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Correlates Associated with Hepatitis C Treatment in Individuals Coinfected with the Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV)

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Correlates Associated with Hepatitis C Treatment in Individuals Co-infected with the Human Immunodeficiency Virus (HIV) and Hepatitis C (HCV)

by

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DISSERTATION

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CORRELATES ASSOCIATED WITH HEPATITIS C TREATMENT IN ADULT INDIVIDUALS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND HEPATITIS C (HCV)

By

Renee Pozza, RN, MSN, APRN, BC

ABSTRACT

Background: Hepatitis C (HCV) infection is reported in approximately 30% of HIV infected patients. Treatment of HCV is crucial to prevent liver decompensation and/or liver failure; however, rates of HCV treatment in this patient population are extremely low. Referral rates for HCV evaluation range from 10-40%, with initiation of therapy at <20%.

Purpose: To determine the patient factors associated with liver disease referral and evaluation for hepatitis C treatment in a cohort of HIV/HCV coinfected individuals.

Methods: A retrospective cohort study was conducted to collect patient demographics, HIV and HCV disease severity, major medical comorbidities, mental health status, substance use, and social context from a group of adult HIV/HCV coinfected individuals seen at a large university based HIV clinic from January 1, 2003 to December 31, 2006. Descriptive statistics, univariate and multivariate logistic regression determined group differences between those referred for HCV evaluation with those not referred (paper three), and between those referred for HCV evaluation who attended their appointment with the group that was nonadherent to liver evaluation (paper four).

Findings: A cohort of 538 HIV/HCV coinfected patients were analyzed for this study. A total of 308 patients (57%) were referred for liver disease evaluation by their HIV provider. In the referred group, 224 patients were seen and evaluated for possible HCV treatment, of which 79 patients went on to receive HCV treatment. Of those patients referred, 84 patients did not attend their liver disease clinic appointment. No referral was received in 230 HIV/HCV coinfected patients.

In the analysis between the HIV/HCV coinfected patients referred for evaluation with those not referred, significant differences were found in liver disease severity, cardiac disease, history of skin cancer, antiretroviral therapy use, psychiatric evaluation, current substance use, homelessness, and history of incarceration. Factors that remained significant in multivariate analysis included liver disease markers, homelessness, and incarceration. For those patients who did not attend liver disease evaluation, differences included age, cirrhosis, current substance use, incarceration, psychiatric evaluation, and nonadherence to HIV medications and/or visits, with only incarceration and psychiatric evaluation remaining significant in multivariate analysis.

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Introduction

In the United States approximately 1 million individuals are infected with the human immunodeficiency virus (HIV). Of those individuals infected with HIV, it is estimated that 30% are also coinfected with the hepatitis C virus (HCV) (Sulkowski, Thomas, 2003; CDC, 2002; Sherman, Roustrer, 2000). In those individuals who contracted their HIV infection through intravenous drug use, studies report a coinfection rate of 70-90% (Sulkowski, et al., 2003). Hepatitis C infection is caused by a single-strand RNA virus that causes inflammation in the liver, liver fibrosis and ultimately end stage liver disease (Talal, Canchis, Jacobson, 2002). Transmission is primarily through blood contact with an infected source (CDC, 2002).

In the HIV infected individual, HCV is considered an opportunistic infection and is one of the leading causes of morbidity and mortality in these patients (Nunez, Soriano, 2004; Martagon, Gordon, 2003). Recent studies demonstrate the progressive rapid nature of liver disease associated with the hepatitis C virus in the HIV/HCV coinfected individual (Pineda, Macias, 2005). In the setting of HIV, HCV behaves more aggressively, with higher rates of viral replication and higher degrees of liver damage (Martagon, et al., 2003). Since the advent of antiretroviral therapy for suppression of HIV, HCV is the leading cause of hospital admissions and death in these patients (Bica, McGovern, Dhar, et al., 2001). Due to the aggressive nature of HCV in the HIV/HCV coinfected individual, national guidelines recommend that all HIV infected patients be screened for HCV (Soriano, Sulkowski, Bergin, 2002; USPHS/IDHS, 1999). Screening is done by

HCV antibody testing through a third generation enzyme-linked immunosorbent assay (ELISA) that has a predictive value of >95% in HIV/HCV coinfected individuals (Pawlotsky, 2002; Bonacini, Lin, Hollinger, 2001; Thio, Nolt, Astemborski, et al., 2000). If found to be HIV/HCV coinfected, appropriate evaluation and testing is recommended to determine HCV treatment candidacy (Alberti, Clumeck, Collins, et al, 2005; Tossing, 2005).

The goal of HCV treatment is to eradicate the hepatitis C virus and halt the progression of liver disease and its associated complications. This can be accomplished in approximately 40-50% of patients with HIV/HCV coinfection (Torriani, Rodriquez-Torres, Rockstroh, et al., 2004). The current approved treatment regimen consists of pegylated interferon, given as weekly subcutaneous injections with ribavirin, a twice daily oral medication, for a period of 48-72 weeks. A successful treatment outcome is a sustained virologic response (SVR) and is determined by negative HCV viral load testing six months after the cessation of medication therapy. HCV treatment is not benign. It is associated with multiple side effects that may occur in varying degrees anytime during the treatment course. Because of the associated side effects, not all patients will be considered candidates for HCV treatment. National guidelines have listed those conditions which are considered contraindications for therapy, those that are relative contraindications and those factors that may be treated or supported prior to the initiation of therapy to ensure good outcomes (Albert, Clumeck, Collins, et al, 2005; Tossing, 2005).

In the HIV/HCV coinfected patient, priority is given to the HIV disease and if HIV treatment is necessary this should be started and stabilized prior to initiation of any HCV treatment regimen. However, due to the accelerated and progressive nature of HCV-associated liver disease, HIV/HCV coinfected patients should be evaluated to determine treatment candidacy. There is not one universally accepted model established to provide this evaluation for the HIV/HCV coinfected patient. Several models of care have been proposed in the current literature (Wagner, Ryan, 2005; Clanon, Mueller, Harank, 2005; Litwin, Soloway, Gourevitch, 2005). These include comanagement between infectious disease and hepatology providers, management by infectious disease providers only, and HCV disease management performed by addiction medicine specialists. It remains to be determined which system is most effective.

There are several challenges that arise in the management of HCV in the HIV/HCV coinfected patient. These include screening, diagnosis and evaluation of HCV in this patient population, as well as in the actual HCV treatment regimen. Historically, evaluation for liver disease and ultimately HCV treatment has been low in this patient population (Clanon, et al., 2005; Fleming, Craven, Thornton, et al., 2005; Rauch, Egger, Reichen, et al., 2005; Fultz, Justice, Butt, et al., 2003). Factors associated with this include provider perceptions, knowledge and familiarity with HCV treatment, access to care and associated system issues as well as patient factors that lead to poor referral rates, poor evaluation of liver disease, and poor HCV treatment rates in HIV/HCV coinfected patients. Due to the nature of HCV treatment with its associated side effects and added treatment

burden, adherence to therapy is an issue. This dissertation attempts to explore some of these HCV evaluation and treatment issues in HIV/HCV coinfected patients.

The overall aim of the dissertation is to describe the factors affecting HCV management in the HIV/HCV coinfected patient population. The methods used to do this are as follows; 1) describe the treatment regimen for hepatitis C management in the HIV/HCV coinfected individual, 2) identify adherence issues related to HCV therapy, 3) describe patient factors that influence referral patterns for liver disease evaluation, and finally, 4) describe patient factors that influence adherence to initial liver clinic evaluation appointment. In order to identify patient factors that influence referral and evaluation for liver disease in HIV/HCV coinfection, a retrospective cohort study was conducted. Subjects from a large urban HIV clinic in the Southern California area were identified. In order to be included in the study, all identified subjects were HIV and HCV antibody positive and were seen in the HIV clinic at least once from January 1, 2003 to December 31, 2006. Patient factors were collected through chart review and data base extraction to identify demographics, disease severity for HIV and HCV, medical comorbidities, psychosocial characteristics, and social context.

Within this comprehensive HIV clinic experienced hepatology providers conduct weekly liver disease evaluation and management clinics. The date of referral for liver disease evaluation from the HIV provider to the liver disease evaluation clinic and the date of actual liver disease evaluation were collected as outcome variables. Descriptive statistics and logistic regression were utilized to

determine patient factors that influenced referral and evaluation for liver disease management in this patient cohort of HIV/HCV coinfected individuals.

The first chapter (Chapter 1) is titled: “Clinical Management of HIV/HCV Coinfection.” The text of this chapter has been submitted for publication and is in revisions with the Journal of the American Association of Nurse Practitioners (JAANP). The article presents a state of the science review of liver disease management for hepatitis C in patients with HIV/HCV coinfection. A review of the literature regarding current HCV treatment regimens and HCV treatment related side effects are included in this article.

The second chapter (Chapter 2) is titled: “Adherence to Therapy: Challenges in HCV Infected Patients.” The text of this chapter has been accepted for publication and will be published in Current Hepatitis Reports (Vol. 6, No. 4). Permission has been granted to include this chapter as part of the dissertation. This article reviews the current literature in the field of adherence research and its application to hepatitis C treatment. The Ickovics and Meisler Model of Adherence is applied in the care of patients undergoing treatment for hepatitis C.

The third chapter (Chapter 3) is titled: “Factors Influencing Referral Patterns for Liver Disease Evaluation in HIV/HCV Coinfection,” by Pozza, Padilla, Holzemer, et al, (In committee review) and will be submitted to the Journal of Clinical Infectious Diseases. This study was conducted to explore the differences between a cohort of HIV/HCV coinfected patients who were referred for liver disease evaluation with a group of patients who were not referred for evaluation. Patient factors such as demographics, disease severity, medical

comorbidities, mental health issues, substance use, and social context were all identified in order to determine patient characteristics that influenced referral for liver disease evaluation.

The fourth chapter (Chapter 4) is titled: “Adherence Issues with Liver Disease Evaluation in HIV/HCV Coinfected Individuals,” by Pozza, Padilla, Holzemer, et al, (In committee review) and will be submitted to Journal of the Association for Nurses in AIDS Care. This analysis explored the patient factors associated with nonadherence to liver disease evaluation after referral from HIV providers in a cohort of HIV/HCV coinfected patients. The study compares a cohort of HIV/HCV coinfected patients who were referred for and underwent liver disease evaluation with a cohort of HIV/HCV coinfected patients who were referred but never attended their liver clinic appointment. This article also includes information regarding HCV treatment in those candidates determined eligible for HCV treatment, as well as reasons for non-eligibility as documented by hepatology providers.

Finally, the fifth chapter (Chapter 5) summarizes findings from the previous articles, identifies gaps in knowledge about adherence to HCV treatment, and outlines the next phase of research in issues in the management of patients with HIV/HCV coinfection.

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Chapter I: Clinical Management of HIV/HCV Coinfection

Clinical Management of HIV/HCV Coinfection

Abstract

Purpose: To review the current management of hepatitis C (HCV) virus in persons coinfected with HIV.

Data Sources: Comprehensive review of current scientific literature derived from electronic databases, article bibliographies and conference abstracts.

Conclusions: Hepatitis C treatment is feasible in the HIV/HCV coinfected individual; however, therapy is complex and requires intensive monitoring and support to achieve the outcome of viral eradication. New strategies to improve HCV treatment rates, adherence to therapy and virological response rates are needed in this patient population.

Implications for Practice: Nurse practitioners are crucial to the management of the HIV/HCV coinfected patient. This patient population needs detailed clinical monitoring, education, side effect management and strategies to improve adherence to therapy.

Key Words: Hepatitis C, HIV, Coinfection, HCV therapy, Adherence

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Introduction

Infection with the Hepatitis C virus (HCV) is quite common among the HIV population. It is estimated that approximately 25-30% of those infected with the HIV virus are also infected with HCV (CDC, 2002; Sherman & Roustrer, 2000). For those individuals who contracted their HIV as a result of intravenous drug use, studies estimate that at least 50% to 90% are infected with HCV (Garlein, Vlahov, Galai, Doherty & Nelson, 1996; Ockenga, 1997). During the last decade and since the advent of the highly active antiretroviral therapy, chronic liver disease became one of the most common causes of morbidity and mortality in HIV/AIDS patients (Martagon, Gordon, 2003; Nunez, Soriano, 2004). Management of chronic liver disease in these patients is essential to prevent further complications, cirrhosis and liver decompensation (Pineda & Macias, 2005).

Overview of Hepatitis C

Hepatitis C infection is caused by a single stranded RNA virus from the Flaviviridae family (Talal, Canchis, Jacobson, 2002). Approximately four million people are infected with the hepatitis C virus in the United States (Alter, Kruszon-Moran, Nainan, McQuillan, Gao, & Moyer, 1999; CDC, 1997). The World Health Organization (1998) attributes hepatitis C infection to 170 million individuals worldwide and the disease ranks 11th in prevalence in the world. Of those acutely infected with the hepatitis C virus about 85% will go on to develop chronic infection. Infection with hepatitis C progresses to cirrhosis and hepatocellular carcinoma and is the main reason for liver transplantation in the United States. Infection rates are higher in minority populations, such as African Americans and Latinos. Sixty-five percent of HCV infection is found in

young adults ages 30-49 (Alter, et al., 1999; CDC, 1997). Parenteral exposure is the most effective route of transmission, and the most common identified risk factors for contracting hepatitis C are intravenous drug use and receiving blood products prior to 1992. Other risk factors include, high risk sexual behaviors, intranasal cocaine use, hemodialysis, occupational exposure, but rarely from tatoos and body piercings. The risk of sexual transmission is felt to be relatively low (CDC, 1997) except in the HIV/HCV co-infected population. Vertical transmission rates are usually low at 0-7%; however, in the co-infected population transmission from mother to baby is higher at rates reaching 25% (Bonacini, Puoti, 2000). In a meta-analysis the risk estimate was found to be 2.82 (95% CI, 1.78-4.45; P=0.00001) from HIV/HCV co-infected mothers compared with HCV positive mono-infected mothers (Pappalardo, 2003).

The hepatitis C virus has been classified into at least six genotypes and more than 50 subtypes (Major, Feinstone, 1997). The most common genotype in the United States is genotype 1 infection which occurs in 75% of the patients (Alter, et al., 1999; CDC, 1997). Most individuals do not experience any symptoms from the infection and accordingly are not aware of it. The main mechanisms responsible for liver injury in HCV infection are not well understood; however, it is becoming clearer how the hepatitis C virus escapes cellular and humoral immune responses (Phillips, Brewer, 2003). HCV main targets are the hepatocytes and possibly B lymphocytes. The rapid replication and high mutation rate of the hepatitis C virus and its ability to inhibit innate interferon stimulated genes may be responsible for the evasion of the immune system and persistence of the infection resulting in chronic liver cell injury (Phillips, et al., 2003; Talal, et al., 2002). HCV-infected hepatocytes may produce as many as 10 trillion virions

per day during the chronic phase of infection, which is greater than that seen with HIV (Zignego, DeCarli, Monti, Careccia, LaVilla, & Giannini, 1995). Mortality results from progressive hepatic fibrosis, cirrhosis and its associated complications (Talal, et al., 2002).

Influence of HIV on HCV

It is estimated that in the setting of HIV, HCV behaves more aggressively, with higher rates of viral replication and higher degrees of liver damage (Martagon, et al., 2003). This leads to; 1) lower rates of spontaneous HCV infection clearance, 2) high viral load, 3) rapid progression of liver fibrosis, 4) increased incidence of cirrhosis, 5) higher rates of liver decompensation after developing cirrhosis, and 6) possibly earlier development of hepatocellular carcinoma (Martagon, et al., 2003).

Progression of Fibrosis in the HIV/HCV Co-infected Individual

Cirrhosis is the end stage complication associated with hepatitis C. It will occur in approximately 20-25% of patients with mono-infection within 20 years of becoming infected with the virus (EASL International Consensus Conference on Hepatitis C, 1999; Feray, Samuel, Gigou, Paradis, David, & Lemonnier, 1995; Lauer, Walker, 2001; NIH, 1997). There have been conflicting data in determining the rate of progression to cirrhosis in the co-infected individual. In a study by Benhamou, et al. (1999) faster progression to fibrosis was reported in the co-infected patient particularly in patients with low CD4 counts (<200/mm), excessive alcohol use (>50 gm/day) and increased age at the time of infection. Mohsen, et al. (2003) found that HIV accelerates liver fibrosis progression 1.4 fold. A further study in Europe found that severe fibrosis was more prevalent in the co-infected population, and fibrosis was associated with increased ALT levels (Martin-

Carbonero, Benhamou, Puoti, 2004). However, two other published studies found no significant progression of fibrosis in the co-infected patients when compared to mono-infected patients (Mehta, Thomas, Torbenson, Brinkley, Mirel & Chaisson, 2004; Sterling, Contos, Sanyal, Luketic, Stravitz & Wilson, et al., 2003). In a study by Monto, there was no difference between the degree of fibrosis or the rate of progression between the co-infected patients and the HCV mono-infected patients (Monto, Kakar, Dove, Bostrom, Miller & Wright, 2006). In a retrospective cohort study of Veterans no difference in cirrhosis was found between HCV/HIV co-infected individuals vs. HCV mono-infected individuals when comparing pre-HAART vs HAART eras, but more cirrhosis was identified in the HAART era (Kramer, Giordano, Soucheck, Richardson, Hwang & El-Serag, 2005). Since acceleration of liver fibrosis seems to be related to the degree of immunodeficiency, there is some evidence that this process may be slowed by the immune reconstitution seen with HAART (Shafran, 2007; Pineda, et al., 2005). In a number of studies, HAART has been shown to reduce liver-related mortality in the co-infected patient (Shafran, 2007; Carosi, Puoti, Antonucci, DeLuca, Maserati & Torti, 2005; Bonacini, 2004; Qurishi, Kreuzberg, Luchters, et al., 2003).

