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HTLV-1/2 infection in Italy: a narrative review of epidemiological studies

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Abstract

The human T-cell leukemia virus type 1 (HTLV-1) was first described in 1980. It is spread in highly endemic regions in the world, such as the Southwestern part of Japan, sub-Saharan Africa and South America, Caribbean, Middle East, and Australo-Melanesia regions. HTLV-1 causes adult T cell leukemia and is associated with many inflammatory conditions, most notably HTLV-1-associated myelopathy/tropic spastic paraparesis. HTLV-2, first isolated in 1982, was recognized as a common infection in intravenous drug users, but a clear association with disease remains elusive. The first estimate of HTLV-1-positive individuals worldwide, in 1993, was around 10-20 millions. Due to the lack of global population-based prevalence studies, this is considered an underestimate at the moment. Furthermore, HTLV-1 prevalence in Europe is impacted by changing migration flows. Particularly, no data on HTLV-1 prevalence in the general population in Italy are available. Here, we report a systematic literature review of studies conducted in Italy on HTLV-1/2 from 1980 to 2023. Based on the criteria we adopted a total of 426 publications were found (64 reviews, 99 epidemiological, and 263 translational studies). The contents of some representative publications are summarized and discussed. Moreover, an approximate estimation of about 26,000 HTLV-1 positive foreigners living in Italy was obtained from updated data of foreigners from each single country officially registered as resident in Italy and from data on HTLV-1 prevalence among the general population in the corresponding countries.

Keywords

HTLV-1. HTLV-2. Italy. Adult T-cell leukemia. Tropic spastic paraparesis.

Introduction

The human T-cell leukemia virus type 1 (HTLV-1) was the first human retrovirus to be identified. HTLV-1 was associated to human oncogenesis since the beginning and was isolated by Poiesz in Gallo's laboratory in fresh and cultured cells from a patient affected by cutaneous T-cell lymphoma around 45 years ago[1,2]. The European Center for Disease Prevention and Control (ECDC) Technical Report on the geographical distribution of HTLV-1 concluded in 2015 that the main highly endemic areas for HTLV-1 were the South-Western part of Japan, some areas of the Caribbean region, South America, sub-Saharan Africa, the Middle East, Romania, and isolated clusters in Australo-Melanesia[3].

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In addition to the other important routes of transmission, such as mother-to-child, mainly through breastfeeding, transfusion of non-leucocyte depleted blood, sharing needles in intravenous drug users (IVDUs)[4], HTLV-1 has finally been recognized as a sexually transmitted infection[5].

Primary HTLV-1 infection is silent. Following a long latency HTLV-1 infection may cause adult T-cell leukemia (ATL) in 5% of all infected persons, increasing to 20-25% in those infected in early life. Inflammation associated with HTLV-1 infection can occur within months of primary infection or more commonly after years of clinical latency. There is a wide range of inflammatory conditions, with damage described in multiple organs, but most commonly the brain and spinal cord (HTLV-1-associated myelopathy/tropic spastic paraparesis. HAM/TSP HTLV-1 infection also impacts on multiple coinfections[6], quality of life even in the absence of HAM/TSP and other overt diseases, and increases the adjusted mortality rate by 57%[7].

HTLV-2 is a human retrovirus related to, but distinct from, HTLV-1 which was first isolated in 1982 in cells from a patient affected by a T-cell variant of relatively benign hairy cell leukemia[8]. However, it was soon recognized as a common infection among IVDUs, lacking a clear etiologic association with disease. Nevertheless, it has been associated with increased rates of urinary and respiratory infections among blood donors in the USA[9].

In 1993, a relatively simple estimate of the number of HTLV-1-positive individuals worldwide was around 10-20 millions[10]. This was updated by Cassar and Gessain in 2012 and again by ECDC in their 2015 report. Based on just 1/6th of the global population (where data exist), 5-10 million people are living with HTLV-1. Even these numbers are mostly based on historical studies and the WHO has called for new data to inform policy[11-13]. This has also led to a lack of understanding of the prevalence of HTLV-1 outside endemic regions[14].

Although there is no routine antenatal screening procedure for HTLV-1 in Europe, the monitoring of the HTLV-1 epidemiological situation in Europe unveiled its presence, linked also to migration from high prevalence areas, in particular from South/Central America to Spain[15] and from Africa and the Caribbean to the United Kingdom, France, and the Netherlands. Conversely, Romania and, most recently described its neighbor Moldova with 0.95% HTLV-1 reactive blood donations, are considered the only endemic areas in Europe[13,16,17]. In Spain, thanks to the nationwide registry created in 1989, it has been reported that ATL has been diagnosed in 7.8% of HTLV-1-positive individuals in 2022[18]. Until the end of 2022, the national registry had reported 451 cases of HTLV-1 and 821 of HTLV-2, with 22 declared cases in 2022[19,20].

