Original Article

Improved Survival of Persons with Human Immunodeficiency Virus Type 1 Infection in the Era of Highly Active Antiretroviral Therapy in Taiwan

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SUMMARY: We assessed the survival of 1,044 HIV-infected persons enrolled in three periods: period 1, 1994 to 1997 (before the introduction of highly active antiretroviral therapy [HAART]); period 2, 1997 to 2000 (early-HAART); and period 3, 2000 to 2004 (late-HAART). As of 30 June 2005, 259 (24.8%) persons had died after a median observation duration of 985 days (range, 2-4,025 days). The mortality rate declined from 33.75 per 100 person-years in the pre-HAART era to 6.51 per 100 person-years in the late-HAART era (P < 0.0001). The adjusted hazard ratios for death in persons with a baseline CD4 count of <200 cells/μl in periods 2 and 3 were 0.605 (P = 0.007) and 0.371 (P < 0.0001), respectively, when compared with persons enrolled in period 1; the adjusted hazard ratio for death was 0.611 for persons enrolled in period 3 when compared to period 2 (P = 0.01).

Our study suggested that the survival of persons in the late stage of HIV infection in Taiwan continued to improve in the late HAART era.

INTRODUCTION

With the introduction of antimicrobial prophylaxis for opportunistic infections and highly active antiretroviral therapy (HAART) for HIV infection, the mortality of persons with early or advanced HIV infection who have access to HAART in Western countries has dramatically declined, and so has the incidence of nearly all AIDS-defining opportunistic illnesses (AIDS-OIs) (1-7). HAART has changed HIV infection from a debilitating fatal disease to a chronic, manageable disease because the risk of HIV progression and death is low in those persons who timely initiate HAART with favorable immunologic and virologic responses (8-13). However, these observations of the benefits of HAART have mainly been reported in Western countries, where the major causes of death have changed from AIDS-OIs to complications of chronic hepatotropic virus coinfection, non-AIDS-related cancers, and metabolic complications (14-18). It is not until recently that such observational studies in defined populations have begun to emerge in Asian countries, where HAART was introduced later and more slowly than in Western countries and where the spectrum of AIDS-OIs (19) and chronic hepatotropic virus coinfection may be different (20,21).

The first case of HIV infection was diagnosed in Taiwan in 1984 (22), and an estimated 10,158 cases with HIV infection had been detected in Taiwan by 31 December, 2005. The rate of increase in newly detected cases of HIV infection was estimated as 10-20% yearly between 1984 and 2003, but the epidemiology of HIV infection began to change in 2004, with the rate of new cases increasing dramatically to 76.7 and 150.2% in 2004 and 2005, respectively. This recent trend of dramatic increase has been propelled mainly by an increase in HIV infection through injecting drug use (IDU) (22). While sexual routes remain the most common route of HIV transmission (27.5% for heterosexuals and 35.5% for men having sex with men), the proportion of HIV-infected persons who are injecting drug users continues to increase significantly. For example, IDU accounted for 2.1% of the 5,221 cases detected between 1984 and 2003, and this rate increased to 31.9 and 71.1% of the cases detected in 2004 and 2005, respectively. Based on previous studies, subtype B and CRF01_AE are the two dominant subtypes in Taiwan, with subtype B (70%) mainly distributing among homosexuals and CRF01_AE (25%) preferentially distributing among heterosexuals (23,24). In association with the rapid increase of infected persons who are injecting drug users, CRF07_BC has emerged as an increasingly common subtype.

Antiretroviral agents were sequentially introduced in Taiwan, with introduction of nucleoside reverse transcriptase inhibitors between 1990 and 1994, followed by protease inhibitors on 1 April 1997, and non-nucleoside reverse transcriptase inhibitors in late 1999 to early 2000. In Taiwan, persons with HIV infection have free access to inpatient and outpatient HIV care, including antiretroviral therapy, at designated hospitals and venereal disease clinics throughout the country. In this study, we aimed to assess the trends of survival of HIV-infected persons who were consecutively enrolled in a university hospital in three different observational study periods: period 1, from 23 June 1994 to 31 March 1997; period 2, from 1 April 1997 to 30 June 2000; and period 3, from 1 July 2000 to 30 June 2004.

