Mortality Analysis of HIV-1 Infected Patients for Prioritizing Antiretroviral Drug Therapy

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Mortality data of patients, classified according to their clinical status and CD4$^+$ cell count status, would be very useful to guide clinicians to prioritizing patients who need antiretroviral drug therapy. In the current study, the authors re-analyzed data derived from a previously published retrospective study of HIV-1-infected individuals at Lampang Hospital in northern Thailand [(1)] . According to the Cox proportional hazard model, compared to asymptomatic patients with a high CD4$^+$ cell count (> 200 cell/μl), the mortality rate of asymptomatic patients with a medium CD4$^+$ cell count (100-199 cell/μl) did not significantly differ. However, the mortality rate of patients with a CD4$^+$ cell count below 100 cell/μl was at least 16 times higher, regardless of the presence of clinical symptoms. Based on these results, the authors produced a Lampang Hospital guideline of antiretroviral drug use; priority of antiretroviral therapy should, therefore, be given to patients with CD4$^+$ cell count < 100 cell/μl.

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Lampang Hospital is a government referral hospital for Lampang province in upper northern Thailand. In October 1995, it established a Day Care Center to provide HIV-1 infected individuals with comprehensive care such as medical treatment and psychosocial support, and to operate various collaborative programs. Up to 31st July 2003, more than 2000 HIV-1 infected individuals had been registered at the center but the clinical practice has been constrained by the limited availability of drugs, particularly antiretroviral drugs. In the past, only a small minority of HIV-1 infected individuals could afford highly active antiretroviral drugs therapy (HAART) due to the high monthly cost of treatment, thus, the vast majority were either not treated or treated with sub-optimum antiretroviral drugs, mostly dual therapy[(1)]. Recently, access to HAART has been dramatically improved, since the Government Pharma-ceutical Organization (GPO) of Thailand started the production of generic antiretroviral drugs such as "GPOvir", which is a combined tablet of stavudine, lamivudine and nevirapine. GPOvir became available in Lampang Hospital around 2002. However, the GPOvir therapy is not yet free for all infected individuals. Many patients still cannot afford the low price of GPOvir, which is about 1,300-1,400 baht per month.

Mortality data would be very useful to guide clinicians to prioritizing patients who need antiretroviral drug therapy. Nevertheless, studies on the mortality rate of HIV-1-infected individuals remain limited in Thailand and other countries in Southeast Asia[(1-3)] . Retrospectively analyzing our experience at the Day Care Center in Lampang Hospital, the authors have reported that clinical status, CD4$^+$ cell count, antiretroviral drug use and year at registration were

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independently associated with death[1]. However, in the previous analysis, the authors did not categorize patients according to clinical status and $CD4^+$ cell count combined, following the way that is generally used for classifying HIV-infected patients by clinicians[4]. The published mortality data was not, therefore, directly applicable in guiding clinicians for antiretroviral drug use. Therefore, in the current study, the authors re-analyzed the data to produce evidence more relevant to clinical practice. Based on the results, a Lampang Hospital guideline of antiretroviral drug use was produced.

Material and Method

The authors used data set derived from the retrospective cohort study at the Day Care Center, Lampang Hospital[1] . Briefly, demographic, clinical, history of antiretroviral drug use and laboratory data were collected from all HIV-1-infected adult patients who attended the center from 2 October 1995 to October 31, 1999. The survival status of patients until October 31, 1999 was ascertained from the hospital, records, mailed letters, and death certificates at the Provincial Health Office. In the current study, mortality of the patients was analyzed after classifying patients according to their clinical status and $CD4^+$ cell count at the first visit to the center. Clinical status at first visit was characterized as either with or without any HIV-related symptom, based on the Thai government's national guideline for the clinical management of HIV infection [5]. $CD4^+$ cell count was categorised into a low CD4 (0-99 cells/μl), a medium CD4 (100-199 cells/μl) and a high CD4 (> 200 cells/μl) group. The effect of other specific variables, including age, sex, antiretroviral drugs use, and year at registration were adjusted by applying the Cox proportional hazard model. All data were double-coded, double-entered and validated using the EpiInfo program. Statistical analysis was done using STATA version 6.0.

Result

A total of 1110 HIV-1 infected individuals attended the clinic during the study period. Demographic data of these patients, median intervals from the first visit to the CD4 test, median $CD4^+$ cell counts, the history of antiretroviral drug, and follow-up durations were described in the previous paper[1].

