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ABSTRACT OF CAPSTONE

Moaz Abdelwadoud

The College of Public Health
University of Kentucky

2017
ADDRESSING BARRIERS TO HEPATITIS C TREATMENT INITIATION IN KENTUCKY CLINIC

ABSTRACT OF CAPSTONE

A Capstone project submitted in partial fulfillment of the requirements for the degree of Doctor of Public Health in the College of Public Health at the University of Kentucky

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ABSTRACT OF CAPSTONE

ADDRESSING BARRIERS TO HEPATITIS C TREATMENT INITIATION IN KENTUCKY CLINIC

Introduction. Hepatitis C virus (HCV) is the most prevalent blood borne infection in the United States and its chronic infection has a high burden on the American healthcare system. Since 2014, the all-oral Directly Acting Antiviral (DAA)-based therapy has been established as the standardized curative treatment for HCV with unprecedented high effectiveness and tolerability. Nevertheless, there is a significant gap between the promise from DAAs benefits and the treatment initiation rates in the United States and Kentucky.

Objectives. The goal of this study is to improve the access to the all-oral DAA-based treatment among HCV patients seeking outpatient treatment services at the Kentucky Clinic.

Methods. This study was conducted from October to December 2016 in the specialized HCV outpatient clinic at the Kentucky Clinic in Fayette County, Lexington, Kentucky. The study utilized a mixed methods approach to address the barriers for initiating HCV treatment. The qualitative analysis explored the current model of care applied to the patients seeking HCV treatment, its tools included: field observations, semi-structured in-depth interviews with healthcare personnel providing administrative and clinical services to HCV patients, and review of relevant administrative forms. The quantitative analysis followed a retrospective cohort design including all chronic HCV patients who had their first visit to the Kentucky Clinic between July 1, 2014 and June 30, 2015. The
observation time for this cohort was calculated from the first visit until treatment initiation or the last day of observation November 30, 2016. To assess the predictors for treatment initiation, we assessed the sociodemographic, clinical, and behavioral variables of the study cohort. Quantitative analysis included descriptive analysis of the patients' explanatory variables comparing those who initiated treatment to those who did not followed by time to treatment analysis for: assessing the cumulative incidence of treatment initiation, constructing Kaplan–Meier time to treatment curves estimating the proportion of patients who initiated treatment at different time points comparing each explanatory variable levels, and identifying the predictive independent variables for treatment initiation over time using Cox Proportional Hazards Regression analysis.

**Results.** Multiple interrelated difficulties in accessing the DAAs treatment were found of relevance to the current model of care and patients' characteristics. The treatment initiation journey is long and hindered by complicated stepwise administrative and clinical procedures. Lack of proper communication between the referring facility, the scheduling center, and the HCV clinic is obvious. Lack of awareness among the patients and their referring provider concerning the treatment initiation procedures add to the difficulty in communication. In general, the HCV treatment services are broken and not properly connected with other services needed by HCV patients. The administrative and clinical procedures are centered around the PA requirements and Medicaid applied restrictive criteria favoring advanced liver disease patients which requires a clinical proof difficult to achieve in border line cases between the mild and advanced liver disease stages. The quantitative results showed that a total of 880 HCV patients visited the HCV clinic at the Kentucky Clinic between July 1, 2014 and June 30, 2015. Only 195 (22.16%) patients initiated the DAAs treatment during the observation period. Time to treatment initiation results are consistent with the long waiting time found in the model of care results. The average number of days to initiate treatment was 263.57 days. Univariate analysis using Kaplan-Meier time to treatment initiation estimates showed significant earlier treatment among males, African Americans, patients who
followed-up at least once, and patients without a history of substance abuse. The disproportionate treatment initiation achievement among the patients born before 1965 was inconsistent under Medicaid coverage and with mild liver disease; patients showed significantly later treatment initiation at different points of time. Bivariate analysis of insurance and liver disease condition showed that Medicaid patients with mild liver disease had the lowest chance for treatment initiation at different time points compared to other groups. The cox model significance results confirmed the previous results on age group, insurance type, and liver disease condition. Medicare baby boomers have almost double and more than quadruple the likelihood of Medicaid baby boomers to initiate treatment at advanced and mild liver disease stages respectively. This likelihood jumps to five and thirteen times respectively on comparing patients born after 1965 with the same characteristics. Likewise, Medicaid baby boomers have less than half the likelihood of private and other insurance patients to initiate treatment at either disease stages. In parallel, the Medicaid patients born after 1965 have nearly quarter the likelihood of private and other insurance patients to initiate treatment at either disease stage. The only significant likelihood difference between Medicare and private and other types of insurance was found among mild liver disease patients born after 1965 where the former group are three times as likely as the latter group to initiate treatment.

**Conclusion.** Access to HCV treatment in the Kentucky Clinic is hindered by a variety of barriers revolving mainly around the model of care, which is greatly influenced by the insurance system. Structural adjustment for the current model of care and prioritizing the disproportionately affected groups of patients by HCV infection is urgently needed. This study proposes a patient centered comprehensive model of care fostering a patient navigation system providing: early linkage and continuity of care, patient education based on a baseline needs assessment, and awareness for the referring provider about the treatment process. In addition, administrative support is mandatory to speed up the process utilizing data linkage with other healthcare facilities and a special prior authorization support system. Integration of HCV services with other services
including primary care, substance abuse management, and other social services. Prioritization should consider Medicaid young patients living in southeast Kentucky with mild liver disease and practicing injection drug use. HCV treatment task shifting to primary providers in the southeastern Appalachian counties is key solution on the long term.

KEYWORDS: hepatitis C, access, barriers, treatment, directly acting antivirals, initiation, prior authorization, Kentucky.

Moaz Abdelwadoud

May 2, 2017
ADDRESSING BARRIERS TO HEPATITIS C TREATMENT
INITIATION IN KENTUCKY CLINIC

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ADDRESSING BARRIERS TO HEPATITIS C TREATMENT INITIATION IN KENTUCKY CLINIC

Moaz Abdelwadoud

College of Public Health
University of Kentucky
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CHAPTER 1
INTRODUCTION

I-  Background

About 3.6 million Americans carry hepatitis C (HCV) antibodies and 2.7 million are chronically infected. This alarming prevalence renders HCV the most prevalent blood borne infection in the United States (US) (Denniston et al., 2014). Moreover, there is a steady increase in acute HCV infections across the nation adding to the problem of its high prevalence (Centers for Disease Control and Prevention, 2016).

Chronic HCV infection is the leading cause of chronic liver disease, hepatocellular carcinoma (HCC) i.e. liver cancer, and liver transplantation (LT) in the US (Ditah et al., 2014). HCV related mortality is continuously increasing with an average annual increase 6.2% (Ly, Hughes, Jiles, & Holmberg, 2016). The burden of HCV on the American healthcare system is a major challenge. Each year HCV patients make more than 2.3 million outpatient visits, 73,000 visits to emergency departments, and 475,000 hospitalizations (Galbraith et al., 2014). This burden is associated with corresponding healthcare costs estimated at $6.5 billion in 2011 (Shah, Younossi, & Opsha, 2015).

Since 2014, the all-oral Directly Acting Antiviral (DAA)-based therapy has been established as the standardized curative treatment for HCV with unprecedented high effectiveness and tolerability. This breakthrough therapy created a promise for the elimination of HCV (American Association for The Study of Liver Diseases, 2016). Clinical outcomes from DAAs are maximized when a cure is achieved; however, all HCV patients gain liver function improvement and a favorable disease prognosis (Rodriguez & Reynolds, 2016; Z. M. Younossi, Birerdinc, & Henry, 2016).

National spending on DAAs showed a tremendous increase since their approval by the US Food and Drug Administration (FDA) in late 2013 (IMS
Institute for Healthcare Informatics, 2016). Although DAAs are costly, their effectiveness outweighs their costs (Z. M. Younossi, Park, Dieterich, et al., 2016). Guidance from specialty organizations calls for expansion of HCV detection and early treatment with DAAs (DeSalvo, Scott, Wolitski, & Dan, 2017).

II- Problem Statement

Unfortunately, the promise of DAAs for HCV elimination is hindered by many challenging barriers. The treatment cascade of HCV from screening to treatment initiation reveals insufficient response from the American health system. The most challenging step in the treatment cascade begins from confirmation of diagnosis and declaring eligibility for treatment until the initiation of the all-oral DAA-based therapy (Yehia, Schranz, Umscheid, & Lo Re, 2014).

At institutional levels, there is a large variability in treatment initiation rates since the interferon (IFN)-based therapy era, suggesting that barriers are diverse and context specific (Denniston et al., 2014; Ditah et al., 2015; Ford et al., 2017; Holmberg, Spradling, Moorman, & Denniston, 2013; Maier, Ross, Chartier, Belperio, & Backus, 2016; Noska, Belperio, Loomis, O'Toole, & Backus, 2017; Stepanova & Younossi, 2015; Vutien, Hoang, Brooks, Nguyen, & Nguyen, 2016; Z. Younossi, Stepanova, Afendy, Lam, & Mishra, 2013). Additionally, the characteristics of HCV patients and their comparative treatment initiation rates have been found to be inconsistent across different contexts and states (Bourgi, Brar, & Baker-Genaw, 2016; Centers for Disease Control and Prevention, 2016; Denniston et al., 2014; Ford et al., 2017; Kanwal et al., 2016)

In Kentucky, the burden of HCV and the characteristics of patients are alarming. This Midwestern state is ranked among the highest states in HCV prevalence and incidence (National Center for HIV/AIDS, Viral Hepatitis, STD, 2015). In particular, the southeastern counties of Kentucky, located in the Appalachian Mountains, possess the highest HCV infection rates due to the predominant use of injection drugs (IDU) (Havens et al., 2013). Moreover, the Kentucky Medicaid program which covers the majority of HCV patients applies very restrictive criteria for DAA-based treatment approval that challenge the most
needy individuals residing in southeast Kentucky who have limited geographical access to HCV treatment specialists (Barua et al., 2015).

The Kentucky Clinic, the setting of this study, reported a significant increase in utilization of specialized services by HCV patients between 2010 and 2015. The profile of these patients revealed that they are predominantly: males, Caucasians, born after 1965, under Medicaid coverage, and reside in rural southeastern Kentucky (Abdelwadoud, Racho, & Rosenau, 2017).

To this end, there appears to be a significant gap between the promise from DAAs benefits and treatment initiation rates. The gap in knowledge and practice for improving HCV treatment initiation rates pertains to influential factors that vary among different contexts. Each context has its specific demand and supply profile; thus, a thorough contextual understanding of the DAAs demand and supply in Kentucky is urgently needed.

III- Study Purpose

The goal of this study is to improve the access to the all-oral DAA-based treatment among HCV patients seeking outpatient treatment services at the Kentucky Clinic. To achieve this goal, this study targeted the following objectives:

1. To describe the administrative and clinical procedures in the Kentucky Clinic applied to HCV patients seeking the standardized DAA-based therapy beginning from their referral until achieving the required approval for treatment initiation.
2. To outline an administrative and clinical flowchart describing the current model of care for HCV patients in the Kentucky Clinic.
3. To determine the sociodemographic, clinical, and behavioral characteristics of HCV patients influencing their initiation of treatment.
4. To develop a proposed comprehensive model of care aiming at improving HCV patients’ access to treatment in the Kentucky Clinic based on the needs identified from the current model of care and the patients’ characteristics.
IV- Research Question
The research question of this study is what are the barriers that prevent, or make it difficult, the Kentucky Clinic HCV patients from initiating the DAA-based treatment?

V- Research Hypotheses
Since the study investigates both the model of care and patients’ characteristics, it assumes two hypotheses:

For the model of care, the null hypothesis assumes that the current model of care perfectly enables the access to DAAs-based treatment and offers no obstacles for treatment initiation.

\( (H_{01}) = \text{there are no barriers associated with the current model of care for DAAs-based treatment initiation in the Kentucky Clinic.} \)

For the patients’ characteristics, the null hypothesis assumes that there is no significant difference in the characteristics of patients who initiate treatment and those who do not initiate treatment.

