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Review

Sex, Age, and Risk Group Variations among Individuals Infected with HIV, HTLV-1, and HTLV-2: Review of Data Records (1983–2017) from a Public Health Laboratory in São Paulo, Brazil

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Abstract: The inaugural AIDS Program in Brazil was established in São Paulo in 1983, with the Instituto Adolfo Lutz appointed for laboratory assistance. Subsequently, research on HIV infections and HIV/HTLV (HIV/HTLV-1 and HIV/HTLV-2) co-infections was conducted. This narrative review focuses on studies from the Immunology Department (1983–2017) that significantly influenced AIDS diagnosis or provided epidemiological data such as prevalence rates, sex, age, and risk factors. Twelve studies, encompassing over 8000 individuals, are discussed. During 1983–1985, nearly all AIDS cases were attributed to homosexual/bisexual men aged 31 years old. Subsequently, heterosexual men and women emerged as risk groups owing to intravenous drug use (IDU) and/or unprotected sexual intercourse with AIDS patients or multiple partners per year. From 1985 onwards, vertical transmission led to child infections. HIV/HTLV co-infection rates decreased over time, initially associated with male IDU, and in the 2010s with female IDU, and individuals aged >40 years. Trends in HIV and HIV/HTLV co-infections among younger men and women (<30 years of age) were observed from 2015 to 2017. The changing characteristics and risk groups for HIV and HIV/HTLV co-infections over the years underscore the necessity for ongoing public policies to prevent retrovirus transmission, particularly among adolescents and young adults.

Keywords: HIV; HTLV-1; HTLV-2; sex; risk factors; prevalence; co-infection; public policies

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1. Introduction

In June 1983, a group of homosexual intellectual men visited the Secretary of Health of the State of São Paulo, to request containment measures against a disease that had been reported in the United States of America (USA) and was beginning to emerge in Brazil [1] (p. 18). This disease was characterised by profound immunosuppression due to a decrease in the number of lymphocytes, mainly the CD4+ T helper lymphocytes (former T4). The initial cases were reported in homosexual men in 1981, followed by reports in heterosexual men who were intravenous drug abusers (of heroin), haemophiliacs, and Haitians [2–6]. Considering the epidemiological bulletins from the Centre for Disease Control and Prevention (CDC) in Atlanta, USA, which showed the widespread nature of the disease, it was termed Acquired Immunodeficiency Syndrome [6]. The acronym was officially adopted in the second half of 1982.

In São Paulo, Brazil, the Secretary of Health approved the first AIDS Program on 25 July 1983 [1] (p. 54) and designated the Instituto de Saúde as coordinator and the Public Health Laboratory—Instituto Adolfo Lutz (IAL) as the reference for laboratory support [1] (p. 55). The implementation of the AIDS Program took place in August 1983 [1] (p. 57), and the Immunology Department of IAL was tasked with analysing the cellular immune profile of suspected AIDS cases [1] (p. 58). During this time, the etiological agent of AIDS had not yet been identified. The serology for the human immunodeficiency virus became

available in Brazil by the end of 1985 and was made mandatory in São Paulo's blood banks in 1986 (Law No. 5190, dated 20 June 1986).

In 1980, a team led by Professor Robert Gallo in the USA discovered the first human T-lymphotropic retrovirus in patients suffering from leukaemia/lymphoma. They named this virus human T-cell leukaemia virus I (HTLV-I) [7]. Two years later, in 1982, the same team identified the second human retrovirus, HTLV-II, from a single case of hairy cell lymphoma [8].

In 1983, Françoise Barré-Sinoussi, a member of a research team led by Professor Luc Montagnier in France, isolated the first T-lymphotropic retrovirus from an AIDS-risk patient. The techniques used for this isolation were similar to those utilised for the detection of HTLV-I and HTLV-II. The patient, a homosexual man, presented with multiple lymphadenopathies, and the virus was isolated from his lymph node. This virus was subsequently named the lymphadenopathy associated virus (LAV) [9].

In 1984, Gallos' team documented the identification, isolation, and ongoing propagation of cytopathic retroviruses (HTLV family) derived from the peripheral blood lymphocytes of numerous AIDS and pre-AIDS patients. These retroviruses were designated as HTLV-III, marking them as the third identified human retrovirus [10,11]. It was later established that LAV and HTLV-III were indeed the same retrovirus linked to AIDS. Consequently, in 1986, it was renamed as the human immunodeficiency virus (HIV).

Significantly, a consensus on the nomenclature of the HTLV family remains elusive. However, the prevalent and recommended terminology is 'human T-lymphotropic virus' followed by an Arabic numeral, such as HTLV-1 and HTLV-2 [12].

HIV, HTLV-1, and HTLV-2 share transmission routes, leading to co-infections that could influence the progression of associated diseases [13–16]. Distinct differences in endemic regions, risk factors and risk groups, and pathogenicity between HTLV-1 and HTLV-2 have been documented [17–22]. For example, HTLV-1 is endemic in Southwestern Japan, sub-Saharan Africa, South America (primarily Brazil), the Caribbean, and specific areas in the Middle East and Australo-Melanesia. It is linked to high morbidity and mortality owing to adult T-cell leukaemia/lymphoma, HTLV-1-associated myelopathy (HAM), and other inflammatory disorders [17,18,21]. Conversely, HTLV-2 is hyperendemic among Amazonian Indians in Brazil, certain African pygmy tribes, and intravenous drug users (IDUs) in urban areas of the USA, Europe, and Latin America, including Brazil [19–22]. Unlike HTLV-1, HTLV-2 has not been associated with a specific disease, although sporadic cases of neurological disorders similar to HAM have been reported [21,22].

The Immunology Department at IAL began its research on HIV/AIDS in 1983, focusing on cellular immunity, diagnosis, and monitoring in both adults and children. In 1991, IAL launched studies on HIV/HTLV-1 and HIV/HTLV-2 co-infections, aiming to determine prevalence rates, affected sex, age, and risk groups susceptible to these retroviruses. This paper presented the most significant studies conducted from 1983 to 2017, discussed potential factors contributing to epidemiological changes, and suggested public policies necessary for controlling and preventing the transmission of these retroviruses.

2. Materials and Methods

2.1. Study Design and Works Selection Criteria

This narrative review displays significant studies conducted by the Immunology Department of IAL from 1983 to 2017, which have left a mark on the history of HIV/AIDS in São Paulo, Brazil. The review included studies that provide epidemiological data on the overall prevalence rates of HIV/HTLV co-infections, segmented by sex, age, and risk groups associated with the acquirement of these retroviruses at specific points in time. Furthermore, it offers a comparative analysis of these epidemiological data over the years and discusses potential reasons for observed changes in the characteristics of infected individuals.

