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HTLV-I VIRUS IN EUROPEANS: THE CONTINUOUS SPREAD. A META-ANALYSIs*

[1]V. MAYER, [2]P. EBBESEN

[1]Institute of Virology, Slovak Academy of Sciences, 842 46 Bratislava, Czechoslovakia, and [2]Dpt. of Virus and Cancer, Danish Cancer Society, DK-8000 Århus, Denmark

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Summary. - Published and unpublished data on the HTLV-I seroprevalence in 13 European countries (sample a total of 79.549 persons) was subject to meta-analysis. HTLV-I infection was significantly associated with intravenous drug use, HIV-I seropositivity, geographical area and immigration from endemic areas outside of Europe. Significant percentage of HTLV-I seropositivity was observed in all groups of HIV-I seropositive individuals studies. The overall HTLV-I seroprevalence was 4.16 % in intravenous drug abusers, 0,66 % in male homosexuals, 0.62 % in immigrants from HTLV-I endemic areas and 0.015 % in the general population. A major problem in these epidemiological considerations is the uncertain delineation of the serology of HTLV-I versus that of HTLV-II. There have, been no reports from Europe of the specific leukaemic and neurologic indicator diseases associated with the HTLV-I seropositivity. Presently, the HTLV-I/HIV-I co-infected individuals represent an urgent medical problem. The information available shows a need for self-exclusion of all blood donor groups at risk for HTLV-I infection and for active seroepidemiological surveillance in all parts of Europe. However, improvements in diagnostic methods, increased knowledge about the pathogenesis of infection by HTLV-I or HTLV-II virus and the probable detection of new human retroviruses may markedly influence the future requirements for preventive measures.

Key words: HTLV-I, seroprevalence, Europe, population groups at risk, indicator disease, viral coinfections, preventive measures.

Introduction

The first exogenous human pathogenic retrovirus was isolated in 1978 following *in vitro* cultivation of T-lymphocytes from a patient with adult T-cell

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leukaemia/lymphoma (Poiesz *et al.,* 1980; reviewed by e.g. Wong-Staal and Gallo, 1985). This virus, a human T lymphotropic virus type I (HTLV-I) with a widespread but uneven worldwide distribution, bears a causal relationship to adult T cell leukaemia (ATL) described earlier in geographically restricted parts of Japan (Takatsuki *et al.,* 1977). The primary aetiologic role of HTLV-I in endemically occurring, slowly evolving myelopathy has been described recently (Gessain *et al.,* 1985, 1989; Osame *et al.,* 1986).

Early clinical and later also seroepidemiological observations indicated that HTLV-I is endemically confined and has a high prevalence in some areas in Japan and the Caribbean Basin, in Africa, Latin America, South East Asia and the South Pacific (e.g. Blattner *et al.,* 1985*a,b*; Delaporte *et al.,* 1988; Garruto *et al.,* 1989; Cortes *et al.,* 1989). This endemicity is claimed to have existed for a long period. Thus, the presence of HTLV-I in Japan is estimated to be at least 60 generations old (Ueda et al., 1988). HTLV-I as a human retrovirus is transmitted by blood (and cellular blood components), sexually, foetomaternally/perinatally and between intravenous drug addicts sharing needles and syringes (e.g. Okuchi *et al.,* 1985; Jason *et al.,* 1985; Kojiyama *et al.,* 1986; Robert-Guroff *et al.,* 1986). The exact mechanisms of perinatal transmission of HTLV-I have not yet been fully elucidated (Lee *et al.,* 1990).

HTLV-I is assumed to have a very low prevalence in general population in Europe.

The present meta-analysis is an attempt to outline the epidemiological characteristics of the HTLV-I spread in Europe, and to evaluate its possible consequences for the European disease pattern. The population-based data in Europe are scant so far. Still, this review of published and unpublished materials may partially elucidate possible trends in the continuous spreading of HTLV-I in some parts of Europe where specific well-defined population strata have been seriously affected by routes of virus transmission being of less importance for spread of infection in endemic regions.

The human T lymphotropic virus type I

HTLV-I belongs taxonomically to the family *Retroviridae,* subfamily Oncovirinae. Like other typical human retroviruses, this enveloped, single-stranded RNA virus can integrate its genome, in the form of DNA transcribed provirus, and thus become part of the host cell genetic material. HTLV-I although being the aetiological cause of the aggressive malignancy of T CD4 cells, i.e. ATL, has no proven oncogene(-s) in the usual sense. Besides its typical structural genes (gag, pol, env) the HTLV-I genome has the unique, 1585 nucleotide long pX region, located between 3'end of the region encoding the envelope gene precursor and the long terminal repeat. The pX region has been shown to contain sequences encoding 3 proteins designated Tax, Rex and p21. The non-structural diffusible Tax protein appears at least to transcriptionally transactivate and/or deregulate both its own LTR and the expression of several cellular genes (Yoshida *et al.,* 1986), including the gene for interleukin-2 and for the α-

subunit of the interleukin-2 receptor (IL 2Rα). The same HTLV-I infected T CD4 cell may therefore produce and utilize interleukin-2, which may trigger a cell proliferation as the first of multiple steps in the oncogenic transformation. Moreover, the Tax protein was recently identified (Tanaka *et al.*, 1990) as a viral oncogene (lacking a cellular homologue) responsible for transformation and leukaemogenesis.

Another human lymphotropic virus, the HTLV-II, is about 50 % homologous with HTLV-I. The lack of specific/suitable reagents in serological tests makes it difficult to say so far how many infections are due to each virus (Rosenblatt *et al.*, 1988). Moreover, concomitant infection with HTLV-I and HTLV-II may also occur (Kaplan *et al.*, 1990). The gene amplification method (polymerase chain reaction, PCR) and HTLV-I/II sequence differentiation by restriction and sequentional analysis has proven productive in resolving this difficulty (Lee *et al.*, 1989 *a,b*) and actually was at first used for screening purposes (e.g. Lee *et al.*, 1990; Wiktor *et al.*, 1990).

