OMNIA RETRORSUM: THE OTHER HUMAN RETROVIRUSES

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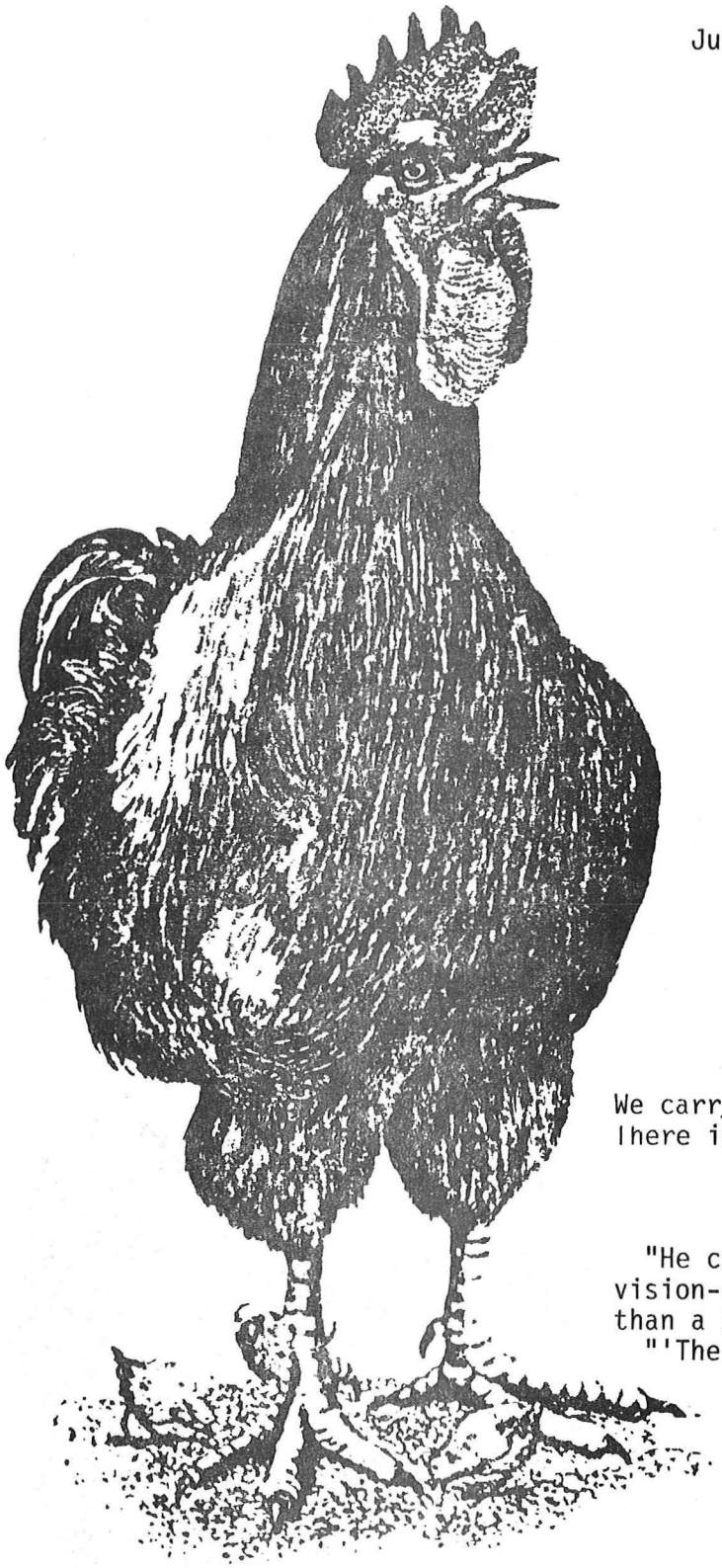

HTLV-I

HTLV-II

STLV-III

HIV-2

We carry within us the wonders we seek without us: There is all Africa and her prodigies in us.

Sir Thomas Browne, Religio Medici

"He cried in a whisper at some image, at some vision--he cried out twice, a cry that was no more than a breath--
"'The horror! The horror!'"
Joseph Conrad, Heart of Darkness

HTLV-I

As armas e os barões assinalados
Que, da ocidental praia Lusitania,
Por mares nunca de antes navegados,
Passaram ainda além a Taprobana,
Em perigos e guerras esforcados
Mais do que prometia a fôrça humana,
E entre gente remota edificaram
Novo Reino, que tanto sublimaram;

[Arms, and those matchless chiefs who from the
shore
Of Western Lusitania began
To track the oceans none had sailed before,
Yet past Taprobane's far limit ran,
And daring every danger, every war,
With courage that excelled the powers of Man,
Amid remotest nations caused to rise
Young empire which they carried to the skies;]

Luis de Camões, Os Lusiadas (1)

In 1415 Prince Henry of Portugal accompanied his father, Joao I, on the successful expedition to capture the North African port of Ceuta (2). Upon his return, Prince Henry, later to be dubbed "the Navigator," dedicated himself to promoting Portuguese maritime exploration. Establishing a school of navigation at the southern port of Sagres, Henry sponosored a series of expeditions to Madeira (1419), the Azores (1427), Cape Bajador (1434), and the Cape Verde Islands (1457), and by the time of Henry's death in 1460, Sierra Leone had been reached by Portuguese mariners. The momentum of Portugal's thrust along the coast of Africa was regained by Bartolomeu Dias, who rounded the Cape of Good Hope in 1487 (3).

Under Manuel I (1495-1521) and João II (1521-1557), Vasco da Gama reached India (1497-98). Alfonso de Albuquerque wrested Malacca, on the Malay Peninsula, from the Arabs in 1511, and a squadron under Rafael Perestrello reached China in 1516. The first Portuguese to reach Japan landed on a Chinese vessel at Kagoshima, in the Satsuma district of the Island of Kyushu, in 1542 or 1543. This contact soon led to regular commercial expeditions from Malacca, with the introduction of firearms to Japan (3, 4).

"But Satsuma offered few export commodities to tempt the Portuguese merchants, while the more morthern provinces of Kyushu were rich in the attractions which Kagoshima lacked....

"For just fifty years after their arrival the Portuguese enjoyed complete freedom from European competition in Japanese markets.... Although a few of the Portuguese merchants found their way at an early date to the imperial capital, the western ports of Kyushu, especially those of Hizen and Chikuzen provinces, were those to which the ships, almost without exception, directed their course. Indeed, throughout the ninety-eight or ninety-nine years (1542 or 1543 to 1641) during which Japan was open to unrestricted

European trade the ports of Kyushu, in spite of the efforts made by eastern daimyo to alter the situation, enjoyed an almost complete monopoly of foreign commerce" (4).

Meanwhile, Portugal was also active in the New World, with voyages to Newfoundland, Greenland, and Labrador and with the discovery of Brazil in 1500. Exploitation of sugar plantations in Brazil during the second half of the Sixteenth Century stimulated the South Atlantic trade in slaves from Africa (3).

In 1974 Junji Yodoi and his colleagues at Kyoto University reported two cases of chronic lymphocytic leukemia (CLL) in Japanese patients. Apart from the rarity of any sort of CLL in Japan, the cases were notable for the demonstration that the neoplastic cells were T lymphocytes rather than B cells. In one of the two patients "a considerable portion of abnormal cells were larger immature cells characteristic of chronic lymphosarcoma-cell leukemia" (5).