The inclusion criteria for selecting the studies were the following: having contributed to the diagnosis of AIDS at a time when its etiological agent was unknown and when the

polymerase chain reaction (PCR) assay for determining HIV RNA was not was available; studies of HIV/HTLV co-infections with the minimum sample size required for statistical analysis and peer-reviewed articles; studies in which the diagnosis of HIV/AIDS was made using tests that identify HIV-1 (Western blot, WB; line immunoassay, LIA and/or HIV-1 genotyping); studies in which HTLV-1 and HTLV-2 were detected via at least two screening assays and two confirmatory assays (WB, LIA and/or PCR). Studies that did not meet these criteria were excluded. It is worth mentioning that all documents from the Ministry of Health and most studies carried out in Brazil use the acronym HIV instead of HIV-1, considering that the AIDS epidemic in Brazil is due to HIV-1.

2.2. Data Presentation and Statistical Analysis

Data were collected from the articles incorporated in this study and the author's personal experience and archives. Tables were constructed and figures were displayed to aid in data visualisation and analysis. In terms of cellular immunity assessment, all leucocyte, lymphocyte, lymphocyte subpopulation counts, and lymphoproliferative responses to mitogens and antigens were presented as mean values. These were compared among groups using the Kruskal–Wallis variance analysis, supplemented with the Dunn multiple comparison test. Prevalence rates were determined via the total number of individuals with HIV/HTLV and separately with HIV/HTLV-1 and HIV/HTLV-2 co-infections at a specific point in time, divided by the total number of individuals examined. The Chi-square test was utilised for prevalence rate comparisons. A 5% level (p-value ≤ 0.05) was considered significant for all statistical analyses.

2.3. Ethics Approval

The IAL's Research Ethics Committee, and when required, the Ethics Committee of collaborating institutions granted approval for all primary studies discussed herein. The study adhered to the Declaration of Helsinki, with data presented in a blinded manner.

3. Results and Commentaries

3.1. Cellular Immune Profile in AIDS (1983–1985)

The Immunology Department at IAL conducted its inaugural study on AIDS, focusing on the cellular immune response in suspected cases. Briefly, between September 1983 and June 1985, 111 individuals who were part of the first AIDS Program in São Paulo, Brazil were referred to IAL for in vitro analyses of their cellular immune responses.

The counts of leucocytes, lymphocytes, T and B lymphocytes, as well as T4 (helper/inducer) and T8 (suppressor/cytotoxic) lymphocytes were ascertained. Subsequently, the T4/T8 ratio was computed. The lymphoproliferative response was also evaluated using T-cell mitogens (phytohaemagglutinin (PHA) and concanavalin A (Con-A), T-dependent B-cell mitogen (pokeweed mitogen (PWM)), and the tuberculin purified protein derivative (PPD) antigen. All laboratory tests were conducted in accordance with the standardisation of the Laboratory of Cellular Immunology and were performed blind, without knowledge of the demographic and clinical attributes of the study population.

At the end of 1985, we undertook a comparative analysis of our results with a CONTROL group. Collaborating with physicians from Instituto de Saúde, we accessed epidemiological and clinical data. Patients were categorised into three groups: RISK (n = 27), lymphadenopathy-associated syndrome/AIDS-related complex (LAS/ARC), n = 37), and AIDS (n = 47), based on the definitions provided by the CDC [6].

The RISK group comprised 23 homosexual/bisexual men and 4 heterosexual women, all of whom had contact with AIDS partners. The LAS/ARC (lymphadenopathy-associated syndrome/AIDS-related complex) group consisted of 36 homosexual/bisexual men and 1 heterosexual woman, all exhibiting persistent unexplained lymphadenopathy and other nonspecific clinical symptoms such as fever, malaise, diarrhoea, and weight loss. The AIDS group included patients suffering from opportunistic infections and/or Kaposi's sarcoma,

all of whom were homosexual/bisexual men. The CONTROL group included 11 lab staff members, consisting of 5 men and 6 women, all of whom were heterosexual.

No significant variation was found among the age groups, with a mean age of approximately 31 years. Regarding sex, it was not possible to perform a comparative analysis for each laboratory test due to the small number of women in each group. A comparison of the mean values for each laboratory test among the groups is presented in Table 1.

Table 1. Number of peripheral blood lymphocytes and values of lymphoproliferative response using PHA, Con-A, PWM mitogens, and PPD antigen in CONTROL, RISK, LAS/ARC, and AIDS groups.

	Groups			
	CONTROL (n = 11)	**RISK (n = 27)**	**LAS/ARC (n = 37)**	**AIDS (n = 47)**
Age (years)	30.4	30.7	31.9	30.8
Leucocytes/mm^3	5263.6	5955.6	5689.2	4763.8 *
Lymphocytes/mm^3	1967.6	2316.7	2264.2	1218.2 *
T lymphocyte (%)	64.0	64.8	62.2	52.1 *
T lymphocytes/mm^3	1247	1509.8	1403.9	662.3 *
B lymphocytes (%)	18.2	16.6	15.0	18.6
B lymphocytes/mm^3	397.3	362.7	307.6	214.4 *
T4 (%)	44.4	37.8	26.3	13.5 *
T4/mm^3	863	833.9	591.4	191.2 *
T8 (%)	21.6	26.6	37.3 *	39.0 *
T8/mm^3	451.9	620.2	797.6 *	550.7
T4/T8	2.3	1.6	0.74 *	0.53 *
PHA 20 μg/mL	255,979.7	233,381.8	175,852.9	118,450.1 *
Con-A 20 μg/mL	172,269.5	136,493.3	111,128.2	54,795.5 *
PWM 20 μg/mL	75,942.8	71,469.8	27,760.5	17,930.1 *
PPD 10 μg/mL	59,989.1	16,696.0	15,505.3 *	7098.8 *

The results for peripheral blood cells are presented as mean values of both percentage and absolute number. The lymphoproliferative response is expressed as mean counts per minute (cpm) following a 3-day culture with mitogens and a 7-day culture with PPD. Statistical significance was determined using the Kruskal–Wallis analysis of variance, supplemented by the Dunn multiple comparison test, with a significance level set at * $p \leq 0.05$.

The demographic and laboratory analyses led to the following conclusions: homosexual men constituted the population most affected by AIDS. The age group most impacted by the syndrome had a mean age of 31 years. The AIDS group exhibited leukopenia, lymphopenia, and a reduced count of T and B lymphocytes, a finding that was statistically significant when compared to other groups. A notable decrease in T4 lymphocytes was observed in the AIDS group, a difference that was statistically significant when compared to other groups. The count of suppressor/cytotoxic T lymphocytes (T8) was significantly higher in the AIDS and ARC groups, a difference that was statistically significant when compared to other groups. A significant inversion of the T4/T8 ratio was detected in the AIDS and ARC groups, a difference that was significant when compared to other groups. The AIDS group showed decreased lymphoproliferative responses to PHA, Con-A, and PWM mitogens compared to those in other groups and diminished lymphoproliferative responses to PPD antigen in the AIDS and ARC groups when compared to those in the CONTROL group. A characteristic cellular immunological profile was established for AIDS cases. These findings were first presented in the author's master's thesis on the cellular immune response in AIDS in Brazil and have since been published [23].

Significantly, the majority of these data were collected during a period when the aetiology of AIDS had yet to be determined and Brazil lacked access to HIV serological tests.

Following the publication, the Laboratory of Cellular Immunology sustained its support for the AIDS Program by quantifying CD4+ and CD8+ T cells until 1993. This 10-year period concluded when the immunofluorescence assay used for these analyses was outdated by flow cytometry, and the routine was transferred to another IAL laboratory.

