HIV-HCV Coinfection: Prevalence and Treatment Outcomes in Malaysia

Ali Akhtar\textsuperscript{a}  Samreen Fatima\textsuperscript{b}  Hamid Saeed\textsuperscript{b}  Chow Ting Soo\textsuperscript{c}  Amer Hayat Khan\textsuperscript{a}

\textsuperscript{a}Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, George Town, Malaysia; \textsuperscript{b}University College of Pharmacy, University of the Punjab, Lahore, Pakistan; \textsuperscript{c}Infectious Disease Unit, Hospital Palau Pinang, George Town, Malaysia

Keywords
Human immunodeficiency virus · Hepatitis C virus · Prevalence · Outcomes · Coinfection

Abstract

Background: Around 130 million infections of hepatitis C virus with 3% overall prevalence are there worldwide. There are approximately 4–5 million persons coinfected with HIV. The main objectives of this study were to determine the prevalence of HCV among HIV-positive individuals and to assess the predictors involved in the outcomes of HIV-HCV coinfected patients. Methods: A retrospective, cross-sectional study was conducted on patients enrolled from 2007 to 2012 at Infectious Disease Unit, Hospital Palau Pinang, Pinang, Malaysia. Sociodemographic data as well as clinical data were collected with the help of a valid data collection form from the patients’ records. Data were entered and analyzed by using statistical software SPSS version 20.0, and \( p < 0.05 \) was considered significant. Results: The overall prevalence of hepatitis C among 708 HIV-infected patients was 130 (16.1 including 541 (76.4\%) males and 167 (23.6\%) females. High prevalence of HIV-HCV coinfection was significantly observed in males (122 [17.2\%]) compared to females (8 [1.1\%]) \( (p < 0.001) \). The main route of transmission among HIV-HCV coinfected patients was heterosexual contact (98 [13.8\%]), followed by homosexual contact (4 [0.4\%]). The statistically significant predictors involved in treatment outcomes of HIV-HCV coinfected patients are gender (OR = 2.015, \( p = 0.002 \)) and intravenous drug users (OR = 2.376, \( p \leq 0.001 \)). Conclusion: The current study shows that HCV infection has an impact on the recovery of CD4 cells of the patients on HAART. Screening of HCV among HIV patients who were smokers and intravenous drug users should be monitored before starting HAART.

Introduction

The human immunodeficiency virus (HIV) has stormed across the world in the past 3 decades. In 2012, several biological, social, and behavioral factors increased the risk of HIV infection to approximately 35.3 million [1]. About 170 million (3\% of the total world’s population) people are infected with HCV. While the estimated rate of HCV infection is 5.3\% in Africa, the highest rates (7.8–18\%) are reported in Egypt, followed by (6\%) sub-Saharan Africa, (2.4\%) West Africa, and (1.6\%) in Eastern and Southern Africa [2]. There is a high prevalence (>3.5\%) of HCV infection in North Africa, Middle East, and Cen-
central and East Asia and moderate occurrence (1.5–3.5%) in South and Southeast Asia, Andean, sub-Saharan Africa, Central and Southern Latin America, Oceania, Caribbean, Australasia, and Eastern, Central, and Western Europe while low prevalence (<1.5%) is reported in the Asia Pacific, Tropical Latin America, and North America [3].

Overall, 3% prevalence of hepatitis C was reported all around the world which constitutes around 130 million infections. There were approximately 4–5 million persons coinfected with HIV. The prevalence of HCV among intravenous drug users (IVDUs) is 72–95%, 1–12% in men who have sex with men, and 9–27% in heterosexuals among HIV-infected persons in the USA and Western countries. Fifteen to 45% persons clear the virus after acute infection and 20–30% of infected individuals with persistent viremia develop liver fibrosis and potentially cirrhosis, followed by liver failure and hepatocellular carcinoma [4]. It is reported in most studies that HIV has adverse effects on the natural history of hepatitis C virus infection. There is an association between HIV infection and higher HCV viral loads, hepatitis B virus persistence, and increased risk of end-stage liver disease in most studies. The levels of HCV-RNA become higher after co-infection with HIV. Some studies showed that in HIV-infected patients, the HCV-RNA levels are higher with lower CD4+ counts than 200/mm$^3$ as compared to patients infected with HIV having higher CD4+ counts [5].