\( (H_{02}) = \text{there is no difference between the characteristics of the patients who initiate the DAAs-based treatment and those who do not initiate the treatment in the Kentucky Clinic.} \)

VI- Study Limitations
There are some limitations in interpreting and applying the results of this study. First and foremost, the results of this study apply to the Kentucky Clinic context as a healthcare facility having a specific model of care, clients, and providers.

While the implications drawn from the results of this study can be valid for health services throughout the Commonwealth of Kentucky, it should be noted that the specific inferences and proposed model of care indicated in this study apply to the Kentucky Clinic in particular. There would be other valid options not proposed in the final model that could be apply to other healthcare facilities.
Another limitation of the study is that the analysis of patients’ characteristics is based on secondary data which could be subject to documentation errors. Additionally, since the measures used for the analysis were limited by the available data in the patients’ medical records, treatment initiation can be influenced and explained by other predictors not included in the analysis.

Finally, given the diversity and complexity of the dimensions of access, influencing factors, and determinants; this study was unable to address them in their entirety.

VII- Organization of This Study

Following this introduction, chapter 2 presents a comprehensive literature review directed at understanding the complexity of access to the DAAs-based therapy for HCV. It illustrates the background of HCV, then reviews the conceptual frameworks proposed in the access to health services literature in order to develop a conceptual framework for assessing access to HCV DAA-based treatment. This framework will guide the study review, methods, results and discussion thereafter. The second part of chapter 2 covers the five access dimensions: availability, affordability, geographical accessibility, acceptance, and accommodation; followed by a description of these dimensions in the Commonwealth of Kentucky; and thirdly concludes with a literature review summary and a comment on the empirical and theoretical bases of this research.

In chapter 3, the research methods employed in this research are illustrated including: study design, study settings, target population, procedures, instrumentation, data analysis strategies, and ethical considerations.

Chapter 4 presents the study results in two sections: qualitative and quantitative analyses, followed by a joint interpretation of these results. Chapter 5 summarizes the results and assesses them, discusses the implications of the study findings, and finally proposes practical recommendations for improving access to HCV treatment in the Kentucky Clinic.
CHAPTER 2

LITERATURE REVIEW

Literature Search Strategy

This review followed a systematic literature search to understand the key concepts and assess the empirical evidence for understanding the factors influencing access to the all-oral, IFN-free, DAA therapy for HCV infection in the US with particular focus on Kentucky. Comprehensive application of the theoretical and empirical knowledge of the health services research discipline was followed in this review.

The search was conducted across the internet databases: Google, MEDLINE, Google Scholar, PubMed, and the Cochrane Systematic Review Database. The search strategy was designed to include all relevant scientific articles; original research; reviews; commentaries; expert opinions; case reports; conference proceedings and posters; doctoral and master's degree dissertations; websites of research projects; and strategies, action plans, and reports published by governmental and non-governmental organizations in the US.

All identified references were reviewed against the study objectives using a process of positive exclusion; first skimming titles and abstracts for relevancy followed by reviewing the full text. Further, the reference lists of collected sources were reviewed to add other relevant sources to the pool.

This review inclusion criteria considered only sources addressing HCV IFN-free treatment initiation in the US using alternatively combined key terms in English: hepatitis C, access, barriers, treatment, directly acting antivirals, interferon free, initiation, uptake, insurance, cost, prior authorization, Kentucky, and United States.

Given the exclusive use of standardized IFN-free therapy during the study period and the fact that the first-generation of DAAs were added to the previous
IFN-based treatment in 2011, followed by the FDA approval for second-generation DDAs use without IFN in December 2013 (Ponziani et al., 2017); the provisional search included knowledge products published from January 2000 till March 2017 to capture all sources relevant to HCV background followed by screening sources published from January 2012 to include only those relevant to the concurrent influencing factors on accessing the standardized DAA-based therapy with special caution in the interpretation of results on combined IFN and DAAs treatment regimens.

**Chapter Overview**

The first section of this chapter provides the background of HCV, including the virus: discovery, virological characteristics, method of transmission, prevention, and natural history. The prevalence and incidence statistics for HCV in the US are then considered followed by the morbidity, mortality, and economic burdens of HCV in the US.

The second section explores access models for HCV services. It provides a critical review of the different conceptual models of access to health services including those specific to chronic diseases and HCV. This analysis concludes with a proposed conceptual framework for assessing access to HCV DAA-based treatment.

The third section is structured around the conceptual framework; it is organized by the five identified dimensions of access to HCV treatment. The influencing factors of these dimensions on HCV DAA treatment in the US are discussed in this section. The first part covers the availability dimension; it starts with introducing the available diagnostic tools that detect patients in need for treatment and then charts the timeline of HCV curative treatment from the discovery of the virus to date with special attention to the health benefits of the DAAs. A discussion of the providers’ availability and DAAs’ prescription requirements then follows. This part continues by examining the treatment cascade and initiation rates in the US at national and institutional levels. The
following item of this section describes the characteristics of HCV patients in different US regions.

The second part focuses on affordability; it commences with the economic benefits of DAAs followed by the national spending on them. Then, this part presents the organizational and administrative procedures for the procurement of DAAs and their estimated prices. It then presents the distribution of HCV patients among different insurance coverages followed by the approval criteria set by these insurers. Given its special approval criteria and broad coverage, this part provides some details on Medicaid, the federally funded and state managed subsidized health insurance plan for low-income citizens including fee-for-service and managed care providers, approval rates at the national, state, and institutional levels followed by evidence from different studies on the cost-value of expansion of Medicaid restrictive approval criteria.

The next part is devoted to geographical accessibility describing the barriers encountered by patients to reach HCV services in the US.

The acceptance dimension is then elaborated on from both the provider and patient aspects including: stigmatization in HCV care, attitudes of providers toward HCV patients, and patients’ cultural acceptance and awareness concerning HCV treatment.

The last part concerning the dimensions covers accommodation. It provides the strategic guidance and best practices for a successful HCV model of care that can ultimately accommodate the needs of patients and it factors in the barriers. It elaborates on this with concrete examples and illustrations of how successful US models were implemented.

The fourth section is devoted for Kentucky special profile. It begins with presenting the volume and characteristics of HCV patients in Kentucky. It then describes the Kentucky Medicaid program approval criteria, and finally the characteristics of HCV patients in the study setting.
This review is then concluded with a fifth section summarizing it and offering the implications of this study within the current literature on DAA treatment for HCV. Finally, the sixth section gives the empirical and theoretical bases for this study and its expected results.

I- Hepatitis C Virus Background

Discovery

In 1975, a new condition of chronic liver inflammation among blood transfusion recipients was reported without association with neither hepatitis A virus (HAV) nor hepatitis B virus (HBV) infections. This condition was labelled non-A, non-B hepatitis until 1989 when the HCV was given its name as a distinguished liver virus after successful cloning (Bukh, 2016).

Virology

HCV is a ribonucleic acid (RNA) enveloped single-stranded virus. It belongs to the flavivirus family that includes hepatitis G, Yellow fever, and Dengue fever viruses (Bukh, 2016). The virus has been detected in most body fluids and tissues including saliva, tears, breast milk, vaginal secretions, and seminal fluid (Patrick, Buxton, Bigham, & Mathias, 2000). The virus has exceptional virological criteria that significantly challenge its control. Scientific efforts to grow HCV in culture has been unsuccessful. The virus replication is extremely rapid producing more than 10 trillion new virion particles per day, even after chronicity, hindering the human body immune-mediated control (Lauer & Walker, 2001). In addition, HCV possesses a high genetic diversity resulting in a major challenge for vaccine and pan-genotypic drug therapy development (Timm & Roggendorf, 2007).

HCV is sub-classified into seven genotypes and several sub-genotypes based on the viral genome phylogenetic and sequence analysis. Genotype 1 is the most common worldwide comprising 46% of all HCV infections followed by genotypes 3 with 22%. Genotypes 2 and 4 are fairly equal in their distribution;
about 13% each (Gower, Estes, Blach, Razavi-Shearer, & Razavi, 2014). Only one historical genotype 7 infection was isolated from a Central African immigrant in Canada (Messina et al., 2015).

Genotype 1 is highly prevalent in North and South America, Europe, and Australia, ranging from 53 to 71% of all cases. Genotype 3 is the leading in Asia with almost 40% of all HCV infections while Genotype 4 accounts for 71% of infections in the Middle East and North Africa (Gower et al., 2014).

**Transmission**

The HCV infection transmission is blood-borne. The most common methods of transmission are: transfusion of contaminated blood or blood products; and percutaneous blood exposure either via medical procedures, tattooing and piercing practices, or sharing a contaminated injection or intranasal drug use device (Manns et al., 2017). The transmission risk of HCV from a single percutaneous blood exposure is intermediate (2.7-6%), compared to HBV (19-30%) and human immunodeficiency virus (HIV) (0.3%) risks (Patrick et al., 2000). Mother to infant HCV transmission is less frequent while sexual transmission is rare (Manns et al., 2017).

Historically, the most common reported method for HCV transmission is blood transfusion prior to the establishment of universal blood screening in 1992 (Lauer & Walker, 2001). It is estimated that 3 million Americans in the baby boomer generation, born between 1945 and 1965, contracted HCV infection through blood, blood products, tissue, or organ donation. Currently, the probability is less than 1 in 1 million blood transfusions may transmit HCV, shifting the most common method of transmission to injection and intranasal drug use practices (Monina Klevens, Hu, Jiles, & Holmberg, 2012).

**Prevention**

Reducing the risk of exposure in medical procedures, tattooing and piercing practices, and injection drug use in addition to protected sexual contact
are the primary prevention methods for HCV (World Health Organization, 2016). There is no prophylactic vaccine for HCV due to the unsuccessful trials till date for antibody-based virus neutralization and T-cell based virus elimination from infected cells (Bukh, 2016). A T-cell vaccine is currently under trial aiming at preventing persistent infection with HCV (Swadling, Klenerman, & Barnes, 2013).

Secondary prevention strategies for HCV include early detection of cases, raising awareness and counselling on treatment options, and immunization against HAV and HBV. Tertiary prevention mandates early treatment with antiviral drugs beside regular monitoring and management of chronic liver affection (World Health Organization, 2016).

**Natural History**

Infection with HCV results in an acute phase within 2 to 24 weeks; however, acute infection passes undiagnosed in about 80% of cases either for being asymptomatic or association with mild general symptoms. Manifest acute symptoms may include fever; fatigue; loss of appetite; nausea and vomiting; abdominal pains; dark urine and clay colored stool; joint pain; or jaundice i.e. yellow eye color. Fulmination of the acute phase is extremely rare (World Health Organization, 2016).

Strong immune response in 15-45% of cases spontaneously clear the HCV within 24 weeks while 55- 85% will acquire persistent viremia and chronic infection with potential progress to liver damage in the form of cirrhosis or liver cell failure between 15 -30% within two or three decades (World Health Organization, 2016). Liver cirrhosis is associated with an annual 1 to 4% risk of HCC. Beside liver affection, various body organs can be affected by HCV due to its autoimmune response. These affections are collectively called extrahepatic manifestations (EHM) (Lauer & Walker, 2001).
Prevalence and Incidence

Hepatitis C virus infection represents a worldwide viral pandemic five times more prevalent than type 1 human immunodeficiency virus (HIV-1) (Lauer & Walker, 2001). The global prevalence of HCV antibodies is estimated at 1.6% of the world population corresponding to 115 million people living with HCV (Gower et al., 2014). In the US, HCV tops the list of prevalent blood-borne infections with estimated 3.6 million Americans carrying antibodies to the virus and 2.7 million chronically infected based on the National Health and Nutrition Examination Survey (NHANES) 2003 to 2010 data (Denniston et al., 2014). Some higher estimates claim that Americans with previous exposure are 4.6 million while those with chronic infection are 3.5 million people (Edlin, Eckhardt, Shu, Holmberg, & Swan, 2015). Reasonable lower estimates factored in the increasing mortality from HCV pointed to 3.2 million antibody carrying Americans (Holmberg, Spradling, Moorman, & Denniston, 2013).