Three years later, the group in Kyoto reported 16 cases of leukemia in which the malignant cells were T-lymphocytes. Characteristics of the cases included onset in adulthood of a subacute or chronic leukemia with a rapidly progressive terminal course, morphologic heterogeneity of the leukemic lumphocytes, with frequent cells having indented or lobulated nuclei, involvement of the skin in many cases, lymphadenopathy without mass disease in the mediastinum, and hepatosplenomegaly. Although 15 of the 16 patients were residents of the Island of Honshu, 13 had been born on Kyushu (6).

In 1978 investigators at the University of Kumamoto reported a case of adult T-cell leukemia (ATL) complicated by hypercalcemia (16.8 mg/dl) in a 56-year-old man from Kyushu. Radiography revealed no lytic foci but demonstrated subperiosteal bone resorption in the pahlanges of the hand. Hypophosphatemia and subnormal tubular reabsoprtion of phosphate were also documented, but serum levels of immunoreactive parathyroid hormone (iPTH) were not evelvated. Supernates of cultures of the patient's leukemic cells had no detectable iPTH, but produced hypercalcemia when injected into chicks (7).

By 1979 interest in the problem of adult T-cell leukemia/lymphoma (ATLL) in Japan culminated in a Symposium on T-Cell Malignancies at the National Cancer Center in Tokyo (8-24). Cultures of peripheral blood cells from patients with ATLL seen in Kagoshima were reported to yield multinucleated giant cells in response to blastogenic stimulation with phytohemagglutin-P or with concanavalin A (19). Isao Miyoshi and his colleagues at Okayama University School of Medicine also announced the development of a leukemic T-cell line, designated MT-1, from a 69-year-old native of Kochi, on the Island of Shikoku, who had ATL (23).

Further investigation in Japan included a multi-center epidemiologic comparison of patients with T-cell lymphoid malignancy with those with B-cell neoplasia. Patients in the T-cell group were relatively likely to be anergic to have a family history of lymphoma or leukemia, to work in agriculture, fishing, or forestry, to have had onset of disease during the summer months, to be anergic to tuberculin, and to succumb to infections (25).

Meanwhile, Bernard Poiesz and his colleagues in the laboratory of Robert Gallo at the National Cancer Institute reported the isolation of a type C retrovirus from T-cell lymphoblastoid cell lines and from fresh peripheral blood lymphocytes from a 28-year-old Black man with mycosis fungoides. The reverse transcriptase and proteins of this retrovirus appeared to be unlike those of known type C viruses from primates. The new virus was designated "HTLV" for "human cutaneous T-cell lymphoma virus" (26).

In 1981 the same group announced the isolation of a second strain of HTLV from the peripheral blood cells of a 64-year-old Black woman with leukemic Sezary's syndrome (27). A radioimmunoprecipitation assay demonstrated specific antibody to the p24 major internal structural protein of HTLV in sera from both the patients with T-cell malignancies from whom the virus had first been isolated as well as in serum from the wife of the man with mycosis fungoides (28). Hybridization experiments indicated that HTLV was not an endogenous (genetically transmitted) retrovirus in man (29).

Later that year, Miyoshi and co-workers in Kochi and Kyoto reported on co-cultivation of cells from a 45-year-old woman who had ATLL with a feeder layer of normal human cord leukocytes. They unexpectedly recovered a T-cell line of cord leukocyte origin, designated MT-2, that produced type C virus particles. These cells were tumorigenic when transplanted into immunosuppressed newborn hamsters (30, 31). Transformation of cord T-cells was subsequently achieved by co-cultivating them lethally irradiated MT-2 cells. The new cell line also produced type C virus particles and expressed ATL-associated antigens (ATLA) (32).

Patients with ATL were found to have antibody to ATLA in MT-1 cells, and extracellular type C virus particles were detected in pelleted MT-1 cells cultured in the presence of 5-iodo-2'-deoxythymidine (33). Among 278 Japanese patients with hematologic malignancies, antibody to ATLA in MT-1 cells was found to be associated with origin in the ATL-endemic area of the Islands of Kyushu and Shikoku and with diagnosis of ATL or ATLL. Seropositivity in patients from outside the endemic area was associated with prior receipt of massive transfusions (34).

Back in the United States, in 1983 Gallo and his colleagues reported four cases of adult T-cell leukemia-lymphoma with seropositivity to HTLV-I in Blacks aged 20 to 30 years who had been born in Alabama, Florida, and Georgia. Five of 26 family members tested also had specific antibody to HTLV-I. Antibody was also detected in two of 95 and one of 189 serum specimens held by the state health departments in Georgia and Floirda, respectively (35).

This virus, now designated "human T-lymphotropic virus type I" (HTLV-I), but also formerly referred to as human T-cell leukemia-lymphoma virus, or adult T-cell leukemia virus (ATLV), has been the subject of numerous reviews (36-40).

The same group later reported that leukemic cells from the patients seen in Kyoto were typable by monoclonal antibodies as mature, peripheral T-cells with an $OKT1^{+}T3^{+}T4^{+}T10^{+}T5^{-}T8^{-}OKIa1^{-}$ phenotype but that these cells lacked helper activity in vitro (41).

Three of five healthy Japanese adults with antibody to ATLA had chromosomal aberrations in cultured T lymphocytes. The aberrations were clonal in two instances and monoclonal in the third (42).

Two of 250 blood donors in Kochi, on the island of Shikoku, were found to have antibody to HTLV-I. An attempt to culture the virus from leukocytes obtained from one of the seropositive donors was successful. The potential for transmission of HTLV-I by transfusion must be of particular concern in the ATL-endemic area of Kyushu (43).

A cohort of pregnant women in Tokyo was screened for antibody to HTLV-I, and one of 81 expectant mothers was found to be seropositive. Cultivation of peripheral blood lymphocytes from this asymptomatic woman revealed that she was a carrier of the virus. At the time of delivery of her baby girl, a sample of cord blood was taken for lymphocyte culture. As in the case of the mother's cells, the cytoplasm of approximately 0.5% of the baby's cultured lymphocytes also revealed HTLV-I p28 core protein antigen by indirect immunofluorescence. This case report is consistent with the hypothesis that vertical transmission of HTLV-I infection can occur (44).

A 37-year-old Japanese woman who carried the diagnosis of AIDS on the basis of Pneumocystis carinii pneumonia, scabies, and severe herpes zoster was found to have a stable antibody titer to HTLV-I. Culture of her peripheral blood lymphocytes yielded a type C retrovirus, and a subpopulation of her cultured cells expressed HTLV-I antigens (45).

In 1982 six cases of ATLL were reported from London and Belfast in Black West Indian and Guyanan expatriates. The clinical characteristics included lymphadenopathy, rashes, hypercalcemia, osteolytic lesions, lymphocytosis, and an aggressive course (Table 1).

Table 1. ATLL in Caribbean Expatriates in the United Kingdom

Age	Sex	Origin	Liver, spleen	Lymph nodes	Rash	Bone lesions	Calcium (mg/dl)	WBC	Survival (months)
55	M	Jamaica	-	+	-	+	22.9	27,000	6
47	M	West Indies	-	+	+	+	16.2	37,000	4
32	F	Grenada	+	+	+	±	9.1	40,000	≥20
31	F	St. Vincent	-	±	-	-	13.2	39,000	4
45	F	Guyana	-	±	-	-	16.3	67,000	3
21	F	Trinidad	+	+	±	-	16.6	31,000	≥2

The malignant lymphoid cells were pleomorphic with irregular nuclei and had surface markers characteristic of mature T lymphocytes. At least four patients had antibody to p24 antigen of HTLV-I, and this virus was isolated from peripheral blood cells from one surviving patient (46).

