group for death from causes other than opportunistic disease, confirming that immunosuppression increases the risk of death among patients with diseases not traditionally believed to be opportunistic in nature. Much, but not all, of the difference in the rates of opportunistic disease or death from any cause between the drug conservation group and the viral suppression group was explained by differences in the CD4+ count and HIV RNA level during follow-up. The hazard ratio for opportunistic disease or death from any cause in the drug conservation group versus the viral suppression group was reduced from 2.6 to 1.5 after adjustment for the latest CD4+ count and the latest HIV RNA level. The reasons for the remaining excess risk are not clear.

Although our findings indicate that the interruption of antiretroviral therapy with the use of higher CD4+ count thresholds than those used in our study may result in lower risks of opportunistic disease or death from any cause, the lack of benefit of our interruption strategy on major adverse events associated with antiretroviral therapy suggests that such strategies should be viewed as carrying a net clinical risk unless proven otherwise in appropriately powered studies.

In summary, our findings provide clear and compelling evidence that the episodic antiretroviral strategy, guided by the CD4+ count, used in the SMART study is deleterious. Our results indicate that some of the excess risk of opportunistic disease or death from any cause in the drug conservation group appears to be attributable to the longer period during which participants had reduced CD4+ counts. Further research is needed to evaluate the effect of interrupting antiretroviral therapy on immune function, inflammation, and other markers.

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Short Communication

Reversal Periods and Patterns from Drug-Resistant to Wild-Type HIV Type 1 after Cessation of Anti-HIV Therapy

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ABSTRACT

Anti-HIV drug-resistant virus reverts to wild type following discontinuation of antiretroviral therapy (ART). This study aimed to determine the reversal period. ART was discontinued in 16 patients harboring drug-resistant viruses. Resistant mutations of reverse transcriptase (RT) and protease (PR) genes of plasma- and peripheral blood mononuclear cells (PBMC)-derived viruses were examined by direct sequencing monthly until the disappearance of mutants (median follow-up period: 8.9 months). Only wild-type virus was detected in 50% of patients at 6.3 months (quartiles, 3.2–20.7 months) and at 9.2 months (quartiles, 5.7–13.8 months) in plasma- and PBMC-derived viruses, respectively, after ART interruption. Among the 133 resistance-associated mutations identified at ART interruption, half the RT and PR mutations shifted to wild type in 3.2 months in plasma, 6.7 months of RT, and 5.7 months of PR in PBMC, respectively. In plasma- and PBMC-derived viruses, the PR mutations reverted earlier than the RT mutations. These results could be relevant as to when to perform drug-resistance testing.

THE EMERGENCE OF DRUG-RESISTANCE-ASSOCIATED MUTATIONS leads to treatment failure and may limit future treatment options. Therefore, inclusion of drug-resistance testing is recommended in anti-HIV-1 treatment guidelines, especially after failure of standard regimens.[1,2] A number of studies showed that drug-resistance testing improved the benefits of antiretroviral therapy (ART).[3–8] For drug resistance testing, plasma and peripheral blood mononuclear cell (PBMC) can be used as clinical specimens.[9] Using direct sequencing, we reported previously the earlier detection of resistant mutations in plasma than in PBMC.[10] Accordingly, we recommended the use of plasma for early detection of drug resistance during therapy in those patients who fail to respond to antiretroviral treatment. Clinically, even when patients develop virologic failure [rebound of plasma HIV-1 viral load (VL)], the CD4 count remains sufficiently high for treatment interruption, at least in some patients. In such cases, the timing of genotypic drug resistance testing is of practical importance. Discontinuation of treatment causes the reversion of resistance mutations to wild-type viruses.[11–18] Previous studies indicated that resistance mutations of plasma viruses could rapidly become undetectable either partially or entirely from 14 days to 4 months after ART cessation.[12–18] The reversion of mutations to wild type is considered to be due to the low replication fitness of mutant variants and outgrowth of wild type viruses when the drug-selective pressure is withdrawn.[17,21–22] However, the time course and pattern of this reversion have not been studied in detail in heavily treated patients. Clarification of this issue will help determine the most appropriate time and sample for performing genotypic-resistance testing after ART cessation.

The study subjects were 16 HIV-1-infected patients who had been known to have drug-resistance virus beforehand and discontinued antiretroviral therapy from August 1998 through December 2002 for a variety of reasons. All patients regularly consulted the AIDS Clinical Center at the International Medical Center of Japan, Tokyo, and gave written informed consent. Their demographic data and clinical characteristics at the time of quitting ART are listed in Table 1. Their blood samples were

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TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS[a]

Pt	*Sex*	*Age (years)*	*Risk factor*	*CD4 cells/μl*	*log_{10} VL month 0*	*log_{10} VL month 1*	*Duration of ART (months)*	*Drugs ever used*	*Reasons of ART stop*
1	M	40	Bisexual	404	5.2	5.3	70.4	AZT, 3TC, d4T, ddI, NFV, RTV, SQH	Virological failure
2	M	23	Hemophilia	103	5	5	46.6	ddC, d4T, 3TC, AZT, ddI, SQH, NFV, IDV	Virological failure
3	M	36	MSM	209	3.5	3.5	91.8	AZT, 3TC, d4T, ddI, NFV	Virological failure
4	M	22	Hemophilia	116	5.1	4.3	71.9	ddC, d4T, 3TC, ABC, ddI, AZT, EFV, SQH, NFV, APV	Virological failure
5	M	26	Hemophilia	30	5.7	5.2	50.2	d4T, 3TC, ddI, AZT, NFV, IDV, RTV	Virological failure
6	M	28	Hemophilia	93	3.6	3.7	129.7	d4T, ddI, AZT, 3TC, ABC, ddC, EFV, RTV, SQH, IDV, NFV, APV	Virological failure
7	M	29	Hemophilia	698	1.7	5	108.6	AZT, 3TC, d4T, ddI, ABC, EFV, RTV, SQH	Side effects
8	M	24	Hemophilia	35	5.1	5.1	67	AZT, 3TC, ddC, SQH, RTV	Virological failure
9	F	42	Heterosexual	690	1.8	4.4	90	AZT, ddI, d4T, 3TC, ABC, EFV, SQH, APV, NFV	Poor adherence
10	M	19	Hemophilia	586	1.8	4.2	107.6	AZT, ddC, d4T, 3TC, ddI, ABC EFV, IDV, RTV, NFV, SQH, LPV/r	Poor adherence
11	M	24	Hemophilia	644	1.7	4.5	117.6	AZT, ddI, 3TC, IDV, RTV	Poor adherence
12	M	22	Hemophilia	138	4.5	4.5	53.4	AZT, ddC, d4T, 3TC, ddI, NVP, SQH, RTV, IDV	Virological failure
13	M	34	Bisexual	276	1.7	3.6	47.6	d4T, 3TC, ddI, ABC, AZT, NFV, IDV, RTV, LPV/r	Poor adherence
14	M	42	MSM	420	4.3	5.3	49.8	AZT, 3TC, d4T, ddI, IDV, RTV, SQH	Virological failure
15	M	39	Hemophilia	544	1.7	4.5	140.8	AZT, d4T, 3TC, NVP, NFV	Side effects
16	M	37	Bisexual	525	4.4	4.6	69.9	AZT, ddC	Virological failure
Mean		30.4		344	3.5	4.5	82		

