

Prevalence and Associated Risk Factors of HTLV/HIV Co-Infection among People who inject Drugs (PWIDs): A Review

Abstract

Human T-cell lymphotropic viruses type 1 and 2 (HTLV1/2) and Human Immunodeficiency Virus (HIV) co-infections show a worldwide distribution. The prevalence varies according to geographic region, racial group and population type. HTLVs and HIV share similar routes of transmission and tropism for T-lymphocytes thus co-infection is common. HTLV-HIV co-infections occur frequently among PWIDs (People Who Inject Drugs) and HIV positive patients. HTLV-1/HIV co-infection has been documented to accelerate progression to Acquired Immunodeficiency Syndrome (AIDS) while HTLV-2 has a protective effect as a result of reduced HIV replication. This review primarily analyzed the global trends of prevalence and associated risk factors of HTLV mono-infection and HTLV-HIV co-infection among PWIDs.

Secondary objectives included an analysis on the global trends in prevalence and risk factors of HTLV/HIV co-infections among HIV positive patients and an analysis on HTLV subtypes present among PWIDs and HTLV-HIV co-infected PWIDs and patients. Based on the three categories, PUBMED and Google Scholar were systematically searched for relevant articles published between January 1988 and May 2017. A total of 67 articles from different countries were reviewed and results were presented in tables. Iran reported the highest HTLV prevalence among PWIDs (52%) while USA (16%) and Kenya (19.3%) reported the highest prevalence among HTLV-HIV co-infected PWIDs and patients respectively. Introduction of subtypes to countries that were previously not endemic suggested transmissions through immigration and travel. Based on the studies, black race and older age were the common risk factors among HTLV-HIV co-infected PWIDs and patients as well as HTLV infected PWIDs. High risk injection and sexual risk factors varied from one study to another. We recommend introduction of regular HTLV screening alongside HIV screening in outpatient clinics that PWIDs attend so as to reduce risk of transmission and to create awareness.

Keywords: HTLV-1; HTLV-2; HIV; PWIDs; Risk factors; Subtypes

Review Article

Volume 6 Issue 1 - 2018

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Received: October 27, 2017 | **Published:** January 02, 2018

Abbreviations: HTLVs: Human T-Cell Lymphotropic Viruses; HTLV-1: Human T-Cell Lymphotropic Virus Type 1; HTLV-2: Human T-Cell Lymphotropic Virus Type 2; HIV: Human Immunodeficiency Virus; STLV-1: Simian T-Cell Lymphotropic Virus Type 1; PWIDs: People Who Inject Drugs; IDU: Intravenous Drug Use; AIDS: Acquired Immune Deficiency Syndrome; HBV: Hepatitis B Virus; HAV: Hepatitis A Virus; HCV: Hepatitis C Virus; ELISA: Enzyme Linked Immunosorbent Assay; PCR: Polymerase Chain Reaction; RIA: Radio Immuno Assay; PA: Particle Agglutination; WB: Western Blot; HAM/TSP: HTLV Associated Myelopathy/Tropical Spastic Paraparesis; ECDC: European Centre for Disease Prevention and Control; WHO: World Health Organization; UNODC: United Nations Office on Drugs and Crime; LTR: NACC: National AIDS Control Commission; Long Terminal Repeat; ICTV: International Committee on Taxonomy of Viruses

Introduction

HTLV-1 was the first retrovirus to be discovered in 1979 from a patient with cutaneous T-cell lymphoma which was later followed by the discovery of HTLV-2 in 1982 from a patient with

hairy cell leukemia [1]. Data shows that at least five to ten million people worldwide are infected with HTLV-1 [2] and between three to five million people worldwide are infected with HTLV-2 [3]. Seroprevalence rates of HTLVs differ depending on the geographic area, socio-demographic composition and individual risk behaviors [1]. Globally, HTLV-1 Seroprevalence rates tend to increase with age and are higher in females than males as sexual transmission occurs more efficiently from men to women than women to men [4].

Regions endemic for HTLV-1 are found mainly in southeastern Japan, the Caribbean, parts of Africa, the Middle East and in the Pacific Islands of Melanesia [5]. The African continent has a population of over one billion and it represents the largest endemic area for HTLV infection but with many data gaps [6]. In Africa, the Seroprevalence increases from the north to the south, varying from 0.6% in Morocco to greater than 5% in several sub-Saharan African countries including Benin, Cameroon and Guinea-Bissau [1]. In Malawi, HTLV-2 prevalence of 1.7% and 1.3% was reported among mothers and their children who had childhood cancers [6]. HTLV-2 is more prevalent among some

Native Americans and some Central African tribes and is relatively common among PWIDs and their sex partners in Europe, North America and other regions of the world [7]. In Europe where HTLV-2 infection is found almost exclusively among PWIDs, about 20,000 to 40,000 persons are estimated to be infected [6]. In Kenya, HTLV prevalence in the general population has not been documented. The first study in Kenya was done on stored serum samples from suspected HIV-infected patients in Nairobi, Mombasa & Kisumu [8].