The infection of hepatitis C virus is frequently prevalent in the population of HIV-infected individuals with one-third of Americans infected with HIV and worldwide 7 million are being coinfected. Now, the leading cause of death is chronic HCV infection after the complications associated with AIDS among the individuals of HIV infection in the regions where highly active antiretroviral therapy (HAART) is available [6]. Several studies have shown that there are higher levels of HCV in the blood of HIV-infected patients coinfected with hepatitis C virus following a rapid progression to liver diseases related to hepatitis C virus and higher risk of liver disease and cirrhosis. HCV is now considered as an adaptable infection in HIV-infected people although it is not regarded as an AIDS-defining illness [7].

Materials and Methods

Study Design, Area, and Period

A retrospective, cross-sectional study was conducted from August 2013 to March 2014 at Hospital Palau Pinang, Penang, Malaysia. The current study evaluated all medical records of HIV patients under treatment between 2007 and 2012. Demographic and clinical data of all HIV patients and coinfected with HCV were analyzed.

Inclusion and Exclusion Criteria

All HIV patients receiving HAART under treatment from 2007 to 2012 with confirmed diagnosis of HCV were included, and patients with HBV and patients before and after the cited duration were excluded from the study.

Data Collection Procedures

Sociodemographic information and other relevant possible risk factors of the study participants were collected with the help of a valid data collection form. All medical records of HIV patients under treatment between 2007 and 2012 were evaluated. Demographic and clinical data of all HIV patients and coinfected with HCV were analyzed.

Data Analysis

The data were entered and analyzed using SPSS Version 20.0 statistical software, and differences in proportions were evaluated by the $\chi^2$ test; a $p$ value of <0.05 was considered as statistically significant. Mean plus standard deviation with 95% confidence interval was used for continuous variables. In order to identify the risk factors associated with the clinical outcomes in HIV-HCV coinfected patients, binary and multiple logistic regression analysis was performed.

Results

The overall prevalence of HCV among all HIV enrolled population was 130 (16.1%) with a mean age of 40 ± 10 years. The majority of the study population was males (541 [76.4%]) as compared to females (167 [23.6%]), and a significant difference was also observed between males and females ($p < 0.001$). The vast majority of the study population was Chinese (427 [60.3%]), followed by Malay (151 [21.3%]), Indian (96 [13.6%]), and other small minorities (34 [4.8%]), and it was also statistically significant ($p < 0.001$) as shown in Table 1. Most of the patients were below 40 years of age (364 [51.4%]). A significant difference was also seen in marital status ($p = 0.001$), education level ($p = 0.050$), smokers ($p < 0.001$), and IVDUs ($p < 0.001$) in which married (338 [47.7%]), with primary education level (289 [40.8%]), smokers (391 [55.2%]), and non-IVDUs (594 [83.9%]) were in majority.

The mean serum levels of AST and ALT in HIV monoinfected study population were 100 μL and 32 μL, respectively, whereas in HIV-HCV coinfected patients, the levels of AST and ALT were raised to 126 μL and 59 μL, respectively. A significant difference ($p < 0.001$) was observed in AST and ALT levels of HIV monoinfected and HIV-HCV coinfected patients as shown in Table 2. The mean CD4 count of HIV-HCV coinfected patients...
was 230 cells/mm$^3$ while in HIV monoinfected patients, the mean CD4 count was raised to 243 cells/mm$^3$.

The regimens of antiretroviral drugs used for the treatment of HIV-HCV coinfected patients are given in Table 3. All the antiretroviral drugs were given in the combination of nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors, but the majority of patients (38 [29.2%]) were on tenofovir + emtricitabine + efavirenz (TDF + FTC + EFV).

