Original article

Survival and prognostic factors of HIV-infected patients receiving antiretroviral therapy

Sumeth Rattanamaneekorn, M.D. Internal Medicine department,
Sawangdaendin Crown Prince Hospital, Sakon Nakhon, Thailand 47110

Abstract

Background: Antiretroviral therapy (ART) for the treatment of HIV infection has been shown to improve survival and reduce HIV associated morbidity and mortality by restoring immunologic function through suppression of viral load. Despite of availability of ART, a substantial portion of HIV-infected patients has continued to die. Studies in many countries have found that differences in clinical, demographic, socio-economic, and behavioral factors related with the survival of HIV-infected patients receiving ART.

Methods: A retrospective cohort study was conducted among HIV-infected patients who were initiated ART during the period from January 2010 to December 2018 at Sawangdaendin Crown Prince Hospital.

Results: A total of 313 patients were studied, 12 (3.8%) patients died. The mean ± SD age was 34.2 ± 10.2 years, and about 63% of them were male. Median (range) baseline CD4 cell count was 104 (0-1253) cell/mm3. Within the first 5 years follow-up, median (range) baseline CD4 cell count had trend to increase from 269 (4-929) to 340 (3-1252), 358 (12-1169), 369 (43-1142) and 375 (13-1031) cell/mm3, each year, respectively and the studied patients had trend to achieve undetectable HIV RNA increasing from 76.5% to 84.2%, 88.9%, 92.5% and 91.7%, each year, respectively. In Kaplan-Meier analysis, the 5-years follow-up time after initiation of ART, 94.7% of patients had probability to survive. From univariate analysis, hemoglobin level at baseline < 11 g/dl (HR 4.113; 95% CI 1.112-15.217; P = .034), hypertension-comorbidity (HR 7.762; 95% CI 1.674-35.999; P = .009), history of previous opportunistic infections including cryptococcal infection or toxoplasmosis (HR 7.140; 95% CI 2.240-22.754; P = .001), adherence to treatment < 95% (HR 3.810; 95% CI 1.112-13.048; P = .033), missed visit within the first 2 years (HR 5.808; 95% CI 1.167-28.899; P = .032) and CD4 cell count at 1 year (HR 0.994; 95% CI 0.990-0.999; P = .029) were statistically significant association with the mortality. From multivariate analysis, only missed visit within the first 2 years had a trend associated with mortality. By the log-rank test, patients who never had missed visit within the first 2 years had survival probability more than who had ever (P = .038).

Conclusion: In the era of ART, which seems to improve survival and reduce HIV associated mortality, a portion of HIV-infected patients receiving ART has continued to die. In this study, patient who never had missed visit within the first 2 years had survival probability more than patient who had ever. So the patients should be emphasized the importance of follow-up especially during the first 2 years, to decrease the mortality rate.

***Key words**: Survival, Prognostic factor, HIV, Thailand*

อัตราการรอดชีวิตและปัจจัยพยากรณ์โรคของผู้ป่วยติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัส

สุเมธ รัตนมณีกรณ์ พ.บ.ว.ว.(อายุรศาสตร์) กลุ่มงานอายุรกรรม
โรงพยาบาลสมเด็จพระยุพราชสว่างแดนดิน จังหวัดสกลนคร 47110

บทคัดย่อ

ที่มา : การรักษาด้วยยาต้านไวรัสเอชไอวีแสดงให้เห็นว่าสามารถเปลี่ยนแปลงการดำเนินของโรคเอดส์ได้อย่างมาก สามารถเพิ่มอัตราการรอดชีวิต ลดการเจ็บป่วยและการเสียชีวิตจากการติดเชื้อเอชไอวี โดยการฟื้นฟูการทำงานของภูมิคุ้มกันผ่านการยับยั้งการเจริญเติบโตของเชื้อไวรัสเอชไอวี แต่ถึงแม้จะมีการรักษาด้วยยาต้านไวรัส ก็พบว่ายังมีผู้ติดเชื้อเอชไอวีจำนวนหนึ่งที่ยังคงเสียชีวิต มีการศึกษาในหลายประเทศที่พบว่าความแตกต่างของปัจจัยทางด้านคลินิก ความแตกต่างทางด้านประชากร เศรษฐกิจสังคม พฤติกรรมการดำรงชีวิต มีความสัมพันธ์กับอัตราการรอดชีวิตของผู้ป่วยที่ติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัส

วิธีวิจัย : เป็นการศึกษาย้อนหลังแบบ cohort study โดยทำในผู้ติดเชื้อเอชไอวีที่มีการเริ่มยาต้านไวรัสระหว่าง มกราคม พ.ศ. 2553 ถึง ธันวาคม พ.ศ. 2561 ที่โรงพยาบาลสมเด็จพระยุพราชสว่างแดนดิน

ผลการศึกษา : จากการศึกษาพบว่ามีผู้ติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัสเข้าร่วมการศึกษาทั้งหมด 313 คน มี 12 คน (3.8%) เสียชีวิต อายุเฉลี่ย 34.2 ± 10.2 ปี และเป็นเพศชายประมาณร้อยละ 63 ค่าเฉลี่ยเม็ดเลือดขาว CD4 เริ่มต้น 104 (0-1,253) เซลล์/ลบ.มม. จากการติดตามผู้ป่วยเป็นระยะเวลา 5 ปี ค่าเฉลี่ยเม็ดเลือดขาว CD4 มีแนวโน้มเพิ่มขึ้นจาก 269 (4-929), 340 (3-1,252), 358 (12-1,169), 369 (43-1,142) และ 375 (13-1,031) เซลล์/ลบ.มม. ตามลำดับ และจำนวนผู้ป่วยที่ตรวจไม่พบเชื้อไวรัสเอชไอวีมีแนวโน้มเพิ่มขึ้นจาก 76.5%, 84.2%, 88.9%, 92.5% และ 91.7% ตามลำดับ จากการวิเคราะห์โดยใช้วิธีของ Kaplan-Meier การติดตามที่ 5 ปีหลังจากการเริ่มยาต้านไวรัส ผู้ป่วยมีโอกาสรอดชีวิตร้อยละ 94.7 จากการวิเคราะห์ด้วย univariate analysis พบว่าปัจจัยดังต่อไปนี้มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการเสียชีวิต ได้แก่ ระดับฮีโมโกลบินเริ่มต้น <11 กรัม/เดซิลิตร (HR 4.113; 95% CI 1.112-15.217; P = .034), โรคประจำตัวความดันโลหิตสูง (HR 7.762; 95% CI 1.674-35.999; P = .009), ประวัติของการติดเชื้อคริปโตคอกโคสิสและการติดเชื้อท็อกโซพลาสโมซิสก่อนหน้า (HR 7.140; 95% CI 2.240-22.754; P = .001), การไม่รับประทานยาอย่างเคร่งครัด (Adherence < 95%) (HR 3.810; 95% CI 1.112-13.048; P = .033) การขาดการรักษาในช่วง 2 ปีแรก (HR 5.808; 95% CI 1.167-28.899; P = .032) และจำนวนเม็ดเลือดขาว CD4 ที่ 1 ปี (HR

0.994; 95% CI 0.990-0.999; P = .029) แต่จากการวิเคราะห์ด้วย multivariate analysis พบว่ามีเพียงปัจจัยเรื่องการขาดการรักษาในช่วง 2 ปีแรกเท่านั้นที่มีแนวโน้มสัมพันธ์กับการเสียชีวิต เมื่อวิเคราะห์ด้วยวิธีของ Kaplan-Meier โดยใช้การทดสอบ log-rank test พบว่าผู้ป่วยที่ไม่ขาดนัดการรักษาในช่วง 2 ปีแรกมีโอกาสรอดชีวิตมากกว่าผู้ป่วยที่ขาดนัดการรักษาอย่างมีนัยสำคัญทางสถิติ (P = .038)

บทสรุป : ในยุคของการใช้ยาต้านไวรัสแสดงให้เห็นว่าสามารถเพิ่มอัตราการรอดชีวิต ลดอัตราตายของผู้ป่วยติดเชื้อเอชไอวีลงได้ ทั้งนี้ทั้งนั้นก็ยังพบว่ามีผู้ป่วยจำนวนหนึ่งที่ยังคงเสียชีวิต งานวิจัยชิ้นนี้พบว่าผู้ป่วยที่ไม่ขาดนัดในช่วง 2 ปีแรกของการรักษามีอัตราการรอดชีวิตมากกว่าผู้ป่วยที่ขาดนัดในช่วง 2 ปีแรกของการรักษาอย่างมีนัยสำคัญทางสถิติ เพราะฉะนั้นผู้ป่วยควรจะถูกเน้นย้ำให้เห็นถึงความสำคัญของการมาตรวจรักษาตามนัดโดยเฉพาะในช่วง 2 ปีแรก เพราะสามารถลดอัตราการเสียชีวิตของผู้ป่วยลงได้

คำสำคัญ *: Survival, Prognostic factor, HIV, Thailand*

Introduction

HIV infection and AIDS continues to be a major global health issue. In 2018 an estimated 37.9 million people were living with HIV.[1]