The samples were analyzed for HTLV-1 using Enzyme Linked Immunosorbent Assay (ELISA) and later confirmed by Western Blot. Out of 913 samples, 3.7% were found positive for HTLV-1 however only 0.44% was confirmed positive by western blot [8]. In Kenya a recent HTLV-1 prevalence of 19.3% was reported from liquid based cytology (LBC) samples among HIV positive women attending Kenyatta National Hospital in Nairobi [9].

The burden of HTLV-2 infection in the world is about 6 to 12 fold lower than that of HTLV-1 [9]. HTLV-1/2 transmission occurs through; unprotected sexual contact, from mother to child via breastfeeding, exchange of contaminated blood products and through intravenous drug use [7]. PWIDs are particularly vulnerable to HIV and other blood-borne pathogens as a result of sharing contaminated syringes and other injecting equipment such as cookers, cotton and rinse water [10]. Given that HTLV and HIV share identical modes of horizontal and vertical transmission, co-infections with these viruses is common in endemic areas [11]. Globally 36.7 million people are infected with HIV whereas in Eastern and Southern Africa, 19 million people are living with HIV. Kenya has an average national HIV prevalence of 5.9% and the prevalence among PWIDs is estimated to be 18.3% [12].

HTLV screening is not routinely performed in many countries and is not always recommended by physicians to outpatients thus Seroprevalence of co-infection may be underestimated [13]. Current evidence suggests a protective role of HTLV-2 and adverse effect of HTLV-1 on HIV infection [7]. This review examined prevalence estimates, risk factors and subtypes among HTLV/HIV co-infected PWIDs and patients together with HTLV-infected PWIDs. The findings will contribute to further understanding of HTLV distribution, risk factors and HTLV/HIV co-infection in PWIDs and HIV positive patients.

HTLV Genotypes and associated diseases

Human T-Cell Lymphotropic virus is a member of the delta retrovirus genus of the retroviridae family [14]. There are four genotypes of HTLV; HTLV-I, HTLV-2, HTLV-3 and HTLV-4. HTLV-1/2 is the most common pathogenic genotypes to humans. They are oncogenic retroviruses that both infect T cells with HTLV-1 infecting mainly CD4+ T cells and HTLV-2 infecting CD8+ T cells. HTLV-2 is especially prevalent among IDUs [15]. HTLV-1 is the causative agent of aggressive adult T-cell leukaemia/lymphoma (ATL) and the progressive chronic, disabling HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) as well as other inflammatory conditions such as infective dermatitis and uveitis. The cumulative risk of a HTLV-1 carrier developing ATL has been estimated at between 2.5% and 5% although a latency period of 50-70 years is typical [6]. Both ATL and HAM/TSP have a low incidence among HTLV-1 carriers. ATL generally presents after a long latency in patients infected during childhood. This is in contrast to HAM/TSP, which is associated with infection later in

life [1]. There is no curative treatment for HTLV-1 or its associated pathologies. An effective vaccine is currently unavailable which puts a heavy social and financial burden on sufferers, their families and the healthcare systems [9]. The pathogenicity of HTLV-2 is low but has occasionally been linked to sub-acute neurological syndromes including HTLV-2-like paraparesis, neuropathies and bladder disturbances [1].

The genotype HTLV-3 was first described in two asymptomatic inhabitants from South Cameroon. Two other cases of HTLV-3 infection in people living in Cameroon have been reported, suggesting that this virus is not extremely rare in the human population living in Central Africa [16]. Only one strain of HTLV-4 has been identified in a person who also lived in Cameroon [3]. No disease has been reported in both HTLV-3 and HTLV-4 infected individuals. HTLV-1 and HTLV-2 have a similar genomic structure and share approximately 70% nucleotide sequence [1].

Epidemiology of HTLV subtypes

T-Lymphotropic virus species are distinguished on the basis of sequence differences and each contains several subtypes. HTLV-1/2 subtypes are clustered according to the geographic region. All HTLV-1 subtypes described have most probably originated from separate interspecies transmissions from simians to humans [14]. HTLV-1a is the only human restricted molecular subtype since the rest of the HTLV-1 subtypes could much more likely imply zoonotic transmission in African regions bordering non-human primate habitat. The other molecular HTLV-1 subtypes from humans in central Africa belong to composite clades that comprise HTLV-1 strains and Simian T-cell lymphotropic virus type 1 (STLV-1) strains derived from non-human primates [17].

