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# Current status of HTLV-1 infection

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**Abstract** It is 30 years since human T-cell leukemia virus type 1 (HTLV-1) was identified as the first human retrovirus. To assess the implications of the virus for human health it is very important to know the past and present prevalence. Most of the estimates of HTLV-1 prevalence are based on serological screening of blood donors, pregnant women and other selected population groups. The widely cited estimate that the number of HTLV-1 carriers in Japan is 1.2 million was calculated from data that are now more than 25 years old. Here I summarize previous reports of prevalence studies in the world and Japan. Then, a recent analysis of seroprevalence of healthy blood donors in Japan will be described in comparison with that of 1988. A decrease in the number of HTLV-1 carriers in Japan was demonstrated, however, it is still more than one million. The number has increased in the metropolitan areas, probably reflecting the migration of Japanese population. I conclude that there is a paucity of general population data in countries where HTLV-1 is endemic, and re-evaluation of HTLV-1 infection is required to understand the virus burden on the human health.

**Keywords** Seroprevalence of HTLV-1 · Vertical and horizontal transmission · Prevention of transmission

## 1 Introduction

Discovery of adult T-cell leukemia (ATL) by Takatsuki's group [1] was followed by the discovery of the first human retrovirus human T-cell leukemia virus (HTLV) and adult T-cell leukemia virus (ATLV) by research groups of the United State and Japan, respectively [2, 3]. In 1980, Poiesz et al. [2] identified HTLV in a T-cell line from a patient with cutaneous T-cell lymphoma. Independently of this, Hinuma and Miyoshi found specific antibodies against ATL cells in the patients' sera [3] and type C retrovirus particles produced by a T-cell line established from peripheral blood of ATL patient in 1981 [4]. In 1982, Yoshida et al. [5] identified ATLV as a human retrovirus. Soon, HTLV and ATLV were shown to be identical at the sequence level and were named HTLV type 1 (HTLV-1) [6, 7].

After the discovery of HTLV-1, related viruses have been isolated and HTLV is now composed of 4 related HTLVs, HTLV-1 to HTLV-4 [8]. However, only HTLV-1 has been convincingly linked to human diseases at present. HTLV-1 has six reported subtypes (subtypes A–F). Diverse studies have been performed on HTLV-1 subtyping but present a minor role in the epidemiological status of the virus. The great majority of infections are caused by the cosmopolitan subtype A, and there is no report of subtype influence on the pathogenic potential of HTLV-1 [9].

## 2 HTLV-1 infection in the world

Approximately 20 million people worldwide are estimated to be infected with HTLV-1 [10]. Among them, more than 90% remain asymptomatic carriers during their lives. Since 1986, HTLV-1 screening has been developed and was slowly implemented worldwide [11]. In 1993, HTLV-1 screening of blood donors was already performed in all developed countries and in many developing countries where HTLV-1 is endemic.

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About the geographic distribution of the virus, a lot of studies have been done in these 30 years. Results indicate that Japan, Africa, the Caribbean islands, and Central and South America are the areas of highest prevalence in the world (reviewed in [12], [13]). However, the data from international prevalence studies should be interpreted and compared with caution as to the population selection criteria, because any difference in the diagnostic strategies can interfere with the final result. Data of the serological screening of healthy blood donors mainly provide basis for the estimation of the global prevalence of HTLV-1, which tends to underestimate the prevalence in the population. The geographic distribution of HTLV-1 infection is shown in Fig. 1 [13].

In addition to Japan, high rates of HTLV-1 infection have been reported for some Caribbean islands in studies of blood donors or segments of the general population. In Jamaica, the prevalence is around 5%. In Africa, the seroprevalence increases from the north to the south, varying from 0.6% in Morocco to greater than 5% in several sub-Saharan African countries, for example, Benin, Cameroon, and Guinea-Bissau, however, more studies are clearly required about these regions in detail. In Europe and North America, the prevalence is low and limited to groups that emigrated from endemic areas. For blood donors, very low rates were found in France (0.0039%) and the United States (0.025%). In South America, the virus was found in all countries, but more studies of the general population are needed to ascertain the real prevalence of HTLV-1. Medium prevalence was found in blood donors from Chile (0.73%) and Argentina (0.07%). In Australia, a prevalence of 14% was reported in a cluster among Aborigines in the Northern Territory, even though the prevalence in blood donors is low. The prevalence of HTLV-1 was highest in the two studies of Japanese islands (36.4%) and lowest in studies from Mongolia, Malaysia and India. In Haiti the prevalence was 3.8%; in Africa between 6.6 and 8.5% in Gabon, and 1.05% in Guinea. Only three studies were from West Africa and none were from the South; the only study from India was from the north of the country. It has to be

