DISCUSSION

The overall estimated survival time from CD4+ lymphocyte count at 200 x 10^6/L to death was 43.4 months, which was a little longer than that from San Francisco Homosexual Cohort Study (3). The median survival time of 38 months from CD4+ lymphocyte count at 200 x 10^6/L to death in San Francisco Homosexual Cohort Study was quite similar to the result from the study of 17 Korean homosexual men (39.7 months). In Multicenter AIDS Cohort Study, 71 % of HIV infected persons with CD4+ lymphocyte count in the range of 101 – 200 x 10^6/L were alive for 2.5 years from 1989 to 1993 (4). In this study, 70.6 % of subjects survived for 2 years and 66.6 % of subjects survived for 2.5 years from the date of CD4+ lymphocyte count at 200 x 10^6/L to death.

The median survival time of 19.8 months from the estimated date of CD4+ lymphocyte count at 50 x 10^6/L to death was somewhat longer than that reported by Elizabeth G. (16 months, >25% at 2 years)(12). Robert Yarchoan showed that the median survival time of HIV infected persons with CD4+ lymphocyte count less than 50 x 10^6/L was 12.1 months (95% confidence interval: 7.2 –19.4 months) (13). According to the previous report that AIDS-defining diseases occurred at CD4+ lymphocyte count of 50 x 10^6/L for diagnoses, we compared our result of survival time from CD4+ lymphocyte count at 50 x 10^6/L to death with other AIDS survival studies. Ninety-seven percentages of AIDS patients survived at 6 months and 86% of them at 12 months in France (14). The median survival time of 16.4 months among homosexual men of MACS shown in table 6 were shorter than the median survival time of 19.8 months from the date of CD4+ lymphocyte count at 50 x 10^6/L to death in this study. Our result was included in the range of median survival time (from 8 months through 28 months) by the studies on AIDS survival time of many countries (Table 6)(15-28).

Difference between the median survival time from the date of CD4+ lymphocyte count at 200 x 10^6/L to death and that from 50 x 10^6/L to death was about 2 years (23.6 months). Our result was supported by the reports that the time from HIV infection to CD4+ lymphocyte count less than 200 x 10^6/L is on average nearly two years less than to manifestation of AIDS defining OI (3, 29).

As mentioned before, 252 (31.1%) of 811 HIV infected Koreans were infected from foreigner abroad. The statistical analysis of survival time from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death depending on the place of infection showed a significant difference (Figure 1). As hazard ratios from CD4+ lymphocyte count at 200 x 10^6/L and 50 x 10^6/L among subjects infected abroad were 2.84 (p=0.0398) and 2.40 (p=0.0444), which was significant different by 95 % confidence interval. This data showed that subjects infected inside Korea survived longer than those infected abroad.

According to the molecular epidemiological study of HIV subtypes in Korea (6), the subtype of HIV-1 from whom infected inside Korea was not only subtype B but also the strains grouped

into distinct subcluster within subtype B which was different with those from North America and Europe. However, the subtypes of HIV-1 from whom infected abroad identified various subtypes: subtype A, E, B, C, D, G, H. As Kanki et al. suggested that HIV-1 subtypes may determine the rates of progression to AIDS (30), it will be of interest to study whether HIV-1 subtype B found in Korea may affect to survival and may also be related to the prognosis or not. Based on those results, we need further studies to identify the factors which may positively influence the survival after CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L. We also need further study on whether the infection was acquires in Korea or abroad is an important factor to determine overall survival time from seroconversion to death or not.

The rate of CD4+ cell loss was significantly associated with survival time from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death. Because the loss of CD4+ cells means the dysfunction of immune system, we could understand that subjects with the higher rate of CD4+ cell loss survived shorter than other groups.

