COMPARISON OF CLINICAL OUTCOMES BETWEEN HIV-INFECTED PATIENTS WITH AND WITHOUT HCV CO-INFECTION IN A RESOURCE-LIMITED SETTING

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Abstract. Hepatitis C virus (HCV) co-infection is common among HIV-infected patients; its treatment is not affordable in resource-limited settings. This study aimed to compare the morbidity, mortality, immunological and virological outcomes of antiretroviral therapy (ART) between HIV-infected patients with and without HCV co-infection in a setting where HCV infection is rarely treated. A retrospective cohort study was conducted among HIV-infected patients attending Ramathibodi Hospital between 1998 and 2008. We studied 171 HIV-infected patients 57 with and 114 without HCV co-infection. The mean age of patients was 34.6 years and 67.3% were males. There were no differences in demographics, HIV staging, CD4 counts, ART use and ART regimens between the two groups (p>0.05). All patients who had a CD4 count <200 cells/mm^3 or had an AIDS-defining illness during following-up were given ART; these consisted of 84.2% and 88.6% of patients with and without HCV co-infection, respectively. Only 4 out of 57 (7%) HCV co-infected patients were treated for HCV infection. During a median (range) follow-up time of 2.9 (1.2-9.8) years, no patients died in either group. The rates of AIDS-defining illnesses and hospitalization in the two groups were similar (p>0.05). In a resource-limited setting where HCV treatment is not affordable, HCV co-infection does not appear to affect morbidity, mortality or treatment responses to ART. ART may have a greater impact than HCV co-infection on the survival of HCV/HIV co-infected patients. Further studies are needed to assess the long-term impact of HCV co-infection on clinical outcomes in HIV-infected patients without HCV treatment.

Keywords: HIV, AIDS, HCV, long-term outcome, antiretroviral therapy

INTRODUCTION

Antiretroviral therapy (ART) has improved the survival and quality of life of HIV- infected patients in various resource settings (Hogg *et al*, 1998; Palella *et al*, 1998; Manosuthi *et al*, 2006; Jongwutiwes *et al*, 2007; Sungkanuparph *et al*, 2008). Hepatitis C virus (HCV) co-infection is common among HIV-infected patients and is now considered a major public health problem worldwide, owing both

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to its high prevalence and to the interactions between HCV and HIV in terms of diagnosis, natural course, and treatment. HCV-associated liver damage appears to be more likely to develop in HCV/HIV co-infected patients than in those with HCV mono-infection (Ragni and Belle, 2001; Goedert *et al*, 2002).

Although increasing data suggests effective treatment of HCV infection results in decreased morbidity and mortality (Kontorinis *et al*, 2005; Aronsohn and Reau, 2009), HCV treatment is not affordable to patients in resource-limited settings. However, some studies have found liver fibrosis and inflammation toxicity scores are lower and fibrosis rates slower in HCV/HIV co-infected patients receiving ART (Dodig and Tavill, 2001; Operskalski *et al*, 2011). A previous study from Taiwan suggested HCV/HIV co-infection was associated with a significantly higher risk for acute hepatitis but has no adverse impact on survival when compared with HIV-infected patients without HCV co-infection (Hung *et al*, 2005). An analysis of HCV/HIV co-infected patients from clinical trials has shown that there is delayed CD4 count recovery among HCV/HIV co-infected patients but this is not sustained, and is not associated with HIV disease progression (Law *et al*, 2004). Morbidity and mortality data and clinical outcomes of HCV/HIV co-infected patients receiving ART in a clinical setting where HCV infection is rarely treated, are limited.

The primary objective of this study was to compare morbidity and mortality between HIV-infected patients with and without HCV co-infection. The secondary objectives were to compare immunological and virological outcomes and adverse effects between HIV-infected patients with and without HCV co-infection.

MATERIALS AND METHODS

A retrospective cohort study was conducted among HIV-infected patients with and without HCV co-infection at Ramathibodi Hospital, a 1,200-bed university hospital. Patients with HCV co-infection were identified from the hospital database, including HIV-infected patients with positive anti-HCV antibodies (Architect i2000 SR, ELISA, Abbott Laboratories, North Chicago, IL) who visited Ramathibodi Hospital between January 1998 and December 2008. Patients without HCV co-infection were randomized from the hospital database of HIV-infected patients at a ratio of 2:1 and matched by year of HIV diagnosis and receiving ART among patients with HCV co-infection during the same study period. Patients with HBV co-infection were excluded. The data were extracted from medical records. All patients were followed through the end of the study period. Information obtained at follow-up visits, such as complaints, adverse events and laboratory investigations, were retrieved. The final decision whether an adverse event developed was determined by the attending physician in the medical records. All data regarding concurrent use of antiretroviral drugs and other prescribed drugs was collected. Patients who were referred or lost to follow-up were contacted by phone or letter to verify survival.