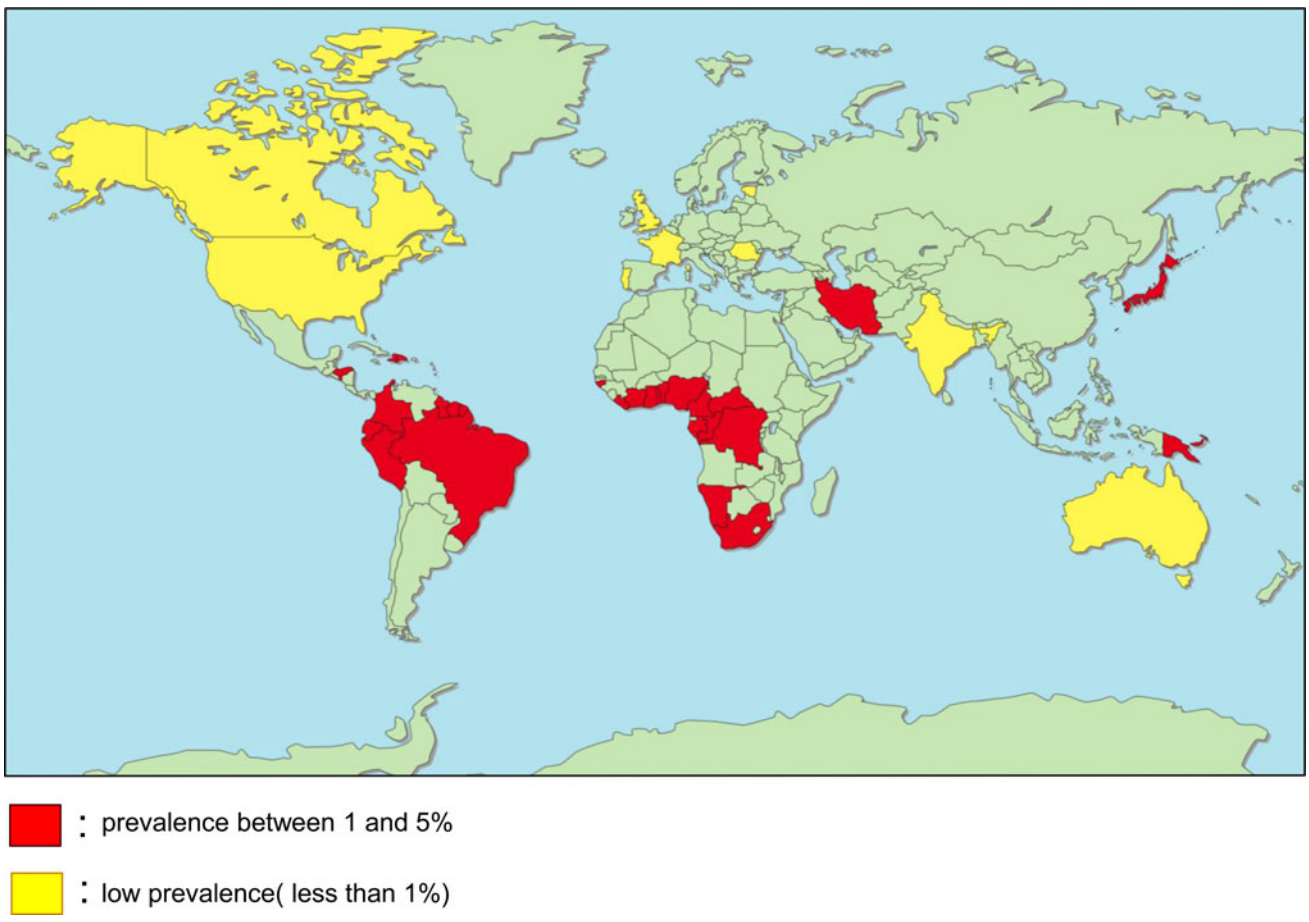


**Fig. 1** Countries with endemic HTLV-I, defined as prevalence between 1 and 5% in some populations, are shown in *red*. Countries with reports of low prevalence (less than 1% in some groups), due mainly to immigration from endemic areas, are shown in *yellow*. It should be noted that HTLV-I endemic areas do not correspond exactly to the country boundaries shown in the map, for example, Brazil, Japan and Iran, where HTLV-I is limited to residents of certain areas of each country (modified from the reference [13])

concluded that there is a paucity of general population data from countries in which HTLV-1 is endemic, and that new studies are required to reevaluate the global burden of infection (reviewed in ref. [12] and [13]).

## 3 HTLV-1 Infection in Japan

### 3.1 Past studies of HTLV-1 carriers

Many efforts have been made to know the number of HTLV-1 carriers since the discovery of the virus in Japan. An example of early nationwide studies is the report of seropositive rates in the 15 blood centers of Japanese Red Cross [14]. It was reported that among 15 blood centers, 7 showed a higher positive rates between 6 and 30%, tested by indirect immunofluorescence assays (IFA). The other report is based on the data of all blood centers in Japan, which was the only study of all areas of Japan before the resent survey by Satake et al. [15]. They studied by IFA about 15,000 samples composed of 200 samples of blood donors aged from 40 to 64 from each center. The highest positive rate of 8% was observed in Kyushu area, and other areas showed positive rates of 0.3–1.2%. Based on these data, authors estimate seropositive rates of blood donors as about 3% in Kyushu and 0.08–0.3% in other areas of Japan. Using this study, Tajima et al., later estimated the total number of HTLV-1 carriers in Japan as 1.2 million [16].

There have been reports of community-based studies on seropositivities in Japan. One of the studies reported a very high seropositive rate (higher than 40%) in the people over 40 years of age [17]. An old study of the Tsushima Island revealed significant differences in the seropositive rate among villages with a high rate of more than 30% [18]. In Okinawa, a very high rate (21%) of HTLV-1 carriers in the general population of older than 40 was reported [19]. In a study of blood donors in Nagasaki prefecture from 