Significantly, in 1995, the CD4+/CD8+ network was established across the state of São Paulo, with numerous laboratories participating under the coordination of IAL.

3.2. HIV Diagnosis in Children (1989–1993)

Following the emergence of AIDS in São Paulo, Brazil, the demographics of HIV-infected individuals moved. An increasing number of women contracted the virus through IDU and unprotected sexual encounters with multiple partners or those with AIDS, particularly during their peak years of sexual and reproductive activity. This trend raised concerns owing to the potential for vertical transmission of AIDS to children, a fear that was subsequently realised.

Maternal antibodies against HIV cross the placenta during pregnancy and can be identified in the offspring from birth until 18 months of age. Consequently, HIV serology is not applicable for diagnosing HIV in children within this age range. Furthermore, in 1989, the polymerase chain reaction (PCR) for detecting HIV-RNA was unavailable in Brazil. Therefore, an alternative method for perinatal HIV diagnosis in children was necessary.

Considering the literature that highlights the polyclonal activation of B lymphocytes in HIV infection [24], along with the spontaneous secretion of HIV antibodies in the supernatant of prolonged lymphocyte cultures [25], we developed an alternative method for use with children. This technique is referred to as in vitro-induced antibody production (IVIAP). Briefly, we developed and standardised an assay for detecting HIV-specific antibodies with high sensitivity and specificity using a 24 h culture of peripheral blood mononuclear cells (PBMC) and a commercial enzyme immune assay (EIA) kit (EIA-LAV Genetic Systems, Seattle, WA, USA). This kit contains disrupted inactivated whole virus adsorbed onto microwell plates as antigens (Figure 1). The assay can discriminate between antibodies present in plasma and those produced by B lymphocytes in both adults and children [26,27].

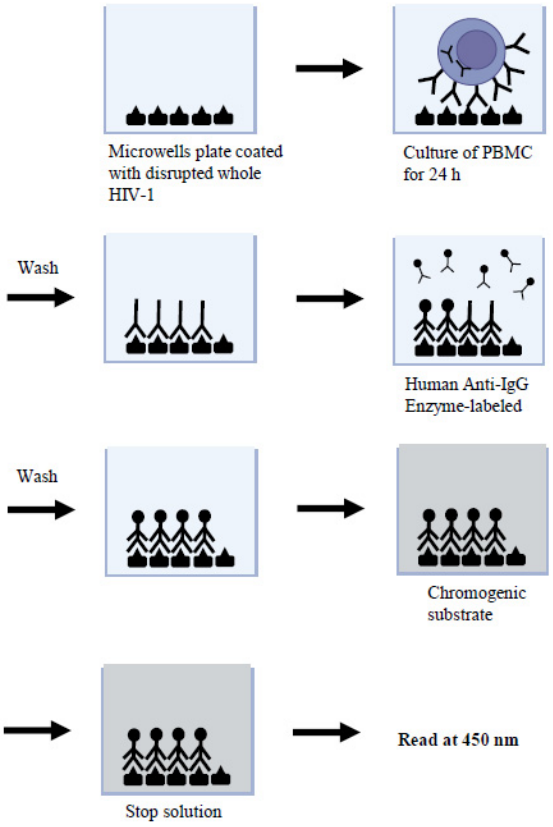


Figure 1. In vitro induced antibody production (IVIAP) steps for detecting the production of specific antibodies by B lymphocytes in HIV-1-infected individuals.

IVIAP was subsequently utilised in a 2-year follow-up study of 57 children born to HIV-infected mothers. False-positive results were detected in children aged <2 months. The sensitivity and specificity of IVIAP when used with children were 96% and 100%, respectively; false-negative results were detected in cases of hypogammaglobulinemia. With adults, the IVIAP sensitivity and specificity was 100%. The results confirmed its applicability in diagnosing children older than 2 months (data not published).

A comparative analysis of the IVIAP and PCR results, the latter conducted at Istituto di Oncologia, Università degli Studi di Padova, Padova, Italy, showed concordance with Kappa index of 0.94 (PhD Thesis from the author, 1993). Most importantly, IVIAP confirmed 30% of HIV-1 vertical transmissions at this point in time, in São Paulo, Brazil.

3.3. HIV/HTLV Co-Infections in Patients Attended by One Hospital of São Paulo (1991–1994)

In the 1990s, our research focused on identifying other human retroviruses (HTLV-1 and HTLV-2) in HIV patients referred to Instituto de Infectologia Emílio Ribas (IIER) in São Paulo, a hospital recognised as a reference centre for HIV/AIDS. Concurrently, studies in the USA and Europe reported cases of HIV/HTLV-2 co-infection linked to IDU [20,28,29]. In São Paulo, we identified both HIV/HTLV-1 and HIV/HTLV-2 co-infections, predominantly in white and mixed-race individuals associated with IDUs [30,31]. This observation is likely attributable to Brazil being an endemic country for HTLV-1 and HTLV-2 [17,18,21,22] and São Paulo's status as a cosmopolitan city attracting migrants and immigrants globally. In summary, the prevalence rate of HIV/HTLV co-infection in samples collected between 1991 and 1992 was 13.2% (7.9% for HIV/HTLV-1 and 5.3% for HIV/HTLV-2) (Table 2) [30], corroborating the prevalence rates detected at this point in time among IDUs from others parts of the world [29].

Table 2. Prevalence rates and demographic characteristics among HIV-1, and HIV-1/HTLV-1 and HIV-1/HTLV-2-co-infected individuals sampled from 1991 to 2016.

Year of Collection	Local/ Group	Number of Cases	Mean Age (Years)	Sex (Number)	HTLV-1/-2 (%)	HTLV-1 (%)	HTLV-2 (%)	Ref.
1991–1992	IIER, SP	471		M (406) F (65)	62 (13.2)	37 (7.9)	25 (5.3)	[30]
	IDU	216	29	M (155) F (61)	57 (26.4)	33 (15.3)	24 (11.1)	
	Homo/Bis	229	34	M (229)	3 (1.3)	2 (0.9)	1 (0.4)	
	Others [a]	26	30	M (22) F (4)	2 (7.7)	2 (7.7)		
1994	IIER, SP	553	32	M (358) F (195)	56 (10.1)	22 (4.0)	34 (6.1)	[31]
	IDU	89	29	M (65) F (24)	25 (28.0)	10 (11.2)	15 (16.8)	
	Hetero	236	33	M (96) F (140)	21 (8.9)	8 (3.4)	13 (5.5)	
	Homo/Bis	139	33	M (139)	5 (3.6)	2 (1.4)	3 (2.2)	
	Others/Unk [b]	89	32	M (58) F (31)	5 (5.6)	2 (2.2)	3 (3.4)	
2001–2002	CRTA-PR	758	36	M (424) F (334)	43 (5.7)	6 (0.8)	37 (4.9)	[32,33]
	Sexual	633			16 (2.5)	2 (0.3)	14 (2.2)	
	IDU	57			17 (29.8)	2 (3.5)	15 (26.3)	
	Sexual + IDU	33			7 (21.2)	1 (3.0)	6 (18.2)	
	Other [c]	35			3 (8.6)	1 (2.9)	2 (5.7)	
1999–2006	CRTAs, SP	1393		M (982) F (411)	81 (5.8)	46 (3.3)	35 (2.5)	[34]
	Clinics, SP	919		M (538) F (381)	121 (13.2)	88 (9.6)	33 (3.6)	
2014–2015	CRTA-SP	1608	44	M (1237) F (371)	50 (3.1)	26 (1.6)	22 (1.4)	[35]
2012–2015	CRTAs, SP	1383	36	M (930) F (453)	58 (4.2)	29 (2.1)	24 (1.7)	[36,37]

M, male; F, Female; [a] multiple transfusion (n = 7) and multiple partners (n = 19); [b] unknown risk (n = 83), blood transfusion (n = 6); [c] combined risk factors of blood transfusion and sexual contact (n = 28), tattooing (n = 5), work accidents (n = 1), and haemophilia (n = 1).