The HIV/AIDS epidemic has remained one of the important public health challenges in Thailand. For current situation in Thailand, there were about 438,336 people living with human immunodeficiency virus (HIV/AIDS) by the end of 2017, accounted for 1.1% of the total population.[2]

ART for the treatment of HIV infection has been shown to profoundly alter HIV disease progression[3-7], including incidence of opportunistic infections in HIV-infected patients.8 The goal of this therapy is to improve survival; to reduce HIV associated morbidity and mortality [9], to increase the quality of life by restoring immunologic function through suppression of viral load.[4],[10-15] Despite of availability of ART, a substantial portion of HIV-infected patients has continued to die from both AIDS-related and non-AIDS-related causes.[16] A number of factors may contribute to those deaths, but the mortality of HIV-infected patients receiving ART varies between countries, depending on several factors such as demographic, socio-economic, behavioral and clinical factors.[4,17-21]

Methods

The study design was a retrospective cohort study involving HIV-infected patients who were initiated ART between January 2010 and December 2018 at Sawangdaendin Crown Prince Hospital, Sakon Nakhon, Thailand. Ethic approval for the study was obtained from Sawangdaendin Crown Prince Hospital ethic committee.

We included the patients with the following criteria: (1) adult patients aged ≥ 15 years old, whom documented with HIV infection, (2) the patients must be initiated ART at Sawangdaendin Crown Prince Hospital, (3) the patients must be initiated ART during January 2010 and December 2018, and (4) the follow-up period of at least 12 months after ART initiation. The patients were excluded if (1) they had initiated ART elsewhere other than Sawangdaendin Crown Prince Hospital and (2) patients whose medical records were not available.

Variables including age, gender, marital status, HIV exposure, employed, weight and hemoglobin level at baseline, comorbidity, hepatitis B and C co-infection, TB co-infection, CD4 cell count and WHO clinical stage at baseline, duration from HIV diagnosis to ART initiation, type of ART regimen and adverse drug effect, cotrimoxazole primary prophylaxis, previous opportunistic infections, adherent to treatment, CD4 cell count and HIV RNA at 1,2,3,4 and 5 years after initiation of ART, Missed visit within the 1st, 2nd, 3rd, 4th and 5th year were reviewed and collected from medical records.

The primary objective of this study was to determine the treatment outcomes of HIV in the HIV-infected patients receiving ART. The secondary objectives were to determine the prognostic factors associated with mortality after ART initiation.

All analyses were performed using SPSS version 21.0. Mean values (± standard deviation,

SD) or median values with range, and frequencies (%) were used to describe the characteristic of patients for continuous and categorical data, respectively. Cox regression analysis was used to determine the prognostic factors associated with mortality after ART initiation. Kaplan-Meier analysis was used to determine the survival probability of HIV-infected patients receiving ART. The log-rank test was used to compare the survival probability of different group. A P value at < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 313 patients were studied, 12 (3.8%) patients died, 26 (8.3%) patients were lost to follow-up, 21 (6.7%) patients were transferred-out to another ART site. The mean ± SD age was 34.2 ± 10.2 years, and 197 (62.9%) patients were male. The mean ± SD baseline weight was 54.5 ± 10.9 kg. The mean ± SD baseline hemoglobin level was 11.4 ± 2.3 g/dl. 9 (2.9%) patients had hypertension as comorbidity. Of 264 patients who were tested for HBsAg, 22 (8.3%) had HBV co-infection. Of the 248 patients who were tested for anti-HCV antibody, 7 (2.8%) had HCV co-infection. Of all, 70 (22.4%) patients had TB co-infection. Risk of HIV infection as heterosexual, homosexual were 78.3%, 21.7%, respectively and none of them had history of intravenous drug use. Baseline WHO clinical stage as stage I, II, III and IV were 39%, 22%, 16%, and 23%, respectively. Among the 313 patients had previous major opportunistic infections including Pneumocystis jiroveci pneumonia (34 patients, 10.9%), cryptococcal infection (19 patients, 6.1%), toxoplasmosis (9 patients, 2.9%), other OIs (cytomegalovirus retinitis and mycobacterium avium complex) (3 patients, 1%). More than half of them (54.3%) had cotrimoxazole primary prophylaxis. Table 1 shows the clinical characteristics of the study patients.

