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Original Article

Prevalence of coinfection with human immunodeficiency virus and hepatitis C virus in Japan

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People with human immunodeficiency virus (HIV) infection are frequently infected with hepatitis C virus (HCV), because of the common transmission routes. Since the dissemination of hyperactive antiretroviral therapy (HAART), the morbidity and mortality associated with HIV infection have declined. However, the reduction in mortality due to opportunistic infection has made HCV-associated liver diseases the leading cause of mortality in Western countries. A similar situation is assumed in Japan, but the status of coinfection with HIV and HCV is unclear. We conducted a nationwide survey to determine the prevalence of coinfection with HIV and HCV by dis-

tributing a questionnaire to the hospitals in the HIV/AIDS Network of Japan. Among 4877 patients reported to be HIV-positive, 935 (19.2%) were also positive for the anti-HCV antibody. Most (84.1%) of the patients coinfecting with HIV and HCV were recipients of blood products. These data, for the first time, show the current status of coinfection with HIV and HCV in Japan. A detailed analysis of the progression and severity of liver diseases in the coinfecting patients is expected.

Key words: coinfection, hepatitis C, HIV, liver disease

INTRODUCTION

H E P A T I T I S C V I R U S (HCV) infection and human immunodeficiency virus (HIV) infection are major public health problems worldwide. In the USA, the estimated prevalence of the anti-HCV antibody is 1.8%, with 2.7 million people having HCV-RNA detected in their blood, indicative of ongoing HCV infection.¹ The prevalence of HIV is <1%, and the virus is estimated to have infected approximately 800 000 people.² Because of the common transmission routes, that is, parenteral ones, many people with HIV infection are also infected with HCV.³ Before the introduction of hyperactive antiretroviral treatment (HAART) in 1996, most people with HIV infection died of HIV-associated opportunistic infections such as *Pneumocystis carinii* (currently called *P. jirovecii*) pneumonia and cytomegaloviral infection. Since the dissemination of HAART, the morbidity and mortality associated with HIV infection have

declined. However, the reduction in mortality due to opportunistic infection has made patients coinfecting with HIV and HCV faced with the menace of progressive liver diseases due to HCV infection in the United States and Europe.^{4,5}

Coinfection with HIV has been shown to increase the HCV load in HCV infection,⁶ being a negative prognostic factor for clearance of HCV in anti-HCV therapy using interferon.^{7,8} It also accelerates the development of cirrhosis and, eventually, hepatocellular carcinoma. Although still controversial, coinfection with HIV and HCV yields a more rapid progression to acquired immunodeficiency syndrome (AIDS) in some cases.^{9,10} Importantly, coinfection with HIV and HCV will increase the morbidity and mortality of HIV-infected patients also in Japan, where the prevalence of HIV infection is increasing in a linear fashion, exceptionally among developed countries.¹¹ There are more than 10 000 HIV-positive people in Japan as of the end of 2004, according to the AIDS National Survey in Japan,¹² and approximately 1.8 million chronic HCV carriers, according to the estimation by the Ministry of Health, Labor and Welfare (MHLW) of Japan. However, unfortunately, the prevalence of coinfection with HIV and HCV in Japan has been unclarified to date. Therefore, we conducted a nationwide study by distributing an

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email-based questionnaire to the hospitals in the HIV/AIDS Network of Japan.

METHODS

IN THE QUESTIONNAIRE, the following information was obtained from hospitals regarding the number of patients who visited the hospitals at least once between January and December 2003: (1) the number of HIV-positive patients; (2) the number of anti-HCV-positive patients among (1); (3) the number of HCV-RNA-positive patients among (2); (4) the number of HIV-positive patients who contracted HIV from blood products; (5) the number of anti-HCV-positive patients among (4); (6) the number of HCV-RNA-positive patients among (5); (7) the number of HIV-positive patients among men who have sex with men (MSM); (8) the number of anti-HCV-positive patients among (7); (9) the number of HCV-RNA-positive patients among (8); (10) the number of HIV-positive patients who contracted HIV through intravenous drug use; (11) the number of anti-HCV-positive patients among (10); (12) the number of HCV-RNA-positive patients among (11); (13) the number of HIV-positive patients whose transmission routes were classified as 'others'; (14) the number of anti-HCV-positive patients among (13); and (15) the number of HCV-RNA-positive patients among (14).

The questionnaire was sent to the 366 hospitals in the HIV/AIDS Network of Japan by email. When emails were returned with a failure of delivery, the questionnaire was forwarded by post. Answers were mostly returned by email, and in some cases by fax. The list of the hospitals in the HIV/AIDS Network of Japan can be browsed at: http://www.acc.go.jp/mLhw/mLhw_frame.htm.

RESULTS

THE QUESTIONNAIRE WAS sent to all 366 hospitals that were on the list of hospitals in the HIV/AIDS Network of Japan in January 2004. One hundred and seventy-six hospitals (48.1%) responded within the indicated period. A collection rate of 47.8% may appear rather low, particularly considering the number of reported HIV-positive people, 10 000, in 2004 according to the statistics of the MHLW of Japan.¹² However, not all the HIV-positive cases are visiting hospitals, and answers to the questionnaire were obtained from most of the major hospitals in the HIV/AIDS Network in big cities around Japan. These factors suggest that not all but

Table 1 Number of hospitals categorized by the number of patients infected with HIV and those coinfecting with HIV and HCV

No. of HIV(+)/HCV(+)	No. of HIV(+)				Total
	0	1-19	20-49	50+	
0	43	52	5	1	101
1-9	0	45	9	3	57
10+	0	2	4	12	18
Total	43	99	18	16	176

a majority of HIV-positive patients in Japan were enrolled in the study.

There were one or more HIV-positive patients in 133 of 176 (75.6%) hospitals; there were no HIV-positive patients in the remaining 43 hospitals (Table 1). Eighteen of 176 (10.2%) hospitals had 20-49 HIV-positive patients, and 16 (9.1%) hospitals had 50 or more HIV-positive patients. On the other hand, there were one or more patients who were coinfecting with HIV and HCV in 75 (42.6%) of 176 hospitals, and there were 10 or more HIV/HCV coinfecting patients in 18 (10.2%) hospitals. HIV/HCV coinfecting patients were concentrated in specific hospitals in big cities around Japan. In particular, in the Kanto area, HIV/HCV coinfecting patients were concentrated in the HIV/AIDS Network hospitals in the Tokyo city area (Fig. 1). Of the 16 hospitals with 50 or more HIV-positive patients and of the 18 hospitals with 10 or more HIV/HCV coinfecting patients, 12 were the same hospitals (Table 1). Hospitals with 10 or more HIV/HCV coinfecting patients, but with less than 50 HIV-positive patients had the characteristic that most HIV-positive patients contracted HIV from blood products.

In total, 4877 patients were reported to be HIV-positive. Among these, 935 (19.2%) were positive for anti-HCV (Table 2). Of these 935 patients, 780 were HCV-RNA-positive, although it should be noted that not all the patients underwent HCV-RNA testing.

HCV prevalence when fractionated by routes of transmission was as follows. Among 811 HIV-positive patients who contracted HIV from blood products such as unheated concentrated coagulation factors, 786 (96.9%) were anti-HCV-antibody-positive. Of 20 intravenous drug users, nine (45.0%) were anti-HCV-antibody-positive. Among 2730 HIV-positive patients who were MSM (men who have sex with men), 114 (4.2%) were anti-HCV positive. In the remaining 1316 HIV-positive patients whose routes of HIV transmission



Figure 1 Nationwide distribution of hospitals in the HIV/AIDS Network of Japan that a number of HIV-positive or HIV/HCV coinfected patients are visiting regularly. Note that in the Kanto area, HIV/HCV coinfected patients were concentrated in the HIV/AIDS Network hospitals in the Tokyo city area. (Δ) hospitals with 1-19 HIV-positive patients; (\square) hospitals with 20-49 HIV-positive patients; (\circ) hospitals with 50+ HIV-positive patients. Hatched figures: hospitals with 10 or more HIV/HCV coinfected patients. Closed figures: hospitals with less than 10 HIV/HCV coinfected patients. For easier visual comprehension, hospitals with 19 or less HIV-positive patients and 9 or less HIV/HCV coinfected patients are omitted from the figure.

were classified as "others", most of whom contracted HIV heterosexually, 26 (2.0%) were anti-HCV-antibody-positive. On the other hand, in HIV/HCV coinfected patients, 786 (84.1%) of 935 patients were recipients of blood products. Thus, the majority of HIV/HCV coinfected patients in Japan are those who contracted HIV, and most likely also HCV, from blood products.