The comorbidities involved in the HIV-HCV coinfected patients are illustrated in Table 4. The majority of the study population was also suffering from pulmonary tuberculosis (58 [54.7%]), followed by pneumocystis pneumonia (12 [11.3%]).

Binary and multiple logistic regression was performed to predict the impact of the number of factors involved in the treatment outcomes of the HIV-HCV comorbid study population as shown in Table 5. This model contains 11 independent variables (gender, age, race, marital status, educational level, employment status, monthly income, smoking, alcohol, IVDU, and risk factors). The model containing all predictors was statistically significant as the Omnibus Tests of Model Coefficients was highly significant ($\chi^2 = 50.116$, $p = 0.001$), which indicates that the model was able to distinguish between the patients improved with the HAART and who were not improved. The model as a whole explained between 0.107% (Cox and Snell R square) and 0.154% (Nagelkerke R squared).

### Table 1. Sociodemographic characteristics and their association with HIV alone and HIV-HCV coinfections

| Variables          | HIV alone, $n$ (%) | HIV-HCV, $n$ (%) | $p$ value |
|--------------------|-------------------|------------------|-----------|
| Gender             |                   |                  |           |
| Male               | 419 (59.2)        | 122 (17.2)       | $<0.001$  |
| Female             | 159 (22.5)        | 8 (1.1)          |           |
| Race               |                   |                  |           |
| Malay              | 75 (10.6)         | 76 (10.7)        | $<0.001$  |
| Chinese            | 391 (55.2)        | 36 (5.1)         |           |
| Indian             | 82 (11.6)         | 14 (2.0)         |           |
| Others             | 30 (4.2)          | 4 (0.6)          |           |
| Age groups, years  |                   |                  |           |
| ≤40                | 304 (42.9)        | 60 (8.5)         | 0.109     |
| >40                | 274 (38.7)        | 70 (9.9)         |           |
| Marital status     |                   |                  |           |
| Single             | 223 (31.5)        | 70 (9.9)         | 0.001     |
| Married            | 294 (41.5)        | 44 (6.2)         |           |
| Divorced           | 30 (4.2)          | 12 (1.7)         |           |
| Widow              | 31 (4.4)          | 4 (0.6)          |           |
| Education status   |                   |                  |           |
| No formal          | 157 (22.2)        | 36 (5.1)         | 0.050     |
| Primary            | 229 (32.3)        | 60 (8.5)         |           |
| Secondary          | 145 (20.5)        | 32 (4.5)         |           |
| Graduation         | 47 (6.6)          | 2 (0.3)          |           |
| Smoking            |                   |                  |           |
| Smoker             | 279 (39.4)        | 112 (15.8)       | $<0.001$  |
| Nonsmoker          | 299 (42.2)        | 18 (2.5)         |           |
| Alcohol use        |                   |                  |           |
| Alcoholic          | 207 (29.2)        | 56 (7.9)         | 0.074     |
| Nonalcoholic       | 371 (52.4)        | 74 (10.5)        |           |
| IVDU               |                   |                  |           |
| Yes                | 38 (5.4)          | 76 (10.7)        | $<0.001$  |
| No                 | 540 (76.3)        | 54 (7.6)         |           |
| Risk factors       |                   |                  |           |
| Heterosexual       | 408 (57.6)        | 98 (13.8)        | 0.183     |
| Homosexual         | 43 (6.1)          | 4 (0.4)          |           |
| Unknown            | 127 (17.9)        | 28 (4.0)         |           |

IVDU, intravenous drug user; HIV, human immunodeficiency virus; HCV, hepatitis C virus.
of the variance in the treatment outcomes of the patients and correctly classified 72.1% of all the cases. In the model, only 2 independent variables had a statistically significant value (gender and IVDU). The strongest predictor involved in the treatment outcomes of the patients was IVDU with an odds ratio of 2.376. This reflected that the patients who were IVDUs were 2.376 times more likely to face treatment failure as compared to non-IVDUs. The odds ratio of 2.015 among the gender group reflected that males were 2.015 times more likely to improve their CD4 counts as compared to females. All predicting factors were effective when controlling all other factors in the given model.