Table1. Baseline characteristics of the study patients

Characteristics	All (*n = 313*)
Age, years, mean ± SD	34.2 ± 10.2
Gender, number (%)	
Male	197 (62.9)
Female	116 (37.1)
Marital status, number (%)	
Married	174 (55.6)
Unmarried/ Seperated	139 (44.4)
Employment status, number (%)	
Employed	237 (75.7)
Unemployed	76 (24.3)
Weight at baseline, kg, mean ± SD	54.5 ± 10.9
Hemoglobin level at baseline, g/dl, mean ± SD	11.4 ± 2.3
Comorbidity, number (%)	
Hypertension	9 (2.9)
Psychiatric disorder	4 (1.3)
Diabetic mellitus	3 (1.0)
Renal calculi	2 (0.6)
Chronic obstructive pulmonary disease	2 (0.6)
Asthma	2 (0.6)
Other*	8 (2.6)
Hepatitis co-infection, number (%)	
HBV *(n = 264)*	22 (8.3)
HCV *(n = 248)*	7 (2.8)
TB co-infection, number (%)	70 (22.4)
Risk of HIV infection, number (%)	
Heterosexual	245 (78.3)
Homosexual	68 (21.7)
IVDU	0 (0)
Baseline WHO clinical stage, number (%)	
Stage I	122 (39)
Stage II	69 (22)
Stage III	50 (16)
Stage IV	72 (23)
History of Opportunistic infections, number (%)	
PCP	34 (10.9)
Cryptococcal infection	19 (6.1)
Toxoplasmosis	9 (2.9)
Other OIs**	3 (1)
Cotrimoxazole primary prophylaxis, number (%)	170 (54.3)

*= gout, hypertriglyceridemia, cervical cancer, ** = Cytomegalovirus retinitis, Mycobacterium avium complex, IVDU=intravenous drug user, HBV=hepatitis B virus, HCV=hepatitis C virus, PCP= Pneumocystis jiroveci pneumonia, OIs=opportunistic infections Treatment outcomes of HIV

Median (range) duration from the diagnosis of HIV to initiation of ART was 47 (0-2707) days. The most common type of ART regimen used was non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen such as efavirenz and nevirapine-based regimens. The NRTI backbone regimen as stavudine plus lamivudine, zidovudine plus lamivudine and tenofovir plus lamivudine or emtricitabine were 22%, 28.8%, and 49.2%, respectively. 85.6% of them were good adherent (≥ 95%) to ART treatment.

Most of them (87.2%) had no missed visits within the first year. Among the 294 patients, 83.3 % had no missed visits within the first 2 years. Among the 149 patients, 81.2% had no missed visits within the first 5 years. Median (range) baseline CD4 cell count was 104 (0-1253) cell/mm3. Within the first 5 years follow-up, median (range) baseline CD4 cell count had trend to increase from 269 (4-929) to 340 (3-1252), 358 (12-1169), 369 (43-1142) and 375 (13-1031) cell/mm3, each year, respectively, shown in Figure1.

Within the first 5 years follow-up, the study patients had trend to achieve undetectable HIV RNA increasing from 76.5% to 84.2%, 88.9%, 92.5% and 91.7%, each year, respectively.

Table 2. Treatment outcomes of the study patients

Variables	All *(n = 313)*
Time from HIV diagnosis to ART initiation, days, median (range)	47 (0-2707)
Type of ART regimen, number (%)	
Efavirenz-based	207 (66.1)
Nevirapine-based	94 (30)
Lopinavir/ritonavir-based	12 (3.8)
NRTI backbone, number (%)	
Tenofovir + Lamivudine or Emtricitabine	154 (49.2)
Zidovudine + Lamivudine	90 (28.8)
Stavudine + Lamivudine	69 (22)
Adherence to treatment, number (%)	
≥ 95%	268 (85.6)
< 95%	45 (14.4)

Variables	All (*n = 313*)
Missed visit within the first year, number (%) *(n = 313)*	
0	273 (87.2)
1	20 (6.4)
2	12 (3.8)
≥ 3	8 (2.6)
Missed visit within the first 2 years, number (%) *(n = 294)*	
0	245 (83.3)
1	20 (6.8)
2	10 (3.4)
≥ 3	19 (6.5)
Missed visit within the first 5 years, number (%) *(n = 149)*	
0	121 (81.2)
1	7 (4.7)
2	4 (2.7)
≥ 3	17 (11.4)
CD4 at ART initiation, cells/mm^3, median (range)	104 (0-1253)
Immunological outcomes	
CD4 cell count, cells/mm^3, median (range)	
at 1 year *(n = 313)*	269 (4-929)
2 years *(n = 291)*	340 (3-1252)
3 years *(n = 225)*	358 (12-1169)
4 years *(n = 189)*	369 (43-1142)
5 years *(n = 149)*	375 (13-1031)
Virological outcomes	
Patients with undetectable HIV RNA, number (%)	
at 1 year *(n = 298)*	228 (76.5)
2 years *(n = 278)*	234 (84.2)
3 years *(n = 216)*	192 (88.9)
4 years *(n = 186)*	172 (92.5)
5 years *(n = 145)*	133 (91.7)
Other outcomes	
Transfer out, number (%)	21 (6.7)
Loss to follow-up, number (%)	26 (8.3)
Death, number (%)	12 (3.8)
Adverse events after ART initiation, number (%)	
Rash	15 (4.8)
No rash	298 (95.2)

