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The Hepatitis C Care Continuum Among Hiv-Infected Patients In A Large Urban Outpatient Clinic: Identifying Barriers To Achieving Optimal Outcomes

Austin Weiss

THE HEPATITIS C CARE CONTINUUM AMONG HIV-INFECTED PATIENTS IN A LARGE URBAN OUTPATIENT CLINIC: IDENTIFYING BARRIERS TO ACHIEVING OPTIMAL OUTCOMES

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ABSTRACT

BACKGROUND: Despite the availability of effective therapies for the treatment of chronic hepatitis C virus (HCV) infection, therapeutic benefits have yet to be experienced by patients affected by the disease, including human immunodeficiency virus (HIV) infected individuals. The aims of this study were to describe the continuum of hepatitis C care among HIV/HCV coinfected patients and identify barriers to achieving optimal management outcomes.

DESIGN AND METHODS: We conducted a retrospective analysis of HIV/HCV coinfected patients under care at an urban HIV referral clinic, comprising patients identified with HCV infection from 2002-2014. Electronic medical records of eligible patients were reviewed, capturing demographic and clinical data. Logistic regression analyses were used to identify predictors of failing to achieve optimal outcomes along key points on the continuum of care.

RESULTS: Of 135 patients in the study, 62% were male, and median age was 56 years. Predominant racial groups were black (48.9%) and white (32.6%), and 91.8% had some form of public insurance. A significant proportion had psychiatric and substance abuse comorbidities that impacted treatment candidacy, including depression (40%), active alcohol abuse (16.3%), and ongoing illicit drug use (22.2%). The majority of patients had HCV genotype 1 disease (1a - 47%, 1b -11.1%), 91.9% were on antiretroviral therapy, and 65% had HIV viral loads < 20 copies/ml. 24.4% of subjects had cirrhosis, 27% of whom had a history of decompensated disease. The

continuum of care showed that of 135 study subjects, 71% were referred for treatment, 67% had a treatment evaluation, 36% were eligible for treatment, 21% were prescribed treatment, and only 13% achieved post-treatment sustained virologic response (SVR). More than half (54%) of patients not referred for HCV treatment evaluation were deemed not to be candidates for treatment by their providers. Predictors of not being referred for HCV treatment evaluation were female gender (odds ratio: 0.240, 95% confidence interval: 0.064 - 0.907, p = 0.035), depression (OR: 0.215, CI: 0.057 - 0.812, p = 0.023), and high HIV viral load (for each 1 log increase in viral load, OR: .608, CI: 0.373 - 0.992, p = 0.046). Predictors of not being prescribed HCV treatment were high HIV viral load (OR: 0.106, 95% CI: 0.025 - 0.458, p = 0.003), and having an acquired immunodeficiency syndrome (AIDS) diagnosis by both CD4 count criteria and history of opportunistic infections (OR: 0.037, 95% CI: 0.001 - 0.924, p = 0.045).

CONCLUSIONS: The number of patients achieving HCV cure remains suboptimal. The benefits of available and effective HCV therapies will not be realized unless effective measures are implemented for dealing with barriers to care. More studies are needed to explore ways to improve modifiable factors associated with suboptimal HCV management outcomes.

CHAPTER 1: INTRODUCTION

1.1) Background: HCV Infection

1.1a) Introduction

The hepatitis C virus (HCV) is an enveloped, single stranded, positive sense RNA virus approximately 55-80nm in size. It is the only member of the *Hepacivirus* genus of *Flaviviridae* family of viruses. [1] In 1975, it was first shown that the majority of cases of transfusion-associated hepatitis were caused by neither hepatitis A virus (HAV) nor hepatitis B virus (HBV), the only two known human hepatitis viruses at the time. This drew attention to the likelihood of a separate etiology. [2] It was nearly a decade and a half later (1989) that the virus responsible for most transfusion-associated non-A non-B hepatitis was identified and cloned, and named hepatitis C virus (HCV). [2]

There are six genotypes of HCV, each with subtypes. The genotypes are numbered 1 through 6, while the subtypes are designated letters a, b, and c. This system of nomenclature for HCV genotypes was first proposed in 1994, as it was recognized that the HCV variants may affect disease progression and response to treatment. [3] The genetic variation between HCV genotypes is significant, with a 31-34% variation in their nucleotide sequence and about a 30% variation in amino acid sequence. [3]

An image of HCV genome is shown below, highlighting the posttranslational cleavages that lead to the production of functional HCV proteins. [4]

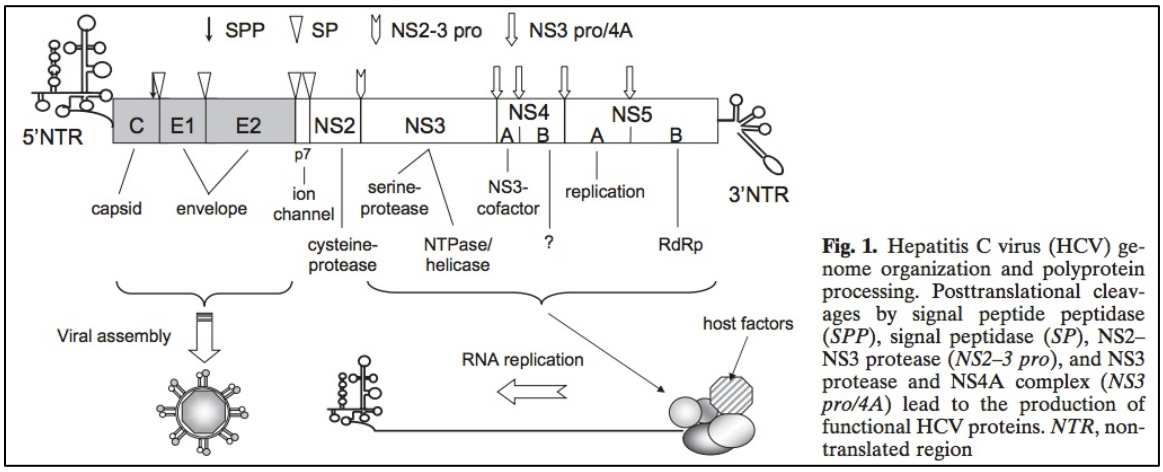


Fig. 1. Hepatitis C virus (HCV) genome organization and polyprotein processing. Posttranslational cleavages by signal peptide peptidase (*SPP*), signal peptidase (*SP*), NS2–NS3 protease (*NS2–3 pro*), and NS3 protease and NS4A complex (*NS3 pro/4A*) lead to the production of functional HCV proteins. *NTR*, nontranslated region

Reprinted from Suzuki et al., 2007 [4]

1.1b) Epidemiology

HCV is a blood-borne virus most commonly transmitted through injection drug use (IDU) through the sharing of injection paraphernalia with a carrier of the virus, in health care settings due to the reuse or inadequate sterilization of medical equipment, especially syringes and needles, and from accidental exposure to infected blood. [5] HCV can also be transmitted by other percutaneous methods, such as tattoos. [6] Some people acquire the infection through sexual transmission typically in persons with high risk behaviors. [2] Vertical transmission (i.e. mother-to-baby) can also occur [7]. HCV is not spread by food or water, saliva, respiratory droplets, breast feeding, or non-sexual physical contact. [2] While HCV is found in saliva, semen, and ascitic fluid, transmission through these secretions is inefficient [8, 9].

Approximately 150-200 million people worldwide and 3.2 million people in the United States have chronic HCV infection. [10] According to CDC surveillance, the incidence rate of HCV infection in the United States peaked in 1992 at 2.4 cases per 100,000. [11] Since then, rates have declined by 88% to 0.3 cases per 100,000 in 2009, amounting to approximately 16,000 new infections per year. [11]

Data from the National Health and Nutrition Examination Survey (NHANES) provide insight into the demographic characteristics of persons with HCV infection in the United States. As of 2010, 67.9% of cases were genotype 1 virus, and 22.1% of cases were genotype 2 infections. [12] The prevalence of HCV was higher in men than women (1.9% *vs.* 1.1%, p <0.001). [12] The burden of HCV infection in the United States occurs disproportionately among those in the birth cohort 1945-1965, as greater than two-thirds (70.1%) of prevalent cases were in the 45 years to 65 years old group in the 2010 survey. The HCV prevalence in this age group was a respectable 3.5%, compared to less than 1.5% prevalence in the 40-44 age group and less than 0.5% prevalence in all other age groups. [12] While there was a decreasing prevalence trend among all races from 2001 to 2010, non-Hispanic blacks bear the greatest burden of HCV infection in the United States. [12]

The strongest risk factors for having anti-HCV antibody included being aged 45 to 65 years old, being born in the United States, having less than a high school education, lifetime history of drug use, abnormal alanine aminotransferase levels (ALT > 39 U/L) and having antibodies to herpes simplex virus type 2. [12] Race, HIV status, service in US military and gender were not predictive of HCV seropositivity. [12]

Before universal HCV antibody screening of blood donors began in 1992, many HCV infections were transmitted through blood, tissue, and organ donation. However, over the past two decades, effective medical interviewing and laboratory screening of blood donors has eliminated this source of new infections. It is now estimated that only 1 in 1 million blood transfusions may transmit HCV. [11]

While blood donation and hemodialysis centers have effectively implemented measures to prevent HCV transmission, such as regular screening and rigorous adherence to infection control practices, not all healthcare facilities have lived up to this high standard. From 1998 to 2008, there were 16 investigated outbreaks which resulted in 275 incident HCV infections. [11] While these outbreaks occurred in a variety of nonhospital healthcare settings, almost all were associated with the reuse of syringes leading to contamination of medicine vials or intravenous fluids. [11]

As transfusion-related and health care associated infections have declined, the contribution of injection drug users (IDUs) in HCV transmission has concurrently increased. Injection drug use remains the strongest risk factor for HCV infection, and the prevalence of anti-HCV antibodies amongst those with lifetime drug use is 37.5% [12]. The CDC estimates that most new cases of HCV infection occur in IDUs. The incidence of HCV infection among IDUs can be as high as 40 cases per 100 person-years, especially among new injectors, with the highest incidence rates occurring early after initiation of injection drug use. [11, 12]

Sexual transmission of HCV used to be controversial. Observational data from HCV-serodiscordant partners in long-term monogamous heterosexual relationships show only slightly higher rates of HCV infection than the general population,

however data obtained from men who have sex with men (MSM) is more compelling. [13] Multiple cross-sectional and cohort studies have reported increased HCV prevalence among MSM, and have highlighted unprotected anal intercourse, multiple sex partners, rough sexual techniques, and coinfection with HIV and other sexually transmitted infections (STI) as potential risk factors. [13]

Vertical transmission is the leading cause of childhood HCV infection. [7, 14] The prevalence of pediatric HCV infection varies from 0.05% to 0.36% in developed countries and between 1.8% and 5% in the developing world. The rate of vertical transmission from mothers with chronic HCV infection to their children is roughly 4 – 7 %. [7, 14] While universal neonatal screening is controversial, all children born to women with anti-HCV antibodies should be checked for HCV infection. [7] Risk factors that increase the likelihood of HCV vertical transmission include maternal intravenous drug use, elevated HCV viral load, and coinfection with HIV. [7] Currently, no clinical intervention has been proven to reduce the risk of vertical transmission of HCV. Cesarean section should not be recommended as a procedure to prevent vertical transmission, and breastfeeding should not be forbidden. [7]

1.1c) Clinical Course

Infection with HCV can result in both acute and chronic hepatitis. Acute HCV infection is usually asymptomatic and rarely causes hepatic failure. [15] Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea,

vomiting, abdominal pain, dark urine, grey-colored feces, joint pain and jaundice. [5] However, acute HCV typically leads to chronic infection, and 50 to 85 percent of cases develop chronic hepatitis, depending on the population and the source of infection. [10]

The high prevalence of chronic infection may be due to the genetic diversity of the virus and its tendency toward rapid mutation, allowing HCV to escape immune recognition. [10] Host factors also influence rates of spontaneous clearance of HCV. One of the most influential factors appears to be certain polymorphisms of a site close to the interleukin-28B (IL28B) gene. The C/C type allele, more common in patients of European ancestry compared with those of African ancestry, has been associated with significantly higher rates of spontaneous HCV clearance than the T/T type allele. [16]

The clinical course of liver disease associated with chronic HCV infection is most often slowly progressive. Approximately 20 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time. A systematic review of 111 studies analyzing the natural history of chronic HCV estimated that the prevalence of cirrhosis 20 years after infection was 16 percent. [17] In the United States, chronic HCV is the most common cause of chronic liver disease and the most frequent indication for liver transplantation. [10]

The risk and rate of progression to cirrhosis varies across different patient populations, and the disease may not be progressive in all patients. Studies have shown that patients who acquire acute hepatitis C from a blood transfusion show no increase in all-cause mortality after 25 years of follow up, while patients who present

initially with symptomatic chronic hepatitis tend to report a more aggressive course with a high risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [10].