Influence of HCV on the Course of HIV Infection

Researchers have examined whether there is an influence of HCV on the course of HIV disease progression with mixed results. Some have demonstrated an association between HCV infection and faster HIV disease progression, while others have not (Daar, Lynn, Donfield, Gomperts, O'Brien & Hilgartner, et al., 2004; Rockstroh, Konopnicki, Soriano, et al., 2004; Llibre, Garcia, Aloy, Valls, 1993; Quan, Krajden, Grigoriew, Salit, 1993; Wright, Hollender, Puo, 1994; Dorrucci, Pezzotti, Phillips, Cozzi-Lepri, Rezza,

1995; Sabin, Teller, Phillips, Bhagani, Lee, 1997; Piroth, Duong, Quantin, 1998; Lessens, Deschenes, Steben, Belanger, Tsouks, 1999). Recent analyses of large data bases which corrected for use of antiviral therapy suggest no negative effect of HCV co-infection on HIV infection (Rockstroh, et al., 2004; Sulkowski, Moore, Mehta, et al., 2002). In relation to the CD4+ count in co-infected individuals, some studies show that co-infected patients have lower CD4+ counts when compared to HIV mono-infected patients, despite similar HIV RNA levels; however, another study failed to show any difference (Moreno, Dronda, 2002; Tedaldi, Baker, Moorman, et al., 2003). HCV may also negatively influence HIV disease through subjection of infected patients to drug toxicities from HAART therapy, requiring drug discontinuation. One study found that the risk of developing HAART related-liver toxicities was 3.7 times greater in co-infected patients compared to HIV mono-infected patients (Sulkowski, Thomas, Chaisson, Moore, 2000). Nunez, et al., observed that this occurs more in patients with Genotype 3, possibly due to the greater steatosis associated with this genotype (2002).

Studies have shown that use of certain protease inhibitors (PI) (ritonavir) and non-nucleoside reverse transcriptase inhibitors (NNRTI) (nevirapine) might increase the risk of hepatotoxicity in co-infected individuals and should be avoided (Dieterich, Robinson, Love, Stern, 2004; Sulkowski, et al., 2000). However, a retrospective analysis done by Sterling et al. (2004) did not find any correlation between use of PI's and NNRTI's and biochemical and histological liver disease. The use of "d-nucleosides" (didanosine, dideoxycytidine) lead to higher rates of hepatic steatosis in the co-infected population and should also be avoided (Sulkowki, Mehta, Moore, 2004; Montessori, Harris, Montaner, 2003). However, recent cohort analyses have shown that immune reconsititution induced

by HAART can improve the course of hepatitis C leading to a decline in liver-related mortality (Rockstroh, et al., 2004). Overall, the benefits of HAART therapy far outweigh the risks of hepatotoxicity which is estimated to occur in 10% of patients (Sulkowski, et al., 2000; Sulkowski, Thomas, Mehta, 2002) and should be offered to HIV/HCV co-infected patients in accordance with the general guidelines for ART in adult patients (Carosi, et al., 2005; Rockstroh, et al., 2004; Yeni, Hammer, Carpenter, et al., 2002).

Diagnostic Testing Available for Hepatitis C

Several laboratory and diagnostic tests may be performed to diagnose hepatitis C infection and determine severity of liver disease. Guidelines published (1999) by The United States Public Health Service (USPHS) and the Infectious Disease Society of America recommend that all HIV-infected individuals be screened for HCV. Available screening tests include detecting HCV antibodies using an enzyme-linked immunosorbent assay (ELISA), or a radioimmunoblot assay (RIBA). This will determine if there has been exposure to the virus, but will not determine viremia or severity of disease. There has been some concern that due to the HIV associated immunodeficiency, false negative ELISA results may be found. However, recent studies have shown that the predictive value of the anti-HCV antibodies detection by the third generation ELISA test is >95% in the HIV/HCV co-infected individuals (Pawlotsky, 2002; Bonacini, Lin, Hollinger, 2001; Thio, Nolt, Astemborski, et al., 2000). Accordingly, third generation ELISA tests screen for HCV in the co-infected individual (Bonacini, et al., 2001; Thio, et al., 2000). Detecting viremia is done by measuring the HCV RNA by polymerase chain reaction (PCR) or branched chain DNA (b-DNA) technology or transcription-mediated amplification (TMA). TMA offers a lower limit of detection to approximately 5-10 IU/ml

(Gish, 2004). HCV RNA detection could be reported as positive or negative (qualitative result) or a value is given which reflects an estimate of the viral load (quantitative results). Overall, higher concentrations of HCV RNA are found in HIV seropositive individuals than in HIV seronegative patients (Sherman, O'Brien, Gutierrez, et al., 1993; Cribier, Rey, Schmitt, et al., 1995). So far, there is no direct correlation between the viral load of HCV RNA in serum and HCV pathogenesis; however, low HCV viral load is one of the predictors of an increased likelihood to respond to treatment (McHutchinson, Gordon, Schiff, et al., 1998; Talal, et al., 2002). Viral genotyping is then performed to determine the appropriate length of drug therapy; however, the different genotypes have no effect on the disease progression.

Liver transaminases such as ALT and AST are not good markers of active disease and not accurate in up to 20% to 30% of patients with active HCV replication, where ALT will repeatedly remain normal (Nunez & Soriano, 2004). A subgroup of patients with HCV have normal aminotransferase levels despite clinically significant fibrosis or cirrhosis (Stanley, Haydon, Piris, et al., 1996). A study by Gonzalez (2006), found that the percentage of HIV/HCV co-infected individuals with advanced necroinflammation was similar whether the patient had normal or elevated ALT levels.

Once infection is confirmed, further testing is pursued to determine the extent of liver damage and disease severity. To determine degree of inflammation and fibrosis in the liver itself, a liver biopsy may be performed. Liver biopsy is the most specific test for grading and staging the disease (Bravo, She, Chopra, 2001). The biopsy is graded on the degree of inflammation present and on the stage of fibrosis (Bedossa, Poynard, 1996; Brunt, 2000). There are numerous scoring systems for grading and staging the disease, of

which the Ishak, Knodell and Metavir scores are the most common (Knodell, Ishak, Black, et al., 1981; Bedossa, 1994; Ishak, 1996) (See Table 1.1).

The need for a liver biopsy in every patient is controversial. Recently several models using laboratory measurements to determine degree of fibrosis in the co-infected patient have been proposed, as well as methods to determine liver elasticity such as the FibroScan; however, most hepatologists recommend the liver biopsy to assess disease severity, plan and time therapy, and determine the prognosis of patients and their follow-up (Al-Mohri, Cooper, Murphy, Klein, 2005; Sterling, Lissen, Clumeck, Sola, Correa & Montaner, 2006; Fouscher, Chanteloup, Vergniol, 2006).

To summarize, aminotransferase and HCV RNA levels have a poor correlation with the extent of histological disease (Talal, et al., 2002), and despite sampling errors, liver biopsy is still the gold standard for grading and staging of the disease and determining the need and timing of therapy. Treatment should be aggressively pursued in those individuals with fibrosis of the liver.

Determining Candidacy for Treatment for Hepatitis C infection in the HCV/HIV Co-infected Patient

Once the evaluation of the HCV is completed, there are several factors that must be considered in determining candidacy for therapy. Disease severity and comorbidities are the main factors for initiation of therapy. To optimize the outcome of therapy and increase viral response, patients are encouraged to adhere to therapy. This goal can be optimized by educating the patients about the disease and its complications and the importance of avoiding drug interruptions. Managing comorbidities and aligning family and social support helps adherence to therapy. Social support systems need to be explored

and optimized, client education and comorbidities should be addressed prior to initiating therapy. Recent international expert panels convened to determine guidelines for initiating HCV therapy and for monitoring response to therapy (Soriano, Sulkowski, Bergen, et al., 2002; Soriano, Puoti, Sulkowski, et al., 2004; Tossing, 2005; Alberti, Clumeck, Collins, Gerlich, Lundgren, Palu, et al., 2005). Their recommendations:

1) HCV treatment should be recommended primarily on the basis of fibrosis (F1-F4) or fibrosis markers in combination with raised serum aminotransferases and positive HCV RNA results.
2) The therapy of choice is the combination of pegylated interferon and ribavirin.
3) Ideal candidates for anti-HCV therapy are patients with CD4-cell counts >350 cells/ul and plasma HIV RNA <50,000 copies/ml, with or without HAART.
4) In patients with CD4-cell counts <350/ul, anti-HCV therapy should be initiated only with caution; ideally HAART should be optimized first.
5) Patients with CD4-cell counts <100-200/ul should receive HAART first before HCV-specific therapy can be initiated.
6) The treatment duration for all HCV genotypes should be 48 weeks.
7) Early virological response to anti-HCV therapy predicts the chance of sustained response; if there is no decrease in serum concentrations of HCV RNA of >2 log after 12 weeks, treatment can be discontinued because of the low likelihood of reaching sustained response.
8) The concomitant use of didanosine and ribavirin should be avoided.

9) Combination of zidovudine or stavudine with ribavirin may increase toxicity; regular follow-up and laboratory safety monitoring are warranted (Rockstroh, Spengler, 2004; Tossing, 2005).

Current Therapies for HCV in the Co-infected Individual

Achieving sustained virological response (SVR) in the co-infected patient is feasible. The results of numerous trials reporting SVR rates have been published. Three major randomized controlled clinical drug trials have been reported in the literature. These studies evaluated the safety and efficacy of pegylated interferon plus ribavirin in the co-infected population. All three of these studies provided 48 weeks of therapy to patients regardless of their genotype (Nunez, et al., 2004). Table 1.2 demonstrates study design and efficacy results for these studies in addition to other smaller trials that have been reported.

The ACTG 5071 trial included 66 patients randomly assigned to receive Peginterferon alfa-2a (Pegasys) 180 mcg SQ weekly along with ribavirin at a dose of 600mg which was increased up to 1000mg 12 weeks later if tolerated. Seventy-seven percent of the patients were Genotype 1, which tends to have a lower response rate to interferon. End of treatment response (ETR) was 41%; however, sustained virological response (SVR) was maintained by 27%. Of those, 14% were in Genotype 1 and 73% were other genotypes (Chung, Andersen, Volberding, Robbins, Liu, Sherman, et al., 2004).

The RIBAVIC trial was a multicenter French cohort which included 205 coinfected patients, each who received weight-adjusted dose (1.5ug/kg/wk) of pegylated interferon alfa-2b (PegIntron) and a fixed dose of 800mg of ribavirin per day. The overall

SVR in this study was 27% (Carrat, Bani-Sadr, Pol, Rosenthal, Lunel-Fabiani, Benzekri, et al., 2004).

The APRICOT trial was the largest multicenter study conducted with 289 patients receiving pegylated interferon alfa-2a (Pegasys) 180mcg per week plus a fixed dose of 800mg of ribavirin per day. The overall SVR in this trial was 40%; however, it was 29% for the Genotype 1 patient (Torriani, Rodriguez-Torres, Rockstroh, Lissen, Gonzalez-Garcia, Lazzarin, et al., 2004). In the Genotype 2 and 3 patients, the ETR was 64% and the SVR was 62% possibly indicating that extending therapy longer in the co-infected patient may reduce rate of relapse (Nunez, et al., 2004).

All three of these trials indicate that the treatment of choice in the HIV/HCV co-infected patient is pegylated interferon and ribavirin. However, response rates for these patients are lower than observed in the mono-infected HCV patients, which have been reported at 54-56% in several large trials (Manns, McHutchinson, Gordon, et al., 2001; Fried, Shiffman, Reddy, et al., 2002). Several mechanisms to explain this have been proposed, including the immune system defects caused by the HIV infection which negatively impact the performance of these immunomodulating drugs (Nunez, et al., 2004). In addition, the three studies used lower doses of ribavirin than recommended for HCV monotherapy. Other factors which may account for lower response rates include poor adherence, larger discontinuation rates in several of the trials (over 30%), more advanced fibrosis, higher viral loads, inadequate T cell response, higher relapse rates, and more steatosis related to alcohol use and antiretrovirals (Frederick & Hassanein, 2004). In the large clinical trials related to antiviral treatment for HCV mono-infection five independent characteristics have been associated with a sustained virological response: 1)

HCV infection with genotype 2 or 3, 2) a baseline viral load less than 3.5 million copies/ml, 3) no or minimal baseline fibrosis on liver biopsy, 4) being of female gender, and 5) age less than 40 years at time of infection (Talal, et al., 2002; McHutchinson, et al., 1998). Predictors determined by the FDA in 2002 using multivariate analysis techniques included genotype, viral load, age, serum ALT, baseline histology, race, weight, ribavirin dose, treatment duration, geographic region and gender. It remains to be determined what the predictive factors for virological response are in the co-infected population. More studies are needed to evaluate the use of higher doses of ribavirin and longer treatment duration in the co-infected population (Mauss, Rockstroh, 2005).

Goal of Therapy and Measurement of Response

Many patients and providers are apprehensive about starting medication treatment for hepatitis C due to the potential drug side effects and possible drug interactions with HIV medications. Unlike HAART or ART therapy, where the goal is viral suppression of the human immunodeficiency virus and the risk is the development of resistance, the goal in drug treatment for the hepatitis C virus is viral eradication. Because the hepatitis C virus does not have a nuclear phase during its replication cycle and does not integrate into the host genome as HIV does, HCV eradiction is a realistic therapeutic goal (Talal, et al., 2002). In long-term follow-up studies individuals who have achieved a sustained virological response are very unlikely to have hepatitis C recurrence (Lau, Kleiner, Chany, et al., 1998; Marcellin, Boyer, Cervais, et al., 1997).

Response to medication therapy may be measured in several ways. The primary measurement is done by determining viral load, usually by measuring HCV RNA at several time points during the course of treatment. All of the major clinical trials in which

pegylated interferon and ribavirin were used considered early virologic response (EVR) at week 12 as an indicator for response. If patients have not achieved a negative viral load or a 2 log drop in HCV RNA levels by week 12, the likelihood of a sustained virological response (SVR) is 1-2% (Chung, et al., 2004, Carrat, et al., 2004, Torriani, et al., 2004). At this point, medication therapy may be stopped if the goal for therapy is viral eradication. There is some interest in determining the prognostic value of achieving a rapid virological response (RVR), defined as negative HCV RNA at week 4. Week 4 HCV viral negativity could predict the recommended duration of therapy when using pegylated forms of interferon in combination with ribavirin. However, in one small study researchers suggested that co-infected individuals have a slower rate of HCV clearance, therefore more data are needed to determine correlation with SVR and to make treatment decisions based on this response (Moreno, Barcena, Garcia-Garzon, Moreno, Quereda, Muriel, et al., 2006). Biochemical response is measured by normalization in the AST and ALT levels; however, they are only used to detect tolerance to therapy. Transaminases may increase after initiation of therapy in some patients, particularly in patients with cirrhosis and hepatic steatosis. Histological response is detected by repeat liver biopsy, though this is rarely done in clinical practice.

Common Side Effects and their Management

Side effects to HCV therapy may contribute to lower response rates, early discontinuation of therapy or dose reduction, and poor adherence rates to therapy and/or clinic visits. Table 1.3 provides a list of the common side effects and some management strategies to assist patients in coping with the effects of the therapy. Some of the side effects are due to the interferon while others have been associated with the ribavirin

therapy. Both drugs carry a black box warning, and providers should read the package insert to become familiar with the warnings.

The most commonly reported side effect due to the interferon treatment is fatigue and flu-like symptoms, such as low grade fever, myalgias, arthralgias, and rigors. These symptoms are worse in the first few weeks after initiating therapy and should decrease as time progresses. Use of limited doses of Tylenol or non-steroidal anti-inflammatory drugs in non-cirrhotics may be helpful, especially one hour prior to the injection time. The injection can be timed for administration at bedtime so the patient sleeps through most of the side effects. Fluid therapy becomes critical for alleviating these symptoms. An increase in water intake is recommended.

Another common side effect due to interferon therapy is depression (Schering and Roche package inserts). Several studies have shown that patients with HCV mono-infection and HIV/HCV co-infection have a higher incidence of depression prior to initiating interferon therapy (Hauser, 2004; Braitstein, 2005). This is especially true in patients with a substance abuse history (Zdilar, Franco-Bronson, Buchler, Locala, Younossi, 2000; Cheung, Ahmed, 2001; El-Serag, Kunik, Richardson, Rabeneck, 2002; Lehman, Cheung, 2002). This becomes further problematic once interferon therapy is initiated. These side effects can result in dose reductions or discontinuation of therapy and can significantly decrease the quality of life (Hauser, 2004). Interferon-induced depression tends to present with a component of anxiety and irritability. These side effects include cognitive, affective and behavioral components that may be challenging to distinguish from each other (Dieperink & Willenbring, 2000). Anti-depressant medications may be initiated several weeks prior to the start of antiviral therapy.

Depression screening tools should be used at each clinic visit to determine presence and severity of depression. Referral to counseling and/or psychiatry may be necessary. If patients have a psychiatric history prior to the start of therapy, some providers recommend psychiatric evaluation and comanagement before initiating therapy.

A common gastrointestinal complaint in the co-infected patient is nausea. This may be caused by the interferon or ribavirin. Timing the ribavirin with food will help mimimize this complaint. Other remedies include having small frequent meals and the use of ginger (ginger ale, ginger snaps, or ginger lollipops), which could help in alleviating the nausea.

Ribavirin has its characteristic side effects such as dry cough, rash, purititis, and anemia. Ribavirin is known to cause birth defects in the developing fetus; accordingly female patients must be screened for pregnancy and need to avoid getting pregnant during therapy and for six months after therapy is completed. Male patients must not father children during and for six months after completion of therapy (Schering and Roche package inserts).

Anemia is a very common side effect due to the ribavirin and could be problematic in the co-infected patient. It is seen early in therapy and within the first 4 weeks a drop of 2-3gm/dl of hemoglobin has been reported in most patients. The anemia is hemolytic in nature due to the lysis of red blood cells caused by the accumulation of the phosphorylated form of ribavirin in red blood cells (McHutchinson & Dev, 2004). Therapy with AZT may further worsen anemia, therefore avoidance of the combination with AZT and ribavirin should be attempted (Frederick, et al., 2004). Many co-infected patients will require the use of growth factors such as erythropoietin to maintain adequate

hemoglobin levels (Dieterich, 2002; Fredrick, et al., 2004). Neutropenia is seen in as many as 95% of patients on antiviral therapy and usually occurs within the first two weeks of therapy (Pegasys package insert). It is mainly induced by the interferon and dose reduction in the interferon or use of growth factors may be helpful to maintain adequate counts, although there are no reports of an increase in infection rates in patients with HCV infection on interferon therapy even if the neutrophil count drops below 750ul/ml (Fredrick, et al., 2004). The overall decrease in absolute CD4+ cell count during interferon and ribavirin therapy reflects the decline in white blood cell counts during therapy; however, the relative percentage of CD4+ cells remains stable or may increase during combination therapy (Rockstroh, et al., 2004; Torriani, et al., 2004).