DISCUSSION

ACCORDING TO THE statistics of the MHLW of Japan, the number of reported HIV-positive people was just over 10 000 in 2004.¹² The total number of HIV-positive patients in the current study is approximately half of that. By a simple calculation, there would be about 1900 HIV/HCV coinfected patients in Japan. However, because HIV-positive patients who contracted HIV from blood products are almost all registered in

Japan and most of them should have been enrolled in this survey, the number of HIV/HCV coinfected patients is likely smaller than 1900. It is regrettable that not all the patients underwent HCV-RNA testing, but it is unavoidable in this type of questionnaire-based study. In some cases, the existence of a positive anti-HCV antibody indicates a memory of a remote HCV infection.

Almost all of the patients who contracted HIV through blood products were also anti-HCV-antibody-positive, suggesting that both viruses were transmitted through the same route. In MSM patients who were HIV-positive, approximately 4% were anti-HCV-antibody-positive, which is about threefold higher than the prevalence of HCV in Japan.¹³ In people aging from 40 to 50 years old in the general Japanese population, whose ages are similar to those of the MSM patients in the current study, the prevalence of HCV is less than 0.5%.¹³ Therefore, an HCV prevalence of 4% in MSM

Table 2 Prevalence of HCV infection in HIV-positive patients

Routes of transmission	No. of patients	Anti-HCV-positive	HCV-RNA-positive†
Blood products	811	786 (96.9%)	667
MSM‡	2730	114 (4.2%)	98
Drug addicts	20	9 (45.0%)	8
Others (heterosexual etc.)	1316	26 (2.0%)	7
Total	4877	935 (19.2%)	780

†Not all patients were subjected to HCV-RNA test. ‡MSM, men who have sex with men.

HIV-positive patients is quite high, suggesting the same route of the transmission of HIV and HCV, and a more intensive exposure to HCV or more susceptibility to HCV in these HIV-positive patients. Similarly, an HCV prevalence of 1.4% in heterosexually transmitted HIV-positive patients is higher than that of the general Japanese population of the same age.

To establish measures that decrease the morbidity and mortality of HIV/HCV coinfecting patients, it is essential to recognize the current status of the coinfection. In the present study, the number and transmission routes of HIV/HCV coinfecting patients in Japan were first described, although detailed information on the progression of HCV-associated liver diseases in HIV/HCV coinfecting patients has not yet been obtained. Undoubtedly, this will be the first step for improving the prognosis and quality of life of patients coinfecting with HIV and HCV in Japan. A detailed analysis of the progression and severity of HCV-associated liver diseases is expected.

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Successful Efavirenz Dose Reduction in HIV Type 1–Infected Individuals with Cytochrome P450 2B6 *6 and *26

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Background. Efavirenz (EFV) is metabolized primarily by cytochrome P450 2B6 (CYP2B6), and high plasma concentrations of the drug are associated with a G→T polymorphism at position 516 (516G→T) of CYP2B6 and frequent central nervous system (CNS)-related side effects. Here, we tested the feasibility of genotype-based dose reduction of EFV.

Methods. CYP2B6 genotypes were determined in 456 human immunodeficiency virus type 1 (HIV-1)-infected patients who were receiving EFV treatment or were scheduled to receive EFV-containing treatment. EFV dose was reduced in CYP2B6 516G→T carriers who had high plasma EFV concentrations while receiving the standard dosage (600 mg). EFV-naïve homozygous CYP2B6 516G→T carriers were treated with low-dose EFV. In both groups, the dose was further reduced when plasma EFV concentration remained high.

Results. CYP2B6 516G→T was identified in the *6 allele (found in 17.9% of our subjects) and a novel allele, *26 (found in 1.3% of our patients). All EFV-treated CYP2B6 *6/*6 and *6/*26 carriers had extremely high plasma EFV concentrations (>6000 ng/mL) while receiving the standard dosage. EFV dose was reduced to 400 mg for 11 patients and to 200 mg for 7 patients with persistently suppressed HIV-1 loads. EFV-containing treatment was initiated at 400 mg in 4 CYP2B6 *6/*6 carriers and one *6/*26 carrier. Two of them still had a high plasma EFV concentration while receiving that dose, and the dose was further reduced to 200 mg, with successful HIV-1 suppression. CNS-related symptoms improved with dose reduction in 10 of the 14 patients, although some had not been aware of the symptoms at initial dosage.

Conclusions. Genotype-based EFV dose reduction is feasible in CYP2B6 *6/*6 and *6/*26 carriers, which can reduce EFV-associated CNS symptoms.

Efavirenz (EFV) is an important anti-HIV-1 agent in current combination treatment and is usually prescribed at a fixed dosage of 600 mg once daily [1, 2].

The plasma concentration of EFV varies widely in individuals, and the prevalence of CNS symptoms is higher in those with high concentrations [3]. EFV is metabolized mainly by cytochrome P450 2B6 (CYP2B6), and its concentration was reported to be associated with the CYP2B6 516G→T genetic polymorphism [4–8]. Previously, we reported that all Japanese patients with the 516TT genotype had extremely high EFV concentrations (>6000 ng/mL), without exception [4]. However, other studies reported some exceptional cases of subjects with the 516TT genotype with normal concentrations, although most of the

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516TT carriers had high concentrations [5–8]. The difference between our data and those of others may reflect polymorphisms other than 516G→T in *CYP2B6*. If this is the case, analysis of other polymorphisms and determination of the *CYP2B6* haplotype may be helpful in predicting EFV plasma levels. In the present study, we determined the *CYP2B6* haplotype of 456 HIV-1-infected patients and analyzed its relationship with EFV concentration in 111 of them. Furthermore, we reduced the EFV dose in 12 patients whose EFV concentrations had been high while receiving the standard dosage. We also used reduced doses of EFV in 5 EFV-naïve patients in whom EFV concentration was predicted to become extremely high while receiving the standard dosage, on the basis of *CYP2B6* haplotype determination.

SUBJECTS, MATERIALS, AND METHODS

Patients. This analysis included 60 previously reported HIV-1-infected individuals at the International Medical Center of Japan (IMCJ) [4] and another group of 396 HIV-1-infected patients who were receiving treatment of the standard dosage (600 mg once daily) of EFV or were scheduled to begin receiving EFV-containing treatment at the following 11 hospitals in Japan: Hokkaido University (Sapporo), Sendai Medical Center (Sendai), Niigata University (Niigata), Higashi Saitama Hospital (Hasuda), IMCJ (Tokyo), Ishikawa Prefecture Central Hospital (Kanazawa), Nagoya Medical Center (Nagoya), Osaka National Hospital (Osaka), Hiroshima University (Hiroshima), Kyushu Medical Center (Fukuoka), and Kumamoto University (Kumamoto). The ethics committee of each hospital approved this study, and each participant gave written informed consent.