Discussion

HCV infection is one of the major diseases of mankind and a serious public health problem all over the world. The objectives of the current study were to determine the prevalence of HCV among HIV-positive individuals who were being treated with antiretroviral therapy and to predict the factors involved in the treatment outcomes of HIV-HCV coinfected patients. The effect of HCV coinfection on the improvement of immune cells and liver enzymes before and after HAART in HIV-positive patients still remains debatable. On the other hand, many studies reported globally suggest that the presence of HIV infection increases the chances of HCV-liver-related diseases in HIV-HCV coinfected patients [8, 9]. T-helper immune response impaired by HIV in turn alters the response of HCV immune cells. Due to this mechanism, HCV replication progresses faster, and greater infection and injury to hepatocytes leads to rapid progression of liver-related diseases [8].

With the above-stated mechanism of these 2 viruses and their complications on the proper management of these coinfected patients, the main objective of the current study is to evaluate the prevalence of HCV among HIV-positive individuals and to predict the factors involved in the treatment outcomes of these coinfected patients in a tertiary care hospital of Malaysia. In the USA and Europe, the prevalence of HIV-HCV coinfected patients ranged from 25 to 50% [10, 11]. In another study, the prevalence of HCV among HIV individuals was 74% [12]. Results of the present study show that the prevalence of HCV was 16.1% in a tertiary care hospital in Malaysia. A study conducted in Iran reported that the prevalence of HIV-HCV coinfected patients was 68% [13]. In a similar study carried out on 620 HIV-positive patients in northern India, the prevalence of HCV among HIV-infected patients was 1.6% [14]. Generally, these prevalence studies were carried out at different parts of the world, so the differences in the prevalence may be due to the types of

| Immunological and liver biomarkers | HIV alone | HIV-HCV | p value |
|-----------------------------------|-----------|---------|---------|
| CD4, mean ± SD, cells/μL | 243±88 | 230±141 | 0.957 |
| ALT, mean ± SD, μL | 32±40 | 59±45 | <0.001 |
| AST, mean ± SD, μL | 100±40 | 126±51 | <0.001 |

HIV, human immunodeficiency virus; HCV, hepatitis C virus.

| Drugs | Class | Frequency |
|-------|-------|-----------|
| 3TC + TDF + EFV | NRTI + NNRTI | 8 |
| d4T + 3TC + EFV | NRTI + NNRTI | 30 |
| AZT + 3TC + EFV | NRTI + NNRTI | 34 |
| d4T + 3TC + NVP | NRTI + NNRTI | 4 |
| AZT + 3TC + NVP | NRTI + NNRTI | 8 |
| TDF + FTC + NVP | NRTI + NNRTI | 8 |
| TDF + FTC + EFV | NRTI + NNRTI | 38 |

HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HCV, hepatitis C virus; d4T, stavudine; 3TC, lamivudine; TDF, tenofovir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; AZT, zidovudine; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors.

| Comorbidities | Frequency |
|---------------|-----------|
| Pulmonary tuberculosis | 58 |
| Pneumocystis pneumonia | 12 |
| Hyperlipidemia | 4 |
| Anemia | 4 |
| Ischemic heart disease | 6 |
| Diabetes mellitus | 4 |
| Hypertension | 2 |
| Oral candidiasis | 2 |
| Liver cirrhosis | 4 |
| Cerebral toxoplasmosis | 6 |
| Virological failure | 4 |

HIV, human immunodeficiency virus; HCV, hepatitis C virus.

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The majority of patients in the current study were males and over 40 years of age as shown in Table 1, indicating that there is an association of the coinfection with gender and age. The higher prevalence in the older group may reflect sexual behavior, chronic nature of the disease, or may be related to immunity and hormonal behavior. These findings are comparable with those of a study reported by Sugimoto et al. [18] that found a higher prevalence of HIV-HCV coinfection in males and over 40 years of age.