A global comparative study published in 2014 estimated that 1.3% of adult Americans has HCV antibodies corresponding to 3,347,000 people and the national viremic rate i.e. chronicity is 76.9% resulting in 1% chronically infected adults equivalent to 2,575,000 Americans. Based on these estimates, the genotypic distribution of HCV in the US is: 46.2% of cases has genotype 1a, 26.3% genotype 1b, 10.7% genotype 2, 8.9% genotype 3, 6.3% genotype 4, 1.1% genotype 6, and 0.5% mixed genotypes (Gower et al., 2014).

The US Centers for Disease Control and Prevention (CDC) surveillance system reported a steady increase in acute HCV infections across the nation from 853 cases in 2010 to 2,194 cases in 2014 projecting a 30,500 real new cases in the United States in 2014 (Centers for Disease Control and Prevention, 2016).

Morbidity and Mortality Burden

Hepatitis C virus infection is the leading cause of chronic liver disease and HCC in the United States. Moreover, liver cell failure from HCV is the most
common indication for liver transplantation (LT) not only in the US but also in North America and Western Europe (Ditah et al., 2014).

A large scale US study on 10 million HCV test results retrieved from 2010 to 2013 showed that 5% of the 2.6 million patients with data on their liver conditions are chronically infected with the virus. About 23% of the chronically infected cases, and 27% among the baby boomer age group, showed signs of advanced fibrosis or cirrhosis at the first diagnosis compared to only 3% among the uninfected cases with HCV (Monina Klevens et al., 2016).

Between 2001 and 2010, HCV patients' healthcare utilization data revealed that they payed annually more than 2.3 million outpatient visits, 73,000 visits to emergency departments, and 475,000 hospitalizations (Galbraith et al., 2014). Extrahepatic HCV manifestations alone lead to an annual 15% increase in HCV patients' hospitalization rate (Monina Klevens et al., 2012).

The mortality from the HCV dramatically increased in the US from 11,051 associated deaths in 2003 to 19,368 in 2013; an average annual increase by 865 deaths equivalent to 6.2% increase per year (Ly, Hughes, Jiles, & Holmberg, 2016). In 2014, the number of deaths associated with the virus reached 19,659, more than half of this number occurred among persons aged between 55 and 64 years. This tremendous increase is the highest among the infectious diseases in the US and exceeds the mortality from more than 60 other infectious diseases combined (Centers for Disease Control and Prevention, 2016).

**Economic Burden**

The economic burden of HCV results from either the direct costs associated with its liver disease sequelae and extrahepatic manifestations; or the indirect costs from chronic HCV patients' productivity loss (Younossi, Birerdinc, & Henry, 2016). In 2011, the total healthcare cost associated with HCV was estimated at $6.5 billion. Based on this estimation, it is projected that this cost will reach $9.1 billion in 2024. The highest expenditures are expected from decompensated cirrhosis (46%), compensated cirrhosis (20%), and HCC (16%)
(Shah, Younossi, & Opsha, 2015). The annual healthcare cost associated solely with HCV EHM is estimated to be $1.5 billion (Younossi, Park, Henry, Adeyemi, & Stepanova, 2016). The indirect economic burden of HCV patients’ productivity loss is estimated to be $7.1 billion per year mainly due to work absenteeism (Baran et al., 2015).

II- Access Models for Hepatitis C Treatment

Applying theoretical models to assess influencing factors, either enabling or hindering, on access to health services is widely debated in the literature. Health services researchers continuously modify the historical access conceptual models to contextualize different health problems, respond to the advances in health services delivery, and address different influencing determinants interacting with health services provision (Ricketts & Goldsmith, 2005).

In their universally applied and critically researched model, Penchansky & Thomas (1981) defined access to health services as a process aiming at an ultimate fit between the demand; i.e. clients’ needs, and the supply; i.e. the healthcare system providing health services. To achieve this goal, Penchansky & Thomas (1981) proposed a five-dimension model to conceptualize access barriers. In this model, the first dimension is the “availability” where the clients’ volume and types of needs are addressed by responsive services and resources including providers, specialized programs, facilities, medicines, and equipment. The second dimension “affordability” encompass costs of services facing the clients’ ability to pay and their health insurance coverage. The third dimension “accessibility” pertains to the client geographical distance and time from the needed health services. Fourth, the “acceptability” dimension represents the mutual expectations and acceptance of attitudes and personal characteristics between the client and the provider. The fifth dimension, “accommodation”, refers to the model of care that health services apply, including organization of resources and administrative procedures, to accommodate the clients’ collective needs from all dimensions (Penchansky & Thomas, 1981).
Peters et al. (2008) contributed to the original Penchansky model by plotting in their framework two key determinants influencing the aforementioned access dimensions: policy and macro-environment as an upstream level determinant; in addition, the client’s household characteristics and individual vulnerability as a downstream level determinant. Jacobs, Ir, Bigdeli, Annear, & Van Damme (2012) identified the key barriers to these dimensions. For the availability dimension, supply side barriers include lack of needed services; e.g. lack of availability of medicines and equipment; and incompetency and low motivation of providers. The demand side barriers revolve around proper client awareness and perceived need. Affordability supply barriers are the direct, indirect, and informal costs of services; and differences between public and private, profit and nonprofit, health facilities. The client’s ability to pay, opportunity costs, insurance coverage, and payment schemes for services influenced by the availability of cash flow within the society are the demand side hindering barriers. Geographical accessibility depends on service location and the transportation means, time, and costs encountered by the client. Acceptance requires proper provider-client relationship where the provider attitude meets the clients’ expectations and build trust. Expected barriers include limited client awareness, information asymmetry between the provider and client, stigma, and low assertiveness from the provider side. Accommodation supply barriers include inadequate continuity of care; e.g. late referrals to specialized services, inconvenient working hours, prolonged waiting times, and improper integration with other needed health services by the clients. (Jacobs et al., 2012; Peters et al., 2008).

Wagner et al. (2001) proposed a specialized chronic care model to guide chronic illnesses care. This model is composed of six components and was developed from practice-based results of a nationwide project involved 104 health services organizations in the US. The first component “Healthcare Organization” emphasizes that in order to improve quality of care the health services facility should gain support and commitment from its leaders. In the second component, “Community Resources”, the model underscores the role of
community participation in cost-efficient expansion and improvement of access to chronic illnesses services. The fourth component “Delivery System Design” complements the second component by highlighting the role of community health workers and case managers in counseling, behavioral change, adherence to treatment, and efficient use of resources. The “Self-Management Support” component maximizes the patient potentials to self-manage his or her condition through individual or group support, encouragement, and self-confidence building. The “Decision Support” component requires integration of chronic illness treatment within a comprehensive care provision. The sixth component, Clinical Information System, provides the tool for decision support and integration of care using patients’ medical records (Wagner et al., 2001).

Sbarigia et al. (2016) applied the concepts of access on HCV studies to develop a conceptual framework for HCV management outcomes. Their linear framework starts with the healthcare system structure and the patient characteristics as key input predictors for the process of care; the intermediate predictor. Collectively, all these predictors contribute the client outcomes. The healthcare system structure mirrors the supply side of all access dimensions in the Penchansky model with special consideration to the provider and model of care characteristics. Client characteristics apply across the board on the demand side including social, demographic, financial, behavioral, and clinical characteristics. The process of care is the performance centered element reflecting the “quality of health services” core in the Peters model. It underscores the effectiveness of management of HCV infection according to the standardized guidelines of care provision. The client outcomes vary from utilization, patient reported outcomes, to ultimately achieving cure (Sbarigia et al., 2016). In HCV management, cure is indicated by sustained virological response (SVR) defined by the absence of detectable HCV RNA in serum; i.e. 50 IU/mL or less for 24 weeks after the end of treatment (Chevaliez & Pawlotsky, 2005).
Collectively from these general and focused conceptual frameworks on HCV, the proposed framework in figure 1 offers a conceptual outline for assessing access to DAA treatment in the following part of this review.
Figure 1. Conceptual framework proposed for assessing access to hepatitis C directly acting antivirals [Adopted from: (Penchansky & Thomas, 1981; Peters et al., 2008; Sbarigia et al., 2016; Wagner et al., 2001)]

<table>
<thead>
<tr>
<th>Availability</th>
<th>Affordability</th>
<th>Geographical Accessibility</th>
<th>Acceptance</th>
<th>Accommodation</th>
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<tbody>
<tr>
<td><strong>Leadership Support and Commitment</strong></td>
<td><strong>Quality of health services</strong></td>
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<tr>
<td><strong>Supply</strong></td>
<td>- Proper diagnosis of HCV</td>
<td>- Direct and indirect costs</td>
<td>- Services' location</td>
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<td></td>
<td>- DAAs availability, effectiveness, and benefits</td>
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<td>- Competency and motivations of providers</td>
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<td></td>
<td>- Volume of eligible patients for treatment vs. patients with perceived need for treatment</td>
<td>- Insurance Coverage Opportunity costs</td>
<td>- Transportation means and time</td>
<td>- Patient education on HCV treatment.</td>
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<td>- Self-management potentials</td>
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<td>- Cultural acceptance</td>
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**Sustained Virological Response**
III- Dimensions and Influencing Factors on Access to Hepatitis C Directly Acting Antivirals in the United States

A- Availability

Hepatitis C Virus Infection Diagnosis

On suspecting HCV infection, the first step is to identify previous infection using serological essays that detect HCV antibodies. While the laboratory-based HCV antibody test is the most reliable; rapid tests are available for real-time screening. In positive cases, a molecular test for HCV RNA is needed to confirm chronic infection and to quantify viral particles load. Some cases, 15-45%, with positive antibody tests show undetectable HCV RNA due to spontaneous clearance of the infection by their immune response. Viral genotyping is another step in the diagnosis that help chose proper treatment regimen and predict its outcome (World Health Organization, 2016).

For disease staging and liver affection, a histologic evaluation of liver biopsy is the gold standard to assess fibrosis level i.e. liver damage; exclude other pathologies; and predict the disease progression. Other less invasive laboratory and radiological investigations e.g. elastography are widely used for assessment of liver function and disease staging (Manns et al., 2017).

Advances in the Curative Treatment for Hepatitis C Virus Infection

The timeline of HCV antiviral treatment begins in 1986 before the virus discovery. Non-A non-B hepatitis patients were recommended three injections of recombinant IFN-α per week. In the following decade, the IFN-α dose and duration increased until it was combined in 1998 with Ribavirin (RBV), a non-specific oral antiviral. For the following decade, from 2001 to 2011, the standardized treatment of HCV was a combination of a modified long-acting PEGylated interferon (PEG-IFN) with RBV. This treatment regimen was applied for 12-72 weeks and showed a wide range of treatment efficacy i.e. SVR, between 40 and 80% depending on the virus genotype. Considerable clinical and
psychological adverse effects of this standardized regimen hindered treatment adherence and outcomes (Manns et al., 2017).

In May 2011, the FDA approved the first-generation of DAAs combination Boceprevir and Telaprevir, to boost the efficacy of the PEG-IFN and RBV protocol. The SVR of this quadruple regimen reached 68-75% in naive cases and 59-88% in treatment experienced cases. The game changer DAA Sofosbuvir has been approved by the FDA in December 2013 as the first second-generation DAA to be used in combination with PEG-IFN and RBV or with RBV alone and showed SVR rates exceeding 85% (Ponziani et al., 2017).

After the unprecedented success of Sofosbuvir, the competitive research on discovery of IFN-free regimens aiming at maximizing SVR rates for different genotypes and liver conditions while reducing adverse effects evolved rapidly. The FDA approved several DAAs to be combined with Sofosbuvir: Simeprevir and Ledipasvir for genotype 1, Daclatasvir for genotype 3, and Velpatasvir. These new combinations reported SVR above 90% for the first time in the HCV history (Ponziani et al., 2017).

Since July 2015, the FDA approved novel DDAs to be prescribed without Sofosbuvir including Paritaprevir, Ritonavir and Ombitasvir, in association with Dasabuvir for genotype 1 and without it for genotype 4. Most recently, in January 2016, the FDA added to the Sofosbuvir-free regimens approval list the Elbasvir/Grazoprevir combination (Ponziani et al., 2017). In June 2016, the FDA approved Sofosbuvir/Velpatasvir as a combined single tablet regimen for all genotypes without the need of RBV (American Liver Foundation, 2016).

