Table 2. (Continued.)

Patient No.	Time of Measurement	Alanine Aminotransferase*	Aspartate Aminotransferase†	γ-Glutamyl-transferase‡	Bilirubin§	Liver Biopsy	
			units/liter		*mg/dl*	*Metavir activity score*¶	*Metavir fibrosis score*‖
14	Baseline	14	23	30	1169		
	Diagnosis	143	106	132	877		
	13-Mo follow-up	126	118	585	994	1	3
Median							
	Baseline	26	23	32	584		
	Diagnosis††	248	115	167	818		
	Follow-up‡‡	59	40	79.5	731		

* Normal values for alanine aminotransferase range from 5 to 34 units per liter.
† Normal values for aspartate aminotransferase range from 3 to 30 units per liter.
‡ Normal values for γ-glutamyltransferase range from 7 to 38 units per liter.
§ To convert values for bilirubin to micromoles per liter, multiply by 17.1. Normal values range from 2 to 21 mg per deciliter.
¶ For assessment of disease activity, a Metavir score of 0 indicates no activity, 1 mild activity, 2 moderate activity, and 3 severe activity.
‖ For assessment of fibrosis, a Metavir score of 0 indicates no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis.
** Patient 2 had substantial alcohol consumption before the acute phase.
†† The differences between values at baseline and at diagnosis are significant for alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase (P=0.001) and for bilirubin (P=0.02).
‡‡ The differences between values at diagnosis and at last follow-up (median, 15 months) are significant for alanine aminotransferase (P=0.003), aspartate aminotransferase (P=0.02), and γ-glutamyltransferase (P=0.03).

nal measurements remained unchanged during the follow-up as compared with preinfection levels (data not shown). HEV seroconversion was observed in four patients with resolving HEV infection (two at 1 month and one each at 3 and 6 months after diagnosis) and seven patients with chronic infection (one at 3 months, two at 6 months, two at 12 months, and one each at 13 and 15 months after diagnosis).

Only six of the eight patients with chronic infection underwent a second liver biopsy (one at 10 months, two at 12 months, and one each at 13, 15, and 18 months after the diagnosis of acute HEV infection). The two remaining patients declined liver biopsy. The mean Metavir activity and fibrosis scores of the six patients who underwent biopsy were 2.0±1.0 and 1.8±0.8, respectively. All biopsy specimens showed features of chronic viral hepatitis, characterized by fibrosis and portal hepatitis, with dense lymphocytic infiltrate and variable degrees of piecemeal necrosis. Lobular hepatitis was mild to moderate in all cases. In the four patients who underwent a liver biopsy during both the acute phase and the chronic phase, the Metavir activity scores progressed from 1.0±0.8 to 2.2±0.9 and the fibrosis scores from 1.2±0.5 to 1.5±0.5.

RESOLVING VERSUS CHRONIC HEV INFECTION

During the acute phase, there were no significant differences between the patients with resolving HEV infection and those with chronic infection in median serum HEV RNA concentrations (5.97 $\log_{10}$ copies of RNA per milliliter [range, 5.79 to 6.44] and 6.18 $\log_{10}$ copies per milliliter [range, 4.92 to 7.28], respectively). There also were no significant differences between the groups in peak liver-enzyme levels. Hepatitis developed later after transplantation in patients with resolving HEV infection than in those in whom the infection progressed. Patients in whom chronic hepatitis developed had significantly lower serum creatinine levels at baseline and significantly lower counts of leukocytes, total lymphocytes, platelets, and CD2, CD3, and CD4 lymphocytes (Table 3). The percentages of patients who received induction therapy at transplantation or who received calcineurin inhibitors, mycophenolate mofetil or sodium, or inhibitors of the mammalian target of rapamycin (mTOR) were similar in the two groups. The dosage and trough levels of immunosuppressive drugs, as well as the proportions of patients with anti–hepatitis A virus, anticytomegalovirus, or IgG antibodies to Epstein–Barr virus, were similar in the two groups (data not shown).

Table 3. Patients with Resolving HEV Infection and Those in Whom the Infection Evolved to Chronic Hepatitis.