MATERIALS AND METHODS

Patients and hospital setting: The trends of survival of HIV-infected persons receiving antiretroviral therapy, including HAART, in Taiwan were analyzed in a prospective...
The Department of Health, Taiwan were searched to identify study period, whichever occurred first. The Vital Statistics of the three study periods (Table 1). At baseline, more than two-thirds of all the persons were diagnosed as having AIDS based on their having CD4 counts of less than 200 cells/µl or based on the presence of AIDS-OIs (56.3%). The median CD4 of the 667 persons who were newly diagnosed as having HIV infection was 67 cells/µl (range, 0-907 cells/µl), and 67.9% of them had a CD4 count of less than 200 cells/µl; the PVL of these individuals was 5.32 log_{10} copies/ml (range, <2.60-5.88 log_{10} copies/ml), and 65.1% of them had a PVL of 5 log_{10} copies/ml or greater (Table 1).

Coinfection with HBV among the 948 persons tested was as high as 21.2%, and there was a trend of decrease in seroprevalence of chronic HBV infection from 28.1% in period 1 to 19.3% in period 3 (Table 1). In contrast, the overall seroprevalence of chronic HCV infection was 8.3%, and there were no statistically significant changes of seroprevalence over the three periods.

The proportion of persons receiving HAART increased in the post-HAART era (Table 1). As of 30 June 2005, more than 80% of all the subjects had initiated HAART; 53.7, 88.8, and 83.9% of the individuals enrolled in periods 1, 2, and 3 had initiated HAART, respectively. The finding that the HAART initiation was lower in period 1 than periods 2 and 3 was attributed to the higher mortality within 6-12 months of enrollment, while the lower rate of HARRT initiation in period 3 compared to period 2 was attributable to the enrollment of more persons with a CD4 count of 350 cells/µl or greater (Table 1).

The median observation duration of the cohort from enrollment to death or the end of this study was 985 days (range, 2-4,025 days) (Table 2). As of 30 June 2005, 259 (24.8%) persons had died. There was a significant decrease in the percentage of death caused by AIDS-OIs; the rates of death due to AIDS-OIs were 88.4, 71.2, and 74.7% of HIV-infected persons in periods 1, 2, and 3, respectively (P = 0.01). Although a substantial proportion of the persons were coinfected with HBV or HCV, the overall rate of liver-related death was 5.8%, without statistically significant changes being observed across the three study periods (P = 0.16) (Table 2).

The crude mortality rates of persons enrolled in periods 1, 2, and 3 at the end of this study were 58.9, 27.2, and 13.8%, respectively (Table 2). More than 40% of all the deaths (44.8%) occurred within the first 6 months of enrollment. In each study period, the crude mortality rate declined with time.

RESULTS

The baseline characteristics of the 1,044 HIV-infected adults are shown in Table 1. The number of enrolled cases increased each year, which was coincident with the trend of the increasing epidemic of HIV infection in Taiwan over the past two decades (22). The majority of the enrolled individuals were males, with the male-to-female ratio being 12.7. The transmission route of HIV was sex between men in more than 60% of subjects, and this value increased from 43.3% in period 1 to 72.1% in period 3; IDU was an uncommon route of HIV transmission in our cohort, accounting for only 2.3% of subjects. Although persons sought HIV care at an increasingly earlier stage over the past 10 years, with the baseline CD4 count increasing from 28 to 117 cells/µl, most of the persons remained at the late stage of HIV infection, with a median CD4 count of 81 cells/µl (range, 0-1,202 cells/µl) (Table 1). At baseline, more than two-thirds of all the persons were diagnosed as having AIDS based on their having CD4 counts of less than 200 cells/µl or based on the presence of AIDS-OIs (56.3%). The median CD4 of the 667 persons who were newly diagnosed as having HIV infection was 67 cells/µl (range, 0-907 cells/µl), and 67.9% of them had a CD4 count of less than 200 cells/µl; the PVL of these individuals was 5.32 log_{10} copies/ml (range, <2.60-5.88 log_{10} copies/ml), and 65.1% of them had a PVL of 5 log_{10} copies/ml or greater (Table 1).

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For example, the rate decreased from 21.7% within the first 6 months of enrollment to 7.4% within 18 to 24 months of enrollment in period 1, from 12.3 to 0.9% in period 2, and from 7.5 to 1.3% in period 3 (Table 2).