Samples collected from the same hospital two years later revealed a relatively low overall prevalence rate of 10.1%, with a higher frequency of HTLV-2 cases (Table 2) [31]. This outcome may be partially attributed to modifications in diagnostic techniques that have increased sensitivity for HTLV-2 detection [28,31]. This was later corroborated by subsequent studies conducted in the laboratory.

Significant findings from these studies revealed high HIV/HTLV prevalence rates among IDUs. In 1992, the prevalence rate was 26.4% (15.3% for HIV/HTLV-1 and 11.1% for HIV/HTLV-2), and in 1994, it increased to 28.0% (11.2% for HIV/HTLV-1 and 16.8% for HIV/HTLV-2) (Table 2) [30,31]. These data underscore the high risk of HTLV-1/-2 infections among this population in São Paulo.

In late 1999, we initiated a search for these co-infections among patients attended by different AIDS reference centres (acronym in Portuguese: CRTA) in São Paulo city and its surrounding areas (state of São Paulo, southeast region of Brazil), as well as in Londrina and its vicinities (state of Paraná, south region of Brazil). Despite the continued detection of HIV/HTLV-1 and HIV/HTLV-2 co-infections, there was a significant decrease in prevalence rates.

3.4. HIV/HTLV Co-Infections in Londrina, Paraná (2001–2002)

During 2001–2002 in Londrina and surrounding areas of Paraná, CRTAs primarily attended white, HIV-infected individuals of both sexes. A preliminary study identified a 6.5% co-infection rate of HIV/HTLV. This co-infection was associated with IDU, hepatitis C virus (HCV) infection, low socioeconomic status, and low educational attainment [32].

Using the Western blot (WB, HTLV Blot 2.4, Abbott Murex, Singapore) as a confirmatory serological assay, a large number of HTLV WB-indeterminate results were identified [32].

To address this problem, patients were asked to return for an additional blood sample collection. This was used for *in-house* PCR confirmatory assays, which amplified the LTR, *env*, and *tax* segments of the HTLV-1 and HTLV-2 genomes. The majority of WB-indeterminate cases were confirmed as HTLV-2 infections via these PCR assays [33]. Consequently, we determined the overall prevalence of HIV/HTLV to be 5.7% (0.8% for HIV/HTLV-1 and 4.9% for HIV/HTLV-2) (Table 2). Notably, and in line with the present data, problems with diagnostic tests for HTLV infections, mostly for HTLV-2, had been previously described in IDUs with AIDS [28,30,31,38].

Significantly, this study highlighted that female IDUs, as well as those with an IDU partner, constitute a critical risk group for acquiring HIV and HTLVs [32].

3.5. HIV/HTLV Co-Infections in Patients of Several CRTAs and Out-Patient Clinics of São Paulo (1999–2006)

Between December 1998 and March 2006, IAL received 2312 serum samples from São Paulo city and its surrounding areas for HTLV-1/-2 serology. Of these, 1393 were from various CRTAs (Group I, HIV-1 infected) and 919 were from HTLV out-patient clinics (Group II, patients treated in specialized health units of haematology, neurology, infectious diseases, and others). These samples were from individuals aged 21–50 years, with the majority falling within the 31- to 40-year age group.

Seven distinct EIA kits were employed for screening during the study period, with the WB (HTLV Blot 2.4) serving as the confirmatory assay. An analysis of samples tested using two EIA kits revealed that no single EIA kit was 100% effective in detecting all true HTLV-1 and HTLV-2 infections (WB positive), corroborating a previous description by other groups of researchers from São Paulo and Italy [28,38]. This underscores the necessity of using two EIA kits with different antigen compositions and formats in HTLV-at-risk populations in São Paulo. Furthermore, a significant number of WB-indeterminate results were confirmed. Overall, HTLV-1/-2 positivity was detected in 5.8% of Group I and 13.2% of Group II (Table 2). In addition, we conducted an analysis of the results, taking into account factors such as sex, age, and the public health units that provided the patients' samples to IAL. A brief overview reveals that both HTLV-1 and HTLV-2 were detected in both groups (Table 2). In the case of seropositive females, HTLV-2 was slightly more prevalent in Group I (HIV-infected, 54.5%), whereas HTLV-1 was more common in patients from Group II (HTLV out-patient clinics, 73.9%). This could be attributed to the fact that Group II individuals were more likely to present with HTLV-1 associated diseases. Male

patients in Group II exhibited a higher percentage of WB-indeterminate results. We found no correlation between HTLV serological results and age. Our temporal analyses revealed a significant number of HTLV WB-indeterminate samples, along with a wide range of WB-indeterminate profiles, many of which were associated with seroconversion to HTLV-1 or HTLV-2 [34].

Considering these findings and the substantial expense associated with the WB test, we emphasised the importance of enhancing serological screening and confirmatory tests for use in Brazil. We suggested PCR as an appropriate confirmatory and discriminatory assay for this geographical region.

3.6. HIV/HTLV Co-Infections in Patients of the Pioneer CRTA-SP (2014–2015)

We conducted a study between 2014 and 2015 to ascertain the prevalence rates and risk factors associated with HIV/HTLV co-infections in São Paulo.

We conducted a study using blood samples from 1608 patients at the pioneering CRTA in São Paulo, with the majority undergoing highly antiretroviral therapy (HAART). Our objective was to detect HTLV-1/2-specific antibodies. To achieve this, we used two EIA kits, namely EIA Murex HTLV-I + II (Diasorin) and Gold ELISA HTLV-I + II (REM). We also employed two immunoblotting methods, HTLV Blot 2.4 (MP Biomedicals) and INNO-LIA HTLV-I/II (Innogenetics). Owing to a high number of HTLV WB-indeterminate results, we incorporated an *in-house* real-time PCR assay to confirm the presence of HTLV-1 and HTLV-2 proviral DNA in blood cells.

The analysis of confirmatory assay results revealed a 3.1% prevalence rate of HTLV-1/-2, with 1.6% of cases being HTLV-1 and 1.4% of cases being HTLV-2 (Table 2). The median age for HIV/HTLV-co-infected individuals was found to be 50 years, compared to 44 years in the general population (p = 0.000). Factors associated with an increased risk of HIV/HTLV co-infection included being female, of black/*pardum* ethnicity, having concurrent HBV or HCV infections, and IDU [35], the same associated factors described elsewhere [29,39].