[a]M, male; F, female; MSM, men having sex with men; VL, HIV-1 viral load in plasma; month 0, time when ART was stopped; month 1, 1 month after ART was stopped. AZT, zidovudine; 3TC, lamivudine; d4T, stavudine; ddI, didanosine; ddC, zalcitabine; ABC, abacavir; EFV, efavirenz; NVP, nevirapine; NFV, nelfinavir; RTV, ritonavir; SQH, saquinavir hard gel capsule; IDOV, indinavir; APV, amprenavir; LPV/r, lopinavir + ritonavir.

collected monthly. Measurements of VL (Amplicor HIV-Monitor, Roche Molecular Systems, Inc., NJ) and CD4 and CD8 lymphocyte counts (monoclonal antibodies and flow cytometry) were performed at each blood sampling.

PBMC were separated by centrifugation from 7 ml EDTA-treated blood. PBMC and plasma were stored at −80°C until sequence analysis. The method of sequence analysis was reported previously.[10] Briefly, total RNA was extracted from 100 μl plasma and DNA was extracted from 1×10^6 PBMCs (SMITEST Ex R&D Kit, Japan). The RNA sample was subjected to reverse transcription (RT) followed by nested polymerase chain reaction (PCR) using primers targeting the RT gene and protease (PR) gene, respectively. A DNA sample was also subjected to nested PCR using the same primers for the same targets. The primers covered 1–100 base pairs of PR and 40–240 base pairs of RT. Sequences of primer sets were published elsewhere.[10] Direct sequencing was performed on a 3730 DNA Analyzer (Applied Biosystems). A heterozygous base sequence was identified when the electrogram showed a minor peak at >50% of the major peak. The amino acid sequence was deduced with the GENETYX-WIN version 4.1 (Software Development, Tokyo) and the amino acid substitutions related to drug resistance were estimated from published data.[2] The clade of HIV-1 was determined by the sequences of RT and PR genes.

The reversal period was defined as the time interval between the date of ART interruption and the date of the disappearance of mutations confirmed by direct sequencing. When mutations (all minor mutations, in some patients) did not revert, the reversal period was defined as the date ART stopped to the date most mutations shifted to the wild-type amino acid sequence (for example, see Table 2; protease residues of plasma virus at month 5.9 of patient 2). As all HIV-1s amplified in this study were HIV-1 clade B, we regarded L63P as the polymorphism. The major mutant residues included M41L, A62V, D67N, K70R, L74V, M184V, G190S, L210W, T215F/Y, and K219E/Q of RT mutations and D30N, L33F, M46I, G48V, V82A/F, I84V, and L90M of PR mutations.[2] The follow-up period was the time interval from when ART was interrupted to when the resistance mutations disappeared.

A Kaplan–Meier survival curve was used to estimate the continuous periods of resistance mutations. The Mann–Whitney U test was used for group comparisons, the Wilcoxon signed rank test was used for paired comparison of the reversal period, the paired t-test was used for changes in CD4 count and HIV-1 viral load, and correlation analysis was used for the relationship between the reversal period and baseline CD4 count or baseline viral load, respectively. StatView version 5 was used for analysis and a p value less than 5% was considered statistically significant.

As shown in Table 1, most patients enrolled in this study had been treated over a long period of time [mean ART period: 82 months (SD, 31.6; range, 46.6–140.8 months)]. The reasons for discontinuation of ART were virologic failure in 10 cases, poor adherence in 4 cases, and side effects in 2 cases. The median follow-up period was 8.9 months (range: 2–25 months) and all patients provided blood samples for testing. None of the patients received any ART during the follow-up period. CD4 counts of 10 patients were more than 200/μl at the time of ART discontinuation. After withdrawal of ART, the CD4 count decreased a mean value of 66/μl 1 month later and continued to decrease until the disappearance of resistant mutations. The VL of 6 patients (patients 7, 9, 10, 11, 13, and 15) who discontinued ART because of side effects or poor adherence ranged from <50 to 650 copies/ml at the time of ART cessation. The VL of these patients rebounded to a mean of 4.2 $\log_{10}$ copies/ml 1 month later (designated as rebounded virus) but showed a plateau level thereafter. The VL of the other 10 patients who discontinued ART for virologic failure was stable after ART cessation.

In all 16 patients, a total of 133 resistance mutation residues with 59 RT and 74 PR were found in plasma and PBMC. The concordance of mutant residues between plasma and PBMC was 96.2% (RT mutations 93.2%, PR mutations 98.6%). All 16 patients possessed RT resistance mutations but 4 of them had no PR mutations (Table 2). In PR, both plasma and PBMC-derived viruses had 26 major resistance and 48 minor resistance residues. In contrast in RT, 52 and 50 major RT residues and 7 and 9 minor RT residues were detected in plasma and PBMC, respectively. The results showed that the resistance mutations could shift to wild type after 1 month or could persist for as long as 22 months after treatment stopped. Interestingly, in 6 patients with viral load rebound, the rebounded viruses in 5 patients (patients 7, 10, 11, 13, and 15) had the same resistant mutations as their predecessor viruses 1 month after ART cessation and then reverted to wild type thereafter. In patient 9, the rebounded virus was a wild-type virus.

As shown in Fig. 1A, after ART interruption, only wild-type virus was detected in 50% of patients at 6.3 months (quartiles, 3.2–20.7 months) and at 9.2 months (quartiles, 5.7–13.8 months) in plasma- and PBMC-derived viruses, respectively. In Fig. 1B, the reversion of 133 resistance mutations is shown by a Kaplan–Meier survival curve. Fifty percent of both PR and RT resistance mutations shifted to wild type in 3.2 months in plasma (quartiles, 1.5–3.7 months for PR, 2–10 months for RT). However, in PBMC, 50% of PR and RT mutations disappeared in 5.7 (quartile, 3.2–6.7 months) and 6.7 (quartile, 3.5–12 months) months, respectively. The reversal period of PR and RT mutations in plasma was 2.5 and 3.5 months, respectively, less than that in PBMC (both $p < 0.05$). Furthermore, the PR mutations shifted to wild type much more rapidly than RT mutations in both plasma and PBMC, although the half life of both mutation residues were the same in plasma (Wilcoxon test $p < 0.05$). In terms of the reversal period of major and minor mutations, there were no difference between them both in the PR and RT regions of plasma- or PBMC-derived viruses. There were no relationships found between the reversal periods of RT and PR mutations and the baseline CD4 cell count, baseline VL, and changes in these two surrogate markers 1 month later (data not shown).