$CD4^+$ cell counts within one year of the first visit were available in 681 HIV-1 infected individuals, of whom follow-up information was available in 674 individuals. These individuals were stratified by both their initial $CD4^+$ cell count and clinical status and their mortality rates were analyzed. A crude mortality rate described as number of deaths per 100 person-year of observation (PYO) was highest in symptomatic patients with a low $CD4^+$ cell count, followed by asymptomatic patients with a low $CD4^+$ cell count, symptomatic patients with a medium $CD4^+$ cell count, symptomatic patients with a high $CD4^+$ cell count and asymptomatic patients with a medium or high $CD4^+$ cell count (Fig.1). The authors found that if patients were asymptomatic, the mortality rate did not significantly differ between patients with a high $CD4^+$ cell count and a medium $CD4^+$ cell count. It was also found that if a $CD4^+$ cell count was lower than 100, the mortality was high regardless of the presence of clinical symptoms at the baseline. Nearly all of the patients had causes of death related to HIV diseases or opportunistic infection. Only two patients died because of a car accident and suicide.

These trends seen in crude mortality rates did not differ when the authors calculated hazard ratios (Table 1). Even after adjusting hazard ratios for other independent risk factor for death such as sex, age, year at registration and antiretroviral drug use, the trends remained the same. The difference in adjusted hazard ratios between asymptomatic patients with a high $CD4^+$ cell count and asymptomatic patients with a medium $CD4^+$ cell count were not significant.

Discussion

The main objective of this analysis was to produce evidence, which guides clinicians to prioritizing patients for antiretroviral drug therapy

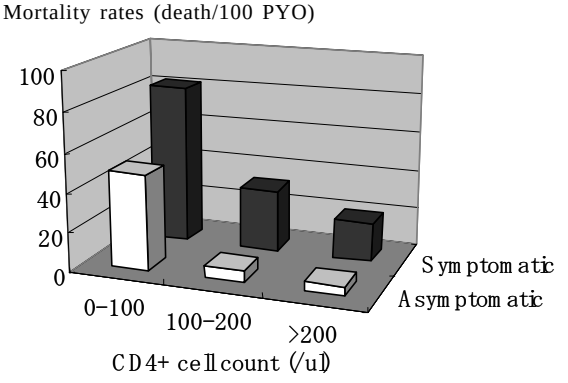

Fig. 1 Mortality rates (number of death per 100 person-year of observation, PYO) of HIV-infected individuals who were categorized by clinical status and $CD4^+$ cell status

Table 1. Mortality analysis of HIV-1 patients stratified by clinical status and $CD4^+$ cell counts

Patient's categories		Patients (N)	Deaths/PYO	Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*	P value from multivariate (univariate) analysis
Asymptomatic	CD4 > 200	224	18/389.9	1.0	1.0	-
Asymptomatic	CD4 100-199	28	3/49.1	1.35 (0.40,4.58)	2.1 (0.62,7.27)	0.237 (0.632)
Symptomatic	CD4 > 200	28	10/50.4	4.22 (1.95,9.15)	4.53 (2.05,10.01)	<0.001 (<0.001)
Symptomatic	CD4 100-199	49	24/75.7	7.04 (3.82,12.98)	7.71 (4.10,14.51)	<0.001 (<0.001)
Asymptomatic	CD4 0-99	16	10/20.5	11.35 (5.22,24.69)	16.79 (7.43,37.96)	<0.001 (<0.001)
Symptomatic	CD4 0-99	329	242/296.2	21.09 (12.91,34.45)	21.02 (12.44,35.52)	<0.001 (<0.001)

* Hazard ratio was adjusted for sex, age group, registered year and antiretroviral drug use according to the previous report (pathipvanich 2003); PYO, person-years of observation; CI, confidence interval

at Lampang Hospital. The authors think that the priority or urgency of antiretroviral drugs should go with the mortality in each clinical stage. In this sense, it is believed that adjusted hazard ratio summarized in Table 1 should be a useful guide. According to the findings, patients with a low $CD4^+$ cell count less than 100 cells/μl should be given the highest priority regardless of clinical symptoms, because the mortality rate was at least 16 times higher compared to that of asymptomatic patients with a high $CD4^+$ cell count (> 200 cells/μl). Whereas, patients with a $CD4^+$ cell count 100 cells/μl or above are less urgent. Particularly, if patients did not have any HIV-related symptom, the mortality did not differ considerably between those with a $CD4^+$ cell count above 200 cell/μl and with a $CD4^+$ cell count 100-199 cell/μl.