Jacobson *et al.*, (1988) described a biologically interesting, but not antigenically different variant of HTLV-I (Shriver *et al.*, 1988). Other data suggest that HTLV-I is significantly more genomically stable (Gallo *et al.*, 1988) than the human immunodeficiency virus (HIV), a lentivirus from the family Retroviridae. In murine leukaemia virus, discrete differences in nucleotide sequences may profoundly change e.g. the neurotropism of the virus (Gardner, 1987).

Diseases caused by or associated with HTLV-I

Adult T-cell leukemia (ATL) has been subdivided by Takatsuki *et al.*, (1977) into five clinical forms: acute (typical), chronic, „smoldering", crisis stage and lymphoma. Death results in ATL from the aggressive spread of leukaemic cells, hypercalcaemia and often from numerous opportunistic infections. These infections are caused by an immunodeficiency linked to the HTLV-I infection. Patients with such disorders have specific anti-HTLV-I antibodies at a frequency of 90–100 % and the cloned HTLV-I DNA provirus has been identified in the tumorous cells (e.g. Clark et al., *1988*).

Chronic cases of ATL have a less aggressive course, but their prognosis is just as poor as that of acute ATL. „Smoldering" ATL shows infiltrative skin symptomatology, but usually do not show any other abnormality (Blattner *et al.*, 1983), until the acute crisis occurs. The lymphoma type of ATL (aleukemic ATL) is a mature T-cell type non-Hodgkin lymphoma in which the malignant cells contain the HTLV-I provirus. Other, rare cases of HTLV-I-associated lymphoma have also been described (Blayney *et al.*, 1983). Studies have also incriminated HTLV-I as associated with an increased risk for the development of B-cell leukaemia/lymphoma. The pathogenetic mechanism exerted here by HTLV-I is not fully elucidated at present, but a chronic antigenic stimulation is suspected to play a role (Blattner and Gallo, 1985*b*).

U.S. reports have recently described sporadic and rare cases of polymyositis linked to HTLV infection (Morgan *et al.*, 1989; Evans *et al.*, 1989) and cases of

HTLV-I-associated myelopathy, which was observed to develop mainly in people of non-Caucasian descent. The same has been the case in Europe since the early 80s, when ATL was diagnosed among individuals from South America, the West Indies and Africa (e.g. Vyth-Dreese *et al.*, 1982).

Intensive studies are being conducted to elucidate the nature and/or influence of HTLV-I infection on the course of infections with HIV, hepatitis B, Epstein-Barr virus and cytomegalovirus (and vise versa), (e.g. Page *et al.*, 1990). *In vitro* observations have invited the hypothesis that at least one HTLV-I pX region-coded product, namely Tax, may activate the HIV provirus or enhance the replication of HIV. Conversely, HIV-induced immunosuppression may influence the course of an existing HTLV-I infection in the same host (Harper *et al.*, 1986).

Transmission modes and selected aspects of the natural history of HTLV-I infection

The blood of asymptomatic HTLV-I carriers is one of the best documented sources of infection (e.g. Okuchi *et al.*, 1984; Jason et al., 1985). Both parenterally administered whole blood, and its corpuscular elements effectively transmit the virus to recipients of transfusion blood and from the mother to child (intrapartum, uteroplacental bleedings). The rate of seroconversion has been shown to surpass 90 % among polytransfused patients (Minamoto *et al.*, 1988) and even among recipients of a single infected blood transfusion (e.g. Okuchhhi *et al.*, 1984). A relatively new mode of HTLV-I transmission rarely met with in the original endemic areas, is via the use among IVDA of HTLV-I contaminated needles of syringes. This mode of virus transmission presently is relatively most prevalent in some southern and northern parts of Europe (e.g. Rome, Neaples, Amsterdam).

Sexual exposure is another important route of HTLV-I transmission. Those most at risk are the sexual partners of HTLV-I seropositive men and to a lesser extent also the sexual partners of infected women. The 10-year probability of HTLV-I transmission from a seropositive husband to his wife is as high as 61 % but from the HTLV-I-carrying wife to her husband it is only 0.4 % (Kojiyama *et al.*, 1986).

The seropositivity rate among homosexual men in HTLV-I endemic areas (Bartholomew *et al.*, 1987*a*), in the U.S.A. (Manns *et al.*, 1988) and in some parts of Europe (e.g. Gradilone *et al.*, 1986; Manca *et al.*, 1989) was lower than that of intravenous drug abusers. However, it remains to be clarified whether specific sexual practices influence the transmission rate between HTLV-I seropositive homosexual men (Ebbesen *et al.*, 1984). The virus transmission is probably facilitated by rectal intercourse which is oftern abrasive. Spreading may also be assisted by cofactors such as the presence of ulcerative sexually transmissible disearses (Murphy *et al.*, 1988).

Together homosexuals, bisexuals, IVDAs and emigrants from endemic areas (see later) form a potential source of HTLV-I infections; a source which

has gained in importance in recent years. The true transmission rate is unknown, however. Promiscuous HIV-infected homosexuals often also have HTLV-I, HTLV-II or other infections such as hepatitis C, or cytomegalovirus (CMV). The possible role of the asymptomatic HIV infection on the transmission rate of HTLV-I in these persons is not known at present. If HTLV-I is acquired sexually in young adults, the time factor may later contribute to the expression of the disease (Murphy *et al.*, 1989). The HTLV-I infection rate among promiscuous homosexuals who have infected partners has been reported to be low (Tedder *et al.*, 1984) and the infection in this group evolves only slowly, which is not without consequences for the general population. Mother to infant transplacental, perinatal or postnatal (breast-feeding, close contacts) HTLV-I transmission also represents a risk for the European population, but it seems at present to be very low. HTLV-I seropositivity has mainly been observed among childbearing mothers and emigrants from endemic regions (e.g. Courtois *et al.*, 1990; Banatvala *et al.*, 1990). It is apparently important in this connection that the HTLV-I seropositivity in children is linked to the mothers seropositivity and not to that of the father (Riedel *et al.*,1989). Familial HTLV-I infection in crowded households has been described, but how it may promote virus transmission is unknown. All factors, contributing to the transmission of HTLV-I clearly have not yet been fully defined (Sarin *et al.*, 1983; Denic *et al.*, 1988; Riedel *et al.*, 1989) and it cannot be established, even in endemic regions, which route of HTLV-I transmission is the most frequent one.