An estimate of 22 500 people of Caribbean or African origin infected with HTLV-1 living in England and Wales was made in 2000, based on seroprevalence rates applicable to region of birth and the seroprevalence among women of different ethnic groups attending antenatal clinics in London at the time[21]. Between 2004 and 2013 HTLV-1 was newly diagnosed in 858 individuals living in England and Wales[22].

In general, understanding the global distribution of HTLV-1 infection, the routes of transmission, the attributable morbidity and mortality, without a specific antiviral therapy and therefore reliant on prevention and public health policy to control viral transmission, scientists call upon the WHO to act[23] resulting in the WHO technical report on HTLV-1/2[24]. In light of this international scenario, this review addresses the need to better understand the prevalence and impact of HTLV-1/2 in Italy.

HTLV-1/2 in Italy: epidemiological historical perspective

Despite the continuous and qualified contribution of some Italian research groups to basic science studies on HTLV-1 over the years, there has been no concerted action to establish and monitor the global presence of HTLV-1/2 in Italy. The lack of such information is easily noticed by checking official public health documents and the scientific literature. Thus, a systematic literature review from 1980 to 2023 on the free database PubMed of the National Center for Biotechnology Information, U.S. National Library of Medicine, National Institutes of Health, in which the words “HTLV” and “Italy” were included as search criteria, revealed 426 papers. Among these publications, in which Italian authors were either co-authors with other Italian colleagues or co-authors with no Italian colleagues, 64 were distinguished by us as reviews, 99 as epidemiological studies describing the patterns of HTLV-1/2 infection in groups of individuals in Italy, and the remaining 263 as generically translational studies. However, all these studies included only specific local realities, isolated case reports, clinical studies on a very limited number of individuals, or preclinical studies, and none addressed the general situation of HTLV-1/2 infection in Italy. Between 1980 and 1990 scattered reports on HTLV-1/2-positive serology and associated disease in local health facilities were published.

In a pioneering study, among 284 sera from IVDUs in Rome and Naples, 63 (23%) were found to be positive

for HIV antibodies, 51 (18%) had antibodies to HTLV-1, and 45 were seropositive for both HIV and HTLV-1, while 6 were positive for HTLV-1 alone. All antibodies were confirmed through immunocompetition and/or Western blot (WB) and no cross-reactivity between the two viruses was detected[25].

To determine the prevalence of HTLV-1 in wider regional areas of Southern Italy such as Apulia, the sera from 3371 volunteers blood donors from 6 centers were examined: 250 randomly from non-hematological/oncological patients from Lecce, 401 from hematological/oncological patients, 331 with different neoplastic diseases, 70 with non-oncological diseases, 76 of whom were polytransfused, 94 from hemophiliacs, 32 polytransfused Cooley patients, 54 from IVDUs all anti-HIV positive at a pre-AIDS stage or with full-blown AIDS. The samples were screened by widely used immunoassay kits followed by confirmatory WB and SDS-PAGE-RIPA to detect HTLV-1 gag protein or gp46 envelope glycoproteins. The substantial negativity to the confirmatory assays suggested that HTLV-1 was not endemic at that time in Apulia[26].

More detailed investigation showed that in North of Italy, Veneto, the trend in HTLV-1 infectivity declined in IVDUs co-infected with HIV between 1985 and 1986[27]. Other studies were carried on in Italy on IVDUs among prisoners. The sera of a total of 523 Italian subjects all men between October 1988 and April 1989 were screened for HTLV-1, HIV antibodies, hepatitis B, and delta markers. Antibodies to HTLV-1 were investigated through commercial EIA and confirmed through WB and RIPA. A repeated reactivity to HTLV-1 was detected by EIA and confirmed through WB and RIPA, mainly versus core proteins, in 25 subjects (4.78%). Among them, 36% were found without no other viral markers while 64% were simultaneously positive for HIV antibodies[28].

Around the 90s, increasing interest in HTLV infection was shown by the inclusion of HTLV-1/2 testing in studies of people at risk for HIV infection. IVDUs remained the preferential screened population for the presence of HTLV-1/2 since it was one of the categories considered most at risk for HIV infection. In general, sera were screened for HIV/HTLV-1/HTLV-2 through enzyme immunoassays such as EIA or ELISA and confirmation by WB with molecular confirmation by PCR. This revealed more frequent HIV/HTLV-2 coinfection in specific areas of Italy. In South Eastern Italy, 8/511 HIV-infected persons were co-infected with HTLV-2[29]. Family clustering of HTLV-1 in the South of Italy was also reported[30] along with a low prevalence of HTLV-1/2 in Sicily, where a total of 921 sera from Sicilian residents either IDVUs or migrants from Africa were examined for HTLV-1/2 antibodies. Sixteen sera were found positive by ELISA. The confirmation by WB revealed 7 indeterminate results, 1 positive for HTLV-1 (a woman from Ghana), and 3 positive for HTLV-2 (a second woman from Ghana and 2 Italian IDVUs). Therefore, the prevalence of HTLV-1 was 0.06% and for HTLV-2 0.18%, respectively[31].