The relatively low prevalence of HIV/HTLV co-infections observed in São Paulo at this point can be partially attributed to initiatives that supply IDUs with sterile needles and syringes, such as the Harm Reduction Program. Additionally, shifts in drug consumption habits, specifically the transition from injecting cocaine to smoking crack cocaine, have also contributed to this reduced prevalence [40,41].

3.7. HIV and HIV/HTLV Co-Infection in Patients of Several CRTAs of São Paulo (2010–2016)

A study carried out in São Paulo examined the characteristics (sex and age) and prevalence rates of HTLV-1/-2 among 1715 HIV-1-infected individuals (1192 men and 523 women). These individuals received care at three AIDS service centres between 2010 and 2016, and their samples were forwarded to IAL for HTLV-1/-2 serology.

We first categorised the study population based on the year of sample collection, from 2010 to 2016, and further divided them by sex into five age groups: G1 (16–25 years), G2 (26–30 years), G3 (31–40 years), G4 (41–50 years), and G5 (>50 years). We observed an increase in HIV infections among men aged 16–25 years (10% in 2010 vs. 43% in 2015–2016), and similarly in the 26–30 years age group (10% in 2010 vs. 25% in 2015–2016). In the female population, although the percentages were lower, there was also an increase in HIV infections among those aged 16–25 years and 26–30 years (Figure 2).

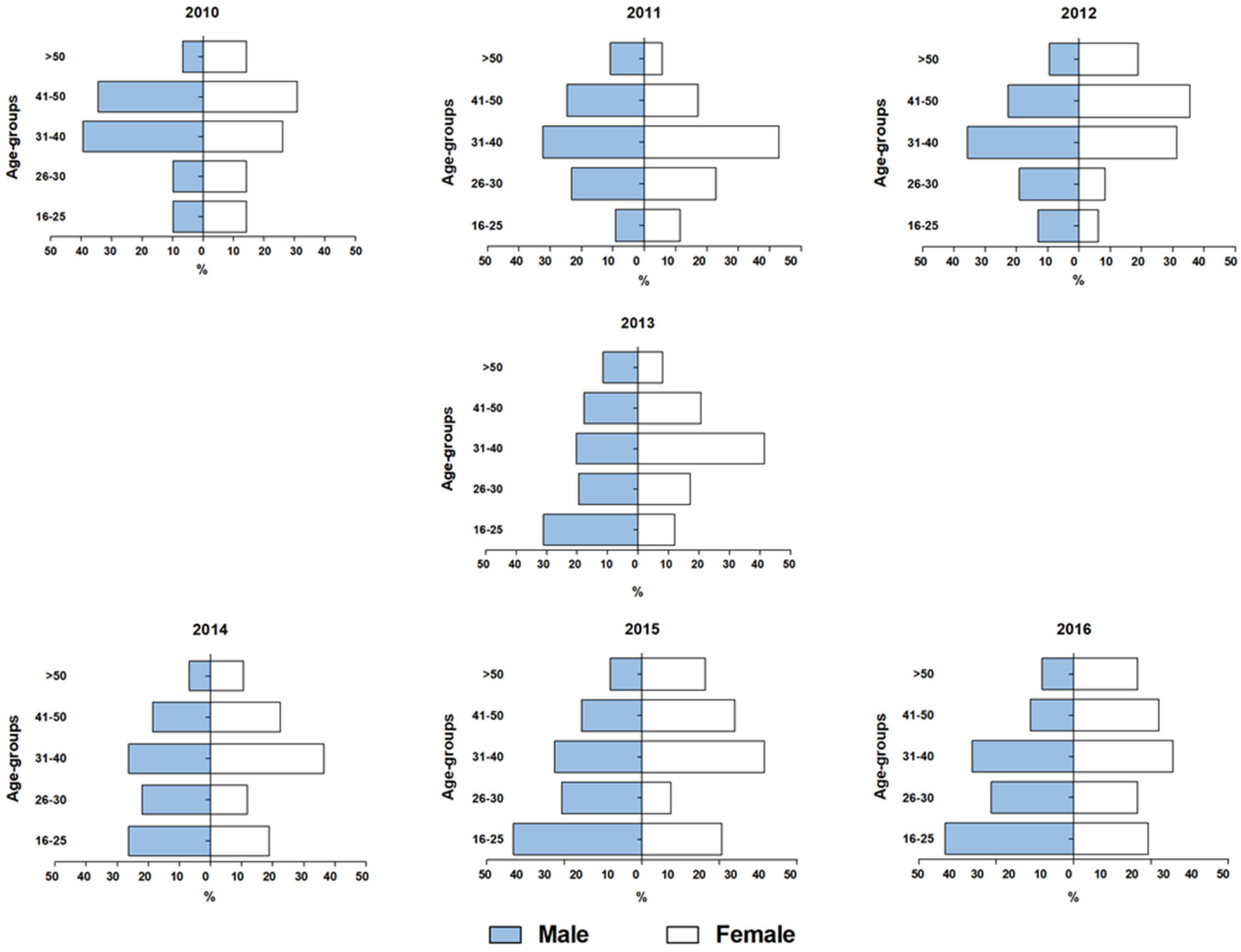


Figure 2. Distribution of the percentages of individuals infected with HIV-1 whose blood samples were sent to Instituto Adolfo Lutz, São Paulo, Brazil, for HTLV-1/-2 infection determination during 2010–2016, according to sex and age groups.

In the context of HIV/HTLV co-infection, 62 individuals (34 men and 28 women) confirmed co-infection; these comprised 33 individuals (18 men and 15 women) identified between 2010 and 2014 in the age group of >30 years (G3, G4 and G5), and 29 individuals (16 men and 13 women) identified between 2015 and 2016, 3 of which were in age groups under 30 years (1 in G1 and 2 in G2). As for HTLV-1/2 infections, the overall prevalence rate was 3.6% (2.0% among men, and 1.6% among women). Despite a higher number of HTLV-positive cases in men, a correlation with the female sex was observed (OR = 1.93, 1.12–3.30) [42]. Noteworthily, HTLV sexual transmission was identified as the main route of transmission from male to female [43]. In summary, the results of this study showed an increase in the number of cases of HIV infection and new cases of HIV/HTLV co-infection in individuals under 30 years of age in the years 2015–2016.

The rise in young individuals utilising AIDS care services in São Paulo corroborated data from the 2016 Epidemiological Bulletin of the Brazilian Ministry of Health. This data indicated an increase in AIDS notifications among individuals aged 15 to 34 years, with a male to female ratio of 2.4:1.0. Sexual exposure was identified as the primary risk factor. Furthermore, 50.4% of men reported homosexual activities; 36.8% reported heterosexual activities; and 9.0% reported bisexual activities. In contrast, 96.4% of women reported heterosexual contact [44].