When the data was censored at death or 12 months after the last enrollment in each study period, whichever occurred first, the mortality rate taking into account of observation duration of periods 1, 2, and 3 was 33.8 per 100 PY (95% CI, 33.03, 34.48 per 100 PY), 15.0 per 100 PY (95% CI, 14.66, 15.35 per 100 PY), and 6.5 per 100 PY (95% CI, 6.37, 6.65 per 100 PY), respectively (P < 0.0001) (Table 2). The mortality rate was lowest in the subjects who had a baseline CD4 count of 350 cells/μl or greater (1.07 per 100 PY), and there were no significant changes across the three study periods. In contrast, among the persons with a baseline CD4 count of less than 350 cells/μl, the mortality rate decreased consistently and significantly across the different CD4 categories from period 1 to period 3 (Table 2).

The survival patterns of HIV-infected persons are shown in Figs. 1, 2, and 3. Persons enrolled in HAART had a significantly longer survival than those in the pre-HAART era (Fig. 1), with an adjusted hazard ratio for death of 0.343 (95% CI, 0.236, 0.500) (P < 0.0001). When compared with persons

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### Table 1. Baseline characteristics of 1,044 non-hemophiliac HIV-infected persons aged ≥15 years between June 1994 and June 2004

<table>
<thead>
<tr>
<th>Variables</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>All patients</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number (N)</td>
<td>175</td>
<td>268</td>
<td>601</td>
<td>1,044</td>
<td></td>
</tr>
<tr>
<td>Age, median (range), yr</td>
<td>34 (15, 75)</td>
<td>35 (20, 83)</td>
<td>34 (17, 81)</td>
<td>34 (15, 83)</td>
<td>0.19</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>91.4</td>
<td>91.4</td>
<td>93.7</td>
<td>92.7</td>
<td>0.38</td>
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<tr>
<td>Risk behavior (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual/bisexual</td>
<td>43.4</td>
<td>49.3</td>
<td>72.1</td>
<td>61.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>47.4</td>
<td>39.9</td>
<td>23.5</td>
<td>31.7</td>
<td></td>
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<tr>
<td>IDU</td>
<td>2.9</td>
<td>3.4</td>
<td>1.7</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6.3</td>
<td>7.5</td>
<td>2.8</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count, median (range), cells/μl</td>
<td>(1, 762)</td>
<td>(0, 1202)</td>
<td>(0, 1063)</td>
<td>(0, 1202)</td>
<td></td>
</tr>
<tr>
<td>Persons with data (N)</td>
<td>152</td>
<td>256</td>
<td>574</td>
<td>982</td>
<td></td>
</tr>
<tr>
<td>&lt;50 cells/μl (%)</td>
<td>65.8</td>
<td>40.2</td>
<td>38.2</td>
<td>43.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50-99</td>
<td>11.2</td>
<td>14.5</td>
<td>8.2</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>100-199</td>
<td>9.2</td>
<td>11.3</td>
<td>14.6</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>200-349</td>
<td>7.9</td>
<td>15.6</td>
<td>15.9</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>≥350</td>
<td>5.9</td>
<td>18.4</td>
<td>23.2</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Baseline PVL, median (range), log10</td>
<td>(5.61, 5.61)</td>
<td>(2.60, 5.88)</td>
<td>(2.60, 5.88)</td>
<td>(2.60, 5.88)</td>
<td>0.76</td>
</tr>
<tr>
<td>Persons with data (N)</td>
<td>1</td>
<td>93</td>
<td>577</td>
<td>671</td>
<td></td>
</tr>
<tr>
<td>PVL&gt;5 log10 copies/ml (%)</td>
<td>100</td>
<td>57.0</td>
<td>56.3</td>
<td>56.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Newly diagnosed with HIV infection (%)</td>
<td>50.3</td>
<td>64.9</td>
<td>67.4</td>
<td>63.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Median CD4 count (range), cells/μl</td>
<td>30.5 (2, 644)</td>
<td>56 (0, 515)</td>
<td>103 (0, 907)</td>
<td>67 (0, 907)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;200 cells/μl (N) (%)</td>
<td>65/78 (83.3)</td>
<td>116/168 (69.1)</td>
<td>250/389 (64.3)</td>
<td>431/635 (67.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Median PVL</td>
<td>NA</td>
<td>5.44</td>
<td>5.26</td>
<td>5.31</td>
<td>0.27</td>
</tr>
<tr>
<td>(range), log10 copies/ml</td>
<td>(2.60, 5.88)</td>
<td>(2.60, 5.88)</td>
<td>(2.60, 5.88)</td>
<td>(2.60, 5.88)</td>
<td></td>
</tr>
<tr>
<td>PVL&gt;5 log10 copies/ml (N) (%)</td>
<td>NA</td>
<td>43/62 (69.4)</td>
<td>253/393 (64.4)</td>
<td>296/455 (65.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Naïve to antiretroviral therapy (%)</td>
<td>59.4</td>
<td>76.5</td>
<td>79.5</td>
<td>75.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Persons with AIDS-OI within 3 m of enrollment (%)</td>
<td>77.7</td>
<td>61.9</td>
<td>47.6</td>
<td>56.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-HCV (+) (N) (%)</td>
<td>12/135 (8.9)</td>
<td>28/257 (10.9)</td>
<td>37/541 (6.8)</td>
<td>77/933 (8.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>HBs antigen (+) (N) (%)</td>
<td>41/146 (28.1)</td>
<td>55/257 (21.4)</td>
<td>105/545 (19.3)</td>
<td>201/948 (21.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Loss to follow-up (%)</td>
<td>14.3</td>
<td>21.6</td>
<td>18.6</td>
<td>18.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Persons ever initiating HAART (%)</td>
<td>53.7</td>
<td>88.8</td>
<td>83.9</td>
<td>80.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median baseline CD4</td>
<td>38</td>
<td>84.5</td>
<td>94.5</td>
<td>82</td>
<td>0.01</td>
</tr>
<tr>
<td>(range), cells/μl</td>
<td>(1, 762)</td>
<td>(0, 1202)</td>
<td>(0, 1063)</td>
<td>(0, 1202)</td>
<td></td>
</tr>
<tr>
<td>CD4≥350 (N) (%)</td>
<td>8/9 (88.9)</td>
<td>44/47 (93.6)</td>
<td>85/133 (63.9)</td>
<td>137/189 (72.5)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