Less commonly reported side effects may include hyperthyroidism, hypothyroidism and retinal abnormalities. Baseline eye examinations are recommended prior to initiating therapy and referral should be made to ophthalmology during therapy for any change in vision or visual disturbances. Thyroid function should be monitored every three months while on therapy. At times supplementation with thyroid replacement medication is necessary.

To summarize, management of side effects are crucial to assist patients through therapy and optimize virological response rates in the co-infected patients. Provider experience and comfort with these antiviral therapies, patient and family education programs, maximizing support systems, and assistance with substance abuse issues are all vital components in the care of these complex patients.

Challenges in the Management of the Co-infected Individual

Issues of Adherence

Adherence to HAART is an issue that has had much attention in the literature and in clinical practice (Reynolds, 2004). However, little has been done to determine adherence or its predictors in the HCV population. While the HIV literature has data to support the importance of >95% adherence to medications for optimal effectiveness, there is little data to determine the criteria for adherence in the HCV population. A retrospective analysis of the early clinical drug trials in HCV mono-infected patients receiving standard interferon and ribavirin was performed to determine criteria for adherence related to virological response (McHutchinson, Manns, Patel, Poynard, Lindsay, Trepo, et al., 2002). This analysis has led to the belief that in HCV infected patients, adherence to the intake of >80% of each drug for >80% of the duration of therapy is required to achieve a sustained virological response. The most frequent reason for nonadherence in this analysis was treatment-related side effects. Flamm, et al. (2002) conducted a prospective, randomized, controlled multi-center interventional trial to determine the effectiveness of patient education, aggressive side effect control and cognitive behavioral therapy in patients with HCV mono-infection on antiviral therapy. Results demonstrated the feasiblity of this type of intervention, showed decreased drop out rates in the first 12 weeks of therapy, and revealed significant improvements in quality of life measures at early time points in the treatment regimen (Flamm, et al., 2002). To date, there have been no studies examining the issues of adherence in the HIV/HCV co-infected population.

Due to the complexity of medication regimens in both disease processes, adherence is a critical issue and must be explored in this patient population. ART or HAART requires daily pill management as well as management of associated side

effects. HCV management takes the regimen to a more complex level. The HCV medication regimen requires twice daily pills (1-3) with a weekly subcutaneous injection and management of associated side effects. Drug interactions must be monitored, side effects monitored and managed to avoid potential complications and interruption of therapy. Another compounding factor is the patient's fear of initiating HCV treatment. One study found that over 30% of the co-infected patients underwent workup for hepatitis C, yet never came back for the drug treatment recommended by the provider (Ilyas, Oliver, Barber, Verbeck, Richards, Carlson, et al., 2005). Another study identified that only 42% of co-infected patients came to their first clinic appointment for HCV treatment after being referred, compared to 66% of those with mono-infection (Shim, 2004). The underlying causes of this fear have yet to be explored, although education and assurance could influence their behavior.

Recent studies have attempted to determine barriers to antiviral treatment for HCV in the co-infected population. Non-adherence accounted for 23% of the identified barriers to treatment in a cohort of 149 HIV/HCV patients in an urban HIV clinic. Other identified barriers included, AIDS, end stage liver disease, psychiatric disease, and illicit drug use (Fleming, Craven, Thornton, 2003). This study identified the primary barriers to treatment for HCV which were low physician referral rates and high clinic no-show rates. Therefore, those with HCV/HIV co-infection are less likely to be treated for HCV than those with HCV mono-infection (Ilyas, et al., 2005; Shim, 2004, Fleming, et al., 2003).

Providers have yet to determine the best systems approach for diagnosis, evaluation and treatment of the HIV/HCV co-infected patient. Should this fall to the infectious disease providers? Should care of these patients be referred out to the liver

disease specialists? Is the hepatologist the best at managing these patients? Is co-management feasible for this patient population? All of these unanswered questions are beginning to be grappled with in clinical practice settings. It is important to remember the patients in this process and their ability to negotiate the complex health care systems and regimens that they are asked to undertake. As nurse practitioners, we need to develop workable processes for co-infected patients and provide support and guidance throughout their care management and treatment regimens.

The Role of the Nurse Practitioner

The nurse practitioner can be very effective in working with this patient population. Table 1.4 outlines a suggested HCV treatment algorithm in order to provide guidelines for therapy and its management. Nurse practitioners are ideally positioned to provide intensive education, support in therapy, side effect management, and clinical evaluation in this population. In collaboration with physicians and other health care team members, nurse practitioners play a vital role in the complex care of the HIV/HCV co-infected individual. A multi-disciplinary team approach can provide improvements in HCV treatment rates, adherence rates and ultimately virologic response rates in the HIV/HCV co-infected population.

Table 1.1 Comparison of Knodell, Metavir, and Ishak Staging Scores

	KNODELL STAGE	METAVIR	ISHAK MODIFIED STAGING
0	None	No fibrosis	No fibrosis
1	Fibrous portal expansion	Fibrosis at portal tract without septa	Fibrous expansion of some portal area with or without short fibrous septa
2		Fibrosis at portal tract with rare septa	Fibrous expansion of most portal areas with or without short fibrous septa
3	Bridging fibrous	Fibrosis at portal tract with numerous septa without cirrhosis	Fibrous expansion of some portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Fibrous expansion of portal areas with marked bridging
5			Marked bridging with occasional nodules
6			Cirrhosis

Table 1.2 Study Design and Outcome Data in Trials Evaluating PEG-IFN in the Treatment of Patients with HIV/HCV Coinfection

Study	Type	N	Regimens IFN (MU TIW), PEG (μ/wk or μg/kg/wk)/ Regimens RBV (mg/d)	ETR (%)	SVR (%)	D/C Rate (%)
Cargnel et al	RT	28 30	PEG-α2b 1.5 X 48 wks PEG-α2b 1.5 + RBV 800 X 48 wks	11 (24w) 35 (24w)	NA	36
Carrat et al	RT	207 205	IFN-α2b 3 + RBV 800 X 48 wks PEG-α2b 1.5 + RBV 800 X 48 wks	27 44	19 27	42 40
Chung et al	RT	67 67	IFN-α2a 3 _ RBV 600-1000 X 48 wks PEG-α2a 180 + RBV 600-1000 X 48 wks	15 (24w) 44 (24w)	12 27	12
Hernandez-Quero et al	RT	70 74	PEG-α2a 180 + RBV 800 X 48 wks PEG-α2a 180 + RBV 1000 X 48 wks	55 (24w) 59 (24w)	NA	6
Mallolas Perez et al	RT	117	IFN-α2b 3 _ RBV 800-1200 X 24-48 wks PEG-α2a 100-150 + RBV 800-1200 X 24-48 wks	PEG>IFN (24w)	NA	NA
Rodriguez-Torres et al*	RT	33 43	PEG-α2a 180 X 24 wks (add RBV X 24w if +resp) PEG-α2a 180 + RBV 800 X 48 wks	18 23	3 6	26
Torriani et al	RT	285 286 289	IFN-α2a 3 + RBV 800 X 48 wks PEG-α2a 180 + Placebo X 48 wks PEG-α2a 180 + RBV 800 X 48 wks	14 31 47	12 20 40	15
Fuster et al	Obs	110	PEG-α2a 180 + RBV 800 x 12 wks If EVR, PEG-α2a 180 + RBV 800 x 12 or 36 wks If no EVR, PEG-α2a 180 + RBV 800 x STD or 72 wks	52.7	41.8	68 (ext arm)
Goelz et al	Obs	22 25	IFN-α2b 5 MU/d X 12 wks, 5 MU/tiw + RBV 1000-1200 X 24-48 wks PEG-α2b 1.5 + RBV 800 X 24-48 wks	NA	23 20	NA
Hopkins et al‡	Obs	40	PEG-α2b 1.5 + RBV 1000-1200 X 24-48 wks	35	32	18
Moreno et al	Obs	35	PEG-α2b 50 + RBV 800	NA	31	20
Myers et al*	Obs	32	Median: PEG-α2b 1.0 + RBV 1000	19	16	47
Perez-Olmeda et al	Obs	68	PEG-α2a 150 X12 wks, 100 X 12-24 wks + RBV 800 X 24-48 wks	40	28	15
Rockstroh et al	Obs	30	PEG-α2b 1.5 + RBV 800 X 48 wks	57 (24w)	NA	47
Santin et al	Obs	66	PEG-α2b 80-150 mcg + RBV 800-1200 x 24 wks (G2-G3) PEG-α2b 80-150 mcg + RBV 800-1200 x 48 wks (G1-G4)	NA	26.7	33.3
Voight et al	Obs	122	PEG-α2b 1.5 mcg + RBV 800 x 24 wks (G2-G3) PEG-α2b 1.5 mcg + RBV 1200 x 48 wks (G1-G4)	52	25	30
Voight et al	Obs	72	PEG-2b + RBV 800 X 48 wks	46	26	17

MU, TIW, million unites thrice weekly; ETR, end-of-treatment virologic response; SVR, sustained virologic response; D/C, discontinuation; RT, randomized trial; Obs, observational study; NA, not available.
*Prior non-responder to interferon trial.
‡66% genotypes 2/3

Table 1.3 Side Effects to Interferon and Ribavirin	
INTERFERON SIDE EFFECTS	**Strategies to Manage Side Effects**
Fatigue	Fluid therapy
Flu-like symptoms	Acetaminophen, NSAIDS
Leukopenia, Thrombocytopenia	Dose reduction, growth factors
Depression	SSRIs, counseling, psych referral
Nausea	Anti-emetics, ginger, small frequent meals
Insomnia	Trazadone, sleep aids
Alopecia	Satin sheets, no hair chemicals
Retinal disease	Eye exam prior to treatment and if symptoms
Anorexia	Supplements, increase calories
RIBAVIRIN SIDE EFFECTS	**Strategies to Manage Side Effects**
Hemolytic Anemia	Dose reduce ribavirin, Growth factors
Cough	CXR if persistent or severe
Pruritis	Creams, oatmeal soaps, anti-pruritic agents
Rash	Dermatological creams-Elidel, Hydrocortisone, Benadryl
Birth Defects	Pregnancy counseling, avoid pregnancy during and for six months following therapy

Table 1.4 Suggested HCV Treatment Algorithm

HCV Treatment and Management	Diagnostic Testing	Provider	Evaluation
Liver Evaluation	Labs, Ultrasound, Possible liver biopsy, Evaluate social support, psych issues, substance abuse issues	MD/NP	Determine Candidacy for HCV Treatment
Treatment Decision	Baseline eye examination Education Class Initiate medication therapy	MD/NP	Initiate HCV Treatment
Treatment Follow-up	Labs, Side Effect Management, Adherence measures, ongoing education Week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	NP, MD Consult if needed	Monitor side effects to therapy Monitor adherence Support patient in therapy
Treatment Response to Therapy	Virological Response to therapy measured by HCV PCR Week 4, 12, 24, 48, 72	NP, MD Consult if needed	Week 4=Rapid virological response (RVR) Week 12=Early virological response(EVR) Week 24=If PCR (+) D/C therapy Week 48=End of treatment (EOT) Week 72=Sustained Virological Response (SVR)

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Chapter II: Adherence to Therapy: Challenges in HCV Infected Patients

Adherence to Therapy: Challenges in HCV Infected Patients

Abstract

While clinicians recognize the importance of adherence to HCV therapy, little research has been conducted to determine actual adherence rates or its predictors in this population. Due to the complexities of the drug regimen, side effects from the medication, frequency of clinical monitoring, variable response to therapy, and potential complications, adherence is a challenge in the HCV infected individual. However, due to the time limited nature of the current medication therapies, multidisciplinary and multifactoral interventional strategies may be designed to positively influence adherence rates, and ultimately, treatment outcomes in this patient population.

Introduction

Chronic infection with the hepatitis C virus (HCV) causes hepatic fibrosis requiring medication therapy in order to achieve the goal of viral eradication. Adherence to HCV medication at rates of >80% has proven to be a strong predictor of virologic response [1]. The 2002 National Institutes of Health Consensus Statement recognized that there would be challenges in adherence in the HCV population due to medication side effects and the complexity of therapy [2]. It seems that while 80% or more adherence to HCV therapy results in good outcomes, very little is know about actual adherence to HCV therapy. But from the few studies available, adherence seems to be a significant problem and should be further studied and addressed in the clinical setting. This article will address the challenges of adherence in the HCV infected individual.

Background on Adherence

Definition of Adherence

Adherence to medications, clinic visits, or prescribed therapies is not a new concept and has been studied and reported in the chronic illness literature. In order to understand the challenges in adherence facing the HCV patient, one must explore the concept of adherence in general. There is no universally accepted definition of adherence in the literature. The historical term for adherence was compliance, defined as "the extent to which a person's behavior (in terms of taking medication, following diets or executing life-style changes) coincides with medical or health advice" [3]. This term has fallen out of favor due to the implied authoritarian relationship between the health care provider and the patient that minimizes the patient's role as a decision maker. Adherence is believed to reflect a more collaborative relationship involving joint decision making,

empowering the patient. Adherence has been defined as "the extent to which the patient continues the agreed upon mode of treatment under limited supervision" [4]. "Patient adherence reflects the extent to which a person's actions or behaviors coincides with advice or instruction from a health care provider intended to prevent, monitor, or ameliorate a disorder" according to Christensen [5].

Adherence to a medication regimen involves several steps. Whether this is for an acute or chronic condition, adherence involves filling the prescription, using the medication as directed, returning for follow-up, reporting side effects and reporting any deviations from the treatment regimen, such as "drug holidays" or missed doses [5]. Medication adherence in general has been the single most important factor linked with treatment failures, illness relapse and complications, increased disability, and premature death [5].

Challenges of Adherence in Chronic Illness

Adherence has been extensively studied in patient populations with chronic illness, such as diabetes, hypertension, asthma, or human immunodeficiency virus (HIV). Adherence to medications and clinic appointments has historically been and continues to be one of the greatest challenges to achieving optimal treatment outcomes [6]. Generally, adherence to medication therapy lessens disease severity and its complications. Despite that, adherence rates to medication therapy in chronic diseases is only approximately 50%, and 30% of patients fail to fill prescriptions [7, 8]. Discontinuation of medication therapy tends to be high in the first several months of therapy, and adherence rates decline for medications, appointment keeping, exercise and diet over time [7]. Economic costs of nonadherence are high, and include increased hospital admissions, greater

emergency department visits, increased physician visits for complications, lost productivity due to reduced work time, and unnecessary prescription costs [6, 5].

Measurements of Adherence

Measurement of actual adherence has historically been a challenge in clinical trials and the clinical practice setting. There is no universally accepted measure of adherence or standard of measurement for adherence behavior [9]. Accurate detection of adherence often provides no insight into factors that influence adherence or lack of it [9]. Most research studies, to date, rely mainly on the patient's self-report as an index of adherence; however, patient reports are often unreliable. When patients admit that they have not taken all of their medications, their estimates usually substantially overestimate their actual adherence [8]. There are multiple other measurement strategies aimed at detecting adherence. These include pill counts, blood level assays, electronic monitoring, outcome measures, and pharmacy refill records. Each measurement system has advantages and limitations.

There is no drug assay used in clinical practice to monitor drug levels of HCV combination therapy. Typical laboratory monitoring includes complete blood count, chemistries and HCV RNA viral loads. Viral loads will give clinicians an estimate of treatment response and potential disease activity; however, they do not give a picture of medication adherence. Patient and disease characteristics will confound the virologic response rates complicating this as a measure of patient adherence.

Factors in Adherence to HCV Therapy

Model of Adherence

The main treatment goal in patients with chronic hepatitis C viral infection is the prevention of progressive hepatic fibrosis by eradicating hepatic and extrahepatic virus [10]. Accordingly, the goal of HCV therapy is viral eradication. The treatment regimen involves a weekly, or at times daily, injectable medication and daily oral medications for a specific period of time; both medications cause significant side effects. Medication adherence to combination therapy has been a challenge in the clinical trials, worse yet in the clinical setting. Patients beginning antiviral therapy are usually asymptomatic from their liver disease and they develop a myriad of drug-related side effects which can be severe in less than 10% of the patients. This has been reported to be a challenge to adherence [5].

In order to address each of the challenges to adherence a conceptual model is useful. There has not been an adherence model cited in the HCV literature. However, in the HIV adherence literature, a frequently cited conceptual model is that of Jeannette Ickovics and Andrew Meisler [9]. Their research was initially conducted to provide a framework for AIDS clinical trials; but was expanded and utilized by many adherence researchers. The model provides the basic building blocks to formulate research studies to further advance knowledge and understanding of adherence. Adherence issues in HIV have long been recognized; however, the issues in adherence and HCV and HIV/HCV co-infection are just beginning to be explored. It is vital to have a similar conceptual framework with which to design adherence studies, determine predictors of adherence, and examine interventional strategies to increase adherence rates to HCV treatment regimen.

In the Ickovics and Meisler [9] conceptual model of adherence there are five key components. These are: 1) the individual, 2) the treatment regimen, 3) the patient-provider relationship, 4) the clinical setting, and 5) the disease. Statistically significant associations across more than one study corroborated these relationships and several factors have consistently been associated with nonadherence to antiretrovirals including symptomatic disease, presence of adverse drug effects, neuropsychological dysfunction, psychological distress, lack of support, increased complexity of drug regimen, low patient self-efficacy, and inconvenience of treatment. Socio-demographic factors are not consistent across research studies. This problem is similarly reported in the general adherence research in other chronic illnesses [11, 12, 13]. Each of the five components in the model describe important categories of factors that affect adherence and can be applied to the care of the patient receiving hepatitis C treatment.

Individual Characteristics

Patient characteristics include sociodemographics, perceived efficacy of treatment, knowledge of treatment regimen, intent to adhere and past adherence, perceived cost and benefits of regimen, social support, and presence of depression and/or substance use. Although most studies show that sociodemographic factors do not predict adherence; others in HIV have found that male sex, white ethnicity, older age, higher income, higher education and literacy correlate with better adherence [14,15,16]. It has been well established in the adherence literature that behavior change and motivation of an individual are important factors influencing adherence [17]. In order to equip patients to be successful, providers must deliver the motivation, tools, knowledge and skills patients need to use treatment and advice. In other words, patients must become good

self-managers; thus fulfilling the definition of "adherence". In addition to education and knowledge, motivation of the individual is important. This includes the readiness to change or sustain behavior and involves the concepts of importance and confidence [18]. In other words, patients may recognize the importance of the necessary treatment or medication, but not have confidence in their ability to successfully manage the regimen. Conversely, the patient may have the confidence, but not recognize the importance of the treatment.