In accordance, the advancements in DAAs led to the availability of standardized IFN-free all-oral protocols for all genotypes and liver disease stages and comorbidities; administered for relatively short duration between 8 and 24 weeks; with high safety and low adverse effects; and achieving cure rates reaching 98% even in historically difficult to cure patients with the IFN-based therapy (Manns et al., 2017).
Given the high efficacy and tolerability of DAAs compared to the old IFN-based therapy, the all-oral DAAs therapy has been established as the standardized curative treatment for all HCV genotypes and disease stages. Different protocols are recommended and continuously updated by the American Association for the Study of Liver Diseases (AASLD) to provide the best options for each category of patients. These protocols recommend either using a specific single or combined DAAs with and without RBV (American Association for The Study of Liver Diseases, 2016).

**Health Benefits of Directly Acting Antiviral Treatment**

Clinical outcomes from DAAs are maximized with achieving SVR; however, all patients at different stages of the disease gain clinical benefits from antiviral treatment in two aspects: liver function and prognosis (Rodriguez & Reynolds, 2016; Younossi, Birerdinc, et al., 2016). The majority of early liver affection patients who achieve SVR develop significant improvements in their liver functions and reversal of mild fibrosis over time. Advanced fibrosis and cirrhotic patients show improved liver function as well with risk reduction of liver cell failure and HCC; need for LT; post transplantation infection recurrence; and increased life expectancy (Rodriguez & Reynolds, 2016).

Chhatwal et al. (2016) projection study anticipated the current DAAs would prevent 8,600 cases of decompensated cirrhosis, 5,400 cases of HCC, 900 LTs, and 9,700 related mortalities, from 2015 through 2050. In addition, they would reduce the HCV prevalence in the United States by more than 80% by 2040 if the treatment initiation rate remained unchanged.

The same study projected the morbidities and mortality from 2015 to 2050 that would be associated with assumed three scenarios: all-oral DDAs regimen, old IFN-based regimen, and no treatment for HCV infection. Findings revealed a significant difference favoring the clinical outcomes of the all-oral DAAs. The projected cumulative incidence for decompensated cirrhosis is 203,000 for the first, 468,000 for the second, and 665,000 for the third scenarios respectively.
Regarding the cumulative incidence of HCC, the results' estimates pointed to 157,000, 305,000, and 415,000 cases respectively for the three scenarios. The number of LTs would be 32,000, 53,000, and 65,000; and the cumulative number of deaths associated with HCV infection are: 320,000, 587,000, and 776,000 as ordered previously (Chhatwal et al., 2016).

Early treatment has been proved beneficial in reducing morbidity and mortality from the chronic HCV infection. A study on 187,860 chronic HCV patients in a Veterans Health Administration (VHA) center showed that treatment initiation in no to mild fibrosis patients would reduce morbidity by 41% and mortality by 36%. Comparing non-advanced fibrosis to advanced fibrosis patients, the study found that the non-advanced group would develop 34% morbidity and 45% mortality risk reduction on treatment initiation while the advanced fibrosis group would develop only 11% and 25% risk reductions respectively (McCombs, Tonnu-MiHara, Matsuda, McGinnis, & Fox, 2015).

The DAAs opened a great opportunity for HCV eradication not only for their curative role, but also for their importance in prevention of transmission. Low serum viral load reduces the risk of HCV transmission significantly. This principal has been established as a successful strategy in HIV prevention resulting in worldwide availability of antiretroviral therapy (ART) (National Academy of Sciences, 2016).

In addition, two challenges for HCV regular primary prevention methods favor the investment in DAAs as prevention. First, there is no available effective vaccine for HCV till date. Second, transmission prevention strategies among people who inject drugs (PWIDs) e.g. syringe exchange, show limited success compared to the escalating incidence among this high risk group. Consequently, the maximum benefit at population level from DAAs for incidence and prevalence reduction will be gained if targeted high risk groups including new and young PWIDs and prisoners. For reduction of morbidity and mortality, the benefit will be at individual level on targeting old PWIDs with low or no injection activity as they
have low risk for infection transmission (Grebely, Matthews, Lloyd, & Dore, 2013).

Nevertheless, a major barrier for using DAAs as a cost-effective prevention strategy in high risk groups is the risk of reinfection (National Academy of Sciences, 2016). The collective estimate for risk of reinfection post SVR from thirteen studies done on PWIDs and men having sex with men (MSM) ranged between 0.9 and 6.1% per 100 person-year. However, these estimates are jeopardized by the probability of relapse after the initial SVR and the difference in intensity of high risk practices and incidence rate among the populations of these studies (Grady, Schinkel, Thomas, & Dalgard, 2013).

Provider Availability and Requirements for Managing Hepatitis C with Directly Acting Antiviral Treatment

The DAAs are specialty drugs that require prescription and full management under supervision of a clinician. Prescriber limitations according to Medicaid requirements in fifteen states mandates a clinical specialist; i.e. gastroenterologist, hepatologist, or infectious diseases specialist for HCV treatment prescription. In fourteen states, Medicaid opens the door for non-specialist clinicians to prescribe or follow hepatitis C patients in consultation with a specialist, while only thirteen states have no Medicaid prescriber limitations on HCV treatment (Barua et al., 2015).

Supporting this restrictive policy, a study conducted by the CDC on the distribution of different providers ordered 1,112,105 HCV laboratory tests revealed the predominance of specialists over non-specialists in HCV care. The overall test to provider ratio was 8.1, the highest ratio was for hepatologists (26.1) followed by infectious diseases specialists (23.7), internal medicine specialists (7.3), family medicine practitioners (6.4), and general practitioners (6.6) respectively (M. Klevens, Pugh, Ward, Thakare, & Holmberg, 2014).

To alleviate this problematic barrier, a joint letter signed by eight clinical associations led by the American Academy of Family Physicians urged the
Centers for Medicine & Medicaid Services (CMS) in April 2016 to rely on the expertise of the provider rather than restricting prescription to specialists considering the latter shortage in rural areas in the US. This policy change would improve access to safe and effective DAAs tremendously and ensure equitable access in rural area where 20% of American citizens live and only 9% of physicians practice. The letter final message to the CMS emphasized that Medicare, the federally subsidized health insurance for elderly citizens above the age of 65 and disabled younger citizens, with its closely tied programs to DAAs prescriptions: Medicare Advantage and Medicare Part D, and Medicaid should not hinder physicians from treating HCV according to their specialty (American Academy of Family Physicians, 2016).

Guidance on Provision of Directly Acting Antiviral Treatment

Several organizations developed guidance reports, recommendations, and action plans emphasizing the importance of identification and treatment of HCV with DAAs. The US Preventive Services Task Force (USPSTF) recommends hepatitis C screening for high risk groups of HCV transmission including individuals who: had history of injection or intranasal drug use, received tattoos under unregulated maneuvers; received blood or blood products prior to 1992; were born between 1945 and 1965; or were born to an infected mother. Due to the severe complications of comorbidity, HCV annual screening is recommended for people living with HIV (Moyer & U.S. Preventive Services Task Force, 2013)

Complementing these recommendations, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America recommend early treatment with IFN-free regimens for all patients with chronic HCV infection except patients with short life expectancy. This exclusion is not only for antiviral treatment but for other radical management interventions including LT. However, the two societies prioritize treatment for high risk morbidity and mortality patients, particularly those with advanced fibrosis or compensated cirrhosis i.e. Metavir fibrosis scores F3 and F4. Second in raw are the patients with high risk for complications especially those with F2 Metavir
fibrosis score, HIV or HBV coinfection, other coexisting liver disease, and insulin resistance diabetes mellitus (American Association for The Study of Liver Diseases, 2016).

Following the AASLD guidelines on early and inclusive treatment for almost all HCV patients, the American College of Preventive Medicine issued a position statement on Hepatitis C Virus infection. The linkage to care recommendations of this position statement pointed to four mandatory steps for HCV discovered patients: early diagnosis confirmation, quantitative HCV RNA test, genotype identification, and evaluation for DAAs eligibility. Responsibility of developing quality and accountability measures for linkage to care should be delegated to the National Committee for Quality Assurance, the Joint Commission, and CMS (Allison et al., 2016).

In the same direction, the National Viral Hepatitis Action Plan for 2017-2020 highlighted in its second goal "Reduce Deaths and Improve the Health of People Living with Viral Hepatitis" the importance of improving access to HCV treatment. To achieve this goal, the action plan called for building the capacities of human resources needed for diagnosis and treatment, special focus on improving HIV/HCV and PWIDs access to treatment, expansion of access to preventive and curative services in incarceration settings, monitoring treatment and its impact, and advancing research for patients’ identification and cure (DeSalvo, Scott, Wolitski, & Dan, 2017).

**Hepatitis C Infection Treatment Cascade and Initiation Rates**

Based on NHANES data that estimates 3.2 million chronically infected Americans with HCV i.e. potentially eligible for treatment, Holmberg et al. (2013) developed a treatment cascade for HCV patients at the national level. In this cascade, about half of the chronically infected patients i.e. 1.6 million populations were discovered, 38% corresponding to 1.2 million were referred to care, while the treatment initiation rate ranged from 7 to 11% i.e. 220,00 to 360,000 patients. These numbers imply that 18.33% to 30% of the patients referred to care
succeeded in initiating treatment. The estimated cured patients ranged from 170,000 to 200,000 i.e. 5-6% of the chronically infected patients. (Holmberg et al., 2013).

Yehia, Schranz, Umscheid, & Lo Re, (2014) developed another cascade (figure 2) starting with 3.5 million infected population considering that NHANES estimations didn’t factor in some high risk groups e.g. homeless and incarcerated population. Accordingly, 1.74 million (49.8%) were diagnosed and aware of their status out of the 3.5 million, 1.51 million (43.3% of the total) are aware and covered by insurance that give them an access to hepatitis C services. Further, 952,726 patients (27.2% of the total) are estimated to be aware, possess access, and confirmed with HCV RNA test. Adding a confirmatory liver biopsy, the latter group narrows down to 581,632 (16.6%) patients. An estimated 555,883 persons (15.9%) passed all previous steps and were prescribed treatment. The final step in Yehia et al. cascade points to 326,859 patients (9.3%) achieved SVR. These numbers imply that out of the patients who were aware, possess access, and confirmed with HCV RNA test; the proportion of the patients who were prescribed the treatment was 58.35% meanwhile the proportion of the patients who achieved SVR was 34.30%. However, the last two steps in this cascade don’t give an answer for the question: how much patients between the treatment prescription (555,883 patients) and SVR (326,859 patients) steps didn’t initiate treatment in the first place, initiated but didn’t complete their regimen, or completed treatment as prescribed but were resistant to therapy (Yehia et al., 2014).
Chhatwal et al., (2016) estimated that in 2015 the HCV infected patients who were aware of their status and had insurance coverage were 923,000, compared to the 1,514,600 million estimates of the previous study. The same study estimated from the reported DAAs market sales that the number of patients who initiated treatment in 2015 were 280,000; a sharp increase from the 150,000 patients estimate in 2014. These numbers reveal that an estimated 33.34% of the theoretically prepared patients for referral (923,00 patients) initiated DAA-based treatment in 2015 (Chhatwal et al., 2016).

The Veterans Health Administration (VHA), the largest provider of HCV care nationwide, had in 2011-2012 DAAs regional initiation rates ranging from 3-7%, the lowest facility initiation rate was below 1% and the highest had 17% initiation rate (Belperio, Backus, Ross, Neuhauser, & Mole, 2014). In 2013, the VHA HCV treatment cascade showed higher rates compared to the national rates. The VHA reported 233,898 infected patients with HCV, 181,168 (77%) were diagnosed, 160,794 (69%) were linked to care, 39,388 (17%) initiated treatment and 15,983 (7%) were treated with HCV antivirals, and 15,983 (7%) achieved SVR. These numbers point to a 24.5% initiation rate among the patients linked to care (Maier, Ross, Chartier, Belperio, & Backus, 2016). In 2015, Noska, Belperio, Loomis, O’Toole, & Backus (2017) estimated that the
number of veterans with HCV infection was 220,605 (32,449 homeless and 188,156 non-homeless). Confirmed diagnosis with HCV RNA was found in 89.6% of homeless vs. 77% of non-homeless veterans. Homeless veterans linked to care represented 79.5% and non-homeless were 72.4%. Treatment initiation rate was 22.9% in the homeless group compared to 31% in the non-homeless group. About 15.5% of the homeless achieved SVR vs. 22.8% of the non-homeless (Noska et al., 2017).