3.8. HIV/HTLV Co-Infections in Recent CRTA Settings in São Paulo (2012–2015)

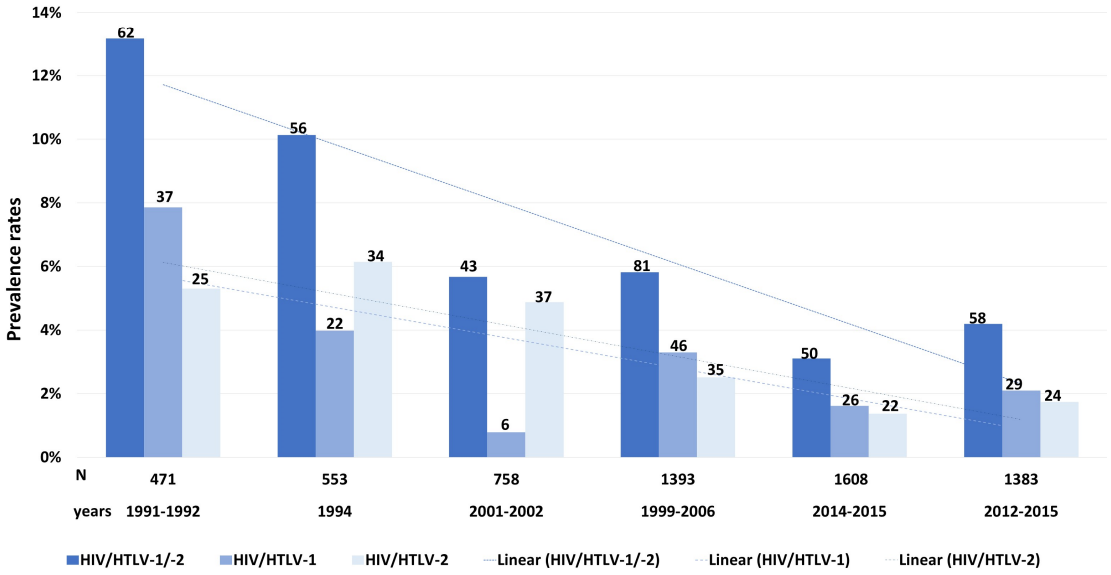
To corroborate and expand upon prior findings, we investigated the presence of HIV/HTLV co-infections in the latest HIV/AIDS service setting in São Paulo. We selected blood samples from 1382 HIV-1 infected individuals (930 men and 453 women; median age 35.6 years) for analysis. These individuals, who had recently contracted HIV through sexual contact and had not yet started HAART, provided the samples between 2012 and 2015.

Following HTLV screening with two EIAs, four confirmatory assays were performed: HTLV Blot 2.4, INNO-LIA, *in-house* qPCR, and PCR-RFLP. The performance of these assays was then comparatively analysed. The overall HIV/HTLV prevalence was 4.2% (2.1% for HTLV-1, 1.7% for HTLV-2, 0.1% for HTLV-1 + HTLV-2, and 0.3% for HTLV) (Table 2). An association between HTLV and women, as well as individuals aged >40 years, was identified [36], supporting the notion that repeated exposure is necessary for HTLV sexual transmission, which is more efficient from male to female [43]. The molecular assays demonstrated low sensitivity, while the LIA showed the best performance in detecting HTLV-1/-2 in these patients. We hypothesised that the negative PCR results might be attributable to the presence of defective provirus and/or low HTLV proviral load in these patients, and the inconclusive WB results could be associated with the seroconversion period [36]; noteworthily, these hypotheses were later confirmed via further studies performed in Japan [45] and in our laboratory.

In a following study, the performance of four HTLV-1/-2 confirmatory tests between two patient groups, those with long-term HIV infection on HAART [35] and those recently infected (HAART-naïve), was compared [36]. Our findings confirmed that LIA showed the best performance in detecting HTLV-1 and HTLV-2 in these patients [37]. Corroborating our findings, a collaborative study for the performance evaluation of HTLV-1 diagnostic assays in Japan established a novel test algorithm, leading LIA to replace the WB as the first confirmatory assay [46].

3.9. Variations in HIV/HTLV Co-Infection Prevalence Rates Regarding the Years of Sample Collection (1991–2015)

Figure 3 was constructed to aid in data visualisation and the statistical analysis of the overall prevalence rates of HIV/HTLV co-infections, as well as separate HIV/HTLV-1 and HIV/HTLV-2 co-infections, based on the years of blood sample collection. Briefly, bars and lines show an overall decline in the prevalence rates of HIV/HTLV co-infections over the time. In the context of HIV/HTLV co-infections, no significant differences were observed between the years 1991–1992 and 1994 ($p = 0.08332$), 2001–2002 and 1999–2006 ($p = 0.8859$), 2001–2002 and 2012–2015 ($p = 0.09996$), and 2014–2015 and 2012–2015 ($p = 0.1025$). However, all other comparative analyses revealed statistically significant differences (all $p < 0.05$) (Figure 3). These findings confirm the variations in HIV/HTLV prevalence rates between the 1990s (higher) and from 2000 onwards (lower). They also supported the period of observed changes in the transmission routes of such retroviruses, as well as shifts in risk factors, sex, and age of infected individuals in São Paulo and Brazil [35,40–42,44].



Chi–square test overall		*p* value	Chi–square test overall		*p* value	Chi–square test overall		*p* value
HIV/HTLV–1/–2		<0.0000001	HIV/HTLV–1		<0.0000001	HIV/HTLV–2		<0.0000001
Chi–square test two points in time	**p< 0.05?**	**Summary**	**Chi–square test two points in time**	**p< 0.05?**	**Summary**	**Chi–square test two points in time**	**p< 0.05?**	**Summary**
HIV/HTLV–1/–2			**HIV/HTLV–1**			**HIV/HTLV–2**		
1991–1992 vs. 1994	No	ns	1991–1992 vs. 1994	Yes	***	1991–1992 vs. 1994	No	ns
1991–1992 vs. 2001–2002	Yes	***	1991–1992 vs. 2001–2002	Yes	***	1991–1992 vs. 2001–2002	No	ns
1991–1992 vs. 1999–2006	Yes	***	1991–1992 vs. 1999–2006	Yes	***	1991–1992 vs. 1999–2006	Yes	***
1991–1992 vs. 2014–2015	Yes	***	1991–1992 vs. 2014–2015	Yes	***	1991–1992 vs. 2014–2015	Yes	***
1991–1992 vs. 2012–2015	Yes	***	1991–1992 vs. 2012–2015	Yes	***	1991–1992 vs. 2012–2015	Yes	***
1994 vs. 2001–2002	Yes	**	1994 vs. 2001–2002	***	***	1994 vs. 2001–2002	No	ns
1994 vs. 1999–2006	Yes	***	1994 vs. 1999–2006	No	ns	1994 vs. 1999–2006	Yes	***
1994 vs. 2014–2015	Yes	***	1994 vs. 2014–2015	Yes	***	1994 vs. 2014–2015	Yes	***
1994 vs. 2012–2015	Yes	***	1994 vs. 2012–2015	Yes	***	1994 vs. 2012–2015	Yes	***
2001–2002 vs. 1999–2006	No	ns	2001–2002 vs. 1999–2006	Yes	***	2001–2002 vs. 1999–2006	Yes	***
2001–2002 vs. 2014–2015	Yes	**	2001–2002 vs. 2014–2015	No	ns	2001–2002 vs. 2014–2015	Yes	***
2001–2002 vs. 2012–2015	No	ns	2001–2002 vs. 2012–2015	Yes	*	2001–2002 vs. 2012–2015	Yes	***
1999–2006 vs. 2014–2015	Yes	***	1999–2006 vs. 2014–2015	Yes	***	1999–2006 vs. 2014–2015	Yes	**
1999–2006 vs. 2012–2015	Yes	**	1999–2006 vs. 2012–2015	Yes	*	1999–2006 vs. 2012–2015	No	ns
2014–2015 vs. 2012–2015	No	ns	2014–2015 vs. 2012–2015	No	ns	2014–2015 vs. 2012–2015	No	ns