Depression and Adherence

Depression has been negatively correlated with adherence to medications and to treatment regimens and recommendations in the literature. Depression, stress and related negative moods have been repeatedly associated with nonadherence across chronic conditions and a major reason for missed medication doses [19, 20]. Depression and mental health issues prevail in the HCV population, represent barriers to treatment with combination therapy, and negatively influence adherence [21,22]. However, numerous studies have shown successful treatment of HCV in patients with depressive symptoms and/or mental health illnesses [23, 24, 25, 26, 27].

Substance Abuse and Adherence

Active alcohol use and/or drug use also negatively influence adherence both in HIV and HCV studies [28, 29]. Abstinence from alcohol use and substance abuse is highly recommended during the treatment phase of hepatitis C due to the compounded damage to the liver and potential for reinfection with intravenous drug use [30]. Substance abusers are also known to have a high frequency of co-occurring psychiatric illness which also influences adherence rates [30]. However, several studies have

demonstrated successful treatment outcomes with HCV combination therapy in patients with active psychiatric illness and substance use disorders although at a lower rate [29]. Careful screening tools and aggressive interventions will need to be in place to assess, treat and evaluate alcohol use, psychiatric illness and substance abuse issues which may all impact adherence to medication and treatment regimens. Taylor has developed a model of care to optimize safety and adherence in the injection drug user HIV/HCV coinfected population and reports 99% adherence to weekly visits for interferon injections [31]. Sullivan and colleagues report treatment response rates in intravenous drug users to HIV or HCV regimens were similar to non-users and that medication adherence and treatment outcomes are optimized with close observation and with substance abuse treatment [32]. Currently underway is a five year study funded by the National Institutes of Mental Health entitled, "Adherence to HCV Treatment in HCV and HCV/HIV Patients." The researcher aims to conduct a prospective cohort study of 100 HCV and 100 HIV/HCV patients initiating combination therapy for hepatitis C treatment. The 200 patients will be followed for 24 weeks to determine if depression, neurocognitive functioning, substance abuse and treatment self-efficacy is associated with early treatment discontinuation [33]. However, it is important to remember that early treatment discontinuation is not always synonymous with medication adherence.

Stigma Associated with HCV Infection

Both HIV and HCV infected patients suffer from stigmatization which impacts their quality of life. Studies have demonstrated that stigma is prevalent in the HIV population and influences adherence to therapy [34]. A few studies demonstrated the impact of stigma on quality of life and well-being in the HCV population [35, 36, 37].

Zickmund reported 57% (N=257) of HCV patients experienced stigmatization that they attributed to the disease [38]. Women were more likely to report perceived stigmatization compared with men (p=<.05). Stigmatization was significantly associated with higher anxiety, depression, worsened quality of life, loss of control and difficulty coping. A qualitative study interviewing women with hepatitis C demonstrated issues with social stigma, sexual transmission, pregnancy and childcare which in turn affected their close relationships and fulfillment of gender roles [39]. In an intervention study to enhance adherence in HIV positive patients, researchers describe the "secrecy and stigma" phenomena associated with preventing others from learning of their diagnosis, which often requires hiding medications from family or friends [40]. The degree of social support, social stability, and self-efficacy influence adherence rates as well [41, 14]. In a study evaluating the impact of HCV diagnosis on social support, 45% of patients reported the loss of at least one relationship due to the disease [42].

The Disease

Another factor is the features of the disease itself, including symptomatology and immunologic status. This factor involves the severity of the disease, as well as the chronicity of the problem. The more comorbidities an individual has that require medication therapy or treatment regimens, the less adherent a patient becomes [5]. The stage of the patient's disease appears to influence treatment adherence [4]. Studies demonstrate the neurocognitive changes that occur with HCV disease and hepatic encephalopathy may impair the patient's ability to adhere to a medication regimen [43, 44]. The presence or absence of symptoms can be either an incentive or a deterrent to adherence to treatment. Some patients are motivated to adhere even with significant side

effects, if their viral load decreases or becomes negative, while others may feel that absence of a viral load and/or symptoms means that they do not need to continue to take their medications.

Treatment Regimen

A key component of the model addresses the characteristics of the treatment regimen and includes factors such as regimen duration or length of treatment, regimen complexity, including dosage frequency and route of administration, and the presence of side effects and their severity. The HCV therapy regimen is complex for patients, requiring the skill of an injectable medication with twice daily pills. Many patients fear self-injection and those with histories of substance abuse may fear needles for different reasons. However, unlike many of the medication regimens to control other chronic illness, HCV therapy is time limited. Although the ideal treatment duration for each patient has yet to be determined, the typical length of HCV therapy is twenty-four to forty-eight weeks, depending on HCV genotype and response to therapy, and this may positively influence adherence rates.

Side effects to the regimen have proven to be a challenge and influence adherence [1]. Fear of treatment related side effects may also negatively influence patient decisions to initiate treatment [45, 46]. Frequently additional medications are used to control side effects further impacting adherence. This may be a positive influence when side effects are controlled or a negative effect as increase pill burden occurs, increasing regimen complexity. When growth factors are necessary to support therapy, additional injectable medication is added to the already complex regimen. In the future, as new medication strategies are developed to improve virologic response rates, the regimen may increase in

complexity as triple or quadruple therapies may become the norm. If the new therapies are determined to have virologic resistance issues such as those seen in HIV, adherence to medication therapy will become an even more pressing issue.

A retrospective secondary data analysis of the key clinical drug trials utilizing interferon and ribavirin was performed to determine criteria for adherence related to virologic response in HCV patients [1]. The researchers evaluated 1,010 patients who were receiving interferon and ribavirin and 511 patients who were receiving peginterferon and ribavirin to determine if dosing at the criteria of 80% of both medications influenced sustained virological response. Researchers eliminated patients from the analysis if they did not take 80% or greater of the 48 week duration of therapy. Overall 80% of the interferon group and 72% in the peginterferon group were considered adherent to 80% or greater of the prescribed dosage of both interferon/peginterferon and ribavirin. Adherence was determined by multiple measures including, pill count, dispensing records and patient diaries. The common reasons for nonadherence in this study were adverse events to the medication therapy (>75%), followed by failure to attend scheduled clinic appointments, withdrawal of consent and nonadherence in the absence of apparent side effects (<25%). Researchers concluded that 80% adherence to prescribed dosages of both medications increased virologic response rates, 44% to 52% in the interferon plus ribavirin group, and 54% to 63% in the peginterferon plus ribavirin group.

This analysis has led to the belief that in HCV infected patients, adherence to the intake of >80% of each drug for >80% of the duration of therapy is required to achieve a sustained virologic response, as measured by a negative viral load six months after

discontinuation of therapy. A second research study was conducted to determine if researchers could replicate the previous data on adherence and its correlation with sustained virological response rates in hepatitis C combination therapy [47]. This study was also a retrospective analysis of data from two multicenter randomized controlled clinical trials using standard interferon and ribavirin conducted in Greece. One trial included naïve patients to therapy (N=301), and the other trial included nonresponders to previous interferon therapy (N=142). Researchers concluded that overall SVR in naïve patients (N=223) was 44% for the adherent group versus 7% ($p=<0.001$) for the nonadherent group. Nonresponder patients (N=116) who were adherent had a 31% SVR versus 11% for the nonadherent group ($p<0.014$). Based on multivariate logistic regression analysis adherent subjects had a significantly higher SVR than those in the nonadherent group, even with adjustment for treatment arm, gender, HCV genotype, age and baseline levels of ALT or HCV-RNA.

The majority of the patients who prematurely withdrew from the studies did so because of side effects and nonadherence to clinic visits. Only 12 patients required dose reduction below the 80% criteria for medical reasons. A multivariate logistic analysis determined prognostic predictors to adherence to therapy. Age at study entry was a strong independent predictor to adherence, with younger subjects having a higher probability of completing therapy. In treatment naïve subjects, those infected through intravenous drug use appeared to have a lower probability of completing therapy compared to those infected through other routes of transmission. Therefore, two research studies have determined that adherence to 80% of the prescribed dosages of both combination medications impacts the likelihood of a sustained virological response to combination

therapy. Adherence to HCV therapy or its predictors has not yet been reported prospectively in the clinical setting nor outside of a clinical drug trial.

Patient-Provider Relationship

Good patient-provider relationships are another factor of the model and have long been recognized in improving adherence to medications and treatment [48]. This factor includes the communication between patient and provider, patient satisfaction, affective tone of relationship, and belief in the skill or knowledge of the provider. Trust in the provider and overall satisfaction are important concepts in patient-provider relationships [48].

Researchers found that a patient's engagement with their HIV provider was significantly related to self-reported medication adherence [49]. Better relationships between the provider and the patient improved the rate of adherence to ART [48]. Schneider and colleagues conducted a study of 554 HIV patients taking antiretroviral medications to determine whether better physician-patient relationships are associated with higher rates of adherence [48]. Researchers measured adherence using a 4 item self-report scale (alpha=0.75) while physician-patient relationships were measured using 6 previously tested scales: general communication, HIV-specific information, participatory decision making, overall satisfaction, willingness to recommend physician, and physician trust (alpha=0.70 for all), and one new scale, adherence dialogue (alpha=0.92). In multivariate models, 6 out of the 7 physician-patient relationship quality variables were significantly ($p=<0.05$) associated with adherence. In all 7 models, poor adherence was independently associated with lower age, not believing in the importance of antiretroviral therapy and worse mental health [48]. Therefore, it is important to recognize that multiple

dimensions of provider-patient relationships will influence adherence to therapy. This issue will be further complicated by multiple providers giving treatment advice to patients related to their HCV therapies. Communication between multiple providers and health care team members must be ensured to maintain trust between patients and their providers. Mixed messages, miscommunication and misinformation may all negatively influence adherence rates [50].

Clinical Setting

The final key factor is the clinical setting. This involves the availability of childcare, scheduling, transportation, confidentiality, and the clinical environment. Access to reliable primary care is related to increased adherence [14], and missed clinic appointments are a strong predictor of virological failure in the HIV population [51]. Strategies to ease access to care, address insurance issues, and target integration and coordination of care will improve disease management [52].

Challenges to Adherence in HIV/HCV Co-infection

HIV/HCV co-infection further complicates the issues of adherence due to the dual therapies required for control of each virus. HIV/HCV co-infection is prevalent in approximately 30% of individuals infected with HIV in the United States [53]. Since the introduction of ART used for viral suppression of HIV, the leading cause of morbidity and mortality in these patients is chronic liver disease [54]. Complexity in therapies, increased pill burden, combined side effects, drug to drug interactions, and hepatotoxicities with the dual therapies provide a challenge to an already strict criteria of medication therapy necessary in HIV therapy. Medication adherence rates of greater than 95% are needed to achieve undetectable plasma HIV RNA levels in 78-84% of HIV

positive patients [55]. Adherence rates of 70-89% have been found to be associated with viral rebound and development of clinically significant viral resistance to ART [56]. Therefore adherence rates to both drug regimens are difficult for patients to achieve and maintain over time, yet vital to achieve successful treatment outcomes. However, in light of the significant liver disease progression and improved virological response rates to pegylated interferon and ribavirin in this patient population, HCV therapy should be considered. Use of multiple providers in this patient population provides an additional challenge in adherence both to clinic visits and medication therapy. Numerous studies report a dismal rate of liver disease evaluation and HCV treatment in the HIV/HCV co-infected population [57, 58, 59, 60, 61,].

Strategies to Increase Adherence in HCV Therapy

Strategies to improve adherence to therapy in the HCV patient need to be targeted at all of the key factors in the adherence model (See Table 2.1). Effective randomized controlled intervention trials to improve adherence rates have been reported in the HIV literature [62, 63]. Interventions that target multiple factors, are multidisciplinary in nature and focus on behavioral domains demonstrate better rates of adherence. Therefore strategies such as education and motivation, proactive side effect management, treatment of comorbid conditions, such as mental health and substance abuse issues, and simplifying the treatment regimen will all be necessary to optimize a successful course of therapy for the HCV patient.

Flamm conducted a prospective, randomized, controlled multi-center interventional trial to determine the effectiveness of patient education, aggressive side effect control and cognitive behavioral therapy in HCV patients on antiviral therapy [64].

Results demonstrated the feasiblity of this type of intervention, showed decreased drop out rates in the first 12 weeks of therapy, and revealed significant improvements in quality of life measures at early time points in the treatment regimen [64].

Implications for Future Adherence Research in Hepatitis C

Future research is crucially needed to examine adherence rates, predictors of adherence and determine the effectiveness of interventions aimed at increasing adherence in the HCV population. Research has demonstrated that drop out rates seem to be the highest in the first 8 weeks of therapy, the period most crucial for the optimal delivery of antiviral therapy [65]. Hepatologists agree that, "A multidisciplinary team approach is required in order to educate and communicate effectively with the patient, individually tailor the prescribed regimen, provide organizational support, develop dispensing aids, and deal with side effects or psychosocial issues," in order to maximize adherence in the hepatitis C population [66]. Therefore, adherence research will be vital in this patient population.

Conclusions

Patient adherence is multi-factorial, complicated and a challenge to adequately measure. Use of a conceptual framework will enhance the ability of clinicians and researchers to identify crucial areas to investigate, develop interventional strategies, and evaluate adherence and treatment outcomes. Due to the time limited nature of HCV therapy, interventional strategies designed to support patients may positively influence adherence rates and ultimately virologic response in these patients. Strategies to assist the patient must be developed to address all of these potential factors which influence adherence. Patients will need to be provided the necessary skills, knowledge, coping and

medical monitoring that will focus on issues of adherence so that optimal patient outcomes can be achieved. Patients will need to be empowered to make decisions, participate in their care, and have the knowledge necessary to negotiate the HCV therapy.

	Individual Characteristics	Treatment Regimen	Patient/Provider Relationship	Clinical Setting	Disease
Challenges in HCV Treatment	Motivation Education Intent to adhere Social support Depression/mental health issues ETOH/Substance abuse issues	Time-limited therapy (+) Virological testing Wk4 12, 24, 48, 72 (+/-) Injectable medication plus twice daily pills Multiple side effects to medications	Multiple providers Various skill levels Comfort with treatment • Hepatology • GI • NP/PA • PCP • ID	Lack of experienced providers Access to providers Insurance coverage issues Transportation Appointment scheduling	Lack of symptoms from HCV Cirrhosis/ESLD • HE • Neurocognitive changes Chronic illness
Strategies to Improve Adherence	Support group Educational classes Educational material Optimize social support Psych/counseling as needed ETOH/substance abuse treatment if needed Prophylactic antidepressant therapy	Proactive side effect management Return demonstration classes for injection Individualized teaching	Knowledgeable multi-disciplinary providers Good communication • Patient-provider • Provider-provider Increase patient satisfaction	Ease of access to providers Patient assistance programs Availability of clinics Ease of scheduling appointments	Disease management strategies

Based on Ickovics & Meisler's Model of Adherence, 1997.

Table 2.1 Challenges and Strategies to Overcome Adherence Issues in HCV Therapy

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Chapter III: Factors Influencing Referral Patterns for Liver Disease Evaluation in HIV/HCV Coinfection

Factors Influencing Referral Patterns for Hepatitis C Evaluation in HIV/HCV Coinfection

Abstract

Background: Hepatitis C (HCV) infection is reported in approximately 30% of HIV infected patients. Treatment of HCV is crucial to prevent liver decompensation and/or liver failure; however, rates of HCV treatment in this patient population are extremely low. Referral rates for HCV evaluation are reported at 30-40%, while initiation of HCV therapy only occurs in approximately 1-20% of HIV/HCV coinfected patients.

Purpose: The aim of this study was to identify the factors that influence liver disease evaluation referral of HIV/HCV coinfected patients from HIV providers in a large university based HIV clinic.

Methods: We analyzed a cohort of 538 HIV/HCV coinfected adult individuals seen during the time period of January 1, 2003 to December 31, 2006. Data was retrospectively collected to identify patient factors such as demographic information, HIV and HCV disease severity, major medical comorbidities, mental health factors, substance use, and social issues. The outcome variable was referral to a liver specialist as defined by a documented referral date from a HIV provider.

Results: Of the 538 HIV/HCV coinfected patients, 308 received a referral for liver disease evaluation, a referral rate of 57%. Of those referred patients, 224 were evaluated for their HCV related liver disease, with 79 (15%) patients initiating HCV treatment. There were 84 referred patients who never attended their liver clinic appointment. There were 230 HIV/HCV coinfected patients who never received a referral for liver care. Patients were more likely to be referred if they were on antiretroviral therapy, had elevated ALTs, had cirrhosis, were infected with hepatitis B, had a history of skin cancer,

and had received psychiatric evaluation. Patients who had cardiac disease, a HCV negative viral load, were currently using intravenous drugs or crystal methamphetamine, or had a history of homelessness or incarceration, were less likely to be referred. Conclusions: Referral rates for liver disease evaluation in HIV/HCV coinfected individuals is dependent on a number of patient factors, including medical variables, substance use, as well as social issues. This illustrates the need for clinical care models that give attention to the complex needs of this patient population.

Introduction

Coinfection with hepatitis C virus (HCV) is prevalent in approximately 30% of individuals infected with the human immunodeficiency virus (HIV) in the United States (Andersson, Chung, 2006; Sulkowski, Thomas, 2003). Since the introduction of antiretroviral medication therapy (ART) for viral suppression of HIV, the leading cause of morbidity and mortality in these patients is chronic liver disease (Soriano, Barreiro, Nunez, 2006; Lewden, Salmon, Morlat, et al., 2005; Bica, McGovern, Dhar, et al., 2001). In an HIV environment, HCV could behave more aggressively, with higher rates of viral replication and more severe liver damage (Martagon, Gordon, 2003). To control or minimize progressive liver disease and the risk of liver toxicity with ART, patients with HCV infection need to be evaluated for treatment (Alberti, Clumeck, Collins, et al., 2005; Benhamou, Bochet, DiMartino, et al., 1999; Sulkowski, Thomas, Chaisson, et al., 2000). Newer medications for the treatment of HCV have demonstrated improved virologic response rates. Studies using the combination of pegylated interferon and ribavirin report sustained virologic response (SVR) rates of 27-50% in the HIV/HCV coinfected population (Chung, Andersen, Volberding, et al., 2004; Torriani, Rodriguez-Torres, Rockstroh, et. al., 2004; Rendon, Nunez, Romero, 2005). Therefore, appropriate screening, diagnosis, evaluation, and treatment for HCV is crucial in this patient population.