The 2016 US Medicine's Use and Spending report proposed a close number for 2015 treatment initiation rate (279,000 patients) while it estimated 170,000 patients in 2014. The total number of patients who initiated treatment in these two years, 2014 and 2015, is 5 times the number of patients who initiated treatment in the prior three years combined (IMS Institute for Healthcare Informatics, 2016b). Drug specific estimates in these two years show that 140,000 and 200,000 patients initiated treatment with either Gilead Sciences products Harvoni® or Sovaldi® in 2014 and 2015 respectively. The more recently approved AbbVie’s Viekira® in December 2014 is estimated to be used by 12,000 patients initiated treatment in 2015 (National Academy of Sciences, 2016).

Organizational based studies show a wide range of variation in treatment initiation rates. Stepanova & Younossi (2015) surveyed 10,799 and 11,840 adult participants from the NHANES 2005–2008 and 2009–2012 and found that HCV infected participants represented 1.19% and 0.94% in the two surveys respectively. The potential access, considering insurance coverage and regimen specific eligibility, to HCV treatment increased from 35.1% for the IFN-based regimen to 66.6 % for all-oral DAAs (Stepanova & Younossi, 2015). Ditah et al., (2015) found that 502 (1.3%) of total 38,025 adult participants sampled from NHANES surveys 2001-2010 were infected with HCV. Out of the 205 participants followed by the study, 67 (40.4%) reported HCV treatment recommendation by a provider and only 18 of them (26.9%) initiated treatment (Ditah et al., 2015). Another study worked on the same NHANES surveys recruited 203 participants
and found that about half of them (101 participants) were aware of their HCV infection prior to their participation in the NHANES survey while only 17% (34 participants) initiated treatment (Z. Younossi, Stepanova, Afendy, Lam, & Mishra, 2013).

A follow up survey with a sample of NHANES participants from 2001 through 2008 showed that 13% of respondents received a treatment for their HCV condition (Denniston et al., 2014). A study on a commercial database of 73,665 insured patients from 2009 to 2013 showed that treatment initiation rate was 10.1% (Vutien, Hoang, Brooks, Nguyen, & Nguyen, 2016).

Secondary data analyses conducted on the records of 13,000 patients in the Chronic Hepatitis Cohort Study (CHeCS) showed that 18% of the study cohort were infected and only 36% of this portion were aware of their condition and initiated a treatment for HCV from 2001 to 2010 (Holmberg et al., 2013).

Results from the New York City Department of Health Check HepC Program between mid-2012 to mid-2013 revealed that 19% (880/4,751 participants) had positive HCV antibody test, 512 participants had a confirmation with HCV RNA i.e. treatment eligible, 435 (85% of confirmed cases) were linked to care, 157 (36%) were checked at a specialized clinic. Forty-seven cases of the 157 checked were identified as good candidates for treatment (30%) and only 14 (30% of the identified candidates) initiated treatment, 3 of them didn’t complete treatment, 5 didn’t follow after completion, and 6 completed and had reported SVR. These numbers mean that 29.8% of the identified eligible (157 patients), who could be comparable to the current linked patients to DAAs treatment, initiated treatment (Ford et al., 2017).

Future estimates for DAAs demand based on the 280,000 initiation rate of 2015 anticipate that the number of patients aware of their condition and have insurance coverage i.e. ready candidates, will fall below the treatment capacity in 2019 on condition that this capacity will remain constant and all stages of liver disease are accepted by insurance. This ambitious estimation projects the
number of these ready candidates to be 55,000 in 2020 and 30,000 in 2030 (Chhatwal et al., 2016).

**Characteristics of Hepatitis C Infection Patients**

1- **Sociodemographic Characteristics**

The CDC national reports from 2010-2014 pointed to a higher incidence of hepatitis C new cases among Caucasians and non-urban residents (Centers for Disease Control and Prevention, 2016). The NHANES results from 2003 to 2010 revealed that hepatitis C infected persons were more likely to be aged between 40 to 59 years, males, and of African American race compared to persons without the virus (Denniston et al., 2014).

Over the period 2009-2013 a commercial multi-state database analysis showed that Caucasians had the highest treatment initiation rate (10.7%) followed by African Americans (8.8%), Hispanics (8.8%), and Asians (7.9%) (Vutien et al., 2016). A VHA study analyzed patients’ data in the first 16 months of all-oral DAAs approval revealed that African American patients were 21% less likely to initiate treatment compared to Caucasians. In this study no significant difference was found among different genders or age groups (Kanwal et al., 2016).

A study on 100 baby boomers visited a Michigan health services group of 21 clinics from mid-2014 to mid-2015 showed that the differential distribution of patients who initiated treatment were 22.6% of males, 42.1% of females, 28% of African Americans, 36% of non-African Americans, 27% of lower income patients, 54.5% of higher income patients. The odds of females were 2.3 times the males for treatment initiation (Bourgi, Brar, & Baker-Genaw, 2016).

The distribution of New York City Department of Health Check HepC Program 4,751 patients recruited for linkage to care and treatment showed that 55% were born after 1965, 44% were baby boomers, and 4.9% were born before 1945. Hispanic patients comprised 48.6%, while African Americans represented
40% and Caucasians were 8.6%. Beside patients with unreported gender, males represented 55.3% while females represented 43.3% of the program participants (Ford et al., 2017).

2- Behavioral Characteristics

Substance abuse is the salient risky behavior among the majority of HCV patients. Based on the NHANES data, in 2011 the HCV infection rate among PWIDs was 43,126 per 100,000 persons aged 40-65. This rate is obviously higher if compared to the HIV infection rate of 2,147 per 100,000 PWIDs in 2010 (Lansky et al., 2014). Some estimates are pointing to an extremely high incidence of HCV infection reaching 40 per 100 person-years supported by the 2009 National viral hepatitis surveillance results that showed 56% (241 of 432) of acute HCV cases reported injection drug use within the previous six months (R. M. Klevens, Hu, Jiles, & Holmberg, 2012). Higher estimates were found in a smaller scale study conducted in Connecticut between 2013 and 2015 where the HCV infection rate among PWIDs reached 60% (Butner et al., 2017).

Older estimates are lower, a study estimated that from 1999 to 2002 the prevalence of HCV infection among young PWIDs aged from 20 to 59 was slightly above 45% (Armstrong et al., 2006).

Disparity in DAA treatment initiation has been found disadvantaging PWIDs. A multi-center study on HCV patients on DAA treatment between January-August 2015 found that patients who were not involved in injection drug use had significantly higher odds for DAAs initiation (Hautamaki et al., 2016).

3- Clinical Characteristics

Klevens et al., (2016) in their 2010-2013 study found that among 150,475 patients diagnosed with HCV there were 59,933 (39.8%) with no or mild fibrosis, 55,524 (36.9%) with moderate fibrosis, and 35,018 (23.3%) with advanced fibrosis or cirrhosis.
Between January 2013 and August 2014, a specialized clinic for co-infected patients with HIV/HCV in Pennsylvania showed that 30% of 128 adult patients was considered eligible by the providers for HCV treatment and only 14% initiated treatment. African Americans and patients with no HCV treatment experience i.e. naïve had significant lower odds for treatment initiation (Cope, Glowa, Faulds, McMahon, & Prasad, 2016).

In Maryland, a specialized clinic in sexually transmitted infections (STI) care screened 2681 patients from June 2013 to April 2014 for HCV infection. About 7% had HCV antibodies and 5.8% confirmed with HCV RNA. About 89% of the confirmed cases followed for treatment consideration, 85% were referred to HCV specialist, and only 52% attended their specialist appointment (Falade-Nwulia, Mehta, et al., 2016).

In Connecticut, a study on HIV clinic revealed that of the 135 HIV/HCV participants: 71% were referred for HCV treatment, 36% had full laboratory results and eligible for treatment, 21% received treatment prescription, and only 13% completed treatment and achieved SVR over the period 2002-2014 (Weiss, 2015).

**B- Affordability**

**Economic Benefits of Directly Acting Antiviral Treatment**

The economic benefits from HCV treatment cannot be measured as a cost-benefit analysis considering only its monetary gain. A sound analysis should factor in the clinical benefits gained by reducing the patients suffering from the infection and its health consequences. Accordingly, the gold standard economic analysis should assess treatment costs per gained quality-adjusted life years (QALYs) reflecting the concept of value based medicine. Nevertheless, a cost-effectiveness analysis interpreting the health gains from the DAAs is always subjected to criticized estimations. First, a widely accepted precise estimation of the clinical gains from the high costs of all-oral DAAs compared to the less expensive old IFN-based therapy is difficult. In addition, there is no consensus on
the societal willingness to pay (WTP) for a single QALY, a historical value of $50,000 has been used for decades in the United States since 1970s; however, a $100,000 estimate has been utilized in many calculations recently (Younossi, Birerdinc, et al., 2016).

Several studies applied modelling methods to estimate the comparative cost-effectiveness of all-oral DAAs therapy. A study used the Quality-adjusted cost of care (QACC) indicator which is calculated by subtracting the increase in QALYs, valued at $50,000 WTP threshold, from the increase in treatment cost. The results showed that all-oral DAAs regimen had a $48,350 higher cost compared to a combined DAAs and IFN regimen. Nevertheless, the high clinical efficacy associated QALY gains of the all-oral DAAs regimen resulted in a favorable QACC of $14,120 compared to the combined therapy. This favorable figure increased significantly on raising the WTP threshold to $100,000 and $300,000 (Z. M. Younossi et al., 2016).

Another study compared the old IFN-based therapy with all-oral DAAs Sofosbuvir/Ledipasvir regimen. The later regimen yielded higher outcomes by 0.56 QALYs at a $55,400 incremental cost-effectiveness ratio (ICER) per additional QALY. Considering the patient previous treatment experience, liver disease stage, and genotype; the ICER would range from $9,700 to $284,300 per QALY. The same study projected that over a five-year time period the costs of DAAs to treat all eligible HCV infected patients in the US will be $65 billion higher than the costs of old IFN-based regimens; however, the cost-offset would reach $16 billion (Chhatwal, Kanwal, Roberts, & Dunn, 2015).

Using the same DAAs regimen i.e. Sofosbuvir/Ledipasvir, a study took the comparison to the direction of estimating the differential cost-effectiveness of treating different stages of liver disease. The study results estimated that treating all stages adds 0.73 QALYs equivalent to $28,899 for an ICER of $39,475 per QALY gained compared to treating advanced patients at fibrosis stages F3 and F4. A stepwise comparison of the four stages of fibrosis reveals that treating F3 patients yields a 2.27 higher QALYs compared with treating patients at F4; F2
treatment yields 0.55 QALYs gain vs. F3 treatment, F1 yields 0.14 QALYs gain vs. F2 treatment, while the lowest stage of fibrosis F0 has a gain of 0.03 over F1 stage treatment (Chahal et al., 2016).

A long term projection estimated that the investment in oral DDAs over a fifty-year time period would generate additional QALYs equivalent to $610 to $1,221 billion and $139 medical expenditure savings on treating all patients at all disease stages with DAAs (Van Nuys et al., 2015).

**Hepatitis C Treatment Spending**

The total US spending on viral hepatitis treatment increased dramatically after the approval of the DAAs in 2014. While the last years of the IFN-based therapy era showed $2.1, $2.9, and $1.9 billion spending in 2011, 2012, and 2013 respectively; the spending escalated to $12.2 and $18.8 billion in 2014 and 2015 ranking the seventh among all non-discounted drug spending in the US. Regarding new brands’ spending, viral hepatitis new drugs had $11.3 and $7 billion spending in 2014 and 2015. Harvoni®, Gilead Sciences’ DAA product, topped the list of all non-discounted medicines in the US in 2015 with $14.3 billion (IMS Institute for Healthcare Informatics, 2016b).