In North-Central Italy, the overall prevalence of anti-HTLV-1/2 antibodies among 1247 IVDUs individuals at high risk for HIV was 4.0%, with the highest prevalence (8.2%) among HIV-infected symptomatic patients[32]. Molecular methods confirmed a higher prevalence of HTLV-2 in comparison with HTLV-1 in Italian IVDUs, mostly HIV-positive in the same years[33]. Nevertheless, these epidemiological investigations also showed a small percentage of HTLV-1/2 indeterminate samples. Multicentric seroepidemiological survey reported a HTLV-2 seroprevalence of 3.6% in HIV-infected IVDUs[34]. A later investigation in 1994 of 599 HIV-infected individuals attending the Institute of Infectious Disease, Ospedali Civili in Brescia (472 Italian and 127 non-European), mostly symptomatic for HIV and believed to be IVDUs in 66%, found that 120 were reactive at the first screening while 116 at the second one. Seventy two out of the 116 samples found HTLV-2 positive by ELISA, were confirmed as positive by the INNO-LIA line immunoassay (62%), which distinguished HTLV-1 from HTLV-2, and 98% were Italian[35].

The long-term impact of HIV and HTLV-2 co-infection remains poorly understood. In a cohort of 522 HIV-infected IVDUs, molecular studies identified five co-infected with HTLV-2, but immunological follow-up showed that HTLV-2 did not affect the natural history of HIV infection[36]. However, subsequent studies focused on a 20-year follow-up of HIV/HTLV-2 IVDUs mostly in the North of Italy concluded that it was unclear whether HTLV-2 co-infection affected HIV progression[37]. Actually, a longitudinal international study on 370 HIV-infected IVDUs with known HIV seroconversion, including 143 cases in an Italian Unit in Rome, suggested that HTLV-2 did not affect HIV progression[38].

In addition to HIV/HTLV-2 co-infection, studies on HTLV-1/2 infection in Italy were extended to other risk categories. A study in the North of Italy included 3017 migrants belonging to the general population and 371 migrants detained in prison. The members of the general population were from the North of Africa (17.9%), Sub-Saharan Africa (27.6%), South and Central America (39.5%), and Eastern Europe (13.2%). Imprisoned individuals were from North of Africa (38%), Sub-Saharan Africa (15.9%), South and Central America (5.9%), and

Eastern Europe (40%). Participants were either IVDUs, had sexually transmitted diseases (STD), or admitted multiple sexual exposures. The prevalence of HTLV-1/2 infection was low, independent of HIV infection. Particularly, in the open population the overall prevalence was 0.3% for HTLV-1 and 0.1% for HTLV-2, while in prisoners, the prevalence for HTLV-1 was 1.4% and for HTLV-2 was 0.8%. Nevertheless, in the absence of any national coordinated HTLV-1/2 survey at that time, the authors suggested a careful evaluation of the presence of HTLV-1/2 among blood donors[39]. Unfortunately, this suggestion went unheeded. Moreover, in 1999, the first case of HTLV-1 infection in an Italian IVDU without co-infection with HIV was described[40].

People with STDs were another group investigated for HTLV infection. A study conducted on 1506 individuals attending 9 STD centers between 1992 and 1993 with an acute STD found a prevalence of HTLV-1/2 infection of 0.13% (2 individuals). One was infected with HTLV-1; she was a woman from Romania, already known as endemic region, who probably contracted HTLV-1 before arriving in Italy. The second was infected with HTLV-2; he was a male co-infected with HIV[41].

A cross-sectional study on 1457 individuals attended large STD urban centers for HIV, HTLV, and HCV. HBV and syphilis surveillance was conducted between January 1994 and June 1996. Within the participants, 69.7% were males, 72.4% Italians, and 19.6% non-European. One thousand seventy-five (74.8%) were non-injecting drug-using heterosexuals, 285 (19.6%) were men having sex with men, and 97 (6.6%) were IVDUs. Eighteen participants were positive for HTLV: nine (0.6%) were found positive for HTLV-1 and nine (0.6%) for HTLV-2 antibodies. The HTLV-1 prevalence was 2.1% in IVDU, 1.4% in homosexual men, and 0.3% in non-injecting heterosexual individuals. HTLV-2 prevalence was 8.2% in IVDUs and 0.09% in non-injecting heterosexual individuals. Overall, 66% of HTLV-1-positive individuals were non-European. Among the 9 HTLV-2 positive individuals, 8 were IVDUs from Italy and one from India. In the univariate analysis, HIV-positive individuals were more likely to be coinfected with HTLV-1 than HIV-negative and non-European IVDUs positive for HCV and antibodies versus treponema pallidum were more exposed to the risk of contracting HTLV-1 infection. Results seem to confirm the origin of HTLV-1 infection in Italy from endemic regions and point out the potentiality of HTLV transmission in Europe through sexual intercourse[42].