Nonhuman primates in Africa could be the source of recurrent zoonotic transmissions of STLV-1 to local human population. STLV-1 found in non-human primates represents a measurable proportion of HTLV-1 infections [17]. There are seven subtypes of HTLV-I which are classified based on geographic distribution and nucleotide diversity of the long terminal repeat (LTR) and env gene sequences: Subtype a which is cosmopolitan, subtype b found in central Africa, central Africa/pygmies subtype c and Australian/Melanesian subtype d. The cosmopolitan subtype found in several geographic regions such as Japan, West and North Africa is the most widespread. Subtypes e, f, g are rare and limited numbers of strains have been reported in central Africa [18]. Subtype A can be divided into five subgroups based on geographical distribution: Transcontinental (A), Japanese (B), West African/Caribbean (C), North African (D) and Black Peruvian (E) [18].

Molecular epidemiology studies have distinguished four main HTLV-2 subtypes. HTLV-2a and HTLV-2b are the most prevalent among PWIDs from urban areas of the Americas and Europe; the subtypes are also prevalent in the indigenous population of the Americas, with sporadic distribution in Asia and Africa [19]. HTLV-2a has been reported in some American Indian tribes of North, Central and South America including; the Navajo and Pueblo in New Mexico as well as the Kayapo, Kraho and Kaxuyana in Brazil [20]. HTLV-2c variant was detected in the indigenous population of the Brazilian Amazon and in PWIDs from urban populations in Brazil [19]. Three different phylogroups within the 2a subtype (AI-AIII) and four different phylogroups within the 2b (BI-BIV) subtype have been described [20].

HTLV among PWIDs

The highest prevalence of HTLV has been observed among PWIDs. HTLV-1/2 infection occurs more frequently among PWIDs [21]. Transmission has been associated with high-risk injection and sexual practices. Needle sharing is hypothesized to be one of the major routes of HTLV-2 transmission among PWIDs in the United States and Europe [4]. The largest number of HTLV-2 infected persons is in the United States (400,000-500,000) reflecting the confluence of endemic Amerindian, hyper endemic PWIDs and secondary sexual spread to the general population [22]. In North American PWIDs where HTLV-2 is endemic, Seroprevalence rates vary between 8.8% to 17.6% [7]. HTLV-1/2 prevalence of 19.1% was reported among PWIDs in Argentina [23]. In Europe, HTLV-2 mainly occurs among PWIDs with prevalence of up to 15% and HTLV-1 among general population with prevalence of less than 1% [7].

HIV among PWIDs

Intravenous drug use (IDU) is an important risk factor for infection with HIV. Studies indicate that PWIDs are at a high risk for HIV transmission through unsafe practices such as sharing non-sterile injecting equipment and unprotected sex. PWIDs often engage in more high-risk sexual behavior with multiple or concurrent partners. This can transfer HIV from PWID to non-PWID populations and extend or prolong the generalized epidemic [24]. One in seven PWIDs is living with HIV [25]. Globally, around 13 million people inject drugs and 1.7 million of them are living with HIV. PWIDs account for approximately 10% of HIV infections globally and 30% of HIV infections outside of Africa.

Regional HIV prevalence rates are high in people who inject drugs in all parts of the world with up to 15.5% in East and Southern Africa [26]. It has been estimated that 17% of new HIV infections at the Kenyan coast are linked to PWIDs. In Kenya, HIV prevalence among PWIDs in Malindi sub-county based was estimated to be 53.1% based on a study involving 211 PWIDs [27]. The efficiency of HIV transmission per injection is six times

higher than for heterosexual route thus HIV prevalence among PWIDs can rapidly reach high levels of more than 50% and up to 90% [28]. HIV prevalence among African PWIDs far exceeds that in the general population, ranging from 9% to 50% [24].

HIV/HTLV Co-infection among PWIDs

HIV/HTLV co-infection is growing worldwide, mainly in South America and Africa [28]. The effects of HTLV-HIV co-infection on humans have been widely studied. HTLV-1 co-infection has been associated with a more rapid progression of HIV-1 disease, higher mortality and increased frequency of opportunistic infections but has also been associated with delaying HIV-1 disease progression [7]. It is generally accepted that HTLV-2 exerts a negative effect on HIV-1 replication. Several authors have associated HTLV-2 co-infection with a better outcome for HIV-1 positive PWIDs as it was observed that co-infected patients showed reduced HIV-1 replication presumably due to lower levels of T cell activation [29].

Trends in the Global prevalence of HTLV/HIV Co-infection among PWIDs

Ten articles that reported HTLV/HIV co-infection among PWIDs from different countries were selected for analysis (Table 1). The country, HTLV virus tested, risk factors analyzed, authors and time were noted. Half of the studies analyzed HTLV-1/2/HIV co-infection while the remaining half analyzed HTLV-2/HIV co-infection. Out of the ten studies, 9 studies analyzed risk factors that were significant with HTLV/HIV co-infection among PWIDs. The trend in prevalence over time showed that HTLV-1/2/HIV co-infection decreased over years as the initial prevalence in 1990 was 14.6% while the last prevalence documented in 2006 was 6.7%. HTLV-2/HIV co-infection decreased steadily between 1995 and 2005 from 5.8% and 0.51%. The highest HTLV/HIV Co-infection prevalence was 16% from USA. Ireland had the second highest co-infection prevalence of 14.6%. The lowest prevalence was 0.51% from Portugal. Half of the studies were done in USA.