Figure 2 shows how the mutation residues disappeared after ART cessation. We roughly divided the reversal process into two patterns. The first pattern was that resistant mutations persisted for some time and then disappeared abruptly (Fig. 2A). Most PR mutations of plasma viruses, 50% of PR mutations of provirus, and 50% of RT mutations in both types of specimens showed this pattern. The second pattern was that of a gradual decrease of mutations followed by their disappearance or persistence (Fig. 2B). One-third of RT mutations showed this pattern. Overall, all major mutations of RT and PR genes disappeared in all patients after withdrawal of ART. In contrast, the minor mutations did not disappear in some patients.

TABLE 2. RESISTANCE MUTATIONS AND REVERSAL PERIOD IN PLASMA AND PBMC AFTER ART CESSATION

Pt	*Sample*	*Months after ART cessation*	*Reverse transcriptase residues*	*Months after ART cessation*	*Protease residues*
1	Plasma	0	41L, 69D, 118I, 210W, 215Y	0	10I, 30N, 33F, 71T, 84I, 88D, 90M
		3.2	—[a]	3.2	—
	PBMC	0	41L, 69D, 118I, 210W, 215Y	0	10I/L, 30N/D, 33F/L, 71T/A, 84I/V, 88D/N, 90M
		3.2	—	3.2	—
2	Plasma	0	41L, 67N, 69D, 118I, 210W, 215Y	0	10I, 20M, 36I, 48V, 54V, 82A
		15.2[b]	41L, 210W/R	5.9	10F, 36I
	PBMC	0	41L, 67N, 69D, 118I, 210W, 215Y	0	10I, 20M, 36I, 48V, 54V, 82A
		15.2[b]	41L, 118I, 215Y	9	10F, 36I
3	Plasma	0	41L, 44D, 184V, 215Y	0	30N, 71V, 77I, 88D
		7	—	4.6	—
	PBMC	0	41L, 44D, 184V, 215Y	0	30N, 71V, 77I, 88D
		8.6	—	4.6	—
4	Plasma	0	41L, 74V, 184V, 215Y	0	10I, 20I/M, 71V, 73S, 84V, 90M
		2.8	—	4.8	—
	PBMC	0	41L, 184V, 215Y	0	10I/L, 20I, 71V/A, 73S/G, 84V/I, 90M
		4.8	—	4.8	—
5	Plasma	0	41L, 44D, 67N, 210W, 215Y	0	10I, 46I, 71T, 73S, 77I, 82F, 90M
		7.9	—	3.3	10I, 77I
	PBMC	0	41L, 44D, 67N, 184V, 210W, 215Y	0	10I, 46I, 71V, 73S, 77I, 82F, 90M
		12.5	—	6.7	10I, 77I
6	Plasma	0	41L, 74V, 184V, 215Y	0	10I, 46I, 54L, 71V, 77I, 84V, 90M
		6.3	—	1.4	77I
	PBMC	0	41L, 74V/L, V118I, 184V/M, 190G/S, 210W, 215Y	0	10I, 20M/K, 46I, 54L/I, 71V, 77I, 84V, 90M
		11.3	—	3.2	77I
7	Plasma	0	67N, 70R, 184V, 219Q	0	N[c]
		1	67N/D, 70R, 184V/M, 219Q/K		
		3.2	—		
	PBMC	0	67N, 70R, 184V, 219Q	0	N
		9.2	—		
8	Plasma	0	41L, 184V, 215F	0	20R, 36I, 54V, 71V, 82A, 90M
		5.7	—	3.7	—
	PBMC	0	41L, 184V, 215F	0	20R, 36I, 54V, 71V, 82A, 90M
		5.7	—	5.7	20R,
9	'Plasma	0	41L, 67N, 70R, 215F, 219E	0	10L/I, 36I, 73S, 77I, 90M
		1	—	1	—
	PBMC	0	67N, 184M/N, 210W, 219E	0	10L/I, 71T/I, 73S, 77I, 90M
		2	—	1	—

10	Plasma	0	41L, 67N, 215F, 219Q	0	10I, 36I, 46I, 53L, 71V, 84V, 90M
		1	41L, 67N, 215F, 219Q		
		8.5[d]	219Q/K	3.7	10I, 36I
	PBMC	0	41L/M, 67N, 70R, 118V/I, 184V/M, 215F, 219Q	0	10I, 36I, 46I, 53L/F, 71V, 84V, 90M
		8.5[d]	67N, 70R, 219Q	7.9	10I, 36I
11	Plasma	0	—	0	N
		1.5	67N, 70R, 219Q		
		24	67N, 69N/D, 219Q		
	PBMC	0	N	0	N
12	Plasma	0	184V, 62V	0	10I, 48V, 71T, 77I, 82A, 90M
		2	—	2.2	71T, 77I
	PBMC	0	184V, 62V	0	10I, 48V, 71T, 77I, 82A, 90M
		2.2	—	5	71T, 77I
13	Plasma	0	67N, 184V	0	10I, 46I, 71V, 77I, 88S
		1	67N, 184V	1	10I, 36M/I, 71V/T
		3.5	—	2.3	10I, 71V/T
	PBMC	0	67N/D, 184V/M	0	10I, 46M/I, 71V/T, 77I
		13.8	—	7.4	10I, 36I/M, 71V/A
14	Plasma	0	184V	0	10I, 20R, 24I, 36I, 53L, 54V, 71T, 82A
		1	—	1	—
	PBMC	0	N	0	10I/L, 20R/K, 24I/L, 36I, 53L/F, 54V, 71V/A, 82V/A
				6.2	—
15	Plasma	0	67N, 70R, 219Q	0	N
		1	67N, 70R		
		20.7	—		
	PBMC	0	67N, 70R, 219Q	0	N
		22.5	67N, 219Q		
16	Plasma	0	67N/D/G, 69A/D, 70R, 219Q	0	N
		19.5	219Q		
	PBMC	0	69A/D, 70R, 219Q	0	N
		19.5	69A/D, 219Q		

[a]—, wild type.
[b]This patient died at this time point with RT mutations detected.
[c]N, no resistance mutations.
[d]New ART was introduced at the time.