Further evidence of sexual transmission was provided by a study conducted between 1996 and 2003 of 393 immigrants to Italy who were either IVDUs or male-to-female transsexual sex workers. They showed a prevalence of 3.6% HTLV-1 positivity in HIV-positive individuals and 0.9% if HIV-uninfected[43]. Although screening of blood donors was not routinely performed in Italy, 1087 individuals attending the transfusion center of Ivrea in 1993, in North of Italy, were routinely screened for HTLV-1/HTLV-2 antibodies. Differentiating molecular studies in PBMC from 11 individuals revealed that three individuals were positive for HTLV-1 and 5 for HTLV-2. The overall prevalence of HTLV infection was 0.73%. This prompted the authors to claim the need for screening blood donors. Among 11 followed until 1995 for discordant anti-HTLV-I/II ELISA assays, through ELISA, WB, and PCR assays, 8 were found to react to some HTLV-1 antigens in WB, but all were negative for anti-rgp46-I and anti-rgp46-II antibodies. After 2 years, only 1/8 developed antibodies against gp46. However, all eight were positive for tax or tax and pol by PCR. Of note, all were living in the same area of Ivrea and none declared any risk exposure to HTLV-1 infection[44].

More recently, in 2018, 1498 immigrants living in Southern Italy, born in sub-Saharan Africa (79.7%) or in southern-Asia (20.3%) were screened for HTLV-1/2. Demographic data on gender, country of origin, age, religion, level of education, risk factors (tattooing, piercing, drug addiction, blood transfusion, tribal rituals), and pregnancy were collected. A chemiluminescent microparticle immunoassay and WB reported 0.07% HTLV-1-positive individuals. One individual, asymptomatic, from Nigeria, who had had unprotected multiple sex partners and a history of drug addiction had anti-HTLV-1 antibodies but was negative for HTLV-1 RNA. This is in accord with data which have shown low prevalence of HTLV-1 RNA-positive patients among the individuals positive for HTLV-1 antibodies[45]. The authors recommended to the Italian Healthcare Authorities to screen for HTLV-1 and HTLV-2 all donors from endemic countries at least to verify the cost-beneficial effect on public health[46]. The conclusions of these studies were based on a variable-sensitive commercial immunoassay used to follow-up HTLV-1 reactivity. On the other side, molecular quantitative investigation about HTLV-1 positivity was performed by introducing molecular studies to prove the presence of the HTLV-1 genome.

A study in North Italy from January 2003 to February 2005 enrolled 3408 HIV-1/2 seronegative immigrants from African countries, living in Italy for < 5 years, referred to the STD clinic, along with 534 blood donors enrolled as control population. Anti-HTLV-1/2 reactivity was detected by ELISA in 9 immigrants and 2 blood donors. In the confirmatory WB, 2/11 (18%) were con-

firmed serologically positive for HTLV-1 antibodies, 3/11 (27%) were HTLV indeterminate, and 6/11 (54%) were negative. Both blood donors were negative, so all the reactivity was among the immigrants, with 5/3408 being either HTLV-1 infected or HTLV indeterminate (0.14%). All 11 ELISA-positive samples were tested for the presence of HTLV-1 DNA by PCR. Real-time PCR demonstrated the presence of HTLV-1 genome only in the two HTLV-1 WB-positive samples. Although the prevalence of HTLV-1 in migrants from endemic areas was low (0.058%), this paper demonstrated that the real-time PCR eliminated any doubts regarding the diagnosis of HTLV-1 positivity based only on ELISA and WB. Subsequent follow-up revealed that one individual, a Nigerian sex worker living in Italy since 2001, developed ATL, while the other a Ghanese sex worker had normal lymphocytes and declined further testing[47].

On the basis that breastfeeding is one of the major routes of HTLV-1 transmission, in 2005, a multicenter European study investigated HTLV-1 and HTLV-2 seroprevalence among more ~ 250,000 pregnant women in European countries including Italy. In the latter, the evaluation was performed between Hospital and University in Padua on 6000 samples of cord blood, for 95% belonging to women born in Europe, 59 in North Africa, 77 in sub-Saharan Africa, 11 in the Caribbean, 2 in Japan, and 153 elsewhere. The seroprevalence of HTLV-1/HTLV-2 was estimated to be 0.33 over 1000 tested samples[48].

