possessed the T242N escape mutation in Gag p24, and six of 15 (40%) of them already had at least one of the compensatory mutations, namely, H219Q, M228I, or G248A [27]. Among HLA-B*58:01 positives, a significantly higher viral load was identified among individuals with these compensatory mutations, compared with the ones without these mutations. However, among HLA-B*57:01, all (3/3) the individuals expressing this allele possessed T242N, but in none of the three there were compensatory mutations present at Gag residues 219/223/228. Although numbers are low, such a high frequency of compensatory mutations in the HLA-B*58:01-positive individuals suggests that it be easier for CRF01_AE's to adapt to immune pressure exerted by this allele.

In conclusion, our study has identified several protective HLA alleles, which affect viral control in HIV-infected individuals in Thailand. This represents a milestone in the study of HIV and HLA alleles from south-east Asia, as our data strongly indicate the existence of a protective effect of HLA-B*57 across ethnic groups, and also highlight for the first time HLA-B*35:05 as an allele protective in this cohort [42]. The identification of protective alleles in each endemic area provides the opportunity to better define the nature of HLA-mediated immune control and, therefore, will be valuable for further CTL vaccine development.

Acknowledgements

The authors would like to thank Dr Naho Tsuchiya, Ms Phattaraporn Orataiwun, Ms Suthira Kasemsuk, Ms Sripai Saneewong-na-Ayuthaya, Ms Katkaew Thamachai, Ms Anongnard Suyasarojna, Ms Nutira Boonna, and Mr Praphan Wongnamnong for their excellent technical assistance at the Lampang hospital. This study was supported in part by JSPS KAKENHI Grant Number 25860367 (Japan), Ministry of Health, Labour and Welfare Grants-in-Aid (US-Japan Cooperative Medical Science Program), and by Imai Memorial Trust for AIDS Research (Japan).

Conflicts of interest

There are no conflicts of interest.

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Jpn. J. Infect. Dis., 66, 375-378, 2013

Original Article

Changing Burden of HIV/AIDS to Clinical Settings in Northern Thailand over 15 Years

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(Received July 30, 2012. Accepted May 7, 2013)

SUMMARY: We conducted a hospital-based descriptive study to describe the changing pattern of patient numbers, characteristics, and mortality rates among human immunodeficiency virus (HIV)-infected patients in northern Thailand over 15 years. The survival status on October 31, 2010 of all HIV-infected adults who attended an HIV center in a government hospital between 1995 and 2010 was ascertained. In total, 3,706 patients were registered, 2,118 (57.2%) of which were male. The survival status of 3,439 patients (92.9%) was available. In addition, 1,543 deaths were identified out of 12,858 person-year-observations (PYO) resulting in a mortality rate of 12.4 deaths/100 PYO (95% confidence interval [CI], 11.3–13.0). An initial decline in mortality rates was observed prior to 1999, probably because of an increase in the proportion of less symptomatic patients. After the introduction of the national highly active antiretroviral therapy (HAART) program, a profound decline in mortality rates was observed, reaching 2.0 deaths/100 PYO (95% CI, 1.4–2.9) in 2010. Simultaneously, the number of patients on follow-up increased by nearly fourfold. Although HAART has drastically improved the survival of HIV-infected patients, the number of patients receiving therapy at this HIV clinic has substantially increased. While referral of HIV patients to general physicians' care should be urged, we cannot overemphasize the importance of preventing new HIV infections.

INTRODUCTION

Thailand has been one of the first Asian countries to be severely affected by the human immunodeficiency virus (HIV) epidemic. Initially, HIV mainly spread between female sex workers and their male clients. These males subsequently transmitted HIV to their wives, who passed it on to their newborn babies (1). The situation was particularly severe in northern Thailand, including Lampang province. Since 1985, when the HIV epidemic began, Lampang province has had the 5th highest prevalence of HIV in Thailand (2). Since the mid-1990s, HIV prevalence in adults has declined from an estimated peak of 2.1% to 1.4% in 2007 (3).

Our first survival survey on HIV-infected patients attending Lampang Hospital completed in October 1999 and suggested a mortality rate of approximately 50/100 person-year-observations (PYO) among patients (4). A number of government initiatives have substantially impacted HIV care in Thailand. The Prevention of Mother-to-Child Transmission (PMTCT) program began in northern Thailand in 1997 (5). As part of this program, the Thai government health services began to screen all pregnant women, allowing the early detection of HIV infections and provision of short-course zidovudine prophylaxis to prevent vertical transmission. Furthermore, the government enhanced the promotion of education on HIV and the development of care and support for HIV-infected patients. In 2003, the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) was launched (6). This improved patient access to highly active antiretroviral therapy (HAART), particularly by the use of a fixed-dose combination of generic drugs (GPOvir®: stavudine, lamivudine, and nevirapine). By December 2007, the estimated antiretroviral drug coverage in Thailand had reached 61% (47–81%) (2).

