

Decline of CD4 Level and Its Correlation with Clinical Events in Chinese HIV-Infected Patients

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Abstract

The occurrence of clinical complications, especially opportunistic infections, in HIV positive patients usually parallels the progressive fall in their CD4 level. The immunologic and clinical course of HIV infection has been widely studied in Caucasians. It has been shown that normal Chinese adults have lower CD4 level than their Caucasian counterparts. Since July 1994, we have undertaken a prospective study to look at the CD4 change and its correlation with clinical presentations in a cohort of Chinese HIV/AIDS patients. In the ensuing 27 months, 187 Chinese patients were recruited into the study. They showed progressive fall in the CD4 level; the decline being faster for those with a higher starting CD4 count and for those who developed symptomatic diseases-AIDS-defining or non-AIDS defining illnesses. Besides rate of CD4 decline, most of our Chinese patients had clinical diseases at low CD4 level; their median count (cells/ μ L) being: Kaposi's sarcoma (60), *Mycobacterium avium intracellulare* (9), *Mycobacterium tuberculosis* (55), *Pneumocystis carinii* pneumonia (53), oesophageal candidiasis (40), *Penicillium marneffeii* (20), cryptococcal meningitis (50), CMV retinitis (18), and oral candidiasis (70). The role of ethnicity in the correlation between immunologic changes and clinical manifestations of HIV-infected people and its implications for patient management need to be further studied. (*J Infect Dis Antimicrob Agents* 1998;15:99-103.)

INTRODUCTION

Human immunodeficiency virus (HIV) infection causes a wide spectrum of disease manifestations in afflicted persons, from a completely asymptomatic state, mildly symptomatic stage, to acquired immunodeficiency syndrome (AIDS)-the late stage of the infection. Progression to AIDS is characterised by the occurrence of major complications, usually opportunistic infections or cancers, which arise because of the underlying immunosuppression.

The number of CD4+ T lymphocytes is a frequently used surrogate marker to measure progression of HIV infection. The course of CD4 change and its impact on the clinical course has been widely studied in Western countries (1,2). Progressive decline in CD4 level has been shown to be associated with increased

risk of developing opportunistic infections, and with mortality (3).

Nevertheless, disease course of the same HIV infection may differ in different ethnic groups, due to a variety of factors. The CD4 changes due to HIV, natural history of disease complications and their interrelationships have not been thoroughly studied in Asian countries. The need for studying the immunologic and clinical course of different ethnic groups is further exemplified by the finding that normal Chinese adults have lower CD4 level than their Caucasian counterparts (4). Given a different CD4 level to start with, it is natural to query whether the subsequent immunologic progression from HIV infection will also differ (5). We undertook this study to look at the CD4 change and its correlation with the development of

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opportunistic diseases during the course of follow-up in a cohort of Chinese HIV/AIDS patients.

SUBJECTS AND METHODS

This prospective study commenced in July 1994 when consecutive adult patients seen at the government HIV clinic (Special Medical Clinic) were recruited and followed up longitudinally. Their immunologic status were documented with serial measurement of CD4 level by flow cytometry at 1-3 months' interval. The patients were categorised into 3 groups according to their CD4 count at entry: >500 cells/ μ L (Gp 1), 200-500 cells/ μ L (Gp 2), and <200 cells/ μ L (Gp 3). Clinical events occurring during follow-up were noted. Within each group, the patients can be further subdivided into two subgroups (designated a subscript s or a) according to whether, at any point of the follow-up period, they have developed clinical events, i.e. symptomatic, (e.g. Gp 1s) or not (e.g. Gp 1a). Patients who had clinical events essentially meant that they were in the 1993 CDC classification of clinical categories B or C (6). *Penicillium marneffe* infection is regarded as an AIDS-defining illness (ADI) locally (7).

The date and immunologic status at which an opportunistic infection and cancer was diagnosed for the first time in a patient was used for analysis. The corresponding CD4 count was recorded within 3 months. The results as at the end of September 1996 were studied and analysed. SAS (version 6.08) was employed for statistical analysis of the data where necessary. Linear regression model was used to study the CD4

change with time.

RESULTS

During the 27-month study period, 230 patients were recruited and 187 (81%) of them were Chinese. Demographic and clinical characteristics of the Chinese patients were shown in Table 1. A majority of them were male who acquired HIV *via* heterosexual contact. About one-third of them had a CD4 <200 cells/ μ L at entry of the study. The patients have been followed up for a mean of 11.2 months (range, 1-27).