More recently infectious disease specialists from Tuscany introduced a strategy to diagnose emerging infectious diseases in non-endemic areas, performing an antenatal screening. In particular, this was proposed by Tuscany Referral Centre for Infectious Diseases in Pregnancy in collaboration with the Tuscany Reference Centre for Tropical Diseases, in Florence, who suggested pregnant women attending a reference center for infections in pregnancy for general problems to complete two questionnaires. The first one focused mainly on country of birth, the second one including five questions on the risk factors such as recent travels abroad also of the partner, origin country of mother, blood transfusion abroad, to identify those women who needed to be tested for specific diseases such as Chagas disease, HTLV-1 infection, malaria, schistosomiasis, and Zika virus infection[49]. Particularly, 429 women were evaluated from March 2019 to November 2020, and 103 (24%) were considered at risk for emerging infectious diseases but no cases of HTLV-1 infection were diagnosed. Recently, the WHO reported that the prevalence of HTLV-1 among pregnant women ranges from 0% to 0.04%[24]. Besides the results, this was an important step in the perspective that the situation could change owe to heterogeneous and unpredictable immigration flux and therefore checking for antenatal HTLV-1 infection belongs to a prevention program. In conclusion of this part of our review, we must recognize that although the prevalence of HTLV infection in Italy seems to be low, long-term follow-up of the single HTLV-positive cases is lacking. It is not known why HTLV-2 was more prevalent than HTLV-1 in IVDUs in Italy but it is likely to be a founder effect. Moreover, the HIV/HTLV-2 double-positive individuals identified were very likely put under the treatment aimed to control HIV infection, and therefore, HTLV was neglected.

HTLV-1/2 in Italy and associated diseases

Besides the above-targeted epidemiological studies, investigating the presence of HTLV-1/2 in defined risk groups in Italy, there are sporadic reports of HTLV-1 infection associated with diseases in this country. Regarding neurological syndromes, one Peruvian male, living in Italy for 7 years, with recurrent meningitis, that was found to be due to strongyloidiasis, tested positive for anti-HTLV-1 antibodies. This, uncommon, but well-documented association between HTLV-1 and strongyloidiasis prompted the authors to declare that more information about neglected diseases, could help clinicians in non-endemic areas in formulating diagnoses in migrants from endemic areas presenting with infections associated with the country of origin. Actually, strongyloidiasis associated with HTLV-1 might have led to a fatal outcome[50]. Two cases of Italians who developed HTLV-1-associated spastic paraparesis were reported. One was a women born and residing in the area of Salerno who developed spastic paraparesis and anti-HTLV-1 antibodies were detected in serum and in CSF. No history of transfusion or risk behavior was reported for this case[51]. Thereafter, a case of an Italian patient with HAM/TSP residing in the area of Pescara/Chieti was reported. The patient received a transfusion in Italy 2 years before the onset of the symptoms. He was found positive for proviral HTLV-1 DNA: gag, pol, and env in lymphocytes despite the absence of anti-HTLV-1 antibodies in serum[52]. Early development of HAM/TSP following transfusion-acquired infection is well documented.

The investigation of a possible association between HTLV infection and neurological syndromes revealed HTLV-2 seropositivity in 13/47 HIV-positive individuals affected by idiopathic polyneuropathy (PN). The prevalence was higher than in non-PN controls, 35% versus

8%, respectively. The presence of HTLV-2 in peripheral blood lymphocytes was confirmed by the detection of HTLV-2, tax, and pol genome by PCR in all 13 seropositive subjects[53].

A well-characterized case of HAM/TSP was reported in a woman born in Cote d'Ivoire but living in Italy for many years. The neurological examination suggested HAM/TSP and anti-HTLV-1 antibodies were detected in CSF and in serum by ELISA and confirmed by WB. HTLV-1 was isolated from peripheral blood lymphocytes and DNA from HTLV-1, *tax,* and *pol* was demonstrated in cultured lymphocytes. HTLV-1 was further confirmed by sequencing. The virological assays were essential as the differential diagnosis of HAM/TSP includes multiple sclerosis[54]. This case demonstrated the presence of HTLV-1 in non-endemic areas and the need to perform a correct diagnosis on the base of virological evidence as well as the need for a high index of suspicion, especially in patients who do not originate in high prevalence regions. In these cases, a careful history of blood transfusion, sexual partners, and other risk factors must be taken. It is not known how the virus infected this patient since she denied blood transfusions, sexual contact, or other exposures with risk. However, she was born in a high prevalence region and may have become infected in early life through breast-feeding[55].