The rate (of occurrence) of ATL or other HTLV-I-associated diseases among virus carriers is low. The average incubation period of tropical spastic paraparesis is supposed to be 18 years, but the period may be as long as 34 years (Cruickshank *et al.*, 1990). It has likewise been observed that ATL may develop over a very long period, up to 30 years (Greaves *et al.*, 1984). Similarly, it has not been definitely clarified, whether the rise in the incidence of HTLV-I seropositivity with age is due to a) a longer latency period before detectable seroconversion, b) repeated exposure (sexual) during adulthood or c) whether contributing factors activate the latent HTLV-I provirus when the seroconversion takes place years after the infection (Cardosa *et al.*, 1989).

In individuals exposed early in life and in whom the amount of antibodies increases with age, the antibody-negative latency period may also stem from other factors such as recurrent T-cell activation due to repeated immunologic stimuli (Blattner *et al.*, 1986). For unexplained reasons there is no HTLV-I antibody expression early in life in men unlike in women (Riedel *et al.*, 1989). The antibody-negative phase, the length of which still is not precisely known, may contribute to a possible underestimation of the number of HTLV-I infected persons outside known endemic regions, which may have relevance to the epidemiology of the European area. (Manzari, ref. personal communication). Moreover, the investigation on the presence of HTLV-I specific antibodies in

blood donors may not give a true picture of the seroprevalence, because these persons in majority are below the age of 40. Along this line d'Auriol *et al.,* (1990) made the important observation that HTLV-I infection could be diagnosed by PCR in seronegative patients with neurological disorders. Moreover, several researchers have concluded that the comercial antibody assays presently available are not satisfactory (e.g. Koprowski and DeFreitas, 1988).

It seems that the host factors may influence the course of infection and also its clinical expression. The genetically encoded magnitude of the immune response would appear to be one of several possible endogenous cofactors. HLA haplotypes associated with a low immune response to HTLV-I have been found in ATL patients, whereas different HLA haplotypes associated with high immune response have very frequently been reported in cases with tropical spastic paraparesis (Usuku *et al.,* 1988). Clinical improvements following the sterois therapy in such patients allows the assumption that it is the presence of a HTLV-I mediated auto-immune mechanism which causes the neurological disorder (McKhan *et al.,* 1989).

The data about the incidence of ATL in seropositive persons from endemic regions show considerable variations; a variation which can only partly be explained by differences in methodology. The prediction of the rate of HTLV-I mediated attacks by other diseases is usually severely obstructed by uncertainty about the time of exposure and by the fact that the age of the carrier also plays a role. The annual ATL incidence calculated for the endemic region of Japan is approximately 1:2000-5000 for seropositive persons (Shimoyama and Watanane, 1979). The annual ATL incidence (Saga, Japan) for 100,000 carriers of HTLV-I aged 40-79 years was 115,9 for men and 66,4 for women, which corresponds to 1 case of ATL for every 860 seropositive men and 1 case for every 1,500 women (Tokudome *et al.,* 1989). It has been proposed (Murphy *et al.,* 1989) that infection with HTLV-I during childhood conditions the development of ATL. On this basis, the estimated cumulative lifetime risk of ATL among persons infected before the age of 20 is 4 %, among men and 4,2 % among women. Assuming this estimation is correct, the impliccations will be important for nonendemic areas and it can be concluded that infection acquired later in the life should carry a lower risk of the ATL development.

HTLV-I overviews in Europe, 1990. Sources of information

The discussion of the presence, spreading and clinical consequences of HTLV-I infection draws on published or otherwise available information from 11 European countries in the period 1982 to June 1990. Individual reports differ widely not only in terms of the number of persons investigated, but also in the terms of sociodemographic patterns of the probands studied. The data used stems from investigations carried out in Czechoslovakia, Finland, France, Greece, Hungary, Italy, the Netherlands, Portugal, Spain, Switzerland and the United Kingdom. Unpublished data has been obtained as personal communi-

Table 1. Known sources of HTLV-I infection (European regions, 1990)

- HTLV-I seropositive persons, especially from groups at high risk (intravenous drug users, homosexual men, bisexual men)
- persons from HTLV-I endemic areas residing in Europe (emigrans, students)
- shared close household/family environment of HTLV-I seropositive persons
- HTLV-I seropositive mothers-neonatal contacts (e.g. breast-feeding)
- small endemic pockets of HTLV-I seropositivity (need further study and surveillance)
- sporadic cases of rare, non-typical illnesses, where laboratory tests have demonstrated an association with HTLV-I (?)

cations from Bulgaria (dr. A. Argirova), Poland (dr. M. Kańtoch) and Hungary (dr. G. Füst, dr. E. Ujhélyi).

Primary attention was paid to those groups which are known sources of the infection (Table 1) and to those which are known to be at a relatively high risk for HTLV-I infection (Table 2). We compared the reported serological status of these groups with that of blood donors drawn from the general population. Serological screening was performed on a total of 79,549 persons, including of whom 8,662 were IVDAs and 2570 homosexual men. HTLV-I has been circulating among IVDAs, at least in Rome, before 1980, i.e. before HIV was introduced into this risk group there (Gradilone *et al.*, 1986). In the U.S.A. HTLV-I was circulating in risk groups, although under different epidemiological circumstances, as early as 1971 (Saxinger *et al.*, 1988). Nevertheless, discussing the European HTLV-I scene, it appears that Portugal and a geographically limited area in southern Italy (part of Apulia) may have a special position in this context. In Portugal (Cardosa *et al.*, 1989), the overall prevalence of HTLV-I seropositive cases is 0.55 % (ranging from 0.7 % among persons who have been residents in Africa for a very long period to 0.36 % among those who have never been to Africa). Although Portugal cannot be considered a true endemic region by the criteria valid for these areas, the seroprevalence is higher than the average HTLV-I seroprevalence found in other European countries. It cannot

Table 2. Persons at risk for HTLV-I infection (European regions, 1990)

- intravenous drug users, especially also for HTLV-II infection (sharing infection equipment)
- homosexual men (more of receptive type?)
- sexual partners of HTLV-I seropositive persons (mainly those of men, to a lesser degree those of women)
- recipients of blood and cellular blood components from HTLV-I seropositive patients, at higher risk are polytransfused persons receiving haemodialysis
- household and family members of HTLV-I seropositive persons (clustering of seropositive cases in families living under poor housing conditions)
- sexual partners of persons who come from a geographical area where HTLV-I is endemically present, or even of persons residing in such areas
- offspring of HTLV-I seropositive mothers

be established from the Portuguese data whether the historical, i.e. colonial, ties to the HTLV-I endemic western African regions in the last several centuries could have played a role similar to the one ascribed to Portuguese seamen who have been suggested to contribute to the importation of the HTLV-I virus to the southern part of Japan (Gallo *et al.,* 1988). It cannot be rejected, however, that available seroprevalence data strongly suggest a more distant spread of HTLV-I virus in Portugal.