Type C retroviral particles have been cultured from peripheral blood lymphocytes from a Jamaican man living in the United Kingdom who had developed adult T-cell leukemia 22 years after leaving the West Indies (47).

Sera from 89 patients attending the hematology service of a teaching hospital in Kingston, Jamaica, were screened for antibody to HTLV-I. Twenty-two samples were positive, including 13 (59%) of 22 from patients with non-Hodgkin's lymphoma, four (29%) of 14 from patients with chronic lymphocytic leukemia, and two (33%) of six from patients with acute lymphoblastic leukemia. The proportion with antibody to HTLV-I was particularly high (11 of 16, 69%) among a consecutive series of incident cases of non-Hodgkin's lymphoma, reflecting the relatively poor prognosis among seropositive patients with this disease. The only other positive sample came from a 69-year-old woman with breast cancer. None of five patients with Hodgkin's disease, hairy cell leukemia, or Sézary's syndrome was seropositive. Antibody-positive patients with lymphoreticular malignancy had many of the same clinical features delineated among ATLL cases in Caribbean expatriates in the United Kingdom and among residents in southern Japan (Table 2) (48).

Table 2. Clinical Features of HTLV-I Seropositive Patients with Lymphoreticular Malignancy, Kingston, Jamaica

Age	Sex	Diagnosis	Liver, spleen	Lymph nodes	Rash	Hyper-calcemia	Marrow
31	F	DPDLL		+	+		+
58	M	DPDLL	+		+	+	
62	F	DPDLL		+	+		
20	F	DPDLL/L	+		+	+	+
22	F	DPDLL/L			+		+
26	M	DPDLL/L			+		+
29	F	DPDLL/L				+	+
44	F	DPDLL/L	+	+		+	+
48	M	DPDLL/L	+	+		+	+
61	F	DPDLL/L			+		
61	M	DLCL		+			
31	M	DLCL/L		+	+	+	+
48	F	DLCL/L	+	+		+	+
48	F	CLL	+				+
56	F	CLL		+			
66	F	CLL		+			+
74	M	CLL	+	+		+	+
16	M	ALL	+	+			+
23	F	ALL		+			+

DPDLL(/L) = diffuse poorly differentiated lymphocytic lymphoma (/leukemia), DLCL(/L) = diffuse large-cell lymphoma (/leukemia), CLL = chronic lymphocytic leukemia, ALL = acute lymphoblastic leukemia

Evidence of HTLV-I infection was demonstrated in a 30-year-old native of Surinam who presented with chronic polyarthritis and T-cell chronic lymphocytic leukemia seven years after emigrating to Holland (49).

An unusual case of Sézary's syndrome was reported in a 55-year-old native of Martinique. Her Sézary cells were found to retain helper function in B-cell differentiation (50).

Evidence for an important association between HTLV-I and lymphoid malignancy has been reported from Martinique. Antibody to HTLV-I was common among patients with non-Hodgkin's lymphoma but rare in most other patients tested (Table 3).

Table 3. Prevalence of Antibody to HTLV-I, Martinique

Diagnosis	No. positive/No. tested
Non-Hodgkin's lymphoma	6/18
Cutaneous T-cell lymphoma	2/2
Chronic lymphocytic leukemia	0/5
Multiple myeloma	1/11
Hodgkin's disease	0/7
Acute lymphoblastic leukemia	0/1
Myeloproliferative diseases	0/5

Fully five of nine patients with non-Hodgkin's lymphoma diagnosed in 1983 were seropositive (51).

The frequency with which chronic lymphocytic leukemia was diagnosed in West Africans under the age of 40 and the preponderance of female patients in this group led to the suggestion that HTLV-I might be involved in lymphoid malignancy in that region (52).

Three cases of apparently typical ATLL in Whites have been reported from Seattle and Oregon, but no information on HTLV-I infection in these cases was presented (53). More data on patients seen in the Washington area, emphasizing the presence of lytic bone lesions, was presented by the group at the National Institutes of Health (54).

A 42-year-old Sicilian woman with leukopenic chronic T-cell leukemia who had massive splenomegaly but less hepatomegaly and minimal lymphadenopathy was found to have IgG antibody to HTLV-I. She responded well to splenectomy followed by combination chemotherapy (55).

In 1982 Saxinger and Gallo reported results of screening serum specimens from the blood bank at the National Institutes of Health for HTLV-I antibody and antigen. Of 126 specimens tested, one contained antibody to HTLV-I as well as detectable HTLV-I p19 and p24 antigen. A second sample was positive in the ELISA test for antibody to HTLV-I but an ELISA assay for competition by purified virus in solution was negative, raising the possibility of a falsely positive test (56). These investigators summarized their findings as showing antigenemia "in about 1% of the sera of normal blood donors" at the blook bank, however the 95% confidence intervals for the binomial distribution of 1/126 can be calculated as equal to 0.02 - 4.35% (57). Saxinger and Gallo advocated screening blood and blood products destined for "high-risk recipient categories" (56).

Antibody to HTLV-I was found in sera from 8 (17%) of 48 hemophiliacs in New York City bled in 1976-1981 and in sera from 5 (11%) of 45 hemophiliacs in Georgia bled in 1982. The positive specimens from New York dated from 1978 and 1979. None of 21 patients receiving chronic hemodialysis and 29 patients with chronic active hepatitis in Georgia was positive (58).

Disturbing new information on HTLV-I seroprevalence in drug abusers has recently been compiled. Sera obrtained from 963 drug abusers in New Jersey in 1984 and from 214 in New Orleans in 1985 were screened (Table 4) (59).

Table 4. Prevalence Rates of Antibody to HTLV-I and HIV-1 in Drug Abusers

	Race					
	Black			Other		
Site	HTLV-I	HIV-1	Both	HTLV-I	HIV-1	Both
New Jersey	30.2%	45.0%	15.5%	8.5%	31.0%	3.2%
New Orleans	49.3%	0.0%	0.0%	6.6%	2.6%	1.3%

Of 2009 sera from adults in selected populations in Asia (China, Indonesia, Israel, Philippines, Korea, Taiwan), Oceania (Solomon Islands), North America (American Indians, Dominica, Puerto Rico), South America (Brazil), and Europe (Denmark, Greece), only ten had antibody to HTLV-I, and at least two of the seropositive subjects were of Japanese ancestry (60).

HIV-1 has a TTNYT pentapeptide (T4-8) that resembles the TDNYT pentapeptide (VIP7-11) of vasoactive intestinal polypeptide (VIP). HTLV-I has an analogous pentapeptide analogous to the HIV-1 TTNYT sequence, which is believed to be a CD4 receptor ligand (61).

Lectin-mediated activation of cells of the Jurkat T-cell line that have been infected with HIV-1 increases promoter activity of the HIV long terminal repeat (LTR). In contrast, T-cell activation does not affect expression directed by the HTLV-I LTR (62).