The complications of chronic HCV infection are mostly confined to patients who have developed cirrhosis, although not all patients with cirrhosis develop complications. A study of 384 patients with compensated cirrhosis due to HCV found that the risk of developing hepatic decompensation was 3.9 percent per year. The most common form of decompensation was ascites, followed by bleeding esophageal varices, encephalopathy, and jaundice, which is almost always a sign of advanced liver disease in patients with chronic HCV. [18] Furthermore, a number of extrahepatic disorders have been associated with chronic HCV infection, including essential mixed cryoglobulinemia, lymphoma, membranoproliferative glomerulonephritis, autoimmune thyroiditis, porphyria cutanea tarda, and lichen planus. [19]

Survival is decreased in persons with chronic HCV. In the aforementioned series of 384 patients with compensated cirrhosis, the 3, 5, and 10-year survival rates were 96, 91, and 79 percent respectively; once decompensated cirrhosis occurred, the five-year survival fell to 50 percent. [18] In 2007, the age-adjusted mortality rate for patients with HCV in the United States was 4.6 per 100,000 persons per year, higher than that of HIV (4.2 deaths per 100,000 persons per year). [20]

Although deaths associated with chronic HCV in the United States are more likely to be due to end stage liver disease (ESLD) rather than hepatocellular carcinoma (HCC), HCV accounts for approximately one-third of HCC cases in the

United States. Estimates of the risk of developing HCC for cirrhotic patients with chronic HCV have varied from 0 to 3 percent per year. In contrast to hepatitis B virus infection, HCC in patients with HCV occurs almost exclusively in those with cirrhosis. [10]

Disease progression in individual patients may be influenced by several host factors, including demographics, behavioral comorbidities, and medical comorbidities. Faster progression of hepatic fibrosis is associated with male gender, non-black race, and acquisition of HCV after age 40. On the other hand, infected children have a decreased risk of disease progression. [10] Behavioral factors negatively impacting disease progression include alcohol use, daily marijuana use, and high levels of dietary cholesterol consumption, while regular coffee consumption has been associated with reduced hepatic fibrosis and slower disease progression. [10] Medical comorbidities leading to greater risk of development and progression of hepatic fibrosis include obesity, diabetes mellitus, insulin resistance, hepatitis B virus (HBV) infection, and HIV infection. [10]

1.1d) Diagnosis

Because acute HCV infection is usually asymptomatic, early diagnosis of the HCV infection is rare. In those people who go on to develop chronic HCV infection, the infection often remains undiagnosed, as symptoms may not develop until serious liver damage has occurred. [5]

Accurate testing to identify chronic HCV infection is important to enable patients and providers to make informed decisions about medical care and options for treatment, to minimize the risk of transmitting HCV to others, and to inform persons who are not currently infected of their status. [21]

Beginning in 1998, the United States Centers for Disease Control and Prevention (CDC) recommended HCV testing for persons with risk factors for HCV infection, and in 2012 they endorsed one-time HCV testing for all persons born during 1945–1965 regardless of other risk factors. [21]

HCV infection is diagnosed in 2 steps. First, screening for anti-HCV antibodies with a serological test identifies people who have been infected with the virus. [5] The main screening test for detecting anti-HCV is the enzyme immunoassay (EIA), which has many advantages including ease of use and automation, low cost, and low variability. [22] In addition to laboratory-conducted antibody assays, alternative point-of-care tests with similar sensitivity and specificity may be utilized. The OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, Pennsylvania), approved by the FDA in 2010, is a rapid assay for fingerstick capillary blood, and provides wider testing access in nontraditional clinical sites. [21]

The qualitative antibody test is reported as either nonreactive (negative) or reactive (positive). A nonreactive anti-HCV result indicates that no HCV antibody was detected. A reactive result indicates either current HCV infection, past HCV infection that has resolved, or may be a false positive result. In low prevalence settings like the healthy blood donor population, the number of false positives by enzyme immunoassay (EIA) may exceed the number of true positives, and

consequently the positive predictive value of the test may fall below 50%. [22] To address this concern, supplemental antibody tests such as the recombinant immunoblot assay (RIBA) were developed for use in resolving false-positive EIA results. [22] In a high-prevalence setting such as a university referral HIV clinic, the positive predictive value of EIA is much higher and supplemental testing is usually not necessary. [22]

A reactive anti-HCV result should be followed by nucleic acid testing (NAT) for HCV RNA. [21] Detection of HCV RNA indicates current HCV infection. If HCV RNA is not detected in a person with a positive antibody test, that indicates either past resolved HCV infection or false HCV antibody positivity. [21] Resolved HCV infection is not uncommon, as approximately 15–45% of people infected with HCV spontaneously clear the infection by a strong immune response without the need for treatment. [5]

1.1e) Evaluation

Given that the hepatic and extrahepatic manifestations of chronic HCV infection cause serious morbidity and mortality, patients may be clinically asymptomatic as they progress to advanced liver disease, and safe and effective treatments are becoming increasingly available, all patients diagnosed with chronic HCV infection should be considered for treatment. [23] The patient's HCV genotype, history of prior treatment, comorbidity burden and degree of liver damage are used to guide treatment decisions and management of the disease. [23]

Those diagnosed with chronic HCV infection should undergo a laboratory test to identify the genotype and subtype of HCV in order to guide choice of antiviral therapy. The six genotypes of HCV respond differently to treatment, and it is possible to be infected with more than one genotype. [5] The most commonly used test method of genotyping is the line probe assay (for example, INNO-LiPA HCV II, Siemens Healthcare Diagnostics, Erlangen, Germany), which provides genotype and subtype. [23]

Patients should be categorized based on their HCV disease status and treatment history, including exposure and response, in order to guide future treatment decisions. Patients who have never received any treatment for HCV are called "treatment naïve". Relapsers are patients who had an undetectable HCV viral load at the end of a prior attempt at treatment (end of treatment response), but who did not achieve a sustained virologic response (SVR), which is defined as negative HCV RNA 12-24 weeks after completing treatment. Partial responders are patients who achieved at least a hundred fold (2 $\log_{10}$) drop in HCV RNA by week 12 of treatment with an interferon-based regimen, but who did not achieve an end of treatment response. Null responders are patients who did not achieve at least a ten fold (1 $\log_{10}$) reduction in HCV RNA by week 4, or a hundred fold (2 $\log_{10}$) drop in HCV RNA by week 12 of treatment with an interferon-based regimen. Partial and null responders tend to have lower SVR rates with the same regimen compared with the treatment-naïve and relapsers. [23]

Clinicians considering initiating HCV treatment for a patient should conduct a thorough evaluation for medical, psychiatric, and social comorbidities that may affect

the treatment plan. The workup should include assessment for renal disease, cytopenias, thyroid disease, autoimmune disease, HIV coinfection, potential drug-drug interactions, pregnancy, psychiatric history, and concurrent alcohol and/or drug use. [23]

Assessment of the degree of liver fibrosis is an important part of a treatment evaluation for chronic HCV. Fibrosis stage can impact the likelihood of response to treatment with interferon-based regimens. [23] The approximate time to development of cirrhosis can be estimated, and treatment can be deferred if little or no fibrosis progression has occurred over a long interval. [23] Furthermore, patients with advanced fibrosis require screening for hepatocellular carcinoma, and patients with cirrhosis require screening for development of complications such as esophageal varices. [23]

Liver fibrosis can be assessed by liver biopsy or through a variety of noninvasive tests. [5, 23] Liver biopsy has historically been the gold standard for assessing fibrosis, but has several limitations. These include sampling error, which leads to misinterpretation in 10 to 15 percent of patients, significant inter-observer variability in interpretation, expense, invasiveness, and risk of complications. [23] As noninvasive markers are becoming more widely available, and as treatment for HCV continues to become less toxic and more effective, there is less need to precisely stage a patient's liver disease with biopsy.

There are several histologic scoring systems for chronic liver disease, many of which assess both grade and stage. Grade indicates the activity or degree of inflammation, and the stage represents the amount of fibrosis. [24] In all systems, the

stages are determined by both the quantity and location of the fibrosis, with the formation of septa and nodules as major factors in the transition from one stage to the next. [24] The most sensitive system for staging is the Ishak fibrosis score, which has seven stages, and can easily be translated to the other scores. [24] Another commonly used system is the Metavir score, which has a five-point fibrosis scale:

- F0: No fibrosis
- F1: Portal fibrosis without septa
- F2: Few septa
- F3: Numerous septa without cirrhosis (bridging fibrosis)
- F4: Cirrhosis

Various noninvasive tests can be very helpful in assessing liver fibrosis, including serologic and radiologic tests. The specific tests chosen will depend on local availability. To improve predictive ability, scoring systems have been developed that combine assays of multiple serologic markers of liver fibrosis. Panels of indirect markers of fibrosis, such as the AST to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores, can be calculated from routine laboratory test results. [23] Specialized noninvasive diagnostic tests include panels of direct serologic markers of fibrosis, such as FibroSpect II, and ultrasound-based transient elastography, such as FibroScan. [23]

Serologic markers of hepatic fibrosis can broadly be categorized as indirect or direct. Indirect markers reflect alterations in hepatic function but do not directly

reflect extracellular matrix metabolism, while direct markers reflect extracellular matrix turnover. [25] Overall, studies of the various panels suggest that they have good ability to differentiate patients with significant fibrosis (F2 to F4) from those without significant fibrosis (F0 to F1). [26]

Potential benefits of these noninvasive tests are ease of administration and lower cost compared to liver biopsy. Also, they can be repeated over time to monitor progress of liver disease. [23] While noninvasive tests are quite reliable for diagnosing cirrhosis as well as for excluding the presence of fibrosis, in the intermediate stages their reliability is limited, and therefore no single test can match the accuracy of liver biopsy in fibrosis quantitation. [27]

The aspartate aminotransferase (AST) to platelet ratio index, or APRI, is based on the AST level and platelet count and is easy to calculate. The APRI is calculated using the AST elevation (which is the AST level divided by the upper limit of normal for the lab) and the platelet count per mm^3 divided by 1000. A meta-analysis of 40 studies found that for predicting significant fibrosis (F2 to F4), an APRI cutoff of 0.7 had a sensitivity of 77 percent and a specificity of 72 percent. [28] For predicting cirrhosis (F4), an APRI cutoff of 1.0 had a sensitivity of 76 percent and a specificity of 72 percent. [28]. However, accuracy was lower in patients coinfected with HIV and HCV. [28]

The FIB-4 index combines platelet count, ALT, AST, and age. In one study of patients with chronic HCV, the FIB-4 index enabled the correct identification of patients with severe fibrosis (F3-F4) and cirrhosis with an area under the receiver operating characteristic curve of 0.85 (95% CI 0.82-0.89) and 0.91 (95% CI 0.86-

0.93), respectively. [29] An FIB-4 index <1.45 had a negative predictive value of 94.7% to exclude severe fibrosis with a sensitivity of 74.3%. [29] An FIB-4 index higher than 3.25 had a positive predictive value to confirm the existence of a significant fibrosis (F3-F4) of 82.1% with a specificity of 98.2%. [29]

FibroTest (Biopredictive, Paris, France), also marketed as FibroSure, is another panel of indirect serologic markers for liver fibrosis that has primarily been studied in patients with hepatitis C. However, as a proprietary test, it has more limited access than the above panels which can be calculated from routine laboratory tests. FibroTest involves assessment of alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gammaglobulin, apolipoprotein A1, GGT, and total bilirubin, while taking into account the patient's age and sex. Results from the individual assays are combined and are used to classify patients having mild fibrosis (F0 to F1), significant fibrosis (F2 to F4), or indeterminate. The sensitivity for detection of significant fibrosis is approximately 60 to 75 and the specificity is approximately 80 to 90 percent, respectively. [25] In one study, the severity of disease was correctly identified as being mild or significant in approximately 46 percent of patients. [30]

FibroSpect II (Prometheus Laboratories, San Diego, California) is a panel that uses a combination of direct serologic markers for liver fibrosis. The panel includes assessment of serum hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1), and alpha-2-macroglobulin. The combination of these assays reliably differentiates patients with chronic HCV with moderate to severe fibrosis from those with no or mild fibrosis. [25] In a validation study with 402 patients with chronic

HCV, the panel had a sensitivity of 77 percent and a specificity of 73 percent for predicting moderate to severe fibrosis. [31]

Ultrasound-based transient elastography, marketed as FibroScan (Echosens, Paris, France), is the predominant radiographic test for assessing liver fibrosis in patients with chronic HCV. Advantages include safety and good inter- and intra-observer reliability, while disadvantages include the difficulty of obtaining successful examinations in obese patients and patients with ascites, and lack of availability in the United States. [25] Overall, for diagnosing significant fibrosis (F2-F4), it has an estimated sensitivity of 70 percent and an estimated specificity of 84 percent. [32] For diagnosing cirrhosis, the sensitivity and specificity are estimated to be 87 and 91 percent, respectively. [32]

1.1f) Treatment

The goal of hepatitis C treatment is to eradicate HCV RNA by achieving sustained virologic response (SVR), defined by the absence of HCV RNA by polymerase chain reaction 12-24 weeks after stopping treatment. An SVR is associated with a 99 percent chance of being HCV RNA negative during long-term follow-up and can therefore be considered cure of the HCV infection. Achievement of an SVR has also been associated with improved clinical outcomes. [33] The cure rate depends on several factors, including patient and viral characteristics as well as the type of treatment given. [5] Regardless of whether or not treatment is prescribed, clinicians should recommend to all patients measures to limit HCV-associated disease

progression, including avoidance or reduction of alcohol intake and vaccination against hepatitis A and B.

Guidelines for HCV treatment were released jointly by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in 2014. [33] Other notable guidelines include treatment recommendations from the European Association for the Study of the Liver (EASL), published in 2014, and United Kingdom consensus guidelines, updated in 2014. [33] The World Health Organization (WHO) also released guidelines in 2014 intended primarily for clinicians and policy-makers in low- and middle-income countries. [33]

Until recently, the standard treatment for HCV was combination antiviral therapy with pegylated interferon and ribavirin, which are effective against all the genotypes of hepatitis viruses. Unfortunately, interferon is poorly tolerated in many patients, with potentially debilitating side-effects like fatigue, flu-like symptoms (fever, headache, muscle aches), and depression. [33] Additionally, ribavirin is highly teratogenic, requiring the use of two forms of birth control in men and women of child-bearing potential, and patients must be monitored regularly for anemia and thrombocytopenia. [33] Management of this regimen is complex, requiring weekly injections for 48 weeks, and many patients fail to complete their treatment. [5] Furthermore, response rates are generally only 40 to 50 percent. [33] In order to optimize administration of a difficult treatment regimen, management decisions focused on identifying patients who would be most likely to respond to therapy or who were most likely to suffer liver-related morbidity and mortality without successful treatment. [23]

Recent advances have led to the development of new antiviral drugs for HCV treatment, known as oral directly acting antiviral agents (DAAs), which are much more effective, safer and better-tolerated than previous therapies. DAAs simplify HCV treatment by significantly decreasing treatment duration and monitoring requirements, and by increasing cure rates, with many studies reporting rates above 90 percent [23, 33]. As a wider range of patients are eligible for treatment with DAAs compared with previous therapies, the vast majority of patients with chronic HCV infection can theoretically be cured with treatment. In spite of this increased population of those eligible for HCV treatment, access to the new treatments remains problematic for many. Although the production cost of DAAs is low, the initial prices set by companies are very high, which has made access to these drugs difficult. [5]

In care settings where access to DAAs is limited, treatment can be prioritized for those who would be most likely to benefit in the near-term, as recommended by the joint guidelines from the AASLD and IDSA. [34] The highest priority patients are those who are at highest risk of substantial morbidity and mortality from untreated HCV infection, namely those with advanced fibrosis or cirrhosis, transplant recipients, and those with severe extrahepatic manifestations of HCV infection. [23, 34] High priority patients include those at high risk of fibrosis progression, such as patients with substantial fibrosis (F2 or greater), HIV coinfection, coexisting liver disease, and diabetes mellitus. [23, 34] The potential for transmission of HCV is an additional consideration that might prioritize treatment. [23, 34] If interferon-free DAA regimens are not yet available for a patient, but are expected to be in the near

future, the guidelines recommend deferring therapy until that time unless there is a compelling reason to initiate treatment earlier. [23]