1990 to 1999, positive rate of HTLV-1 antibodies decreased from 3.39 to 2.78% during 10 years. When focusing on the birth year of the donors, positive rates showed a decrease from 13.14 to 0.81% over the years from 1928 to 1983 [20]. On the other hand, the seroprevalence rate in Kumamoto prefecture was reported to be 3.6 or 4.7% in 1987–1988 [21, 22]. A survey on the general population was reported in Hokkaido. The average seropositive rate was 0.8% (male 0.6% and female 0.9%), with some regions showing higher seroprevalence rates as much as 5.2% [23].

Taken together, studies in 1980s and 1990s were mostly community-based ones using sera of blood donors. The oldest nationwide survey of the seroprevalence of HTLV-1 in blood donors and estimation of the number of HTLV-1 carriers [15, 16] had been referred to as the only published information until recently.

### 3.2 Recent studies of HTLV-1 infection in Japan

Based on the numbers of seropositive blood donors, Satake et al. have estimated the number of HTLV-1 carriers in Japan [15]. They analyzed data of blood donors who donated for the first time in 2006 and 2007, because Japanese Red Cross Blood center has notified the donors with the results of screening tests since 2000. This notification would have caused a bias in the population of total blood donors reducing the number of HTLV-1 carriers. In Satake's study, the total of number of tested was 1,196,321 (M: 704,074; F: 492,247), among them, HTLV-1 antibody was confirmed to be positive in 37,787 (M: 2,115; F: 1,672). Thus, the positive ratio was 0.32% for both male and female. Since the ages of blood donors were limited between 16 and 64, they estimated the seropositive rates of the peoples of younger than 15 or older than 65 by an assumption that the positive rate will increase exponentially in the young population, and for the aged people, by adding the average increase in the percentage in each age group in 20 years comparing with the data in 1988. Consequently, the estimated number of HTLV-1 carriers in 2007 was 1,078,722. The number of HTLV-1 carriers was estimated to be 492,582 in Kyushu area (including Okinawa), 171,843 in Kinki area (containing city areas of Osaka, Kyoto, Kobe) and 190,609 in Kanto area (containing the greater Tokyo area). The percentages of carriers in these areas among the total carriers were 45.7, 15.9 and 17.7%, respectively.