Table 5. Predictors affecting the treatment outcomes of the HIV-HCV comorbid study population

| Variables                      | Univariate analysis |          |          |          | Multivariate analysis |          |          |
|-------------------------------|---------------------|----------|----------|----------|-----------------------|----------|----------|
|                               | odds ratio | p value | 95% CI lower | 95% CI upper | odds ratio | p value | 95% CI lower | 95% CI upper |
| Gender                        |           |          |          |          | Gender                |           |          |
| Male                          | 2.187     | <0.001   | 1.443    | 3.314     | Reference             |           |          |
| Female                        | Reference |          |          |          | 2.015                 | 0.002    | 1.297    | 3.130      |
| Race                          | Race      |          |          |          | Race                  |          |          |
| Malay                         | Reference |          |          |          | Reference             |           |          |
| Chinese                       | 1.819     | 0.044    | 1.017    | 3.254     | 1.618                 | 0.118    | 0.886    | 2.957      |
| Indian                        | 1.121     | 0.568    | 0.758    | 1.656     | 0.941                 | 0.775    | 0.618    | 1.431      |
| Others                        | 0.773     | 0.506    | 0.361    | 1.653     | 0.499                 | 0.097    | 0.220    | 1.135      |
| Age groups, years             | Age groups, years |       |          |          | Age groups, years     |          |          |
| ≤40                           | Reference |          | 0.006    | 0.465     | Reference             | 0.635    | 0.007    | 0.456      | 0.884      |
| >40                           | 0.639     |          |          |          | 0.635                 | 0.007    | 0.456    | 0.884      |
| Marital status                | Marital status |       |          |          | Marital status        |          |          |
| Single                        | Reference |          |          |          | Reference             |           |          |
| Married                       | 1.020     | 0.909    | 0.729    | 1.427     | 1.618                 | 0.118    | 0.886    | 2.957      |
| Divorced                      | 0.695     | 0.282    | 0.358    | 1.348     | 0.941                 | 0.775    | 0.618    | 1.431      |
| Widow                         | 1.181     | 0.673    | 0.545    | 2.359     | 0.499                 | 0.097    | 0.220    | 1.135      |
| Education status              | Education status |       |          |          | Education status      |          |          |
| No formal                     | Reference |          |          |          | Reference             |           |          |
| Primary                       | 0.686     | 0.056    | 0.466    | 1.010     | 0.635                 | 0.007    | 0.456    | 0.884      |
| Secondary                     | 1.372     | 0.178    | 0.866    | 2.174     | 0.635                 | 0.007    | 0.456    | 0.884      |
| Graduation                    | 1.219     | 0.581    | 0.603    | 2.466     | 0.635                 | 0.007    | 0.456    | 0.884      |
| Monthly income, RM            | Monthly income, RM |       |          |          | Monthly income, RM    |          |          |
| ≤1,000                        | Reference |          |          |          | Reference             |           |          |
| 1,000–2,000                   | 1.484     | 0.091    | 0.939    | 2.346     | 1.618                 | 0.118    | 0.886    | 2.957      |
| 2,001–3,000                   | 1.182     | 0.679    | 0.536    | 2.606     | 0.941                 | 0.775    | 0.618    | 1.431      |
| >3,000                        | 0.857     | 0.762    | 0.316    | 2.326     | 0.499                 | 0.097    | 0.220    | 1.135      |
| Smoking                       | Smoking   |          |          |          | Smoking               |          |          |
| Smoker                        | Reference |          |          |          | Reference             |           |          |
| Nonsmoker                     | 1.304     | 0.103    | 0.948    | 1.796     | 1.618                 | 0.118    | 0.886    | 2.957      |
| Alcohol                       | Alcohol   |          |          |          | Alcohol               |          |          |
| Alcoholic                     | Reference |          |          |          | Reference             |           |          |
| Nonalcoholic                  | 1.189     | 0.294    | 0.860    | 1.645     | 0.941                 | 0.775    | 0.618    | 1.431      |
| IVDU                          | IVDU      |          |          |          | IVDU                  |          |          |
| Yes                           | Reference |          |          |          | Reference             |           |          |
| No                            | 2.583     | <0.001   | 1.718    | 3.885     | 2.376                 | <0.001   | 1.541    | 3.664      |
| Risk factors                  | Risk factors |       |          |          | Risk factors          |          |          |
| Heterosexual                  | Reference |          |          |          | Reference             |           |          |
| Homosexual                    | 1.221     | 0.558    | 0.627    | 2.376     | 0.499                 | 0.097    | 0.220    | 1.135      |
| Unknown                       | 0.873     | 0.483    | 0.597    | 1.276     | 0.635                 | 0.007    | 0.456    | 0.884      |