***CYP2B6* genotype.** DNA samples were extracted from peripheral blood specimens obtained from participants, and genotyping of *CYP2B6* 64C→T (*rs8192709*), 415A→G (*rs12721655*), 499C→G (*rs3826711*), 516G→T (*rs3745274*), 777C→A (*rs* number not available), 785A→G (*rs2279343*), 1375A→G (*rs* number not available), and 1459C→T (*rs3211371*) was performed by allele-specific fluorogenic 5' nuclease chain reaction assay with predesigned primers and TaqMan MGB probes (TaqMan SNP Genotyping Assay; Applied Biosystems) or previously published primers and MGB probes [4]. In subjects confirmed to carry 499C→G, all 9 exons of the *CYP2B6* gene were amplified with previously published primers [9], and their DNA sequences were directly determined. For haplotype analysis of the *CYP2B6* allele, PCR amplification of the genomic region (3130 bp) containing exons 4 and 5 was performed using sense primer 5'-AACTGTACTCACTCCAGAGT-3' and antisense primer 5'-CTCCCTCTGTCCTTTCATTCTGT-3'. The amplified PCR product was subjected to subcloning, and the DNA sequence of each clone was determined. For genotyping of *CYP2B6* 983T→C (*rs28399499*), new primers and probes were designed as follows: forward primer, 5'-GCCTGAAATGCCCTTTAAA-

ATGAGATTC-3'; reverse primer, 5'-GCGATGTGGGCCAATCAC-3'; VIC probe for 983T, 5'-CTGTTCAATCTCCC-3'; and FAM probe for 983C, 5'-CTGTTCAATCTCCC-3'. The obtained genotyping results of *CYP2B6* 983T→C for >10 patients were confirmed by direct sequencing of exons 7 and 8 with use of primers published elsewhere [9].

Plasma EFV concentration. Samples of peripheral blood were collected during a daytime office visit (9–16 h after the patient took EFV) from the patients who had received EFV treatment at 600-mg dose at bedtime for >4 weeks. EFV concentration was measured by the reverse-phase high-performance liquid chromatography (HPLC) method [10]. For cases of EFV-dose reduction, plasma concentration was measured >2 weeks after the change in EFV dose. Differences in EFV concentrations between groups were examined for statistical significance with Student's *t* test. A *P* value <.05 denoted the presence of a statistically significant difference.

RESULTS

Novel *CYP2B6* allele. The *CYP2B6* genotype was analyzed in 456 HIV-1-infected patients, including 442 Japanese, 8 other Asians, and 6 others. During the analysis, we noticed that some patients had the *CYP2B6* 499C→G polymorphism, substituting Ala for Pro at the 167th amino acid, which is already registered in the SNP Database, although the *CYP2B6* allele containing 499G had not been determined yet. TaqMan Genotyping Assay indicated that *CYP2B6* 449G was heterozygous with 499C in 12 individuals (2.6%), who were all Japanese (table 1). Direct sequencing of all the exons confirmed the results of TaqMan Genotyping Assay and showed that 8 subjects had 516GT, 785AG, and 1375AA genotypes; 3 had 516TT, 785GG, and 1375AA genotypes; and 1 had 516GT, 785AG, and 1375AG genotypes without any other mutation. Subcloning analysis of the PCR products confirmed that 499G always coexisted in the same allele with 516T and 785G (figure 1). Therefore, it was concluded that the novel haplotype containing 499C→G had 2 other single-nucleotide polymorphisms (SNPs): 516G→T and 785A→G. We formally registered this novel allele with the Human Cytochrome P450 Allele Nomenclature Committee, and it was designated "*CYP2B6* *26" (<http://www.cypalleles.ki.se/>). With use of this nomenclature, the *CYP2B6* haplotype of the twelve 499C→G carriers were identified as eight *1/*26 heterozygotes, three *6/*26 heterozygotes, and one *23/*26 heterozygote (table 1). The allelic frequency of *26 was 1.3% in our study participants.

***CYP2B6* haplotype determination.** In 456 HIV-1-infected individuals, we determined the genotypes of 9 SNP positions (64C→T, 415A→G, 499C→G, 516G→T, 777C→A, 785A→G, 983T→C, 1375A→G, and 1459C→T) in *CYP2B6* (table 1). No *CYP2B6* genetic polymorphism was detected in 211 patients, and their haplotype was determined to be *1/*1. The haplotypes

Table 1. CYP2B6 haplotype and allele frequencies in study participants.

CYP2B6 status	CYP2B6 genotype at nucleotide position								No. (%) of subjects	
	415	499	516	777	785	983	1375	1459	All*	Japanese
Haplotype:										
*1/*1	AA	CC	GG	CC	AA	TT	AA	CC	211 (46.3)	205 (46.4)
*1/*2	AA	CC	GG	CC	AA	TT	AA	CC	30 (6.6)	30 (6.8)
*1/*4	AA	CC	GG	CC	AG	TT	AA	CC	43 (9.4)	42 (9.5)
*1/*5	AA	CC	GG	CC	AA	TT	AA	CT	4 (0.9)	3 (0.7)
*1/*6	AA	CC	GT	CC	AG	TT	AA	CC	104 (22.8)	101 (22.9)
*1/*23	AA	CC	GG	CC	AA	TT	AG	CC	2 (0.4)	2 (0.5)
*1/*26	AA	CG	GT	CC	AG	TT	AA	CC	8 (1.8)	8 (1.8)
*2/*4	AA	CC	GG	CC	AG	TT	AA	CC	6 (1.3)	5 (1.1)
*2/*5	AA	CC	GG	CC	AA	TT	AA	CT	1 (0.2)	1 (0.2)
*2/*6	AA	CC	GT	CC	AG	TT	AA	CC	5 (1.1)	5 (1.1)
*4/*4	AA	CC	GG	CC	GG	TT	AA	CC	5 (1.1)	5 (1.1)
*4/*6	AA	CC	GT	CC	GG	TT	AA	CC	12 (2.6)	12 (2.7)
*5/*5	AA	CC	GG	CC	AA	TT	AA	TT	1 (0.2)	1 (0.2)
*5/*6	AA	CC	GT	CC	AG	TT	AA	CT	1 (0.2)	1 (0.2)
*6/*6	AA	CC	TT	CC	GG	TT	AA	CC	19 (4.2)	17 (3.8)
*6/*26	AA	CG	TT	CC	GG	TT	AA	CC	3 (0.7)	3 (0.7)
*23/*26	AA	CG	GT	CC	AG	TT	AG	CC	1 (0.2)	1 (0.2)
Total									456	442
Allele:										
*1	A	C	G	C	A	T	A	C	613 (67.2)	596 (67.4)
*2	A	C	G	C	A	T	A	C	42 (4.6)	41 (4.6)
*4	A	C	G	C	G	T	A	C	71 (7.8)	69 (7.8)
*5	A	C	G	C	A	T	A	T	8 (0.9)	7 (0.8)
*6	A	C	T	C	G	T	A	C	163 (17.9)	156 (17.6)
*23	A	C	G	C	A	T	G	C	3 (0.3)	3 (0.3)
*26	A	G	T	C	G	T	A	C	12 (1.3)	12 (1.4)
Total									912	884

* Including 442 Japanese, 8 other Asians (5 Thai, 2 Koreans, and 1 Filipino), 4 Hispanics, and 2 non-Hispanic whites.

of single-SNP carriers with 64CT, 785AG, 1375AG, and 1459CT were determined to be *1/*2, *1/*4, *1/*23, and *1/*5, respectively. Those of homozygous polymorphism carriers with 785GG only, 1459TT only, and both 516TT and 785GG were determined to be *4/*4, *5/*5, and *6/*6, respectively. When the fact that *2 is the only allele harboring 64C→T is considered, patients with 64CT and 785AG; 64CT and 1459CT; and 64CT, 516GT, and 785AG were identified as *2/*4, *2/*5, and *2/*6 heterozygotes, respectively. Patients with both 516GT and 785GG genotypes but without other polymorphisms were determined to have *4/*6 heterozygotes. There were 104 patients (22.8%), including 101 Japanese, who held both 516GT and 785AG genotypes without other polymorphisms. There were 2 possible haplotypes, *1/*6 and *4/*9, in this genotypic pattern. When the fact that *9 had not been reported in Japanese subjects was considered [11], we found that all 101 Japanese were *1/*6 heterozygotes. Haplotype analysis by subcloning of PCR products described above was performed in the 3 others, and their haplotype was determined as *1/*6. One Japanese patient

had 516GT, 785AG, and 1459CT genotypes without other polymorphisms, and there were 2 possible haplotypes, *1/*7 and *5/*6, in this genotypic pattern. Because *7 had not been reported in Japanese subjects [11], the haplotype in this patient was determined to be *5/*6. Overall, the allelic frequency of *6 was 17.9% in our study participants. The 415A→G, 777C→A, and 983T→C polymorphisms, which are the determinants of *8, *3, and *18, respectively, were not observed in our subjects.