In this study, we describe the changing pattern of patient numbers, characteristics, and mortality rates among HIV-infected patients in northern Thailand and accordingly discuss the effect of the introduction of NAPHA and other government programs on HIV care in northern Thailand.

MATERIALS AND METHODS

We present data from a hospital-based descriptive study conducted in a large hospital in northern Thailand. Lampang Hospital is the only government

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referral hospital with approximately 800 beds in Lampang province, located 100 km south of the city of Chiang Mai. In October 1995, an HIV center, locally called a day care center, was established at this hospital to provide comprehensive care to HIV-infected patients, including psychosocial care and support for patient self-help groups. This center functioned as a referral outpatient clinic and provided medical care to by far the largest number of HIV patients in the province. All HIV-infected patients registered at the center from October 2, 1995 to October 31, 2010 were included in the present study. Demographic and clinical information at the time of registration was obtained from medical charts and hospital records. For this analysis, we ascertained the survival status of all HIV-infected patients over 16 years of age who attended the HIV clinic in Lampang Hospital during that time using hospital records, death certificates from the Lampang Provincial Health Office, and postal letters as well as by contacting their families or relatives. Patients known to be attending other hospitals within Lampang province and having no death certification by the Lampang Provincial Health Office were regarded as being alive. If the exact date was unknown, the death was assumed to have occurred on the 15th of a month (if the day of the month was missing) and in June (if information on the month was missing). Loss of follow-up was defined as patients no longer residing within Lampang province, those whose survival status was unknown, or those who died but the year of death was not available. We calculated the number of patients and mortality rate over the period of October 2, 1995 to October 31, 2010. We present changes in crude survival rates at 12-month intervals over the study period in patients attending the center during each 12-month period. The number of patients who began HAART was shown to investigate the impact of HAART on the change in mortality rates.

This study was conducted as part of the Lampang HIV-Cohort Phase I and Lampang and Phayao HIV Cohort Phase II studies, which were approved by Thai Ministry of Public Health Ethics Committee.

RESULTS

Between 1995 and 2010, a total of 3,706 patients received care at the day care center. Of these, 2,118 (57.2%) were male, and the median age was 33.8 years (interquartile range [IQR], 33.5–34.1; range, 15–84). Approximately 95% of transmission routes were attributed to heterosexual intercourse (4,7,13). There was no significant change in the median age over time. Baseline CD4 cell counts were obtained from 3,111 patients (83.9%). The median CD4 cell count was 81 (IQR, 22–262). Figure 1A shows the number of newly registered patients at the HIV clinic for each 12-month study period. At the beginning of the study period, the number of the newly registered male patients was twofold greater than that of female patients. The gap gradually decreased as more women who were infected by their partners attended the HIV clinic. A temporal increase was observed from 2000 to 2003, possibly due to the effect of our prospective cohort that began in July 2000 and the initiation of NAPHA. Thereafter, the number of newly registered patients has gradually declined. Figure 1B shows the proportion of patients stratified by a CD4 cell count of <50 cells/μl, 50–200 cells/μl, and >200 cells/μl at the first visit. The proportion of patients with a CD4 cell count >200 cells/μl temporally increased around 2,000 (38.1%) and then stabilized since 2008, reaching 40% in 2010.

The survival status on October 31, 2010 was available for 3,439 patients (92.9%). In total, 267 patients were lost to follow-up. The median follow-up duration was 1,689 days (IQR, 799–2,680; range, 0–4,318). A total of 1,543 deaths were identified out of 12,858 PYO, resulting in an overall mortality rate of 12.4 deaths/100 PYO (95% confidence interval [CI], 11.3–13.0). Figure 1C shows temporal changes in the mortality rate in the total population, stratified by gender, at 12-month intervals. Mortality rates declined from 54/100 PYO (95% CI, 47–63) in 1998 to 33/100 PYO (95% CI, 28–40) in 1999, remaining around this level until about 2002. HAART was first conducted among a restricted number of patients around 2000 as a pilot phase and has been broadly provided by NAPHA since 2003. Consequently, the number of patients on HAART has been continuously increasing (Fig. 1D). Following the introduction of NAPHA, a further pronounced decline in mortality rates was observed from 2003, reaching as low as 2.0 deaths/100 PYO in 2010 (95% CI, 1.4–2.9). The mortality rate of males was higher than that of females, particularly before the HAART era. A decline in mortality rates prior to the introduction of HAART was greater in males than in females. Figure 1E shows the proportion of patients who died within 3 months after the first visit, stratified by gender. Before 2005, male patients were more likely to die early than female patients. Interestingly, there was a sharp increase in this trend after 2008. The cumulative number of patients on active follow-up remained stable before 2001 (Fig. 1F). From 2001 to 2010, particularly after NAPHA was initiated in 2003, the number of patients being actively followed-up drastically increased by nearly fourfold.