The age distribution of carriers showed a shift of the peak to the aged population. In 1988, the largest number of carriers was observed in the age group of 50–59, whereas in 2007 it was in the age groups of 60–69 and 70–79. The number of carriers in the age groups between 0–9 and 50–59 showed a significant decrease. This decline could be explained by changes in the life styles of Japanese people such as smaller number of children per family and shorter period of breast feeing. However, the exact reasons remain to be elucidated, especially considering the same tendency observed in the study of Brazilian people [24] and the age-dependent increase in the seropositivity in the colony of Japanese monkeys [25, 26].

Comparison of the regional distribution of the carriers in the present study with that reported by a Japanese study group in 1990 [27] revealed a significant decrease of the HTLV-1 carriers in Kyushu area (50.9 to 45.7%) and an increase in Kanto area (10.8 to 17.7%). The observed changes were considered to be mainly due to the migration of Japanese people from the Kyushu/Okinawa area to the metropolitan areas (Fig. 2). This interpretation is supported by the observation of Uchimaru et al. [28], who studied HTLV-1 carriers in Tokyo area and revealed that many of HTLV-1 carriers in Tokyo are either born in

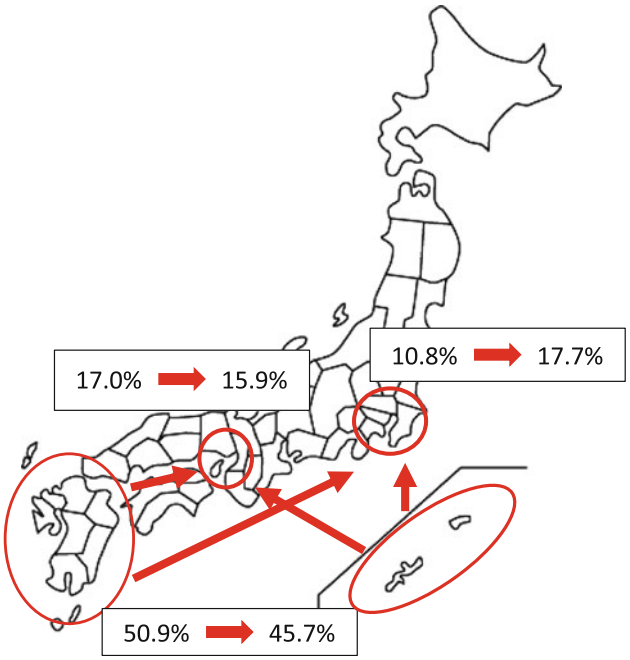


**Fig. 2** Distribution of HTLV-1 carriers in Japan. Migration to the metropolitan areas is apparent. The number of HTLV-1 carriers in the endemic areas is still the largest, however, those in the great Tokyo area is significantly increasing

the endemic areas or the descendants of migrants from those areas.

## 4 Remaining problems and future directions

We have attributed the decrease in the HTLV-1 prevalence in Japan to the modernization and westernization of life styles of Japanese people. However, when we consider the same tendency in Brazil and age-dependent increase of seropositive rates in Japanese monkeys, we have to be cautious about interpretation of the observed data and may have to re-evaluate the meaning of the age-dependent carrier rates.

Another point that was raised by Satake's study is unexpectedly high increase in the positive rates in 20 years in the age-cohort [15]. This indicates the presence of horizontal transmission of the virus, probably through sexual contacts. This mode of infection should have contributed, at least to some extent, to the age-dependent increase in the positive rates. Thus, epidemiological studies on the horizontal transmission are definitely required; however, no such studies are now under way in Japan.