Table 1: Summary of HTLV/HIV Co-infection prevalence among PWIDs 1990-2006.

Country	Type of HTLV	P (%)	Risk Factors	Authors	Year
Ireland	HTLV-1/2	15	Black race p<0.01, older age p<0.01	Lee et al. [31]	1990
USA	HTLV-1/2	2.7	Black race p>0.001, older age p<0.001, females p< 0.001	Cantor et al. [32]	1991
USA	HTLV-2	5.8	Black race p<0.05, older age p<0.05, female gender p<0.05, HIV infection p<0.05	Briggs et al. [33]	1995
USA	HTLV-2	3.3	None of the factors were significant	Giacomo et al. [34]	1995
USA	HTLV-2	2.3	None of the factors were significant	Hershow et al. [35]	1996
Brazil	HTLV-1/2	8.8	Black race p<0.001, old age p<0.001, longer duration of IVD use p<0.001, CD4:CD8 cell ratio p<0.001	Lentino et al. [21]	1997
Italy	HTLV-2	1.8	None of the factors were significant	Egal et al. [36]	1999
USA	HTLV-1/2	16	Risk factors not determined	Guimaraes et al. [37]	2001
Portugal	HTLV-2	0.5	None of the factors were significant	Silva et al. [38]	2005
Italy	HTLV-1/2	6.7	HCV serology p<0.0001, older age p<0.0001, CD4:CD8 cell ratio p<0.0001	Turci et al. [39]	2006

P(%)-Prevalence percentage, HCV-Hepatitis C virus, All the studies analyzed the blood samples using ELISA followed by confirmation with western blot except the study by Turci et al. [39], that used PCR (polymerase chain reaction). No published studies for the period 2007 to 2017 were retrieved.

In USA, co-infection prevalence increased from 2.7% in 1991 to 16% in 2001. In Italy, prevalence of 1.8% and 6.7% were recorded in 1999 and 2006 respectively. The reduced HTLV/HIV co-infection prevalence over the years could be attributed to the establishment of harm reduction measures such as provision of free needles and syringes, education awareness, provision of condoms and HIV testing and counseling. All these measures play a major role in mitigating spread of the virus among the PWIDs. United States together with countries such as China, Russian Federation and Brazil are estimated to have the largest populations of PWIDs and together account for 45% of the total estimated worldwide population of PWIDs. Given that HIV infections are high among PWIDs in all areas of the world, HTLV rates could also be higher due to similar transmission patterns. These could all be possible explanations for the high prevalence observed in USA.

The origin of the HTLV-2 epidemic is not entirely defined but it is likely that the initial HTLV-2 epidemic in the United States occurred in PWIDs as early as the late 1960s [30]. This could explain why most of HTLV-2 studies focused on PWIDs. The low prevalence of 0.51% recorded in Portugal is attributed to the fact that this was the first time HTLV-2 cases were identified in

Portugal [31]. This indicates that Portugal may not be an endemic area for HTLV-2. In addition it could imply that there are very few immigrants from endemic regions. Older age and Black race were reported in five studies as the main significant risk factors [21,32-35]. Others included female gender [33,34], longer duration of PWID [21], HCV infection 35 [39] and high CD4:CD8 T-cell ratio [21,35].

Trends in the Global prevalence of HTLV/HIV Co-infection among Hospital patients

Studies from different countries published between 2001 and 2017 were examined as summarized in (Table 2). Only fifteen studies that had analyzed HTLV-HIV co-infection among hospital based patients were selected. The country, HTLV virus tested, risk factors, authors and time were noted. Out of the twelve studies, eight analyzed HTLV-1/2/HIV Co-infection, five analyzed HTLV-1/HIV Co-infection and two analyzed HTLV-2/HIV Co-infection. Nine studies were from Brazil, three from Mozambique and one study each from Mexico, Nigeria and Kenya. Ten studies analyzed risk factors associated with HTLV/HIV co-infection among hospital based patients. The trend in prevalence over time showed that there was a decrease in HTLV-1/2/HIV co-infection from 5.0% in 2005 to 4.2% in 2017.

Table 2: Summary of HTLV/HIV Co-Infection prevalence among HTLV-HIV Co-infected Patients 2001-2017.