There was progressive fall in CD4 count with time, but the rate varied (Fig. 1). Patients in Gp1 has the steepest slope of decline (8 cells per month) while Gp3 had the slowest rate (1.5 cells per month).

Table 1. Demographic and clinical characteristics of 187 HIV-infected Chinese patients.

Mean age at entry (year)	35.4
Male : female	173:14
Risk factor for HIV	
heterosexual	123
homo-/bi-sexual	49
blood transfusion	11
injecting drug user	3
unknown	1
CD4 (cells/ μ L) at entry	
>500 (Gp 1)	39(21%)
200-500 (Gp 2)	85(45%)
<200 (Gp 3)	63(34%)

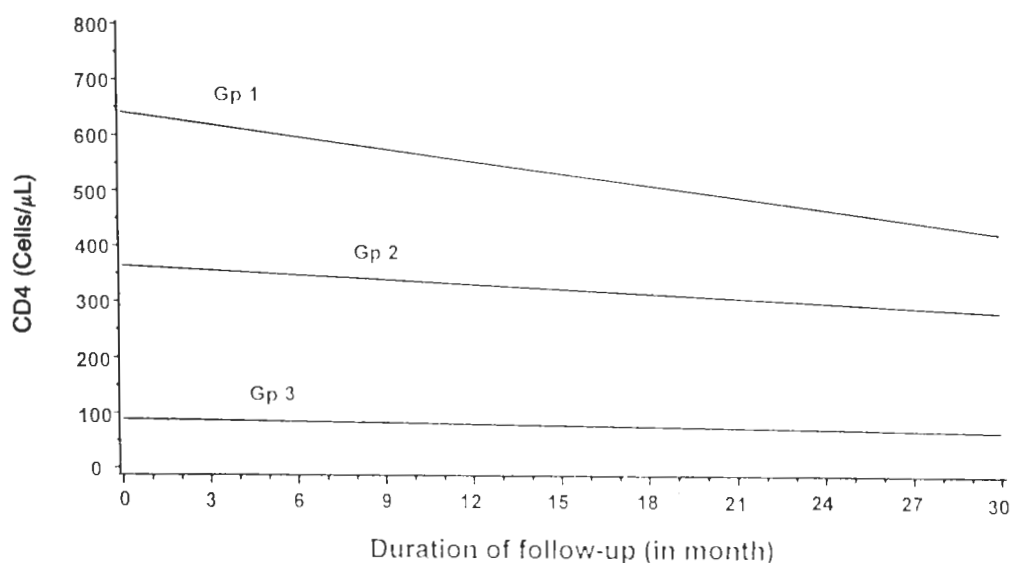


Fig. 1 Decline in CD4 count in HIV positive Chinese patients. Patients stratified into 3 groups according to CD4 level at entry: Gp1->500 cells/ μ L, Gp2- 200-500 cells/ μ L, Gp3-<200 cells/ μ L.

The rate of CD4 decline with time also differed for the symptomatic (either ADI or non-AIDS defining diseases) and the asymptomatic subjects regardless of their initial CD4 count. Patients who were symptomatic had a greater loss of CD4 cells with time (Fig. 2) and the loss was greater in Gp1s (12 cells per month) than

Gp2s (7 cells per month) than Gp3s (2 cells per month).

The CD4 count at the occurrence of the opportunistic complications is shown in Fig. 3. In general, non-AIDS defining diseases occurred at a higher CD4 level than the ADI. But still only herpes zoster, bacterial pneumonia and genital wart appeared at a