Taken together, we have to realize that we do not have enough data about the prevalence of HTLV-1 even in Japan, where serological data of blood donors are the only information to estimate the prevalence. Serological screening of the pregnant women that started in 2011 will provide valuable information about young females in Japan. Since the number of carriers who develop ATL is estimated about 1,200 per year in Japan, we have to expect more than 20,000 ATL patients from the present carriers in the future. In addition to the screening for the blood donors, prevention of mother-to-child infection by stopping breast feeding will greatly reduce the vertical transmission, nonetheless, there still remain other modalities of HTLV-1 infection, that are sexual transmission and possible trans-uterine infection. Neutralizing antibodies are often observed in carriers of HTLV-1 [29–32]. Furthermore, previous reports suggest that a primed immune response can be protective or prevent infection postviral exposure and challenge. It was shown that maternally acquired antibody protect infants from HTLV-1 infection in the early months of life [33]. A vaccine candidate based on an envelope expressing vaccinia virus provides protection to experimentally challenged primates [34, 35], and an attenuated viral strain provides long-term protection against the closely related bovine leukemia virus [36]. Taking all these into consideration, a costeffective vaccine may be a viable objective for prophylactic intervention in HTLV-1-endemic areas.

## References

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood. 1977;50:481–92.
2. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA. 1980;77:7415–9.
3. Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA. 1981;78:6476–80.
4. Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature. 1981;294:770–1.
5. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci USA. 1982;79:2031–5.
6. Watanabe T, Seiki M, Yoshida M. Retrovirus terminology. Science. 1983;222:1178.
7. Gallo RC. History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. Oncogene. 2005;24:5626–930.
8. Mahieux R, Gessain A. The human HTLV-3 and HTLV-4 retroviruses: new members of the HTLV family. Pathol Biol (Paris). 2009;57:161–6.
9. Ono A, Miura T, Araki S, Yamaguchi K, Takatsuki K, Mori S, et al. Subtype analysis of HTLV-1 in patients with HTLV-1 uveitis. Jpn J Cancer Res. 1994;85:767–70.