CYP2B6 and EFV concentration. We determined the CYP2B6 haplotype in 251 patients at IMCJ and in 205 patients at the other 10 hospitals. Of the 251 genotype-analyzed patients at IMCJ, 101 were being treated or were beginning treatment with a standard dose of EFV during this study period (figure 2). Plasma EFV concentrations were measured in all 101 patients, including sixty-seven 516GG holders, twenty-eight 516GT holders, and six 516TT holders. To clarify the effect of the 516TT genotype, EFV concentration was also measured in ten 516TT holders undergoing treatment with the standard dose of EFV at other hospitals. The mean concentration (\pm SD)

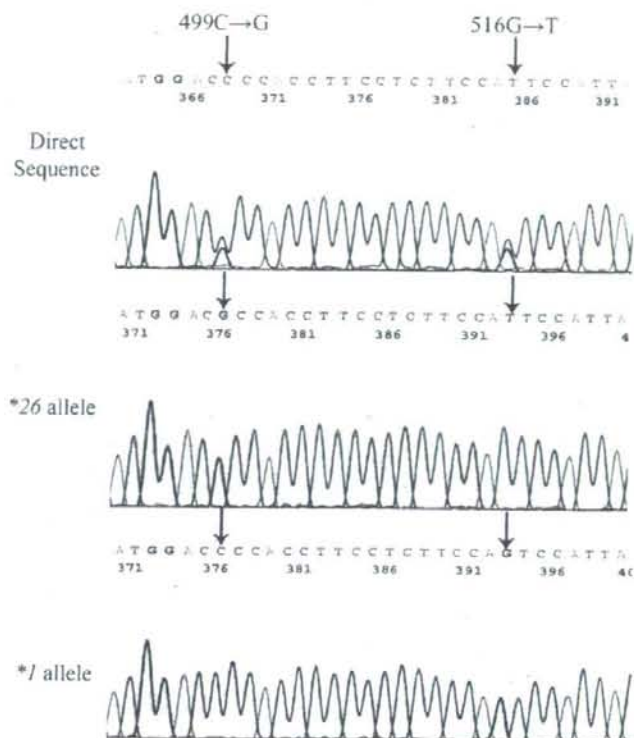


Figure 1. Direct (top panel) and subclonal (middle and bottom panels) sequences of *CYP2B6* in 499C→G carriers. The genotypes 499G, 516T, and 785G (not shown) exist in the same allele, newly designated as "*CYP2B6* *26." The same results were obtained in all 9 patients with the 499CG, 516GT, and 785AG genotypes, and the patients were identified as eight *1/*26 carriers and one *23/*26 carrier. Although shown are the sense-strand sequences only, both strands were sequenced. Arrows indicate the variant nucleotide positions 499 and 516.

of EFV in all patients was 3740 ± 2800 ng/mL. When divided by the genotype of position 516, striking discreteness was observed (figure 3). All (95% CI 91.1%–100%) of the 16 carriers of 516TT genotype, including fourteen *6/*6 carriers and two *6/*26 carriers, had extremely high EFV concentrations (>6000 ng/mL). Their mean concentrations (9500 ± 2580 ng/mL) were many orders of magnitude higher than those of the other genotype carriers ($P < 10^{-4}$). There was no significant difference in EFV concentration between *6/*6 carriers and *6/*26 carriers. On the other hand, there were only 2 patients who had such high EFV concentrations among the other genotype carriers. One was a *1/*6 carrier (7140 ng/mL), and the other was a *1/*26 carrier (9710 ng/mL). Direct sequencing of all *CYP2B6* exons showed no polymorphism other than 499C→G, 516G→T, and 785A→G in these individuals. The mean concentrations of EFV of the twenty-eight 516GT carriers, including twenty-five *6-heterozygotes (3320 ± 1240 ng/mL; $P < 10^{-4}$) and three *26-heterozygotes (5470 ± 3840 ng/mL; $P < 10^{-4}$), were signifi-

cantly higher than those of the sixty-seven 516GG genotype carriers (2450 ± 770 ng/mL). None (95% CI 0%–0.1%) of the 516GG carriers had a high EFV concentration (>6000 ng/mL). Considered together, it was concluded that high plasma EFV concentrations were associated with *CYP2B6* *6 and *26 and that *CYP2B6* *6/*6 and *6/*26 carriers had extremely high plasma EFV concentrations at standard dosage, without exception.

EFV dose reduction from 600 mg. To determine whether the EFV dose can be reduced in patients who have a high concentration while receiving the standard dose, a dose-reduction protocol was applied in 12 patients with high plasma concentrations (>6000 ng/mL [range, 6170–14,690 ng/mL]), including one *1/*26 heterozygote, nine *6/*6 homozygotes, and two *6/*26 heterozygotes. Before the dose reduction, plasma HIV-1 load was undetectable (<50 copies/mL) in all patients for >1 month with treatment of a standard antiretroviral regimen containing 600 mg of EFV. In these 12 patients,

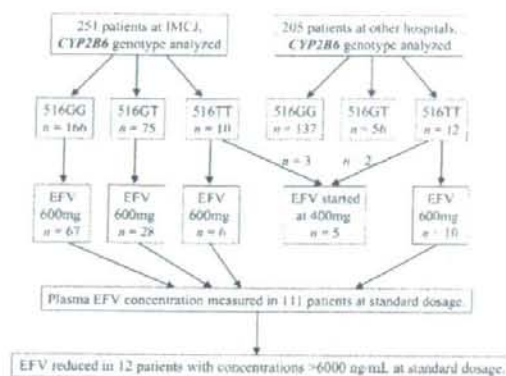


Figure 2. Flow diagram of study participants. The *CYP2B6* genotype was analyzed in 251 patients at the International Medical Center of Japan (IMCJ) and in 205 patients at other hospitals. Standard dosage of EFV was administered in 101 patients at IMCJ, including sixty-seven *CYP2B6* 516GG, twenty-eight 516GT, and six 516TT holders, whose EFV concentrations were measured. Ten 516TT holders at the other hospitals were administered standard dosages of EFV, and their EFV concentrations were also measured. A reduced-dose (400 mg) regimen of EFV was initiated in 5 other 516TT holders.

the EFV dose was reduced from 600 to 400 mg in 11 subjects and was further reduced to 200 mg in 7 of them who consented to further reduction. The plasma EFV concentrations decreased by approximately one-third (36%–46%), to 3720–6160 ng/mL, with dose reduction from 600 to 400 mg in 10 of 11 subjects, and further decreased by approximately one-half (51%–59%), to 1620–2960 ng/mL, with reduction from 400 to 200 mg in 6 of 7 subjects (figure 4). In one patient who had a markedly high EFV concentration (14,690 ng/mL) at the standard 600-mg dose, however, the concentration decreased unexpectedly by 69%, to 4500 ng/mL, with the reduction to 400 mg and further decreased by 82%, to 790 ng/mL, lower than the recommended range (>1000 ng/mL) [1], with the reduction from 400 to 200 mg. Therefore, the dose was increased in this patient back to 400 mg. In another patient who had reported severe dizziness during treatment with the standard dose (600 mg), the dose was reduced immediately to 200 mg at the patient's request. The plasma EFV concentration was also markedly high in this patient (14,360 ng/mL) during treatment with the standard dosage. However, it decreased by 83%, to 2410 ng/mL, with the dose reduction to 200 mg. Consequently, the final EFV dose was 400 mg in 5 subjects and 200 mg in 7 subjects. The determined dosage for each patient was continued for >6 months (the longest was 26 months for a patient who received the 200-mg dose), and the plasma HIV-1 load was continuously undetectable in all patients.

