improve the treatment of these conditions which, though rare in Europe, cause considerable morbidity and mortality.

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