In addition to causing T-cell malignancies, HTLV-I may sometimes play an indirect role in B-cell leukemogenesis. In the West Indies, where HTLV-I infection is endemic, the prevalence of antibody to HTLV-I is higher among patients with chronic lymphocytic leukemia (CLL) than among the general population. CLL cells from two HTLV-I-seropositive Jamaicans have been fused to a human B-lymphoblastoid cell line. The resulting hybridoma cells produce IgM antibody that specifically reacts with the p24 or gp61 antigens of HTLV-I. These data suggest that the CLL cells represented a malignant transformation of antigen-committed B cells in response to HTLV-I infection, perhaps abetted by immunosuppression induced by infection of T cells by HTLV-I (63).

Antibody to HTLV-I has been detected in four of nine Nigerian patients with CLL. This prevalence contrasts with seropositivity in six (3.7%) of 161 blood donors and in one of five patients with non-Hodgkin's lymphoma and one of eight patients with Burkitt's lymphoma. Fifteen Nigerians with chronic granulocytic leukemia, acute nonlymphoblastic leukemia, Hodgkin's disease, splenomegaly of unknown origin, or acute lymphoblastic leukemia were seronegative, as were 11 monkeys of three different species (64).

Recent reviews have addressed the subjects of myeloneuropathies of undetermined origin that occur in tropical countries (65) as well as the role that retroviruses may play in neurologic disease of man and other vertebrates (66).

In 1964 Montgomery and co-workers reviewed their accumulated experience with the clinical and patholgical findings in a chronic neurologic disorder of adults seen in Jamaica, Trinidad, Barbados, Montserrat, Antigua, and El Salvador. They referred to this disorder as "Jamaican neuropathy," and distinguished between two subgroups, one ataxic and one spastic. According to them, "Thre true causes and interrelationships of the syndromes remain to be defined. In the Jamaican spastic cases there are few overt indications of malnutrition, and toxic factors have not been directly implicated." At the time, these investigators suspected that the spastic form might be attributable to a treponematosis (67).

Tropical spastic paraparesis is a slowly progressive myelopathy in which involvement of the pyramidal tracts predominates over distal sensory deficits and impairment of sphincter function. The disease is recognized in Colombia, Jamaica, Martinique, South Africa, and southern India. Two-thirds of patients with TSP diagnosed at the Regional Hospital Center in Fort de France, Martinique, had antibody to HTLV-I, whereas seroprevalence rates were much lower in control groups (Table 5) (68).

Table 5. Prevalence of Antibody to HTLV-I, Fort de France, Martinique

Subjects	Proportion with antibody to HTLV-I	
	ELISA	Western blot
TSP patients	15/22 (68%)	15/22 (68%)
Other neurology patients	1/24 (4%)	1/14 (7%)
Healthy medical staff	1/27 (4%)	not tested
Blood donors	11/252 (4.4%)	not tested

Twenty-five patients with TSP and antibody to HTLV-I have been reported from Martinique, in the French West Indies. All were women. The mean age of onset was 45 years, with a range of 25 to 60. All 11 patients tested also had antibody to HTLV-I in the CSF. The minimal incidence rate of HTLV-I-associated TSP in Martinique was estimated to be 1/100,000 inhabitants per year, with a minimal prevalence of 8/100,000. Seventeen percent of asymptomatic family members of the patients were also seropositive. Initial symptoms included lower extremity weakness, lumbar and thoracic backache, and lower extremity dysesthesias, paresthesias, and arthralgias. Physical findings included spastic paraparesis or paraplegia, upper limb spasticity, bladder dysfunction, and minimal sensory loss (69).

High prevalences of antibody to HTLV-I in serum and CSF have also been reported in TSP patients from Jamaica (Jamaican neuropathy) and the coastal Tumaco region of Colombia (Pacific spastic paraparesis) (Table 6) (70).

Table 6. Prevalence of antibody to HTLV-I in TSP Patients in Jamaica and Coastal Colombia

Source		ELISA			
		Positive	Borderline	Negative	Total
Jamaica	serum	16 (67%)	4 (17%)	4 (17%)	24
	CSF	15 (56%)	3 (11%)	9 (33%)	27
Colombia	serum	3 (100%)	0 (0%)	0 (0%)	3
	CSF	16 (73%)	3 (14%)	3 (14%)	22

Fifty cases of tropical spastic paraparesis were reported from Tumaco, a port on the Pacific Coast of Columbia, in 1985. The estimated prevalence rate in one town was 98/100,000 population. The sex ratio was 1.4:1, and all cases were in adults. Onset was characterized by dysesthesias of the feet, lower extremity stiffness, and bladder spasticity. Men were impotent. Typical cases exhibited spasticity and weakness in the lower extremities, but the Achilles reflex was diminished. Vibratory sensation was imparied in the feet. The clinical cause was characterized by slow progression without attributable mortality. The epidemic curve of the cases in Tumaco extended back to 1952, but most cases had had onset since 1972, with an apparent peak in incidence 1977 (71).

Data including antibody prevalence in control subjects was presented in a subsequent report on TSP in Tumaco, Colombia. Seventeen (94%) of 18 TSP patients had antibody to HTLV-I, whereas all neighbors tested were seronegative. Antibody was also detected in 25% of spouses, 20% of children, and 33% of other relatives in the households of patients with TSP. Only one of 55 subjects from an area 1000 km to the north of Tumaco had antibody to HTLV-I. This was a woman who had developed TSP one year after marrying a man from the TSP-endemic area. Sexual transmission of HTLV-I in coastal Colombia has been hypothesized to explain the absence of cases of TSP among children and the sequential occurrence of the disease in spouses in that area (72).

Seroepidemiologic data indicate that HTLV-I infection is commoner among patients with tropical spastic paraparesis TSP in Martinique, Jamaica, Colombia, Trinidad, and the island of Mahe in the Seychelles than among the general population in these areas. HTLV-I seropositivity is also high among patients in Jamaica who have polymyositis (73).

High-signal lesions in the white matter, chiefly in the periventricular areas, were found by magnetic resonance imaging (MRI) of the brain in two women in France who had TSP with positive ELISA and Western blot tests for antibody to HTLV-I in serum and cerebrospinal fluid (CSF). One woman had been born in Guadeloupe, but the other was a native of France. In both patients, the disease was initially misdiagnosed as multiple sclerosis (74).

Small foci of abnormally increased signal anterior and lateral to the lateral ventricles were detected by MRI in an asymptomatic Colombian woman. Both she and her husband, who had TSP, were seropositive for HTLV-I, but she was clinically normal except for absent ankle jerks and bilateral extensor plantar reflexes (75).

A 32-year-old native of the Ivory Coast with spastic paraplegia, bladder dysfunction, and CSF pleocytosis was found to have antibody to both HTLV-I (p19, p24, p42, gp45, p55, and gp61) and HIV-2 (HTLV-IV) (p24, gp32, and gp120). This case raises the question of whether infection with multiple retroviruses might present a higher risk of neurologic disease than does infection with a single neurotropic agent (76).

In 1986 Osame and colleagues reported the existence of an illness that resembled tropical spastic paraparesis among inhabitants of Kagoshima Prefecture in Japan, an area of high endemicity for ATLL. They described four women and two men, aged 25-58, who had developed the gradual onset of a progressive myelopathy over a period of three months to 11 years. The

patients had spastic paraparesis with mild sensory and sphincter disturbances without abnormalities detectable by myelography, computerized tomography of the spine, and magnetic resonance imaging. All patients had high titers of antibody to HTLV-I in serum and CSF, whereas seropositivity was detected in only 12 (15%) of 78 control subjects with other neurological disorders, only one of whom had specific antibody in the CSF. These workers proposed the term "HTLV-I associated myelopathy" (HAM) for the disorder. Hematologic abnormalities in patients with HAM were confined to the presence of a few atypical lymphocytes. Striking improvement in gait was reported in all four patients treated with prednisolone (60 mg qd initially, followed by tapered reduction to a lower maintenance dose) (77).