In parallel, Medicaid spending on DAAs escalated. In 2014, 14 states’ Medicaid programs spent on Sovaldi® more than any other drug and 33 programs spent on it as one of its top five pharmaceutical expenditures’ list (Rubin, 2016). In Medicare, Part D plans’ spending on DAAs increased from $283 million in 2013 to $4.5 billion in 2014, more than $3 billion were spent on Sovaldi® alone (Jung, Feldman, Cheong, Du, & Leslie, 2016).

**Hepatitis C Drugs Supply Chain and Payment Procedures**

The pharmaceutical supply chain of DAAs is linear and has many contributors. It starts with the pharmaceutical company producing the drug. These companies sell their products to the wholesale distributors who store drugs and distribute them among pharmacies and medical facilities. While large
hospitals and clinics, and federal medical facilities purchase their drugs from the wholesale distributors; chain pharmacies purchase directly from pharmaceutical companies and play the role of the whole sale distributor. Finally, the pharmacy dispenses the drug to patients and manage billing with insurers (Rosenthal & Graham, 2016).

The payment pathway is more complex than the supply chain. Basically, there is a third party for price negotiation beside the supply chain contributors. This third party is the Pharmacy Benefit Managers (PBM) who negotiate prices for the insurers. Payment has two pathways; first, the initial payment is done in reverse order of the supply chain starting with the PBM who pays the pharmacy. Usually the initial payment is a percentage of the total payment based on its timing and purchase power of the payer. The second pathway is the rebate where the pharmaceutical companies rebate to PBMs, pharmacies, and government organizations. Companies formulary payments i.e. rebate to their PBM, are done for the later role in giving market preferences against competitors e.g. better copayment offers. In addition, some companies provide a market share rebate when the PBM succeed to entice the consumers to purchase their products. Other forms of rebates include volume-based discounts for achieving a predetermined target sale volume. Some companies encourage payers to pay their initial payments within earlier time period by offering prompt pay rebates (Rosenthal & Graham, 2016).

Governmental healthcare bodies possess high negotiation power for their huge number of beneficiaries and nationwide distribution of contracted medical facilities. Accordingly, they gain special offers in drug prices, initial payments, and rebates from pharmaceutical companies to include their drugs in their formularies. Price negotiations revolve around average price paid by wholesale distributors to pharmaceutical companies i.e. Average Manufacturer Price (AMP), which publically unavailable (Rosenthal & Graham, 2016).

Medicare run its drug purchase process under Medicare Part D plans. Private insurers or PBMs manage these plans setting the formularies, prices, and
discounts for Medicaid is prohibited by law from negotiating prices and receives the higher rebate from either a 23.1% of the AMP or the difference between the AMP and the best-price i.e. lowest price paid by a private payer. An equivalent pricing is given to the 340B pharmacies and non-federal entities servicing indigent populations who are covered by Medicaid (Rosenthal & Graham, 2016). However, states’ Medicaid plans negotiate DAAs rebates with pharmaceutical companies either by themselves or through a PBM resulting in different contracts and accordingly different access potentials for patients (Canary, Kleven, & Holmberg, 2015).

The Federal Supply Schedule (FSS) manages drug pricing for the VHA, Federal Prisons, Public Health Services, Department of Defense, and Indian Health Services. These discounts offered to the FSS is higher than those offered by private insurers to Medicaid Part D plans. Besides, the initial price paid by the FSS has to be under the federal ceiling counted as the AMP minus 24%. Moreover, the negotiation power of the FSS on rebates result in a final lower prices (Rosenthal & Graham, 2016).

State incarceration systems don’t have negotiation powers like Medicare, Medicaid, and the FSS. Consequently, they pay the highest prices and contribute to elevating the market best-price (Rosenthal & Graham, 2016).

Specialty pharmacies are financially incentivized by pharmaceutical companies, insurers, or PBMs to offer drug adherence supporting services, side effects management, and outcomes evaluation e.g. discontinuation and SVR rates (American Association for The Study of Liver Diseases, 2015).

**Directly Acting Antiviral Drugs Prices**

Pharmaceutical companies predominantly target the maximum possible profit from their DAA product based on market analysis considering multiple internal factors including: cost of research and drug development; manufacturing and marketing costs; novelty and effectiveness of the drug; cost-effectiveness and budget impact models; and shareholders expectations. External factors
include: prices offered by competitors; availability of generic drugs; and the
negotiation power of different purchasers. Collectively, these factors determine
the sticker price for the DAA which is commonly known as the Wholesale
Acquisition Cost (WAC). This price doesn’t represent a simple targeted return on
investment nor consider access to consumers with low payment ability
(Rosenthal & Graham, 2016).

The WAC of IFN-free DAA regimens timeline stared with the Gilead
Sciences’ novel DAA Sovaldi® (Sofosbuvir) in late 2013. Sovaldi® was publically
known as the $1,000 pill drug with a 12-week course of treatment set at WAC of
$84,000. Harvoni® (Ledipasvir/Sofosbuvir), more effective and broadly prescribed
Gilead Sciences’ drug, course of treatment was set at $94,500 WAC in 2014.
AbbVie competed with its combined DAAs Viekira Pak®
(Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir) setting a WAC at $83,319.
Bristol-Myers Squibb produced Daklinza® (Daclatasvir) to be combined with
Sovaldi® for a total WAC of $147,000. Merk competed with a lower WAC
combination, Zepatier® (Grazoprevir/Elbasvir), for $54,000. Together, Harvoni®
and Viekira Pak® possess 80 % of the current DAA market in the United states
(Rosenthal & Graham, 2016).

While the WAC and payment pathway are known, the final DAAs prices
for different purchasers are not publically announced leading to non-transparent
DAAs market (Konerman & Lok, 2016; Rosenthal & Graham, 2016). This is
attributed to the fact that negotiations for DAAs prices are confidential business
contracts except the FSS mandated rebates (Saag, 2015).

Market competition and negotiating power of different purchasers played
major role to tame the WAC overtime. In average, the estimated negotiated
discounts on the DAAs WAC increased from 22% in 2014 to 46% in 2015
(Wyden & Grassley, 2015). The highest estimates for Sovaldi® and Harvoni®
discounts reached 55% in 2015 (IMS Institute for Healthcare Informatics, 2016a).
Aggressive market competition resulted in great reduction in Gilead Sciences’
products final prices. To keep the company leading position, Harvoni® and
Sovaldi® courses’ average net prices i.e. final prices after negotiations, were as low as $50,400 and $44,520 respectively for a 12-week course in 2015. Based on these prices and an estimated 236,874 patients treated with these two drugs in 2015, the total net spending on standard courses using Harvoni® and Sovaldi® was $10.9 billion (IMS Institute for Healthcare Informatics, 2016a). This net total is way less than the estimated 2015 $14.3 billion spending on Harvoni® alone; however, the difference might be attributed to other costs of HCV services beside the drug cost (IMS Institute for Healthcare Informatics, 2016b).

A retrospective cohort study conducted at a VHA medical center between October 2014 and September 2015 found that the average DAAs spending to cure was $40,135 per patient. Cirrhotic patients’ DAAs spending to cure was higher ($41,907) than non-cirrhotic patients ($38,431), and treatment-experienced patients had higher spending to cure ($39,482) compared to naïve patients ($39,179) (Yang, Britt, Hashem, & Brown, 2017).

In addition to the type of insurance coverage and final price ambiguity, other factors affect the direct cost burden on patients. Pharmacy plans apply copayment plans on patients for the DAAs; however, the patient assistance programs may cover part or all copayments for different patients according to their ability to pay (Saag, 2015). In 2015, the mean out-of-pocket spending on DAAs ranged from $6,297 to $10,889 for Medicare Part D plans beneficiaries with no subsidy. Low-income subsidy group spent significantly lower out-of-pocket expenditure between $1,080 and $1,191 (Jung et al., 2016).

One of the major consequences of DAAs pricing complexities is the limitations on patients’ options for DAAs choice due to the exclusive deals between their insurers and pharmaceutical companies. The majority of the current exclusive deals aiming at cost reduction are done with Gilead Sciences for Harvoni®, few are with AbbVie for Viekira Pak®, and only one reported deal with both companies (Wittkop, Rosenberg, Garfield, & Greenwald, 2015).
Two decades before the approval of the DAAs, NHANES data from 1988 to 1994 revealed that 29.6% of HCV infected Americans had no insurance coverage while less than half this percent (12.2%) of non-infected citizens are uninsured (McGowan & Fried, 2012).

Recently, it is estimated that 86.9% of HCV infected Americans who are aware of their status are insured while only 60.4% of unaware infected persons are insured (Yehia et al., 2014). Another study followed identified HCV positive patients by the NHANES from 2001 to 2010 revealed that 19.4% attributed their failure to initiate the treatment to its high costs. Besides, the only significant independent variable for treatment was lack of health insurance coverage (Ditah et al., 2015).

An analysis of NHANES data to quantify the distribution of confirmed HCV RNA positive patients according to their affiliation to different health insurers in 2013 showed that the uninsured patients comprised the highest portion (1,012,000 patients) followed by those under the coverage of private insurers (779,000 patients), incarceration system (450,000 patients), Medicaid (377,000 patients), VHA (302,000 patients), both Medicaid and Medicare (201,000 patients), Medicare (117,000 patients), and other military coverage (10,000 patients) (Bruce Pyenson & Engel, 2013). Another study estimated that of the 68 million Medicaid enrollees in 44 states, about 700,000 have positive antibodies to HCV (Wyden & Grassley, 2015).

In 2015, the estimated proportion of HCV infected patients under private insurance coverage was 38% followed by 24% Medicare, 13% Medicaid, 6% other public insurance, and 19% uninsured (Chhatwal et al., 2016).

The 2013 NHANES analysis pointed to the shift of HCV patients towards Medicare overtime. The distribution of HCV RNA prevalence by year of birth from 1910 to 2010 pointed to the fact that the high prevalence of HCV among baby boomers will result in their inclusion under Medicare, by the age rule, when they
turn 65 between 2010-2030. Given the natural history of HCV infection progression towards liver affection, a young patient at the time of contacting the infection would probably fall under Medicare coverage in advanced stage of liver disease (Bruce Pyenson & Engel, 2013). In the same direction, another study claimed that this aging phenomenon resulted in increasing Medicare HCV infected enrollees from 18% in 2010 to 24% in 2015. Besides, the Affordable Care Act (ACA) shifted the uninsured HCV infected patients from 26% down to 19% yet these uninsured patients are the least enabled group to access treatment and consequently would comprise the highest proportion of HCV patients by 2019 (Chhatwal et al., 2016).

Different Insurers’ Approval Criteria and Barriers for the Directly Acting Antiviral Treatment

1- Commercial Insurance

As the ACA prohibited refusal of coverage for preexisting health conditions; private insurers may fear adverse selection where HCV patients opt for enrollment in the generous plans rather than the stricter ones. Consequently, private insurers would be reluctant in covering the costly DAAs in their plans. The National Academies of Sciences, Engineering, and Medicine 2016 report “Eliminating the public health problem of hepatitis B and C in the United States: Phase one report” underscored this dilemma as a threat for private insurance market failure in HCV treatment (National Academy of Sciences, 2016).

Additionally, the ACA out-of-pocket (OOP) expenses limits in 2016 were $6,850 for individuals and $13,700 for families hindering the HCV patients from DAAs costly treatment (Rodriguez & Reynolds, 2016).

Commercial health insurers are steadily shifting the costs of specialty drugs and costly healthcare costs including DAAs services to their beneficiaries under different titles: premiums, deductibles, co-payments, and co-insurance (Spiro, Calsyn, & O’Toole, 2015). With these cost-sharing variations and titles, DAAs are unequally offered across private insurers’ plans (Rodriguez &
Moreover, the DAAs are classified as specialty drugs and often placed among the drug formulary high cost-sharing tier. In 2015, more than 25% of Silver plans nationwide placed DAAs on specialty tiers (Pearson, 2015). In Massachusetts, two commercial insurance plans who applied adverse tiring to DAAs revealed that more than half of two plans, Silver and regular, placed DAAs either at the highest rank formulary tiers or didn’t cover them (Wittkop et al., 2015).