Variable	Patients with Resolving Infection (N=6)	Patients with Chronic Infection (N=8)	P Value
	median (range)		
At diagnosis			
Time since transplantation — mo	78.5 (25–168)	37.5 (6.0–63.0)	0.03
Leukocyte count — $\times 10^{-3}/mm^3$	8.85 (6–9.66)	4.31 (2.19–7.20)	0.004
Lymphocyte count — $\times 10^{-3}/mm^3$			
Total	1.73 (1.12–2.33)	0.75 (0.63–1.04)	0.004
CD2+	1.59 (0.84–2.25)	0.66 (0.58–0.92)	<0.001
CD3+	1.54 (0.70–1.88)	0.61 (0.49–0.79)	0.01
CD4+	0.93 (0.49–1.07)	0.22 (0.16–0.40)	0.004
Platelet count — $\times 10^{-3}/mm^3$	261 (190–285)	155.5 (75.0–250.0)	0.01
Serum creatinine — mg/dl*	2.15 (1.31–2.84)	1.33 (1.08–1.89)	0.01
At last follow-up			
Aspartate aminotransferase — IU/liter	25.5 (7–35)	55.5 (39.0–238.0)	0.002
Alanine aminotransferase — IU/liter	25 (13–45)	108.0 (59.0–298.0)	0.002

* To convert values for creatinine to micromoles per liter, multiply by 88.4.

DISCUSSION

HEV infection is transmitted by the fecal–oral route and may be a zoonosis in industrialized countries. It has a mortality rate of about 1% in the general population and 30% in pregnant women.[13] HEV-induced acute hepatitis may be fulminant,[14] but we are not aware that any cases of chronic hepatitis have previously been reported. Recently, the diagnosis of many cases of acute HEV hepatitis in nonimmunocompromised patients in southwest France[15] prompted us to look systematically for HEV in recipients of solid-organ transplants who had unexplained hepatitis. Of the 14 patients with acute HEV infection whom we report on here, 8 underwent progression to chronic hepatitis. In addition, in this issue of the *Journal*, Gérolami et al. report a case of HEV-related cirrhosis in a kidney-transplant recipient.[16]

After all other causes of hepatitis had been ruled out, the serum of 14 patients, none of whom had traveled outside France in the previous year, was found to be positive for HEV RNA. We did not identify any source of contamination. The peak aminotransferase levels were lower than in nonimmunocompromised patients.[17,18] Histologic lesions (mainly spotty lobular necrosis) that are characteristic of classic acute viral hepatitis were seen; these lesions were less severe than those typically seen in nonimmunocompromised patients. These findings could be related to the immunosuppressive therapy in transplant recipients.

HEV infection resolved in 6 of the 14 patients within 6 months after the end of the acute phase. In contrast, HEV infection in eight patients evolved to chronic hepatitis, as indicated by persistently elevated liver-enzyme levels and detectable serum HEV RNA at a median of 15 months (range, 10 to 24) after the end of the acute phase. Liver biopsies performed at a median of 12.5 months (range, 10 to 18) after the acute phase revealed signs of chronic viral hepatitis. The histologic lesions — dense lymphocytic portal infiltrate with constant piecemeal necrosis — were similar to those observed in patients chronically infected with hepatitis C virus. None of the patients received any specific therapy; in particular, none received antiviral therapy. Immunosuppressive therapy was not modified after the diagnosis of HEV. In the absence of available therapeutic recommendations for patients infected with HEV, we only performed close monitoring of liver-enzyme levels.

There were no significant differences between patients with resolving HEV infection and those with chronic HEV infection in demographic or clinical features, including treatment with immunosuppressive agents before the acute phase. However, the immunologic status of the patients may have had a role in the evolution to chronic dis-

ease. In patients in whom the infection became chronic, the time from transplantation to the development of infection was significantly shorter — and consequently, the total lymphocyte counts and the CD2, CD3, and CD4 lymphocyte counts were significantly lower — than in patients in whom HEV infection resolved. Hence, the T-cell response seems to have a role in HEV clearance, as does the B-cell response.