DISCUSSION

In the present study, we described changes in mortality rates among HIV-infected patients and the healthcare burden, such as numbers and characteristics of patients, over 15 years in northern Thailand. Although we demonstrated that the mortality rate declined with an increase in the number of patients on HAART (Fig. 1C and 1D), it may not be explained by the direct effect of HAART alone. Particularly, the initial decline in mortality well before the launch of NAPHA, was thought to be due to an increased proportion of less symptomatic patients. During the early phase of the HIV epidemic, before the Thai government launched various programs against social stigmatization of HIV/AIDS (6), patients often did not seek care until they were critically ill. We believe that unfavorable treatment-seeking behavior related to the social stigma of HIV/AIDS contributed to the very high mortality rate prior to 1999. The extended national PMTCT program, promotion of education on HIV, and development of care and support for HIV-infected patients have also played a role in the increase in the number of less symptomatic patients attending the HIV clinic. Apart from its effect on viral load, the mere

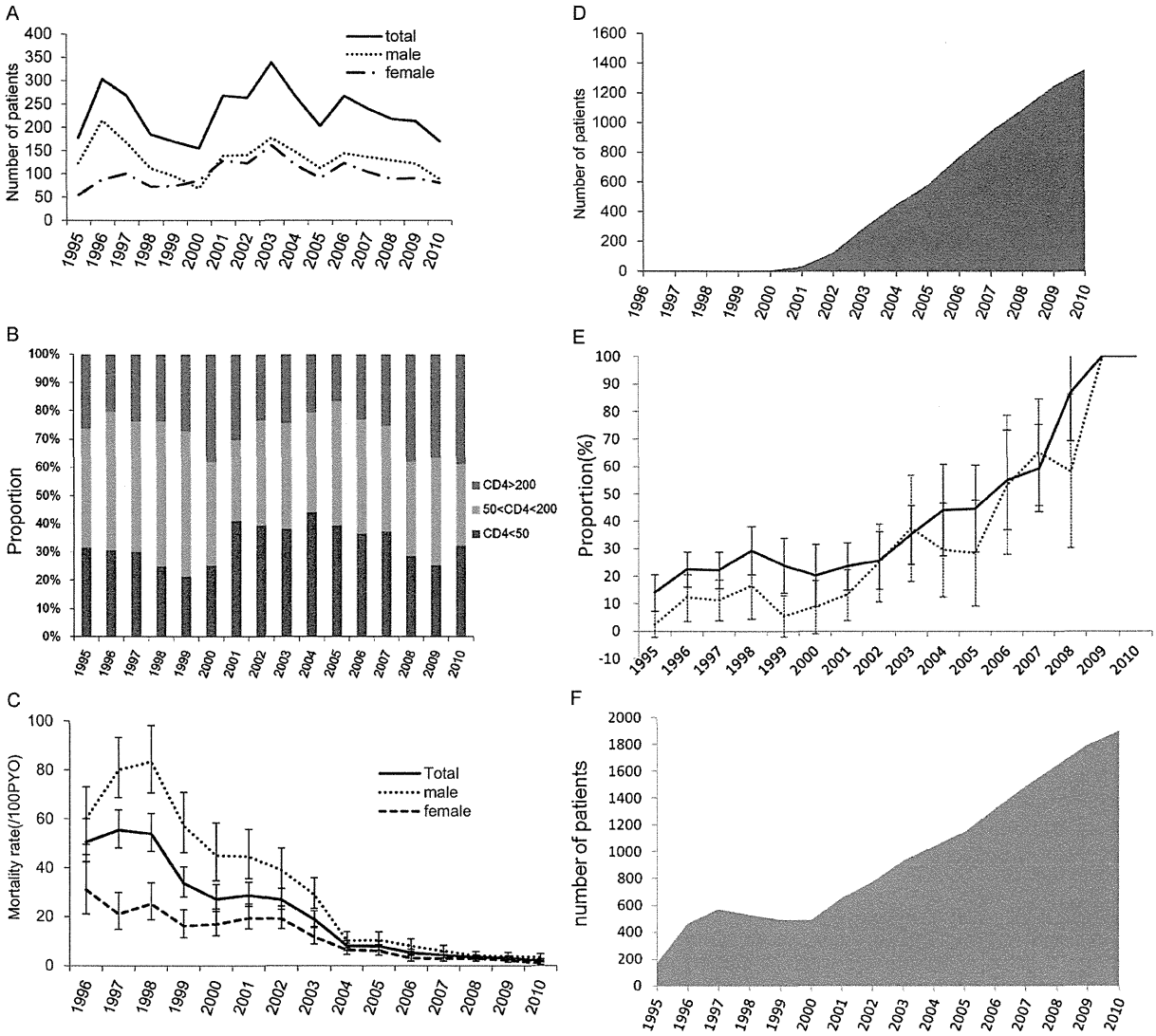

Fig. 1. (A) Number of newly registered patients. (B) Proportion of patients stratified by a CD4 cell count at enrolment. (C) Mortality rate with 95% confidence interval. (D) Number of patients on highly active antiretroviral therapy. (E) Proportion of deaths which occurred within the first 3 months of registration; denominator is the number of total death each year. (F) Cumulative number of patients on active follow-up. The pilot phase of access to antiretroviral therapy program started in 2000. The National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) was launched universally in 2003.

availability of HAART may have improved survival after 2003 by encouraging HIV-infected patients to seek support from healthcare and possibly from social services. Our previous qualitative study showed that the availability of HAART had a positive impact on the attitudes and self-confidence of HIV-infected patients, including a markedly lower perceived sense of stigmatization (7). The availability of treatment also changed the practice of healthcare professionals; their morale was boosted and awareness toward the diagnosis of opportunistic infections was heightened because death from AIDS-related infections is no longer perceived as unavoidable.

Despite the many positive effects of improving access to HAART, we identified a number of issues of concern. First, the local healthcare staff perceive that the long-term side effects of antiretroviral drugs are becoming a major problem (8). It has been shown that among the active substances in GPOvir®, only stavudine is known to frequently cause lipodystrophy (9,10). The longer patients are on antiretroviral therapy, the higher the risk of long-term side effects or metabolic changes (11), resulting in regimen modification. Given that the choice of salvage regimen is still limited in low- and middle-income countries, further studies investigating the long-term outcomes of HAART and its predictors are warranted.