HTLV-I integrated provirus sequences and/or specific HTLV-i antibodies have been recovered (Pandolfi *et al.,* 1986) both in some of 16 very peculiar cases, e.g. chronic T-cell lymphoma/leukaemia, who mostly originated from southern Italy, and in a woman with spastic paraparesis. (Annunziata *et al.,* 1987). Moreover, the aggregation of 23 seropositive cases in a small area in southern Apulia suggests an endemic presence of the agent. The data therefore imply that a special variant of the HTLV-I virus could be at work in these cases (Manzari *et al.,* 1985, Manzari, personal communication). It is difficult to explain what has caused this aggregation, but it is remotely possible that it can be linked to an African endemicity (Pandolfi *et al.,* 1986).

Intravenous drug abusers - Europe

On the basis of a published seroepidemiological study of 8,662 serum samples collected from IVDAs in the 1984–89 (except 21 sera collected in the years 1978-89 from IVDAs in Rome). Data from 7 countries show an average HTLV-I seroprevalence of 4,16 % i.e. 361 IVDAs with confirmed specific HTLV-I antibodies (Table 3).

The data are characterized by a noticeable uneven distribution of seropositive cases not only in various large urban areas, but even in their different sectors. The best example may be the Italian studies. HTLV-I carriers are mainly prevalent in certain Italian cities, sometimes reaching a HTLV-I seropositivity as high as 27 % in cohorts investigated (e.g. Gradilone *et al.,* 1986; Manca *et al.,* 1989). The most interesting finding was that of a relatively high prevalence of HTLV-I infection in HIV-I seropositive IVDAs. Among 3,075 HIV-I positive IVDAs (i.e. 35 % from the total number of IVDAs investigated), 292 individuals showed also the HTLV-I seropositivity (80,8 % of the total of 361 HTLV-I seropositive IVDAs). There were 69 HTLV-I seropositive persons (19 % of the total of 361 HTLV-I seropositive in this group) and the 5,587 seronegative IVDAs (65 % of the total, i.e. from 8662 IVDAs studied). The percentage of HTLV-I seropositive individuals was about 7.6 times higher in the smaller group of HIV-seropositive persons than in the approximately 1.8 times larger group of HIV-seronegative persons.

It has been suggested that the reason for this is either a higher promiscuity among IVDAs (Rezza *et al.,* 1988), IVDAs of homosexual or bisexual orientation, or possibly co-contamination of injection equipment. A hypothetical possibility is that the HIV infection may affect the latency of the HTLV-I virus.

Table 3. Prevalence of HTLV-I and HTLV-I/HIV - concomitant infections in some European regions in intravenous drug users

Region	Time period	HTLV-I + / HIV -		HTLV-I + / HIV +		HTLV-I + total		References
		n	%	n	%	n	%	
Austria	1987	0/100				0/100		Fuchs *et al.*, 1988
France	1985–1989	7/1690	0.41	2/909	0.22	9/2599	0.34	Deforges *et al.*, 1988 Tamalet *et al.*, 1989 Lemaire *et al.*, 1989
Germany (West)	1985–1988	0/554				0/554		Marcus *et al.*, 1989 Ehm *et al.*, 1989
Italy	(1978–1980) 1985–1988	52/1983	2.6	287/1835	15.5	339/3818	8.8	Gradilone *et al.*, 1986 Manca *et al.*, 1989 Quarto *et al.*, 1989 Rezza *et al.*, 1988 Tamburrini *et al.*, 1988 Titti *et al.*, 1988
Spain	1985–1989	6/949	0.63	3/331	0.4	9/1280	0.7	Cour *et al.*, 1989 Genesca *et al.*, 1989 Soriano *et al.*, 1989 Tor *et al.*, 1989
Switzerland	1984–1985	0/198				0/198		Schüpbach *et al.*, 1988
United Kingdom	1982–1984	4/113	3.5			4/113	3.5	Tedder *et al.*, 1984

For explanations see Tab. 5

Serological testing used at present does not distinguish which virus type (I or II) the infected persons got first.

There have been no reports of diseases aetiologically linked to the HTLV-I as known from endemic regions, among the 361 HTLV-I seropositive IVDAs. Until the spring of 1990, HTLV-I linked frank disease was not observed, not even in Rome, though this is possibly the city with the relatively highest number of HTLV-I seropositive IVDAs in Europe (Titti, personal communication). Actually, the total of 361 HTLV-I seropositive IVDAs (data pooled from 17 individual reports) represents a relatively small group if compared with considerably greater cohorts of HTLV-I seropositive people in endemic areas. Taking into consideration the already mentioned low incidence and the low cumulative lifetime risk of ATL in infected persons in HTLV-I endemic areas, it would appear that the risk of a disease of neoplastic character (ATL/lymphoma) in the discussed IVDAs is rather low. Nevertheless, it seems as somewhat premature simply to apply the experience from endemic areas here. This may show as relevant for only 69 HTLV-I seropositive individuals among HIV-seronegative IVDAs. It should be born in mind that the HTLV-I associated diseases are characterized by a longer latency than for HIV-I and their natural history is not yet completely understood.

