3. Current Status of HIV Infection in the AIDS Clinical Center (ACC)

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Introduction
HIV infection was first reported in 1981 in USA. It has been 20 years since then. Owing to the understanding of the pathogenesis of this disease and development of new drugs such as HIV-specific protease inhibitor (PI), the prognosis of the disease has been improving. Especially after 1997 in Japan, the strategy of anti-HIV treatment shifted from a two-drug combination to a three-drug combination, which is called highly active antiretroviral therapy (HAART). HAART has been so effective that the prevalence of HIV-associated opportunistic infections has decreased dramatically (Fig. 1). Mortality among hospitalized HIV-1-infected patients in ACC has also decreased from 6.7% in 1996 to 2.6% since then (Fig. 2). However, 80% of patients receiving HAART suffered from side effects and in 15% of these patients, it was necessary to change their treatment due to side effects. Furthermore, an unexpected side effect, namely lipodystrophy syndrome (LDS), emerged among patients who were receiving HAART for more than one year. LDS was first reported as re-distribution of lipid such as central obesity with or without lipo-atrophy from extremities and/or face. Not only cosmetic change, but also it is associated with an elevation of lipid and glucose levels. Therefore, patients with LDS face risk of ischemic heart diseases. Our survey indicated that the rate of LDS in Japanese patients was almost the same as that of Caucasian patients reported elsewhere (1).

Drug resistance
HIV infection has been well controlled by HAART but it does not mean cure. Patients on HAART must adhere to their treatment completely, otherwise resistant virus can appear in their clinical course (2), causing treatment failure (3). Therefore, an assay to detect the resistant virus has become important clinically, although it is likely very expensive. Current means of detection of drug resistance are classified into three methods; genotypic, phenotypic (4), and recombinant virus assays. Among them, the genotypic assay is widely used in many laboratories because it is relatively rapid and easy. In order to investigate the indicative point of the assay, we prospectively examined nucleotide sequence of PR region of plasma RNA virus in a total of 128 patients, whose plasma viral load (VL) was 10,000 copies/ml or more at baseline. This study clearly demonstrated that examination of the PI-resis-

Figure 1. Annual prevalence of opportunistic infections in ACC.

Figure 2. Mortality among hospitalized HIV-1-infected patients in ACC.

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tance at 3 months after the start of therapy is beneficial for PI-naïve patients to predict their prognosis if VL remained at 10^3 order/ml at that time (5).

**Opportunistic infections associated with HIV infection**

Treatment for HIV infection consists of two major arms; one is the use of anti-HIV drugs to prevent the development of AIDS as described above and the other is diagnosis, treatment, and prophylaxis of opportunistic infections. There are five very important opportunistic infections; *Pneumocystis carinii* pneumonia (PCP), cryptococcus meningitis, toxoplasma encephalitis, cytomegalovirus (CMV) infection, and Mycobacterium avium complex (MAC) bacteremia. If these five infections can be precisely diagnosed, a patient can survive under the appropriate treatment. On the other hand, if these are not diagnosed, the patient will die of AIDS. After introducing HAART, the number of cases of CMV retinitis, MAC bacteremia, and AIDS dementia complex was decreased. However, the number of PCP remained high because PCP is the first indicator disease of AIDS if the patient does not know his HIV status. The first choice of drug is sulfamethoxazole/trimethoprim (ST) for PCP treatment. If the patient is in severe respiratory failure, corticosteroid is used concomitantly. Treatment is usually continued for 3 weeks. We have successfully treated 45 out of 47 cases of PCP for 4 years. However, those patients treated with ST for 3 weeks were limited to only 35% due to the very high rate of side effects of ST (6). If the patient was intolerant to ST, treatment was switched to pentamidine. After finishing the treatment, the patient is to be treated with a 5-day course of oral desensitization to ST (7). A protocol of our method is shown in Table 1. More than 80% of patients who were previously intolerant to ST successfully obtained tolerance by this method.

**Future treatment**

The main cause of immunodeficiency in HIV-patients is attributed to qualitative and quantitative abnormalities of CD4 lymphocytes. We previously reported that the production of IL-2 from CD4 lymphocytes in the advance stage of patients is significantly decreased (8). IL-2 increases number and function of CD4 lymphocytes. According to these properties of IL-2, the international clinical trial of subcutaneous administration of IL-2 is on going. This is one of the immune-based therapies administrating cytokines. Another immune-based approach is structured treatment interruptions (STI). This new strategy is to maintain the immune function to HIV by maintaining a very low level of HIV with repeated interruptions of drugs. ACC has a plan to start STI in primary infected patients. HAART can not cure HIV infection. Immune-based therapies which allow patients to long-term non-progressors will be used to support HAART in the future.

**References**


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**Table 1. A Protocol of a 5-day Course of Desensitization to Sulfamethoxazole/trimethoprim (ST)**

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