EFV initiation at 400-mg dose. Our analysis showed that *CYP2B6* *6/*6 and *6/*26 carriers had extremely high EFV concentrations, without exception (figure 3), and that dose reduction was possible in patients with high EFV concentration with retention of therapeutically effective anti-HIV-1 activity (figure 4). In the next phase of our study, we used an antiretroviral regimen containing a reduced dose (400 mg) of EFV in 5 EFV-naïve patients (four *6/*6 homozygotes and one *6/*26 heterozygote). Before the introduction of low-dose EFV-containing regimen, the plasma HIV-1 loads had been undetectable during receipt of the previous protease inhibitor-containing regimen in all 5 patients. Their EFV concentrations were 4080–9450 ng/mL, and all such concentrations (95% CI, 99.5%–100%) were therapeutically adequate (>1000 ng/mL) at the 400-mg dose (figure 5). One *6/*6 homozygote developed severe dizziness, necessitating discontinuation of EFV-treatment at day 16. His EFV concentration was 5430 ng/mL. In one *6/*26 heterozygote, severe thrombocytopenia emerged, probably because of overdosage of rifabutin prescribed for the treatment of coinfection with *Mycobacterium intracellulare*, and EFV treatment was stopped at day 15. The EFV concentration was 5770 ng/mL. Two of the remaining 3 patients still had extremely high EFV concentrations (6760 and 9450 ng/mL) at the 400-mg dose, and their dose was subsequently reduced to 200 mg. The plasma EFV concentrations decreased to 2690 and 3660 ng/mL (i.e., by 60% and 61%, respectively). Consequently, 2 subjects

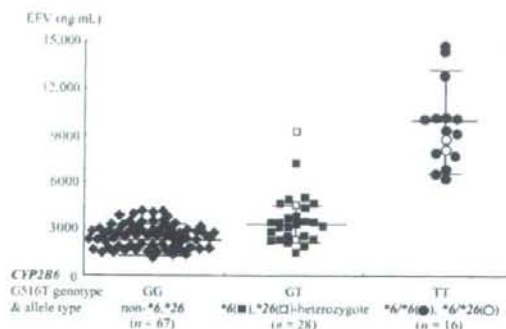


Figure 3. Plasma efavirenz (EFV) concentrations measured during EFV treatment with standard dose (600 mg). A total of 111 HIV-1-infected patients treated with EFV-containing regimens were divided into 3 groups on the basis of nucleotide genotype at *CYP2B6* position 516 (GG, GT, or TT), and their plasma EFV concentrations were compared. Blackened squares, *6 heterozygote with allele other than *26; unblackened squares, *CYP2B6* 499C→G carriers (*26 heterozygote with allele other than *6); blackened circles, *6 homozygote (*6/*6); unblackened circles, *CYP2B6* 499C→G carriers (*6/*26 heterozygotes); blackened diamonds, other genotype carriers. Horizontal lines represent the mean (± SD) plasma EFV concentrations for each group.

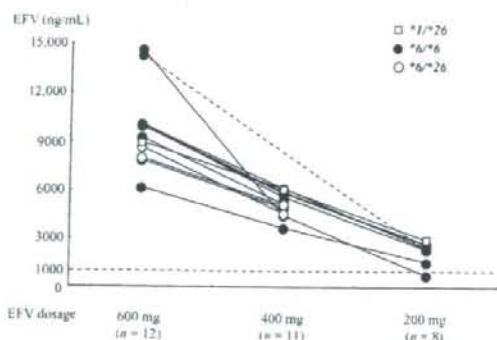


Figure 4. Dose reduction of efavirenz (EFV) in 12 patients whose concentrations were extremely high while receiving treatment with standard dose (600 mg). EFV dose was reduced from 600 to 400 mg in 11 patients and was further reduced, to 200 mg, in 7 patients. In one patient who had severe CNS symptoms while receiving treatment with standard dose, EFV dose was directly reduced to 200 mg (concentrations connected with a dotted line). The suggested minimum target concentration (1000 ng/mL) is indicated by the thin line.

discontinued the EFV-containing regimen, and 3 subjects continued low-dose EFV-containing regimen (400 mg for 1 patient and 200 mg for 2 patients). The low-dose regimen was continued for >6 months, and the plasma HIV-1 load was persistently undetectable in all 3 patients.

Improvement of CNS symptoms. As described above, the EFV dose was reduced from 600 to 400 and 200 mg as the final dose in 5 and 7 subjects, respectively (figure 4), and it was decreased from 400 mg as the initial dose to 200 mg for 2 other subjects (figure 5). To delineate the changes in CNS symptoms associated with the decrease in EFV concentration, a questionnaire survey of these 14 patients was conducted regarding 6 items: dizziness, strange dreams, depression, irritability, concentration problems, and sleep difficulty. More than 1 month after the dose had been reduced to the lowest dose, the patients were asked to judge the 6 CNS symptoms above at initial and final doses, with use of a 5-grade system ("none," "slight," "sometimes," "often," and "always"). Ten (71%) of the 14 patients had some of the aforementioned CNS symptoms during treatment with the initial dose (table 2). The most common symptom was dizziness (57%), followed by strange dreams (50%). Interestingly, all the symptoms improved after dose reduction in the 10 patients. Furthermore, dizziness and concentration problems disappeared during treatment with the final dose in one-half of the patients, although strange dreams and sleep difficulty were still reported by all the patients who had those difficulties at the initial dose. Finally, when the patients were asked whether they wanted to reincrease EFV to

the previous dose, all 10 patients with CNS symptoms at the initial dose answered "no" (9 answered "absolutely no").

DISCUSSION

In this study, we identified a novel *CYP2B6* allele, *26, which includes 499C→G, 516G→T, and 785A→G in 12 Japanese patients, and we showed that, without exception, all *6/*6 and *6/*26 carriers, all holding 516TT, had extremely high plasma EFV concentrations while receiving the standard dose (600 mg) [4]. In other reports, however, there were some exceptional subjects with 516TT who had normal concentrations of EFV, and the discreteness of the EFV concentration with the position 516 genotype was not as clear as it was in our patients [5–8]. This difference may be because some of the 516TT carriers had other *CYP2B6* alleles, such as *7 (containing 516G→T, 785A→G, and 1459C→T), *9 (containing 516G→T only), and *13 (containing 415A→G, 516G→T, and 785A→G). Those alleles could not be found in our subjects, and their effects on EFV concentration were not well described. Because numerous additional *CYP2B6* variants with impact on expression and/or function were recently reported [12–18], correct determination of *CYP2B6* haplotype seems indispensable for prediction of EFV plasma levels.

We reduced the EFV dose in 12 patients whose plasma EFV concentrations were extremely high while receiving the standard dose, and we initiated EFV treatment at a 400-mg dose in 5 EFV-naïve *6/*6 and *6/*26 carriers. In most patients, the plasma EFV concentration decreased proportionally with the dose-reduction ratio. In 2 subjects, however, the concentrations decreased much more than expected, given the dose reduction

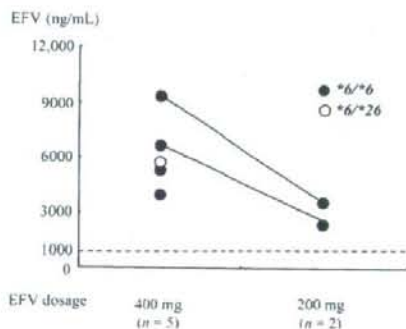


Figure 5. Introduction of low-dose efavirenz (EFV)-containing antiretroviral regimen to *CYP2B6* *6/*6 and *6/*26 carriers. Treatment was started in 4 EFV-naïve carriers *CYP2B6* *6/*6 and one *6/*26 carrier, with 400-mg EFV-containing regimens. EFV dose was further reduced, to 200 mg, in 2 patients whose EFV concentrations were >6000 ng/mL while receiving treatment with the 400-mg dose.

Table 2. Changes in CNS-related symptoms after reduction of efavirenz dosage.

Symptom	No. (%) of subjects who reported symptom status during efavirenz treatment		
	Present ^a (n=14)	Improved ^b	Disappeared ^b
Dizziness	8 (57)	8 (100)	4 (50)
Strange dreams	7 (50) ^c	7 (100) ^c	0 (0)
Depression	5 (36)	5 (100)	1 (20)
Irritability	5 (36)	5 (100)	1 (20)
Concentration problem	4 (29)	4 (100)	2 (50)
Sleep difficulty	3 (21)	3 (100)	0 (0)
Any of the above	10 (71) ^c	10 (100) ^c	4 (40)

^a Including the 4 grades "slight," "sometimes," "often," and "always" at the initial dosage. Includes 2 patients whose efavirenz treatment was originally 400 mg and was reduced to 200 mg.