with a baseline CD4 count of 350 cells/µl or greater, the adjusted hazard ratios for death were 6.504 (95% CI, 2.677, 15.800), 8.538 (95% CI, 3.428, 21.267), 14.867 (95% CI, 6.207, 35.608), and 14.930 (95% CI, 6.638, 33.582) in persons with a CD4 count of 200 - 349, 100 -199, 50 - 99, and <50 cells/µl (P < 0.0001 in all comparisons), respectively (Fig. 2).

The risk for death decreased significantly from period 1 to period 3, regardless of CD4 stratifications (<350, <200, <100, or <50 cells/µl) (Table 2). When compared with persons with a baseline CD4 count of less than 200 cells/µl in period 1, the adjusted hazard ratio for death was 0.605 (95% CI, 0.420, 0.870) for period 2 (P = 0.007) and 0.371 (95% CI, 0.256, 0.538) for period 3 (P < 0.0001); the adjusted hazard ratio for death was 0.611 (95% CI, 0.411, 0.908) for persons in period 3 when compared to period 2 (P = 0.01) (Fig. 3).

Similarly, the adjusted hazard ratios for death were 0.566 (95% CI, 0.385, 0.832) (P = 0.004) and 0.423 (95% CI, 0.288, 0.620) (P < 0.0001) for persons enrolled in periods 2 and 3, respectively, compared with persons in period 1 who had a baseline CD4 count of 200 - 349, 100 -199, 50 - 99, and <50 cells/µl in period 1, the adjusted hazard ratio for death was 0.605 (95% CI, 0.420, 0.870) for period 2 (P = 0.007) and 0.371 (95% CI, 0.256, 0.538) for period 3 (P < 0.0001); the adjusted hazard ratio for death was 0.611 (95% CI, 0.411, 0.908) for persons in period 3 when compared to period 2 (P = 0.01) (Fig. 3).
CD4 count of less than 100 cells/μl. The adjusted hazard ratios for death were 0.638 (95% CI, 0.414, 0.983) ($P = 0.04$) and 0.403 (95% CI, 0.263, 0.619) ($P < 0.0001$) for persons enrolled in periods 2 and 3, respectively, compared with persons in period 1 who had a baseline CD4 count of less than 50 cells/μl.