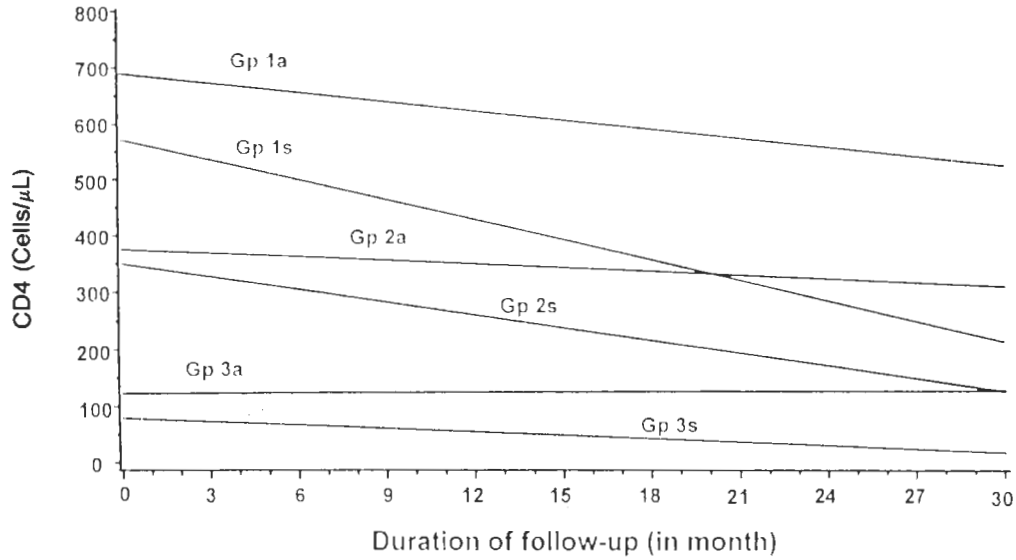


Fig. 2 Decline in CD4 count with time according to CD4 level at entry and symptomatic disease or not: Gp1a->500 cells/μL & asymptomatic, Gp1S->500 cells/μL & symptomatic, Gp2a- 200-500 cells/μL & asymptomatic, Gp2s- 200-500 cells/μL & symptomatic, Gp3a-<200 cells/μL & asymptomatic, Gp3s-<200 cells/μL & symptomatic.

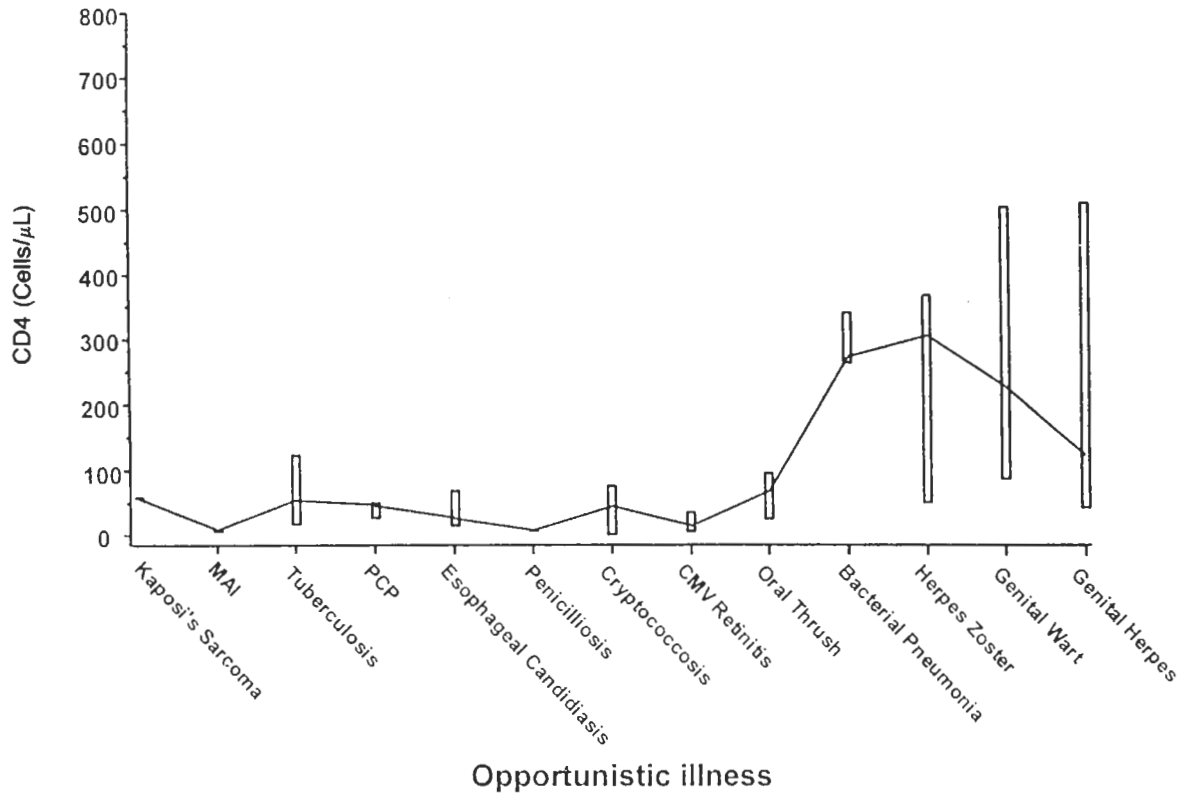


Fig. 3 CD4 lymphocyte count (shown as Boxplot of the median, first and third quartile) at the time of the development of opportunistic disease in Chinese HIV infected subjects.

median CD4 count of >200 cells/ μL . All the ADIs occurred at a median count of <100 cells/ μL .