Selection of the optimal HCV treatment regimen for a given patient depends mainly on HCV genotype, history of prior treatment, potential drug-drug interactions, and insurance coverage. For patients with genotype 1 infection, choice of regimen may differ between treatment-naïve and treatment-experienced patients. [33] For both groups, there are three regimens with comparably high expected efficacy and safety: ledipasvir-sofosbuvir, simeprevir plus sofosbuvir, and ombitasvir-paritaprevir-ritonavir plus dasabuvir with or without ribavirin. [33] Choosing between them depends primarily on potential drug-drug interactions and insurance coverage. [33] These interferon-free combination regimens have reported SVR rates in excess of 90 percent for patients with genotype 1 infection, a major achievement as genotype 1 infection responded poorly to treatment with interferon and ribavirin. [33]

The first-ever FDA approved HCV single-tablet combination drug regimen, Ledipasvir-sofosbuvir regimens results in SVR rates of approximately 95 percent or higher with only mild to moderate side effects, most commonly fatigue or headache. [33] The duration of ledipasvir-sofosbuvir treatment depends on HCV viral load, prior treatment history, and the presence of cirrhosis, and ranges from 8-24 weeks. [33] Ombitasvir-paritaprevir-ritonavir plus dasabuvir with or without weight based ribavirin also achieves SVR rates of 95 percent of higher. [33] It is especially effective for subtype 1b infection, and duration ranges from 12-24 weeks. [33] Adverse effects are common but typically mild in severity. Simeprevir plus

sofosbuvir for 12-24 weeks is also highly effective, but the data supporting its use are more limited than for the previous two regimens. [33]

In contrast to patients with genotype 1 infection, those with genotype 2 or 3 infection achieve relatively high SVR rates (65 to 80 percent) with only 24 weeks of therapy with interferon and ribavirin. [35] However, many of these patients went without treatment due to contraindications as well as patient and provider reluctance to initiate a lengthy and highly toxic treatment. [35] For all patients with genotype 2 and 3 infection, the recommended regimen is sofosbuvir and ribavirin, with duration ranging from 12-24 weeks based on genotype, treatment history, and presence of cirrhosis. [35] SVR rates with this regimen among these populations range from 83 to 97 percent. [35]

Notably, none of the recommended treatment regimens include the first generation HCV protease inhibitors boceprevir and telaprevir. While the development of these agents led to higher treatment eligibility rates and improved treatment outcomes, the newer DAAs are much better tolerated. [36] Boceprevir and telaprevir have recently been pulled from the market as they have fallen out of favor with providers and patients. [36]

To monitor for potential toxicity with interferon-free regimens, complete blood count, basic chemistry panel, and liver enzyme and bilirubin levels are recommended at weeks 1 to 2, 4, 8, and 12, with more frequent monitoring for concerning results or trends. [33, 35] Virologic cure in response to treatment should be assessed by checking the viral load at 12 to 24 weeks following the cessation of therapy. Patients who achieve SVR who do not have bridging fibrosis or cirrhosis do

not require any specific follow-up for their HCV. Patients who fail to achieve an SVR should be followed for signs of progression of their liver disease, and patients with bridging fibrosis and cirrhosis, regardless of treatment response, require ongoing monitoring for hepatocellular carcinoma and other complications of advanced liver disease. [33]

1.2) Background: HIV/HCV Coinfection

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) represent two highly prevalent chronic viral infections worldwide and the United States. The CDC estimates that there are upwards of 3.2 million Americans living with HCV, and upwards of 1.2 million living with HIV/AIDS. [37] The intersection of these two epidemics presents special challenges for patients with HIV/HCV coinfection and their health care providers.

The viral kinetics of HCV are altered by concomitant HIV infection. During the chronic stage of HCV infection, a relatively stable viral load or "set point" is maintained. However, in the setting of HIV coinfection, HCV RNA levels increase starting from HIV seroconversion and continue to increase over time compared with patients with HCV alone. [38] While increases in the HCV viral load do not affect liver disease severity, they do have an impact on HCV treatment response. [38]

Coinfection with HIV and HCV is common since both infections share similar routes of transmission. In the United States, the prevalence of HCV is especially high among HIV infected patients (30-35%), and similar rates have been reported in

Europe. [38] As the relative efficiency of transmission differs according to route, the prevalence of coinfection varies markedly among various risk groups. In one study, HCV seroprevalence in HIV-infected injection drug users (IDUs) was 73 percent, and in the low-risk group was 4 percent. [39] Compared to patients with HCV and HIV monoinfection, coinfection is associated with more severe psychiatric illness, ongoing drug use, poverty, homelessness, and incarceration. [40] Additionally, the order in which the two infections are acquired tends to differ by transmission route, as IDUs typically acquire HCV before HIV infection while men who have sex with men (MSM) usually are infected with HIV before they acquire HCV infection. [38]

The seroprevalence of HCV in HIV-infected MSM in the United States ranges from about 4 to 8 percent, higher than the general population (1.8 percent). [38] Data suggest that an increased risk of HCV transmission exists among MSM whose predominant risk factor is unsafe sex. [38] In recent years, new HCV infections appear to be especially common among HIV-infected MSM; HCV transmission may be enhanced by mucosal injury and/or concomitant sexually transmitted diseases. [38] Among MSM, unprotected anal sex, fisting, group sex, and recreational gamma-hydroxybutyrate (GHB) use are associated with HCV acquisition. [38] The importance of mucosal damage as a risk factor for HCV acquisition was highlighted in a report in which 18 of 20 MSM reported either genital ulcerative disease (lymphogranuloma venereum, syphilis, or HSV-2) or fisting within the period of acute HCV seroconversion. [13]

Vertical transmission of HCV infection is increased in HIV-coinfected mothers. Meta-analyses have shown that the risk of vertical transmission of HCV to

children of HCV RNA-positive women was 5.8% for children of HIV-negative women and 10.8% for children of HIV-positive women. The study also found that maternal HIV coinfection was the most important determinant of vertical transmission risk (adjusted odds ratio: 2.56). [41]

In patients with chronic HCV infection, concomitant HIV infection is associated with higher rates of morbidity and mortality related to liver disease. [38] HIV/HCV coinfected patients are less likely to clear viral infection, have more rapid rates of fibrosis, and have a higher risk of hepatic decompensation compared with HCV monoinfected patients. [38] In a large European cohort of coinfected patients, liver-related death accounted for 27% of all deaths, on par with AIDS as the leading cause of death. [42] Therefore, all HIV-infected individuals should be screened for HCV with an anti-HCV antibody test on entry into HIV care. [40]

While chronic HCV infection increases the risk of hepatotoxicity from antiretroviral therapy (ART) for HIV, the clear benefit of ART outweighs the risk of liver injury. [38] Studies also support the positive impact of ART on hepatic fibrosis progression in HIV/HCV-coinfected patients, and the CCR5 receptor antagonist maraviroc may halt or even reverse the progression of hepatic fibrosis. [43, 44]

Because of the faster progression to advanced liver disease in the setting of HIV infection, coinfection is one reason to prioritize a patient for HCV antiviral therapy. [36] In ART-naïve HIV/HCV coinfected patients, ART should be initiated regardless of CD4 count, with regimen choice taking into account the potential drug-drug interactions with HCV antiviral therapy if treatment is planned. [36] Treatments for HCV and HIV should not be started simultaneously, so that patients can adjust to

each regimen sequentially. [40] For patients already on ART, a regimen switch may be warranted if some components cannot be used with the planned HCV treatment regimen. [36]

HCV antiviral regimen selection for HIV/HCV coinfected patients is generally the same as for HCV monoinfected patients, and coinfected patients with preserved immune function should not be thought of as a special population that has lower response rates compared with the monoinfected population. [33, 36] Although studies with peginterferon and ribavirin therapy showed that HIV/HCV coinfected patients had lower response rates compared with HCV monoinfected patients, SVR rates with regimens that contain a direct-acting antiviral appear to have comparable treatment outcomes. For example, in coinfected patients with genotype 2 or 3 infection, sofosbuvir based combinations are associated with high cure rates, similar to those observed in subjects with HCV monoinfection. [35, 45]

Several important drug interactions between ART and HCV antiviral agents should be considered when assessing a HIV/HCV coinfected patient for HCV treatment. [36] Sofosbuvir can be safely used with most commonly prescribed antiretroviral agents. Ledipasvir-sofosbuvir should not be used with the combination of elvitegravir, cobicistat, tenofovir, and emtricitabine, and caution is warranted when using other tenofovir-containing regimens as it may result in elevated tenofovir levels. [36] Ombitasvir-paritaprevir-ritonavir plus dasabuvir (with or without ribavirin) should not be used with darunavir, rilpivirine, efavirenz, or lopinavir-ritonavir. [36] Significant drug-drug interactions have also been observed with simeprevir, which should not be used with HIV protease inhibitors, including

ritonavir, or the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine. [36]

1.3) Problem Statement

While newer DAA based antiviral treatment regimens for the treatment of HCV have shown high cure rates in randomized controlled trials (RCTs), cure rates may be much lower in real-world community-based practice settings. People with chronic HCV infection need to fulfill several steps along a care continuum to achieve optimal health outcomes (disease cure). First, persons must be aware of their HCV diagnosis and linked to care with a provider who is knowledgeable and willing to manage their infection. Once in care, patients should have HCV RNA confirmation testing and undergo liver fibrosis staging to help make decisions regarding HCV therapy. Lastly, individuals must receive and maintain good adherence to HCV treatment to achieve SVR. This HCV treatment cascade, or care continuum, provides a framework for monitoring and identifying gaps in care.

1.4) Goals and Objectives

We conducted a cross-sectional survey of HIV-positive patients from the Nathan Smith Clinic who have been diagnosed with HCV infection. We characterized each patient's progression along the HCV care continuum, identifying barriers to progression at each step, and characterizing each outcome as optimal or suboptimal.

We aimed to identify disparities in care related to demographic and clinical characteristics of patients, such as gender, race, and medical and psychiatric comorbidities.

1.5) Hypothesis

Large gaps currently exist between current real-world practice and optimal treatment goals for people with HIV and chronic HCV infection, with progression along the HCV cascade of care varying widely in different clinical settings and among patient groups. The care continuum approach to assessing points of engagement and progression along the spectrum of HCV management will enable identification of points along the continuum of care where optimal management gaps exist, and highlight specific factors contributing to suboptimal patient outcomes. Data from the HCV cascade will also help assess for disparities in care among patient groups based on their demographic and clinical characteristics.

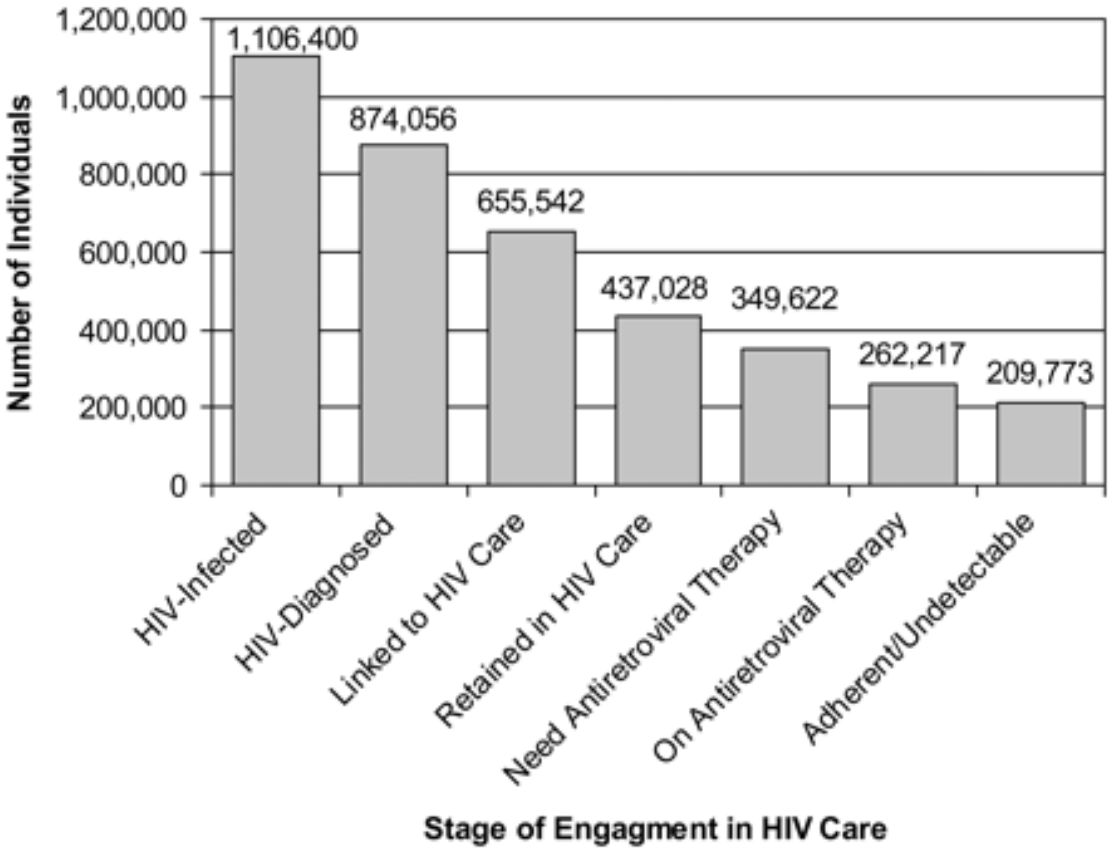
CHAPTER 2: REVIEW OF THE LITERATURE

2.1) The HCV Care Continuum

The "care continuum" concept, also known as "cascade of care" and "spectrum of engagement in care" was introduced by Gardner et al. in 2011, in order to explore the effectiveness of test-and-treat strategies for HIV prevention. The test-and-treat approach proposes that expanded testing and earlier treatment of HIV infection markedly decreases ongoing HIV transmission, stemming the HIV epidemic. [46] However, Gardner et al. realized that poor engagement in care for HIV-infected individuals would substantially limit the success of such strategies.