Categorical data are presented as frequencies and percentages. Continuous data are presented as means and standard deviations (SD), or medians and ranges, for data with and without normal distribution, respectively. Categorical variables in the two groups were compared using the chi-square or Fisher's exact test where appropriate. Continuous variables were compared using the Student's *t*-test or

Table 1
Clinical characteristics of HIV-infected patients with and without HCV co-infection.

Characteristics	HCV co-infection		*p*-value
	Yes (*n*=57)	No (*n*=114)	
Age, years, mean ± SD	35.1 ± 8.7	34.3 ± 8.4	0.938
Male gender, number (%)	44 (77.2)	71 (62.3)	0.050
Risk of HIV infection, number (%)			0.001
Homosexual	4 (7.0)	2 (1.8)	
Heterosexual	28 (49.1)	110 (96.4)	
Intravenous drug users	23 (40.4)	2 (1.8)	
Receipt of blood products	2 (3.5)	-	
HIV disease staging, number (%)			0.924
AIDS (A3, B3, C1-3)	30 (52.6)	62 (54.4)	
Non-AIDS (A1-2, B1-2)	27 (47.4)	52 (45.6)	
Baseline CD4, cells/mm^3, median (range)	209 (13-464)	232 (22-877)	0.388
Receiving ART, number (%)	48 (84.2)	101 (88.6)	0.419
ART regimen, number (%)			<0.001
NNRTI-based	40/48 (83.3)	100/101 (99.0)	
PI-based	8/48 (16.7)	1/101 (1.0)	

ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Mann-Whitney *U* test, where appropriate. All analyses were performed using SPSS program version 16.0 (SPSS, Chicago, IL). A p-value < 0.05 was considered statistically significant. The study was approved by the institutional review board.

RESULTS

We studied a cohort of 171 patients; 57 were HCV/HIV co-infected patients and 114 were HIV mono-infected patients. The overall mean age (SD) was 34.6 (8.6) years and 67.3% of patients were males. Table 1 shows the baseline characteristics in the patients with and without HCV co-infection. There were no differences in demographics, HIV staging, CD4 cell counts, ART use or ART regimens between the two groups. Intravenous drug use (IVDU) was significantly more common among patients with HCV co-infection (p<0.05).

All patients who had a CD4 cell count <200 cells/mm^3 or had an AIDS-defining illness during the follow-up period were given ART; these constituted 84.2% of patients with HCV co-infection and 88.6% of patients without HCV co-infection. Most of the patients received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. Protease inhibitor (PI)-based regimens were more commonly used among patients with HCV co-infection. Only 4 out of 57 (7%) HCV co-infected patients were treated for HCV infection. All 4 patients had clinical hepatitis, elevated ALT levels (median, 164 U/l), and high HCV viral loads (median, 998,441 copies/ml). Pegylated interferon and ribavirin were used in these 4 patients and all achieved an early and sustained

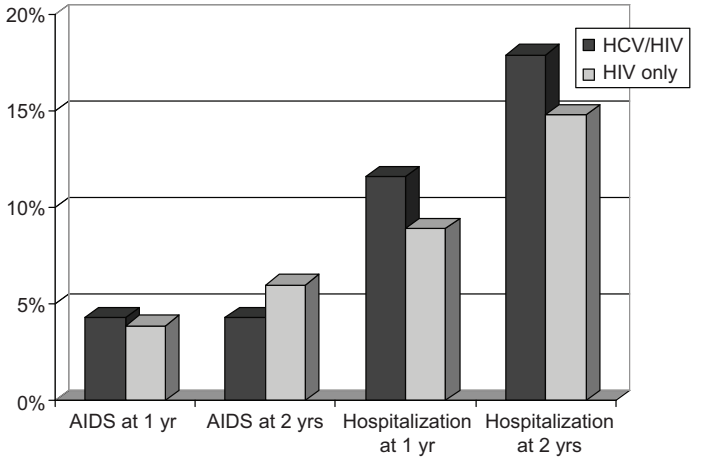

Fig 1–Rates of AIDS-defining illness and hospitalizations in HIV-infected patients with and without HCV co-infection.