A case was reported of a 20-year-old patient from Brazil born in a family with no history of neurological diseases. He had normal development until he was 11 years old. He then complained of difficulties in climbing, mood disturbance, and difficult interaction with school rules. At age 17 years, neurological examination showed lower-limb weakness and cognitive impairment. Serological analysis of him and his mother revealed the absence of reactivity to HIV antibodies while detecting anti-HTLV-1 antibodies by ELISA and WB, in both serum and CSF. In addition, the presence of tax-rex, pol, and LTR was found through nested PCR in both their peripheral blood mononuclear cells. Both mother and son were infected with the same cosmopolitan HTLV-1 subtype. This case has reported for the 1st time a juvenile form of a co-existence of motor and cognitive syndrome associated with HTLV-1 infection. An important aspect to be highlighted is that presumably the young patient contracted the HTLV-1 infection during prolonged breastfeeding since he was breastfed up until he was 3 years old[56]. In the past 30 years (1993-2023), HTLV-1 was checked in lymphoid malignancy beside ATL reported as associated with HTLV-1 in the world. One controversial and debated issue was the association between HTLV-1 infection and mycosis fungoides (MF) since some presentation of ATL mimic MF. Actually, some authors reported the association of MF with HTLV-1[57,58], while other did not detect HTLV-1 in French and Portuguese patients affected by MF[59]. Sequences of HTLV1/2 were found in mononuclear cells from 10 of 29 patients affected by MF living in Northern Italy with no origin from endemic areas. Conversely, no positivity for p24 or RT was found[60]. The authors of this article hypothesized that the virus in MF patients was bearing deletion that limited or inhibited viral replication. The analysis of the sample was repeated 6 months later obtaining the same results. In addition, the authors claimed the absence of HTLV-1-infected cell line in the laboratory, thus excluding the possibility that the results were distorted by possible contamination. More recently, a study on Italian patients diagnosed with MF was conducted in the region of Friuli Venezia Giulia between 1993 and 2003, at the Dermatology Unit of University of Trieste. Skin biopsies for multiple viruses were performed. Nineteen out of 23 MF patients with multiple infections were positive for HTLV-1 tax sequences. However, the authors also detected HTLV-1-like sequences in 12% of healthy donors. Therefore, the role of HTLV infection as co-factors in MF remained controversial. Importantly detection of HTLV DNA was not associated with MF progression[61].

A few cases of ATL, occurring in 2-5% of HTLV-1-infected individuals who show symptoms after 15-20 years from infection[62], have been identified in Italy. It is worthwhile to distinguish between cases in individuals living in Italy and cases from endemic areas. About the latter, a case of acute ATL in a female sex worker from Nigeria leaving in Italy since 2001 was reported. The patient presented exfoliative dermatitis followed by deterioration of her conditions with a high number of white blood cells, lymphocytosis, and hypercalcemia. She was admitted to the Oncology division which suspected a diagnosis of ATL owe to the presence of flower-shaped lymphocytes. The diagnosis of ATL was confirmed when the presence of HTLV-1 antibodies was detected in serum by ELISA and confirmed in WB. The presence of HTLV-1 proviral DNA was confirmed through semi-nested PCR. She was treated with two cycles of chemotherapy and prednisone followed by vindesine, epoxide, carboplatin, and prednisone. This was followed by treatment with antivirals: the nucleoside analogs zidovudine, and didanosine plus interferon-alpha which after an initial control of symptoms were unable to reduce the reservoir of HTLV-1-infected leukemic cells[63].

In 1990, another case of ATL diagnosed in Northern Italy was reported[64]. ATL occurred in a young woman of Italian origin and no history of known risk behaviors for HTLV-1 infection, blood transfusion, or travel to HTLV-1 endemic regions. She presented lymphadenopathy, splenomegaly, hypercalcemia, and renal failure. The diagnosis of ATL was confirmed by the presence of 60% of abnormal peripheral blood leukocytes with "flower-shaped nuclei". Phenotypic analysis of peripheral mononuclear cells showed high expression of CD4 and CD25 markers. HTLV-1 infection was detected by ELISA and confirmed by WB. Her family and husband were found negative for HTLV-1 antibodies. Unfortunately, no other information on this case was disclosed in the following time.