^b Percentage of those who initially reported "present."

^c Including 1 patient whose efavirenz dose was originally 400 mg and was reduced to 200 mg.

ratio. Both of these patients had markedly high concentrations at standard dosage. Hasse et al. [19] reported a patient with excessively high plasma EFV concentration at standard dose, which decreased to one-thirtieth following dose reduction from 600 to 200 mg. Long-term exposure to such excessively high concentrations may induce CYP2B6 enzymatic expression in the liver, which could result in an unexpectedly large decrease in plasma EFV concentration by dose reduction if deinduction of the enzyme takes several weeks. At the 400-mg dose, the plasma concentrations of EFV were therapeutically adequate in all the treated *6/*6 and *6/*26 carriers in this study. Regarding the reduced dose, it is noteworthy that a phase II study during EFV development supported the use of a lower dose [20]. The same study indicated that the 600-mg dose of EFV is associated with a high rate of adverse events that could lead to discontinuation, which suggests that the lower dose of 400 mg may be almost as effective without the high discontinuation rate. In the present study, associated with the dose-reduction regimen, a significant number of patients experienced improvement of CNS symptoms, which was unexpected on the basis of previous reports [5, 21, 22]. Interestingly, some of these patients did not appreciate their clinical state and considered themselves to have no CNS-related symptoms during the standard-dose treatment. However, after the dose reduction, they reassessed the status and evaluated symptoms during the treatment with the standard dose as associated with CNS symptoms and indicated that the reduced dose of EFV relieved them of such symptoms. Because EFV-treated patients often stick to the regimen, previous reports of symptom questionnaires conducted during the standard treatment might have underestimated the EFV-associated CNS symptoms [5, 21, 22]. However, this finding might be confounded by placebo effect, because the patients were told

that their EFV levels were high while receiving the initial dose and decreased throughout the dose-reduction protocol. Because of this possible placebo effect, a double-blind, placebo-controlled study would best address this question.

EFV dose reduction and initiation of EFV treatment at reduced dose is possible with therapeutic anti-HIV-1 potency retained in CYP2B6 *6/*6 homozygotes and *6/*26 heterozygotes, which could relieve the patients of the EFV-associated CNS symptoms. It may also decrease the risk of development of EFV-resistant HIV-1 after mandatory treatment discontinuation, such as abdominal surgery [23], and reduce the treatment cost, an important issue in developing countries [24]. After dose reduction, however, careful monitoring is necessary until larger studies confirm the safety of reduced dose in such specific genotype carriers.

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Potential conflicts of interest. All authors: no conflicts.

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Process and Contents of Telephone Consultations Between Registered Nurses and Clients with HIV/AIDS in Japan

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Antiviral therapy is essential for HIV/AIDS patients, but many variables impede patients' adherence to therapy. To facilitate adherence, trained registered nurses in Japan provided consultation by phone at the AIDS Clinical Center. This study describes the process and content of this intervention and explores the predictors for length of time of phone consultations. The study was completed over 1 month using a time study, checklist, and medical record inquiry. A total of 175 consultations were described. Mean time was 4.8 ± 3.8 min, and longer for patients with complications or comorbidity. Although the contents of conversations differed according to the phase of highly active antiretroviral therapy, major identified themes included need for medical consultation, symptom control, provision of information, and active listening. The results are useful for those trying to find ways to use telephone consultation effectively to reinforce adherence.

Key words: specially trained nurses for HIV/AIDS consultation, telephone consultation, nursing consultation, support for medication adherence

In Japan, an increase in the number of patients with HIV infection has recently become a serious problem in terms of cost of health care (Ministry of Health, Labour, and Welfare, 2006b). Currently in Japan,

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the cumulative number of patients reached 11,680 at the end of 2005 (annual increase rate, 6%) (Ministry of Health, Labour, and Welfare, 2006a). Thus, creating prevention services at the primary, secondary, and tertiary levels is a task of pressing urgency. The health care system needs to consider continuous support of therapeutic self-care behaviors in outpatients (Ishihara, 2000) as a preventive approach. Self-care is a significant and reasonable approach in designing prevention services in Japan because it has the potential to prevent the extension of HIV illness to AIDS as well as decrease the transmission of HIV to others. Because of the uniqueness of each HIV/AIDS client's needs (including economic, social, psychological, familial), special consideration is needed to provide care tailored to assessed self-care needs, which include medical care.

Currently, the main therapy for HIV/AIDS is highly active antiretroviral therapy (HAART), oral medication combining more than three kinds of antiretroviral drugs on a daily basis. Continuation of oral administration of these drugs has enabled long-term inhibition of HIV growth and favorable maintenance and reconstitution of patients' immune levels (Crum et al., 2006; Hogg et al., 1998; Krentz, Kliever, & Gill, 2005; Pallella et al., 1998, 2006; Sabin et al., 2006; Wong, Chan, & Lee, 2004). To maintain the benefits of HAART, medication adherence such as consistency in self-administration is essential. According to the previous reports, patients need to maintain an adherence rate of 95% or more throughout their lifetime to suppress HIV and maintain a favorable CD4 count (Montaner, Hogg, Raboud, Harrigan, & O'Shaughnessy, 1998; Paterson, 1999; Research Group for Therapy of HIV Infection, 2002; Yeni et al., 2004). Lack of medication adherence leads to a formidable prognosis and the evolution of drug-resistant viruses, which can lead to a decrease in future drug options for patients because of cross-resistance. Despite the benefits of taking HAART medications regularly, there are many challenges that patients face in maintaining self-care. The challenges are (a) patients are not likely to notice the benefits of HAART but do experience side effects (such as diarrhea, eruption, and nausea), which leads to a decrease in the credibility of drug efficacy; (b) patients fear the possibility that self-medication might disclose their HIV status to others who are significant in their life; and (c) the burden of taking the medications, including dosage schedules and administration

of the doses such as large size and large number of drugs (Research Group for Therapy of HIV Infection, 2002; Watanabe, 2001).

An adherence rate of 80% or higher is typically defined as good. But some previous research shows that only 63% (Singh et al., 1996) of patients and 41% of juvenile patients (Murphy, Wilson, Durako, Muenz, & Belzer, 2001) achieved good adherence. Therefore, it is necessary for medical professionals to support patients so that they may deal with the problems of HAART adherence. Nurses who have relationships with patients can be key advocates for enhancing self-care related to HAART adherence in a clinical setting.

Nurses as Self-Care Adherence Advocates: The Use of Telephone Consultation

In Japan, the AIDS Clinical Center (ACC) was established in 1997 in the International Medical Center of Japan as a center of research and medical care for patients with HIV/AIDS. It has been cooperating in its activities with hospitals nationwide. Besides physician specialists, six full time coordinator nurses (CNs) for patients with HIV/AIDS work at the ACC. Their main role has been to support patient self-care at the outpatient clinic since HAART was established. The key area of support is helping patients with self-administration of medications for HIV/AIDS (Watanabe, 2001). The specific activities of CNs in the ACC focus on (a) supporting the patient-doctor relationship, (b) enhancing informed consent for therapy, and (c) providing educational guidance for patients beginning with their initial visit. The frontline leaders of these activities are the CNs. They are expected to enhance patients' adherence to HAART through a self-care model. The activity of CNs has become a model for outpatient care in hospitals in Japan. CNs are assigned per patient, and they support patients and their families by phone in addition to face-to-face consultation at the outpatient clinic. In addition to answering phone calls from patients or their family members at any time, CNs may also place calls so that serious situations as a result of missed appointments or emergency care needs can be avoided. Based on these CNs' roles and activities, the outcome of HAART at ACC was that about 90% of patients reached an undetectable level of HIV-RNA a year after the initiation of

therapy and subsequently maintained this rate for 4 years (Fukuyama et al., 2004; Tachikawa et al., 2003). In addition, the rate of missed appointments at ACC was 16% (Ikeda & Kawamura, 2004), which is very low compared with another report (Lim, Dong, & Hart, 2003). It is likely that the outcome of therapy and consultation continuation at ACC show the effects of support for adherence by CNs, including face-to-face consultations at the outpatient clinic and phone consultations.