Gardner et al. described engagement in care as being comprised of multiple stages: individuals need to know that they are HIV infected, be linked to and retained in regular HIV care, and receive and adhere to effective antiretroviral therapy. [46] Gardner et al. proposed that understanding the proportion of the HIV-infected population that passes through each stage, and the percentage that drops off, is crucial for estimating the potential impact of interventions to improve engagement in care. [46] In creating this framework to better characterize engagement in care, Gardner et al. laid the foundation that has since been adapted for use across various patient populations, health care settings, and chronic disease treatment paradigms.

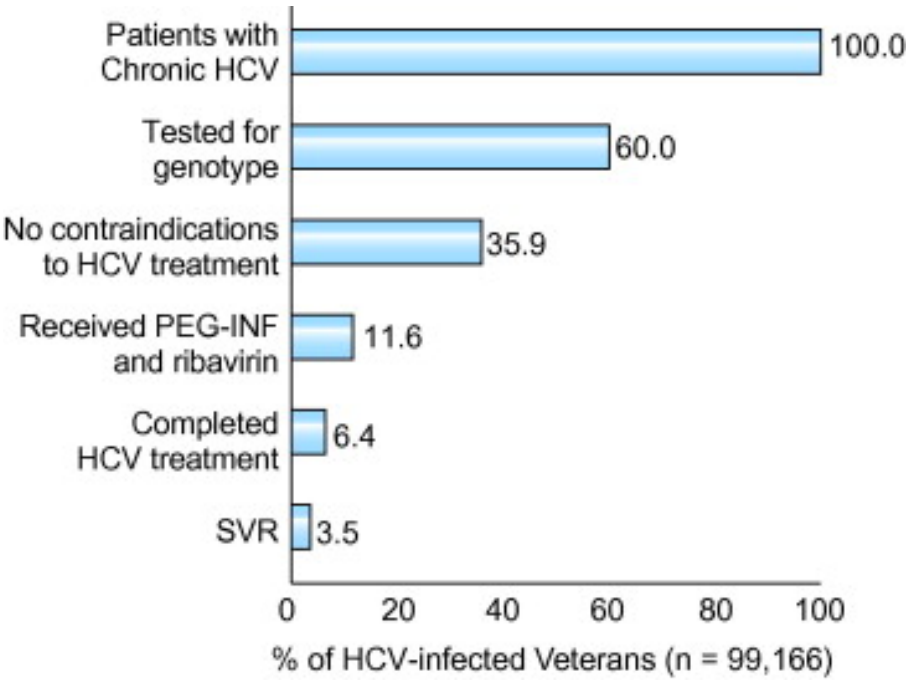
The spectrum of engagement in HIV care in the United States is shown below:



Reprinted from Gardner et al., 2011 [46]

One of the most notable studies to apply the spectrum of engagement in care concept to individuals with chronic HCV infection was Kramer et al. in 2012, which aimed to explore the effectiveness of HCV treatment in Veterans Administration (VA) hospitals nationwide. [47] Using the nationwide VA HCV Clinical Case Registry (CCR), Kramer et al. examined a cohort of veterans who had HCV viremia between 2000 and 2005, and identified patients who received treatment with pegylated interferon (PEG-INF) and ribavirin. [47] The effectiveness of treatment was measured as the proportion of patients who achieved SVR in the entire cohort,

and among patients who initiated and completed treatment. [47] Kramer et al. identified 99,166 patients with HCV viremia. Of those, 11.6% received PEG-INF with ribavirin and 6.4% completed treatment. [47] Contraindications were present in 57.2% of the patients that did not receive treatment. SVR was documented in 39.9% and 58.3% of patients who completed treatment; 23.6% and 50.6% of patients who initiated treatment; and 3.9% and 11.2% of the entire HCV cohort for genotype 1 or 4 and 2 or 3, respectively. [47] Overall, only 3.5% of the entire HCV viremic cohort had a documented SVR. [47] A major strength of this study was its size, as it remains one of the largest studies to examine HCV treatment effectiveness in a community practice setting. Another strength was that it was able to characterize the proportion of patients with various contraindications to receiving HCV treatment. Some limitations of the study are that it did not capture patient-physician interactions, such as patients declining treatment or physicians recommending deferred treatment, and that the population of the VA system is not representative of the general population, as men and African-Americans are overrepresented.



Reprinted from Kramer et al., 2012 [47]

In 2014, Yehia et al. performed a systematic review and meta-analysis of studies describing the treatment cascade for persons with chronic HCV infection in the United States. [48] The analysis included articles published between January 2003 and July 2013, and studies were excluded if they were conducted outside of the United States, did not present original data, only analyzed data collected prior to 2000, involved a single site, or focused on special populations. [48] Data from each included study were extracted into tables stratified by HCV treatment cascade step. [48] Overall, 3.5 million people in the United States were estimated to have chronic HCV infection, 50% (95% CI 43-57%) were diagnosed and aware of their infection, 43% (CI 40-47%) had access to outpatient care, 27% (CI 27-28%) had HCV RNA confirmed, 17% (CI 16-17%) underwent liver fibrosis staging, 16% (CI 15-16%) were prescribed treatment, and 9% (CI 9-10%) achieved SVR. [48] These results

confirmed the existence of large gaps between current practice and treatment goals for people with chronic HCV infection. While the main analysis focused on non-VA studies, a separate analysis was conducted using VA-specific data in order to highlight differences between U.S. veteran and non-veteran populations. [48] Among chronic HCV-infected veterans in care, the proportion of those who received hepatic fibrosis staging by liver biopsy and who were prescribed HCV treatment was 22% and 19% lower, respectively, compared to the general population. [48] Similarly, among veterans with chronic HCV infection who were prescribed pegylated interferon plus ribavirin, a smaller proportion achieved SVR compared to the general population (44% vs. 58%). [48] One limitation of this systematic review was the relatively small number of studies identified, particularly for earlier steps in the cascade. Furthermore, because studies of special populations were excluded, this analysis fails to describe certain populations disproportionately affected by chronic HCV infection, such as homeless individuals and prisoners. Lastly, estimates for each step in the HCV treatment cascade could not be determined by sex, race/ethnicity, socioeconomic status, injection drug use, and HIV status, preventing assessment for disparities in care, because these data were not available in the included studies. [48]

2.2) The HCV Care Continuum in HIV Coinfected Patients

Several studies have aimed to characterize the HCV care continuum in those with HCV/HIV coinfection. In 2011, Butt et al. compared the rates for HCV treatment eligibility among a national cohort of HCV and HIV/HCV

coinfected veterans in care from 1998-2003. [49] Overall, HIV/HCV coinfected persons were less likely to be evaluated by a gastroenterologist or hepatologist and less likely to be eligible for treatment compared with the HCV-monoinfected subjects. Of the 27,452 subjects with HCV and 1225 with HIV/HCV coinfection, 74.0% and 84.6% had indications for therapy and among these, 43.9% of HCV monoinfected and 28.4% of HIV/HCV coinfected subjects were eligible for treatment. [49] In exploring the conditions that led to treatment ineligibility, Butt et al. found that anemia, decompensated liver disease, renal failure, active psychiatric disease, and recent drug abuse or dependence were 1.5 to 2 times more prevalent in the coinfected group. [49] This analysis was significant for being the first national study to evaluate HCV treatment eligibility and directly compare HCV-monoinfected and HIV/HCV coinfected persons. Limitations of this study include that it focuses only on veterans engaged in the VA healthcare system, and that indications and contraindications for HCV treatment have evolved significantly since 2003, especially since the introduction of DAAs.

The benefit of conducting analyses of large databases is clear, in that observations can be made with greater statistical power. However, the limited information available in these databases means that certain barriers in the care continuum, such as reasons for non-referral for HCV therapy, can be better evaluated by studies focused on single care settings. Cachay et al. (2014) conducted a retrospective cohort analysis of HIV-infected patients in care at the UCSD Owen Clinic from 2008-2012, identifying reasons for not referring for and not initiating HCV therapy after completion of HCV treatment staging. [50] Electronic medical

records were reviewed to ascertain reasons for not initiating HCV therapy, and logistic regression analyses were used to identify factors associated with lack of referral for HCV therapy. [50] Of 4725 total HIV-infected patients, 4534 (96%) were screened for HCV, 748 (16%) had reactive serum HCV antibodies, and 542 (11%) had active HCV infection. Lack of engagement in care was the most important predictor of non-referral for HCV therapy (OR: 5.08, 95% CI 3.24-6.97, p <0.00001). [50] Other significant predictors included unstable housing (OR: 2.26), AIDS (OR: 1.83), having a detectable HIV viral load (OR: 1.98) and being non-white (OR: 1.67). [50] The most common reason (40%) for not initiating or deferring HCV therapy was the presence of ongoing barriers to care, including ongoing illicit drug or alcohol use, ongoing uncontrolled neuropsychiatric disease, and poorly controlled HIV disease. [50] A major strength of this study was its ability to characterize these barriers to care. One weakness of the study was that it restricted the analysis of reasons for not initiating HCV therapy to only those patients who finished HCV clinical staging. However, a significant proportion of patients referred for HCV therapy, 53 of 303 (17%), either never showed up for their HCV appointment or did not return after their first HCV appointment, and were excluded from their analysis. [50] Additionally, as with all single site studies, these results may not be generalizable across care settings with different patient populations.

Maier et al. (2014) aimed to estimate the impact of the availability of DAAs on the care continuum for HIV/HCV coinfected persons, with a focus on treatment eligibility. Maier's analysis is the first to use a multi-year, statewide, population-based sample to estimate HCV treatment eligibility in HIV/HCV coinfected patients,

and the first to estimate eligibility in the setting of an interferon-free regimen. [51] Of 161 coinfected patients living in Oregon during 2007-2010, 21% were eligible for HCV therapy, and eligibility assuming an interferon-free regimen increased only to 26%, mostly due to numerous simultaneous contraindications. [51] Active alcohol abuse was the most common contraindication (24%), followed by uncontrolled mental health (22%), recent injection drug use (21%), and poor antiretroviral adherence (22%). [51] Additional strengths of this study include use of both medical record abstraction and a structured interview as data sources, and use of data from the modern antiretroviral time period. Limitations of the study include assumption of chronic infection given anti-HCV positivity, as few patients had HCV viral load testing, and lack of generalizability of results to other geographical areas.

While the retrospective cohort studies described above are able to provide estimates of the care continuum at a given point in time, prospective studies are able to shed light on changes in the care continuum over time. Grint et al. (2013) conducted a prospective cohort study in association with EuroSIDA, a cohort of 18,295 HIV-positive individuals in 105 centers across Europe, Israel and Argentina. [42] Grint et al. studied all patients in EuroSIDA with viremic HCV infection, and used Poisson regression was used to identify temporal changes
and regional differences in HCV treatment uptake. [42] The study included a total of 1984 coinfected patients, of whom 501 (25.3%) received HCV therapy. [42] Treatment incidence rose from 0.33 (95% CI 0.16-0.50) per 100 person-years of follow-up in 1998 to 5.93 (95% CI 4.49-7.38) in 2007, and fell to 3.78 (95% CI 2.50-5.07) in 2009. [42] A CD4 cell count > 350 cells/μL and liver fibrosis ≥ F2 were

predictors of anti-HCV treatment initiation on adjusted analyses. [42] A strength of this study is its ability to record patients' HCV status over time and to associate demographic and clinical characteristics with treatment initiation and completion. Limitations of this study include failure to characterize contraindications for initiating treatment (i.e. substance abuse) and reasons for discontinuing treatment (i.e. adverse events).

CHAPTER 3: STUDY METHODS

3.1) Study Design

We conducted a retrospective review of the medical records of patients reported as having HCV infection at the Nathan Smith HIV clinic of Yale-New Haven Hospital from June 2002 through January 2014 (n = 135), collecting data points for each patient including: demographics, clinical characteristics related to HCV and HIV, other medical comorbidities, linkage to care, prescription of HIV and HCV treatment, HCV treatment course, and outcomes. Clinical data collected for each subject were the current or most recent at the time of their most recent HCV treatment evaluation, unless no evaluation occurred, in which case data were collected from the most recent clinical encounter at the Nathan Smith Clinic.

This study is unique amongst prior published studies of the HCV care continuum in two ways. First, it examines a large sample of HIV/HCV coinfected patients in the DAA era. Second, it classifies care outcomes as optimal or suboptimal, in order to better characterize factors impacting optimal management outcomes.

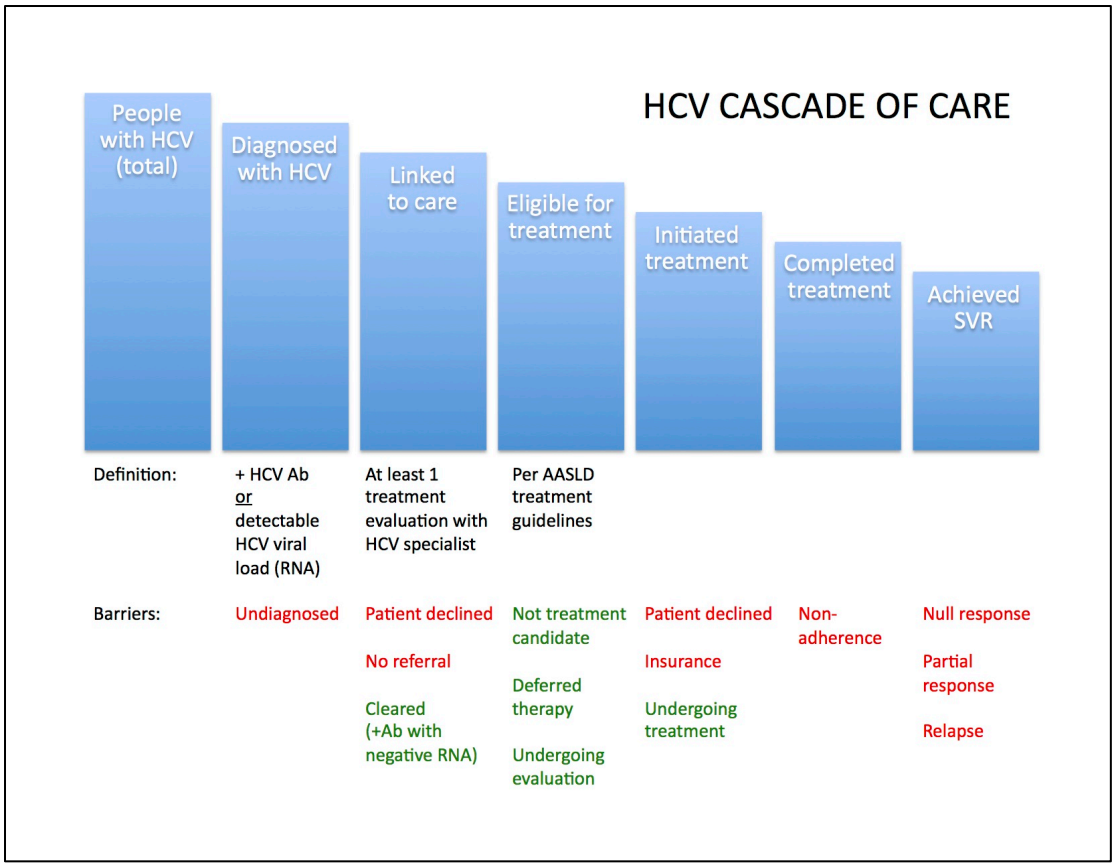


Figure 1: The HCV Cascade of Care, showing steps of the cascade, definitions of each step, and barriers to care at each step. Text in red indicates suboptimal outcomes, while text in green indicates optimal outcomes. HCV = hepatitis C virus, SVR = sustained virologic response, Ab = antibody, AASLD = American Association for the Study of Liver Diseases.