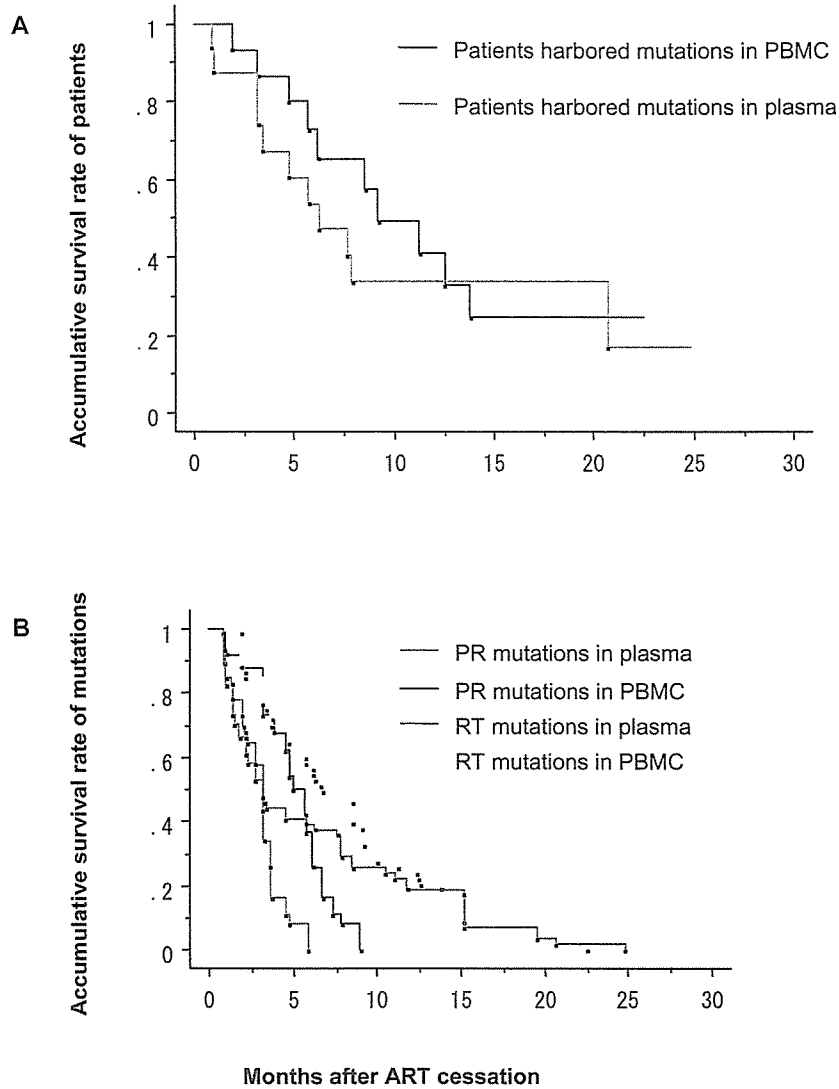

FIG. 1. (**A**) Kaplan–Meier curves showing percent of 16 patients with drug resistance mutations in plasma or PBMC. (**B**) Kaplan–Meier curves showing percent of 133 drug resistance mutations (59 RT and 74 PR) in plasma or PBMC. PR, in plasma vs. in PBMC ($p < 0.05$); RT, in plasma vs. in PBMC ($p < 0.05$); PR vs. RT ($p < 0.05$).

We designed the present study with the main objectives of determining the duration of the reversal period from the presence of resistant viruses to wild-type viruses and of elucidating the reversal patterns of plasma- and PBMC-derived viruses after discontinuation of ART. To determine the duration of the reversal period (i.e., from resistant mutations of RT and PR genes of plasma viruses and proviruses to wild type), sequential specimens of plasma and PBMC from patients with resistance mutations were sequenced after ART was interrupted. We found that the PR and RT resistance mutations shifted to wild type much more rapidly in plasma than in PBMC after ART cessation. In 3.2 months after ART stopped, 50% of the resistance mutations in plasma-derived viruses shifted to wild type and 50% of the major mutations of both RT and PR regions were undetected by direct sequencing. This period was similar to that reported by other investigators.[13,14,16–20] However, 50% of the mutations of RT and PR were detected by 6.7 and 5.7 months, respectively, when PBMC samples were used. Accordingly, when the patient develops virologic failure and drug resistance testing is performed using plasma sample after 3.2 months of ART cessation, the results of the test should be interpreted with caution, especially when deciding subsequent ART regimens, because 50% of mutation residues were undetectable by testing. When a resistant virus is not detected by drug-resistant testing, therapy using the same antiretroviral drugs or the same class of agents that reveal cross resistance is usually associated with early drug failure by previously acquired resistant viruses.[23,24] Therefore, like other recommendations,[1,2] drug-resistance testing should be performed soon after ART cessation. However, according to our data, the testing period could be postponed for 2.5 months (from 3.2 to 5.7 months) after ART withdrawal if PBMCs are used instead for plasma. In this regard, PBMC is a suitable candidate specimen for drug-resistance testing during off therapy.

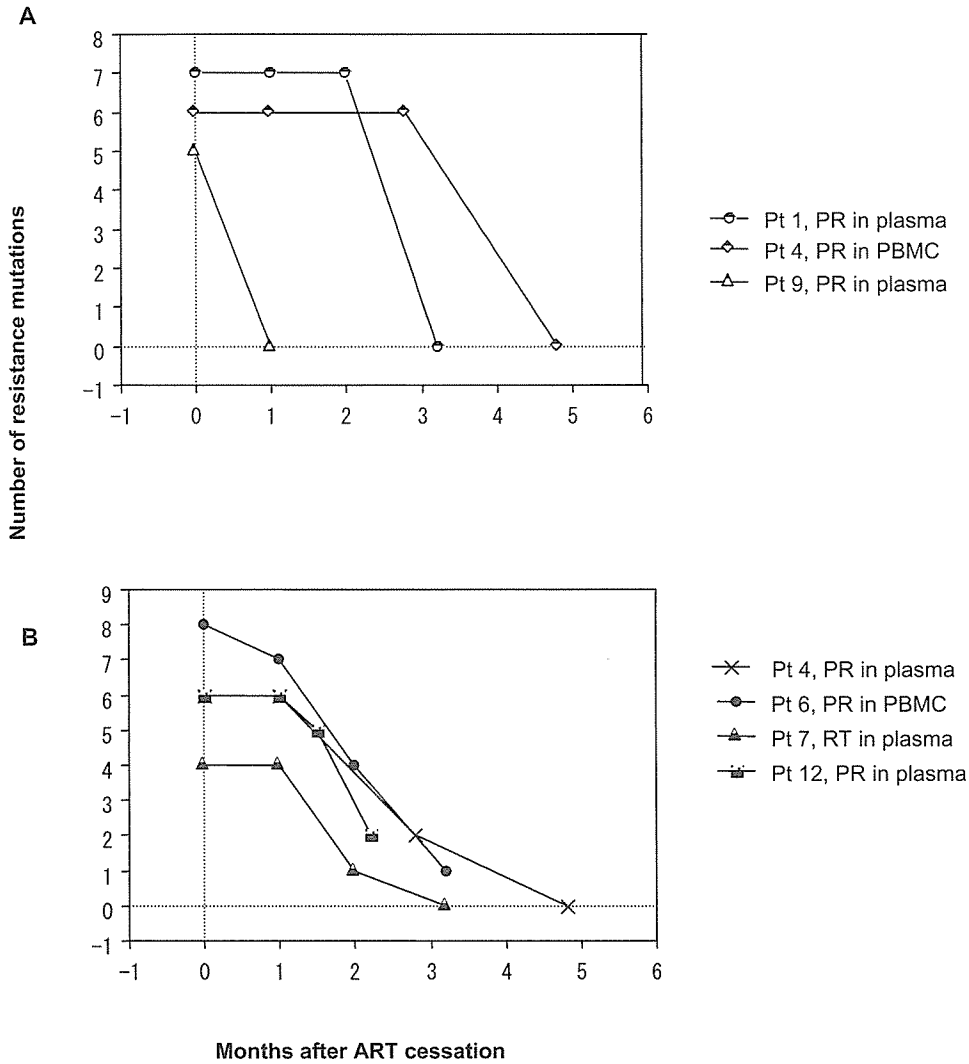

FIG. 2. Two Representative patterns of resistance mutations reverted to wild type after ART cessation. (**A**) Steep disappearance pattern of resistance mutations; (**B**) gradual reversal pattern of resistance mutations. RT, reverse transcriptase; PR, protease.