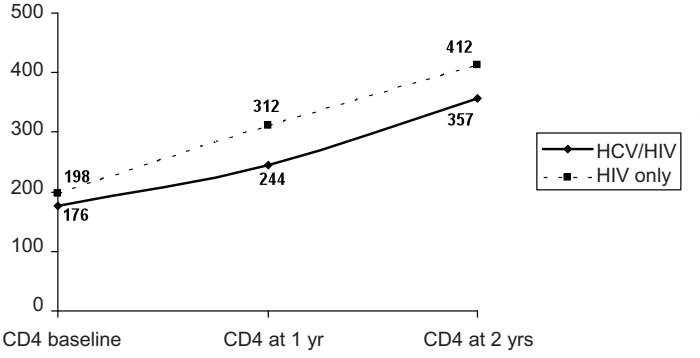

Fig 2A–Immunological response (median CD4 cell count) to ART among HIV-infected patients with and without HCV co-infection.

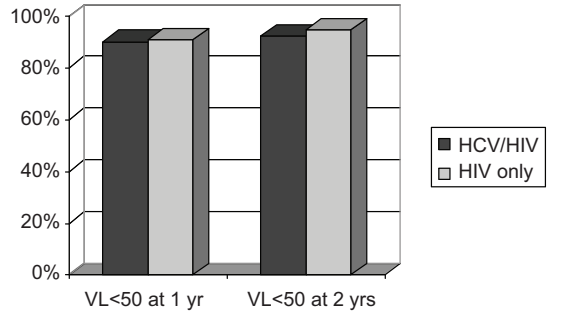

Fig 2B–Virological response to ART among HIV-infected patients with and without HCV co-infection.

virological response.

During a median (range) follow-up time of 2.9 (1.2-9.8) years, no patients died in either group. Fig 1 shows the rates of AIDS-defining illnesses and rates of hospitalizations from any cause in patients with and without HCV co-infection. There were no differences in clinical outcomes between the two groups (p >0.05). Causes of all hospitalizations were due to HIV-related opportunistic infections. Regarding hepatotoxicity, there were significantly higher rates of grade 3-4 elevated liver enzymes among HIV-infected patients with HCV co-infection at 6 months, one year and two years (p <0.05). Two patients, one with and one without HCV co-infection, developed cirrhosis during the study period.

Fig 2 shows immunological and virological responses of patients receiving ART in both groups.

DISCUSSION

HCV/HIV co-infection has a negative impact on the natural history of HCV infection, including higher rates of viral persistence, increased viral load and more rapid progression to fibrosis, cirrhosis, and death (Operskalski *et al*, 2011). The current standard for HCV treatment is pegylated interferon with ribavirin among both HCV mono-infected and HCV/HIV co-infected patients (Soriano *et al*, 2007; Iorio *et al*, 2010).

However, this treatment is not affordable in many resource-limited settings, including Thailand. The clinical outcomes of HCV/HIV co-infected patients who are not treated for HCV infection are still questionable. Some physicians are reluctant to plan long-term care for these patients.

Our results demonstrate in a setting where ART is given, morbidity and mortality were not different between HIV-infected patients with and without HCV co-infection. The virological and immunological responses were similar between the two groups. Early ART may protect co-infected patients from liver fibrosis progression and may reduce the risk of liver disease and related morbidity and mortality. Many recent studies support the concept of ART as HCV therapy, particularly when specific treatment for HCV infection is not affordable. ART can significantly decrease liver HCV necroinflammatory activity in HCV/HIV co-infected patients, possibly by inhibiting HIV replication in the liver or decreasing the level of proinflammatory cytokines (Pascual-Pareja *et al*, 2009). Recent HIV treatment guidelines recommend ART be initiated earlier in patients with HCV/HIV co-infection (Sungkanuparph *et al*, 2010; Thompson *et al*, 2010).

HCV/HIV co-infected patients may experience liver enzyme elevation following ART initiation (Price *et al*, 2009). However, the results from the present study show severe liver impairment, such as cirrhosis, is not different between HIV-infected patients with and without HCV co-infection. Although close monitoring of liver function test is suggested after initiation of ART among HCV/HIV co-infected patients, HCV itself should not discourage physicians from initiating early ART in these patients.

There were limitations in the present study: it was retrospective, had a relatively small sample size and small number of HCV/HIV co-infected patients. However, this retrospective cohort study provides information in the clinical setting. We included HCV/HIV co-infected patients over a 10-year period when HAART was available in order to increase the sample size. Since HCV RNA was not tested in all patients, the morbidity and mortality of HCV co-infection could be underestimated.

In conclusion, HCV co-infection does not appear to affect morbidity, mortality or treatment responses to ART in resource-limited settings where HCV treatment is not affordable. ART may have a greater impact than HCV co-infection on the survival of HCV/HIV co-infected patients. Further studies are needed to assess the long-term impact of HCV co-infection among patients without HCV treatment.

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