3.2) Study Population, Eligibility and Sampling

The study population included all HCV-positive patients from the Nathan Smith Clinic of the Yale-New Haven Hospital, an urban HIV referral clinic in New Haven, CT associated with the Yale Medical Group and the Yale School of Medicine.

Eligibility criteria were defined as patients in care from June 2002 through January 2014, and having a current diagnosis of HCV by ICD-9 code, verified by current anti-HCV positivity and/or detectable HCV viral load in the clinical record.

3.3) Study Variables and Measures

Definitions of HIV/HCV coinfection

- HCV diagnosis: The subject must have at least one positive anti-HCV antibody test and/or HCV RNA (the latter accepted for active cases)
- Chronic HCV infection: The subject must have persistent HCV RNA, i.e. at least one HCV RNA result greater than undetectable > 6 months from time of first diagnosis
- HIV infection: The subject must have at least one positive anti-HIV 1 or 2 antibody result
- AIDS Diagnosis by low CD4 count only: The subject must have at least one CD4 count under 200 cells / µl and no recorded history of opportunistic infection
- AIDS Diagnosis by low CD4 count and OI: The subject must have at least one CD4 count under 200 cells / µl and a recorded history of at least one opportunistic infection, per CDC guidelines of AIDS-defining criteria [52]

Definitions of medical comorbidities

- All medical comorbidities were identified by provider documentation from a primary care provider and/or an HCV treatment specialist, by ICD-9 code and/or explicit mention in a provider note

Definitions of care continuum stages

- Referral to care: The subject must have a provider note explicitly stating referral to an HCV treatment specialist, have a clinical appointment scheduled with an HCV treatment specialist, or attend an evaluation with an HCV treatment specialist
- Treatment evaluation: The patient must have had at least one clinical encounter with an HCV treatment specialist for the purpose of HCV treatment evaluation
- Treatment eligibility: The subject must be evaluated by an HCV treatment specialist and either explicitly deemed to be a candidate for treatment, be recommended to initiate treatment, or be prescribed treatment

Definitions of suboptimal care outcomes

- Patient declined: The subject must have declined to be referred for treatment evaluation or declined to be prescribed treatment, while the provider recommended referral or prescription of treatment, as explicitly stated in a provider note
- Loss of linkage to care: The subject must have at least one clinical encounter to establish care with a primary care provider or HCV specialist, but fail to

present to future scheduled appointments without being in regular contact with the clinic

- No referral, reason unknown: The subject must have no documentation in the clinical record of having been referred for HCV treatment AND have no documented reason for non-referral

Definitions of optimal care outcomes

- Infection cleared: The subject must have at least one positive anti-HCV antibody result and an undetectable HCV RNA at most recent laboratory evaluation in the absence of treatment
- Not treatment candidate: The subject must have been deemed "not a candidate for treatment" as explicitly stated in a provider note from a primary care provider or HCV treatment specialist
- Awaiting initial evaluation: The subject must have been referred for HCV initial treatment evaluation and have a future scheduled appointment for this evaluation
- Undergoing evaluation: The subject must have had an initial evaluation with an HCV treatment specialist, but no decision had yet been made at the time of data collection regarding treatment eligibility
- Deferred therapy: The subject must have had at least one HCV treatment evaluation, with a provider note from the encounter explicitly recommending deferred therapy

- Undergoing therapy: The subject must have initiated HCV treatment but not yet completed the prescribed treatment course

Definitions of treatment outcomes:

- Partial response: ≥ 2 log $_{10}$ reduction from baseline HCV RNA at week 12, but virus remains detectable through week 24 or end of treatment (applies to therapy with interferon based regimens and first generation DAAs boceprevir and telaprevir)
- Null-response: <2 log $_{10}$ reduction from baseline HCV RNA during treatment (applies to therapy with interferon based regimens and first generation DAAs boceprevir and telaprevir)
- End-of-treatment response (ETR): undetectable HCV RNA at the end of planned treatment course
- Sustained virologic response (SVR): undetectable HCV RNA at 12-24 weeks after treatment completion
- Relapse: undetectable viremia during treatment and/or at the end of treatment, but subsequent viremia typically occurring within 24 weeks following treatment cessation

3.4) Data Collection

All data collection was conducted by the author of this thesis. Clinical data were abstracted over the period -August 2014 to December 2014- from electronic

medical records of identified eligible patients into an electronic case report form and/or password protected MS Excel © database. Each patient was assigned a unique code prior to entry of data into the case report form and/or study database to minimize risk of patient identification. The master lists linking patient names/identifiers to the study database were stored in an encrypted password protected file, known only to the research team. Similarly, all electronic study data was stored in encrypted and password-protected laptop computers. Electronic data without PHI was stored on an encrypted USB drive that is password protected, available only to the principal investigator, sub-investigators, and research coordinators.

3.5) Data Analysis / Statistics

All data analysis was conducted by the author of this thesis. The number of patients progressing through each stage of the treatment cascade were expressed as proportions of the total study population (simple frequencies and/or percentages). Reasons for failure of progression ("drop-offs") along the HCV treatment cascade were captured and reported as optimal or suboptimal outcomes, including the number of patients who met the pre-defined criteria for the outcomes. Binary logistic regression analyses were conducted to investigate factors associated with not being referred for HCV treatment evaluation and not being prescribed HCV treatment, while adjusting for other related variables, using SPSS version 22 (IBM, Armonk, New York). Bivariate analyses were conducted to obtain unadjusted data for factors

shown to be significant predictors in the regression analyses. A p value ≥ 0.05 was considered statistically significant.

3.6) Timeline and Resources

Study conception and design occurred from April 2014 to July 2014 with subsequent study approval obtained from the Yale University Institutional review Board (Human Investigations Committee - HIC). Data collection was then conducted over the period from August 2014 to December 2014. Data analysis was performed from December 2014 to February 2015. Drafting and multiple revisions of the thesis occurred over the period of January 2015 to February 2015. Funding for the study was provided by the Yale School of Medicine Office of Student Research, on a monthly basis, over the period of June 2014 to December 2014.

3.7) Subject Protection and Confidentiality

All portable devices and desktop computers contained encryption software by Yale University Information Technology Services (ITS). Data was maintained as accessible only to the investigator and study personnel listed on the Human Investigation Committee (HIC) application. The principal investigator was responsible for monitoring the data and assuring protocol compliance. Either the principal investigator or the HIC maintained the authority to stop or suspend the study

or require modifications. In compliance with the ICH/GCP guidelines, the investigators took measures to prevent accidental or premature destruction of these documents or loss of data. When the project is complete, the password encrypted data and/or identifiers will be destroyed by electronically and securely deleting all information in its entirety using approved software.

CHAPTER 4: RESULTS

4.1) Study Subject Demographics

The majority of the study population was male (62.22%), and the male-to-female ratio was 1.65 to 1 (see Table 1a). The median age of the population was 56 years, and the interquartile range was 50.9 years to 59.4 years. The majority of the study population was 55-64 years of age (51.85%), most subjects were between 45 and 64 years of age (89.63%), and 4.44% were elderly (age ≥ 65). The population was racially diverse, with the highest proportion identifying as black (48.89%) followed by white (32.59%) and Hispanic/Latino (17.04%), and no patients identified as Asian. Only 8.15% of the study population was homeless, and none were incarcerated while in care. The vast majority of subjects had public insurance (91.85%), most were unmarried (82.96%), and the majority of the study population was unemployed (65.19%). While more than half resided in New Haven (56.30%), a large amount (43.70%) commuted to the clinic from surrounding areas.

Table 1a: Demographic characteristics of study population

		N or median	% or IQR
Gender	Male	84	62.22%
	Female	51	37.78%
Age	Median Age	56	50.92 - 59.42
	< 45	8	5.93%

	45-54	51	37.78%
	55-64	70	51.85%
	≥ 65	6	4.44%
Race / Ethnicity	White	44	32.59%
	Black	66	48.89%
	Latino	23	17.04%
	Asian	0	0.00%
	Other	2	1.48%
Housing Status	Personal Residence	114	84.44%
	Extended Care Facility	10	7.41%
	Homeless	11	8.15%
	Prison	0	0.00%
Insurance	Public	124	91.85%
	Private	9	6.67%
	Uninsured	2	1.48%
Marital Status	Married	23	17.04%
	Single/Other	112	82.96%
Employment	Employed	22	16.30%
	Unemployed	88	65.19%
	Unknown	25	18.52%
Resident City	New Haven	76	56.30%

Other	59	43.70%

The majority of study subjects had no significant medical comorbidity (52.59%) (see Table 1b). The most common medical comorbidity among the study subjects was diabetes mellitus (16.30%), followed by portal hypertension (14.81%) and anemia (11.11%). No patients were pregnant at their most recent treatment evaluation or most recent clinical encounter. More than half of patients had at least one psychiatric comorbidity or substance abuse disorder (60.00%), with the most common comorbidities being depression (40.00%), active drug abuse (22.22%) and active alcohol abuse (16.30%).

Table 1b: Comorbidities of study population

	N	%
Medical Comorbidities		
Hepatic Decompensation	9	6.67%
Portal Hypertension	20	14.81%
Diabetes Mellitus	22	16.30%
Renal Disease	12	8.89%
Chronic Obstructive Pulmonary Disease	12	8.89%
Heart Failure	2	1.48%
Thyroid Disease	5	3.70%
Anemia	15	11.11%

Leukopenia	4	2.96%
Thrombocytopenia	10	7.41%
Hemophilia	2	1.48%
Autoimmune Disease	2	1.48%
Malignancy	9	6.67%
Pregnancy	0	0.00%
None	71	52.59%
Psychiatric / Social Comorbidities		
Depression (or other mood disorder)	54	40.00%
Schizophrenia	5	3.70%
Active alcohol abuse	22	16.30%
Active drug abuse	30	22.22%
None	54	40.00%

Of the patients with known HCV viral load (88.63% of study population), the median HCV viral load was 2,430,000 copies/µl (IQR: 521,000 - 6,448,647), 72.73% had HCV viral load greater than 600,000 copies/µl, and 28.93% had HCV viral load greater than 6,000,000 copies/µl (see Table 1c). The majority of patients had genotype 1 infection (71.11%), with nearly half of the study population having subtype 1a infection (47.41%). There were small numbers of patients with genotypes 2 (3.70%), 3 (6.67%), and 4 (2.22%) infection. For the majority of patients, the IL-28B genotype was unknown (65.19%). Injection drug use (IDU) was the most

commonly reported risk factor for HCV acquisition (69.63%). Most patients (84.44%) had never previously received HCV treatment.

Table 1c: HCV-related clinical characteristics of study population

		N or median	% or IQR
HCV Viral Loads	Median VL	2,430,000	521,000 – 6,448,647
(copies/µl of blood)	> 600,000	88	72.73%
	> 6,000,000	35	28.93%
	Unknown	14	10.37%
HCV Genotype	1a	64	47.41%
	1b	15	11.11%
	1 (subtype unknown)	17	12.59%
	1 (total)	96	71.11%
	2	5	3.70%
	3	9	6.67%
	4	3	2.22%
	Unknown	22	16.30%
IL-28B Genotype	CC	9	6.67%
	CT	25	18.52%
	TT	13	9.63%
	Unknown	88	65.19%

Mode of HCV Acquisition (Risk Factors)			
	Injection Drug Use	94	69.63%
	Sexual	6	4.44%
	Blood Products	7	5.19%
	Intranasal Cocaine	4	2.96%
	Tattoo / Scarification	2	1.48%
	Health Care Associated	0	0.00%
	Unknown	30	22.22%
Treatment Naïve	Yes	114	84.44%
	No	21	15.56%

The most commonly reported risk factors for HIV transmission were injection drug use (69.63%) and heterosexual contact (37.04%) (see Table 1d). The median CD4 count of the study population was 521 cells/µl (IQR: 304 – 787.5). The majority of patients had serum HIV viral loads less than 20 copies/ml (65.93%), and 42.96% had undetectable serum HIV viral loads. The majority of patients had never been diagnosed with AIDS (52.59%), and only 23.70% had a history of opportunistic infection. The majority of subjects (91.85%) were on antiretroviral therapy (ART), and 8.15% were not taking any ART. Broken down by classes, the antiretroviral therapy for 22.22% included a non-nucleoside reverse-transcriptase inhibitor (NNRTI), 51.85% included a protease inhibitor (PI), and 35.56% included an integrase strand transfer inhibitor (INSTI).

Table 1d: HIV-related risk factors and clinical characteristics of study population

		N or median	% or IQR
Mode of HIV Acquisition (Risk Factors)			
	Injection Drug Use	94	69.63%
	Homosexual	7	5.19%
	Heterosexual	50	37.04%
	Blood Products	4	2.96%
	Vertical	0	0.00%
	Health Care Associated	0	0.00%
	Unknown	13	9.63%
CD4 Count	Median CD4 Count	521	304 – 787.5
HIV Viral Load	< 20 (includes undetectable)	89	65.93%
(copies/ml)	Undetectable	58	42.96%
AIDS Diagnosis	Low CD4 count	32	23.70%
	OI only	0	0.00%
	Both (low CD4 and OI)	32	23.70%
	None	71	52.59%
ART	On ART	124	91.85%
	Not on ART	11	8.15%
	NRTI Total	117	86.67%
	3TC only	2	1.48%

TDF only	1	0.74%
ABC / 3TC	20	14.81%
ABC / TDF	1	0.74%
AZT / 3TC	2	1.48%
TDF / FTC	91	67.41%
NNRTI Total	30	22.22%
EFV	17	12.59%
ETR	2	1.48%
NVP	2	1.48%
RPV	9	6.67%
PI Total	70	51.85%
ATV	6	4.44%
ATV / RTV	35	25.93%
DRV / RTV	23	17.04%
LPV / RTV	5	3.70%
NFV	1	0.74%
INSTI Total	48	35.56%
RAL	30	22.22%
DTG	8	5.93%
EVG + cobicistat	10	7.41%

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

About one quarter (24.44%) of the study population had known cirrhosis (see Table 1e). Of patients with cirrhosis, 27.27% had decompensated disease. The most commonly experienced complications of cirrhosis were ascites (36.36%) and esophageal varices (36.36%). The proportion of patients having liver fibrosis evaluation was 41.48% for liver biopsy and 27.41% for Fibrospect II. Metavir and Fibrospect II scores were unknown for the majority of patients (58.52% and 72.59% respectively). Of patients with known Metavir scores, 76.79% had F2 or greater fibrosis, and of patients with known Fibrospect II scores, 72.97% had F2 or greater fibrosis.