In a more complete report by the same group, the authors described "adult T-cell leukemia-like cells" in peripheral blood of the patients with HAM (78).

An autopsy was performed on a 59-year-old woman from southern Japan who had died of congestive heart failure after a 2½-year course of HAM, which had begun six months after she had received blood transfusions for cardiac surgery. Her serum and CSF had been positive for antibody to HTLV-I. Pathologic findings included capillary proliferation, lymphocytic perivascular cuffing, demyelination, axonal degeneration, astrocytic proliferation, and infiltration by foamy macrophages. Changes were most pronounced in the lateral and anterior columns of the thoracic cord. Perivascular cuffing was also present in the medulla, pons, and cerebral and cerebellar white matter. Evidence of chronic arachnoiditis and of a chronic vasculitis were also noted. These findings were considered to be similar to those described in cases of TSP and distinct from the neuropathologic effects of HIV-1 infection (79).

Southern blots of Pst I digests of DNA from peripheral blood lymphocytes of patients with HAM were indistinguishable from DNA from a patient with adult T-cell leukemia when hybridized with a probe containing the whole sequence of HTLV-I. The provirus integration sites appeared to be randomly located in the lymphocytes of HAM patients (80).

The question of whether retroviruses may be also involved in multiple sclerosis and methodologic aspects of this area of research have recently been reviewed (81).

Evidence has been offered of an association between HTLV-I and multiple sclerosis in Key West, Sweden, Japan, and Finland (73). The high incidence of genuine multiple sclerosis, as distinct from tropical spastic paraparesis, in Key West has been emphasized (82). However, negative findings regarding HTLV-I seropositivity in patients with multiple sclerosis have been reported from Milwaukee, Richmond, Paris, Martinique, England, Sweden, Japan, and Italy (73).

Only one of 125 workers at the National Institutes of Health tested for antibody to HTLV-I because of work with infected patients or with virus-containing specimens was found to be seropositive. She was a 51-year-old native of Jamaica whose pre-employment serum specimen also had a high titer of antibody to HTLV-I. These results support the adequacy of P-2 isolation precautions for work with this virus (83).

The Public Health Laboratory Service in London has detected low prevalence rates of antibody to HTLV-I in asymptomatic West Indian patients at sexually transmitted disease clinics, West Africans, and intravenous drug abusers as well as in West Indians with hematologic or neurologic disease (Table 7) (84).

Table 7. United Kingdom: Specimens Screened for Antibody to HTLV-I

Source or condition	Number positive by at least two methods*/Number tested	Proportion
Hematologic disease	2/27	7%
Neurologic disease	2/9	22%
STD clinic patients		
African origin	0/123	0%
West Indian origin	2/58	3%
Sickle-cell anemia	0/90	0%
Hemophilia	0/103	0%
Intravenous drug abuse	3/106	3%
West Africans	9/188	5%

*Particle agglutination, competitive radioimmunoassay, indirect immunofluorescence, ELISA

Eighteen of 20 monkeys captured in various parts of Japan had specific antibody to HTLV-I-infected MT-2 and Si-1 cells. Cultured mononuclear leukocytes from four of four seropositive and neither of two seronegative monkeys expressed ATLL antigens. Type C retroviral particles were detected when one of the antigen-positive cultures was examined by electron microscopy. These results suggest that infection with HTLV-I may be widespread among wild monkeys in Japan (85, 86).

Japanese investigators have reported antibody to HTLV-I in cynomolgus monkeys (M. fascicularis) captured in Indonesia. The seroprevalence varied notably as a function of the site of the animal's procurement (87).

Twenty-two (82%) of 27 African green monkeys (Cercopithecus aethiops) brought to Germany from Kenya had antibody to HTLV-I. Lymphocyte cultures were prepared from blood from five of these animals and yielded ATLL antigens detectable by immunofluorescence, indicating infection with HTLV-I or a closely related virus. Thirteen rhesus monkeys (M. mulatta) and twelve chimpanzees were seronegative. A survey of over 1000 sera from healthy and leukemic Germans and from the handlers caring for the monkeys revealed none with antibody to HTLV-I (88).

Viral isolates of simian origin that resemble HTLV-I are now referred to as simian T-lymphotropic virus type I (STLV-I). Antibody to STLV-I was detected in 4 (4%) of 114 African green monkeys collected in central Ethiopia in 1973, in 25 (29%) of 85 of those collected near Kampala, Uganda, in 1966, and in 149 (44%) of 336 collected in central and southern Kenya in 1978 and 1979. Among the Kenyan monkeys seropositivity was more frequent among females (54%) than males (37%) and rose from 16% in infants under nine months

to 69% in adults over 42 months of age. Only one of three infants of seropositive mothers had seroconverted. Seropositivity did not appear to be associated with impaired health in these animals (89).

A female Japanese macaque (M. fuscata) seroconverted to HTLV-I within eight weeks of mating with a seropositive male. In a companion experiment, one male monkey who had been mated with a seropositive female remained seronegative at least 15 weeks thereafter (90).

Gallo and co-workers have emphasized the relationship between HTLV-I and bovine leukemia virus and the differences between these organisms and most other animal retroviruses. Commenting upon the geographic distribution of HTLV-I-associated disease in man and upon the evidence for infection with HTLV-I or similar viruses in Old World, but not New World monkeys, these investigators have suggested that HTLV-I may have been introduced to the Western Hemisphere by infected Black Africans and into coastal Japan by 16th-Century Portuguese travelers (91).

Remarkably, the nucleotide sequence of the LTR of HTLV-I has been found to show greater homology (95%) to that of STLV-I from African green monkeys and chimpanzees (African subtype) than to the LTR (90% homology) of STLV-I from Asian macaques (Asian subtype). That is, the human viruses from Japan are more similar to simian viruses from Africa than they are to simian viruses from Japan (92).

Purine and pyrimidine analogs bearing 2',3'-dideoxyribose can inhibit the replication of HTLV-I in vitro (93).

The MT-4 cell line, which is infected with HTLV-I, is susceptible to lytic infection by strains of HIV-1. Thus, MT-4 cells can be used to assay the concentration of HIV-1 in samples, and HIV-1 isolates can be cloned from plaques produced on MT-4 cultures (94).

Leukocytes from a Japanese macaque (M. fuscata) were co-cultivated with lethally irradiated MT-2 cells, a line established from HTLV-I infected leukemic cells from a patient with ATLL. Monkey lymphocytes were transformed by the co-cultivation experiment, and the resulting line, designated Si-1, was shown to be infected with type C retroviruses and to express ATLL-associated antigens (95).

HTLV-II

In 1978 Golde and colleagues reported a case of hairy cell leukemia in a 37-year-old White man from Seattle. Although the patient had typical clinical and pathological findings of hairy cell leukemia, including neoplastic cells in tartrate-resistant acid phosphatase, the malignant lymphocytes had T-cell, instead of B-cell, characteristics (96). Four years later Gallo and his associates reported the isolation of a novel virus from a cell line established from this patient's neoplasm. Although this virus showed antigenic relatedness to typical HTLV-I strains from the United

States, the Caribbean, and Japan, immunologic cross-reactivity tests with HTLV-I p24 major internal core protein revealed the Seattle isolate to represent a new subtype, which was accordingly designated HTLV-II (97).