Country	Type of HTLV	P (%)	Risk Factors	Authors	Year
Brazil	HTLV-1	4.7	Risk Factors not determined	Ferreira et al. [41]	2001
Brazil	HTLV-1/2	5	Tattooing P=0.035, alcohol abuse P=0.008, history of blood transfusion P=0.039	Galetto et al. [29]	2005
Brazil	HTLV-1/2	13.4	IDU P<0.01, HCV seropositivity P<0.01, non-white race P<0.01, Low level of education P<0.01	Etzet et al. [5]	2006
Brazil	HTLV-1/2	2.4	injecting cocaine(OR=5.2, P<0.001), older age (OR=1.7, P<0.001), HIV (OR=3, P<0.001)	Barcellos et al. [42]	2006
Brazil	HTLV-1/2	6.4	HCV (OR=22.6, P<0.05)	Morimoto et al. [43]	2006
Brazil	HTLV-1/2	3.11	female gender (OR=3.26, P<0.05), black/pardo race (OR=2.21, P<0.05), HCV (OR=24.4, P<0.05) IDU (OR=30.01 P<0.05)	Caterino de Araujo et al. [44]	2010
Nigeria	HTLV-1	4.9	Risk factors not determined	Nasir et al. [45]	2012
Brazil	HTLV-1/2	0.79	None of the factors were significant	Kozlowski et al. [11]	2014
Mexico	HTLV-2	12.5	Candidiasis p=0.0004, AIDS P=0.02	Castro Sansores et al. [46]	2015
Mozambique	HTLV-1	4.5	Risk factors not determined	Bhatt et al. [47]	2015
Brazil	HTLV-2	9.7	HCV P=0.006, Male gender P=0.03, IDU P=0.0005	Posada et al. [48]	2016
Kenya	HTLV-1	19.5	HIV P<0.01, Smoking p<0.01, high number of marriages p<0.01, high number of sexual partners p<0.05	He et al. [9]	2016
Mozambique	HTLV-1/2	1.55	Female gender	Augusto et al. [49]	2017
Mozambique	HTLV-1	3.9	Risk factors not determined	Ivan et al. [50]	2017
Brazil	HTLV-1/2	4.2	Risk factors not determined	Campos et al. [51]	2017

HTLV testing was done using enzyme linked immunosorbent assay (ELISA) followed by confirmation with western blot in all studies except the study by Galetto et al. [29], and He et al and Ivan et al which used PCR polymerase Chain Reaction and Campos et al which used INNO-LIA, Western Blot and PCR, IDU-intravenous drug use, HCV-Hepatitis C virus, HIV-Human Immunodeficiency Virus

HTLV-1/HIV co-infection decreased from 4.7% in 2001 to 3.9% in 2017. The highest and lowest co-infection prevalence of 19.5% and 0.79% were recorded in Kenya and Brazil respectively. An increased HTLV/HIV co-infection among patients suggests involvement in high risk behaviors such as unprotected sex, multiple sex partners and high risk injection behaviors which aggravate the risk of infection. In addition, HIV infection increases the risk of HTLV transmission due to similar modes of transmission and tropism towards CD4 and CD8 T-Cells. Decreased co-infection prevalence could be due to establishment of harm reduction measures such as provision of free needles and syringes, education awareness, provision of condoms and HIV testing and counseling which play a major role in mitigating spread of the virus among the HIV-positive patients.

In Africa, Kenya had the highest prevalence of 19.5% followed by Nigeria and Mozambique with 4.9% and 4.5% respectively [9,36,37]. Africa is considered to be a large reservoir for HTLV-1 infection. The fact that the highest co-infection prevalence was documented in Kenya reinforces the finding that Kenya may be endemic for HTLV-1. This further confirms the association between HTLV-1 and HIV since HIV increases the risk of acquiring HTLV [9]. In Brazil, HTLV-1/2 Seroprevalence is relatively high in HIV- positive patients and according to the Brazilian regions that analyzed these rates; it is documented that they could reach 20% in some studies [29]. This explains why majority of the studies are conducted in Brazil for continuous monitoring of the prevalence rates.

The public health system in Brazil provides prevention programs as well as free and universal access to antiretroviral treatment for HIV/ AIDS [11]. This could account for the lowest prevalence documented in Brazil. Socio-demographic factors significantly associated with HTLV/HIV co-infection include older age, low level of education and non-white race. Significant risk factors for HTLV-HIV co-infection among Patients included; tattooing, alcohol abuse, history of blood transfusion, injecting cocaine, smoking, high number of marriages and high number of sexual partners. Infections such as HIV, HCV and candidiasis were also significantly associated with HTLV/HIV co-infection among hospital-based patients.

Trends in the Global prevalence of HTLV among PWIDs

A total of 29 studies that had analyzed HTLV infection among PWIDs were selected. The studies were summarized according to country, HTLV virus tested and risk factors analyzed as summarized in (Table 3). Majority (38%) of the studies were done in USA. There were two studies each from El Salvador, Argentina, Italy, Sweden and Spain. There was one study each from the following countries; Scotland, Mexico, Brazil, Indonesia, Iran and Estonia. Out of 29 studies, 4 studies analyzed HTLV-1 among PWIDs, 11 analyzed HTLV-2 among PWIDs and 14 analyzed HTLV-1/2 among PWIDs.