Background

Despite the seriousness of HIV/HCV coinfection and the encouraging improvements in virologic response rates to HCV therapy, the rates of HCV treatment in the clinical setting in this population are alarmingly low. Studies demonstrate only 30-

41% of HIV/HCV coinfected individuals are referred for evaluation of their liver disease (Fleming, Craven, Thornton, et al., 2005; Adeyemi, Jensen, Attar, et al., 2004; Fultz, Justice, Butt, et al., 2003). Most studies report a dismal rate of 1-8% of HIV/HCV coinfected patients actually receiving medical treatment for their HCV infection (Fleming, et al., 2005; Clanon, Mueller, Harank, 2005; Rauch, Egger, Reichen, et al. 2005; Fishbein, Lo, Reinus, et al., 2004; Fultz, et al., 2003). Recently some studies reported HCV treatment rates of 15%, 26% and 27% respectively in HIV/HCV coinfected individuals (Restrepo, Johnson, Widjaja, et al., 2005; McGovern, Fiore, Wurcel, et al., 2005; Ilyas, 2005). Yet, national guidelines recommend HCV screening and evaluation for HCV treatment in all HIV infected individuals. Recommendations from an International Consensus panel regarding care and treatment of patients with HIV/HCV coinfection identified barriers to HCV treatment. Identified barriers involve both patient and health care provider issues and include active substance abuse, lack of information and familiarity with hepatitis C therapy, difficulty of treatment, and the lack of patient commitment and motivation (Soriano, Sulkowski, Bergin, et al., 2002). In order to address some of these challenges, HIV providers have implemented programs for HIV infected individuals to increase awareness of HCV, and to provide better screening, diagnosis and referral for liver disease evaluation in order to determine candidacy for HCV treatment. The aim of this study is to determine if there are differences in patient factors including demographics, comorbidities, disease severity, mental health issues and social issues between a group of HIV/HCV coinfected adults referred for liver disease evaluation and those not referred.

Materials and Methods

Study Design and Population

A retrospective cohort study was conducted utilizing patient chart review and data extraction from an HIV clinic computer database of HIV/HCV coinfected adult individuals. Six hundred and fifty five HIV/HCV coinfected subjects were identified within the Owen clinic, a large university based HIV clinic in California. Within this comprehensive clinic, HIV providers and support staff manage care for HIV patients and refer liver disease evaluation and management to the hepatology specialists. Since 1999, hepatologists have conducted weekly liver disease management clinics within the Owen clinic to ease accessibility to care and continuity for the HIV/HCV coinfected patients. To be included in this study, adult subjects with consent were identified by a documented HIV and HCV antibody test by ELISA and had an HIV clinic visit between January 1, 2003 and December 31, 2006. The Institutional Review Boards of the University of California San Francisco and the University of California San Diego approved this study.

Subject Assessments

Data were collected by chart review on 538 HIV/HCV coinfected individuals. One hundred and seventeen subjects were excluded from data collection due to lack of access to the complete patient record as a result of clinic inactivity, defined as no clinic attendance in the HIV clinic for over one year, or patient death. Patient demographics and laboratory measures were collected by data extraction from the clinic database system using SAS statistical software. All other patient factors were collected by retrospective chart review by a single researcher. The outcome variable for this study was referral for liver disease evaluation as measured by a documented date of referral from the HIV provider to a liver specialist. In order to capture the period of decision making for liver

disease evaluation referral by the HIV provider, patient characteristics were measured within 90 days to the initial hepatitis C viral load draw date.

Descriptive patient factors are grouped into three main categories: 1) demographics, 2) clinical characteristics, and 3) mental health, substance use and social context. Demographic data include gender, race, and age. Clinical characteristics include chronic comorbidities and HIV/HCV parameters. Comorbities are renal disease, diabetes, hypertension, cardiac disease including myocardial infarction, congestive heart failure and/or coronary heart disease, seizures, respiratory disease including asthma and/or chronic obstructive pulmonary disease and excluding tuberculosis diagnosis or treatment, skin cancer including basal cell carcinoma and/or Kaposi's sarcoma lesions, hematologic cancers including leukemia and/or lymphomas, Kaposi's sarcoma with pulmonary involvement, and finally end stage liver disease as defined by provider documented cirrhosis or fibrosis score on liver biopsy. HIV/HCV laboratory parameters are measured at date of or within 30 days of initial hepatitis C viral load blood draw and include CD4 count, HIV viral load, HCV viral load, and liver enzymes.

Mental health, substance use and social context were identified by chart review. These factors include: history of alcohol abuse, current alcohol abuse, history of intravenous drug use, current intravenous drug use, history of crystal methamphetamine use, current use of crystal methamphetamine, evidence of drug rehabilitation or sober living documentation, current methadone use, diagnosis of depression or anxiety, diagnosis of schizophrenia, diagnosis of bipolar disorder, documented suicide attempt, documented evidence of homelessness, documented evidence of incarceration, and documentation by the HIV provider of nonadherence to clinic visits or medications.

Current use of alcohol, intravenous drugs or crystal methamphetamine was defined as use within a six month time period from date of initial hepatitis C viral load draw. The HIV clinic utilizes a self report questionnaire to assess general well-being at each clinic visit. Patients score themselves on a scale of 0-100, with 0 being the worst imaginable health state and 100 the best imaginable health state. A single score was captured for this study. In 95% of the subjects, this score was collected within 30 days of the initial HCV viral load draw date.

Analyses

Analyses were performed to determine differences in patient characteristics between those HIV/HCV coinfected patients referred for liver disease evaluation with those HIV/HCV coinfected patients not referred for liver evaluation. Descriptive statistics such as chi- square or the t-test were performed to assess bivariate relationships between demographics, clinical characteristics, mental health, substance use and social context, and liver disease. Univariate logistic regression was performed to examine the association between not being referred for liver disease evaluation and each patient characteristic. Multivariate logistic regression was performed utilizing twelve predictive factors in the model. Only patient factors that were statistically significant in univariate analyses were included in the model. The potential for collinearity in the multivariate model was assessed by determining the correlation between pairs of independent variables. No pair of variables included in the same regression model was highly correlated (no correlation was greater than 0.50). All analyses were performed with SPSS Version 15 statistical software.

Results

Study Sample

Of the 3,363 adults with HIV who attended the Owen HIV clinic from 2003 to 2006, 655 patients met the study inclusion criteria of HIV/HCV coinfection (Figure 3.1). Complete data was collected on 538 HIV/HCV coinfected patients who constitute the analyzable study sample. A referral for liver disease evaluation from their HIV provider was documented in 308 patients (57.2% of the study sample). Of these 308 patients, 84 (15.6% of the study sample) did not attend their liver clinic appointment. HIV providers did not refer 230 patients (42.7% of the study sample) with HIV/HCV coinfection for liver disease evaluation (Figure 3.1). Of those who were referred for evaluation, and were subsequently evaluated, 79 (14.7% of the study sample) actually received treatment for their HCV (Figure 3.1). There were 42 HIV providers within the Owen clinic who provided primary care for a case load of HIV infected patients. There was no difference in provider referral rates between specific providers or types of providers, such as physicians, physician assistants or nurse practitioners. Those HIV providers who provided care to a greater number of HIV/HCV coinfected patients within their total case load trended toward higher rates of referral; however, this was not statistically significant.

Demographic Data

The patients were predominantly male (82%) with a mean age of 45 years. No significant differences in age, gender or race/ethnicity were detected between the not referred and referred groups (Table 3.1).

Clinical Characteristics

HIV status. CD4 count was below 200 in 139 patients (25.8% of the study sample). Univariate analyses showed no significant difference between the not referred and referred groups in severity of HIV disease. However, subjects were more likely to be referred if they were on antiretroviral therapy at the time of initial HCV viral load testing (Table 3.2). Forty one percent of the study sample self-reported intravenous drug use as their primary risk factor for their HIV infection.

HCV status. Univariate analyses showed that subjects were significantly more likely to be referred if they had elevated liver enzymes, had a diagnosis of cirrhosis, and were coinfected with hepatitis B. Liver biopsy was performed in 110 patients with 41 patients (7.6% of the study sample) demonstrating mild liver disease (fibrosis score 0-1). Cirrhosis was documented in 28 patients (5.2% of study sample) identified by provider documented diagnosis or biopsy proven evidence.

Of the total study sample, 18% of patients tested HCV viral load negative. Of those not referred, 83 (46.4%) had an initial negative HCV viral load by PCR, indicating viral clearance or prior treatment for HCV. However, in the same not referred group, 36 patients (16%) never received HCV viral load testing. Subjects were significantly less likely to be referred if they had negative HCV viral load (Table 3.2).

Comorbidities. Patients with a history of skin cancer or evidence of Kaposi's sarcoma skin lesions were significantly more likely to be referred; while subjects with cardiac disease were significantly less likely to be referred (Table 3.2).

Psychosocial Characteristics

Psychosocial characteristics were grouped into three main categories: 1) mental health issues, 2) substance use and social factors, and 3) HIV provider perception of

nonadherence to HIV clinic visits and/or medications. Referred patients were significantly more likely to have had a psychiatric evaluation compared with those patients not referred; however, there was no difference between the groups in all other measures of mental health (Table 3.3). HIV/HCV coinfected patients were significantly less likely to be referred for evaluation of their liver disease if they had evidence of current intravenous drug use, current crystal methamphetamine use, were homeless or had a history of incarceration. History of substance abuse including alcohol use and intravenous drug use was not different between the not referred and referred groups. Likewise, provider perception of nonadherence to clinic visits and/or medications was not different between the not referred and referred groups.

Patient Predictors of Non-Referral

In the multivariate model, 75 patients had missing data on at least one factor, therefore, 463 patients were included in this analysis. In order to determine patient characteristics that predict the likelihood of being in the not referred group, twelve factors that were statistically significant in the univariate analysis were included in the multivariate model. These factors include patient diagnosis of cardiac disease, skin cancer, hepatitis B, cirrhosis, ALT per 100 IU/L increase, HCV negative by PCR, on antiretrovirals, had a psychiatric evaluation, homelessness, history of incarceration, current use of intravenous drugs, and current use of crystal methamphetamine. The overall model is significant (Chi-square = 186.740, $p<0.01$). Of the twelve original patient factors, five remain significant in the multivariate model and include ALT per 100 IU/L increase, hepatitis B, homelessness, incarceration and negative HCV viral load (Table 3.4). In other words, patients were more likely to be in the not referred group if

they were homeless, had a history of incarceration, or had a negative HCV viral load. Patients were less likely to be not referred for every 100 point increase in their ALT, or if they had a diagnosis of hepatitis B.

Discussion

This study provides information regarding referral rates from HIV providers to liver care specialists in order to provide liver disease evaluation and determine HCV treatment candidacy in a group of HIV/HCV coinfected patients. As we gain further understanding into the factors that influence referral and evaluation in this group of patients, clinicians and researchers can develop further systems to support the care of these complex patients.

The overall rate of referral to a liver disease provider in this study was higher than the range of 30% to 41% referral rates in most previously reported studies (Fishbein, et al., 2004; Fultz, et al., 2003). This may be a result of the liver disease providers being located within the HIV clinic system thus allowing patients familiar access to care, in a familiar setting, with consistent clinic staff and resources. Both providers are easily accessible to each other in order to enhance communication, collaboration, consultation and education in evaluation and management of both liver disease and HIV in this patient population. Of those patients who were referred for liver disease evaluation, 79 (14.7% of study sample, Figure 3.1) patients went on to receive HCV treatment in this cohort. It is interesting to note that there was no difference in HIV provider referral rates between physicians, physician assistants or nurse practitioners. There was a trend toward higher referral rates with those HIV providers who had a greater percentage of HIV/HCV coinfected patients in their entire case load.

It is clear that HIV providers paid attention to liver disease markers such as elevated liver enzymes, evidence of cirrhosis, or coinfection with hepatitis B. However, liver disease progression from the hepatitis C virus often does not present with clinical symptoms. It has been well documented that serum ALT and HCV viral load levels provide only limited information related to HCV disease severity (Sulkowski, 2007; Fanning, Kenny, Sheehan, et al., 1999). Therefore, this should not be a marker used to determine referral for HCV evaluation. Current national and international guidelines indicate that all HIV/HCV coinfected patients should be evaluated for possible HCV treatment (Soriano, et al., 2002; Alberti, et al., 2005). HIV providers may be more aware of abnormal liver function tests and refer patients for hepatotoxicity concerns secondary to antiretrovirals in this patient population which is seen in about 10% of HIV-infected patients on ART. Chronic hepatitis C has been associated with an increased risk of drug-induced hepatotoxicity (Sulkowski, Benhamou, 2007). Although current national guidelines for ART therapy in HIV infection cite that there is no evidence that ARTs are inherently more hepatotoxic in HIV/HCV coinfection (Hammer, Saag, Schechter, et al., 2006).

In the group that was not referred for liver disease evaluation 46% had positive HCV antibodies, but tested negative for HCV viral load. This would indicate that while some of these patients may have cleared the virus without antiviral therapy, many of these patients may have been previously treated for their HCV. Our study was not able to accurately identify outside referrals, if patients sought liver care elsewhere, or if they were treated while incarcerated. Most patients had HCV viral load testing prior to a referral for liver care; however, this was not always the case. In 36 of the 230 (15.6%)

patients that were never referred, no evidence of viral load testing was found. In patients who were referred for liver evaluation, HCV PCR testing found 14 (4.7%) to be HCV viral load negative.

Other clinical variables that were significant in the univariate model, like cardiac disease and skin cancer, did not remain significant in the multivariate model. It is unknown why more patients who had a history of skin cancer would be referred for liver evaluation. This relationship may not have anything to do with referral patterns. More patients with cardiac disease were not referred for liver disease evaluation indicating that some comorbidities may take precedence over HCV treatment. It is possible that these patients would not be appropriate candidates for interferon therapy because of the known contraindication of interferon and ribarvirin use in this patient population. Ribavirin use is limited in patients with coronary artery disease due to its hemolytic effects and its effects on lowering of hemoglobin concentration which could increase the risk of myocardial infarction in patients with advanced coronary artery disease.

As is reported in other studies, our cohort of patients had both a history of and current substance abuse issues, to both alcohol and intravenous drug use. Of the total study sample (Figure 3.1), 85 (15.8%) were actively drinking alcohol, 83 (15.4%) were currently using intravenous drugs, and 143 (27%) were using crystal methamphetamines, as reported by HIV providers. A history of alcohol use and those currently drinking alcohol was not significantly different between those referred for evaluation and those not referred. However, in the univariate analysis, those currently using intravenous drugs or crystal methamphetamines were less likely to be referred. This did not remain significant in multivariate analysis. Historically, current substance abuse has been considered a

relative contraindication for HCV treatment by providers (Kresina, Bruce, Cargill, et al., 2005; Sylvestre, Litwin, Clements, et al., 2005; Fishbein, et al., 2004). However, current guidelines state that active drug use should not be an absolute exclusion criterion and several studies have demonstrated effective HCV treatment in this population, although possibly at a lower rate of success (Alberti, et al., 2005; Sylvestre, et al., 2005). Therefore, it remains crucial to provide substance abuse treatment and implement systems for coordinated care with a multidisciplinary approach for this group of patients. Palepu (2006) reports longitudinal research to examine the influence of substance abuse treatment on referral for liver disease evaluation by primary care providers. Palepu's study did not detect a significant association between substance abuse treatment and receipt of specialty care for their HCV (Palepu, Cheng, Kim, et al., 2006). However, the researchers found that if HIV/HCV coinfected patients were on ART, had liver complications in the past six months, and were currently not using alcohol, they were more likely to seek liver specialty care (Palepu, et al., 2006). These findings are similar to those found in this study.

Fishbein (2004) reports that HIV positive drug users were significantly less likely to accept referral for liver evaluation (OR 0.51, CI 0.30-0.88). In this study, 84 patients who were referred by their HIV provider never attended their liver evaluation appointment. Many studies have reported nonadherence to clinic visits as a barrier to HCV evaluation and treatment (Fleming, et al, 2005; Taylor, 2005, Ilyas, et al, 2005).

Clearly new models of care are needed to address this issue in this patient population. Litwin (2005) reports a multidisciplinary model of care integrating substance abuse treatment and psychiatric care that led to increased rates of HCV evaluation and

treatment in mono-infected individuals. Methadone treatment programs have been proposed to enhance access to HCV care and provide systems to successfully treat HCV patients (Walley, White, Kushel, et al., 2005; Sylvestre, et al., 2005). Fleming reports their experience with a coordinated coinfection clinic (2005). Close to 50% of the patients evaluated in the coinfection clinic were actively using intravenous drugs and 24% were engaging in hazardous drinking. They determined that 30% of their patients would be eligible for HCV treatment; however, two-thirds of those eligible for treatment declined (Fleming, et al., 2005). Kresina (2005) reports on three types of models for care of injection drug users coinfected with HIV/HCV. One model is similar to that reported here with the liver specialty team housed within the HIV clinic. A second model integrates care for HCV infection into primary care for HIV infection, while a third model utilizes methadone treatment programs to coordinate care for HCV infection (Kresina, et al., 2005). It has not been determined which model of care is more effective for referrals, evaluation or HCV therapy.

Issues such as evidence of homelessness or history of incarceration have been identified as potential barriers to care in this patient population. In this study, both were significant patient factors associated with poor referral rates, based on both univariate analysis and the multivariate model. Several of the HIV providers noted that patients who had marginal living situations or were currently homeless had no access to refrigeration for medications, or secure places to keep their medications. A few patients in this cohort were living in cars or moving from shelter to shelter, some while caring for small children. In order to effectively treat this group of HIV/HCV coinfected patients, new systems such as direct observed therapy may be necessary, in addition to resource

identification for this high risk group. In a cohort study of homeless and marginally housed in the San Francisco area, primary care providers were questioned regarding HCV treatment in this population (Thompson, Ragland, Hall, et al., 2005). Over 70% of these patients were deemed ineligible for treatment with the average of 3.2 reasons cited per patient. Provider perception of poor adherence (50%), perception of patient refusal (49%), depression (46%), drug use (33%) and alcohol use (19.1%) were the most frequently cited reasons for treatment ineligibility (Thompson, et al., 2005). McGovern (2005) reports successful treatment in the incarcerated HIV/HCV coinfected population. Within this system, 28% of their referred population received HCV treatment with >80% adherence to medications. The researchers report that offering HCV treatment in this setting is highly efficient, allowing underserved minority patients access to this type of care (McGovern, Fiore, Wurcel, et al., 2005). Since these social issues may change over time, providers need to continue to re-evaluate the patient both from a clinical standpoint and a social standpoint so that as situations change or improve, appropriate referral and evaluation may be undertaken.