2- Medicare Program

Medicare DAAs coverage is provided under Medicare Part D. To have DAAs covered, patients need to be enrolled in prescription drug plan covered by a private insurer. The two pathways for prescription coverage are: Medicare Prescription Drug Plan beside the original plan or a Medicare Advantage Prescription Drug plan. In reality, most Medicare patients have these prescription coverages and are able to initiate DAAs therapy once their clinical provider complete their assessment (Cross, 2016; Rosenthal & Graham, 2016).

3- Medicaid Programs

State Medicaid programs cover the majority of HCV patients in need for DAAs; however, they apply the most restrictive approval criteria among insurers. These approval criteria are applied in the “Prior Authorization (PA)” approval. The pharmacy or prescribing clinician have to submit a request documenting that the patient is compliant with the required criteria. The insurer either accept or deny the request and in case of denial, an appeal can be filed by the request provider. This process is complex both clinically and administratively and requires time (National Academy of Sciences, 2016).

The PA criteria are inconsistent among Medicaid programs and may include:

**Proof of Advanced Liver Disease.** Approval criteria for most Medicaid program target the AASLD ranked “highest priority” patients while neglecting all
other high priority patients in need. These restrictive criteria are applied in 33 states and require an evidence of advanced liver disease attested by a METAVIR fibrosis score of F3 or F4 for Sovaldi® approval. Moreover, 4 states require an invasive liver biopsy rather than imaging and laboratory investigations (Canary et al., 2015). About 81% of Medicaid programs apply this role in general terms i.e. evidence of advanced fibrosis and 74% accept only METAVIR fibrosis score of F3 or above (Barua et al., 2015).

**The Sobriety Role.** Most Medicaid programs (88%) require abstaining from substance abuse i.e. illicit drug use and/or alcohol for a period ranging from 3 to 12 months. The argument behind this role is to ensure success of treatment and to avoid reinfection. For complying to this role, patients in 64% of programs have to undergo drug screening either before or periodically during treatment, and in some programs complete substance abuse treatment program or join an addiction counselling program with a specialist is also required (Barua et al., 2015; Wittkop et al., 2015).

**Provider Restrictions.** About 69% of Medicaid programs requires a specialist to prescribe or at least be consulted in DAAs regimens. This requirement challenges many patients in underserved areas lacking specialist services (Barua et al., 2015).

**Special Treatment for HIV/HCV Patients.** About one quarter (24%) of Medicaid programs require HIV/HCV patients to be engaged in HIV ART or provide and evidence of HIV RNA suppression (Barua et al., 2015).

Facing these restrictions, the Center for Medicare and Medicaid Services (CMS) published a guidance report in November 2015 to encourage and remind state Medicaid programs of their legal responsibility toward HCV patients. Basically, the report pointed out that Medicaid programs’ cost containment strategies restricting HCV effective treatment are against the federal law. In this report, “Assuring Medicaid Beneficiaries Access to Hepatitis C Drugs”, the CMS underscored three elements coupled opportunities for feasible implementation
mechanisms. First, the DAAs are both necessary and effective giving no other option neither for the patients nor their insurance. As a reminder and key solution, Medicaid managed care programs enrollees should benefit from the DAAs covered in approved state plans. The second key element in the CMS report highlighted the mechanisms that can help reduce DAAs cost via either including them in the managed care contracts or apply capitation rates or carve-out supplementary plans. Third, the CMS pointed to the importance of the opportunity resulting from the competition among pharmaceutical companies in reducing the DAAs prices and offering better rebates for Medicaid programs (Centers for Medicare & Medicaid Services, 2015).

The National Academies of Sciences, Engineering, and Medicine 2016 report offered a benchmarking solution that can help leverage access to DAAs through delegation of the federal government to negotiate discounts for low-income patients reference to the Vaccines for Children program (National Academy of Sciences, 2016).

Medicaid Prior Authorization Approval Rates

A study investigated the PA approval rates and predictors among Massachusetts Medicaid program during the following year after the approval for Sofosbuvir® in December 2013 revealed that about 5% of patients had a PA request and 90% of them were given the PA. About 71% of approved patients’ request were for all-oral DAAs while the remaining proportion was for combined IFN and DAAs regimens. Each of the infectious diseases (ID) and gastroenterology specialists’ groups requested 37% of the approved PAs. Hepatologists requested 21%, and internal and family medicine practitioners requested 4% of the PAs. PA requests were higher among Caucasians, males, those aged between 50 and 64 years, the disabled, those having the standard Medicaid plan, and those in advanced stage of liver disease. Lower percentages of PA requests were associated with homelessness, drug abuse, and primary care community health center engagement. The most common PA disapproval
reason was lacking complete information required from the provider (Clements et al., 2016).

Another study explored the distribution and predictors among a sample of privately insured patients nationwide who had PA request between March and June 2014. In this study, 59.4% of the PA requests were for IFN-free regimens and 90% of PA requests came from either a gastroenterology or hepatology specialist. The distribution of patients showed that 61% were males, mean age was 55.4 years, and their geographical distribution was as follows: 38.2% from southern states, 21% from northeastern states, 20.4% from western states, and 20.4% from Midwestern states (Tambourine et al., 2016).

At Yale University Liver Center, a study examined the PA rates for Harvoni® during October-December 2014 found a 91.4% total PA rate (77.5% PA rate without appeal and 13.9% after the first appeal). The average time to PA was 22.9 (SD ± 21.2) days. Significant independent predictors for approval were public insurance i.e. Medicare or Medicaid, and HCV RNA load over 6 million IU/mL (Do et al., 2015).

A study on University of California Los Angeles all payer HCV treatment services between October 2014 and July 2015 revealed a total 81% PA approval rate were distributed among public (63.7%) and private (36.7%) pharmacies. PA approval was given to 75.6% of approved PAs without appeal, 10.4% after the first appeal, and 1.2% after the second appeal. The mean time from PA request submission to drug approval was 28.1 (± 46) days. According to type of insurance, Medicare patients had the highest approval rate (92%), followed by Medicaid patients (80%), non-Medicaid health maintenance organizations patients (78%), and private insurance patients (70%). Higher approval rates were among males (58.1%), middle-income group (67.1%), advanced liver condition (51%), and employed (43.1%) patients. Adjusted significant independent predictors included Medicare insurance, advanced liver disease, and lack of other comorbidities (Saab et al., 2016).
A four-state study conducted on a specialty pharmacy chain database found 16.2% PA denial rate between November 2014 and April 2015. The most common reasons for denial included lack of sufficient information supporting medical need (35.5%), lack of medical necessity (35%), failure in drug screening test (4%), and prescription of a non-preferred DAA by the pharmacy (2.7%). Among Medicaid patients, 46.3% received denial while 10.2% of privately insured and 5% of Medicare patients were denied. Adjusted variables significantly associated with PA denial included Medicaid insurance and non-advanced liver disease identified by absence of cirrhosis (Lo Re et al., 2016).

A single center study in Michigan found that between December 2013 and May 2014 the PA approval rate for the combination Simeprevir (Olysio®) and Sofosbuvir (Sovaldi®) was 67.7% (George, Weick, Moonka, Segovia, & Jafri, 2014).

Cost-Value for Medicaid Expansion of Approval Criteria

Several studies proved the cost-effectiveness of full-access to DAAs for Medicaid beneficiaries. A study compared the cost-effectiveness of restricted versus full-access policies Medicaid policies on beneficiaries aged 40-55 revealed that the currently applied restrictive policy is costlier by $9,200 per patient with 0.84 lower QALYs. In addition, the full-access policy is estimated to prevent 5,994 HCC cases and 121 liver transplants per 100,000 patients. On the long term, the study projected a cost saving exceeding $3.5 billion for the estimated 450,000 HCV Medicaid patients if the full-access policy replaced the current restrictive policy (Chidi et al., 2016). Another study projected additional 0.84 life-years per patient and prevention of 36,752 cirrhotic cases; 1,739 liver transplants; 8169 HCC cases; and 16,173 HCV-related deaths per patient in case of providing Harvoni® to all patients compared to treating advanced liver disease patients only with the same drug. The cost saving according to this study scenario is expected to reach $3.8 (Zobair Younossi et al., 2017). Considering the additional burden of high risk groups, a study factored in treating PWIDs, men having six with men, and HIV co-infected patient in estimating the cost-
effectiveness of the full-access scenario. Treatment expansion including all types of patients at all stages would reduce new infections by more than half (55%) and prevalence by 93% over two decades. Moreover, it will add 1.15 QALYs with $1,626 reduction of costs per patient over the same time frame. Considering a $150,000 WTP value, the net social benefits would reach $500 billion over two decades (Moreno et al., 2017).

Denied Medicaid beneficiaries are expected to fall under Medicare in the future with probably full coverage of HCV treatment including DAAs and liver disease complications. Based on this inevitable scenario, a study estimated the cost reduction of treating Medicaid patients on future Medicaid expenses in Pennsylvania. First, the study estimated that Medicaid expansion of treatment to include one more fibrosis stage i.e. Metavir F2 score patients, this limited expansion would add $273 Medicaid spending over a decade with limited effect on liver disease morbidity but a reduction of the expected costs of treatment under Medicare by 10%. Full-access scenario including all patients would cost Medicaid additional $693 million over the same time period; however, it would reduce the future patients in need for treatment under Medicare coverage by 46% and consequently the costs by 23% plus significant reduction of morbidities (Kabiri et al., 2016).

C- Geographical Accessibility

Services Locations and Patients Distance from Different Providers

Unequal distribution of HCV treatment centers and specialists is one of the major obstacles for DAAs mass provision and elimination of the disease. The CDC recognizes this obstacle and supports training of primary care providers in remote and rural areas to overcome the geographical accessibility barrier to specialized HCV services (M. Klevens et al., 2014).

A study conducted by the CDC to explore the distance of HCV patients from different providers ordering HCV laboratory tests showed that the patient to provider median distance was 12.1 miles. The shortest median distance was to
primary care providers: internal medicine specialists (8 miles), general practitioners (10 miles), and family medicine practitioners (11.5 miles). HCV specialists had the highest distance from patients; the hepatologists median distance was 22.7 miles and for the gastroenterologists it was 12.4 miles (M. Klevens et al., 2014).

Another study compared the major barriers from the patient side after referral for HCV treatment at a centralized academic medical center with a community based clinic in North Carolina. Results revealed that the only significantly different barrier between the two clinics was the distance. Nearly 40% of the academic medical center patients identified distance as a problematic barrier compared to 17% of the community based clinic patients (Evon et al., 2010).

D- Acceptance

Stigma

HCV stigma is rooted in the association of the infection with substance abuse and HIV. Stigmatization and social rejection are identified major barriers to accessing HCV care in almost all contexts. Stigmatizing HCV patients is not limited to society but extends to healthcare settings. When patients feel stigmatized by their providers, they lose interest in follow-up and their probability to initiate and adhere to providers’ recommendation falls down significantly (Evon et al., 2010; McGowan & Fried, 2012).

Providers’ Attitudes

Providers’ negative attitudes towards PWIDs represent a critical bias in HCV treatment. These attitudes are associated with providers’ mistrust in PWIDs adherence to treatment plans, fear of possibility of reinfection, and negative perception about psychological problems rendering them difficult to treat patients (Zeremski et al., 2013).
A survey conducted among HCV treatment prescribing clinicians in 2014 showed that only 52% were willing to treat abstaining PWIDs for 6 months or more, 35% for 1-6 months abstaining period, and 15% were willing to treat HCV patients who are active drug users i.e. had an injection within the prior 30 days. The odds of willingness to treat PWIDs increased proportionally with abstinence period. The odds ratio for 1-6 abstinence period was 4.8, 17.1 for 6-12 months, and 17.5 for 12 or more months (Asher et al., 2016).

Trust in providers’ competences is another barrier to HCV treatment. A study identified lack of trust in providers’ competence as a perceived barrier by HCV patients hindering treatment initiation and adherence (Evon et al., 2010).