The effective CD8+ cell-mediated immune response has been closely linked to a beneficial host response to infection with retrovirus. Recent studies have suggested that the $CD8^+$ T cell is an important lymphocyte subset in pathogenesis of HIV infection and is correlated with disease outcome (2-4). A strong HIV-specific immune response can prevent the quantitative and qualitative immune defects of disease progression by HIV-infection. CD8+ T cells can suppress HIV replication in peripheral blood mononuclear cells (PBMCs). The antiviral effect of CD8+ T cells is mediated by HIV suppressor factors secreted from CD8+ T cells such as stromal cell-drived factors (SDF-1), eotaxin, monocyte chemotactic proteins (MCP-1), macrophage-derived chemokine (MDC), CD8+ cell antiviral factor (CAF), and interleukin 16 (IL-16) et al. Recent studies also suggested that beta-chemokines (RANTES, MIP-1 α and MIP-1 β) produced by CD8+ T cells showed a synergistic effect leading to the suppression of HIV replication *in vitro*. $CD8^+$ T cells with anti-HIV activity, especially CTLs, decreases as an HIV-infected person progresses from a healthy state to an AIDS condition. Therefore, the high rate of CD8+ cell loss affected the survival from CD4+ lymphocyte count at 200 x 10^6/L. But the rate of CD8+ cell loss did not affect the survival from CD4+ lymphocyte count at 50 x 10^6/L. We need to study the characterization of CD8+ T cells in detail to explain our result that the rate CD8+ cell loss was lower affect in survival from CD4+ lymphocyte count at 50 x 10^6/L than at 200 x 10^6/L.

Gender, age, infection route and AZT treatment did not affected statistically on the survival time from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death.

Age was identified as a cofactor of HIV progression, and the effect of age was subsequently confirmed in many studies (31, 32). The median survival time from CD4+ lymphocyte count at 200 x 10^6/L to death was slightly shorter among group over age 34 than under age 34. Hazard ratio for over age 34 was 0.82 (p=0.6332) on survival after CD4+ lymphocyte count at 200 x 10^6/L and that for over age 38 was 1.12 (p=0.7560) on survival after CD4+ lymphocyte count at 50 x 10^6/L, after adjustment for other factors. However, we could not find a statistically significant difference by age in our study. The interpretation of these results was that age did not

affect on survival time from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death, though the differences of age between younger and older groups was about 10 years.

Longer survival time and lower hazard ratio from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L were demonstrated among subjects infected through transfusion or blood product than those infected sexually.

Our univariate estimate showing longer survival among subjects infected through transfusion or blood product were different from other studies which survival trends of hemophiliacs were similar to those of homosexual men and intravenous drugs users with AIDS (17, 33, 34). But the infection route did not affect significantly on survival from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death since the number of subjects through transfusion or blood product was small.

After AZT was licensed, many studies was reported that AIDS cases treated with AZT had a median survival of more than 20 months, compared with about 10 months for AIDS cases not treated (35-38). But some studies reported that early initiation of antiretroviral therapy might have little effect on overall survival time (39, 40). Our results showed that AZT treatment did not affect the median survival after CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L. However, some studies suggested that AZT treatment affected the rate of CD4+ cell loss (41, 42). It is possible that AIDS incubation period was extended because the rate of CD4+ cell loss was lower before AIDS onsets. Since 1997 in Korea, the percentage of HIV infected persons who receive the combination therapy including protease inhibitor has increased rapidly. It has been reported that the combination therapy had a significant effect on lengthening survival time (43, 44) but the extent of effect of combination therapy on survival is still uncertain. Although AZT treatment did not show a positive effect on survival after CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L, we need a longitudinal study to investigate the effect of the combination therapy including AZT monotherapy on survival among HIV infected persons.

This study is the first report on the survival time and survival rate from AIDS indicated level to death in Korean. The median survival time after AIDS indicated level is similar with results of studies in other countries. While we had the limitation that the number of subjects included in survival study was small, we found interesting characteristic that HIV infection inside Korea had significantly longer survival time from CD4+ lymphocyte count at 200 x 10^6/L or 50 x 10^6/L to death. We need further to study identify which factors affect the natural history of HIV infection from seroconversion to death.