The phenomenon of concomitant HTLV-I/II and HIV I and perhaps also other viral infections and their eventual impact on the progression and/or outcome of HIV and/or HTLV-I/II infection (comorbidity) has been intensively duscussed (e.g. Ognjan *et al.,* 1988). Several studies have concluded that a dual infection by HTLV-I and HIV I (and vice versa) does not seem to aggravate the course of the asymptomatic phase of the long-latency diseases they cause (Brown *et al.,* 1988; Feigall *et al.,* 1988; Koshiwagi *et al.,* 1988; Mildwan *et al.,* 1988; Van de Perre *et al.,* 1988; Tamburrini *et al.,* 1988). During the first three years of the follow up Bartholomew et al., (1987*b*, 1988, 1989) observed a faster progression to AIDS in some cohorts of coinfected men when compared with the men infected by HIV only (similarly, Weis *et al.,* (1989)). Nevertheless, this difference in progression, as supported by a very recent report (Bartholomew *et al.,* 1990) was not maintained after 72 months of observation. HIV-HTLV-I/II coinfected IVDAs from Miami, Florida, however, (Page *et al.,* 1990) were three times more likely to die from AIDS during the 2.3 years long follow-up (since recruitment) than those infected by HIV-I only. This study clearly warrants continuation.

Chermann (1990) and Kobayashi *et al.* (1990) hypothesize about the mechanisms of a possible acceleration of the HIV disease, discussing the effects of HTLV-I in *in vitro* systems (Rossi *et al.,* 1986). The Tax-encoded proteins seem to be most effective (Chermann, personal communication).

By 31st of March 1990, a total of 34,967 European AIDS cases were reported (WHO Collaborating Center on AIDS, Paris). According to this source, the incidence of cases diagnosed in 1989 in the homo/bisexual group was similar to

Table 4. Prevalence of HTLV-I an HTLV-I/HIV - concomitant infections in some European regions in homosexual men

Region	Time period	HTLV-I + / HIV -		HTLV-I + / HIV +		HTLV-I + total		References
		n	%	n	%	n	%	
Finland	1989	0/446		0		0		Leinikki *et al.*, 1989
France	1984–1985			2/416	0.48	2/416	0.48	Eme and Audrieu, 1988 Deforges *et al.*, 1988
Germany (Berlin-West)	1988	0/526		0		0		Ehm *et al.*, 1989
Italy	1985–1989	5/64	7.8	2/24	8.3	7/88	0.79	Tamburrini *et al.*, 1988 Manca *et al.*, 1989
Switzerland	1984–1985	1/284	0.35	0		1/284	0.35	Schüpbach *et al.*, 1988
United Kingdom	1982–1984	2/621	0.32	5/189	2.64	7/810	0.86	Tedder *et al.*, 1984

For explanations see Tab. 5

Goudsmit *et al.*, (1987) found in 1984 from 697 Dutch homosexual men 5 HTLV-I seropositive (3 were HIV seronegative, 1 was HIV seropositive and 1 immigrant was coinfected also). For in remaining individuals was not specified their HIV status, the data was not possible to include into this overview.

that in IVDAs. The cumulative number of AIDS cases in Europe in the former group was 16,600 (46.2 % of the total number of AIDS cases) and in the latter group 10,660 (30.5 %). Interestingly, in the group of homo/bisexual IVDAs, the number of AIDS cases only constituted 2 %. The projected cumulative number of AIDS cases among IVDAs is expected to lie in the range of 23,000-33,000 at the end of 1991.

According to WHO, the number of IVDAs is steadily increasing in some parts of Europe, e.g. in Switzerland. In France (Tamalet et al., 1990) an estimate for the number of IVDAs is about 70,000, a figure which will imply that in certain regions France up to 50 % of these cases will acquire AIDS. In Italy about 60 % of the AIDS cases are found among IVDAs (Luzi *et al.,* 1988) and a steady increase in the number of HIV-infected IVDAs has been noted in Scotland (Robertson et al., 1988). The problem seems similar in Spain (Soriano *et al.,* 1989; Merino *et al.,* 1990). To date the central and some eastern parts of Europe seem less affected; the HTLV-I infected persons found until now are exclusively among aliens (e.g. Mayer, 1990).

Nevertheless, the data strongly suggests that in certain parts of Europe the conditions favour an increased circulation of retroviruses among high risk groups, in particular IVDAs. A similar picture has been portrayed in the U.S.A. (e.g. Manns *et al.,* 1988; Gaudino *et al.,* 1990).

Homosexual men - Europe

The sexually active homo/bisexual men (HSX) appear as a second subpopulation at risk for HTLV-I infection in the Caucasian general European population. The data reviewed (Table 4) mainly originated from the same reports as IVDA data and therefore reflects at the situation roughly in the same time and epidemiological settings. The serologically studied sera were, however, more than 3 times less in number than those of IVDA. Nine individuals were co-infected with HTLV-I (53 % of the total number of HTLV-I seropositive HSXs) among the 629 HIV-I seropositive persons (24 % of the total of HSXs investigated) (Table 6). Among the 1941 HIV-I seronegative persons (76 % of the total number of HSXs investigated) specific antibodies were detected in 8 persons (i.e. only in 0,41 %). Data from 5 countries (Table 4) indicate a significantly lower prevalence of HTLV-I and HIV in HSXs than in IVDAs suggesting a less efficient transmission by rectal intercourse than via blood (Burzcak *et al.,* 1988; Peralta *et al.,* 1988; Kelen *et al.,* 1989). The HIV and HTLV-I prevalence among European HSXs (0.027 %) is approximately half that reported among similar persons living in the U.S.A. (0.8 per 1000 persons) as reported by Manns *et al.,* (1988).