A 48-year-old Black man from Los Angeles was hospitalized with pancytopenia and splenomegaly without enlargement of liver or lymph nodes. He was found to have a chronic T-cell leukemia that initially responded to splenectomy but later relapsed. The patient's serum contained IgG antibody specific for HTLV-II (55).

A subsequent report of the identification of HTLV-II in a second case of T-cell hairy cell leukemia has been reported (98). At least nine isolates of HTLV-II have been made, including five associated with hairy cell leukemia, two in intravenous drug abusers with HIV-1 infections and dermatopathic lymphadenopathy, one in a a case of prolymphocytic leukemia, and one from a hemophiliac with HIV-1 infection who had no malignancy (98, 99).

Like HTLV-I, HTLV-II has an alalog of the TTNYT pentapeptide that is the CD4-receptor ligand of HIV-1 (61).

STLV-III

> Not in innocence, and not in Asia was mankind born. The home of our fathers was that African highland reaching north from the Cape to the Lakes of the Nile. Here we came about--slowly, ever so slowly--on a sky-swept savannah glowing with menace.
>
> Robert Ardrey, African Genesis

> The Arabs came to East Africa in the seventh century A.D., in search of gold, ivory, spices, and slaves. But the Arabs were merchant seamen and did not venture inland. They called the interior Zinj--the Land of the Blacks--a region of fable and fantasy. There were stories of vast forests and tiny men with tails; stories of mountains that spewed fire and turned the sky black; stories of native villages overwhelmend by monkeys, which would have congress with the women...."
>
> Michael Crichton, Congo

In 1985, investigators from the laboratory of Myron Essex at the Harvard School of Public Health and the New England Regional Primate Research Center in Southborough, Massachusetts, reported the isolation and characterization of a simian retrovirus from sick macaques at the Center. The virus was designated simian T-lymphotropic virus type III (STLV-III) because of its

antigenic similarity to HTLV-III (HIV-1) (100, 101). STLV-III is cytotoxic for infected target cells in vitro (102). A rhesus monkey naturally infected with STLV-III developed immunosuppression and an oligoclonal or polyclonal B-cell lymphoproliferative disease characterized by diffuse infiltration of lymph nodes, spleen, bone marrow, thymus, lung, liver, kidney, salivary glands, pancreas, thyroid, stomach, and tongue with plasmacytoid lymphoblasts (103).

Antibody to STLV-III was detected in 28 (42%) of 67 wild African green monkeys (C. aethiops) but in none of 60 captive chimpanzees or baboons. Cross-reacting antibody was also present in sera from 17 (53%) of 32 persons with antibody to HIV-1 but in none of ten HIV-1 seronegative cancer patients. The green monkeys appeared healthy, leading to the suggestion that "STLV-III may be non-pathogenic in this species, allowing for efficient transmission through these primates. Furthermore, C. aethiops is more likely than other non-human African primates to be found close to and interacting with human populations....STLV-III of African green monkeys may have been transmitted to man coincident with the recognition of AIDS in central Africa. An HTLV-III related virus has thus been found in two species of Old World primate; in the Asian macaque it is associated with immunodeficiency whereas in the African green monkey the virus is apparently non-pathogenic" (104, 105). Up to half the African green monkeys caught in the wild have antibody to STLV-III (105), also known as SIV (106).

Ten (83%) of 12 rhesus monkeys (M. mulatta) inoculated intravenously with STLV-III developed a transient maculopapular rash involving the face, groin, and trunk within one to three weeks after injection. Skin biopsies revealed a superficial perivascular mononuclear cell infiltrate associated with endothelial cell hypertrophy and degeneration (107).

Four of six rhesus monkeys inoclated intravenously with STLV-III died within 160 days of injection with an AIDS-like syndrome consisting of weight loss, opportunistic infections, a primary retroviral encephalitis, and immunologic abnormalities including a decrease in circulating T4+ cells (108).

The nucleotide sequence of STLV-III$_{AGM}$ and HIV-1 reveal similar genome structures. In comparison to HIV-1, however, both STLV-III and HTLV-IV (see below) show truncation of a transmembrane glycoprotein (109). STLV-III resembles HIV-1 in terms of tropism for the CD4 receptor, production of syncytia in CD4-positive lymphocytes infected in vitro, ultrastructure, magnesium dependence of the reverse transciptase, and antigenic similarity of the gag, env, pol, and 3'-orf gene products. The 3' 4.2 kb of the STLV-III genome has been cloned and found to resemble the corresponding segment of HIV-1, with up to 55% homology of regions identified as constant domains in the HIV-1 env gene and analogous positioning of all of 18 cysteine residues in HIV-1. In addition, other regions, including art and tat, which encode regulatory products, are preserved in STLV-III (110).

A report from Sweden indicates that human sera containing antibody to HIV-1 demonstrable by Western blot vary in seropositivity to STLV-III$_{MAC}$ antigens. Cross-reactions with STLV-III appeared most common in sera from African subjects (111).

The hypothesis that simian retroviruses could be transmitted to man by folk practices has been suggested on the basis of an anthropologist's report that inhabitants of the Great Lakes area of Africa take injections of monkey blood for aphrodisiac purposes (112).

HIV-2

> Unde etiam vulgare Graeciae dictum "semper aliquid novi Africam adferre."
>
> [Whence it is commonly said among the Greeks that "Africa always offers something new."]
>
> Pliny, Historia Naturalis

> "They were dying slowly--it was very clear. They were not enemies, they were not criminals, they were nothing earthly now,--nothing but black shadows of disease and starvation, lying confusedly in the greenish gloom. Brought from all the recesses of the coast in all the legality of time contracts, lost in uncongenial surroundings, fed on unfamiliar food, they sickened, became inefficient, and were then allowed to crawl away and rest. These moribund shapes were free as air--and nearly as thin."
>
> Joseph Conrad, Heart of Darkness

In 1985 Myron Essex of the Harvard School of Public Health and his colleagues reported a serologic study performed on prostitutes and surgical inpatients in the West African country of Senegal. Twenty (6.9%) of 289 prostitutes and five (4.1%) of 122 surgical inpatients in Dakar had positive ELISA tests for antibody to HIV-1 (HTLV-III). Western blot analysis of positive sera against lysates of HIV-1 and of STLV-III_{AGM} revealed that the speciticities of the Senegalese antibodies differed from those of ELISA-positive sera from Burundi and the United States in showing preferential binding to STLV-III_{AGM} antigens rather than to those of HIV-1. The reactions with the sera from the Senegalese subjects resembled those produced by sera from healthy African green monkeys and macaques (Table 8). These workers emphasized that both the monkeys from which HTLV-III_{AGM} has been isolated and the seropositive Senegalese lack any signs of immunodeficiency and suggested that STLV-III_{AGM} might be less virulent than HIV-1, with possible implications for vaccine development (113).