Second, the incidence of early death (within 3 months after recruitment) (Fig. 1E) drastically increased during the HAART era, reflecting that while the total number of deaths decreased, most involved cases who had advanced AIDS prior to their first visit and died soon after the recruitment period. Although the cause of death is generally difficult to obtain in a busy government hospital, our previously published studies with active investigations indicated that most deaths were attributed

to HIV-related illnesses that occurred during both the pre- and post-HAART era (7,12,14). Our previous study revealed the highest incidence of opportunistic infections during the first year of HAART, particularly among patients with a low CD4 cell count (13). Some patients died before initiating HAART. Even during the HAART era, special attention should be paid to the management of newly registered patients, and we should continue to make an effort to reduce the number of undiagnosed HIV-infected patients.

Third, this study demonstrated that the rapid increase in the number of outpatients in this setting shortly after NAPHA was a result of the increase in the number of patients on HAART and decrease in the mortality rate. The HIV clinic is now faced with a large number of patients, which has resulted in a higher workload for the staff. At the same time, the number of inpatients with opportunistic infections has considerably declined. Since the initiation of NAPHA, the AIDS ward of Lampang Hospital became redundant and closed in January 2004. Overall, it remains unclear whether the overall workload due to HIV has increased or decreased following the introduction of HAART. However, the burden of care at this HIV clinic will continue to increase unless the actual number of newly infected patients substantially decreases. While we cannot overemphasize the importance of preventing new HIV infections, referral of HIV-patients to general physicians' care once their first-line therapy is stabilized should be urged; however, this will require additional training resources to build on the success of the ongoing programs for ensuring adequate care for HIV-infected patients in Thailand.

Acknowledgments This study was supported by Japan International Co-operation Agency (JICA), Japan Health Science Foundation, and the Department of Medical Sciences of Ministry of Public Health of Thailand and partially by Global COE Programme, Nagasaki University.

We would like to thank all the patients and staff at Lampang Hospital especially Ms. S Kasemsuk, Ms. S Seneewong-Naayudhaya, Ms. A Suyasarojna, Mr. P Wongnamnong, and Ms. K Yoddumnern, Ms. K Lor-yont, Mr. W Khaewkarnka, Mr. S Umnajsirisuk, and Mr. S Niyom-thai.

Conflict of interest None to declare.

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