Table 1e: Liver disease severity of study population

		N	%
Cirrhosis	Yes	33	24.44%
	No	37	27.41%
	Unknown	65	48.15%

Cirrhosis Classification	Compensated	24	72.73%
	Decompensated	9	27.27%
	Total	33	
Cirrhosis Complications	PSE	9	27.27%
	SBP	0	0.00%
	Ascites	12	36.36%
	Varices	12	36.36%
Metavir Score	Known	56	41.48%
	0	3	5.36%
	1	10	17.86%
	2	19	33.93%
	3	9	16.07%
	4	15	26.79%
	Unknown	79	58.52%
Fibrospect II Score	Known	37	27.41%
	F0-F1	10	27.03%
	F2-F4	27	72.97%
	Unknown	98	72.59%

4.2) The Care Continuum

Of 135 total patients diagnosed with chronic HCV, only 96 were referred for HCV treatment evaluation, a drop-off of 29% (see Figure 2). Of the 96 referred, 91 had a treatment evaluation, a decrease of 5%. Of the 91 evaluated, 49 were deemed eligible for HCV treatment, a decline of 46%. Of the 49 eligible for treatment, only 28 were prescribed HCV treatment, a drop-off of 43%. Finally, 17 subjects achieved SVR, with a decrease of 39%.

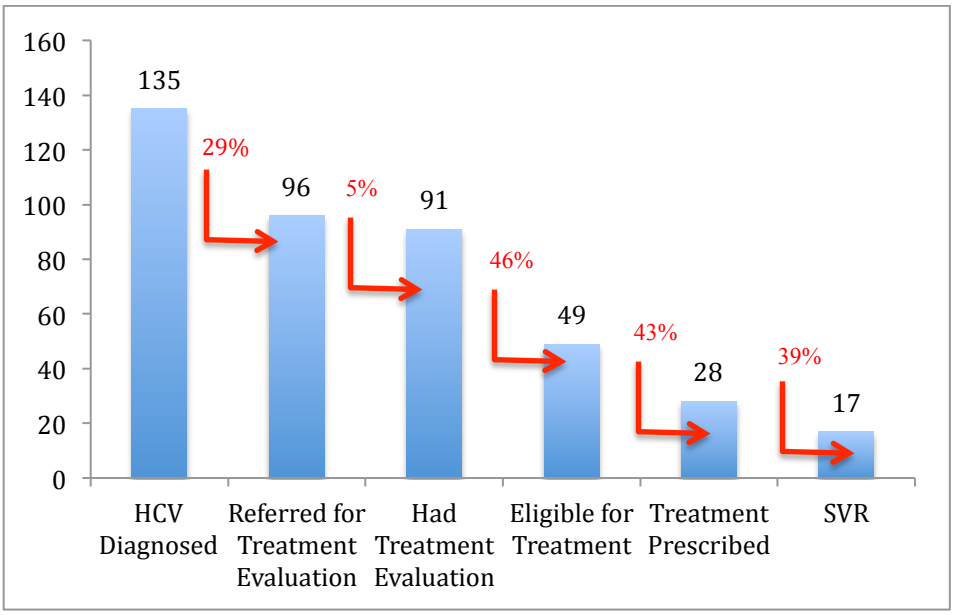


Figure 2: The HCV Care Continuum among HIV/HCV Coinfected Patients at the Nathan Smith Clinic, 2002-2014. The horizontal axis represents the sequential steps of the continuum. The vertical axis denotes the number of patients progressing through each step of the continuum, labeled in black numbers above each column. The red arrows and percentages designate the proportion of patients from the previous step who drop off before achieving the next step. HCV = hepatitis C virus, SVR = sustained virologic response.

4.3) Factors Impacting Optimal Management Outcomes

Of 135 total patients in the study population, 71% were referred for treatment, 67% had a treatment evaluation, 36% were eligible for treatment, 21% were prescribed treatment, and 13% achieved SVR (see Figure 3). More than half (54%) of patients not referred for treatment were deemed not to be candidates for treatment, and 13% of patients not referred for treatment had cleared their HCV infection. Some of these patients (10%) declined to consider treatment, and others (18%) had no discernable reason for lack of referral. Of the 42 patients who have been evaluated for HCV treatment but not deemed eligible for treatment, 64% were deemed not a treatment candidate while 31% were still undergoing evaluation. Of the 21 patients deemed eligible for HCV treatment but not prescribed treatment, 71% were recommended to defer therapy, 24% declined to undergo treatment, and 5% could not receive treatment due to a problem with insurance coverage. Of the 11 patients prescribed HCV treatment that did not achieve SVR, 55% were still undergoing therapy and 45% had an end-of-treatment response.

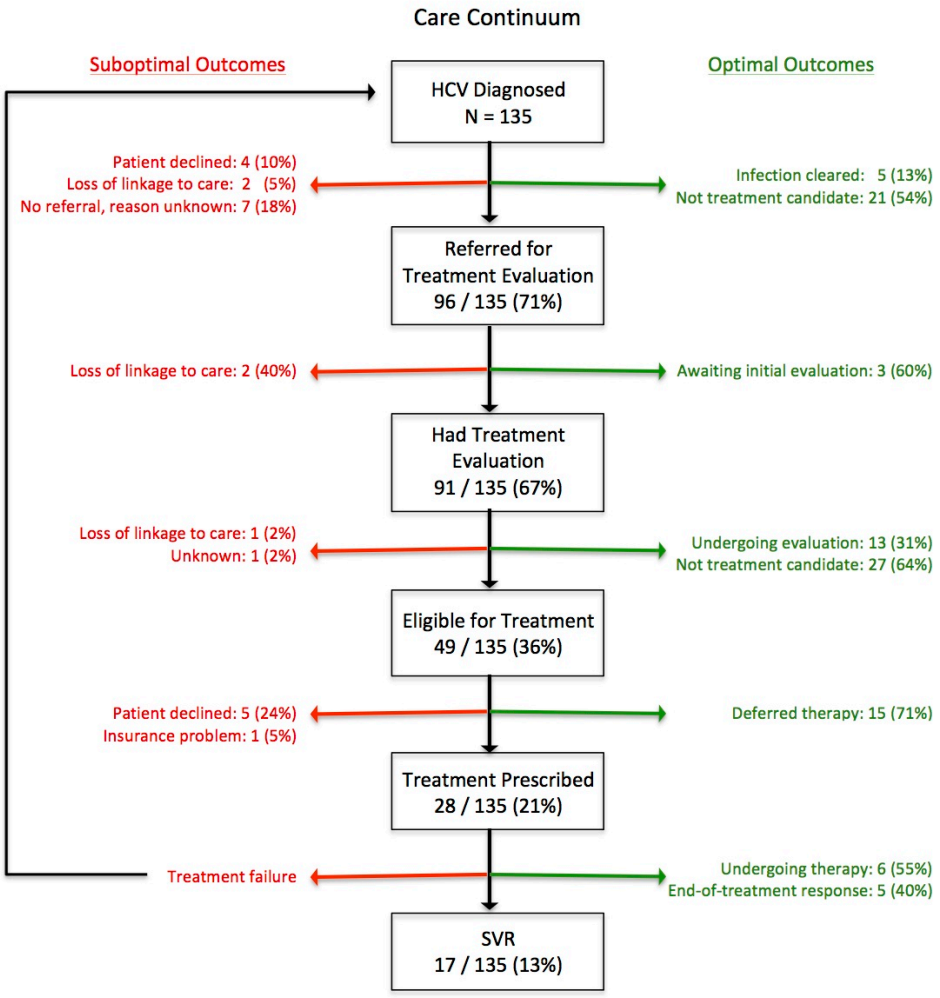


Figure 3: Optimal and Suboptimal Outcomes in the HCV Care Continuum. Percentages for each outcome describe the proportion of the patients who drop off the continuum at the designated location due to the designated outcome. Patients experiencing treatment failure return to the beginning of the care continuum.

Of the 107 patients who were not prescribed HCV treatment, the most common reason for not initiating treatment was not being deemed a treatment candidate (45.79%) (see Table 2a).

Table 2a: Reasons for not initiating treatment

	N	%
Infection cleared	5	4.67%
Awaiting initial evaluation	3	2.80%
Undergoing evaluation	13	12.15%
Deferred therapy	15	14.02%
Patient declined	9	8.41%
Not candidate	49	45.79%
Loss of linkage to care	5	4.67%
No referral for treatment evaluation (reason unknown)	7	6.54%
Lack of insurance coverage	1	0.93%
Total	107	

Of patients deemed not to be treatment candidates, the most common reasons given were non-adherence to ART / poorly controlled HIV (51.02%), active drug abuse (40.82%), and active alcohol abuse (26.53%) (see Table 2b).

Table 2b: Reasons for non-candidacy for HCV treatment

	N	%
Active alcohol abuse	13	26.53%
Active drug abuse	20	40.82%

ART non-adherence / poorly controlled HIV	25	51.02%
Decompensated cirrhosis	5	10.20%
Uncontrolled depression	4	8.16%
Uncontrolled Diabetes Mellitus	3	6.12%
Malignancy	3	6.12%
End Stage Renal Disease	2	4.08%
Thrombocytopenia	1	2.04%

4.4) Predictors of Suboptimal Outcomes across the Care Continuum

Using a binary logistic regression model, significant predictors of not being referred for HCV treatment evaluation include female gender (odds ratio: 0.240, 95% confidence interval: 0.064 - 0.907, p = 0.035), depression (OR: 0.215, 95% CI: 0.057 - .812, p = 0.023), and high HIV viral load (for each 1 log increase in viral load, OR: 0.608, 95% CI: 0.373 - 0.992, p = 0.046) (see Table 3a). Having a higher number of medical comorbidities was positively associated with HCV treatment referral (for each additional comorbidity, OR: 2.054, 95% CI: 1.084 - 3.892, p = 0.027). These predictors were significant after controlling for the other variables in the model. Age, race, transmission risk factors, alcohol and drug abuse, HCV genotype, HCV viral load, CD4 count and AIDS diagnosis were not predictive of treatment referral in this model.

Table 3a: Predictors of treatment referral using a binary logistic regression model

	Odds Ratio (OR)	95% C.I. Lower	95% C.I. Upper	p-value
Demographic Information				
Age	0.968	0.870	1.078	0.555
Female gender	0.240	0.064	0.907	0.035
Black	0.843	0.208	3.405	0.810
Latino	1.785	0.248	12.818	0.565
Homeless	2.669	0.169	42.217	0.486
Married	1.064	0.150	7.539	0.951
Lives outside New Haven	0.979	0.275	3.483	0.974
Injection Drug Use	0.716	0.147	3.491	0.680
Blood Products	0.639	0.033	12.207	0.766
Homosexual	0.487	0.034	6.987	0.596
Comorbidities				
Depression	0.215	0.057	0.812	0.023
# of Medical Comorbidities	2.054	1.084	3.892	0.027
Active Alcohol Abuse	3.306	0.427	25.625	0.252
Active Drug Abuse	0.361	0.081	1.618	0.183
HCV Information				

Genotype 2	3.836	0.205	71.686	0.368
Genotype 4	0.881	0.050	15.530	0.931
Genotype unknown	0.032	0.001	1.182	0.062
log10(HCV Viral Load)	0.842	0.501	1.415	0.516
HIV Information				
CD4 Count	1.002	1.000	1.005	0.088
AIDS: CD4 only	1.346	0.210	8.646	0.754
AIDS: CD4 + OI	1.269	0.244	6.590	0.777
log10(HIV Viral Load)	0.608	0.373	0.992	0.046

Cox & Snell R square: 0.332, Nagelkerke R square: 0.492

Using bivariate analysis, female gender (OR: 0.334, 95% CI: 0.155 - 0.721, p = 0.005), depression (OR: 0.284, 95% CI: 0.131 - 0.617, p = 0.001), and high HIV viral load (OR: 0.695, 95% CI: 0.544 - 0.889, p = 0.004) remained significant predictors of not being referred for HCV treatment evaluation (see Table 3b). The number of medical comorbidities was not a significant predictor of treatment referral using this analysis, which does not control for any other variables in the study.

Table 3b: Predictors of HCV treatment referral using bivariate analysis

	Odds Ratio (OR)	95% C.I. Lower	95% C.I. Upper	p-value

Female gender	0.334	0.155	0.721	0.005
Depression	0.284	0.131	0.617	0.001
# of Medical Comorbidities	1.321	0.938	1.861	0.111
log10(HIV Viral Load)	0.695	0.544	0.889	0.004

Using a binary logistic regression model, significant predictors of not being prescribed HCV treatment include black race (compared to white, OR: 0.018, 95% CI: 0.001 - 0.307, p = 0.006), high HIV viral load (OR: 0.106, 95% CI: 0.025 - 0.458, p = 0.003), and having AIDS diagnosis by both CD4 count and history of opportunistic infection (OI) (OR: 0.037, 95% CI: 0.001 - 0.924, p = 0.045) (see Table 3c). These predictors were significant after controlling for the other variables in the model. Age, gender, date of treatment evaluation, number of number medical comorbidities, depression, alcohol and drug abuse, cirrhosis, HCV genotype, HCV viral load, and ART regimen were not predictive of being prescribed HCV treatment in this model.