Because of a high turn-over rate of doctors working in community hospitals, doctors working in the community are inevitably less experienced. In order to maximize the benefit of antiretroviral drugs in our clinic as well as in the community hospitals in Lampang, the authors made a Lampang Hospital guideline of antiretroviral drug use, especially targeting patients who can not afford any anti-retroviral drug other than GPOvir. Retrospective mortality data was used as supporting evidence when the guideline was produced. The summary of the guideline is shown in Table 2. This guideline is available for free upon request to the corresponding author.

Table 2. Clinical management according to CD4 count and clinical status

	Clinical status		
CD4+ cell status	Asymptomatic	Early symptomatic	AIDS#
> 200/μl	Observation	Treat O.I.	Treat O.I. PCP prophylaxis Consider ARV
100-199/μl	PCP prophylaxis Consider ARV	Treat O.I. PCP prophylaxis Recommend ARV	Treat O.I. PCP prophylaxis Recommend ARV
< 100/μl	PCP, Crypt. Toxo. prophylaxis Strongly recommend ARV	Treat O.I. PCP, Crypt. Toxo. prophylaxis Strongly recommend ARV	Treat O.I. PCP, Crypt. Toxo. prophylaxis Strongly recommend ARV

AIDS defining illness is as follows: Penumocystis carinii pneumonia, Toxoplasma encephalitis, Cryptococcosis (meningitis or disseminated), Penicilliosis, pulmonary TB, extrapulmonary TB, CMV retinitis, Candida esophagitis, recurrent pneumonia, disseminated atypical mycobacterium infection, Herpes simplex virus (persistent mucocutaneous or visceral), non-typhid Salmonella septicemia, HIV wasting syndrome, Histoplasmosis, Cryptosporidiosis with diarrhea > 1 month, progressive multifocal leukoencephalopathy, CMV esophagitis or colitis, lymphoma, Kaposi's sarcoma, HIV encephalopathy, cervical cancer

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แนวทางการพิจารณาเริ่มยาต้านไวรัสในผู้ติดเชื้อ HIV โดยใช้ผลการวิเคราะห์การเสียชีวิตของผู้ติดเชื้อ HIV-1 ที่มารับการตรวจที่ศูนย์ดูแลผู้ป่วย HIV ที่โรงพยาบาลลำปาง

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การศึกษาครั้งนี้ได้นำข้อมูลบางส่วนจากงานศึกษาย้อนหลังเกี่ยวกับผู้ติดเชื้อ HIV-1 ในโรงพยาบาลลำปาง ที่ได้เคยลงตีพิมพ์ไปแล้ว[1] มาวิเคราะห์ข้อมูลการเสียชีวิต โดยพิจารณาตามลักษณะอาการและค่า CD4 เพื่อใช้เป็นประโยชน์สำหรับแพทย์ในการเรียงลำดับผู้ป่วยที่จำเป็นต้องได้รับยาต้านไวรัส ซึ่งเป็นการวิเคราะห์ในรูปแบบ Cox proportional hazard model โดยเปรียบเทียบกลุ่มผู้ป่วยที่ไม่มีอาการและมีค่า CD4 สูง ≥ 200/ml กับกลุ่มที่ไม่มีอาการเช่นกันแต่ค่า CD4 อยู่ในระดับกลาง 100-199/ml ทั้งสองกลุ่มนี้มีอัตราการตายไม่แตกต่างกัน แต่เมื่อพิจารณากลุ่มที่มีค่า CD4 ต่ำ < 100/ml พบว่ากลุ่มนี้มีอัตราการเสียชีวิตสูงกว่า 2 กลุ่มแรกประมาณ 16 เท่า โดยไม่ขึ้นกับอาการแสดงของผู้ป่วย จากพื้นฐานนี้เอง นำไปสู่การเสนอแนวทางการเริ่มยาต้านไวรัสของ Lampang Hospital Guideline ในกลุ่มที่มี CD4 < 100/ml เป็นกลุ่มแรก