HEV seroconversion occurred later in patients with chronic infection than in those with resolving infection. This difference may be related to the reduction in the humoral immune response caused by treatment with mycophenolate, inhibitors of mTOR, or both. These drugs are known to decrease the synthesis of antibodies[19,20] and to inhibit the cell-cycle progression and differentiation of human B lymphocytes.[21] The humoral immune response is necessary to clear HEV and to prevent hepatitis. Bryan et al. have shown that antibodies to the HEV capsid can be protective against hepatitis E.[22] Passive immunoprophylaxis studies in cynomolgus monkeys have confirmed that the antibody to the HEV capsid may prevent HEV infection in humans.[23] Recently an HEV recombinant protein vaccine was found to be effective in preventing HEV infection.[24]

Further studies are required to determine the incidence of chronic HEV infection in transplant recipients who live in areas where the disease is not endemic. Vaccination against HEV could be proposed to patients before or after organ transplantation. However, the efficacy of vaccination in these populations should be addressed.

In conclusion, our data suggest that HEV should be considered an etiologic agent of hepatitis in organ-transplant recipients. We have demonstrated that HEV infection can evolve to chronic hepatitis, at least in organ-transplant recipients. A longer follow-up is required to assess the outcome of HEV infection in organ-transplant recipients.

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研究報告の概要

○フランスの新規HIV診断例におけるHIV-2、HIV-1のグループO型の感染率:2003～2006年
新規HIV診断例のHIV血清型を同定するため、フランス国内で調査用に採取された乾燥血清spotsを用いた。2003年1月～2006年6月に、10,184の新規診断例が報告された。HIV-2、HIV-1のグループO型感染の割合は、それぞれ1.8、0.1%であった。これら症例のほとんどは、異性との接触により感染した流行地域出身の患者であった。HIV-2感染の3症例は、男性との性交渉を持つ非アフリカ系男性で報告された。

報告企業の意見	今後の対応
2003年1月～2006年6月に、フランスにおいて10,184の新規HIV診断例が報告され、HIV-2、HIV-1のグループO型感染の割合は、それぞれ1.8、0.1%であったとの報告である。	日本赤十字社では、HIV抗体検査に加えて20プールでスクリーニングNATを行い、陽性血液を排除している。また、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)の導入を順次進めている。さらに、HIV-2及びHIVグループOの検出が可能な次世代NATの導入に向けた準備を進めている。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

Prevalence of HIV-2 and HIV-1 group O infections among new HIV diagnoses in France: 2003–2006

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French national surveillance of new HIV diagnoses included the collection of dried serum spots to identify HIV serotypes. Between January 2003 and June 2006, 10 184 new diagnoses were reported. The proportions of HIV-2 and HIV-1 group O infections were 1.8 and 0.1%, respectively. Most of these cases occurred in patients infected through heterosexual contact and originated from the corresponding endemic areas. Three cases of HIV-2 infections were reported in non-African men having sex with men.

HIV-2, first suspected by serological findings in west African residents, was isolated from patients with AIDS originating from Cape Verde and Guinea Bissau [1,2]. Although HIV-2 causes AIDS, it is clearly less pathogenic than HIV-1 [3,4]. The viral load is significantly lower in HIV-2-infected patients, and consequently HIV-2 is less transmissible [5,6]. The precise diagnosis of HIV-2 has implications, particularly for monitoring RNA levels, as no specifically dedicated commercial assays are currently available, and for the choice of antiretroviral treatment, because HIV-2 strains are naturally resistant to non-nucleoside reverse transcriptase inhibitors and fusion inhibitors, and are less sensitive *in vitro* to some protease inhibitors [7,8]. HIV-2 is endemic in west Africa. Most cases described outside Africa have been traced to contacts with individuals from this endemic region. This has been particularly observed in European countries with historical links with west Africa such as France, the United Kingdom and Portugal [9–11]. No extensive epidemiological surveys have, however, allowed the determination of the exact prevalence of HIV-2 in these European countries. Similarly, HIV-1 group O variants are restricted geographically, mainly to Cameroon and the surrounding areas [12]. Rare cases have been reported in industrialized countries, but the exact prevalence of these variants among HIV-1-infected patients is unknown. Similar to HIV-2, most of the commercially available assays for the quantification of HIV-1 RNA do not detect viral sequences from HIV-1 group O variants [13], and non-nucleoside reverse transcriptase inhibitors are inefficient at controlling HIV-1 group O replication [14].