DISCUSSION

Despite a predominantly Chinese community, the population of Hong Kong has a heterogeneous mixing of people of different ethnicities. The first few AIDS cases in Hong Kong were found among Caucasian patients in 1985. Today, however, a majority of our patients are local Chinese (8). The high proportion of Chinese HIV-infected patients in Hong Kong and also in our clinic offers a good chance for us to study the course of HIV disease in this ethnic group, and to compare it with overseas findings.

A vast majority of the patients in our cohort did not have their HIV infection diagnosed during the seroconversion stage. Thus they were recruited into the study at variable duration after the infection and monitoring of the rate of their CD4 decline with time from time of seroconversion was not possible in this study. Nevertheless, a baseline documentation at time of entry, albeit of different disease stage, provides information for the subsequent immunologic and clinical course. Regular monitoring of CD4 level at about 3-month interval afterwards proved to be even more informative.

Similar to overseas findings in Caucasians, we have found that there is an obvious trend of progressive fall, with time, in CD4 count of HIV-infected Chinese individuals. The fall was more marked in patients with a higher initial CD4 level, regardless of whether they had or subsequently developed symptomatic diseases or not. This may be related to the CD4 cell reserve, being greater for those with a higher CD4 count to start with. However, even a slower rate of decline in the severely immunosuppressed patients, e.g. Gp3, means a greater percentage loss of the total CD4 cells. This may be very significant in terms of the disease progression; in particular the emergence of major life-threatening complications generally occur at low CD4 level.

The decline in CD4 count over time was more prominent in symptomatic than asymptomatic patients in all 3 groups. The correlation of a more rapid decline in CD4 count with diseases development may thus be used for the prediction of occurrence of complications (9). This finding echoed the overseas reports of the prognostic significance of rate of CD4 cell decline. On the other hand, the disease itself may

cause a further fall in CD4 level and thus be a contributing factor to the steeper fall in CD4.

It was recognised that the frequency and severity of opportunistic illnesses in HIV-infected patients depend on the degree of immunosuppression and increases as CD4 cells are gradually depleted. The absolute CD4 level is actually useful for predicting the risk for development of individual complication (10). For example, the risk of having *Pneumocystis carinii* pneumonia (PCP) is substantially higher when the CD4 count was below 200 cells/ μL (11). On one hand, this finding greatly aids the suspicion and diagnosis of PCP should clinical cases arise. On the other hand, it proved invaluable in providing basis for studying the efficacy of PCP prophylaxis which in turn led to important recommendation on it becoming standard of HIV management (12). The occurrence of *Mycobacterium avium intracellulare* often at CD4 count of less than 75 cells/ μL has also led to the recommendation of initiating prophylaxis when CD4 falls below this level (13).

Though not too many of our patients had clinical complications during the study period, the CD4 enumeration did shed light on the correlation of immunosuppression with opportunistic diseases in Chinese HIV-infected people, similar to that in overseas studies. In general, most of the complications that occurred at a very low CD4 count were major life-threatening conditions.

The CD4 count at which our Chinese patients had opportunistic diseases was in general quite low. A majority of the ADI occurred at advanced immunosuppression with a median CD4 of below 50 cells/ μL . These levels of CD4 counts were lower than the figures documented for HIV-infected Caucasians in late 1980s or early 1990s (10). But they were more comparable to the CD4 levels for the same diseases reported in other Western cohorts of the recent 2-3 years (14,15). This discrepancy may have been due to advances in the prophylaxis for opportunistic complications, antiretroviral therapy, as well as more comprehensive patient management. These factors all contributed to improved survival of patients towards very advanced stage of immunosuppression. However, the possibility of our Chinese patients having susceptibility at a lower CD4 level for the same disease complication as compared with the Caucasian counterparts cannot be excluded.

In conclusion, we have demonstrated the natural history of HIV infection in Chinese in terms of a

progressive decline in CD4 level, which was paralleled by the development of clinical diseases. Apart from a lower absolute CD4 count, a more rapid rate of fall of CD4 level also correlated with the occurrence of complications. Regular monitoring of this surrogate marker will thus be informative of the disease status. Our patients tended to have clinical events at an advanced stage of immunosuppression. Whether ethnicity plays a role in the relationship between immunologic deterioration and clinical manifestations would have to be addressed by a prolonged longitudinal study of a bigger cohort.

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