**DISCUSSION**

In this study, we found that the survival of persons in the late stage of HIV infection was significantly improved in Taiwan in the era of HAART, and this observation of a consistent improvement in survival from the early to late HAART era was similar to the trends in Western countries (6,7). The cause of improvement is likely to be multifactorial, and may include consecutive enrollment of more persons with higher CD4 counts and transmission of HIV through routes other than IDU (Table 1); initiation of antimicrobial prophylaxis; accumulation of clinical experience in the management of AIDS-OIs and adverse effects of antiretroviral therapy; and, most importantly, introduction of HAART with resultant immune restoration (1-7).

Most of the enrolled persons in our cohort before and after introduction of HAART had AIDS-OI, lower baseline CD4 counts and higher PVL (Table 1), all of which were found to be negative prognostic factors of HIV disease progression and death in the pre- and post-HAART era (28,29). Although viral suppression and immune restoration may be delayed in those persons with high PVL and low CD4 count following institution of HAART (30), risk for HIV progression and death can be significantly reduced (3,6).

Although many studies in Western countries have demonstrated that the proportion of deaths due to causes other than AIDS-OIs is increasing in the post-HAART era, AIDS-OIs remain the leading cause of death in persons who have limited access to HIV care and develop delayed virologic and immunologic responses or failure to HAART (14-18). In our cohort, nearly half of the deaths occurred within 12 months of diagnosis, and a substantial proportion of persons died of AIDS-related OIs. Those who died had low CD4 counts despite initiation of HAART, suggesting incomplete and delayed immune recovery of those persons in whom detection of HIV infection and seeking HIV care are delayed (9).

In our cohort, IDU accounted for only 2.3% of the enrolled persons and seroprevalence of chronic HCV infection was significantly lower than in the studies of Western countries. For example, IDU often accounted for more than 20-30% of enrolled persons in population studies assessing HIV infection and survival (1-7). Persons who were active injecting drug users are generally considered to be at high risk for disease progression and mortality due to deaths from substance overdose, chronic liver diseases, delayed initiation of HAART, and poorer adherence and responses to HAART (7,13,31).

An increasing number of observational studies in persons receiving HAART have demonstrated that the improved survival allows liver-related deaths due to alcoholism or HBV or HCV coinfection to emerge (14,15,32-34). In this study, we found that deaths related to chronic liver disease did not increase over time, despite the fact that the seroprevalence of chronic HBV coinfection was higher than that reported in Western countries. The finding of a lower rate of liver-related deaths may have been related to the anti-HBV effect of nucleoside reverse transcriptase inhibitors, such as lamivudine and tenofovir, and the lower rate of chronic HCV coinfection in our cohort when compared with studies in Western countries; in addition, HAART may also reduce long-term liver-related mortality (35).

Our study has several limitations inherently present in the observational study design and consecutive enrollment of study subjects. Although we tried to adjust for potential confounding factors, unmeasured factors might have been involved in this study, which lasted more than 10 years. We did not collect data on the adherence and responses to HAART.

Previous studies in Western countries have demonstrated that baseline PVL and initial responses and adherence after initiation of HAART were strongly predictive of HIV disease progression and mortality (8,11,12,29). In our previous observational study assessing the virologic and immunologic responses to HAART in 276 antiretroviral-naïve persons with or without concurrent tuberculosis (36), 72.8% with PVL > 5 log10 copies/ml at baseline, we found that more than 72% achieved a viral suppression to less than 400 copies/ml, even in persons receiving anti-tuberculous therapy, which resulted in significant treatment difficulties due to an increased pill burden and drug-drug interactions. Despite the higher PVL and lower CD4 counts, the virologic responses in the present study were comparable to those of observational studies outside of clinical trial settings (12).

The provision of HIV care at designated hospitals and clinics, including HAART, was free of charge in Taiwan, and thus our findings may not be generalizable to other Asian countries where such HIV care is not readily available. We do not know the duration of HIV infection and we did not analyze the CCR-5Δ32 allele of the enrolled persons in our cohort, and most of them were diagnosed as having HIV infection very late. Therefore, we were not able to assess the rate of and genetic predisposition to HIV progression in this Taiwanese cohort before and after introduction of HAART. However, we think that the CCR-5Δ32 homozygous allele did not have a significant role, because none of the 181 normal controls, 152 high-risk HIV-uninfected persons, and 64 HIV-infected persons had the CCR-5Δ32 homozygous allele in an investigation of Taiwanese Chinese (37).

In conclusion, we found consistent and significant improvement with time after introduction of HAART in a cohort of Taiwanese persons in the late stage of HIV infection.

**REFERENCES**