The fact that 0.41 % of European HIV-seronegative HSXs were HTLV-I carriers indicate that the HTLV-I circulates independently of HIV in this group and that it probably took a longer time for HTLV-I to become introduced in this group (Gradilone *et al.,* 1986). This finding is in an agreement with known transmission routes of human retroviruses, as suggested earlier (e.g. Tedder *et*

Table 5. Prevalence of HTLV-I and HTVL-I/HIV-1 concomitant infections in some European regions in various groups of population tested

Region	Time period	HTLV-I + / HIV -		HTLV-I + / HIV +		HTLV-I + total		References
		n	%	n	%	n	%	
Czecho-Slovakia	1985–1987	0/231 (HF) 2/476 (IM)	0.42	-		0/231 2/476	0.42	Mayer, 1991
Finland	1989	0/5317 (BD, HF, GP, NS)		-		0/5317		Leinikki *et al.*, 1989 Ranki *et al.*, 1989
France	1985–1990	3/48062 (BD, HP, PT GP, HF)	0.006	2/567	0.35	5/48629	0.01	Agius *et al.*, 1989 Coste *et al.*, 1990 Courtois *et al.*, 1990
		14/2038 (IM)	0.68	2/170	1.17	36/6014	0.59	Deforges *et al.*, 1988 Eme and Audrieu, 1989 Lemaire *et al.*, 1989 Patey *et al.*, 1989 Tamalet *et al.*, 1989
Greece	1989	3/949 (BD, GP)	0.31	-		3/949	0.31	Derivianaki *et al.*, 1989
Hungary	1988	0/33 (HP)		-		0/33		Koike *et al.*, 1988
Italy	1984–1987	0/750 (BD, GP)		-		0/750		

continued next page

Nether-lands	1986–1990	3/95 (HF, GP)	4.16	–		3/95	4.16	Doornum *et al.*, 1990 Goudsmit *et al.*, 1986
		3/472 (IM)	0.42			3/472	0.42	
Portugal	1985–1989	9/2487 (BD)	0.36	–		9/2487	0.36	Cardosa *et al.*, 1990
		21/2988* (BD-AFR)	0.70	–		21/2988	0.70	
Spain	1989	0/53 (PT)				0/53		Soriano *et al.*, 1988
		1/102 (IM)	0.98	–		1/102	0.98	
Switzer-land	1984–1988	0/292 (BD)		5/795	0.62	5/1087	0.45	Schüpbach *et al.*, 1988
		0/70 (IM)				0/70		
United Kingdom	1982–1984	0/1051 (BD,HF,GP)	0	–		0/1051		Banatvala *et al.*, 1990 Cruikshank *et al.*, 1990
	1988–1990	20/3806 (IM,NS)	0.56	–		20/3806	0.56	Tedder *et al.*, 1984

If the period of sera collection is not indicated in the original paper, the year of publiaction is used.
Nominator: number of HTLV-I seropositive persons, denominator: number of persons investigated
Abbreviations: BD – Blood donors, BD-AFR – Portuguese blood donors after living in Africa by residence, HF – haemophiliacs, IM – Immigrants, NS – nonspecified, PT – polytransfused patients, GP – general population
X = Portuguese African connection (BD-AFR) considered as IM for relative high number of HTLV-I seropositive persons
+ = seropositive, – = seronegative (accoring the detection method used)
* Because the percentage of HTLV-I seropositive in 2,298 Portuguese was as high as 0.7 %, the persons living for more than a decade in endemic region of West Africa, were considered as „Immigrants".

al., 1984; Goudsmit *et al.*, 1987; Manca *et al.*, 1989). The fact that a higher percentage (here 3,5 times) of HTLV-I infection cases occur among HIV seropositive HSXs seems important, too. Some of the situations which may have caused the low level of HTLV-I seroprevalence among HSXs have already been mentioned when IVDAs were discussed; but it does seem probable that HTLV-I circulates at a low pace among HSXs. Taking into account the recent data on the genetic information of HTLV-I in cases where classical serology is negative, a similar verification in HIV-seronegative HSX may reveal further information (D'Auriol *et al.* 1990) important for the understanding of HTLV-I/host organism interactions, and it is also needed for a more satisfactory evaluation of HTLV-I epidemiology.

Emigrants from endemic regions - Europe

The compiling of data on the HTLV-I infection prevalence unexpectedly revealed that this virus was in a greater extent present in the groups of immigrants originating from endemic geographic areas (Table 6). The data available were limited to investigations carried out in 6 countries (western, southern and central Europe) and a certain bias is therefore unavoidable (Table 5). The above result stems from the fact that 4 of these countries - France, the Netherlands, Portugal and the United Kingdom - maintained colonies in endemic regions in the first half of this century and had a certain presence there in the last few of decades, coupled with the fact that a substantial number of white people returned to their country of origin following the proclamation of independence by these colonies (Cardosa *et al.*, 1989)*. Therefore as pointed out by e.g. Courtois *et al.*, (1990), the HTLV-I seropositivity and the vast majority of viruse carriers are confined almost exclusively to individuals from endemic areas (Table 1 and 2).

For comparison, the reported number of HTLV-I seropositive persons from Spain, Switzerland and Czechoslovakia (foreign students, Mayer, 1991) was 3 out of 648 persons investigated (0,46 %). In Europe, United Kingdom and Netherlands in a total of 37 persons (0.58 %) from the 6,316 persons investigated (the data reported by Goudsmit *et al.*, 1987, are not included- see Table 4). When data from Portugal were added, these four countries contributed with 58 HTLV-I seropositive individuals out of a total of 9304 emigrated persons studied (average 0,62 %, range 0.52-0.72 %).

If compared with the 378 HTLV-I seropositive individuals reported from the IVDA and HSX groups (i.e. from together 11,232 persons) the 63 HTLV-I seropositive individuals found in 10,122 immigrants is striking. They represent a source of infection for the general population or they make up more segregated groups of HTLV-I infected persons, especially in countries with ties to endemic areas (e.g. Cruikshank *et al.*, 1990). The HTLV-I seroprevalence in emigrants approaches thus that of HSXs, as calculated from the analysed reports.

It does not seem surprising that among HIV-seronegative emigrants 61 were found to be HTLV-I seropositive, i.e. 96,8 % of all such persons from this immigrants group. It should be mentioned, however, that data about emigrants did not specify their sexual preference and the 170 HIV-seropositive individuals of whom 2 were double infected with HTLV-I, thus could have had homosexual experiences, be IVDA, have been infected by heterosexual intercourse or by other modes of transmission. It is most likely that persons from this particular group emigrated from their country at a young age (e.g. Robert-Guroff *et al.,* 1984).

The majority of HTLV-I seropositive immigrants was detected when serving as blood donors or found by screening programs. Undoubtedly, they represent a non-negligible risk as donors for blood recipients or for dialysis units in Europe (Table 2), as already observed in the U.S.A. (e.g. Minamoto *et al.,* 1988; Perez *et al.,* 1988).