Mandatory anonymous HIV case reporting was implemented in France in 2003, with which virological monitoring using dried serum spots was associated. The procedures and the first results of this surveillance system have been described elsewhere [15]. In brief, any HIV-positive serology confirmed for the first time by a clinical laboratory must be reported, with a unique anonymous code for each patient. Clinical and epidemiological details are supplied by the physicians in charge of the patients. For each case, the laboratory is asked to send dried serum spots collected on filter papers from the serum sample obtained for the original diagnosis to the National Reference Centre (NRC). Although HIV notification is mandatory, virological surveillance is based on volunteer participation by both microbiologists and patients. The patient's consent for virological surveillance is obtained by the reporting clinician through the HIV notification form. Serological identification of the type and group of HIV is performed by enzyme-linked immunosorbent assay at the NRC, as described [16]. Results from the NRC are then linked to the epidemiological data in the HIV national database using the patient's anonymous code. Any specific diagnosis of infection by either HIV-2 or HIV-1 group O implies transmission of the information to the clinical laboratory of origin in order to adapt the clinical, biological and therapeutic management of the patient.

Here we report the results of the HIV-2 and HIV-1 group O infections that were identified among new HIV diagnoses during the past 3 years. Between January 2003 and June 2006, 10 184 new diagnoses with participation in the virological surveillance were reported. Among these, 186 were from patients infected by HIV-2 [1.8%; 95% confidence interval (CI) 1.6–2.1], of which 164 (1.6%; 95% CI 1.4–1.9) were HIV-2 only and 22 (0.2%; 95% CI 0.1–0.3) were probable dual infections. The serological diagnosis of dual infection was based on similar high antibody binding to both the immunodominant epitope of gp41 and the V3 region of both HIV-1 and HIV-2 [16,17]. Such a stringent criteria was validated earlier [17], and more recently on a panel of samples for which single or dual infections were diagnosed by type-specific polymerase chain reaction (data not shown). Patients infected with HIV-2 were mostly citizens of a west African country (65%; $n=121$), mainly Côte d'Ivoire ($n=64$), Mali ($n=19$) and Senegal ($n=12$), but there were also 22 European individuals, 20 from France and two from Portugal (Fig. 1). The majority of cases was observed in women (63%; $n=118$). Although the risk factor was unknown for 26% ($n=48$) of cases, 72% ($n=134$) of HIV-2 infections were caused by heterosexual transmission. HIV-2 was, however, identified in three men who have sex with men (MSM), one from France and two from the Americas.

Twelve patients (0.1%; 95% CI 0.1–0.2) were infected with HIV-1 group O variants. Most of them originated from the sub-Saharan endemic area: nine from Cameroon and one from Chad (Fig. 1). Two of those patients had dual M/O infection; those two cases have been described in detail earlier [18]. The two other cases were French