Twenty two studies analyzed risk factors associated with HTLV infection among PWIDs. Over time, there was a general increase in HTLV-1 prevalence from 6.6 % in 1988 to 52% in 2004 [38,39]. There was a general decrease in HTLV-2 prevalence from 10.7% in 1989 to 3.2% in 2011 [40,41]. There was also a decrease in HTLV-

1/2 prevalence from 12.2% in 1990 to 0.3% in 2016 [7,32]. From USA, there were six studies each on HTLV-2 and HTLV-1/2. There was also a general increase in HTLV-2 prevalence unlike HTLV-1/2 where there was a decrease.

The highest documented prevalence of HTLV among PWIDs was 52% from Iran [39]. This could possibly be due to the increasing rate of addiction and injection drug use in Iran together with risky behaviors such as needle sharing, front loading, tattooing and multiple sexual partners [39]. The lowest prevalence recorded was 0.0% from Scotland. This could be explained by free needles and syringes which were made available to the PWIDs thus reduced needle sharing [42].

Estonia recorded a low prevalence of 0.3% [7]. This might be explained by three reasons. First, there are very few immigrants from HTLV-1/HTLV-2 endemic regions living in Estonia. Second, the PWIDs population in Estonia is relatively closed. Third, the studied PWIDs were relatively young (25-34) whereas HTLV causes lifelong infection and the prevalence is usually higher among older people [7]. The fact that HTLV-2 studies were only done in USA and Sweden supports the view that HTLV-2 is more frequent among (PWIDs) in United States and Europe [19]. This could also account for the majority of HTLV studies on PWIDs being done in USA.

Socio- demographic risk factors significantly associated with prevalent HTLV infection among PWIDs included increasing age, female gender, black race, Mexican American race and African-American race [21,32,33,43-45]. Injection related risk factors included needle sharing, longer duration of PWID, speed balling, tattoo, injecting opiates, frontloading and back loading [4,38,39,46,47]. Sexual risk factors included commercial sex and sexual promiscuity [38,46]. Prior history of HIV-1, HBV (Hepatitis B virus), HCV (Hepatitis C virus) and Syphilis infection was also significantly associated with HTLV seropositivity among PWIDs [4,23,44,45].

Analysis of HTLV Subtypes present among HTLV mono-infected PWIDs and HTLV-HIV co-infected PWIDs and Hospital based patients

Thirteen studies on HTLV subtypes were retrieved (Table 4). Only those studies on HTLV subtypes that focused on HTLV infected PWIDs, HTLV-HIV co-infected patients and HTLV-HIV co-infected PWIDs were selected for review. A total of eleven studies evaluated HTLV-2 subtypes: one was on HTLV-1 and two were on HTLV-1/2 subtypes. Only one study from USA that focused on HTLV infected PWIDs determined risk factors associated with HTLV-2a subtype. These included older age and black and white race [48]. HTLV-2 subtypes identified among HTLV/HIV co-infected PWIDs included HTLV-2a and HTLV-2b while HTLV-2a, 2b and 2c were identified among HTLV/HIV co-infected patients. HTLV 2a and 2b were identified among HTLV-2 infected PWIDs. HTLV-1 subtype a subgroup A (cosmopolitan) was identified among HTLV-HIV co-infected patients in Brazil. Prevalence of HTLV-2a and 2b subtypes among PWIDs in North America, South America and Europe reinforces the theory that HTLV-2a and 2b subtypes are endemic among PWIDs in the Americas and Europe [19].

Table 3: Summary of HTLV prevalence among PWIDs 1988-2016.