General population - Europe

The sample of HIV-seronegative persons in the general European population (Table 5) represent in this review 56,833 persons of Caucasian origin. The group mainly consisted of blood donors and are therefore mostly adults or young adults. The composition of this sample may have influenced the rate of seropositivity (Manzari, personal communication). From this group, 9(0.015 %) were found to be seropositive - excluding Portuguese data for the reasons explained above. In the comprehensive U.S. Red Cross study (Williams et al., 1988), there were 10 seropositive donors (out of 40,000 healthy donors studied - prevalence 0,025), and only one seropositive was a Caucasian female. In the present analysis of the European situation, the 0.015 % HTLV-I seroprevalence was calculated for the HIV-seronegative part of the general population (Table 6). A higher percentage of HTLV-I seroprevalence (i.e. 0.51 %) was also found in the 1362 HIV-seropositive individuals from the general population. Seven persons from the group of HIV-seropositive were co-infected which suggests that the medical histories of these Caucasians have been rather incomplete, also with respect to their sexual preference. The early study by Hunsman *et al.,* (1985) has been excluded in this overview because it deals with 2,048 persons with AIDS or at risk for AIDS. Among those only one had HTLV-I antigen-reactive serum (0.048 %).

As a very low HTLV-I seroprevalence was noted in HIV-seronegative European Caucasians (encompassed in this review). Nevertheless, also this prevalence has varied in certain parts of the continent. Alghough the evidence is not substantial, it may indicate that HTLV-I did not readily penetrate into the general Caucasian population in Europe and only started to do so in the last 2-4 decades. This conclusion is in agreement with the fact that marker diseases known to be caused by this virus (onco-haematological and progressive neurological disorders) are virtually non-existent, except for the very few case reports which seemingly have not been directly related to the spreading of HTLV-I

Table 6. HTLV-I seropositive persons – European data [11 countries, (1982) 1984 – June 1990]

Groups of persons investigated	HTLV-I + / HIV -		HTLV-I + / HIV +		HTLV-I + total	
	n	%	n	%	n	%
Intravenous drug users	69/5 587[x]	1.23	229/3 075	9.4	361/8 662	4.16
Homosexual men	9/1 941	0.41	9/629	1.43	17/2 570	0.66
General population						
Immigrants[xx]	612/9 952	0.61	2/170	1.17	63/10 122	0.62
Caucasians	9/56 833	0.015	7/1362	0.51	16/58 195	0.027
(South Apulia, 23/273, not included into the number of Caucasian population – see text)						

Total of 79.549 persons investigated (see Tabs. 3, 4, 5)
x = Nominator: number of HTLV-I seropositive persons; denominator: number of persons investigated
xx = including the African connection of Portugal (see text)
The seropositivity rates in individual groups differed significantly ($p < 0.01$ or < 0.001) (Mikulecký *et al.*, 1990)

among the risk groups witnessed during the 80s. However, the HIV seropositivity of 2.3 % and the HTLV-I seropositivity of 0.015 % found in the general European population of Caucasian descent normally considered to be a non-risk group seem to signal a beginning spreading of human retrovirus to other groups than those usually considered at risk; in a manner similar to that of the HIV into the general European population (Ebbesen *et al.,* 1988).

In 1989 the WHO Collaborating Centre on AIDS in Paris reported the largest increase in the number of AIDS cases in the heterosexual transmission group.

HTLV type I and HTLV type II

Commercially available serological tests cannot in their present form distinguish HTLV-I infections from those caused by HTLV-II virus, as mentioned above, and the results of serological testing are therefore not rarely designated as valable for HTLV-I/II. Consequently, there is doubt about the specificity of the earlier tests and data concerning how many infections are due to each virus has been ambiguous in previous studies. In some parts of Europe, the prevalence of HTLV-I, as defined in this report, has increased comparatively within the last decade, especially in some of the population groups at risk. A similar trend is currently noted at least in some areas of the U.S.A. Robert-Guroff *et al.* (1966) described an antibody prevalence in New York among IVDAs of 9 % for HTLV-I infected persons and 18 % for HTLV-II infected persons. Data on the sero-epidemiology of HTLV-I was limited to surveys of populations at risk and blood donors, but the specificity found in these groups has recently been reconsidered (Blattner, 1989). The frequently encountered cross-reactive HTLV-II virus (e.g. Eble *et al.,* 1990; Feigall et al., 1990; Gaudino *et al.,* 1990) has complicated efforts to differentiate between the aetiological role of HTLV-I and HTLV-II in various diseases. Recent methodological progress (e.g. PCR) has made it possible to ascertain that HTLV-II is much more prevalent than HTLV-I in certain areas among IVDAs and an epidemic spreading of HTLV-II has been detected among IVDAs in several major cities in the U.S.A. (e.g. Agbalika *et al.,* 1990; Lee *et al.,* 1990; Yajko *et al.,* 1990). Comprehensive data about the seroprevalence of HTLV-II in the general population is not available at present.

The possibility of distinguishing between HTLV-I and HTLV-II infections opens a completely new perspective for in-depth understanding of the biology, spreading and pathological changes caused by these agents, not to be confused with serological cross-reactivity. In the context discussed, the pathogenetic meaning of co-infection (HTLV-I/II; HTLV-I/HIV; HTLV-II/HIV) and the diverse clinical manifestations caused by simultaneous infection will probably increase our understanding of the mechanisms involved. In addition to retroviruses, hepatitis C virus, cytomegalovirus and the Epstein-barr virus are also relevant in this context (Sunita *et al.,* 1990).