Recently an atypical case of cutaneous presentation of a HTLV-1 associated ATL was reported in Italy in Turin. A 32-year-old Nigerian male who travelled to Italy through Libia in 2016 attended the dermatology clinic with painful vesicular bullae and a history of vesicular skin lesions. A skin swab revealed herpes simplex virus 2 (HSV-2) DNA, Streptococcus agalactiae, and methicillin-resistant *Staphylococcus aureus*. Immunophenotyping showed an expansion of CD4+, CD25+, and HLA-DR+ T-lymphocytes. Anti-HTLV-1 antibodies were detected by ELISA and WB and in the bone marrow biopsy, typical "flower cells" were detected. The patient was treated with acyclovir, antibiotics followed by zidovudine + IFN. Due to zidovudine and IFN, toxicity treatment was switched to tenofovir. This treatment induced clinical remission but after 52 months, the patient presented fever and erythematous plaques. Skin and bone marrow biopsies, biochemistry and CT scan confirmed a recurrence of ATL. Therefore, the patient was treated with chemotherapy including etoposide, prednisone, vincristine, and cyclophosphamide[65]. This was the first case with an atypical presentation of HSV-2-positive skin infection associated with HTLV-1 infection and successively to the development of ATL. In this case, the antiviral treatment induced a prolonged remission and delayed the full-blown disease. Therefore, this unique evidence disclosed a possible involvement of skin lesions precociously in HTLV-1 infection and the need to train dermatologists and in general clinicians to diagnose infections which a common in endemic areas and are thus found among immigrants. This could let the Italian health-care organizations find themselves in front of new disease manifestations and to take appropriate actions, as has already be done in other European countries such as the UK, where testing migrants from high prevalence areas for HTLV-1/2 is now recommended.

HTLV-1/2 in Italy in 2024

To envisage the possible future scenario of HTLV-1 diffusion in Italy, based on the above-reported data and on the current knowledge of the state HTLV-1 infection in the world, we think that careful attention should be addressed to the latest migration flows from endemic areas to Italy. Actually, as mentioned before, there is no national register for HTLV-1/2 in Italy. In a technical report from the ECDC, in 2015, about the geographical distribution of areas in which high prevalence of HTLV-1 infection occurred[3], Europe, except for Romania, was reported as an area with low prevalence or no presence of HTLV-1 infection. In the case of most of Central and Eastern Europe, in fact, there were no data. In this document, the ECDC recommended testing for anti-HTLV-1 antibody donors living in or originating from HTLV-1 high prevalence areas.

The last WHO document on HTLV-1 goes back to June 2023. In this document, the WHO refers that studied prevention strategies include, in addition to cessation of breast feeding and breast milk freeze-thaw method, for women with HTLV-1 antibody screening among blood donors which has been implemented in 23 countries (not Italy) and leukoreduction. In this document, the WHO affirms to work for implementing surveillance, improving testing approaches in low-income countries and, in general, to better define the risks. Unfortunately, these warnings have not been taken equally in all the European countries. Regarding Italy, due to the lack of certain data on the presence of HTLV in the country, we thought that, nevertheless, it was possible to make a theoretical estimation of the putative HTLV-1-infected individuals at the moment at least for foreign people living in Italy, based on existing data reported in the literature and by international health agencies in other parts of the world. In fact, as there is no reason to believe that the HTLV-1 prevalence in foreign citizens residing in Italy differs from that in their countries of origin, we have estimated the number of people living with HTLV-1 in Italy for each country officially registered as resident in Italy and, from existing data on % prevalence of HTLV-1 among the general population in the different countries in the world, as detailed below. Data on the numbers of foreigners by country of citizenship officially registered as resident in Italy on January 1st, 2024, were obtained from the website of ISTAT, the Italian National Institute for Statistics (http://dati.istat.it/Index.aspx, accessed on January 17, 2024). Data on % prevalence of HTLV-1 in the

general population of different countries in the world were mainly derived from the "Human T-Lymphotropic Virus Type 1: Technical Report", published by the WHO[24]. In particular, the putative number of HTLV-1-positive individuals in Italy by country of citizenship was calculated only for countries for which a value > 1% was obtained as the arithmetic average between the minimal and maximal % prevalence in the general population, as reported in the "WHO Technical Report". An arbitrary zero prevalence/number of HTLV-1-positive individuals was assigned to countries for which the mean prevalence was < 1% or no data was available. The number of putative HTLV-1-positive foreigners in Italy by continent of origin in the world was then calculated by taking the sum of the available, putative numbers of positive citizens of the countries located in the various continents. These calculation criteria were adopted for all countries except the following: (i) Romania, for which, although no numerical prevalence value could be found in the "WHO Technical Report", an arbitrary HTLV-1 prevalence of 1% was assigned due to its classification among high prevalence (i.e. > 1%) countries in the "Technical Report: geographical distribution of areas with a high prevalence of HTLV-1 infection" published by the ECDC in 2015[3] (note that Romania is the only country which, based on the above indicated criteria, contributed to the putative number of HTLV-1 positives in Italy from European countries); (ii) Peru for which the prevalence obtained from a recently published study focused on this specific subject[66], was preferred to that reported in the "WHO Technical Report"; (iii) Argentina, Jamaica, Guyana, and Haiti for which the prevalence of the prenatal screening indicated in the "WHO Technical Report" was preferred to that of the general population, being the former slightly, but inexplicably, higher; (iv) Trinidad Tobago for which only the estimated prevalence in blood donors was available. Mean, minimal, and maximal numbers of putative HTLV-1-positive individuals from different countries were calculated using mean, minimal, and maximal % prevalence values, respectively, except for Romania, South Africa, and Trinidad and Tobago for which only the mean % prevalence values were available. Here are the lists of the countries, divided by continent, for which, accordingly to the above-detailed criteria, a putative number of HTLV-1-positive individuals officially resident in Italy could be estimated and contributed to the overall estimation. Europe: Romania. Africa: Benin, Cameroon, Congo, Democratic Republic of Congo, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Nigeria, Senegal, South Africa, Togo. Asia: Iran. America: Argentina, Brazil, Colombia, Jamaica, Guyana, Haiti, Honduras, Panama, Peru, Trinidad and Tobago.