NRTI=Nucleoside Reverse Transcriptase Inhibitor

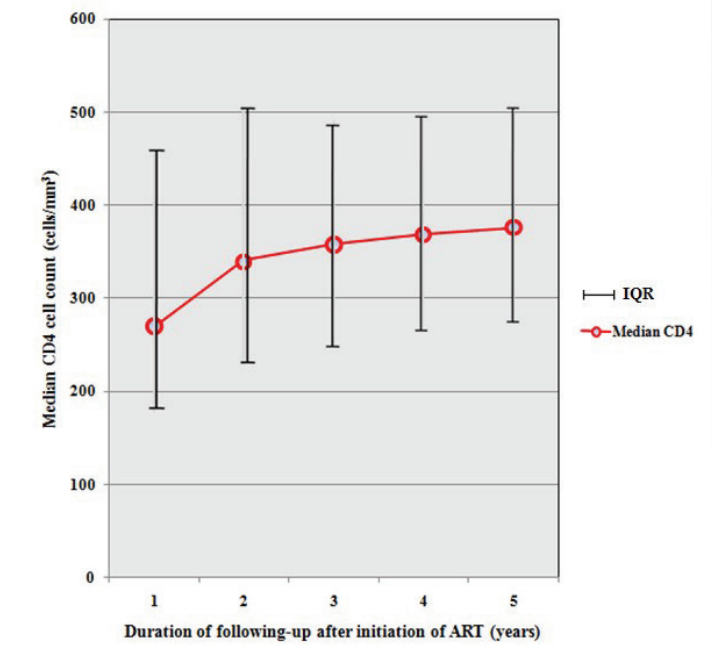

Figure 1. Graph showing the median (IQR) CD4 cell count of the study patients

In Kaplan-Meier analysis, Figure 2 shows probability of survival after 5 years of ART. At 5-year follow up time after initiation of ART, 94.7% of patients had probability to survive.