Table 8. Western Blot Reactions of Serum Specimens with Positive Radioimmunoprecipitation Tests for HIV-1 or STLV-III$_{AGM}$

Origin of Sera	No. tested	No. reacting with HIV-1		No. reacting with STLV-III$_{AGM}$	
		p24	gp41	p24	p32
Monkeys	5	2	0	3	5
Humans					
Senegal	8	8	0	8	8
Burundi	3	3	3	3	0
United States	11	11	11	5	1

In 1986 Essex and his colleagues reported the isolation of a retrovirus from healthy inhabitants of Senegal. This strain showed close antigenic relatedness to multiple protein and glycoprotein antigens of STLV-III$_{AGM}$ but shared fewer common epitopes with HIV-1 (114).

That same year Luc Montagnier of the Institut Pasteur and his associates reported the isolation of a new human retrovirus from two West Africans with AIDS. The first patient was a 32-year-old married man from Guinea-Bissau who had been hospitalized in Lisbon in 1985 with a two-year history of diarrhea and weight loss. On admission, he was found to have fever, lymphadenopathy, esophageal candidiasis, and cryptosporidiosis. Immunologic abnormalities included inversion of the T4/T8 ratio, hypergammaglobulinemia, and cutaneous anergy. The second patient, a 32-year-old divorced native of the Cape Verde Islands, was hospitalized in Paris in 1983 with ARC. Over the ensuing two years he developed cryptosporidiosis, infection with Isospora belli, and cerebral toxoplasmosis (115).

A retrovirus, designated LAV type II, was isolated from peripheral blood lymphocytes from each patient and was found to produce syncytia in T-cell lines. These isolates failed to hybridize under stringent conditions with an RNA probe containing the whole genome of HIV-1. Weak hybridization was observed under less stringent conditions with subgenomic probes containing the HIV-1 pol and gag RNA sequences. Neither patient had antibody to HIV-1 detectable by ELISA, although inconstantly positive results were seen by using the more sensitive technique of radioimmunoprecipitation to detect antibody to HIV-1 p34. Both patients had antibody against the homologous isolate detectable by Western blot (115).

The hydrophilic glycoprotein of LAV-II had the same molecular weight (130,000-140,000) as that of STLV-III, and these molecules share antigenic similarities, suggesting a closer relationship between LAV-II and STLV-III than between LAV-II and HIV-1 (115).

Retroviruses that are closely related to STLV-III have been recovered from inhabitants of West Africa. Designations in use for these strains include HTLV-IV (or HTLV-4), LAV-2, HIV-2, SBL-6669, and West African retroviruses (WAR). In contrast to the epidemiology of HIV-1 infection, evidence for infection with STLV-III-like viruses in Central African populations has been absent. High seroprevalence rates in female prostitutes

suggest transmission by sexual contact. Essex has stressed the view that these infections are characteristically asymptomatic, paralleling the experience with STLV-III infection in monkeys (105).

In contrast to Essex, Montagnier has emphasized an association between human infection with HIV-2 (formerly LAV-2) and AIDS and related conditions in West African countries including Guinea-Bissau, Senegal, The Gambia, and Ivory Coast (102, 106). His group and their Portuguese colleagues have recently summarized their experience with HIV-2 infection in 12 men and 18 women, including 26 from Guinea-Bissau and two from the Cape Verde Islands. Of these 30, 17 had AIDS; four had ARC; one each had persistent generalized lymphadenopathy without constitutional symptoms, pulmonary tuberculosis, and neurosyphilis; and six were asymptomatic. Chronic diarrhea associated with I. belli was the most prevalent opportunistic infection (116).

HIV-1 and HIV-2 share similar morphologies and are both tropic and cytopathic for CD4-positive cell lines and lymphocytes, despite antigenic differences between their envelope glycoproteins. Nucleotide sequence analysis of HIV-2 reveals that the organization of its genome resembles that of HIV-1 except for the presence in the former of insertions in the LTR. Whereas the gag and pol genes of the two viruses show 50% conservation of sequences, greater divergence (less than 30% conservation) is present in the genes for the env glycoprotein and for the F and Q proteins (106).

Cloning of the HTLV-IV provirus has revealed overall nucleotide sequence homology with HIV-1 of approximately 40%, with similarities in the env, 3'orf, and LTR sequences. A peptide sequence (coded by the 3' portion of the env gene), which has been implicated in the cytopathic effect produced by HIV-1 is strongly conserved (12 of 14 amino acids) in HTLV-IV (117).

The LAV-2 genome has also been cloned, and MboI restriction endonuclease digests reveal divergences from those of HIV-1 (102).

There are antigenic similarities between the internal components of HTLV-IV, LAV-2, and SBL-6669 and those of HIV-1 strains. However, the envelope glycoproteins of HTLV-IV, LAV-2, and SBL-6669, which are closely related to each other, are markedly different from envelope glycoproteins in HIV-1 isolates. These differences, which are apparent in assays of antibody-dependent cell cytotoxicity, have obvious implications for work on immunodiagnostic testing and vaccine development (118).

LAV-2 and SBL6669, which have been associated with an immunodeficiency syndrome, kill infected target cells in vitro, as does STLV-III. In contrast, HTLV-IV, isolated from asymptomatic West Africans, does not display killing of CD4-positive target cells in vitro (102).

Patients infected with HIV-2 develop low titers of cross-neutralizing antibody to HIV-1. Patients infected with HIV-1 do not demonstrate antibody that cross-neutralizes the LAV-2 strain of HIV-2, but this isolate is poorly neutralized even by homologous antiserum (119).

Three cases of AIDS and one of ARC due to virologically-proven infection with HIV-2 have been reported from Paris (Table 9).

Table 9. AIDS and ARC with HIV-2 Infection, Paris

Age	Sex	Origin	Risk factors	Clinical manifestations
32	M	Cape Verde Islands	none	Candida esophagitis Cryptosporidium enteritis Isospora enteritis pulmonary tuberculosis Toxoplasma encephalitis
32	M	Guinea-Bissau, Senegal	none	oral candidiasis Toxoplasma encephalitis
34	M	Senegal, Guinea-Bissau	not stated	chronic diarrhea diffuse lymphadenopathy Salmonella typhimurium enteric fever
58	F	Portugal	transfusion, asymptomatic huband also seropositive	Candida esophagitis chronic diarrhea cortical atrophy herpes zoster Toxoplasma encephalitis

None of the patients had antibody to HIV-1 by ELISA or Western blot. The three African men were all carriers of HB_sAg. Of note, the Cape Verde Islander survived over three years after the diagnosis of AIDS, and the Portuguese woman was still alive and able to live at home 38 months after onset of her first opportunistic infection (120).

Several publications have reported evidence of HIV-2 infection in populations in West Africa.

Antibody to HIV-2 was found in two women with AIDS and thirteen asymptomatic persons among 236 subjects from the Cape Verde Island of Praia-Santiago. None of 144 residents of the Island of Sal was seropositive (121).

Studies of HIV-1 and HIV-2 antibody prevalence in Ivory Coast prostitutes, prisoners, and hotel staff suggest that seropositivity is specific for infection with the homologous virus and not due to cross-reacting antibody (122, 123). Antibody to HIV-2 is widespread in the Ivory Coast despite the rarity of AIDS in that country. Seropositivity rates to both HIV-1 and HIV-2 are particularly high among native and Ghanaian prostitutes of low socioeconomic status (124). Of 200 patients with pulmonary infections assoicated with asthenia and weight loss, 19% had antibody to HIV-1, and 8% had antibody to HIV-2; antibody to both viruses was detected in 13% (125).