Using logistic regression. HIV, human immunodeficiency virus; HCV, hepatitis C virus; IVDU, intravenous drug user.
In the present study, there is no statistically significant difference observed in HIV monoinfected and HIV-HCV coinfected study participants. However, a mean CD4 count of 230 cells/mm³ was found in HIV-HCV coinfected patients. Similar studies were conducted in Nigeria and India in which the mean CD4 count was reported as 260 cells/mm³ and 288.6 cells/mm³, respectively [14, 19]. The mean CD4 count of HIV-HCV coinfected patients was relatively lower than that of the HIV monoinfected study participants. This low CD4 count may be due to increased HIV and HCV replication, indicating the immunosuppressed state.

A significant difference was observed in the mean levels of liver enzymes between the HIV monoinfected and HIV-HCV coinfected patients as shown in Table 2. There is an increase in the levels of liver enzymes in HIV-HCV coinfected patients as compared to HIV monoinfected patients. In a similar way, a study carried out in South Africa reported that 70% of HIV-HCV coinfected patients have significant elevated ALT and AST levels as compared to HIV monoinfected patients [20]. Similarly, a study conducted in India reported a significant elevated ALT level in 20% of the HIV-HCV coinfected patients [14]. The differences in the levels of liver enzymes of the coinfected patients in different studies may be due to the duration of viral hepatitis as well as patient’s social habits of alcoholism or drug addiction that further develops in liver fibrosis and elevated liver enzymes.

The statistically significant predictors involved in treatment outcomes of HIV-HCV coinfected patients are gender (OR = 3.818, p = 0.011), smoking (OR = 0.528, p = 0.025), and IVDUs (OR = 4.342, p ≤ 0.001) as shown in Table 5. Similar studies in different parts of the world reported that smoking and needle sharing for drugs were the strongest predictors in the treatment outcomes of the HIV-HCV coinfected patients [21–23].

**Strengths and Limitations of the Study**

There are some limitations of the present study that should be considered when interpreting the study findings. The first and the most obvious limitation of the present study is the retrospective study design. However, the study was unable to supplement information with prospectively collected data acquired during other prospective studies. Furthermore, the extent of liver damage among viral hepatitis-positive participants could not be determined because liver biopsies were not performed. Other limitations might include the lack of liver biopsy and genotype data for hepatitis cases and relatively short follow-ups. In addition, these data will only represent the population found in Hospital Pulau Pinang and therefore will not represent the whole Malaysian population.

**Conclusion**

The current study shows that HCV infection has an impact on the recovery of CD4 cells of the patients on HAART. Screening of HCV among HIV patients who were smokers and IVDUs should be monitored before starting HAART.

**Statement of Ethics**

The current study was conducted after the approval from the National Institutes of Health and Medical Research and Ethics Committee, Malaysia (NMRR-13-1284-16473). As it is a retrospective cross-sectional study, data were collected from the medical records, so there was no need of consent from the patients.

**Conflict of Interest Statement**

The authors state that they have no conflicts of interest.

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None.

**Author Contributions**

A.A. was the principal investigator of the study, designed the study protocol, collected the data from the hospital, and wrote the manuscript. A.H.K. was the supervisor and supervised the whole study. H.S. was the co-supervisor and helped in data analysis. C.T.S. was the field supervisor in the hospital and helped in the collection of data from the hospital. S.F. helped in formatting of the manuscript and data collection. All authors read and approved the final manuscript.

**Data Availability Statement**

All the required data is available within the article.
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