Table 3c: Predictors of being prescribed HCV treatment using a binary logistic regression model

	Odds Ratio (OR)	95% C.I. Lower	95% C.I. Upper	p-value
<u>Demographic Information</u>				
Age	1.260	0.990	1.602	0.060

Female gender	0.370	0.049	2.810	0.337
Black	0.018	0.001	0.307	0.006
Latino	0.447	0.025	8.026	0.585
Evaluated after 12/6/2013	0.558	0.095	3.269	0.518
Comorbidities				
Depression	0.518	0.074	3.643	0.509
# of Medical Comorbidities	0.773	0.362	1.653	0.507
Active Alcohol Abuse	1.345	0.075	24.250	0.841
Active Drug Abuse	0.130	0.008	2.037	0.146
Cirrhosis	2.243	0.166	30.315	0.543
HCV Information				
Genotype 2	3.227	0.022	469.629	0.645
Genotype 3	0.071	0.003	1.526	0.091
Genotype 4	0.345	0.000	10067	0.839
Genotype unknown	0.026	0.000	115.781	0.394
log10(HCV Viral Load)	0.625	0.194	2.019	0.433
HIV Information				
AIDS: CD4 only	1.311	0.149	11.556	0.807
AIDS: CD4 + OI	0.037	0.001	0.924	0.045

log10(HIV Viral Load)	0.106	0.025	0.458	0.003
ART: TDF / FTC	0.070	0.000	43.479	0.418
ART: ABC / 3TC	0.008	0.000	5.286	0.146

Cox & Snell R square: 0.464, Nagelkerke R square: 0.662

Using bivariate analysis, high HIV viral load (OR: 0.518, 95% CI: 0.320 - 0.840, p = 0.008) and having AIDS diagnosis by both CD4 count and history of OI (OR: 0.182, 95% CI: 0.040 - 0.838, p = 0.029) remained significant predictors of not being prescribed treatment for HCV (see Table 3d). Black race compared to white was not a significant predictor of being prescribed HCV treatment in this analysis, which does not control for any other variables in the study.

Table 3d: Predictors of being prescribed HCV treatment using bivariate analysis

	Odds Ratio (OR)	95% C.I. Lower	95% C.I. Upper	p-value
Black	0.447	0.171	1.172	0.102
log10(HIV Viral Load)	0.518	0.320	0.840	0.008
AIDS: CD4 + OI	0.182	0.040	0.838	0.029

CHAPTER 5: DISCUSSION

5.1) Key Findings

Our results show that in a real-world setting, an urban outpatient HIV clinic, few HIV-infected individuals diagnosed with chronic HCV infection achieve virologic cure of HCV, and that there are multiple barriers that lead to significant drop-offs between stages along the HCV care continuum.

In our analysis, only 13% of the study population achieved SVR. While low, this is higher than the proportion reported by Kramer et al. (3.5%) and Yehia et al. (9%). [47, 48] However, these results may not be directly comparable due to differences in study population. Kramer et al. studied HCV monoinfected patients in the VA healthcare system. Yehia et al. also studied monoinfected patients, and used an estimate of all patients with chronic HCV infection, not a group of individuals with diagnosed HCV infection, as the denominator for their proportion. When readjusted as a percentage of only those with diagnosed chronic HCV infection, the proportion achieving SVR in their analysis was 18%.

Cachay et al., a study of a similar patient population (HIV/HCV coinfected patients in care at an HIV-referral clinic), reported that only 7% of patients diagnosed with chronic HCV achieved SVR. [50] Since Cachay et al. captured data from as recently as 2012, the improved cure rates in our study may reflect the positive impact of introduction of DAAs in the recent two years.

In our analysis, 36% of the study population had a treatment evaluation and were found to be eligible for HCV treatment, similar to the eligible proportion found by Kramer et al. (35.9%), but higher than that reported by other studies of HIV/HCV coinfected subjects, including Butt et al. (28.4%) and Maier et al. (21%). [47, 49, 51]

Our results may reflect an improvement in treatment eligibility in the era of DAAs which became available and were used in the last two years of the study period. Compared to regimens containing interferon and ribavirin, treatment eligibility is vastly improved for the currently recommended DAA-based regimens as there are less clinical and laboratory contraindications to use of the drugs. While the analysis of Butt et al. used data from 2003, and that of Maier et al. used data from 2010, our study captured clinical interactions as recently as December 2014. [49, 51] In fact, more than 67% of the treatment evaluations recorded in our study occurred after December 6, 2013, the date of FDA-approval of sofosbuvir (table 4).

Table 4: Treatment Evaluation in the era of DAAs

Treatment Evaluation after 12/6/13	N	%
Yes	61	67.03%
No	30	32.97%

One of the strengths of our study was the ability to describe factors impacting drop-off between stages in the HCV care continuum. We identified three major drop-offs points in the cascade: between HCV diagnosis and HCV treatment

referral/evaluation, treatment evaluation and treatment eligibility, and lastly, treatment eligibility and prescription of antiviral treatment.

Of the 135 HIV-infected individuals diagnosed with HCV, while 71% were referred for HCV treatment evaluation, 67% had a formal evaluation by a HCV specialist. These proportions compare favorably to other analyses. Kramer et al. found that 60% of those diagnosed with HCV were evaluated for treatment. [47] Cachay et al. reported a 50% evaluation rate for patients with HIV/HCV coinfection. [50] Yehia et al. found that only 54% of those diagnosed with chronic HCV even had HCV RNA confirmation, and that only 34% had liver fibrosis evaluation. [48]

Of the factors influencing drop-off between diagnosis and referral, the most common was not being deemed a treatment candidate (54%). Notably, the determination of treatment candidacy was typically determined by a patient's primary care provider. The most common reasons for non-candidacy were non-adherence to ART / poorly controlled HIV (51.02%), active drug abuse (40.82%), and active alcohol abuse (26.53%). These factors are comparable to those identified by Maier et al., who found that the most common contraindications to therapy were active alcohol abuse (24%), uncontrolled mental health (22%), recent injection drug use (21%), and poor antiretroviral adherence (22%).

While the above factors are relative contraindications to receiving HCV therapy, they become absolute when they preclude referral for treatment evaluation, eliminating any chance that treatment will be prescribed. This, however, may not be an optimal outcome, as history of non-adherence to ART may not be entirely predictive of non-adherence to HCV treatment, especially with new and better

tolerated DAA regimens that are prescribed for relatively short treatment durations. Furthermore, while ART non-adherence and substance abuse are difficult to treat, they are amenable to intervention, and if adequately addressed may indirectly increase HCV treatment referral.

Of the suboptimal outcomes influencing drop-off between HCV diagnosis and treatment evaluation referral, the most common were patients not referred for evaluation by providers for unknown reasons (18%) and patients declining referral (10%). The former is provider-driven barrier, while the latter is patient-driven. There are numerous reasons why a provider may fail to refer a patient with chronic HCV for treatment evaluation: the provider may not be aware of the diagnosis, may not be aware of indications for treatment referral, or may not be aware of available and effective HCV treatment options or willing to prescribe them. These factors may be mitigated by increasing providers' familiarity with HCV disease and its management, and development and implementation of HCV referral and treatment protocols. Patients declining to meet with an HCV treatment specialist need further education regarding the consequences of untreated chronic HCV infection in the context of HIV co-infection and the availability of safe and well-tolerated treatment regimens of short durations.

The second major drop-off in our HCV care continuum was between treatment evaluation and treatment eligibility. Only 36% of the study population was deemed eligible for treatment, a decline of 46% from the group of patients who had a treatment evaluation. Kramer et al. reported a similar decline (40%) between evaluation and eligibility. Again, the primary reason for this drop-off was not being

deemed a treatment candidate. As discussed above, interventions targeting the primary reasons for non-candidacy (non-adherence and substance abuse) may indirectly improve HCV treatment eligibility. Promisingly, 31% of the decline at this point was due to patients still undergoing treatment evaluation who may yet progress further through the cascade. As progression through this stage is dependent on provider subjectivity, strict algorithms for evaluation and prescription of treatment may help eliminate this barrier to care. However, not all reasons for treatment non candidacy can be easily modified, including comorbid conditions such as abnormal renal function, severe cytopenias, and decompensated liver disease.

The final major drop-off was between treatment eligibility and prescription of treatment. Our results show a decline of 43% at this step, which was significant but not as drastic as that reported by Kramer et al. (67.7%). [47] The major reason for failure to progress through this step was deferred therapy (71%), meaning that the patient was eligible for treatment but that the provider recommended deferral of prescription of treatment in the best interest of the patient. Deferring therapy may be a provider's choice if they have knowledge of impending availability of new regimens that are safer, more effective, and/or better tolerated than those currently available, or if the patient needs to complete evaluation or treatment for another serious medical comorbidity, such as malignancy. In the era of interferon therapy, lack of severe liver disease was sometimes a reason to defer therapy, as the risk of harms resultant from highly toxic treatment was greater than the benefit of potential HCV cure for those with low risk of progression to cirrhosis. However, with newer well-tolerated and more effective regimens available, all patients with chronic HCV infection should be

considered for treatment. The concern for deferring HCV therapy is the possibility of progression of liver disease or risk of developing extra-hepatic complications of HCV infection.

Other factors which may contribute to non-prescription of HCV treatment for potentially eligible individuals include drug-drug interactions between HCV and ARV drugs, particularly those of the protease inhibitor class (51.9% of our study population on ART). Furthermore, no or insufficient insurance coverage may also limit use of newer DAAs as it is factored into clinician decisions on whom to initiate therapy.

The primary suboptimal outcome influencing drop-off between eligibility and treatment was patients declining to receive treatment (24%). The reasons for this observation is unclear. This is probably related to patients' perception that they are at low risk of complications from HCV infection, or that treatments would result in significant side effects. Again, educating patients and providers about the availability, safety, efficacy and short duration of new treatment regimens will help to mitigate drop-off at this point in the continuum.

By conducting logistic regression and bivariate analysis, we were able to identify demographic and clinical factors predictive of not being referred for treatment and not being prescribed treatment. Female gender, depression, and high HIV viral load were predictive of not being referred for treatment, while high HIV viral load and having AIDS diagnosis by both low CD4 count and history of opportunistic infection (OI) were predictive of not being prescribed treatment. Cachay et al. reported similar factors to be predictive of failing to achieve optimal

outcomes. Their analysis found that lack of engagement in care, unstable housing, having AIDS diagnosis, having detectable HIV viral load and being non-white were predictive of non-referral, while ongoing illicit drug or alcohol use, ongoing uncontrolled neuropsychiatric disease, and poorly controlled HIV disease were predictive of not receiving HCV treatment. [50]

Our study found that female patients were much less likely to be referred for HCV treatment. There is evidence that women clear HCV infection more commonly than men, and experience slower rates of liver disease progression when chronically infected with HCV. [53, 54] Women also face unique barriers to treatment, including active pregnancy or the requirement for contraception for those with pregnancy potential to limit the risk of teratogenic effects from HCV drugs such as ribavirin. [55] The factors certainly impact HCV treatment evaluations and treatment eligibility. Lower rates of HCV treatment referral for female patients may reflect bias among primary care providers, as females who were evaluated for treatment were not less likely to be prescribed treatment by HCV treatment specialists. It may also indicate the presence of a confounding variable that was not included in the logistic regression analysis.

Depression was found to be predictive of non-referral, but in practice should not prevent referral for HCV treatment. This was probably driven by treatment evaluations performed when interferon based regimens were the only treatment options, as even a history of depression or mood disorder was a serious contraindication to interferon therapy. However, newer DAAs are not associated with

causing or exacerbating mood disorders, but primary care providers may retain the notion that depression precludes HCV treatment.

It was not surprising that our study found that having a high HIV viral load is predictive of both not being referred for evaluation and not receiving HCV treatment. It is plausible that patients who are prescribed ART and found with high viral loads are likely not engaged in regular care and/or not adherent to ART. For these patients, control of their HIV disease is often prioritized by providers over treatment of HCV infection. Furthermore, patients non-adherent with ART may also be non-adherent with HCV therapy. Having AIDS diagnosis by both low CD4 count and history of OI was also predictive of not being prescribed treatment, and this also likely reflects a group of patients with poor engagement in care and possibly poor adherence to ART.

5.2) Real world obstacles to optimal HCV management

There are numerous real world obstacles to HCV management, some of which were not captured in our analysis. The population in our study included only patients with diagnosed chronic HCV infection, but poor testing rates can lead to large numbers of undiagnosed individuals. To address poor testing rates, New York State passed legislation that requires the offering of a HCV screening test to every individual born between 1945 and 1965 in both inpatient and outpatient care settings. [56] While similar legislation in other states or at the federal level will likely help to reduce the number of people with undiagnosed chronic HCV infection, as of yet no

study has tested whether this will lead to net clinical benefit or harm in screened populations. [57]

There are also multiple factors leading to lower eligibility rates for HCV treatment among HIV-infected patients compared to non HIV-infected clinical trial populations. As seen in our results, HIV-coinfected populations have higher rates of mental health disorders and substance abuse disorders than the general population. In addition, drug-drug interactions remain a major challenge for prescribers of HCV treatment. Patients may decline HCV therapy if they are unwilling to switch their ART regimen to one compatible with the planned HCV treatment regimen. Issues of drug-drug interaction are extremely common. Among our study population, 51.9% of subjects were on ART containing a protease inhibitor (PI), many of which have significant interaction with the currently recommended DAA-based regimens. Potentially, care algorithms could be designed to transition HIV-infected patients with known chronic HCV infection to compatible ART in anticipation of future HCV treatment.

The prohibitive cost of newer treatments is another major obstacle to HCV management. The new DAA regimens can cost as much as $150,000 per treatment course, and recently, there has been a decision by many state Medicaid programs, to limit treatment only to individuals with advanced (F3 or F4) liver fibrosis. [58] Medicaid and Medicare insure a large proportion of HIV/HCV coinfected patients and such drug coverage decisions may weigh heavily on the patient population. As an example, 92% of our study population had public insurance. While those without advanced liver disease may not immediately suffer harm from untreated infection,

there remains a risk of transmission of HCV. Furthermore, while limiting access to treatment may yield short-term cost savings, it may lead to more patients requiring expensive liver transplants in the future.

5.3) Study Limitations

One limitation of the HCV continuum of care model is the large amount of overlap of the stages of engagement in care. While we attempted to address this by creating strict definitions for each stage of the cascade, the imposed definitions used in allocating patients may limit inter-study comparisons. Also, as study data was collected retrospectively from pre-existing medical records, accuracy of study results is dependent on quality of documentation. As with any single-center study, it is unclear whether patients have been evaluated or treated at other centers.