There are several studies that indicate telephoning can be an effective and economical means to support patients with HIV/AIDS (Kinsella, 1998; Morrison & Black, 1998; Morrison et al., 1997; Nakanishi et al., 1997). After the establishment of HAART in 1996, Lim et al. (2003) reported the effects of salvage therapy on virologic and immunologic markers through a phone consultation service (Warmline), rather than through the patients themselves.

Measuring Adherence Outcomes Using Telephone Consultation

Although CNs' telephone consultation activity in the ACC has been studied informally (Kato et al., 2004a, 2004b), a detailed investigation had not yet been conducted. No survey had previously determined details such as (a) the times that patients call CNs and CNs call patients, (b) the mean length of these conversations, (c) the frequency and content of these conversations relative to HAART treatment phase, and (d) relationships between telephone conversation data and demographic or disease-related data.

This study's aims were to (a) describe the actual circumstances surrounding the phone consultation activities provided to patients as routine practice by CNs, (b) describe the contents of dialogue with patients according to differences in HAART phase, and (c) understand the relationship between the length of telephone consultation and patients' demographic data and other treatment-related factors.

Methods

Study Design

Design of this study was descriptive and correlational.

Sample. A convenience sample was composed of seropositive patients who received phone consultation services provided by CNs as ACC's routine practice and who were registered with ACC over a period of 1 month in October 2004. It was difficult to anticipate reasonable estimates of parameters, such as the semipartial coefficient between independent variables, needed for calculating adequate sample size for multiple regression analysis (Maxwell, 2000) because this is the first research on CN phone consultation for patients with HIV/AIDS. Thus, the authors estimated a sample size above 114 to achieve a power of .80 using Green's (1991) rule of thumb ($N = 104 + \text{number of independent variables}$).

Setting. Three types of phone devices were used for consultation: (a) the hospital's lightweight cordless mobile phones, Personal Handyphone System (PHS), (b) desk phones at ACC, and (c) a cellular phone dedicated to the CNs' use. The telephone number of the hospital PHS was the main switchboard number of the facility, and a CN was appointed to answer. The ACC desk phone numbers were announced to the public. There was one cellular phone, and CNs took turns carrying it around after office hours; this phone number was disclosed only to patients registered with ACC.

Procedure

The survey was approved by the ethical committee of the International Medical Center of Japan. CNs posted and presented a letter asking patients to consider being involved in the study at the outpatient clinic and describing the sample tool. The letter described (a) the purpose of the study, (b) how the contents of the dialogue with patients would be recorded (by checklist), (c) a statement about inquiry into medical records only with the patient's consent, (d) a guarantee of confidentiality, and (e) permission to refuse to participate with no penalty. For interested patients, permission to participate was validated by telephone after CNs informed them of the contents of the letter.

Each CN in charge of phone consultation collected data using (a) a stopwatch to time consultations, (b) a pretested checklist regarding content of conversations, and (c) medical record inquiry. Data on the circumstances and contents of conversations were collected just after each consultation. With

Table 1. Study Measures: Contents of Phone Consultation

Item	Explanation
Consultation needs of patients (10 items)	
• Self-administration of medication:	Cases of forgetting to take medication or losing medicines and whether or not antiretroviral drugs are used.
• Condition of disease:	Continuous consultation on changes in physical condition.
• Symptoms:	Consultation on poor physical condition at the time of the call, such as abdominal pain, diarrhea, headache, etc.
• Anxiety:	Variety of anxieties experienced in coping with HIV/AIDS.
• Consultation with other divisions/institutions:	Consultation or reference to institutions and/or organizations other than ACC.
• Daily life:	Consultation in matters affecting daily life such as diet, maintaining activities and behavioral patterns, and sex life.
• Human support:	Consultation on human support formation on whether patients should inform close acquaintances or family about their infection.
• Economic support:	Consultation on aspects related to economic support, including use of social resources.
• Medical consultation:	Necessity for medical consultation.
• Other:	Free description of any other relevant topics.
CNs' interventions/responses (8 items)	
• Education:	Specific and detailed advice.
• Explanation:	Provision of facts/knowledge or information.
• Referral to other division.	
• Active listening.	
• Recommendation of medical consultation.	
• Clerical communication.	
• Request of contact.	
• Other:	Free description of any other relevant topics.

NOTE: ACC = AIDS Clinical Center, CN = coordinator nurse.

permission obtained from each patient, medical records were surveyed the day after the consultation.

Measures

The following three measurement elements were contained in the survey.

1. *Circumstances of phone consultations.* Actual circumstances of phone consultations were collected using a checklist. These included day of the week, time in conversation, time zone, and incoming or outgoing call. Time zone was recorded using three categories: a.m. (weekdays 8:30 a.m. to 12:00 noon), p.m. (12:00 noon to 5:00 p.m.), and other (weekdays 5:00 p.m. to 8:30 a.m. of the following day, and around the clock on Saturdays, Sundays, and public holidays).
2. *Contents of conversations.* Contents of conversations were recorded from two perspectives: consultation needs of the patient and the CNs' interventions/responses. Possible contents were listed in the checklist as consultation needs of patients (10 items) and CNs' interventions/responses (8 items), as shown in Table 1. These items were developed based on previous research using the methods of content analysis (Ogane, Watanabe, Ikeda, & Ishihara, 2002). Multiple choices were allowed for both needs and interventions/responses.
3. *Demographics and treatment-related factors.* For demographic background, sex, nationality, and age were recorded. Treatment-related factors of the patients are shown in Table 2. The HAART process was classified into four phases: before the introduction of HAART, within 2 weeks of

Table 2. Study Measures: Backgrounds and Treatment-Related Factors of AIDS Clinical Center Patients

- HAART phase^a
 - Before the introduction of HAART
 - Within 2 weeks of introducing HAART
 - Within 6 months of introducing HAART
 - After 6 months of introducing HAART
- Infection route (five categories)
 - Men who engage in homosexual sex
 - Heterosexual sex
 - Blood products
 - Other routes (blood transfusion, needle punctures, etc.)
 - Unknown
- Stage of disease^b
 - Asymptomatic carrier stage
 - AIDS stage
- Presence or absence of complications/comorbidity
 - Tuberculosis, mental disease, hepatitis, diabetes, etc.
- Recent CD4-positive lymphocyte counts (cells/ μ L)
- Recent viral load (copies/mL)
- Day of initial medical examination/consultation at the AIDS Clinical Center

NOTE: HAART = highly active antiretroviral therapy.

a. This classification refers to the research result that viral load in blood at 4 to 6 months after the initiation of HAART can be considered one of the indices for evaluation of HAART effectiveness (Ishihara, 2000). In addition, at the AIDS Clinical Center, the patients were required to report the side effects and the situations of self-administration of medication over the phone a week after HAART introduction and to undergo the first medical examination/consultation 2 weeks after the initiation of self-administration of medication.

b. According to Japanese criteria, asymptomatic carriers are infected HIV patients with no experience of opportunistic infection or malignancies listed as AIDS indicator diseases/conditions, and if they have experienced any of these once, they are classified as AIDS patients, even with no symptom at present.

introducing HAART, within 6 months of introducing HAART, and after 6 months of introducing HAART.

Survey Tool

For data collection, a survey tool was developed as shown in the appendix. This was a pocket-sized checklist for convenience in surveying, and to maintain confidentiality, the upper part of the tool was cut off for data analysis.

Data Analysis

First, descriptive statistics in actual circumstances were tabulated. Second, independent *t*-tests were used for exploration of differences between groups in required time.

To describe the contents of conversations and to explore the relationship between the length of telephone time and patients' demographic data or treatment-related factors, the authors used only episodes with patients from whom permission for access to medical records was obtained. The number of each content item checked by CNs was counted and compared according to HAART phase for both needs and interventions/responses.