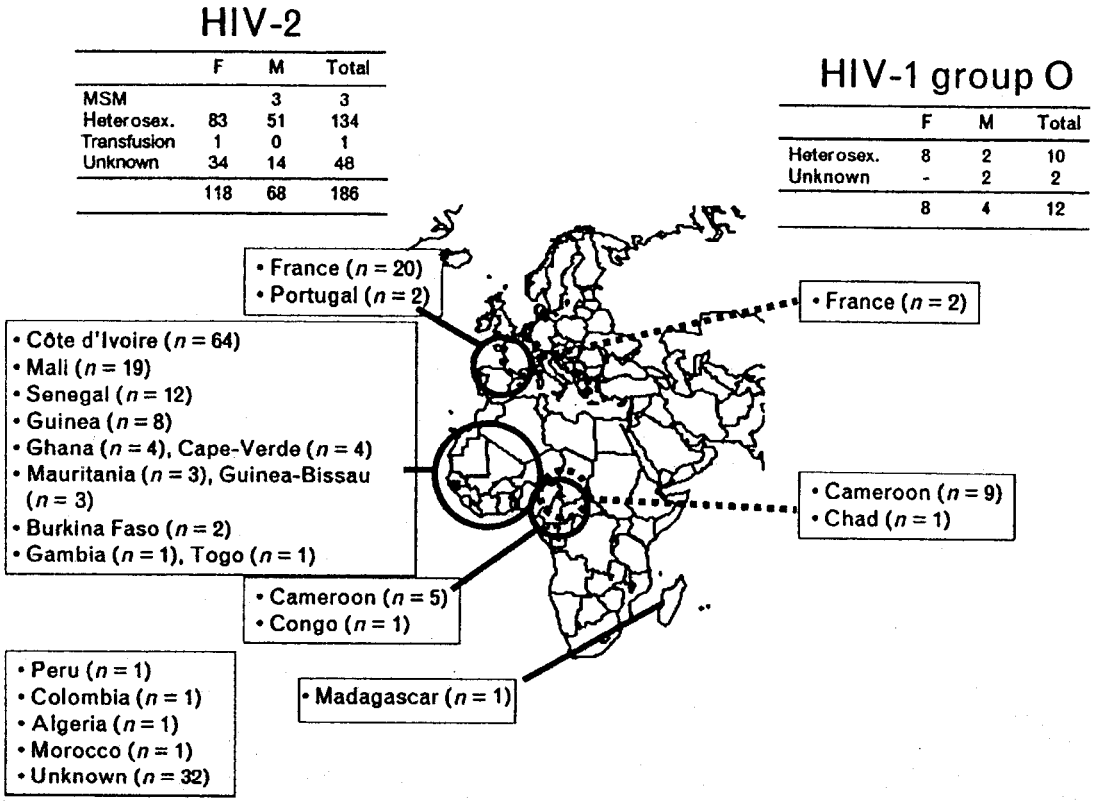

Fig. 1. Nationality and mode of transmission of patients identified as infected by HIV-2 (left) and HIV-1 group O (right) in France, 2003–2006. F, Female; Heterosex., heterosexual transmission; MSM, men who have sex with men; M, male.

citizens who had probably been infected through heterosexual intercourse.

A specific serological diagnosis of HIV-2 infection may be missed if adapted confirmation tools are not routinely used in clinical laboratories, a situation that is frequent in non-endemic areas. There is a frequent use of HIV-1 Western blots for confirmatory diagnosis, on which serum samples positive for antibodies to HIV-2 may cross-react, even on envelope glycoproteins, leading to a misclassification as anti-HIV-1 positives [19]. Similarly, HIV-1 group O infections are not systematically diagnosed as such, except if there are dissociations between clinical and biological findings in an HIV-1-positive patient; for example, AIDS stage with undetectable viral load. This is because there is no commercially available specific serological tool for this purpose. Therefore, there are no data that would provide estimates of the prevalence of these rare variants in western countries. The French national surveillance of new HIV diagnoses included the collection of dried serum spots to identify HIV serotypes with dedicated peptide immunoassays [16,17]. This allowed, for the first time, the provision of reliable estimates of the proportion of these rare variants in a European country. The results indicate that most of the cases diagnosed during this 3-year period still occurred in patients originating from the endemic areas, west Africa and Cameroon, for HIV-2 and HIV-1 group O, respectively. Three cases of HIV-2 infections were, however, reported in MSM, an observation that should deserve further attention because of the persistent high-risk behaviours in some individuals in the gay community.

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研究報告の概要

○1999～2006年の長崎における日本人献血者ヒトT細胞向性ウイルス1型 (HTLV-1) 感染率の傾向

HTLV-1の流行地域である日本の長崎では、1986年から献血者のルーチンの血清スクリーニング検査、1987年からウイルスキャリアの母親からの乳汁媒介伝播予防のために長崎県ATL ウイルス母子感染防止研究協力事業(APP)が実施されている。本試験では、1999年1月～2006年12月に献血を行った初回献血者の年齢別、出生年別、および期間別HTLV-1血清陽性率の傾向分析を行った。初回献血者55,668名(献血時年齢16～65歳、出生年1934～1990)のうち、718名はHTLV-1検査陽性であり、全体的な血清陽性率は1.29% (95%CI, 1.20-1.39)であった。陽性率は男性よりも女性の方が高かった(1.53%vs.1.13%; OR; 1.36, 95%CI; 1.17-1.57)。血清陽性率は、年齢が高くなるにつれ有意に上昇し、献血時年齢16～25歳では0.70%、献血時年齢56歳以上では7.34% (χ2乗検定、P<0.0001)であった。年間感染率は1999年が1.32、2002年が1.31、2006年が1.37であり、期間中に有意な経年傾向がないことが示された(P for trend=0.99)。献血時年齢の解析では、陽性率は56歳以上(P for trend=0.02) と16～25歳 (P for trend=0.0007)では有意に減少したが、出生年別解析では、1981～90年出生群で1999年の1.22%から2006年の0.44%へ減少(P for trend<0.0001)したことを除き、陽性率の経時的変化は見られなかった。1985～90年出生群の解析では、血清陽性率は1985～86年出生群の0.75% 、1987～88年出生群の0.31%から1989～90年出生群の0%に減少した(P for trend=0.0002)。