Unique illnesses attributable to HTLV-II are already appearing (e.g. T-cell CD8 infiltration and ichthyosis of the skin, leukaemia, etc.), adding to the

possibility of evaluating the epidemiologic status of population groups at risk (Kaplan *et al.,* 1990). It seems perfectly possible that the tracing of HTLV-II epidemical spreading in Europe will uncover data not already available for methodological purposes and may prove important for institution of specific preventive measures. Similarly, progress may be expected in the field concerning the suggested existence of HTLV-I antigenetic variants in different parts of the world – a supposition based on numerous seroepidemiological studies. These variants may be related, but they differ from the HTLV-I virus (e.g. Burczak *et al.,* 1988; Shriver *et al.,* 1988) and they have different biological properties (e.g. Jacobson *et al.,* 1988). An example of this deviation is the presently inexplicable, weak and atypical reactivity detected relatively frequently in sera of Swiss blood donors (Schüpbach *et al.,* 1988).
The existence of additional, new human retrovirus(-es) cross-reacting with HTLV-I or HTLV-II cannot be ruled out (Schüpbach, personal communication). It is very probable that PCR may be very helpful in answering the still open question of the reliability of tests used for the detection of HTLV-I and HTLV-II infection (Blattner, 1989; Georgopoulu *et al.,* 1990; Lentino *et al.,* 1990).

Concluding remarks and recommendations

HTLV-I is a serious medical and public health problem in endemic regions such as southern Japan, the Caribbean Basin, and parts of Africa and South America. In the U.S.A., the HTLV-I seropositivity is mainly seen among the black and Hispanic minorities. The marker diseases of HTLV-I are adult T-cell leukaemia/lymphoma and a slowly progressing form of myelopathy. Seroconversion from negativity to positivity may occur several years after infection. The HTLV-I transmission rate is rather low and the occurrence of the above marker diseases among seropositive HTLV-I carriers is extremely infrequent. Furthemore, the marker diseases do not become manifest until after an unusually long incubation period (20–30 years). HTLV-I virus is transmitted by ways and modes typical for human retroviruses. Transmission by the blood is the most efficient; thus seroconversion is observed in 50–60 % of those who receive infected blood from a donor. Retrospective serological studies have shown that HTLV-I was circulating among IVDAs in the U.S.A. in 1971 (Saxinger *et al.,* 1988, 1989) and in Italy in the period 1978–90 (Gradilone *et al.* 1986); in both cases before AIDS was discovered in these populations. The emerging picture is that the spreading of HTLV-I is not confined to specific groups in non-endemic regions, and that in recent years it has been spreading alongside with HIV through IVDA, sexual contact and via contaminated blood. The pooled data, mainly published in the second half of the 80s suggest a marked spread of infection by HTLV-I persons in specific subpopulations in some parts of Europe, i.e. IVDAs, homosexual men and the immigrants from endemic areas of this infection are considered to be a source of HTLV-I. However, in the European population the HTLV-I indicator diseases have not

been observed (i.e. excluding the extremely rare, clinically related and sometime atypical, sporadic cases, e.g. ATL in immigrants). This strongly suggests that HTLV-I has not been endemic in these areas in the last 20–40 years. In spite of this, the data collected seeem to indicate interesting trends. In a sample of the general population (58,195 persons), the HTLV-I seroprevalence was calculated to 0.027 %, i.e. 154 times less than that found in IVDAs (4.16 %). In a sample of HIV-seronegative European population (56,833 persons) the HTLV-I seroprevalence was 0.015 %, i.e. 627 times less than that found in HIV-seropositive IVDAs (Table 6). HTLV-I seroprevalence in homosexual men was calculated to 0.66 % and for the immigrants with links to endemic areas (10,122 persons) as 0.62 %. The seroprevalence is lower in Europe than in the U.S.A., probably mainly due to the higher HTLV-I seroprevalence in American black and Hispanic minorities (e.g. Gaudino *et al.,* 1990; Kaplan *et al.,* 1990; Lentino *et al.,* 1990; Sunita *et al.,* 1990; Williams *et al.,* 1988). To date (June 1990) there has not been a consistent evidence linking HTLV-I seropositivity in European IVDAs and homosexual men to any of the HTLV-I related indicator diseases. Because no occurrence of these diseases has been reported, the risk of transmission of these diseases remains unknown. It may appear that insufficient time has elapsed following exposure or that the risk of ATL development is lower in persons who became infected as adults (Murphy *et al.,* 1989). The percentage of HTLV-I seropositive individuals was sigificantly higher in HIV-seropositive IDAs and homosexual men than in HIV-seronegative persons (Table 6). The natural history of HTLV-I infections in HIV-infected individuals has not yet been established. Both viruses have long latency periods, but recent evidence suggests an acceleration of immune deficiency progression in doubleinfected individuals, but never in persons with ATL (e.g Page *et al.,* 1990).

Data suggests that the HTLV-I seroprevalence observed in Europeans at risk does not results in an increased risk of ATL or other oncologic conditions among specific subpopulations. Especially in IVDAs, this „man-made-epidemic" of HTLV-I infection has remained clinically dormant for more than a decade. It cannot be excluded that HIV-infected persons may develop the final phase of the disease (AIDS) without clinical manifestations of HTLV infection. It seems interesting that the „transactivating" mechanisms during continued development of HIV in the organism of the coinfected individuals do not affect the latency of the HTLV-I as the reverse is supposed. According to the data reviewed, the sexual transmission (homosexual men not using drugs intravenously) did not seem to play a major role in HTLV transmission. Although HTLV-I infection in Europe is an emerging problem, it is still sufficiently limited to assume that an intervention programme would be effective.

Preventive measures may include

a) strict self-exclusion of IVDAs, homosexual men and of immigrants from HTLV-I endemic areas as blood and organ (bone marrow!) donors. This step is

recommended because recent findings show HTLV-I sequences in persons with HTLV-I indicator disease, but seronegative by current assays (d'Auriol *et al.*, 1990).

b) Screening of donated blood in European countries where an increment in the number of HTLV-I seropositive individuals in the general population has been noted.

c) An active sero-epidemiological surveillance in all persons suspected to be possible sources of HTLV-I infection may be immediately useful because otherwise accumulation of the relevant epidemiological data may take years (HTLV-I disease). Moreover, the elucidation of the spectrum of HTLV-II pathogenicity is urgent for the European situation, as well as finding a definition for the possible HTLV-I and HTLV-II disease, encompassing the whole period from exposure to the final phases using new methodological tools and finally the development of more efficient laboratory tests to help detect HTLV-I and HTLV-II infections.

The data reviewed and outlined may serve as an „early alert" in order to institute appropriate responses to this continuous medical challenge.

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