Figure 3. Comparative analyses of the prevalence rates of HIV/HTLV-1/-2 and HIV/HTLV-1 and HIV/HTLV-2-co-infected individuals sampled from 1991 to 2015. The bars denote the prevalence rates determined by the number of individuals with HIV/HTLV co-infections (numbers above the bars) divided by the total number of individuals examined (numbers below the bars). The lines show the decline in HTLV prevalence rates. Differences that are statistically significant are depicted using the Chi-square test. *p*-values depicted as asterisks correspond to * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$, ns. not significant.

In the context of HIV/HTLV-1 co-infection, no significant differences were observed between 1994 and 1999–2006 ($p = 0.2754$), 2001–2002 and 2014–2015 ($p = 0.1422$), and 2014–2015 and 2012–2015 ($p = 0.3037$). All other comparisons revealed significant differences (all $p < 0.05$) (Figure 3). The lowest prevalence of HIV/HTLV-1 was found in the cohort sampled in 2001–2002. This observation could be partially attributed to the fact that the state of Paraná is not an endemic region for HTLV-1 infection in Brazil [47] (pp.51–54), joined with the high proportion of IDUs in the population that is more susceptible to HTLV-2 infection [21,32,33]. In fact, the prevalence rate of 4.9% of HIV/HTLV-2 co-infection was identified in this patient cohort in the 2000s. With respect to the prevalence rates

of all HIV/HTLV-2 co-infections, no significant differences were found between groups in 1991–1992 vs. 1994 (p = 0.8040), 1991–1992 vs. 2001–2002 (p = 0.3151), 1994 vs. 2001–2002 (p = 0.1685), 1999–2006 vs. 2012–2015 (p = 0.1236), and 2014–2015 vs. 2012–2015 (p = 0.3838). All other comparisons yielded $p < 0.05$ Table 3**.** Prevalence rates of HIV/HTLV-co-infected individuals, and individually HIV/05 (Figure 3). The observed decline in prevalence rates results could be attributed in part to changes in drug usage patterns and a decrease in the number of IDUs involving shared infected needles and syringes [40,41], joint with education programs to prevent HIV transmission/acquisition and free access to antiretroviral treatment.

Table 3. HTLV-1- and HIV/HTLV-2-infected individuals from different regions of Brazil at different points in time.

Location	Year of Collection	Number of Samples	HIV/HTLV (%)	HIV/HTLV-1 (%)	HIV/HTLV-2 (%)	Risk Factors/ Associations	Ref.
North							
Belém, Pará	1994–1996	149	7.4	2.7	4.7	Homosexual/bisexual men, IDU	[48]
Belém, Pará	2005	117	5.1	1.7	3.4	Unknown	[49]
Belém, Pará	2016–2017	368	1.4	1.4	0	Female, sexual contact, sporadic condom use	[50]
Northeast							
Salvador, Bahia	1994–1995	123	20.3	17.1	3.2	IDU	[51]
State of Bahia	2004–2013	1733	2.4	2.1	0.3	Female, sexual contact, from Salvador	[52]
State of Piauí	2012	805	1.6	1.1	0.5	Blood transfusion, surgeries, >40 years	[53]
João Pessoa, Paraíba	2015	401	1.5	1.5	0	None	[54]
Southeast							
Santos, São Paulo	1997–1998	499	13.4	6.0	7.4	Male, IDU, HCV, no condom use	[55]
Ribeirão Preto and São Paulo, São Paulo	2001	319	4.7	0.6	4.1	IDU, HCV	[56]
South							
Porto Alegre, Rio Grande do Sul	1996	2985	2.4	1.4	1.0	IDU, >30 years	[57]
Canoas, Rio Grande do Sul	2008–2009	580	2.9	1.9	1.0	Blood transfusion, tattoo, alcohol abuse	[58]

IDU, intravenous drug use; HCV, hepatitis C virus infection.

For comparative analyses of HIV/HTLV prevalence rates presented herein and those detected in other regions/populations from Brazil, we have to consider differences in the demographic, sociocultural, and economic status of individuals, the variability in HTLV-1 and HTLV-2 endemic regions, and the years of sample collection. Table 3 presents studies conducted in Brazil, confirming the decline in HIV/HTLV prevalence rates over time, and more cases of HIV/HTLV-1 and HIV/HTLV-2 co-infections in populations/regions endemic for HTLV-1 and HTLV-2, respectively. In addition, it agrees with changes in retrovirus transmission routes, and different associated factors [48–58].

Taken together, studies carried out in Brazil confirm a decline in HIV/HTLV prevalence over time and emphasise differences in the type of HTLV that circulates in different regions of this country.

4. Discussion

Brazil has earned global acclaim for its efforts against AIDS, offering universal, free access to antiretroviral treatment for all patients and implementing education programs to prevent virus transmission/acquisition [59,60]. The success of HAART, initially in reducing AIDS-related hospitalisations in Brazil and subsequently in controlling HIV disease progression and transmission (evidenced by a decrease in HIV viral load to undetectable levels and a stable maintenance of CD4+ cell counts), has been instrumental in preventing HIV

transmission/acquisition and the onset of AIDS in infected individuals. Additionally, the Harm Reduction Program, which provides sterile needles and syringes to IDUs, along with changes in drug use patterns in Brazil, has contributed to a decrease in HIV prevalence rates [40,41], although new HIV/AIDS cases continue to arise. Several other significant measures have enhanced our understanding of the HIV/AIDS situation in Brazil. These include (i) the mandatory reporting of AIDS cases (Ministry of Health Ordinance No. 542, dated 22 December 1986), (ii) the compulsory notification of HIV infection in pregnant women, parturient or puerperal women, and children at risk of vertical HIV transmission (Ministry of Health Ordinance No. 993, dated 4 September 2000), and (iii) the inclusion of HIV in the List of Diseases of Compulsory Notification and in the Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação, Sinan), per Ordinances No. 1271, dated 6 June 2014, and No. 1984, dated 12 September 2014, following through with other information systems: Mortality Information System (Sistema de Informações sobre Mortalidade, SIM); CD4 and viral load Laboratory Tests Control System (Sistema de Controle de Exames Laboratoriais CD4 e CV, Siscel); and Drug Logistic Control System (Sistema de Controle Logístico de Medicamentos, Siclom). These systems provide real-time updates on the HIV/AIDS situation in Brazil, contribute to epidemiological bulletins, and aid in establishing measures to control virus dissemination.