Drug-resistance testing is not advised for patients with VL <1000 copies/ml since amplification of the virus is unreliable.[1,2] However, if ART has to be discontinued because of ART-related toxicities and VL was undetectable at the time of discontinuation, the timing of the test is a practical question. Others report[17] a sharp reduction in the number of mutations at the time of viral load increase in patients during structured treatment interruption. Our results showed that at 1 month after ART cessation, VL dramatically increased from <1000 copies/ml to >4 $\log_{10}$ copies/ml in 6 patients who stopped treatment due to causes other than ART failure. However, the rebounded viruses in 5 of these 6 patients were still resistance mutant but not the wild-type virus. We previously reported that drug resistance mutations emerged gradually when therapy failed.[10] In contrast, the results here showed that nearly 50% of the mutations disappeared abruptly when ART completely stopped. Thus, waiting for several months after ART withdrawal until stabilization of the VL may potentially result in missing important information for selecting the subsequent therapeutic regimen. Therefore, in such situations, drug-resistance testing should be performed after 1 month to obtain a reliable result after ART withdrawal.

We previously studied the emergence of drug resistance during therapy and reported that the appearance of drug resistance in plasma viruses precedes that in proviruses by more than 1 year and recommended the use of plasma samples for drug-resistance testing during therapy.[10] Considering the high concordance of resistance mutations between plasma and PBMC, and the long persistence period of mutations in PBMC, we conclude that when ART stopped, if PBMC could be used as the sample for resistance assay, the test period may be postponed for 3 months.

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glomerular filtration rate 15 ml/min per 1.73 m^2) avoiding the need for renal replacement therapy. In addition, there was a dramatic decline in proteinuria from an estimated 5 g to 1 g per 24 h.

Epidemiological studies have shown a correlation between increasing HIV viral load, decreasing CD4 cell count and the occurrence of proteinuria and renal failure [1], as well as a reduction in the incidence of HIVAN in patients treated with HAART [2]. Previous case reports have demonstrated a reversal of acute renal failure and histological changes on biopsy after short courses of antiretroviral therapy [3]. Several observational cohort studies have demonstrated a decreased need for renal replacement therapy for patients treated with antiretroviral therapy compared with those not so treated [4–6]. This case supports the hypothesis that HIVAN can be treated by the suppression of viral replication with HAART, and when initiated early may remove the need for renal replacement therapy and provide long-term stabilization of disease. Unlike the previous reported cases, this case suggests a risk of relapse of disease after discontinuing HAART. This suggests that a history of HIVAN alone may be an indication for indefinite HAART, even with an adequate CD4 cell count and despite mild to moderate side effects.

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HLA-Cw8 primarily associated with hypersensitivity to nevirapine

We read with interest the report by Littera *et al.* [1] about human leukocyte antigen (HLA)-dependent hypersensitivity to nevirapine in Sardinian HIV patients. The authors state that high levels of genetic homogeneity and linkage disequilibrium make the Sardinian population particularly suitable for genetic association studies, and they observed a statistically significant association between a nevirapine-hypersensitivity reaction and the HLA-Cw*0802-B*1402 haplotype. In the Sardinian population, however, HLA-Cw*0802 and B*1402 are in such strong linkage disequilibrium that they could not establish which one of these two alleles is primarily associated with the hypersensitivity reaction to nevirapine. Considering that HLA-B14(65) can not be found in the Japanese population, it might be helpful to analyse the patients in our clinic for a determination of the primarily associated HLA allele [2–5].

In our outpatient clinic, a total of 326 HIV-1-infected individuals (309 were Japanese) had given written informed consent for HLA analysis and the study of its association with HIV-1 disease progression and drug-induced adverse events. High resolution typing of the alleles at the HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1 loci had been performed by polymerase chain reaction amplification using sequence-specific primers in all of them. The allele frequency of HLA-Cw8 and HLA-B14 was 13 and 0%, respectively, which is compatible with previous reports of HLA frequency in the Japanese population [2–5]. Forty-three of the analysed patients were on nevirapine treatment or had a history of nevirapine treatment. One of them died of malignant lymphoma 4 weeks after the introduction of nevirapine-containing treatment. In another patient, nevirapine-containing treatment was terminated 17 days after initiation because of granulocytopenia probably induced by co-administered zidovudine. These two patients were excluded from further analysis and the remaining 41 patients were divided into two groups; a nevirapine-hypersensitive group and a nevirapine-tolerant group (Table 1). The nevirapine-hypersensitive group included 11 patients who experienced extensive skin rash (accompanied by fever $> 38^{\circ}C$ in three) and one patient with chronic hepatitis C who developed nevirapine-induced hepatotoxicity with aspartate aminotransferase/alanine aminotransferase values three times above the baseline. The nevirapine-tolerant group included 29 others who had been treated with nevirapine for a period of more than 6 months and did not develop any hypersensitive reaction [1]. There were no significant

Table 1. Demographics and immunological variables in the nevirapine-hypersensitive group and nevirapine-tolerant group.

Variable	Nevirapine hypersensitive ($n=12$)	Nevirapine tolerant ($n=29$)	P value
Mean age, years (SD)	33	40	0.07
Sex, *n* (%)			
Male	11 (92%)	26 (90%)	>0.99
Female	1 (8%)	3 (10%)	
Ethnicity, *n* (%)			
Japanese	11 (92%)	28 (97%)	0.50
Mean weight, kg (SD)	62 (13)	61 (8)	0.88
Plasma HIV-1 RNA, *n* (%)			
>400 copies/ml	9 (75%)	14 (48%)	0.17
Immunological status, cells/μl (SD)			
CD4	306 (186)	291 (184)	0.81
CD8	587 (246)	765 (416)	0.17
HLA, *n* (%)			
Cw8	5 (42%)	3 (10%)	0.03

differences in age, sex, ethnicity, weight, HIV-1 viral load, CD4 and CD8 cell counts between the two groups (Fisher's exact test for dichotomous variables, Student's *t*-test for continuous variables). The frequency of HLA-Cw8-positive patients in the nevirapine-hypersensitive group was 42%, which was significantly higher than those of the nevirapine-tolerant group (10%) and the general Japanese population (9–14%) [2–5]. In the nevirapine-hypersensitive group, four patients including one who developed hepatotoxicity had HLA-Cw*0801 and one had HLA-Cw*0803. In the nevirapine-tolerant group, three patients had HLA-Cw*0801. HLA-Cw*0802 was not identified in the patients we analysed. There was no significant difference in the frequency of the other HLA alleles between the two groups.