Country	Type of HTLV	P (%)	Risk Factors	Authors	Year
Italy	HTLV-1	6.6	sexual promiscuity (OR=5.3, 95% CI 1.2-22.3), needle sharing (OR=31.9, 95% CI 1.03-64.9)	Titti et al. [52]	1988
USA	HTLV-2	10.7	Risk factors not determined	Ehrlich et al. [53]	1989
USA	HTLV-1/2	12.2	Black race p<0.05, Older age p<0.01	Lee et al. [31]	1990
Egypt	HTLV-1`	0.7	None significant	Constantine et al. [54]	1991
USA	HTLV-1/2	16.8	black race p<0.0001, increasing age, longer duration of IDU older age p<0.0001	Lentino et al. [21]	1991
USA	HTLV-2	11.5	increasing age P<0.001, female gender P<0.001, Black race P<0.001	Cantor et al. [32]	1991
USA	HTLV-2	8	Older age P<0.01	Khabbaz et al. [55]	1991
Italy	HTLV-1/2	4	HIV-1 seropositivity P<0.002, increasing age P<0.001 longer duration of IDU P<0.05	Zanetti et al. [56]	1992
Mexico	HTLV-1/2	21	None significant	Guerena-Burgueno et al. [57]	1992
USA	HTLV-1/2	1.7	Risk factors not determined	Palumbo et al. [58]	1992
Sweden	HTLV-2	3.2	HIV infection p<0.05, HAV infection p<0.05, age p<0.05 injecting opiates p<0.05 longer duration of IDU p<0.05,	Krook et al. [59]	1994
Italy	HTLV-2	1.6	Risk factors not determined	Giacomo et al. [34]	1995
Spain	HTLV-1/2	2.5	Risk factors not determined	Henrard et al. [60]	1995
USA	HTLV-2	15.1	older age p<0.001, female gender p<0.001, black race p<0.001	Briggs et al. [33]	1995
USA	HTLV-2	10.2	Back loading (OR=6.52, 95% C1 1.94-21.95),Female gender (OR=5.77, 95% C1 1.33-25.05) commercial sex (OR=3.36, 95% CI 1.32-8.57)	Vhalov et al. [61]	1995
USA	HTLV-1/2	19.3	Age p<0.05	Freeman et al. [62]	1995
Brazil	HTLV-1	35.2	needle sharing (OR=7.94, 95% C1 1.32-47.6), duration of IDU(OR=3.30, 95% C1 1.60-6.80) HIV-1 infection (OR=7.52, 95% C1 2.61-12.34), syphilis (OR=5.68, 95% C1 2.61-12.34)	Dourado et al. [63]	1999
El Salvador	HTLV-1/2	16.6	Risk factors not determined	Guimaraes et al. [37]	2001
Scotland	HTLV-1/2	0	Risk factors not determined	McIntyre et al. [64]	2001
Argentina	HTLV-1/2	16.8	None significant	Wessein bacher et al.[65]	2003
USA	HTLV-2	21	None significant	Trachtenberg et al. [66]	2004
Iran	HTLV-1	52	needle sharing 49%, frontloading 20%, Tattoo 57%	Rahbar-Rowhani et al. [67]	2004
USA	HTLV-2	7.4	Speed balling (OR=1.79, P<0.001), female gender (OR=3.17, P<0.001),African-American race (OR=8.80, P<0.001), longer duration of IDU (OR=3.7, P<0.001), HBV Infection (OR=2.58, P<0.001) HCV infection (OR=12.76, P<0.001)	Zunt et al. [4]	2004
Spain	HTLV-2	2.8	HIV-1 seropositivity (OR=5.7, 95% CI 2.2-14.8), injected in last 30 days,(OR=6.5, 95% CI 1.4-29.8)	Fluente et al. [68]	2006
Argentina	HTLV-1/2	19.1	Young age (OR=10.7 P=0.004), Low education level (OR=6.7 P=0.048)	Berini et al. [22]	2007
El Salvador	HTLV-1/2	4	None significant	Nunes et al. [69]	2007

Sweden	HTLV-2	3.2	Risk factors not determined	Malm et al. [70]	2011
Indonesia	HTLV-1/2	3.7	None significant	prasetyo et al. [71]	2013
Estonia	HTLV-1/2	0.3	Risk factors not determined	Jogeda et al. [7]	2016

HTLV testing was done using enzyme linked immunosorbent assay (ELISA) followed by confirmation with western blot in all studies except the study by Jogeda et al. [7] which used PCR-polymerase chain reaction. The study by Guereña-Burqueno et al. [57] and Ehrlich et al. [53] used RIA-radioimmunoassay and PA-particle agglutination in addition to Elisa and WB, HAV-hepatitis A virus, HBV-hepatitis B virus, HIV-1-Human immunodeficiency virus type 1, IDU-intravenous drug use, OR-odds ratio

Table 4: HTLV subtypes among different populations 1995-2016.

Country	Population	Type of HTLV	Sub Types	Authors	Year
Italy	HTLV infected IDUs	HTLV-2	HTLV-2a, HTLV-2b	Salemi et al. [72]	1995
USA	HTLV infected IDUs	HTLV-2	HTLV-2a	Murphy et al.[73]	1998
Portugal	HTLV-HIV Co-infected IDUs	HTLV-2	HTLV-2b	Silva et al. [38]	1998
Europe	HTLV infected IDUs	HTLV-2	HTLV-2a,HTLV-2b	Salemi et al. [20]	1998
Brazil	HTLV infected IDUs	HTLV-2	HTLV-2a	Alcantara et al. [74]	2003
Ireland	HTLV-HIV Co-infected IDUs	HTLV-2	HTLV-2a	Egan et al. [36]	2004
Spain	HTLV infected IDUs	HTLV-2	HTLV-2b	Toro et al. [75]	2005
Brazil	HTLV-HIV Co-infected patients	HTLV-1/2	HTLV-1a subgroup a, HTLV-2c	laurentino et al. [76]	2005
Argentina	HTLV-HIV Co-infected IDUs	HTLV-2	HTLV-2a, HTLV-2b	Berini et al. [23]	2007
Brazil	HTLV-HIV Co-infected patients	HTLV-1/2	HTLV-1a subgroup A, HTLV-2c	Rego et al. [18]	2010
Spain	HTLV-HIV Co-infected IDUs	HTLV-2	HTLV-2b	Abad et al. [77]	2011
Brazil	HTLV-HIV Co-infected patients	HTLV-2	HTLV-2a, HTLV-2b, 2c	Magri et al. [19]	2013
Indonesia	HTLV-HIV Co-infected patients	HTLV-2	HTLV-2a	Prasetyo et al. [71]	2013
Brazil	HTLV-HIV Co-infected patients	HTLV-1	HTLV-1a subgroup A	Kozłowski et al. [11]	2016