The spectrum of engagement in care as characterized in this high-risk, HIV-coinfected patient population may not be generalizable to the total patient population with chronic HCV or to populations outside of the United States and in resource limited settings due to different patient and provider characteristics. Furthermore, the care continuum at the Nathan Smith Clinic may not be reflective of a typical community clinic, as it has a pool of providers who are familiar with and actively engaged in HCV management, and is affiliated with an academic center with access to clinic trials.

Although a strength of our analysis was the ability to designate care outcomes as optimal and suboptimal, there remain limitations to this approach. Patients undergoing treatment evaluation and undergoing therapy were classified as having

optimal outcomes at the time of data collection, but it is possible that these patients may not progress forward through the cascade and will not be captured by our analysis. Controversially, one may argue it is an optimal outcome not to treat an HCV-infected patient with a low risk of progression to cirrhosis, and therefore not at risk for developing HCC. However, this was a stronger argument when HCV treatment was more toxic and less effective, therefore, the risk-benefit calculus was more weighted toward risk. In the era of DAAs, the pendulum is swinging in the other direction with less risk of harms with treatment and high success rates. Lastly, we considered it an optimal outcome when a patient is deemed not a treatment candidate because it represents optimal management of the patient at the time of evaluation, but leaving chronic HCV infection untreated is certainly not optimal for the health of the patient or for the public health as there remains a risk of disease transmission.

5.4) Conclusions and Recommendations

In conclusion, the number of patients achieving HCV cure remains suboptimal, and the benefits of available and effective HCV therapies will not be realized unless effective measures are implemented for dealing with barriers to care. Our study findings suggest that emphasis should be placed on improving HCV treatment referrals and treatment eligibility, including development and implementation of referral and treatment protocols. More studies are clearly needed to explore ways to improve modifiable factors which have been identified as resulting in suboptimal HCV management outcomes. Future research should also focus on

defining the best candidates for treatment using cost effectiveness models based on real world data, and expanding care delivery models including those that support medication adherence in hard-to-treat populations such as substance users and individuals with mental health disorders.

APPENDICES

Appendix A: Data Collection Worksheet

Patient ID: _____

Reviewed by: _____

Date Reviewed:

_____

Demographics

DOB: _____

Sex: ❑ M ❑ F

Race / Ethnicity:
❑ White ❑ Black
❑ Asian ❑ Latino
❑ Other: _____
❑ Unknown

Housing Status:
❑ Personal residence
❑ ECF ❑ Prison
❑ Homeless
❑ Other: _____
❑ Unknown

Insurance:
❑ Public ❑ Private
❑ Uninsured

Marital Status:
❑ Single ❑ Married
❑ Unknown ❑ Other

Employment Status:
❑ Employed
❑ Unemployed
❑ Unknown

Resident City:
❑ New Haven
❑ Other: _____

HCV Data
Date of Diagnosis
(or first HCV Ab +):

_____

HCV Viral Load (RNA):

❑ _____
❑ Unknown

HCV Genotype:
❑ 1 ❑ 2 ❑ 3
❑ 4 ❑ 5 ❑ 6
❑ Unknown

Subtype:
❑ a ❑ b ❑ c
❑ Unknown or N/A

IL-28B Genotype:
❑ CC ❑ CT
❑ TT ❑ Unknown

Mode of HCV Acquisition:
❑ IVDU ❑ Sexual
❑ Blood Products
❑ Intranasal Cocaine
❑ Tattoo / Scarification
❑ Health Care
❑ Unknown

HIV Data
Date of Diagnosis:

_____

Mode of HIV Acquisition:
❑ IVDU
❑ Homosexual
❑ Heterosexual
❑ Blood Products
❑ Vertical
❑ Health Care
❑ Unknown

CD4 count at HCV treatment evaluation:

❑ _____
❑ Unknown

HIV Viral Load at HCV treatment evaluation:

❑ _____
❑ Unknown

AIDS Diagnosis:
❑ OI ❑ CD4
❑ Both ❑ None
❑ Unknown

HIV Treatment (HAART):
❑ NRTI: _____
❑ NNRTI: _____
❑ PI: _____
❑ INSTI: _____
❑ Other: _____
❑ None ❑ Unknown

Patient ID: _____

Comorbidities:

Medical comorbidities:
❑ Hepatic decompensation
❑ Portal Hypertension
❑ DM ❑ Renal Disease
❑ COPD ❑ Heart Failure
❑ Thyroid ❑ Anemia
❑ Leukopenia
❑ Thrombocytopenia
❑ Hemophilia
❑ Pregnancy
❑ Autoimmune disease
❑ Other: _____
❑ None

Psychiatric / Social comorbidities:
❑ Depression
❑ Schizophrenia
❑ Active alcohol abuse
❑ Active drug abuse
❑ Other: _____
❑ None

Linkage to care

Treatment referral:
❑ Yes ❑ No
❑ Unknown

Date of treatment eval. with HCV specialist:

❑ _____
❑ None

Liver Fibrosis Evaluation:
❑ Serum markers
❑ Liver biopsy
❑ Other: _____
❑ None

Cirrhosis:
❑ Compensated
❑ Decompensated
❑ Yes, unspecified
❑ No ❑ Unknown

Cirrhosis complications:
❑ PSE ❑ SBP
❑ Ascites ❑ Varices
❑ Other: _____
❑ None

Metavir score:
❑ 0 ❑ 1 ❑ 2
❑ 3 ❑ 4
❑ Unknown

Fibrospect score:
❑ F0 – F1 ❑ F2 – F4
❑ Unknown

Treatment prescribed:
❑ Yes ❑ No
- If not, reason:
❑ Undergoing eval
❑ Infection cleared
❑ Patient declined
❑ Deferred therapy
❑ Not candidate
❑ Insurance
❑ Other: _____
❑ Unknown

Ineligible for treatment at prior evaluation:
❑ Yes ❑ No
- If yes:
Year: _____

Reason:

_____

Patient ID: _____

Treatment Course 1

Treatment start date:

_____

Treatment Regimen:
- ❑ Interferon (IFN) alone
- ❑ IFN + ribavirin (RBV)
- ❑ Telaprevir +IFN+RBV
- ❑ Daclatasvir +IFN+RBV
- ❑ Sofosbuvir +IFN+RBV
- ❑ Sofosbuvir + RBV
- ❑ Sofosbuvir/simeprevir
- ❑ Other: _____
- ❑ N/A

Completed treatment:
- ❑ Yes ❑ No ❑ N/A
- ❑ Undergoing therapy

- If not, reason:
- ❑ Side effects
- ❑ Insurance
- ❑ Loss of linkage to care
- ❑ Non-adherence NOS
- ❑ Other: _____
- ❑ Unknown

Duration of Treatment:

- ❑ _____
- ❑ N/A

Treatment end date:

_____

Treatment outcome:
- ❑ EOT
- ❑ SVR 12
- ❑ SVR 24
- ❑ Relapse
- ❑ Partial response
- ❑ Null response
- ❑ Undergoing therapy
- ❑ Other
- ❑ N/A

Treatment Course 2

Treatment start date:

_____

Treatment Regimen:
- ❑ Interferon (IFN) alone
- ❑ IFN + ribavirin (RBV)
- ❑ Telaprevir +IFN+RBV
- ❑ Daclatasvir +IFN+RBV
- ❑ Sofosbuvir +IFN+RBV
- ❑ Sofosbuvir + RBV
- ❑ Sofosbuvir/simeprevir
- ❑ Other: _____
- ❑ N/A

Completed treatment:
- ❑ Yes ❑ No ❑ N/A
- ❑ Undergoing therapy

- If not, reason:
- ❑ Side effects
- ❑ Insurance
- ❑ Loss of linkage to care
- ❑ Non-adherence NOS
- ❑ Other: _____
- ❑ Unknown

Duration of Treatment:

- ❑ _____
- ❑ N/A

Treatment end date:

_____

Treatment outcome:
- ❑ EOT
- ❑ SVR 12
- ❑ SVR 24
- ❑ Relapse
- ❑ Partial response
- ❑ Null response
- ❑ Undergoing therapy
- ❑ Other
- ❑ N/A

Appendix B: CDC Testing Recommendations for Hepatitis C Virus Infection

Available at: http://www.cdc.gov/hepatitis/hcv/guidelinesc.htm

CDC Testing Recommendations for Hepatitis C Virus Infection
Testing should be initiated with anti-HCV. For those with reactive test results, the anti-HCV test should be followed with an HCV RNA.

Persons for Whom HCV Testing Is Recommended

- Adults born during 1945 through 1965 should be tested once (without prior ascertainment of HCV risk factors)
- HCV-testing is recommended for those who:
    - Currently inject drugs
    - Ever injected drugs, including those who injected once or a few times many years ago
    - Have certain medical conditions, including persons:
        - who received clotting factor concentrates produced before 1987
        - who were ever on long-term hemodialysis
        - with persistently abnormal alanine aminotransferase levels (ALT)
        - who have HIV infection
    - Were prior recipients of transfusions or organ transplants, including persons who:
        - were notified that they received blood from a donor who later tested positive for HCV infection
        - received a transfusion of blood, blood components or an organ transplant before July 1992
- HCV- testing based on a **recognized exposure** is recommended for:
    - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
    - Children born to HCV-positive women

Note: For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended.

Persons for Whom Routine HCV Testing is of uncertain need

- Recipients of transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, sperm)
- Intranasal cocaine and other non-injecting illegal drug users
- Persons with a history of tattooing or body piercing
- Persons with a history of multiple sex partners or sexually transmitted diseases
- Long-term steady sex partners of HCV-positive persons

Persons for Whom Routine HCV Testing Is Not Recommended

(unless other risk factors present):

- Health-care, emergency medical, and public safety workers
- Pregnant women
- Household (nonsexual) contacts of HCV-positive persons
- General population

Appendix C: AASLD and IDSA Recommendations for Testing, Managing and Treating Hepatitis C

Available at: http://www.hcvguidelines.org/full-report-view

Appendix D: Guidelines for the use of Antiretroviral Agents in HIV-1 infected Adults and Adolescents - Considerations for Antiretroviral Use in Patients with HCV/HIV Coinfection

Available at: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/26/hiv-hcv

Panel's Recommendations
• All HIV-infected patients shold be screened for hepatitis C virus (HCV) infection. Patients at high risk of HCV should be screened annually and whenever HCV infection is suspected. • Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury (DILI). Therefore, ART should be initiated in most HIV/HCV-coinfected patients, regardless of CD4 T lymphocyte (CD4) cell count **(BII)**. • Initial ART combination regimens recommended for most HIV/HCV-coinfected patients are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, consideration of potential drug-drug interactions and overlapping toxicities should guide ART regimen selection or modification (see discussion in the text below and in Table 12). • Combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden, and toxicities. Although ART should be initiated for most HIV/HCV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until HCV treatment is completed **(CIII)**. • In patients with lower CD4 counts (e.g., <200 cells/mm^3), ART should be initiated expeditiously **(AI)** and HCV therapy may be delayed until the patient is stable on HIV treatment **(CIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Appendix E: Recommendations for Concomitant Use of Selected Antiretroviral Drugs and All Food and Drug Administration (FDA)-Approved Drugs for Treatment of Hepatitis C in HIV-Infected Adults

Available at: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/26/hiv-hcv

Select ARV Drugs by Drug Class	**HCV Drugs**						
	HCV Direct-Acting Antiviral Agents					**HCV Non-Direct-Acting Antiviral Agents**	
	NS5B Inhibitor	**Co-Formulated NS5A/NS5B Inhibitor**	**HCV Protease Inhibitors**				
				No Longer Recommended by HCV Guidelines			
	Sofosbuvir	Ledipasvir/Sofosbuvir	Simeprevir	Boceprevir	Telaprevir (Discontinued from U.S. market in October 2014)	Ribavirin	Pegylated interferon alpha
Nucleoside Reverse Transcriptase Inhibitors							
FTC	√	√	√	√	√	√	√
3TC	√	√	√	√	√	√	√
ABC	√	√	√	√	√	√	√
TDF	√	√[b]	√	√	√ Modify for TDF toxicity due to ↑ TDF level.	√	√
ZDV	√	√	√	**X**[a]	**X**[a]	**X**[a]	**X**[a]

HIV Protease Inhibitors							
ATV, ATV/r, or ATV/cobi	√	√[b]	**X**	**X**	√	√	√
DRV/r or DRV/cobi	√	√[b]	**X**	**X**	**X**	√	√
FPV or FPV/r	√	√[b]	**X**	**X**	**X**	√	√
LPV/r	√	√[b]	**X**	**X**	**X**	√	√
SQV/r	√	√[b]	**X**	**X**	**X**	√	√
TPV/r	**X**	**X**	**X**	**X**	**X**	√	√
Non-Nucleoside Reverse Transcriptase Inhibitors							
EFV	√	√ If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑ TDF level.	**X**	**X**	√ ↑ teleprevir dose to 1125 mg q8h	√	√
ETR	√	√	**X**	√ ***EXCEPTION*** ETR + boceprevir **is not recommended** when coadministrated with drugs that may further decrease ETR (e.g., TDF, DVR/r, LPV/r, SQV/r).	√	√	√
NVP	√	√	**X**	**?**	**?**	√	√
RVP	√	√	√	√	√	√	√

Integrase Strand Transfer Inhibitors							
DTG	√	√	√	√	√	√	√
EVG/cobi/TDF/FTC	√	**X**	**X**	**X**	√	√	√
EVG + (PI/r without cobi)	Refer to recommendations for specific ritonavir-boosted PI						
RAL	√	√	√	√	√	√	√
CCR5 Antagonist							
MVC	√	√	√ ↓ MVC dose to 150 mg bid	√ ↓ MVC dose to 150 mg bid	√	√	√

[a] Concomitant use of ZDV with boceprevir, telaprevir, or ribavirin is not recommended because of potential for worsening anemia; concomitant use with pegylated interferon is not recommended because of potential for worsening neutropenia.

[b] Concomitant use of ledipasvir/sofosbuvir with TDF and an HIV PI/r (or ATV/cobi or DRV/cobi) may lead to increased TDF exposure; consider alternative HCV or ARV therapy, especially in patients at risk of renal injury. If co-administration is necessary, monitor for TDF-associated adverse reactions.

Key to Symbols:
√ = ARV agent and HCV drug that can be used concomitantly
↑ = Increase
↓ = Decrease
X = Concomitant use of the ARV agent and HCV drug **is not recommended**
? = Data limited or not available on PK interactions between the ARV and HCV drugs

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; ATV/cobi = atazanavir/cobicistat; cobi = cobicistat; DRV/r = darunavir/ritonavir; DRV/cobi = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FDA = Food and Drug Administration; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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