The relationship between time and each patient's factors was analyzed in the following steps: univariate analysis was conducted by *t*-test or analysis of variance for categorical data and by regression analysis for numeric data. Then, multiple regression analysis was completed to see if there were demographic or treatment-related predictors of time on the telephone (dependent variable) with the CNs. Independent variables were the factors at $P < .2$ by univariate analysis. All of the statistical analysis was performed using a statistical software program, SAS version 9.1 (SAS Institute, Inc, Cary, NC), and the level of significance was set at $p < .05$.

Results

Number of Telephone Consultations and Consent From Patients

During one month, 175 phone consultation episodes with patients were collected, including both incoming and outgoing calls. Among these, consent for use of medical records was obtained from 161 episodes; excluding patient duplications, the number of patients giving consent was 118.

Circumstances Surrounding the Telephone Consultations

The circumstances of 175 phone episodes are shown in Table 3. There were nearly 9 episodes per day on weekdays and .18 per day after office hours

Table 3. Patient Circumstances During Coordinator Nurses' Phone Consultations

	Total Number of Calls (N = 175)
	n (%)
Time zone ^a	
a.m. (weekdays 8:30 a.m. to 12:00 noon)	73 (41.7)
p.m. (weekdays 12:00 noon to 5:00 p.m.)	79 (45.1)
Other ^b	15 (8.6)
Device ^c	
Hospital PHS	98 (56.0)
Desk phones at ACC	45 (25.7)
Cellular phone dedicated to CNs	27 (15.4)
Incoming/outgoing ^d	
Incoming	130 (74.3)
Outgoing	43 (24.6)
	Mean ± SD
Number of calls (per day)	
Mon.–Fri.	8.60 ± 3.15
Sat., Sun., and holiday	.18 ± .4
Call time (min)	
Mean	4.75 ± 3.78
Incoming/outgoing	
Incoming	5.44 ± 3.95
Outgoing	2.64 ± 2.37

NOTE: ACC = AIDS Clinical Center, CN = coordinator nurse, PHS = Personal Handyphone System.

a. Information was not obtained for 8 calls.

b. Weekdays 5:00 p.m. to 8:30 a.m. of the following day, and around the clock on Saturdays, Sundays, and public holidays.

c. Information was not obtained for 5 calls.

d. Information was not obtained for 2 calls.

and on weekends/holidays. The hospital PHS was the vehicle for more than half of all calls, and the cellular phone was used for another 15.4% of calls. The number of incoming calls was nearly three times greater than that of outgoing calls. The average time per consultation was 4.8 ± 3.8 minutes, with a significantly longer time for incoming calls (5.4 ± 4.0 min) than for outgoing calls (2.6 ± 2.4 min) ($P < .0001$).

Contents of Telephone Consultation According to Highly Active Antiretroviral Therapy Phase

Table 4 shows patients' needs and CNs' interventions/responses according to the difference in HAART phase for 161 episodes. Because the number

of consultations was small *within 2 weeks* after introduction of HAART (4 episodes), this phase was combined with the *within 6 months* phase.

Major needs in the phase *before introduction of HAART* were medical consultation (34.7%), followed by symptoms (13.9%) and anxiety (11.1%). For these needs, the most frequently cited interventions/responses were recommendation of medical consultation (34.7%) and explanation (33.3%). In the phase *within 6 months* after HAART introduction, symptoms (42.3%) was the most conspicuous need and other needs were anxiety (19.2%), self-administration of medication (15.4%), and condition of disease (15.4%). In this phase the most frequently cited interventions/responses were active listening (42.3%), explanation (38.5%), and recommendation of medical consultation (30.8%). There were no conspicuous needs or interventions/responses in the *after 6 months* phase; patients' needs were medical consultation (22.2%), symptoms (15.9%), and condition of disease (12.7%). Interventions/responses were explanation (25.4%), active listening (15.9%), and recommendation of medical consultation (14.3%). In addition, many other needs and interventions/responses that were not included in the checklist were collected as free description, regardless of the HAART phase. There were a few needs or conversations in this group that were obtained from more than two phone calls.

Through all phases, medical consultation (26.1%) and symptoms (19.3%) were major needs of patients. The leading interventions/responses by CNs were explanation (31.1%), recommendation of medical consultation (26.1%), active listening (19.3%), and referral to other division (13.7%).

Relationships Between Telephone Time and Demographic/Treatment-Related Factors

Of 161 episodes, 153 were analyzed, excluding episodes without time data (Table 5). From univariate analysis between the length of telephone conversation and each factor, five variables were selected. Time required was longer when the age was higher ($P = .012$), when HAART phase was within 6 months of introduction ($P = .01$), when patients had complications/comorbidities ($P = .02$), and

Table 4. Patients' Needs and CNs' Interventions/Responses Depending on Highly Active Antiretroviral Therapy Phase (Multiple Choice) (*N* = 161)

	HAART Phase			Total <i>N</i> (%)
	Pre-HAART	Within 6 Mo.	Over 6 Mo.	
	<i>n</i> (%) 72 (100)	<i>n</i> (%) 26 (100)	<i>n</i> (%) 63 (100)	
Need				
Self-administration of medication	2 (2.8)	4 (15.4)	5 (7.9)	11 (6.8)
Condition of disease	3 (4.2)	4 (15.4)	8 (12.7)	15 (9.3)
Symptoms	10 (13.9)	11 (42.3)	10 (15.9)	31 (19.3)
Anxiety	8 (11.1)	5 (19.2)	5 (7.9)	18 (11.2)
Consultation with other divisions/institutions	2 (2.8)	0 (.0)	2 (3.2)	4 (2.5)
Daily life	1 (1.4)	1 (3.8)	1 (1.6)	3 (1.9)
Human support	1 (1.4)	0 (0)	2 (3.2)	3 (1.9)
Economic support	3 (4.2)	1 (3.8)	2 (3.2)	6 (3.7)
Medical consultation	25 (34.7)	3 (11.5)	14 (22.2)	42 (26.1)
Other	21 (29.2)	12 (46.2)	22 (34.9)	55 (34.2)
Intervention				
Education	7 (9.7)	4 (15.4)	5 (7.9)	16 (9.9)
Explanation	24 (33.3)	10 (38.5)	16 (25.4)	50 (31.1)
Referral to other division	12 (16.7)	2 (7.7)	8 (12.7)	22 (13.7)
Active listening	10 (13.9)	11 (42.3)	10 (15.9)	31 (19.3)
Recommendation of medical consultation	25 (34.7)	8 (30.8)	9 (14.3)	42 (26.1)
Clerical communication	10 (13.9)	3 (11.5)	5 (7.9)	18 (11.2)
Request of contact	5 (6.9)	1 (3.8)	5 (7.9)	11 (6.8)
Other	11 (15.3)	5 (19.2)	21 (33.3)	21 (13.0)

NOTE: HAART = highly active antiretroviral therapy.

when viral load was lower ($P = .014$). In the two categorized stages of disease (asymptomatic carrier or AIDS), no significant difference in time was reported ($P = .099$). Among these five variables, the stage of disease was strongly related to HAART phase ($\chi^2 = 13.1, P = .0014$). Therefore, multiple regression analysis for telephone time was performed using the above four variables, excluding the stage of disease. As a result, the only predictive factor of telephone time was the presence of complications/comorbidities (β ; partial regression coefficient = 1.23, $P = .044$, $R^2 = .11$).

Discussion

Circumstances Surrounding the Telephone Consultation

The number of CNs' phone consultations with patients, 175, was higher than the average monthly

number of face-to-face consultations at the ACC outpatient clinic, 89 (Kato et al., 2004a). Compared with consultation at the outpatient clinic, which was available only on the scheduled consultation day, the telephone consultation system, which was always available, seemed to be valued by the patients.

Phone consultations were mostly conducted during working hours on weekdays, with durations of around 5 minutes per person. Considering the result that almost all phone calls were placed during office hours, hospital PHS and desk phones at ACC were able to respond to nearly all consultations. However, a few consultations were sought after office hours and on weekend/holidays. When CNs met patients on their first visit to the outpatient clinic, they confirmed a convenient time and phone number. However, many patients underwent HAART while still at work (Kato et al., 2004a), and some had not disclosed information about their infection even to their family. Therefore, a phone consultation system outside of office hours is considered essential