Considering our data together with that of Littera *et al.* [1], HLA-Cw8 antigen rather than specific alleles of other genes linked with HLA-Cw*0801 or HLA-Cw*0802 may be primarily associated with a nevirapine-hypersensitivity reaction. Nevirapine or nevirapine metabolite coupled with HLA-Cw8 antigen may be expressed on the cell surface and may induce hypersensitive reactions including skin rash and hepatotoxicities. We totally agree with Littera *et al.* [1] that a careful choice of drugs in susceptible patients identified by HLA typing would considerably reduce the risk of severe and sometimes life-threatening hypersensitive reactions.

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K65R development among subtype C HIV-1-infected patients in tenofovir DF clinical trials

A recent study demonstrated a greater propensity for HIV-1 subtype C to develop a K65R mutation under in-vitro selection with tenofovir compared with subtype B or other non-B subtypes [1]. The mechanistic basis for this in-vitro observation was not clear because the single nucleotide change is identical for the K65R substitution in either subtype B or subtype C. For subtype B, a switch from AAA to AGA occurs. For subtype C, a switch from AAG to AGG occurs. The third codon position, however, is different for subtype C, reflecting redundancy in the genetic code for lysine and a natural variation among different HIV-1 subtypes. The authors speculate that this third codon position difference or other genetic changes may influence the propensity for the development of K65R in subtype C HIV-1.

We evaluated patients with subtype C, subtype B, and other non-B HIV-1 subtypes for virological failure and the development of resistance in two phase III clinical trials of tenofovir disoproxil fumarate (DF). These studies enrolled patients primarily from the United States, Europe and South America. Within these studies, approximately 7% of the 1200 patients enrolled were infected with non-B HIV-1 subtypes. Study 903 assessed the combination of tenofovir DF with lamivudine and efavirenz, and study 934 assessed the combination of tenofovir DF with emtricitabine and efavirenz. Although neither study was statistically powered to address efficacy in patients with non-B subtypes, the virological failure rates were similar between patients with subtype B or non-B HIV-1 subtypes (15.5 versus 19%, respectively,

Acute Schizophrenic Symptoms as the Initial Manifestation of HIV Infection that Respond to Highly Active Antiretroviral Therapy

To THE EDITOR—We read with a great interest an article in your journal by Shah et al. [1] that showed successful treatment of a case of HIV encephalopathy. Here, we report a case of a patient who had schizophrenic symptoms as the initial manifestation of HIV infection and had a regression of mental abnormalities following the initiation of HAART.

A previously healthy 25-year-old Japanese woman presented to Hokkaido University Hospital with psychotic symptoms, such as hallucinations and persecutory and somatic delusions. She had no history of abusing drugs or alcohol. Her Mini-Mental State Examination score was 27/30. The initial diagnosis was schizophrenia, defined according to International Classification of Diseases and Related Health Problems, 10th edition [2]. Although she was treated with quetiapine fumarate (300 mg daily), her psychotic symptoms did not show any improvement. Then, recurrent fever of unknown origin was observed and systemic examinations were performed. Radiography of the chest had no findings and tests for collagen diseases, vasculitic syndromes, and herpes groups viruses had negative results, but HIV-1 antibodies were present on ELISAs and Western blots. Her $CD4^+$ T lymphocyte count was 2 cells/mm^3. The plasma HIV-1 RNA load (Amplicor HIV-1 Monitor assay; Roche Molecular Systems) was 140,000 copies/mL. Enhanced MRI of the brain revealed no abnormalities. A lumbar puncture showed 3 lymphocytes/mm^3 without atypia, a normal protein concentration of 25 mg/dL (normal concentration, <45 mg/dL), and a glucose concentration of 57 mg/dL. CSF cultures for bacteria, mycobacteria, and fungi were negative. Specific PCRs of CSF, including HIV, JC virus, cytomegalovirus, and varicella-zoster virus, were not done. Neurologically, coordination and all sensory and motor modalities were preserved. However, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) at rest revealed diffuse diminished metabolism in the patient's brain (figure 1). Because treatment with quetiapine fumarate did not improve the patient's symptoms, the diagnosis of HIV-associated psychosis presenting as a schizophrenic form was suspected.

HAART with lamivudine (300 mg

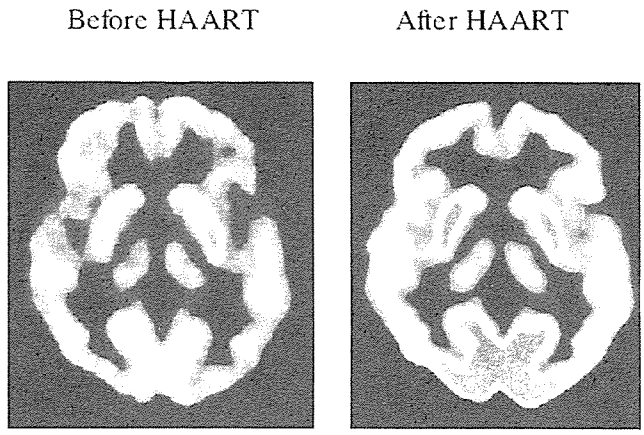

Figure 1. ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography scans before HAART *(left panel)* and after HAART *(right panel)*.

daily), sanilvudine (60 mg daily), and lopinavir-ritonavir (400 mg/100 mg daily) was started. After 8 weeks of HAART, the patient's HIV load was undetectable in plasma. The $CD4^+$ cell counts increased to 74 cells/mm^3. The patient showed a substantial improvement in her mental status within 8 weeks of beginning treatment. In particular, there was a significant improvement of hallucinations and delusions. After 3 months of HAART, the patient's Mini-Mental State Examination score improved to 30/30, and she was in good clinical condition with no evidence of mental abnormality. At this time, FDG-PET at rest showed the recovery of brain metabolism, especially in the occipital lobe (figure 1). The patient was able to perform all daily living activities with no psychiatric agents.

HIV is neuroinvasive and neurovirulent, and neurological complications are seen at all stages of HIV infection. HIV encephalopathy is one the most well-known psychiatric syndromes that usually occurs as a consequence of HIV disease. HIV encephalopathy is defined by severe impairment of specific cognitive functions, such as memory recall and speed of information processing, and by extensive neuronal atrophy. On the other hand, acute onset of schizophrenic symptoms as a first manifestation of HIV encephalopathy was reported [3–6]. However, because these symptoms were mainly reported before the HAART era, treatment for HIV-related psychiatric symptoms has not yet been well defined. In our patient, antipsychiatric agents did not improve her symptoms. Instead, HAART dramatically reversed her characteristics almost completely to what they had been before HIV infection was diagnosed. Because of this, the diagnosis of HIV-induced psychiatric symptoms seems to be justified.