Table 1. Theoretical estimation of HTLV-1-infected foreign residents in Italy by continent in the world calculated from data on foreign residents in Italy and % HTLV-1 prevalence in the general population of their country of origin

Foreign residents in Italy on January 1st, 2024*		
Continent by country citizenship	**Total**	**Estimated HTLV-1+**
All countries of the world	5,141,341	26,024 (15,932-36,786)†
Europe	2,417,811	10,818
Africa	1,151,433	9,252 (3,656-14,840)
Asia	1,181,236	247 (49-429)
America	388,227	5,707 (14,09-10,699)
Oceania	1,991	0
Stateless	643	0

*Foreigners officially registered as resident in Italy, as reported by ISTAT, the Italian National Institute for Statistics.
†Mean, and minimal and maximal (in brackets) total number of putative HTLV-1-positive individuals by continent of the world. Data refer to the sum of values for each single country of the continent, calculated from mean, minimal, and maximal % HTLV-1 prevalence in the general population of the countries, were available.

The results of this arithmetical estimation are reported in table 1, where data have been collectively represented by continent of origin in the world of foreigners resident in Italy, and in supplementary table 1, where the arithmetical estimation of the putative positive cases, based on the above reported arbitrary criteria, is represented in detail for each country of origin of foreigners officially residing in Italy. Strikingly, the results of this estimate led to the belief that between 15932 and 36786 foreign individuals residing in Italy are living with HTLV-1 at the moment.

Conclusions

Our narrative historical review of the course of HTLV-1 infection in Italy and the arithmetical estimation of foreigners possibly infected with HTLV-1 at this time in Italy could contribute to counteract, at least in part, the absence of definitive data on the presence of the virus in the Italian territory. Interestingly, our theoretical estimation indicates that we can expect that about 26000

people are living with HTLV-1 in Italy, counting only those who have been registered as foreigners living in Italy. However, we must be aware that the numbers reported in table 1 and supplementary table 1 most likely underestimate the actual presence of HTLV-1 in Italy. In fact, the theoretical estimation has taken into account only the number of foreigners officially registered as residing in Italy. All other foreigners, and particularly those possibly native from HTLV-1 endemic areas, actually present in Italy but lacking an official registration, such as irregular migrants or migrants during the long phase of regularization, are missing from the calculation. Moreover, native foreigners who arrived in Italy but after regularization opted for Italian citizenship, including their children born in Italy, also escaped from the calculation. In addition, the restrictive criteria we adopted to assign a prevalence to different countries, such as the arbitrary assignment of 0% prevalence to countries with a reported prevalence < 1 or to countries for which, including Italy, a prevalence was not available in official documents or scientific publications, may have contributed to underestimate the actual number of HTLV-1-infected individuals in Italy. Moreover, based on our theoretical estimates, we can also deduce that HTLV-1-associated diseases are rarely reported in Italy. In fact, taking into account, numbers of our estimate of individuals living in Italy with HTLV-1 and percentages of HTLV-1-infected people who develop HTLV-1 associated diseases over the years, as well documented by several studies, we must assume that what was supposed for ATL in the Netherlands, i.e., ATL presumably misdiagnosed as T-cell non-Hodgkin lymphomas[67], as well as what could occasionally occur for HAM/TSP, misdiagnosed as MS, is frequently taking place in Italy.

In conclusion, we propose that the time has come to urge the Italian health authorities and medical environment to change the present state of things and to start, similarly to what has been done in other European countries, to perform serious surveillance on HTLV-1/2 in Italy, beginning from a centralized, mandatory reporting of all HTLV-1/2 performed tests.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.24000007. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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