Psychiatric illness and mental health issues have been frequently identified as barriers to HCV treatment both in HCV mono-infection and HIV/HCV coinfection (Alberti, et al., 2005; Soriano, et al., 2002). It is interesting to note that there is no difference between the referred and not referred groups among the mental health variables. The only significant difference was found in the number of referred patients who had received a psychiatric evaluation or were engaged in psychiatric care. This finding, based on a univariate analysis, was not significant in the multivariate model. This may indicate that HIV providers are aware of pre-existing mental health issues, are

attempting to address them, and recognize the importance of this component prior to HCV evaluation and possible treatment. It is well known that HCV treatment may exacerbate underlying psychiatric conditions and these may lead to poor adherence both to medications and clinic visits (Fumaz, Munoz-Moreno, Ballesteros, et al., 2007; Guadagnino, Trotta, Carioti, et al., 2006). However, studies have shown that HCV positive patients with pre-existing psychiatric illness during HCV treatment are no more likely to experience depressive symptoms, discontinue HCV therapy, or have higher drop out rates (Schaefer, Schmidt, Folwaczny, 2003; Pariante, Orru, Baita, 1999).

While a strength of this study is the fact that it was conducted at a single center site with very experienced HIV providers and hepatologists, who had access to a comprehensive HIV support system, such as social workers, drug counseling, case management, insurance coverage, transportation, and pharmacists to support care for these patients, it is also a limitation as it may not be generalizable to other centers without similar resources. Accordingly, it is more effective to have coinfected patients managed in the HIV care centers. This study does serve as a workable model for others involved in the care of this population. Another limitation to this study is the lack of access to the records of 117 patients due to clinic inactivity or patient death. We recognize that this group may be different and may warrant further investigation in this area. Another area for further research would be to explore the reasons for nonadherence to the liver disease evaluation in the 84 patients who did not attend their appointment. It was difficult to capture when patients did not want referral or refused referral and/or HCV treatment. Therefore, there may be some patients in the not referred group who the HIV provider would have referred, but the patient refused for some reason. We also recognize that this

study was conducted retrospectively and captures a snap shot of what was occurring with the patient and is limited to what was documented in the record. While this data gives us a glimpse into the different factors influencing referral for liver disease evaluation, these factors are not static and may change over time, thereby warranting continuous evaluation and re-evaluation for appropriateness of referral, evaluation and possible HCV treatment.

In conclusion, this study showed that by providing a designated coinfection clinic within the HIV clinic system, liver disease referral and evaluation rates improved compared with other previously reported rates. However, HCV treatment rates continue to remain low in this cohort of patients. Future research will need to be conducted to determine underlying issues related to HCV treatment reluctance in this patient population. This study also demonstrated that patients with HIV/HCV coinfection have multiple patient factors that influence referral from their HIV providers to liver disease evaluation. Multidisciplinary models of care will need to be developed, implemented and evaluated in order to provide the necessary care for these complex patients.

Figure 3.1 HIV/HCV Coinfected Cohort 2003-2006

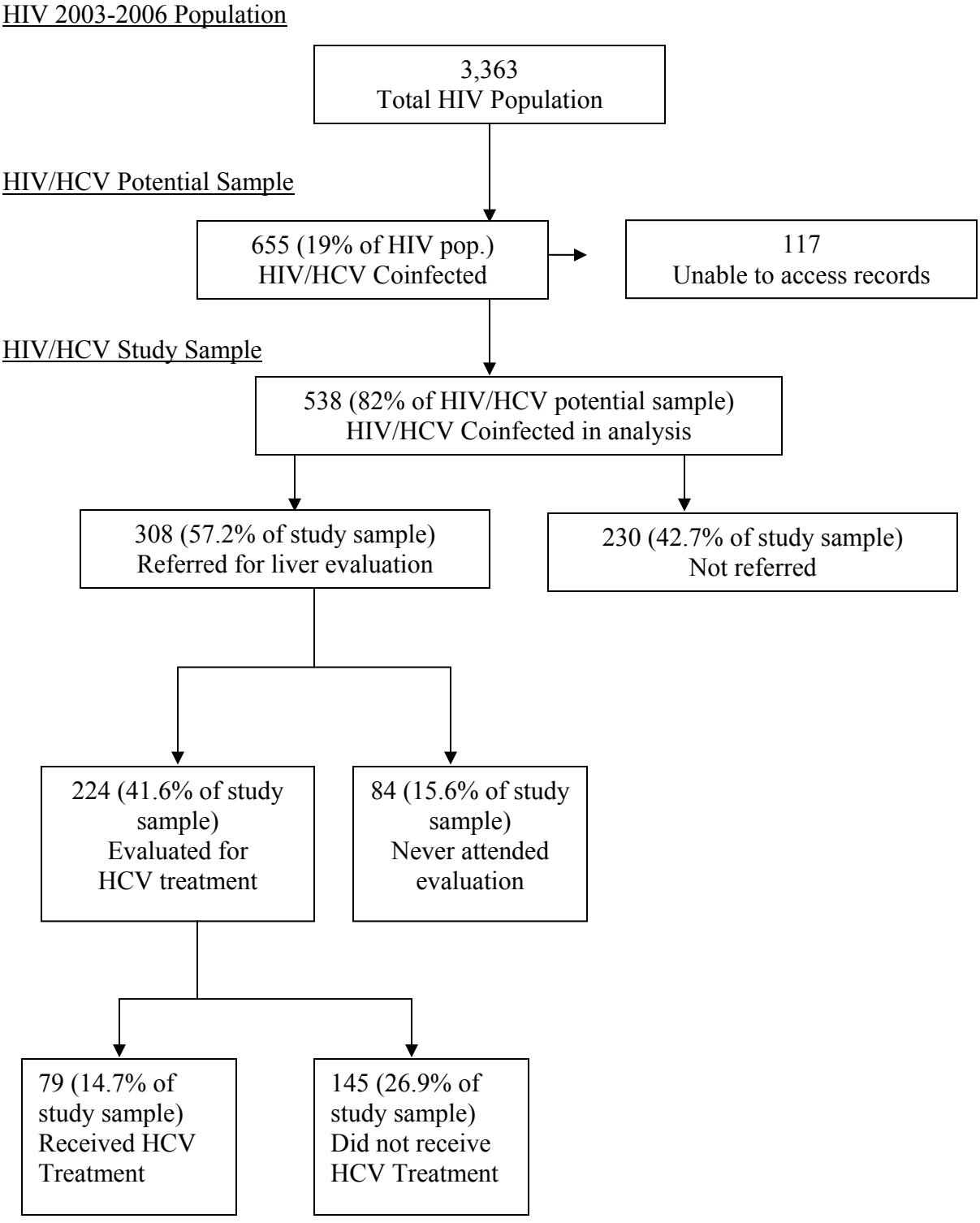

Table 3.1. Demographic Characteristics of HIV/HCV Coinfected Individuals (N=538)

Demographic Characteristics	Not Referred $N = 230$		Referred $N = 308$		p Value
Gender	n	(%)	n	(%)	0.58
Male	188	(81.7)	252	(81.8)	
Female	40	(17.4)	50	(16.2)	
Other	2	(0.9)	6	(1.9)	
Race					0.37
White	130	(56.5)	156	(50.6)	
Hispanic	50	(21.7)	77	(25.0)	
Black	37	(16.1)	62	(20.1)	
Other	13	(5.7)	13	(4.2)	
Age in years	Mean	(SD)	Mean	(SD)	0.85
	45.40	(± 7.47)	45.53	(± 8.01)	

Table 3.2. Clinical Characteristics in a Cohort of HIV/HCV Coinfected Individuals (N=538)

Clinical Characteristic	**Not Referred**			**Referred**			***p* Value**
HIV Status	N			N			
CD4 count	217	M= 389	SD ± 279	305	M= 394	SD ± 255	0.81
CD4 count <200	217	F = 63	29%	305	F = 76	24.9%	0.32
HIV viral load	216	M= 49,830	SD ± 125,734	305	M= 41,960	SD ± 136,243	0.50
On ART	230	F = 98	42.6%	308	F = 183	59.4%	<0.01*
HCV Status							
HCV viral load Copies/ml	179	M= 1,383,700	SD ± 5,000,436	297	M= 1,693,266	SD ± 4,176,469	0.47
HCV negative viral load	179	F= 83	46.4%	297	F= 14	04.7%	<0.01*
ALT	175	M=46.10	SD ± 44.86	299	M= 114.78	SD ± 214.40	<0.01*
Cirrhosis	230	F= 4	01.7%	308	F= 24	07.8%	<0.01*
HBV	230	F= 2	00.9%	308	F= 13	04.2%	0.03*
Liver biopsy performed	230	F= 3	01.3%	308	F= 107	35.6%	<0.01*
Comorbidities							
Renal	230	F= 11	04.8%	308	F= 10	03.2%	0.38
Diabetes	230	F= 17	07.4%	308	F= 30	09.7%	0.36
Hypertension	230	F= 40	17.4%	308	F= 53	17.2%	1.00
Cardiac disease	230	F= 21	09.1%	308	F= 14	04.5%	0.04*
Seizures	230	F= 12	05.2%	308	F= 15	04.9%	0.85
Respiratory	230	F= 25	10.9%	308	F= 34	11.0%	1.00
Skin cancer	230	F= 11	04.8%	308	F= 30	09.7%	0.03*
Hematologic cancers	230	F= 3	01.3%	308	F= 04	01.3%	1.00
KS pulmonary	230	F= 0	00.0%	308	F= 03	01.0%	0.26
Hemophilia	230	F= 6	02.6%	308	F= 15	04.9%	0.26

F=Frequency
M=Mean $\pm$ SD (Standard Deviation)
*=Alpha significant ≤ 0.05

Table 3.3. Psychosocial Characteristics in a Cohort of HIV/HCV Coinfected Individuals (N=538)

Characteristic	Not Referred *N* = 230 n(%)	Referred *N* = 308 n(%)	*p* Value
Mental Health			
Depression / Anxiety	113 (49.1)	171 (55.5)	0.16
Schizophrenia	15 (6.5)	17 (5.5)	0.71
Bipolar disorder	28 (12.2)	31 (10.1)	0.49
Ever had suicide attempt	11 (4.8)	14 (4.5)	1.00
Psychiatric evaluation	73 (32)	130 (42.5)	0.02*
State of Well-being score (Mean, SD)	(*n* = 169) 59.70 ± 26.69	(*n* = 275) 63.01 ± 26.33	0.20
Substance Use and Social Context			
History of ETOH	49 (21.3)	81 (26.3)	0.19
Current ETOH use	38 (16.5)	47 (15.3)	0.72
History of IVDU	123 (53.5)	159 (51.6)	0.73
Current IVDU	46 (20.0)	37 (12.0)	0.02*
History of crystal meth use	109 (47.4)	147 (47.7)	1.00
Current crystal meth use	76 (33)	67 (21.8)	<0.01*
Drug rehab	28 (12.2)	32 (10.4)	0.58
Methadone use	7 (3)	9 (2.9)	1.00
Homelessness	32 (13.9)	18 (5.8)	<0.01*
Incarceration	61 (26.5)	54 (17.5)	0.01*
Provider Perception			
Nonadherence to HIV meds/visits	43 (18.7)	41 (13.3)	0.09

* significance <0.05 level

Table 3.4. Multivariate logistic regression model for factors associated with non-referral for liver disease evaluation (N = 463)

Factors associated with non-referral for liver disease evaluation	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*p* Value
Cardiac disease	2.11 (1.05 – 4.25)	2.56 (0.96 – 6.84)	0.06
Skin cancer	0.47 (0.23 – 0.95)	0.71 (0.27 – 1.84)	0.48
Hepatitis B	0.20 (0.04 – 0.89)	0.05 (0.01 – 0.29)	0.001
Cirrhosis	0.21 (0.07 – 0.61)	0.52 (0.16 – 1.75)	0.29
ALT*	0.21 (0.12 – 0.38)	0.49 (0.30 – 0.82)	0.006
HCV viral load negative	17.48 (9.50 – 32.22)	26.50 (12.16 – 57.77)	< 0.01
On ART	0.51 (0.36 – 0.72)	0.79 (0.48 – 1.28)	0.33
Ever had psychiatric evaluation	0.64 (0.45 – 0.91)	0.64 (0.39-1.05)	0.07
Current IVDU	1.83 (1.14 – 2.93)	1.21 (0.59 – 2.50)	0.60
Current crystal methamphetamine user	1.78 (1.21 – 2.61)	1.39 (0.75 – 2.57)	0.30
Homelessness	2.60 (1.42 – 4.80)	2.90 (1.29 – 6.53)	0.01
History of incarceration	1.70 (1.12 – 2.57)	2.27 (1.28 – 4.02)	0.005

* ALT is divided by 100 IU/L in logistic regression

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Chapter IV: Adherence Issues with Liver Disease Evaluations in HIV/HCV Coinfected Individuals

Adherence Issues with Liver Disease Evaluation in HIV/HCV Coinfected Individuals

Abstract

Background: Hepatitis C (HCV) infection is reported in approximately 30% of HIV infected patients. Evaluation for treatment of HCV in HIV/HCV coinfected patients is crucial to prevent liver decompensation and/or liver failure. However, rates of HCV treatment in this patient population are still extremely low, despite improvement in referral rates for HCV evaluation and potential treatment.

Purpose: The aim of this study was to identify the factors that contributed to the failure of HIV/HCV coinfected patients pursuing evaluation of their HCV liver disease in a large university HIV clinic.

Methods: We analyzed a cohort of 538 HIV/HCV coinfected adult individuals seen during the time period of January 1, 2003 to December 31, 2006. Data was retrospectively collected to identify patient factors such as demographic information, HIV and HCV disease severity, major medical comorbidities, mental health factors, substance use, and social issues. The outcome variable was attendance at their liver disease evaluation appointment after referral from their HIV provider.

Results: Of the 538 HIV/HCV coinfected patients, 308 received a referral for liver disease evaluation, a referral rate of 57%. Of those referred patients, 224 were evaluated for their HCV related liver disease, with 79 (15%) patients initiating HCV treatment. There were 84 referred patients who never attended their liver clinic appointment. There were 230 HIV/HCV coinfected patients who never received a referral for liver care. Patients were more likely to attend their evaluation appointment if they were older, had a diagnosis of cirrhosis and had received psychiatric evaluation. Patients were more likely

to miss their appointment if they were currently drinking alcohol, using crystal methamphetamines, had a history of incarceration, and were nonadherent to HIV medications and/or HIV clinic visits, as perceived by their HIV provider.

Conclusions: The interest of HIV/HCV coinfected patients in liver disease management is affected by a number of patient factors including substance abuse and nonadherence. Strategies to assist HIV/HCV coinfected patients in accepting referral for liver disease evaluation will need to be developed in order to enhance referral rates and ultimately HCV treatment in this patient population.

Introduction

Approximately 30% of individuals infected with the human immunodeficiency virus (HIV) are coinfected with the hepatitis C virus (HCV) in the United States (Rockstroh, Mocroft, Soriano, et al., 2005). Those who acquire infection via contaminated blood, such as in intravenous drug use, have rates up to 75% for HIV/HCV coinfection (Sherman, Rouster, Chung, et al., 2002). End stage liver disease and its associated complications are now considered one of the leading causes of hospital admissions and death in the HIV infected patient since the use of antiretroviral therapy (Bica, McGovern, Dhar, et al., 2001; Martin-Carbonero, Soriano, Valencia, et al., 2001). Newer medications for treatment of HCV have demonstrated improved response rates to HCV therapy in the HIV/HCV coinfected patient (Kim, Dorn, Bouajram, et al., 2007). Recent guidelines have been published highlighting the importance of HCV treatment in this patient population (Alberti, Clumeck, Collins, et al., 2005). However, there are numerous reports of significant challenges in the treatment of HIV/HCV coinfection (Wagner, Ryan, 2005; Mehta, Thomas, Sulkowski, et al., 2005; Scheft, Fontenette, 2005; Sulkowski, Benhamou, 2007).

The challenges with HCV treatment in HIV/HCV coinfection involve referral and eligibility for treatment, the treatment regimen and associated side effects, and barriers to care for patients. Historically, patients with HIV/HCV coinfection are evaluated for liver disease management at a very low rate. Studies report that less than 50% of HIV/HCV coinfected patients are actually evaluated to determine HCV treatment candidacy (Fultz, Justice, Butt, et al., 2003; Fishbein, Lo, Reinus, et al., 2004). Even fewer numbers of HIV/HCV coinfected patients actually receive HCV treatment once evaluated. HCV

treatment rates from infectious disease providers and liver disease clinics in the United States are reported at 1-15% (Fultz, et al., 2003; Adeyemi, Jensen, Alter, et al., 2004; Clanon, Mueller, Harank, et al., 2005; Restrepo, Johnson, Widjaja, et al., 2005; Fleming, Tumilty, Murray, et al., 2005). In light of the seriousness of liver disease in this population and the improvement in drug regimens used to eradicate the hepatitis C virus, it is crucial to evaluate HIV/HCV coinfected patients for HCV treatment. The aim of this study is to describe and compare the characteristics of a group of HIV/HCV coinfected patients who were referred for liver disease evaluation and attended their appointments with a group of HIV/HCV coinfected patients who are referred but did not attend their appointment.

Methods

Setting and Design

In order to improve access to care and increase referral rates for liver disease evaluation and ultimately HCV treatment rates, a large urban HIV clinic implemented a specialty liver disease clinic located within the HIV clinic. The Owen HIV clinic is university-based and serves a large HIV population in Southern California. Care is provided by a multidisciplinary staff which serve over 3500 HIV infected patients. The liver disease clinic is run by the hepatology team from the University of California San Diego. The team provides weekly access to liver evaluation and treatment management.