FDG-PET studies showed abnormal glucose metabolic patterns in the brains of HIV-seropositive patients, compared with healthy, HIV-seronegative individuals [7]. These patterns included were diffuse hypometabolism and subcortical hypermetabolism [8]. On the other hand, a number of studies on schizophrenia have found lower glucose uptake in the prefrontal cortex of patients with schizophrenia [9]. Our patient showed diffuse hypometabolism in the cortex that reverted to normal with improvement of her symptoms during HAART. There is a controversy as to whether HAART can change metabolic concentrations [10]. In this respect, more studies are needed to conclude definite patterns of brain metabolism or changes with HAART in patients who develop psychotic symptoms as a first manifestation of HIV infection.

In conclusion, this case suggested that HIV infection should not be ruled out as a diagnosis for new-onset schizophrenia. In addition, such a case report shows the need for longitudinal studies to assess the efficacy of HAART in the treatment of schizophrenic symptoms associated with HIV.

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Potential conflicts of interest. All authors: no conflicts.

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AIDS/HIV NEWS LETTER

東北ブロックHIVニュースレター

Vol.3 No1

●発行日／平成18年9月 ●発行／厚生労働科学研究費補助金エイズ対策研究事業「HIV感染症の医療体制の整備に関する研究」班 分担研究者 佐藤功
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はじめに

1年ぶりにニュースレターの発行となりました。動態調査では7月初めで、東北の非血友病の感染者は250人を超え、全国と同様右肩上がりと増加傾向が続いています。
各県の様々な取り組みも記事に盛り込みました。拠点病院紹介は最近患者急増中の青森県立中央病院です。今後ともHIV感染症の診療レベルの向上、HIV感染拡大防止活動など推進したいと思いますので、よろしくお願い申し上げます。

平成18年度東北ブロック・エイズ拠点病院等連絡会議

国立病院機構仙台医療センター 統括診療部長 佐藤 功

東北ブロック・エイズ拠点病院等連絡会議は平成18年6月21日㈬、岩手県盛岡市（マリオス）で開催されました。66名の参加者（内岩手県が32名）でありました。初めに、仙台医療センターの菊地副院長から、「最近は東北地方においてもHIV感染者が増加している。今日の講演で学んだことを取り組みに役立てて欲しい」とのご挨拶がありました。特別講演では国立国際医医療センターエイズ治療・研究開発センター医療情報室長の立川夏夫先生からHIV/AIDS最近の治療の工夫という演題で、1. HIV感染症の治療について 2. 副作用の問題について 3. 耐性発現について 4. 今後発売される新薬について。5. いきなりエイズ発症等について御講演を頂きました。次いで国立国際医療センターエイズ治療・研究開発センター患者支援調整官の池田和子さんからHIV/AIDSケア up to date の演題名で「疫学、若者での性のネットワーク化、予防対策の重要性、患者教育、服薬、患者支援体制」等のお話を頂きました。

次に岩手県の取り組みについて、医療の立場から1）岩手医科大学医学部血液内科教授 石田陽治先生から「岩手医科大学におけるHIV感染症診療の現状、予防活動（学校教育について、生と性及びエイズ教育を考える会との活動、指導者講習会等熱心な取り組みについて）」のお話を伺いました。2）岩手県立中央病院副院長の武内健一先生に「岩手県立中央病院におけるHIV診療の現状と思い出に残る症例等について」のお話を頂きました。行政の立場からでは岩手県保健福祉部保健衛生課、健康予防担当 技術副主幹兼主査 藤尾 修氏から岩手県のHIV/AIDS患者数の推移、エイズ対策事業（予防普及啓発、人材育成、相談HIV検査、医療体制の整備、

HIV対策推進体制）についてのお話がありました。最後に原告団からの連絡としまして「治療の歴史的な経緯で困難さが現在、現れている。今後とも対応宜しく御願いしたい。イベントなどでは行政、医療関係者に加えて、患者を交えた取り組みを御願いしたい。」等でした。最後に国立病院機構盛岡病院長の山口一彦先生が、おわりのご挨拶をされ終了しました。

今回はいつもに増して熱心に討論され、大変有意義な会議となりました。

平成18年度東北ブロック・エイズ拠点病院等連絡会議
〈プログラム〉平成18年6月21日㈬13時～ マリオス 18階 188会議室

Ⅰ あいさつ
国立病院機構仙台医療センター副委員長 菊地 秀

Ⅱ 講 演
1.「HIV/AIDS最近の治療の工夫」
国立国際医療センター エイズ治療・研究開発センター 医療情報室長 立川 夏夫
2.「HIV/AIDSケアup to date」
国立国際医療センター エイズ治療・研究開発センター 患者支援調整官 池田 和子
3.「岩手県の現状と取り組み」
～医療の立場から～
1）岩手医科大学医学部血液内科教授 石田 陽治
2）岩手県立中央病院副院長兼診療部長 武内 健一
～行政の立場から～
3）岩手県保健福祉部保健衛生課 健康予防担当 技術副主幹兼主査 藤尾 修

Ⅲ 地域原告団連絡事項

Ⅳ 終わりに
国立病院機構盛岡病院長 山口 一彦

平成17年度東北ブロック各地域の取り組み

平成17年度の東北各地域での取り組みをまとめました。東北ブロックでは「東北HIV診療ネット」(各県2～3施設のHIV診療担当医師を世話人とした組織) を立ち上げ、活動を行っております。

【青　森】

○平成17年7月2日　青森土曜の会の集い

○平成17年9月6日
青森県HIV迅速検査導入に向けての事前研修会(青森県健康福祉部主催)、於：青森市、講演「青森県HIV即日検査導入に向けて－HIV即日検査におけるカウンセリングについて－」講師　大館市立総合病院　高橋義博

○平成17年10月12日
青森県エイズ予防対策情報交換会議

○平成18年1月13日
エイズ/HIV感染症出張公開セミナー、仙台医療センター HIV診療スタッフによる出張講演会、於：弘前大病院

【秋　田】

○平成17年9月9日
第3回秋田県HIV治療研究会、秋田市・秋田ビューホテル、一般演題：HIV感染の発見動機　秋田赤十字病院　内科　三浦一樹　特別講演：中高生の性意識の実態とこれからの予防教育のあり方について～テーラーメイドの予防対策/教育の導入～講師　京都大学大学院医学研究科社会健康医学系専攻社会疫学分野　助教授　木原雅子

○平成17年10月25日
平成17年度エイズ教育（性教育）研修会－若者をエイズから救うために－(秋田県教育庁主催)、於：秋田県総合教育センター、講演『学校性教育におけるエイズ教育の留意点』講師：大館市立総合病院　高橋義博

○平成17年12月4日　秋田県世界エイズデー
希望者に無料・匿名で個別相談及びHIV抗体迅速検査

【岩　手】

○平成17年8月27日　みちのくクエスト

○平成17年12月7日
講演会①「アフリカでのHIV/AIDS患者の看護を経験して」講師：岩手医科大学看護師　上平明美
②「アメリカ・アフリカ南北エイズ事情」講師：コロンビア大学附属セントルークス・ルーズベルト病院　内科リウマチ学教室　稲田頼太郎、於：岩手医科大学歯学部講堂