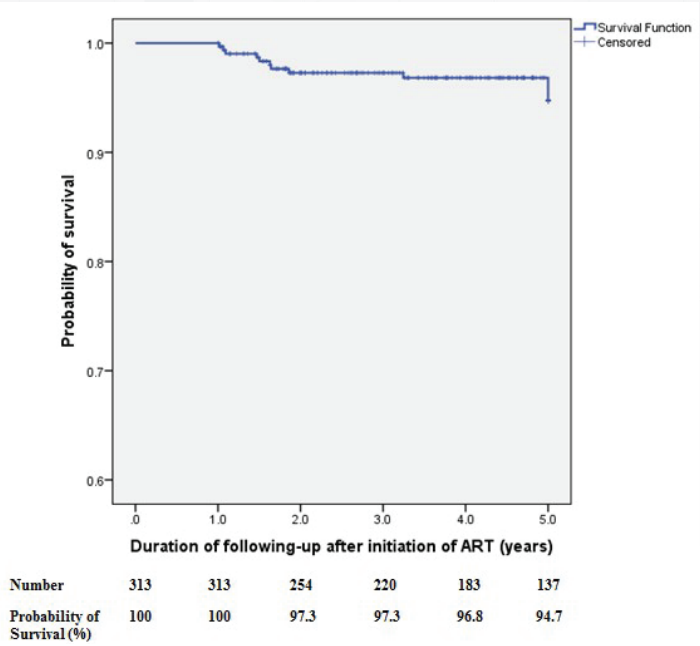

Figure 2. Kaplan-Meier survival curve of the study patients

Table 3 shows the hazard ratios from the univariate analysis of the association between the prognostic factors of mortality and risk of death. From univariate analysis, hemoglobin level at baseline < 11 g/dl (HR 4.113; 95% CI 1.112-15.217; P = .034), hypertension-comorbidity (HR 7.762; 95% CI 1.674-35.999; P = .009), history of previous opportunistic infections including cryptococcal infection or toxoplasmosis (HR 7.140; 95% CI 2.240-22.754; P = .001), adherence to treatment < 95% (HR 3.810; 95% CI 1.112-13.048; P = .033), missed visit within the first 2 years (HR 5.808; 95% CI 1.167-28.899; P = .032) and CD4 cell count at 1 year (HR 0.994; 95% CI 0.990-0.999; P = .029) were statistically significant association with the mortality and NRTI backbone (HR 0.285; 95% CI 0.074-1.095; P = .068), cotrimoxazole primary prophylaxis (HR 3.650; 95% CI 0.797-16.711; P = .095), CD4 cell count at 3 years (HR 0.952; 95% CI 0.985-1.000; P = .052) , CD4 cell count at 5 years (HR 0.985; 95% CI 0.971-1.000; P = .053) and undetectable HIV RNA at 2 years (HR 0.256; 95% CI 0.056-1.161; P = .077) had a trend associated with the mortality. Age, gender, marital status, employment status, weight at baseline, HCV co-infection, TB co-infection, risk of HIV infection, baseline WHO clinical stage, time from HIV diagnosis to ART initiation, type of ART regimen, history of PCP and baseline CD4 cell count were not associated with the mortality (P > .1). From multivariate analysis, only missed visit within the first 2 years had a trend associated with mortality as shown in Table 4. By the log-rank test, patients who never had missed visit within the first 2 years had survival probability more than who had ever (P = .038) as shown in Figure 3.

Table 3. Univariate analysis of prognostic factors associated with mortality for the study patients

Factors	Univariate analysis		
	HR	95% CI	*P* value
Age (years)	1.023	0.967-1.083	0.429
Male gender	1.188	0.357-3.952	0.779
Unmarried/seperated vs Married	0.945	0.299-2.981	0.923
Employed vs Unemployed	0.648	0.195-2.154	0.479
Weight at baseline (kg)	0.998	0.946-1.053	0.940
Hemoglobin level at baseline < 11 g/dl	4.113	1.112-15.217	0.034
Presence of hypertension-comorbidity	7.762	1.674-35.999	0.009
Presence of HCV co-infection	3.829	0.474-30.920	0.208
Presence of TB co-infection	0.562	0.122-2.586	0.459
Heterosexual contact	2.624	0.338-20.378	0.356
Baseline WHO clinical stage II-IV vs stage I	1.147	0.342-3.839	0.824
Time from HIV diagnosis to ART initiation (days)	1.000	0.999-1.001	0.528
Lopinavir/ritonavir vs Nevirapine or Efavirenz-based	2.172	0.278-16.993	0.460
Stavudine or Zidovudine vs Tenofovir	0.285	0.074-1.095	0.068
History of PCP	0.041	0.000-103.061	0.424
History of cryptococcal infection or toxoplasmosis	7.140	2.240-22.754	0.001
Cotrimoxazole primary prophylaxis	3.650	0.797-16.711	0.095
Adherence to treatment with < 95% vs ≥ 95	3.810	1.112-13.048	0.033
Missed visit within the first 2 years	5.808	1.167-28.899	0.032
Baseline CD4 cell count (cells/mm^3)	0.999	0.995-1.003	0.559
CD4 cell count at 1 year (cells/mm^3)	0.994	0.990-0.999	0.029
CD4 cell count at 3 years (cells/mm^3)	0.952	0.985-1.000	0.052
CD4 cell count at 5 years (cells/mm^3)	0.985	0.971-1.000	0.053
Undetectable HIV RNA at 2 years	0.256	0.056-1.161	0.077

Table 4. Multivariate analysis of prognostic factors associated with mortality for the study patients

Factors	Multivariate analysis		
	HR	95% CI	*P* value
Hemoglobin level at baseline < 11 g/dl	2.455	0.442-13.655	0.305
Presence of hypertension-comorbidity	3.739	0.323-43.308	0.291
History of cryptococcal infection or toxoplasmosis	1.703	0.250-11.608	0.587
Missed visit within the first 2 years	4.772	0.939-24.255	0.060