IDUs-intravenous drug users OR-Odds Ratio CI-Confidence interval

Since HTLV subtypes are geographically dispersed, subtypes were analyzed according to the resident country. From Brazil, subtypes identified included HTLV-2a and 2b both from HTLV-infected and HTLV-HIV co-infected PWIDs. HTLV-1a cosmopolitan and HTLV-2c were also identified from HTLV-HIV co infected patients in Brazil. HTLV-2a is the most predominant subtype subtype in Brazil [23]. The finding of subtype 2a among PWIDs by clearly indicates that these PWIDs had little interaction with individuals or blood products from other geographic areas and also with PWIDs co-infected with HIV/HTLV-2 outside Brazil [49]. HTLV-2b in Brazilian States indicates spread of this subtype from the state of Rio Grande do Sul where this subtype is prevalent [19]. HTLV-1a subgroup A (transcontinental) is in agreement with studies reported in HIV1-infected patients in Brazil in whom this HTLV1 subgroup is predominant [11].

Recent studies suggest that the introduction of the transcontinental subgroup is probably the result of the Bantu population's migration over the last 3000 years from Central Africa to Southern Africa, then eventually to the State of Bahia [18]. Data from Brazil indicate that the HTLV-2c molecular variant was formerly present in native Indian tribes with posterior dissemination to the urban population of Brazil. Possibly this

occurred through inter-ethnic contact by sexual intercourse and is maintained in Indians mostly by breast feeding [19]. From Argentina, HTLV-2a and 2b subtypes have been reported among HTLV-HIV co-infected PWIDs. HTLV-2b is the major strain circulating in an urban population of Argentina. Its presence may be due to the increasing internal migration of aborigines from the northeast region where subtype 2b is endemic to large urban centers [23].

HTLV-2a could have been introduced from endemic South American countries such as Brazil and because of contact with other populations such as PWIDs from Europe through migration and tourism [50]. HTLV-2a in Indonesia could have been introduced from USA where the subtype is common since the isolates resembled the USA subtype a [51]. HTLV-2a and 2b subtypes were identified from Portugal, Italy, Spain and Ireland (Europe) among HTLV-infected and HTLV-HIV co-infected PWIDs. HTLV-2b is the prevalent subtype in Western Europe (Italy, Spain and Portugal) where co-infection with HIV-1 is frequent. HTLV-2a is the main circulating variant in North America and Eastern Europe-Ireland [52-79]. HTLV-2a from Italy implies introduction from Brazil, North America or Eastern Europe where the subtype is predominant.

Conclusion

This review has focused on prevalence, risk factors and subtypes among HTLV-HIV positive PWIDs, HIV positive patients and HTLV positive PWIDs. The prevalence varied between and within countries and population groups. Concerning HTLV-HIV co-infection among PWIDs, there has been a general decrease in prevalence over time. The highest documented prevalence was 16% from USA while the lowest was 0.51% from Portugal among HTLV-HIV co-infected PWIDs. Both HTLV-2/HIV and HTLV-1/HIV co-infection among HIV positive patients showed a decreasing trend over years. The highest HTLV-HIV co-infection prevalence among HIV infected patients was 19.3% from Kenya while the lowest was 0.79% from Brazil. There was a general decrease in HTLV-2 infection among PWIDs unlike HTLV-1 where an increase was observed.

Highest and lowest HTLV prevalence among PWIDs were 52% and 0.0% from Iran and Scotland respectively. Majority of the studies focused on HTLV-HIV co-infected and HTLV infected PWIDs were from USA. HTLV subtypes are geographically dispersed and an introduction of a new subtype to a particular geographical region indicates contact through immigration or tourists. Older age and black race were the main risk factors for HTLV-HIV co-infection among PWIDs, HIV positive patients and HTLV infected PWIDs. Other socio-demographic, injection and sexually related factors varied from one study to another.

Recommendations

The epidemic of HTLV-HIV co-infections among PWIDs and HIV positive patients constitutes a major public health problem and should be addressed to prevent further spread in the community. Harm reduction measures such as provision of free needles and syringes, HIV counseling and treatment coupled with educational programmes could be explored. Regular serological testing of HTLV-1/2 should be introduced among HIV-infected PWIDs especially in clinical settings where PWID is a major mode of HIV transmission. Frequent HTLV-HIV testing will assist in continuous monitoring of the prevalence rates. More research on HTLV infection is imperative for generating data on prevalence, elaborate public policies on educational and prophylactic measures, increase the awareness of the infection and reduce the viral transmission and infection-related disease.

Acknowledgment

None.

Conflict of Interest

None.

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