Antibody to HIV-2 was sought in 4,248 serum specimens from Senegal, Guinea, Guinea-Bissau, Mauritania, Burkino Faso, and the Ivory Coast. Seropositive subjects were identified in five of the six countries, but the prevalence rates varied from 1% to 32%. AIDS was found to be associated with infection with HIV-1, but evidence for a link between HIV-2 and AIDS was not apparent (126).

LAV-II seropositivity was documented in a lifelong resident of Mali. This 35-year-old soldier, who denied homosexuality, presented with weight loss from 77 to 32 kg over a period of two years and a three-month history of diarrhea. He was found to have Candida esophagitis and enteritis; intestinal infections with Salmonella typhimurium, Isospora belli, and Cryptosporidium; and cytomegalovirus ileitis. The concentration of leukocytes, lymphocytes, and CD-4 cells was low. No fever, hepatosplenomegaly, peripheral adenopathy, or hypergammaglobulinemia was found. Antibody to HIV-1 was not detectable (127).

Evidence of HIV-2 infection has also been reported from Central Africa. In a study from the Central African Republic, 14 of 82 asymptomatic mothers living in poverty were seropositive for antibody to HIV-1 by ELISA and Western blot. Of these 14, 11 had reactive HIV-2 ELISA antibody tests; three of these were shown by Western blot to represent double infection to HIV-1 and HIV-2, whereas eight apparently represented cross-reactions to the HIV-2 p26 antigen. Similarly, eight positive HIV-2 ELISA tests were found among 12 patients with AIDS who had antibody to HIV-1; these eight included three double infections and five cross-reactions (128).

Evidence of transmission of HIV-2 infection in European populations has also been sought.

In the United Kingdom, no evidence of infection with HIV-2 was detected in 520 sera from hemophiliacs, homosexual and heterosexual patients with other sexually transmitted diseases, and parenteral drug abusers, including 44 subjects admitting recent sexual contact in Africa. However, evidence of cross-reactivity with HIV-2 in a competitive ELISA assay was seen in some samples testing positive for antibody to HIV-1 (129).

Evidence of HIV-2 infection has been found in West Germany. Particular attention has been given to persons at high risk for AIDS in whom ambiguous results were obtained in tests for antibody to HIV-1 (chiefly positive reactions to the p24 and p52 core proteins and the p66 polymerase). Of over 300 such sera tested, nine were primarily reactive with HIV-2, and one showed evidence of infection with both viruses. One seropositive subject had apparently had a West African sex partner. Two seropositive persons had signs of ARC. Antibody to HIV-2 was found in specimens dating back to 1984 (130).

Asymptomatic infection was discovered in a promiscuous German woman, one of whose sex partners in Wiesbaden had been a Senegalese man who had later died of slim disease. The man had repeatedly been negative for antibody to HIV-1, but the woman's HIV-1 serologic results were equivocal. Immunoblot testing showed that the woman had specific IgG antibody to HIV-2 (131).

The Retrovirus Study Group of the French National Society of Blood Transfusion has tested sera from a number of sources with initially negative results in attempts to detect samples positive for HIV-2 (Table 10) (132).

Table 10. HIV-1 and HIV-2 Seropositivity in France

Date	Source	Number of Specimens	HIV-1 Seropositive	HIV-2 Seropositive
1985-1986	intravenous drug users*	375	1	0
	multiply-transfused*	210	0	0
	hemophiliacs*	164	0	0
	other AIDS risk groups*	20	0	0
	blood donors+	177	1	0
	imprisoned Africans	184	9	0
	imprisoned drug addicts	61	19	0
1987	blood donors			
	"non-selected"	6573	3	0
	military personnel	1706	0	0
	mobile unit in Paris	545	0	0
	formerly in Africa	189	0	0
not stated	prisoners	319	42	0

*Previously screened for antibody to HIV-1 with negative results.
+Previously screened for antibody to HIV-1 with equivocal results.

However, more recently, five seropositive blood donors have been identified in France; one was Senegalese and the other four had links to the Ivory Coast (133).

Seroconversion to HIV-2 was documented in a Moroccan living in Paris who had been hospitalized with immune thrombocytopenic purpura and found to have pulmonary tuberculosis. Transmission may have occurred through blood transfusions administered during his hospitalization. Alternatively, he may have become infected by contacts with African (probably Ghanaian) prostitutes, since HIV-2 infection may occur in Ghana (134).

Serologic testing performed on patients in Milan revealed that only one of 42 patients with AIDS was positive by ELISA for antibody to HIV-2, and Western blotting suggested that the result was attributable to cross-reaction from anti-HIV-1 antibody. In contrast, 20 of 68 patients with ARC had positive HIV-2 ELISA tests, and eight of these were confirmed by Western blotting. All subjects with antibody to HIV-2 were also seropositive against HIV-1. None gave a history of travel to Africa or of sexual contacts with Africans. Of interest, three patients with AIDS and six with ARC had no antibody to either HIV-1 or HIV-2 (135).

Related Retroviruses in Man

Swedish workers have reported three blood donors with positive ELISA tests for antibody to HIV-1 whose sera were repeatedly positive for antibody to HIV-1 p24 and p55 antigens by Western blot. These reactions were considered to be falsely positive in view of absence of antibody to other HIV-1 antigens on Western blots, negative competitive ELISA testing, negative immunofluorescence testing using H9 cells infected with HIV-1, and negative exposure histories. No antibody to HUT 78 cells infected with HIV-2 (HTLV-IV) was detectable in the sera. In addition to cross-reactions to ribonucleoproteins or other normal cell constitutents, the possibility of cross-reaction with other hypothetical human retroviruses was suggested as an explanation for the anomalous results (136).

Workers in Paris have described blood donors with falsely positive ELISA tests for antibody to HIV-1 in which Western blotting revealed antibody only to p24-25 and p55 (FP25, 11 men and 12 women) or to p18 and p 55 (FP18, three men and five women). These patterns were found in 0.05 per 1000 and 0.15 per 1000 units tested, respectively, in comparison with a proportion of 0.86 per 1000 units giving positive ELISA tests with confirmatory immunoblots. Tests of these anomalous sera for antibody to STLV-III and HIV-2 were negative, as were attempts to culture retroviruses from the donors' lymphocytes. No risk factors for HIV infection or abnormalities in CD4 and CD8 counts and IgG levels were detected in these donors (137).

Gallo has recently announced the isolation of another human retrovirus from Nigerian patients with AIDS. This virus displays antigenic relatedness to core proteins from HTLV-I and HTLV-II and from HIV-1 and HIV-2 (99).

Related Retroviruses Without Primate Hosts

> Olim quod vulpes aegroto cauta leoni
> Respondit referam: "quia me vestigia terrent,
> Omnia te adversum spectantia, nulla retrorsum."
>
> [The wary fox in the fable answered the sick lion:
> "Because I am frightened at seeing that all the
> footprints point towards your den and none the
> other way.]
>
> Horace, Epistles

Bovine immunodeficiency-like virus (BIV) is an infectious retrovirus that was isolated from the leukocytes of a cow that was ill with persistent lymphocytosis, lymphadenopathy, lesions of the central nervous system, weakness, and emaciation. This agent shares morphologic and antigenic characteristics with HIV-1 and cloned BIV provirus hybridizes with pol gene probes made from HIV-1 and visna viruses (138).

The virus (EIAV) that causes equine infectious anemia also demonstrates morphologic, antigenic, and genetic relatedness to HIV-1 (139).

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HTLV-I

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