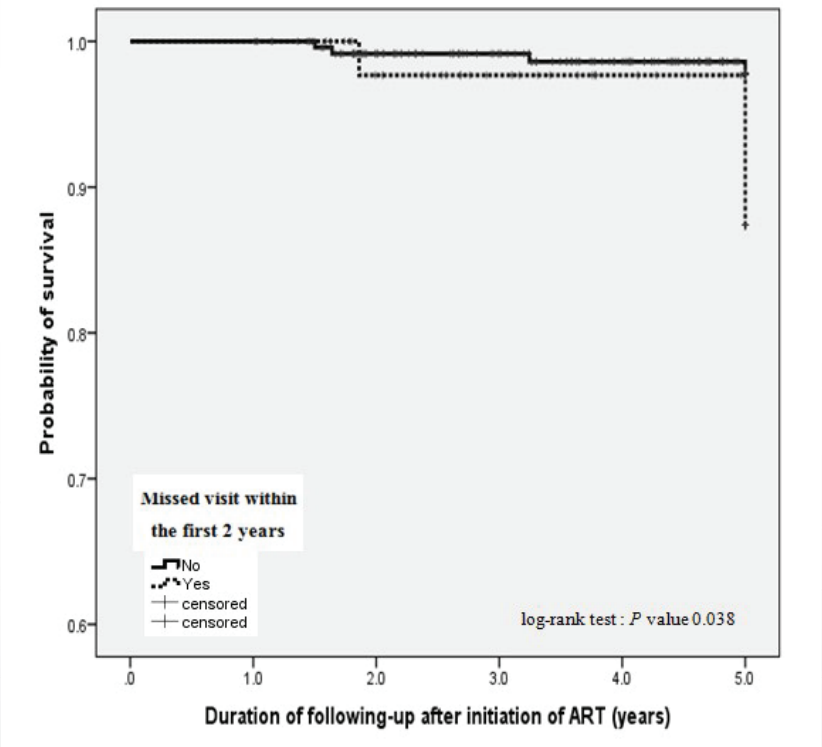

Figure 3. Kaplan-Meier survival curve among patients who missed versus no missed visit within the first 2 years

Discussion

In the era that ART was widely accessible, multiple studies had demonstrated that early ART was associated with prolonged survival of HIV-infected patients, resulting in successful immune restoration and reduction in morbidity and mortality.[4,22] However, survival time and mortality of HIV-infected patients receiving ART varied in different countries and regions, which depended on adherence of therapy, baseline CD4 cell count, demographic characteristics of the patients, and quality of service.[23-25]

However this study was among the very first study to analyzed survival outcomes and explored the prognostic factors of mortality and risk of death among HIV-infected patients receiving ART at Sawangdaendin Crown Prince Hospital, Sakon Nakhon, Thailand.

From our data, hemoglobin level at baseline <11 g/dl, hypertension-comorbidity, history of previous opportunistic infections including cryptococcal infection and toxoplasmosis, adherence to treatment < 95%, missed visit within the first 2 years and CD4 cell count at 1 year were found to be statistically significant factors associated with higher mortality in HIV-infected patients receiving ART. In univariate analysis, NRTI backbone, cotrimoxazole primary prophylaxis, CD4 cell count at 3 and 5 years, undetectable HIV RNA at 2 years, had trend to be statistically significant association with higher mortality in the patients.

This study had disclosed that these factors eg. age, gender, marital status, weight at baseline, TB co-infection, risk of HIV infection, baseline WHO clinical stage, time from HIV diagnosis to ART initiation, baseline CD4 cell count and virological outcome had represented as statistically non-significant covariates of survival of HIV-infected patients receiving ART.

Hemoglobin level of less than 11 g/dl at baseline was also associated with higher mortality. Several previous studies revealed that anemic problem was an independent predictor of mortality in HIV patients.[14,24,26-30] The anemia feature could be explained as part of the advanced clinical staging, especially it may indicated the secondary outcome of latent opportunistic infections, but the exact cause of anemia was impossible to determine. The causes of anemia in HIV patients are likely to be multifactorial such as nutritional deficiency, hemolytic anemia, bone marrow suppression, etc. History of previous opportunistic infections including cryptococcal infection and toxoplasmosis was found to be statistically significant prognostic factor of higher mortality. It might reflect delayed diagnosis and/or delayed treatment in patients who had advanced disease (CD4 cell count < 100 cells/mm^3) and had advanced clinical symptoms (WHO clinical stage IV) at the time of treatment initiation. Other factors such as HIV-related stigma and discrimination may have played a vital role in delaying diagnosis and/or treatment.