A retrospective cohort study was performed to identify referral patterns, treatment evaluation and HCV treatment rates and outcomes for all HIV/HCV coinfected patients seen within the Owen HIV clinic from January 1, 2003 to December 31, 2006. To be included in the study, previously consented patients had a documented positive HIV

antibody test and a positive HCV antibody test and had at least one clinic visit in the Owen HIV clinic. Data were collected by patient chart review and data extraction from the HIV clinic electronic database. The Institutional Review Boards of University of California San Francisco and University of California San Diego approved this study.

Subject Assessments

Initially 655 HIV/HCV coinfected subjects were identified that met study inclusion criteria. Chart review was completed on 538 HIV/HCV coinfected individuals to collect patient major medical diagnosis, mental health characteristics, substance use and social issues, and provider perception of adherence to HIV medications and clinic visits. One hundred and seventeen subjects were excluded from data collection due to lack of access to complete patient records. Patient demographics and laboratory data were collected through data extraction from the electronic HIV clinic database using SAS statistical software. All laboratory data were captured on the date of or within 30 days of the initial HCV viral load draw date. The date of referral from an HIV provider was captured in addition to the date of the liver disease clinic appointment. The outcome variable for this analysis is patient attendance at the liver disease evaluation appointment. Treatment outcomes for those patients who received liver disease evaluation and HCV treatment were recorded. For those patients who were evaluated but did not receive HCV treatment, the primary reason for not receiving treatment was recorded. For patients with multiple reasons for non-eligibility for HCV treatment, only the primary reason as documented by the hepatology provider was also recorded. For those patients who did not attend their initial liver clinic appointment the primary reason as documented by the HIV provider was recorded.

Analyses

Analyses were performed to determine differences in patient characteristics between those HIV/HCV coinfected patients who were referred and attended their liver disease evaluation with those who did not attend their appointment, and to describe reasons for non-treatment and treatment outcomes. Descriptive statistics such as chi-square or t-test were performed to assess bivariate relationships between demographics, clinical characteristics, mental health, substance use and social context, and the outcome, attendance at liver disease evaluation. Frequency distributions were employed to describe treatment outcomes and reasons for non-treatment. Univariate logistic regression was performed to examine the association between not attending liver disease evaluation and each patient characteristic. Multivariate logistic regression was performed utilizing seven predictive factors in the model. Only patient factors that were statistically significant ($p<0.05$) in univariate analyses were included in the model. Model fit was assessed with goodness-of-fit tests. The potential for collinearity in the multivariate model was assessed by determining the correlation between pairs of independent variables. No pair of variables included in the same regression model was highly correlated (no correlation was greater than .30). All analyses were performed with SPSS Version 15 statistical software.

Results

Of the 538 HIV/HCV coinfected patients in this cohort a total of 308 (57%) patients were referred by their HIV provider for liver disease evaluation. Two hundred and twenty-four patients received liver disease evaluation and determination of HCV treatment candidacy. There were 84 (27%) patients who never attended their liver disease

evaluation clinic appointment (Figure 4.1). Thirty five of these patients had documentation in their HIV record as recorded by their HIV provider addressing their missed appointment, while 49 (58%) had no documentation. Reasons documented by the patient's HIV provider are listed in Figure 4.1 and include active drug use, patient refusal, nonadherence to HIV clinic visits, patient treated elsewhere, patient incarceration, and other reasons.

Demographic and Clinical Characteristics

The total sample of 308 HIV/HCV coinfected patients referred for liver disease evaluation included 252 (82%) males, with a mean age of 44.8 years. Fifty one percent of the subjects were Caucasian, 25% were Hispanic, 20% were African American, and 4% were from other ethnic groups. Data in Table 4.1 shows that there is no difference in gender or race/ethnicity between those patients who were evaluated for their liver disease and those patients who did not attend their appointment. There is a significant age difference between the groups. Subjects who attended their appointment were approximately 3 years older than those patients who did not attend their evaluation appointment. The univariate odds ratio indicated that for every year older the patient was, the patient was 95% more likely to attend the evaluation appointment.

Within the total sample of 308, the patients had fairly well controlled HIV disease with a mean CD4 cell count of 396. However, 75 patients (24%) had CD4 cell counts below 200. One hundred eighty three (59%) of the total sample were taking antiretroviral therapy at the time of their referral for liver disease evaluation (Table 4.2). The majority of the sample had HCV viral load testing performed. Twenty-four patients had evidence of cirrhosis with most (23, 96%) being in the group that was evaluated. The mean ALT

value for the total sample was 112 IU/L indicating that HIV/HCV coinfected patients were referred when liver function tests were elevated. Thirteen patients in the total sample also had evidence of hepatitis B disease. Other major medical comorbidities were captured for this cohort. There were no significant differences between the groups in HIV status, HCV status or medical comorbid conditions, with the exception of cirrhosis as previously indicated (Table 4.2).

Mental Health and Substance Use

Fifty six percent of the total sample had evidence of depression and/or anxiety, 10% had bipolar disease, 6% had a diagnosis of schizophrenia, and 5% had documentation of a previous suicide attempt. However, there was no significant difference between the two groups in these mental health characteristics (Table 4.3). One hundred and four patients (46.6%) in the group that were referred for evaluation and attended their appointment had evidence of psychiatric evaluation, while only 26 patients (31.3%) in the group that was not seen in the liver clinic had psychiatric evaluation (p=0.02). In univariate analysis those patients who had received a psychiatric evaluation were more likely to have attended their liver disease evaluation appointment than those who had not received a psychiatric evaluation (OR 0.52, CI=0.31-0.89). The total sample mean score on a patient self-reported State of Well-Being questionnaire was 62.64 out of a possible 100 points (100 being the optimal or best state of well-being).

Within the total sample, 26% had a history of alcohol use, 52% had a history of intravenous drug use, 48% had a history of using crystal methamphetamine, and 12% were currently using intravenous drugs. However, there was no difference between the groups in current intravenous drug use. There were significant differences between the

groups in terms of current alcohol and current crystal methamphetamine use. Those patients who were currently drinking alcohol were two times more likely not to attend their liver clinic appointment by univariate analysis. Those patients who were currently using crystal methamphetamine were 2.8 times more likely not to attend their appointment. Nonattendance at their liver clinic appointment was also associated with nonattendance at their HIV clinic appointments and nonadherence to their HIV medications as reported by HIV providers. If patients were nonadherent to their HIV medications and/or HIV clinic appointments they were 2.7 times more likely to miss their liver clinic appointment. Patients who had a history of incarceration were 3.1 times more likely to be nonadherent to their liver disease evaluation.

HCV Treatment Candidacy

Of the 224 patients who received liver disease evaluation, 79 (35%) went on to receive HCV treatment. Sustained virologic response (SVR), as defined by a negative HCV viral load 6 months after HCV treatment is completed, is 41% in this cohort of HIV/HCV patients. For those 145 patients who did not receive HCV treatment the primary reason as documented by the hepatology provider is current substance abuse (18%), either to intravenous drugs or crystal methamphetamine. Nonadherence to subsequent liver clinic appointments (17%) was the second most frequently cited reason for non-treatment (Table 4.5). Of the 224 patients who were evaluated for their liver disease, 58 (26%) patients had either canceled or had multiple no shows to their initial liver disease clinic appointment, some as many as five missed appointments. In 60% of the sample (134 patients) the average time from HIV provider referral to the initial liver clinic evaluation appointment was less than three months, with 30% of the sample (78

patients) waiting less than six weeks between referral and their liver clinic evaluation appointment.

Factors Associated with Nonadherence to Liver Disease Evaluation

Multivariate logistic regression was performed to examine patient factors that would determine the probability of being in the group that did not attend their liver disease clinic appointment. Two patients from the total sample had missing data, one patient from the referred with evaluation group and the other from the referred but not evaluated group. Therefore, the total analysis includes 306 patients. Seven factors were included in the multivariate model. Patient factors were only placed in the model if they were statistically significant in the univariate analysis. These patient factors were: patient age, diagnosis of cirrhosis, had a psychiatric evaluation, current alcohol use, current crystal methamphetamine use, a history of being incarcerated, and provider perception of nonadherence to HIV medications and/or HIV clinic visits. The overall model was significant (Chi square=42.76, $p<0.01$). Only two patient factors remained significant in the overall model while holding constant for all other factors. These were history of incarceration and having psychiatric evaluation (Table 4.4).

Discussion

Some of the challenges in the care of patients with HIV/HCV coinfection has been in screening, diagnosis, evaluation and treatment of HCV. Many studies have highlighted difficulties in terms of patient factors, provider factors and system issues. Patient factors have included active substance use, current alcohol use, nonadherence to clinic visits and medications, and evidence of a chaotic lifestyle, all leading to difficulty in HCV treatment (Nunes, Saitz, Libman, et al., 2006; Pelapu, Cheng, Kim, et al., 2006;

Fishbein, et al., 2005; Fultz, et al., 2003; Adeyemi, et al., 2004). Several studies have examined provider barriers and include provider lack of knowledge about HCV treatment, and difficulty in referral or access to specialty care (Thompson, Ragland, Hall, et al., 2005; Clanon, et al., 2005). However, national guidelines recommend that all HIV/HCV coinfected patients be evaluated for the possibility of HCV treatment (Albert, et al., 2005; Soriano, et al., 2002). Even so, referral rates and ultimately HCV treatment rates have been very low clearly identifying an ongoing problem.

The findings reported here continue to highlight these barriers to treatment for HCV. The study was conducted in a setting where care of HIV/HCV coinfected patients is optimized. A multidisciplinary team is accessible to coordinate care and provide financial and social resources to enhance patient outcomes. Specialty care for liver disease is located within the HIV clinic at least weekly. HIV providers screen HIV infected patients for HCV (>95%) and refer HIV/HCV coinfected patients for liver disease evaluation at a rate of 57%. In the group of patients that was not referred for liver disease evaluation, 46% had undetectable HCV viral load. However, even with these systems in place, only 73% of the referred group actually attended their evaluation appointment. While this study highlights a significant adherence problem, the underlying reasons for nonadherence to liver disease evaluation are still not clearly understood.

There was no difference between those evaluated for their liver disease and the group that did not attend their appointment in the status of their HIV disease, their medical comorbidities, or their mental health status. Patients that had a diagnosis of cirrhosis were more likely to attend their liver evaluation appointment. This is consistent with other reported studies. Strathdee (2005) found that in HCV infected drug users those

patients that perceived the threat of progression of their liver disease and were not using alcohol were more likely to accept referral for HCV treatment evaluation. Gender and race did not make a difference in attendance at their liver clinic appointment; however, age was significantly different. The group that did not attend their appointment was approximately three years younger. Fishbein (2004) reported that older HIV/HCV coinfected patients were more likely to keep their HCV evaluation appointments. These findings are similar to most adherence literature, which shows that younger as compared to older patients are less likely to adhere to a variety of regimens including appointments (Reynolds, 2004; Jani, 2002).

It is interesting to note that those patients who did not attend their evaluation appointments were more likely to be currently using alcohol or crystal methamphetamine. Current intravenous drug use was not different between the two groups in our study. Thirty-seven patients (12%) were currently using intravenous drugs, as documented by their HIV provider, in our total study sample. Our study did not attempt to quantify alcohol use through use of a standardized measurement tool such as the CAGE questionnaire. Alcohol use was documented by the HIV provider as an issue in HIV care. In a recent study of HIV/HCV coinfected patients with alcohol problems, heavy alcohol use was found to be the single most important contraindication to HCV treatment (Nunes, et al., 2006). However, this was also associated with other barriers such as depression, current drug use, poorly controlled HIV disease, and decompensated liver disease. Not all of the barriers to HCV treatment identified by Nunes (2006) were found to be significant in our study. Other studies have also highlighted the presence of substance use and/or

alcohol use as a main contributing factor to lack of treatment in this population (Palepu, et al., 2006; Adeyemi, et al., 2004; Fultz, et al., 2003).

While the mental health characteristics of the groups were not significantly different, the groups were different in terms of psychiatric evaluation. This was significant in the univariate analysis as well as the multivariate model. Patients who had been evaluated by psychiatry were more likely to attend their liver clinic appointment. This may point to the fact that attendance in psychiatric care or counseling can influence the patients willingness to be evaluated for their liver disease. Historically, providers have been hesitant to begin HCV treatment in HIV/HCV coinfection due to the high prevalence of existing psychiatric disease and substance use disorders (Weiss, Gorman, 2006).

In this sample, HIV/HCV coinfected patients who had a history of incarceration, either with jail time or prison records, were significantly more likely to not attend their liver disease evaluation appointment. This highlights the prevalence of the chaotic lifestyle of many of these coinfected patients. In our study, of those patients referred for liver disease evaluation, 54 patients (18%) had evidence of incarceration and 18 patients (6%) experienced periods of homelessness. These barriers to HCV evaluation have been found in other studies as well (Thompson, et al., 2005; Adeyemi, et al., 2004). It is estimated that one-third of all those infected with HCV in the United States cycle through the prison or jail system every year (Hammett, Harmon, Rhodes, 2002). McGovern (2005) reports a model for care including screening, education, counseling and HCV treatment of the incarcerated patient population in order to address this issue. To address HCV and its associated liver disease in these patients, providers will need to continuously

re-evaluate, provide continuous education of the importance of evaluation and re-refer these patients for evaluation.

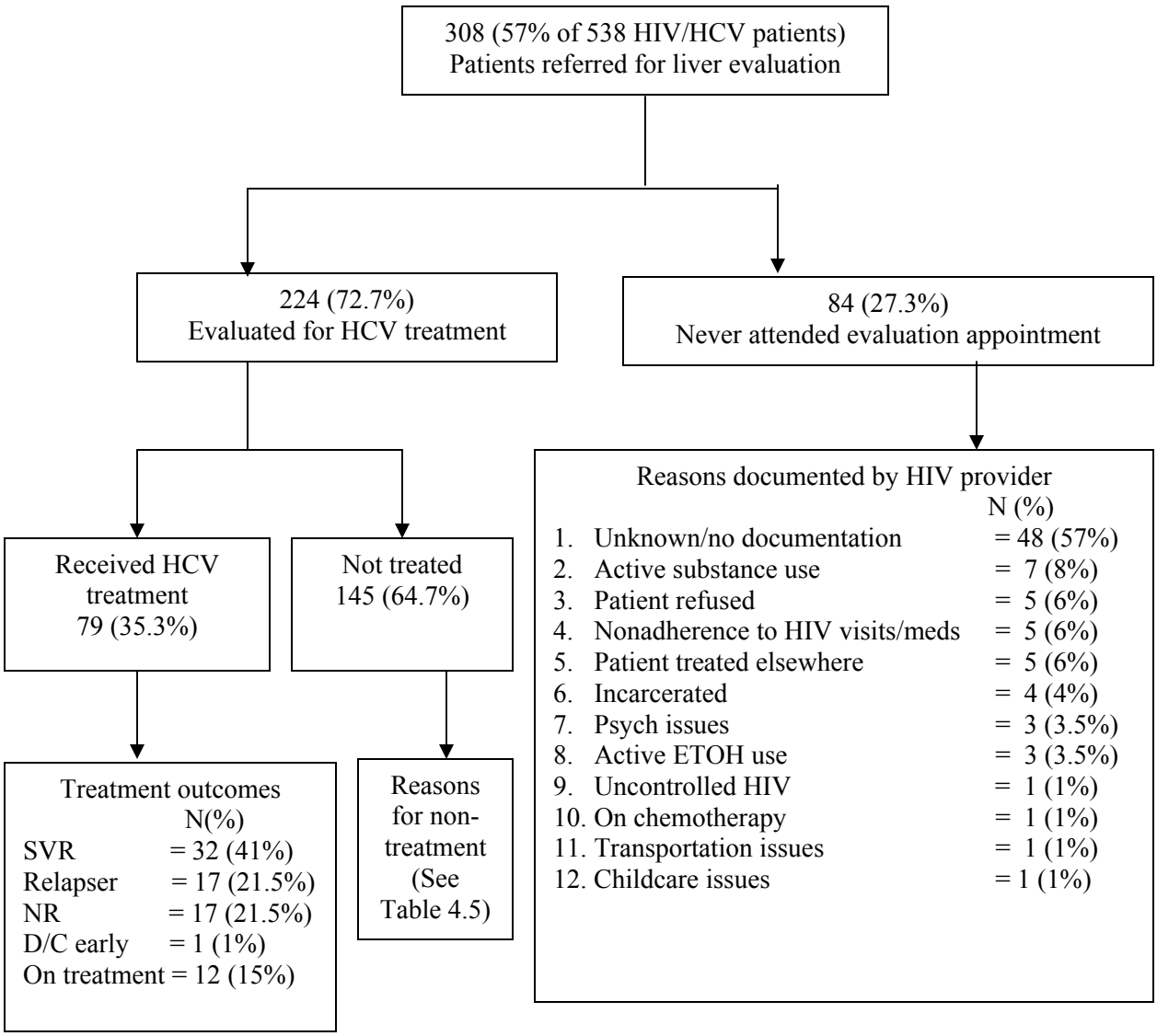
Initiation of HCV treatment continues to be a challenge in the HIV/HCV coinfected population. Within this cohort of 538 HIV/HCV patients, 57% were referred for liver disease evaluation. Of this group, 73% went on to receive evaluation for HCV management and HCV treatment candidacy. Within this evaluated group, 79 patients received HCV treatment, 35% of the referred group; however, if you calculate this from the original sample, this is an HCV treatment rate of 6.8%. Unfortunately, this is consistent with other published studies (Table 4.6). Hepatology providers documented reasons for HCV treatment ineligibility in 123 patients (Table 4.5). The primary reasons for non-treatment included current substance abuse, nonadherence to subsequent liver clinic appointments, minimal disease on liver biopsy, and patient refusal. Many of the reasons listed by hepatology providers are modifiable, such as substance use, nonadherence to visits, and patient refusal, and these reasons warrant intervention to assist the patient with successful evaluation and appropriate HCV treatment.

Recent studies cite nonadherence to clinic visits as one of the primary factors influencing poor referral and HCV treatment rates (Ilyas, et al., 2005; Clanon, et al., 2005; Shim, et al., 2004). Our study clearly identifies an issue in HIV/HCV coinfected patients accepting referral for liver disease evaluation and even once referred and evaluated becomes an issue for the initiation of HCV treatment. HIV providers documented some comments from patients regarding their lack of acceptance for liver disease evaluation referral. Patient concerns included fear of HCV treatment and its associated side effects, fear of needles or the liver biopsy as well as social concerns.