HTLV-1血清陽性率は、APP開始後の1987～90年に生まれた献血者では、1985～86年に生まれた献血者と比較して有意に低かった。以上の結果は、ほとんどのウイルス伝播が幼児期に起こるため、HTLV-1陽性率の出生年解析が経年傾向の評価に適切であると考えられることを示し、ウイルスキャリアの母親の授乳を避けることを指導した県をあげての対応が、当該地域のHTLV-1血清陽性率の減少に貢献していることを示している。

報告企業の意見	今後の対応
1999～2006年の長崎における献血者のヒトT細胞向性ウイルス1型感染率は、1987～90年に生まれた献血者では1985～86年に生まれた献血者と比較して有意に低く、ウイルスキャリアの母親の授乳を避けることを指導した県をあげての対応が陽性率の低下に貢献していることが示されたとの報告である。	日本赤十字社では、HTLV-1のスクリーニング検査を行っている。今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(二)

Basic Science and Clinical Practice in Blood Transfusion

Basic Science and Clinical Practice in Blood Transfusion

Trend in Prevalence of Human T-Lymphotropic Virus Type-1 (HTLV-1) Infection in Japanese Blood Donors, Nagasaki, 1999 to 2006.

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Abstract

To aluate time-trend of HTLV-1 prevalence and the effect of preventative measure against the viral transmission are important in the virus endemic regions. In Nagasaki, Japan, an endemic area of HTLV-1, a routine serological virus screening for blood donors and a prefecture-wide intervention project (the ATL Prevention Program; APP) to prevent milk-borne transmission for the virus carrier mothers have been conducted since 1986 and 1987, respectively. However, the effects of both projects on the virus seroprevalence have not been well evaluated. In this study, we conducted trend analyses of age-specific, birth-year-specific, and period-specific seroprevalence of HTLV-1 for first-time blood donors who donated between January 1999 and December 2006. Among 55668 first-time donors (age at donation; 16–65 years, birth year; 1934–1990), 718 were test positive for HTLV-1, indicating that the overall seroprevalence was1.29% (95%CI, 1.20–1.39). Prevalence was significantly higher in women than men (1.53% vs. 1.13%; OR; 1.36, 95%CI; 1.17–1.57). Seroprevalence increased significantly with increasing age at donation from 0.70% at 16–25 years to 7.34% at over 56 years (Chi-square test, $P < 0.0001$). The annual prevalence was 1.32 in 1999, 1.31 in 2002, and 1.37 in 2006, indicating that there was no significant secular trend during 1999–2006 (P for trend=0.99). In analyses by age at donation, trends of HTLV-1 prevalence significantly de ied among age over 56 years (P for trend=0.02) and age 16–25 years (P for trend=0.0007), whereas in birth-year-specific analyses, there was no apparent change of the prevalence over time, except in birth year 1981–90 group in which the prevalence declined from 1.22% in 1999 to 0.44% in 2006 (P for trend < 0.0001). In analyses for limited birth year from 1985 to 1990, the seroprevalence declined from 0.75% in birth year 1985–86 group, 0.31% in 1987–88 group, to zero% in 1989–90 group (P for trend =0.0002). HTLV-1 seroprevalence was significantly lower among donors born in 1987–90 (after APP) than 1985–86 (before APP). These results indicate that a birth-year-specific analysis for HTLV-1 prevalence may be appropriate to evaluate secular trend since the virus mostly transmit during infancy, and that a prefecture-wide intervention, the refraining from breast-feeding by the virus carrier mothers, contributes a declining HTLV-1 seroprevalence in our region.

Footnotes

Disclosure: No relevant conflicts of interest to declare.