○平成18年2月26日
岩手レッドリボンネットワークプロジェクト（主催：IWATE:生と性及びエイズ教育を考える会)、於：エスポワール岩手、①HIV即日検査②HIV啓発活動報告③講演発表　講師：岩手医科大学細菌学講師　吉野直人

【山　形】

○平成17年12月12日
講演会「HIV感染症/AIDSへのアプローチ～特にHAARTについて～」於：山形県立中央病院、講師：仙台医療センター　伊藤俊広

○平成17年12月22日
講演会「AIDSの話題について（サンフランシスコ見聞録)」
於：山形大学医学部臨床研究棟第5講義室　講師：米沢市立病院内科科長　八幡芳和

【宮　城】

○平成17年5月23日
仙台医療センター地域医療研修センター講演会「感染症治療の原則」講師：㈱サクラ精機・感染症コンサルタント　青木 眞

○平成17年7月6日
エイズリリーフセミナー(東北大感染症呼吸器内科)

○平成18年1月28日
第2回エイズと日和見感染症研究会（東北大感染症呼吸器内科）

○平成17年6月22日
東北ブロック・エイズ拠点病院等連絡会議
於：秋田市・秋田県総合保健センター　協力：秋田大学第三内科
講演：「HIV／HCV重複感染の治療について」
エイズ国立国際医療センター ACC病棟医長 菊池嘉
発表：（仙台医療センター症例報告）仙台医療センター内科医長　伊藤俊広
（秋田県の取り組み）秋田県健康福祉部健康対策課、秋田大学第三内科、大館市立総合病院

○平成17年6月24日
東北エイズ/HIV看護研修"基礎編"

○平成17年6月25日
HIV/AIDS Case Study～初級・中級・上級編～
＊エイズ財団主催研究成果発表会

○平成17年8月28日
宮城のHIV検査を考える学習会
＊厚科研・宮城県臨床検査技師会協力

○平成17年10月30日
東北エイズ/HIV臨床カンファレンス　＊厚科研・地域医療研修センター共催　特別講演:「エイズに合併する寄生虫症」国立国際医療センター研究所部長　狩野繁之、東北ブロック内症例7演題発表

○平成17年11月21日
東北ブロック・エイズ拠点病院等連絡会議

○平成18年1月27日
東北エイズ/HIV看護研修
発表:「HIVの基礎」佐藤功（統括診療部長）「HIV/HCV重複感染について」
千田信之（総合内科部長）「外来看護」菅原美花（看護師）「病棟看護」伊藤ひとみ（副病棟師長）、於:仙台医療センター

○平成18年1月28日
東北AIDS/HIV心理・福祉研修会
（歯科・薬剤師合同特別講演）「HIV感染症による長期療養者の課題～今後の支援のあり方を考える～」講師：桃山学院大学社会学部教授　小西加保留
「HIVカウンセリングの実際～心理支援のいろいろ」講師：千葉県派遣カウンセラー石川雅子、東京都派遣カウンセラー神谷昌枝

○平成18年1月28日
東北AIDS/HIV歯科診療研究会・協議会

○平成18年1月28日
東北AIDS/HIV薬剤師研修会「抗HIV薬と服薬援助」講師：大阪医療センター調剤主任　吉野宗宏
「HIV診療における薬剤師の関わり」講師：名古屋医療センター薬剤科　奥村直哉

○平成18年2月6日
山形県立中央病院より薬剤師2名の実地研修受け入れ（仙台医療センター）

○平成18年3月11日
東北HIV診療ネットワーク会議
【診療ネット参加施設】14施設：青森県立中央病院、弘前大病院、秋田大病院、大館市立病院、山形大病院、山形県立中央病院、岩手医大病院、岩手県立中央病院、国立病院機構西多賀病院、東北大病院、福島医大病院、太田西ノ内病院、磐城共立病院、仙台医療センター

【福　島】

○平成17年7月16日　**みちのくクエスト**、郡山市熱海

○平成18年2月3日
HIV講演　於：太田看護専門学校　講師：太田西ノ内病院　松田信

○平成18年2月14日　**福島県エイズ対策推進協議会**（会長　松田信）、於福島県庁

○平成18年3月22日
福島県エイズ拠点病院情報交換研究会

海外研修～サンフランシスコ研修を終えて～

国立病院機構仙台医療センター 外来看護師　疋田　美鈴

平成18年1月14日から29日までHIV海外研修に参加して、サンフランシスコという非日常の中で、HIV・AIDSについて勉強することは自分が想像していたよりもインパクトの強いことが数多くあったように思う。

中でも、特に印象に残ったことは、HIV外来を長年行っているカイザー病院での受診の流れ、各部門との関わりです。患者は医師の診察後、看護師兼ケースマネージャーのところへ行き、必要に応じてソーシャルワーカーや教育担当、栄養士、薬剤師のところへ行きます。初診の患者について受診するところを見学させていただいたが、どこに行くにもスタッフが次のコメディカルの方への情報シェアを行い、患者が外来で一人になることがないように配慮されていた。又、日本ではスタッフの役割が処方は医師、薬に関しては薬剤師のように狭く線引きされているが、カイザー病院では線引きの幅が広く、オーバーラップしているところが多いと感じた。HIV看護を長年してきたメンバーだからこそ、そのようなチームワークが出来ているのだろうと思われた。

HIV・AIDSは現在慢性疾患になりつつある。慢性疾患を持った人たちが病気とうまくつき合っていくためにセルフマネジメントが重要になってくる。セルフマネジメント（自己管理）ということで、自分なりの目標や問題解決法などを自らが決めていき、行動につながることで自信へとつながる。私達は様々な治療法、問題解決法を患者が生活の中に取り入れることが出来るように助ける必要があることを学んだ。

行動変容を支援するピア・カウンセリングという方法がある。ピアとは仲間・同志という意味で、その人（患者）が問題を持っているのであれば、その人は一番よくその問題について知っている。解決する力も持っている。様々な問題があるので今は解決する力が抑えられているため、その手助けをしましょうという方法で、治療ではなく自己決定の中で進めていく。患者が今どの立場にいるのかを把握し、必要に応じて情報を提供し、聞き上手になることで相手は気持ちをうち明けるという考えである。

又、カウンセリングのスキルとは、日々、慌ただしい時間の中で患者と接することが多く、はい、いいえのクローズドクエスションによる質問が多かったが、5W1Hの使用により、開かれた質問をすることで多くの情報を得ることが出来ることを学んだため、日々の仕事の中で取り入れ、患者の思いをきちんと捉えることができるように、自分なりに再学習していく必要があると思う。

当院のHIV外来業務での役割は、今はまだ分からないことがほとんどだが、外来業務の流れ、各部門の役割を把握し、患者の情報を各部門でシェア出来るように、又、入院時には病棟スタッフとも情報交換が持てるような関わりを少しでも学んできたことを活かしながら取り組んでいきたい。