In this study, poor adherence to ART (< 95%) was also significantly associated with a higher risk of mortality. This finding is supported by several previous studies, which had shown higher

risk of mortality among non-adherent patients (<95%).[24-25,31-34]

Patients who had missed visit within the first 2 years after receiving ART were also significantly associated with a higher risk of mortality. This finding was supported by previous studies.[35-37] The association between adherence to clinic visits during the first 2 years after receiving ART and mortality might be explained by two major reasons. First, adherence to clinic visits in the early period after receiving ART could predict adherence to clinic visits later on. Secondly, adherence to clinic visits may be associated with adherence to antiretroviral drugs. Previous studies have shown that adherence to clinic visits is correlated with drug adherence in patients with chronic illnesses.[38]

From univariate analysis, cotrimoxazole prophylaxis before ART initiation had trend to be statistically significant association with higher mortality but the difference was not statistically significant in multivariate analysis. However, some studies had revealed that taking cotrimoxazole prophylaxis before ART initiation was a significant factor associated with reduction of mortality as compared to not taking the prophylaxis.[26,39-40]

Our study did not find any significant association between an increased age with an increased death hazard rate. These results are consistent with findings from multiple studies showing no association between the age at the ART initiation with death.[33] However other previous studies had revealed relationship of an increased age at the onset of ART treatment with higher mortality rate.[31-32]

The significance of gender in determining the survival time until death was variable in many studies. Previous studies had reported that the mortality rate seems to be higher in males than in females.[24-25] However our study did not find any association of survival time until death between genders similar with other studies.[26-27,32]

In contrast to other studies in which baseline TB infection was an important predictor of mortality[33], our study did not demonstrate an association between baseline TB infection and mortality similar with the study.[32] It might be because all of the HIV-TB co-infected patients had received TB treatment, adhered to the DOTs treatment guidelines.

We had found no significant association between baseline WHO clinical staging and CD4 cell count with survival, in contrast to the previous studies which shown significant association between them.[14,33]

From multivariate analysis, missed visit within the first 2 years was the only factor that had trend to be statistically significant association with higher mortality. By the log-rank test, patients who never had missed within the first 2 years had survival probability more than patients who missed visit during that period.

Other factors which found to be statistically significant determinants of mortality in univariate analysis did not show any statistical significance in multivariate analysis, might be due to small sample size. Future study should be conducted with larger sample size at the provincial or national level by multi-centers design.

Strength & Limitation

The main strength of this study is the follow-up time which was long enough to estimate survival and its determinants. All of our enrolled patients were treatment-naive, so our results could not be confounded by previous antiretroviral therapy. The limitations of this study included the nature of a retrospective study and it lacked of the detailed information about the causes of death. Moreover, the mortality outcomes of patients who loss to follow-up in this study were unknown.

Conclusion

This retrospective cohort study had provided the information about prognostic factors of death in HIV-infected patients receiving ART in Sawangdaendin Crown Prince Hospital. In the study, patients who never had missed visit within the first 2 years had more survival probability than patient who had ever missed visit. So the patients should be emphasized the importance of follow-up especially during the first 2 years, to decrease the mortality rate.

The findings can be applied and redesigned clinical management of high risk patients and ultimately improving their survival and quality of life. Educating a community regarding HIV testing services is essential for obtaining an earlier diagnosis, earlier initiation of ART, successful enrollment in ART treatment services and self-awareness of adherence.

กิตติกรรมประกาศ

งานวิจัยฉบับนี้สำเร็จลุล่วงไปได้ด้วยดี ด้วยความกรุณาช่วยเหลือแนะนำอย่างดียิ่งจาก ศาสตราจารย์นายแพทย์สมนึก สังฆานุภาพ สถาบันการแพทย์จักรีนฤบดินทร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล ที่ได้ให้คำปรึกษาแนะนำและข้อคิดเห็นต่างๆในงานวิจัยตลอดจนแก้ไขข้อบกพร่องต่างๆมาโดยตลอด ผู้วิจัยขอกราบขอบพระคุณเป็นอย่างสูง

ขอขอบพระคุณนางเทพวาณี ร่างกาย และนางสาวขนิษฐา มิกทา พยาบาลประจำคลินิกผู้ติดเชื้อเอชไอวี เจ้าหน้าที่ศูนย์ข้อมูลสารสนเทศที่ได้ให้ความร่วมมือเป็นอย่างดีในการช่วยค้นหาข้อมูล ขอขอบพระคุณนายแพทย์วิโรจน์ วิโรจนวัธน์ ผู้อำนวยการโรงพยาบาลสมเด็จพระยุพราชสว่างแดนดิน ที่คอยเป็นกำลังใจ และช่วยเหลืองานวิจัยให้สำเร็จลุล่วงไปได้ด้วยดี

สุดท้ายนี้ ขอกราบขอบพระคุณเป็นอย่างสูง สำหรับบิดา มารดา คณาจารย์ทุกๆ ท่าน ที่อบรมสั่งสอน และประสิทธิ์ประศาสตร์วิชาแก่ผู้วิจัยเป็นอย่างดีตลอดมา

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