10. de Thé G, Kazanji M. An HTLV-I/II vaccine: from animal models to clinical trials? J Acquir Immune Defic Syndr Hum Retrovirol. 1996;13(Suppl 1):S191–8.
11. Inaba S, Sato H, Okochi K, Fukada K, Takakura F, Tokunaga K, et al. Prevention of transmission of human T lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus. One-year experience. Transfusion. 1989;29: 7–11.
12. Goncalves DU, Proietti FA, Ribas JGR, Araujo MG, Pinheiro SR, Guedes AC, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 2010;23:577–89.
13. Proietti FA, Anna Bárbara, Carneiro-Proietti F, Bernadette C, Catalan-Soares, Murphy EL, et al. Global epidemiology of HTLV-I infection and associated diseases. Oncogene. 2005;24: 6058–68.
14. Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, et al. Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. Int J Cancer. 1982;29:631–5.
15. Satake M, Yamaguchi K. Annual report of the group study for survey of HTLV-1 infection and HTLV-1 related diseases in Japan. 2009 (in Japanese) (Manuscript submitted).
16. Tajima K. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. Int J Cancer. 1990;45:237–43.
17. Kohakura M, Nakada K, Yonahara M, Komoda H, Imai J, Hinuma Y. Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. Jpn J Cancer Res. 1986;77:21–3.
18. Tajima K, Kamura S, Ito S, Ito M, Nagatomo M, Kinoshita K, Ikeda S. Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL-endemic island: a report of the community-based co-operative study in Tsushima, Japan. Int J Cancer. 1987;40:741–6.
19. Kohakura M, Nakada K, Yonahara M, Komoda H, Imai J, Hinuma Y. Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. Jpn J Cancer Res. 1986;77:21–3.
20. Chiyoda S, Kinoshita K, Egawa S, Inoue J, Watanabe K, Ifuku M. Decline in the positive rate of human T-lymphotropic virus type-1 (HTLV-1) antibodies among blood donors in Nagasaki. Intern Med. 2001;40:14–7.
21. Lee SY, Mastushita K, Machida J, Tajiri M, Yamaguchi K, Takatsuki K. Human T-cell leukemia virus type I infection in hemodialysis patients. Cancer. 1987;60:1474–8.
22. Iida S, Fujiyama S, Yoshida K, Morishita T, Shibata J, Sato T, et al. The seroprevalence of anti-HTLV-1 antibodies in patients with various liver diseases. Hepatogastroenterol. 1988;35:242–4.
23. Kwon KW, Yano M, Sekiguchi S, Iwanaga M, Fujiwara S, Oikawa O, et al. Prevalence of human T-cell leukemia virus type 1 (HTLV-I) in general inhabitants in non-adult T-cell leukemia (ATL)-endemic Hokkaido, Japan. In Vivo. 1994;8:1011–4.
24. Barcellos NT, Fuchs SC, Mondini LG, Murphy EL. Human T lymphotropic virus type I/II infection: prevalence and risk factors in individuals testing for HIV in counseling centers from Southern Brazil. Sex Transm Dis. 2006;33:302–6.
25. Ishida T, Yamamoto K, Kaneko R, Tokita E, Hinuma Y. Seroepidemiological study of antibodies to adult T-cell leukemia virus-associated antigen (ATLA) in free-ranging Japanese monkeys (Macaca fuscata). Microbiol Immunol. 1983;27:297–301.
26. Hayami M, Komuro A, Nozawa K, Shotake T, Ishikawa K, Yamamoto K, et al. Prevalence of antibody to adult T-cell leukemia virus-associated antigens (ATLA) in Japanese monkeys and other non-human primates. Int J Cancer. 1984;33:179–83.
27. Tajima K, Itoh S, Itoh T, Kinoshita K, Shimotohno K. Epidemiology of ATL and HTLV-1. In: the annual report of the group study "Inhibition of mother-to-child infection and ATL" (1990). 1991 (in Japanese).
28. Uchimaru K, Nakamura Y, Tojo A, Watanabe T, Yamaguchi K. Factors predisposing to HTLV-1 infection in residents of the greater Tokyo area. Int J Hematol. 2008;88:565–70.
29. Astier-Gin T, Portail JP, Londos-Gagliardi D, Moynet D, Blanchard S, Dalibart R, et al. Neutralizing activity and antibody reactivity toward immunogenic regions of the human T cell leukemia virus type I surface glycoprotein in sera of infected patients with different clinical states. J Infect Dis. 1997;175:716–9.
30. Londos-Gagliardi D, Armengaud MH, Freund F, Dalibart R, Moze E, Huet S, et al. Antibodies directed against a variable and neutralizable region of the HTLV-I envelope surface glycoprotein. Leukemia. 1997;11(Suppl. 3):38–41.
31. Hadlock KG, Rowe J, Perkins S, Bradshaw P, Song GY, Cheng C, et al. Neutralizing human monoclonal antibodies to conformational epitopes of human T-cell lymphotropic virus type 1 and 2 gp46. J Virol. 1997;71:5828–40.
32. Hadlock KG, Rowe J, Foung SK. The humoral immune response to human T-cell lymphotropic virus type 1 envelope glycoprotein gp46 is directed primarily against conformational epitopes. J Virol. 1999;73:1205–12.
33. Takahashi K, Takezaki T, Oki T, Kawakami K, Yahiski S, Fujiyoshi T, et al. Inhibitory effect of maternal antibody on mother-to-child transmission of human T-lymphotropic virus type I. Int J Cancer. 1991;49:673–7.
34. Kazanji M, Heraud JM, Merien F, Pique C, de The G, Gessain A, Jacobson S, et al. Chimeric peptide vaccine composed of B- and T-cell epitopes of human T-cell leukemia virus type 1 induces humoral and cellular immune responses and reduces the proviral load in immunized squirrel monkeys (*Saimiri sciureus*). J Gen Virol. 2006;87:1331–7.
35. Kazanji M, Tartaglia J, Franchini G, de Thoisy B, Talarmin A, Contamin H, Gessain A, de The G, et al. Immunogenicity and protective efficacy of recombinant human T-cell leukemia/lymphoma virus type 1 NYVAC and naked DNA vaccine candidates in squirrel monkeys (*Saimiri sciureus*). J Virol. 2001;75:5939–48.
36. Kerkhofs P, Gatot JS, Knapen K, Mammerickx M, Burny A, Portetelle D, Willems L, Kettmann R. Long-term protection against bovine leukaemia virus replication in cattle and sheep. J Gen Virol. 2000;81:957–63.