The latest HIV-AIDS Epidemiological Bulletin from the Brazilian Ministry of Health, 2022, reveals that from 1980 to June 2022, 1,088,536 AIDS cases in total were reported, with 310,099 cases originating from São Paulo [61]. The rate of AIDS cases has fluctuated over time. In 2011, the rate was 22.5 cases per 100,000 inhabitants, which decreased to 15.6 cases per 100,000 inhabitants in 2021. This reduction was more pronounced in women (43.6%) than in men (16.2%). A similar decline in AIDS cases was observed in São Paulo, with 21.4 cases per 100,000 inhabitants in 2011 compared to 13.4 cases per 100,000 inhabitants in 2022 [61]. However, despite the overall decrease in new AIDS cases in Brazil, there has been a concerning increase among adolescents and young adults. This is particularly evident among homosexual men aged 20 to 29 years, who accounted for 57.1% of AIDS cases in this age group in 2015, a figure that rose to 62.4% in 2021 [61]. The same situation was described in Puerto Rico (Caribbean region), where in the years 2010 to 2014 an increase of 53% in new HIV diagnoses was observed among men and women aged 13 to 24 years, which was more pronounced in men who had sex with men [62]. In addition, similar circumstances have recently been described in USA; in recent years, increased rates of sexually transmitted diseases such as chlamydia, gonorrhoea, and primary and secondary syphilis have been observed among men and women aged 15 to 24 years, and approximately one in five new HIV diagnoses have been observed among males aged 13 to 24 years, of which 93% were attributable to homosexual activity, emphasising the need for a continuing education program for these age groups [63].

Interestingly, the UNAIDS Global AIDS update 2023 reported different figures of new HIV infections from 2010 to 2022 across the world. The rise in new HIV infections continued in Latin America (8% increase), Eastern Europe and central Asia (49% increase), and the Middle East and North Africa (61% increase). On the other hand, decreases in the numbers of new HIV infections were detected in Eastern and Southern Africa (57% reduction) and Western and Central Africa (49% reduction), but adolescent girls and young women in many parts of sub-Saharan Africa still have high risks of HIV infection. The decline in new HIV infections was also observed in western and central Europe and North America (23% decline), the Caribbean (15% decline), and Asia and the Pacific (a 14% decline, although in some countries in Asia and the Pacific the number of new HIV infections is rising alarmingly). In summary, the HIV pandemic continues to affect key populations more than it does the general population worldwide. In 2022, comparative analyses among adults in the general population (aged 15–49 years) revealed a HIV prevalence rate that was 11 times higher among homosexual men, 4 times higher among sex workers, 7 times higher among people participating in IDU and 14 times higher among transgender people [64]. In this regard, governments must provide treatment and prevention and

prioritise inclusive approaches that respect people's human rights and involve affected communities throughout the HIV response.

Unfortunately, concerns and the strategies, policies, information systems implemented for HIV/AIDS were not extended to HTLV-1 and HTLV-2 infections/diseases elsewhere, including Brazil, despite the high morbidity and mortality rate of HTLV-1-associated diseases and the absence of curative treatment for HTLV-1/-2. Nevertheless, while specific interventions for IDUs have not been established for HTLVs, the measures taken for HIV have significantly decreased the incidence of HIV/HTLV co-infections among people participating in IDU in urban regions [30–33,35]. In addition, some progress has been observed since the publication of a call for action to WHO [65], which in 2021 included a global consultation and the publication of a technical report and fact sheet [65,66].

Furthermore, a recent review article by an HTLV study group from Brazil and the United Kingdom examined the transmission routes of HTLV-1/2 and strategies to prevent its continued spread in Brazil. This review scrutinised public health policies implemented in Brazil since 1993, when HTLV serology became mandatory in blood banks (Ministry of Health Ordinance No. 1376, dated 19 November 1993). Additional policies included HTLV screening for organ and tissue donors and recipients (Ordinance No. 2600, dated 21 October 2009) and gamete donors (Resolution—RDC No. 23, dated 27 May 2011). The review also addressed recommendations for HTLV-seropositive mothers to avoid breastfeeding and the incorporation of HTLV into the national program for sexually transmitted infections [67]. Moreover, the review proposed several public health policies for HTLV, such as (i) universal antenatal screening, (ii) confirmatory testing for those reactive in screening tests, (iii) mandatory reporting, (iv) the establishment of multidisciplinary reference centres, (v) the provision of HTLV testing for high-risk populations, and (vi) public education to enhance the awareness of HTLV infection/diseases [67].

A subsequent review article examining the analysis of strengths, weaknesses, opportunities, and threats for the implementation of HTLV-1 public health policies in Brazil identified several weaknesses: (i) inadequate HTLV knowledge, (ii) insufficient epidemiological data, (iii) a deficiency of patient care reference centres, (iv) the limited availability of confirmatory tests, (v) the absence of universal antenatal screening, and (vi) a lack of cost-effectiveness studies [68]. Consequently, numerous studies have been initiated or are underway in Brazil to address these deficiencies.

In Japan, an HTLV-1 endemic country, horizontal transmission has emerged as the primary route of virus transmission, particularly among adolescents and young adults residing in urban areas. This trend is attributed to the migration of these age groups from rural to urban areas, influenced by superior education and employment prospects, coupled with more liberal social and sexual norms. Unprotected sexual encounters, especially with multiple partners, and transmission via contaminated needles, including drug injection or tattooing, have been identified as significant HTLV-1 transmission pathways in Japan [69]. This situation mirrors, to some extent, the circumstances in São Paulo and Brazil, where adolescents and young individuals, predominantly homosexual men, are exposed to retroviruses through unprotected sexual activity and promiscuity, often under the influence of substances such as alcohol, marijuana, crack, amphetamines, and hallucinogens.

The limitations of the present study included the analysis of samples from different cohorts, in different time periods, with different diagnostic tools and algorithms. However, it is worth highlighting that during these years, IAL's laboratory always used two HTLV-1/-2 screening tests and two HTLV-1/-2 confirmatory assays, which somehow covers some gaps and differences in diagnosis. Another limitation of this study is the lack of longitudinal studies for confirming trends in HTLV infection acquisition among adolescents and young adults. Unfortunately, since 2017, the routine for HTLV-1/-2 diagnosis was decentralised from IAL to other labs across the state of São Paulo, but lectures and personal communications during HTLV-related Conferences and Congress confirm this tendency, and agree on the situation in Japan [69].

Despite the limitations of the present study, the studies discussed herein, coupled with data from the Brazilian Ministry of Health [44,61] and the author's expertise in HIV/AIDS and HTLV-1/-2 infections in Brazil suggest a concerning lack of awareness among the general population, especially among adolescents and young adults regarding the transmission methods and implications of these retroviral infections. Consequently, it is imperative to promptly initiate ongoing informational and awareness campaigns targeting these age and risk groups in Brazil, with the aim of curbing the spread of these retroviruses within the country.

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