Health care providers will need to more effectively address these patient concerns in order to increase acceptance of referral and evaluation for HCV related liver disease.

This study has several limitations. Data was retrospectively collected from chart review and may not represent all of the factors that influence attendance at liver clinic evaluation appointments. Further research into this area will require patient input as important insights may be gained from this approach. This study represents a single cohort sample from a single center and therefore, may not be generalizable to other clinics and patient populations. However, this data provides insight into referral and liver disease evaluation patterns for the treatment of HCV in HIV/HCV coinfected patients. Further study will need to be conducted to determine strategies to assist patients in recognizing the importance of liver disease evaluation. Multidisciplinary interventions, such as education and counseling, adherence strategies, substance abuse treatment, and resource identification will need to be provided in this patient population in order to impact rates of referral, evaluation and ultimately HCV treatment.

Figure 4.1. Outcomes for HIV/HCV Coinfected Patients Referred for Liver Evaluation between January 1, 2003 and December 31, 2006.



SVR=Sustained Virologic Response
NR=Non-responder
D/C=Discontinued therapy

Table 4.1 Demographic Characteristics of HIV/HCV Coinfected Individuals Referred for Liver Disease Evaluation (N=308)

Demographic Characteristics	**Not Evaluated No Show *N* = 84**		**Evaluated *N* = 224**		*p* Value
Gender	n	(%)	n	(%)	0.22
Male	71	(84.5)	181	(80.8)	
Female	10	(11.9)	40	(17.9)	
Other	3	(3.6)	3	(1.3)	
Race					0.32
White	45	(53.6)	111	(49.6)	
Hispanic	19	(22.6)	58	(25.9)	
Black	14	(16.7)	48	(21.4)	
Other	6	(7.1)	7	(3.1)	
Age in years	Mean	(SD)	Mean	(SD)	<0.01
	43.21	(±8.08)	46.39	(±7.83)	

Table 4.2 Clinical Characteristics in a Cohort of HIV/HCV Coinfected Individuals Referred for Liver Evaluation (N=308)

Clinical Characteristic	Not Evaluated (No Show)			Evaluated			*p* Value
HIV Status	N			N			
CD4 count	84	M=400	SD ± 241	221	M= 392	SD ± 261	0.82
CD4 count <200	84	F =16	19%	221	F =59	26.7%	0.18
HIV viral load	84	M= 31,203	SD ± 78,113	221	M= 46,049	SD ± 152,600	0.39
On ART	84	F =43	51.1%	224	F =140	62.5%	0.09
HCV Status							
HCV viral load Copies/ml	80	M= 2,150,408	SD ± 5,729,532	217	M= 1,524,734	SD ± 3,433,790	0.25
ALT	80	M=108	SD ± 200	219	M= 116	SD ± 220	0.78
Cirrhosis	84	F=1	1.2%	224	F= 23	10.3%	<0.01*
HBV	84	F=4	0.5%	224	F=9	0.4%	0.76
Comorbidities							
Renal	84	F= 4	0.5%	224	F= 6	0.3%	0.50
Diabetes	84	F= 6	0.7%	224	F=24	10.7%	0.40
Hypertension	84	F= 10	12%	224	F=43	19.1%	0.17
Cardiac disease	84	F= 3	3.5%	224	F=11	0.5%	0.77
Seizures	84	F=4	0.5%	224	F=11	0.5%	1.00
Respiratory	84	F=14	16.7%	224	F=20	0.9%	0.07
Skin cancer	84	F=8	9.5%	224	F=22	9.8%	1.00
Hematologic cancers	84	F=0	0%	224	F=4	1.8%	0.58
KS pulmonary	84	F=1	1.2%	224	F=2	0.9%	1.00
Hemophilia	84	F=4	4.8%	224	F=11	4.9%	1.00

F=Frequency
M=Mean $\pm$ SD (Standard Deviation)
*=Alpha significance $\leq$0.05

Table 4.3 Psychosocial Characteristics in a Cohort of HIV/HCV Coinfected Individuals Referred for Liver Disease Evaluation (N=308)

Characteristic	Not Evaluated N=84 (No Show) N (%)	Evaluated N=224 N (%)	*p* Value
Mental Health			
Depression / Anxiety	39 (46.4)	132 (58.9)	0.052
Schizophrenia	7 (8.3)	10 (4.5)	0.26
Bipolar disorder	10 (11.9)	21 (9.4)	0.53
Ever had suicide attempt	4 (4.8)	10 (4.5)	1.00
Psychiatric evaluation	26 (31.3)	104 (46.6)	0.02*
State of Well-being score (Mean, SD)	(*n* = 76) 61.79 ± 25.67	(*n* = 199) 63.48 ± 26.62	0.64
Substance Use and Social Context			
History of ETOH	23 (27.4)	58 (25.9)	0.77
Current ETOH use	19 (22.6)	28 (12.5)	0.03*
History of IVDU	39 (46.4)	120 (53.6)	0.31
Current IVDU	14 (16.7)	23 (10.3)	0.17
History of crystal meth use	42 (50)	105 (46.9)	0.70
Current crystal meth use	30 (35.7)	37 (16.5)	<0.01*
Drug rehab	7 (8.3)	25 (11.2)	0.54
Methadone use	1 (1.2)	8 (3.6)	0.45
Homelessness	8 (9.5)	10 (4.5)	0.11
Incarceration	26 (31)	28 (12.5)	<0.01*
Provider Perception			
Nonadherence to HIV meds/visits	19 (22.6)	22 (9.8)	<0.01*

* significance <0.05 level

Table 4.4. Multivariate logistic regression model for factors associated with nonadherence to liver disease evaluation (N = 306)

Factors associated with non-adherence to liver disease evaluation	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	***p* Value**
Age	0.95 (0.92 –0.98)	0.97 (0.93 – 1.00)	0.05
Cirrhosis	0.11 (0.01 – 0.79)	0.14 (0.02 – 1.08)	0.06
Psychiatric Evaluation	0.52 (0.31 – 0.89)	0.52 (0.29 – 0.93)	0.03
Current ETOH use	2.05 (1.07 – 3.91)	1.81 (0.89 – 3.69)	0.10
Current Crystal Methamphetamine use	2.81 (1.59 – 4.96)	1.79 (0.92 – 3.46)	0.08
History of incarceration	3.14 (1.71 –5.77)	2.08 (1.06 – 4.11)	0.03
Nonadherence to HIV meds/visits	2.68 (1.37 – 5.27)	1.89 (0.88 – 4.07)	0.11

* ALT is divided by 100 IU/L in logistic regression

Table 4.5. Primary reasons for HCV treatment ineligibility in a HIV/HCV Coinfected cohort

Primary Reason for HCV Treatment Ineligibility	*N*	*N*=145 (%)
1. Current substance abuse	27	(19%)
2. Nonadherence to liver clinic appointments	25	(17%)
3. Unknown	22	(15%)
4. Minimal disease on biopsy	17	(12%)
5. Treatment planned in future	17	(12%)
6. Patient refused treatment	13	(9%)
7. Negative HCV PCR	6	(4%)
8. End stage liver disease	5	(3.5%)
9. Current ETOH use	4	(3%)
10. Uncontrolled HIV	3	(2%)
11. Acute HCV – patient cleared	3	(2%)
12. Transportation issues	1	(0.07%)
13. On chemotherapy	1	(0.07%)
14. Homeless	1	(0.07%)

Table 4.6. Summary of referral and initiation of therapy identified in treatment of HIV/HCV coinfected patients

Authors	Total HIV/HCV coinfected patients	Pts refrred for HCV *n*(%)	Not referred *n*(%)	Treated *n*(%)	Not treated *n*(%)	Reasons for no treatment						
						Non-adherence with clinic visits	Drug/ alcohol	ESLD	Psych	Un-controlled HIV	NL Bx	Other
Nunes, et al. 2006	*n*=200 Cohort with ETOH, Boston	200	NA	21 (18%)	147 (88%)	NA	87 (52%)	14 (8%)	63 (38%)	27 (16%)	NA	NA
Cacoub, et al. 2006	*n*=300 Multicenter specialized clinic, France	380	NA	175 (46%)	205 (54%)	NA	46 (43%)	NA	45 (73%)	NA	35 (32%)	NA
Butt, et al. 2006	*n*=6502 National VA database, USA	6502	NA	468 (7.2 %)	6034 (92.8%)	NA	NA	NA	NA	NA	NA	NA
Ilyas, et al. 2005	*n*=758 Single site urban referral clinic, San Diego	313 (41%)	445 (59%)	85 (27%)	228 (73%)	170 (75%)	16 (7%)	4 (2%)	8 (3%)	2 (1%)	12 (5%)	16 (7%)
Clanon, et al. 2005	*n*=228 HIV County Care Network, No. California	228	NA	2 (1%)	226 (99%)	27 (12%)	36 (16%)	NA	NA	NA	NA	NA
Thompson et al.. 2005	*n*=133 Homeless cohort, San Francisco	133	NA	4 (3%)	129 (97%)	NA	49 (52%)	NA	41 (43.6%)	NA	20 (21.3 %)	NA
Restrepo, et al. 2005	*n*=104 Liver clinic, urban NY	104	NA	16 (15%)	88 (85%)	30 (40%)	11 (15%)	10 (13%)	6 (8%)	NA	NA	31 (35%)
Rauch, et al. 2005	*n*=135 HIV clinic, Switzerland	107	NA	9 (8%)	98 (92%)	34 (32%)	35 (33%)	NA	13 (12%)	NA	NA	17 (16%)
Fleming, et al. 2005	*n*=260 Specialized coinfection clinic, Boston	149	NA	21 (8%)	239 (92%)	24 (23%)	24 (23%)	13 (12%)	22 (21%)	14 (13%)	NA	36 (27%)
McGovern, et al. 2005	*n*=164 Subpecialty coinfection clinic (under-served / incarcerated), Boston	164	NA	46 (28%)	118 (72%)	18 (15%)	8 (7%)	3 (3%)	16 (13%)	NA	20 (17%)	53 (45%)
Adeyemi, et al. 2004	*n*=110 Single site urban referral clinic, Chicago	110	NA	14 (13%)	96 (87%)	15 (14%)	14 (13%)	4 (4%)	4 (4%)	7 (6%)	3 (3%)	41 (43%)
Fishbein, et al. 2004	*n*=125 Single site urban referral clinic, NY	61 (48.8 %)	64 (51.2 %)	1 (<1%)	124 (99%)	40 (66%)	NA	NA	NA	NA	NA	NA
Fultz, et al. 2003	*n*=300 Multicenter (3) VA clinics, Cleveland, Houston, Manhattan	90 (30%)	210 (70%)	2 (2%)	88 (98%)	NA	11 (12%)	11 (12%)	19 (21%)	NA	NA	36 (41%)

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Chapter V: Conclusions and Next Steps

Conclusion and Next Steps

In summary, hepatitis C related liver disease and its associated complications is a major problem for individuals coinfected with the human immunodeficiency virus and the hepatitis C virus (HIV/HCV). In light of the progressive nature of liver damage caused by HCV, it is vital that HIV/HCV coinfected individuals be screened, diagnosed, evaluated and treated for the hepatitis C virus. Research highlights the importance of early identification and evaluation for HCV in the setting of HIV/HCV coinfection. As part of the evaluation process, HCV treatment necessity and patient candidacy is determined. In those patients who are deemed appropriate for HCV treatment, strategies to improve HCV treatment regimens, manage treatment related side effects, improve adherence to medications and clinic visits, and ultimately enhance treatment outcomes are needed. Strategies are also needed to modify those factors that will enable more HIV/HCV coinfected patients to undergo HCV treatment. These strategies will include multidisciplinary resources to address issues such as substance use, access to care, patient and provider knowledge of the importance of HCV treatment as well as the HCV treatment regimen, and adherence to liver disease evaluation and the HCV treatment.

Key Findings

Model of Care

Several models of care have been identified in the literature to improve the awareness of HCV, to enhance referral for liver disease evaluation and to increase rates of HCV treatment in HIV/HCV coinfection. These studies attempted to determine the effectiveness of a designated HIV/HCV coinfection clinic located within a large HIV clinic. Five hundred and thirty eight HIV/HCV coinfected adult patients were identified

and analyzed from an urban HIV clinic, from January 2003 to December 2006. Data were collected to determine patient characteristics in this cohort of HIV/HCV coinfected patients. Collected data includes demographic information, HIV and HCV disease severity, major medical comorbidities, mental health issues, substance use and social context. HIV providers referred 308 HIV/HCV coinfected patients for liver disease evaluation, a 57% referral rate. This is one of the highest reported referral rates for liver disease evaluation to date indicating the effectiveness of locating hepatology providers within the HIV clinic system. Of those HIV/HCV coinfected individuals who were not referred for liver disease evaluation, 43% were found to be HCV viral load negative, therefore, referral was not indicated. Since hepatology providers are accessible and available within the HIV clinic, this may heighten HIV provider awareness of HIV/HCV coinfection, allow for consultation and ease of referral for liver evaluation, as well as provide a familiar system for patients to access care.

Adherence Issues in HIV/HCV Coinfection

Of the 308 HIV/HCV coinfected patients referred for liver disease evaluation, 84 patients did not attend their liver clinic appointment. The patients that did not attend their appointment were found to be significantly younger, were currently using alcohol and/or crystal methamphetamines, and had a greater likelihood of a history of incarceration ($p<0.05$). Other underlying reasons for lack of attendance at their appointment has yet to be determined and will require further study. This investigation clearly identifies the issue of nonadherence to liver clinic appointments in this population. Even within the group that initially attended their appointment, many of them had previous cancellations or no shows to prior appointments. Nonadherence to subsequent liver clinic appointments

was identified by hepatologists as the second leading cause for non-treatment in those patients referred for liver disease evaluation. Other research studies have found similar issues with nonadherence in the HIV/HCV coinfected population leading to difficulties in HCV treatment initiation. Further research will need to be conducted to explore patient perceptions of HCV-related liver disease, of HCV treatment, and of the personal consequences of non-treatment. Once underlying reasons for nonadherence are more clearly understood, interventional strategies may be designed to address these barriers to adherence.

Patient Factors in Referral

A significant finding from this research is that patient factors such as severity of HIV disease, most major medical comorbidities, and mental health factors were not significantly different in either the group that was referred for liver disease evaluation and those not referred. This finding is consistent with national guidelines in care of patients with HIV/HCV coinfection which recommends all HIV/HCV coinfected individuals be evaluated to determine treatment candidacy. In this study, those patients with significant cardiac disease or a history of skin cancer or Kaposi's skin lesions were less likely to be referred for HCV evaluation highlighting the recognition that some medical comorbidities take precedence over HCV treatment. Patient factors that influenced referral for liver disease evaluation included indicators of liver disease, such as the presence of hepatitis B, cirrhosis, elevated liver function tests, and HCV viral load results ($p<0.05$). Patient factors found to influence non-referral included substance use, history of incarceration, and homelessness ($p<0.05$). These results highlight the fact that HIV providers perceived social factors indicative of a chaotic lifestyle to be deterrents to

candidacy for HCV treatment. However, research has indicated that successful HCV treatment is possible despite these negative social factors, albeit at a lower rate and requiring adequate support systems to achieve treatment adherence. Further research is needed to find more effective strategies to support patients with substance use issues, as well as chaotic lifestyles, such as homelessness and incarceration.

Patient Factors in Evaluation

In order to determine patient factors associated with nonadherence to liver disease evaluation, descriptive statistics, univariate and multivariate logistic regression were performed. Factors that were found to be both significant in univariate and multivariate analysis were history of incarceration (OR 2.08, CI 1.06-4.11) and psychiatric evaluation (OR .52, CI .29-.93). Those patients with a history of incarceration were less likely to attend their appointment. Patients who had received psychiatric evaluation were more likely to attend their liver clinic appointment. Other factors considered clinically significant, and also found to be statistically significant in univariate analysis included age, presence of end stage liver disease, current alcohol use, current crystal methamphetamine use, and nonadherence to HIV medications and/or HIV clinic visits. Older patients and those with significant liver disease were more likely to attend their liver evaluation appointment. Those patients with current alcohol or crystal methamphetamine use, and those patients with documented adherence issues to their HIV clinic visits or HIV medications were more likely to miss their liver disease evaluation appointment. Neither disease severity, gender, race, medical comorbidities, nor mental health issues were different between the groups that did and did not attended their liver disease appointment. There appear to be some underlying reasons for nonadherence to

liver disease evaluation appointments that this study was not able to capture. In order to understand the reasons for missed appointments, patient focus groups would need to be conducted to enable researchers to gain insight into patient concerns and other factors influencing missed appointment for liver disease evaluation.

Limitations

This investigation had several limitations. The study was conducted at a single center site with very experienced providers to both HIV and HCV disease. Patients had access to various support systems to enhance their treatment options and ultimately their outcomes. This may influence the generalizability of this study to other clinics and models of care for patients with HIV/HCV coinfection. Research was only conducted for a specified period of time and may not have captured those patient factors that change over time, such as mental health issues, substance use and social context. This calls for providers to continuously re-evaluate HIV/HCV coinfected patients for candidacy for referral, evaluation and potential HCV treatment. The study did not address the appropriateness of referral by HIV providers or liver disease evaluation in the cohort of HIV/HCV coinfected patients and further research will be necessary to determine this factor.

Future Directions

This research study gives insight into the patient issues associated with liver disease referral and HCV evaluation in a cohort of HIV/HCV coinfected patients. Certain challenges such as substance use and social issues continue to be a major problem in this patient population and influence their ability to obtain referral, liver disease evaluation, and ultimately HCV treatment. Health care providers working with HIV/HCV coinfected

patients will need to maximize systems to address these needs. HCV treatment in the setting of HIV is complex and will require new strategies, not only in newer treatment regimens with better virologic outcomes and more tolerable medications, but in holistic patient care to meet the needs of this patient population.

Future research will need to be conducted to determine issues of adherence to clinic visits as well as medication adherence. As HIV/HCV coinfected patients add a complex HCV treatment regimen to their management of HIV disease, new interventions to assist them in navigating these issues will be vital. Input from the patient's perspective is necessary as clinicians and researchers aim to improve systems to support patients in evaluation and treatment for their liver disease.

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