Cultural Acceptance

There is a paucity of studies conducted on cultural acceptance of all-oral DAA therapy; however, it is anticipated that oral therapy is convenient for most of population groups. Nevertheless, cultural acceptance is closely tied to awareness among the community about the efficacy and tolerance of DAAs.

Patient Education

Patients’ limited awareness and misunderstandings about the DAAs treatment encounters most of the patient side barriers to treatment initiation and adherence (Grebely, Oser, Taylor, & Dore, 2013). Treatment fears have been identified major factors since the IFN-based therapy era, these fears revolve around treatment efficacy and side effects (McGowan & Fried, 2012). It is estimated that 65-75% of HCV-infected PWID are neither aware of their infection nor aware of the effectiveness of DAAs in HCV cure (Zeremski et al., 2013).

A study explored the motivating and hindering factors for patients to initiate and adhere to HCV treatment showed that most salient motivating factors for patients in order are: fear of negative health outcomes of HCV, patient’s personal will, provider’s advice, fear of HCV impact of quality of life and achieving future life goals, and receiving laboratory results and success likelihood of
treatment. Major hindering factors were nonspecific side effect and possible need for injection therapy (Fusfeld et al., 2013).

Reassurance and proper awareness about the current all-oral regimens are mandatory to resolve this problem. Consequently, patient education is very crucial to help patients initiate treatment and ensure adherence to treatment plans. Prior to DAAs, the liver specialty clinic of San Francisco’s safety net healthcare system in California mandated a formal HCV education class to all HCV patients referred to the clinic before evaluation for treatment. The education curriculum was delivered by specialized nurse practitioner in a two-hour presentation in English with availability of interpreter for other languages when needed. The content of this presentation included information on HCV transmission, diagnosis, symptoms, natural history, impact on liver, eligibility for treatment, treatment response rates, and potential adverse effects of treatment. Outcomes of this education program showed significantly shorter time to treatment initiation compared to patients who didn’t join the program. Positive provider attitude was significantly associated with the referral rate to the program. About 70% of specialists reported increase knowledge among patients after the program, 52% reported increased interest in treatment, and 56% acknowledged improved communication with patients (Lubega, Agbim, Surjadi, Mahoney, & Khalili, 2013).

E- Accommodation

Linkage to Care

The national viral hepatitis action plan 2017-2020 recommends mainstreaming of HCV screening and linkage to care as standard practices in the healthcare settings (DeSalvo et al., 2017). The primary point of care and the fostering healthcare setting for patients are diverse. For instance, PWID start their healthcare navigation through urgent and emergency services. Accordingly, the American College of Preventive Medicine recommends linkage to HCV testing and treatment through utilization of all possible facilities including federally
qualified health centers, patient centered medical homes, inpatient settings, and emergency departments (Allison et al., 2016).

In 2012, the Congress allocated funds to the CDC toward improving viral hepatitis testing and linkage to care. Accordingly, the CDC launched the Hepatitis Testing and Linkage to Care (HepTLC) initiative that provided 25 grants to HCV focused health organizations. Components of this initiative included HCV services in community health centers, testing in PWID settings, and both testing and linkage to care in other settings. Between September 2012 and September 2014, the initiative tested 57,570 participants for HCV antibodies in 15 states and districts, 4,765 were tested for HCV RNA, 3,449 were confirmed with chronic infection. Out of 2,798 received 2,624 were referred to specialty care and 1,509 made a visit to HCV specialist. Results showed that the maximum benefit of linkage to a one-facility comprehensive care was among homeless PWIDs (Ramirez et al., 2016).

Beside these regular settings, mobile clinics can be a standardized starting point for linking HCV patients to care especially in high prevalence underserved remote areas. In Connecticut, a mobile clinic-based program from 2012 to 2013, included HCV screening in routine health assessment. The program offered two HCV testing choices for participants: rapid onsite test and regular laboratory-based tests. Identified HCV-infected participants were linked to care by the program. Results showed that HCV patients who opted for rapid testing were more likely to be linked to HCV treatment (Morano et al., 2014).

**Patient Navigators**

Patient navigation is a supportive intervention using community healthcare workers or social workers to support continuity of care. Navigators help overcome the healthcare system barriers hindering effective access to prevention and treatment services especially among: difficult to reach populations for a stigmatized risky behavior, disadvantaged underservices populations in
geographically remote areas, and those unaware of their status or how to approach curative treatment (Ford, Johnson, Desai, Rude, & Laraque, 2016).

The CDC fostered HepTLC initiative is following the patient navigator model. The initiative results revealed that counselors and patient navigators ensured adherence to medical appointments through awareness and facilitating transportation. Besides, navigators from the patients' local community who speak the same language could deliver culturally accepted health awareness and linkage to care message (Ramirez et al., 2016).

At state level, the New York City Department of Health and Mental Hygiene have implemented, with private sector fund, its patient navigation program “Check HepC” since 2012. Under supervision of an onsite-supervisor, four navigators were recruited over two years, two of them were fluent in Spanish. Each navigator worked closely with a multidisciplinary team either in on-site clinical care facilities or off-site substance abuse harm reduction settings. The navigators' tasks started with comprehensive assessment of patients' needs followed by developing an individualized care plan for each patient. Navigators provided education messages, counselling, insurance and PA approval and appeal support. The treatment initiation rate among Check HepC patients reached 33% from March 2014 through January 2015. On-site patients showed higher odd of treatment initiation compared to their off-site counterparts (Ford et al., 2016).

One of the pioneer HCV patient navigation interventions have been conducted in Pennsylvania and showed successful results in facilitating access from testing to cure with support from both patient navigators and clinical social worker. This community-based intervention reached out to 1,301 random participants via mobile clinics from February 2012 to February 2014 and could identify 52 participants with HCV antibodies. The program navigators succeeded to identify HCV antibody carriers, conduct confirmatory HCV RNA testing, and link chronically infected patients to specialized HCV services. Patient navigators reached patients for follow-up by phone and home visits to non-respondents. To
achieve linkage to care, the navigators could help enroll the uninsured Medicaid eligible patients and link them to a primary provider through the program support. Once the patient had insurance coverage and a primary provider, navigators supported patients in getting referral to HCV specialist either through illustrating the process, reminding patients to contact their primary providers, or requesting in person the referral on behalf of the patient (Trooskin et al., 2015).

In North Carolina, an interventional study from December 2012 to February 2014 used counselors as patient navigators to provide post-test counseling beside linkage to care. The counselors either reached out to patients through phone calls, in person meetings, and community visits. Moreover, the interventional study let the HCV specialists provide medical assessment and follow-ups to patients in substance abuse services facilities and health departments to ensure patients adherence. Incarcerated patients were included in the intervention as well, either linked to care after release or referred within the incarceration healthcare system. The overall linkage to care rate of the study reached 51% (Seña et al., 2016).

In 2014, a pilot patient navigation program in Chicago, Illinois identified three major healthcare barriers to HCV treatment in HIV co-infected patients: low rate of HCV confirmatory tests, referral to specialists for evaluation, and PA processing capacities. Individual barriers according to the study are substance abuse, mental health problems, and lack of permanent housing. The study navigators commenced their work with patients’ needs assessment, and connection to HCV treatment facilities in addition to substance abuse and mental health providers. The program succeeded to increase confirmatory testing rate from 50% to 100%. Referral rate was 67.5%, PA requests were sent for 23.9% of patients and 19.6% initiated treatment (Glick, Armstrong, Tobin, & Allgood, 2016).

To compare the cost-effectiveness of different linkage to care models, a study simulated four hypothetical intervention strategies in DAAs therapy: linkage to care through five visits to a case manager over three months; treatment
initiation through visits to a physician, nurse, and a case manager over three months after referral to treatment; integrated case management through visits to a case manager over six months to pursue the first two interventions steps i.e. linkage to care and treatment initiation; and peer navigator intervention through hand in hand peer support over twelve to eighteen months from HCV discovery to treatment completion. The peer navigator intervention showed the best ICER among all interventions ($16,200 per QALY reference to standard of care), a 22.49 years’ life expectancy, 11.32 QALYs, and $207,300 reduction in life time medical costs (Linas et al., 2014).

Integration of Care

Given the syndemic of HCV, HIV, and substance abuse; care for these related health problems requires synchronized services’ provision. A multidisciplinary team of healthcare workers involved in management of these three problems is fundamental to care coordination and better clinical outcomes. This team should ultimately include clinical providers trained in co-management of HIV/HCV, substance abuse counselors, mental health specialists, case managers, and community health workers (Reece et al., 2014). Peer support has been proved efficient in improving access to HCV treatment in high risk group and could be integrated within the multidisciplinary team. The hosting healthcare setting for multidisciplinary services can be a community based primary care center, a substance abuse therapy center, or a specialized hospital based outpatient clinic (Bruggmann & Litwin, 2013).

The national viral hepatitis action plan 2017-2020 emphasized the importance of integration of care for effective prevention of infection, early identification of HCV, and linkage to specialized care. According to the action plan, care coordination should engage primary and specialized clinical care, public health programs, mental healthcare, and substance abuse and risk reduction e.g. syringe exchange services. In parallel, integration should involve all health problems having blood-borne or sexual transmission linked risky behavior i.e. HIV and HBV. Accordingly, these health problems related
behaviors should be under one umbrella of assessment and activities including counseling and education; vaccination against HAV and HBV; testing for HIV, HBV, and HCV; and linkage to treatment. To ensure quality improvement, integrated services should develop and utilize best practices in integrated models of care and apply a comprehensive clinical monitoring process to should guide these activities (DeSalvo et al., 2017).

The US Department of Health and Human Services (HHS) action plan for the prevention, care and treatment of viral hepatitis fostered a similar integration of care model especially for high risk patients with HIV or practicing injection drug use. The HHS plan called for integrating HCV testing and treatment within substance abuse and HIV programs in addition to management of other comorbidities (US Department of Health and Human Services, 2011). This integrated care model avoids the limitations of isolated vertical programs e.g. financial shortage and limited time frame of funding. Besides, integration of care matches the holistic approach to health which helps DAAs providers manage their patients comprehensively especially for patients residing in rural and low-resource settings (DeSalvo et al., 2017).

The American College of Preventive Medicine echoed the national action plan and called for integration of behavioral counseling before and during DAAs therapy. In addition, counsellors should advocate for patients and assist with linking them to DAA treatment (Allison et al., 2016).

An expert view calls for organizing partnerships at all levels between HCV and substance abuse services’ providers for co-provision of prevention, screening, and curative services (Edlin, 2016). To implement this partnership, a multidisciplinary care team should be established and substance abuse and HCV services should be co-localized. In accordance, HCV-infected patients will be easily identified and linked to onsite comprehensive HCV services or offsite specialty services (Zeremski et al., 2013). In contrast to this opportunity, the National Drug Abuse Treatment Clinical Trials Network found a significantly unconnected substance abuse and HCV testing, counseling, and treatment
services either in a comprehensive single facility or through referrals to specialized HCV facility (Bini et al., 2012).

In Connecticut, a comprehensive onsite treatment program (OTP) for substance abuse included HCV testing and linkage to care within its services. Confirmed HCV cases were offered support from a social worker and a psychiatrist for counselling and arrangement of HCV evaluation concurrently with substance abuse treatment. The OTP program multidisciplinary primary care team included two primary care physicians with HCV treatment experience managed the HCV patients and provided guidance to the program. In addition, the program offered an optional family member involvement and close contacts screening for identified patients (Butner et al., 2017).

In New Jersey, a substance abuse facility institutionalized HIV, HCV, and HBV screening for all opioid abuse patients. Identified HCV infected patients were evaluated, counseled on treatment, and referred to proximal HCV providers to their homes. Outcomes from October 2014 to June 2015 showed that 8.6% could follow-up with an HCV treatment provider and 1.6% initiated treatment (Akyar et al., 2016).

Multiple evidences from studies in the US, and other regions of the world, underscored that integration of care should include other social services based on the patient needs. The intensive case management model showed successful results in prevention and treatment of HIV and HCV as well but with limited applications. This model is more applicable to PWIDs with special healthcare needs including health insurance coverage, substance abuse and other comorbidities management; and socioeconomic needs e.g. housing (Meyer et al., 2015).

**Task shifting**

According to the World Health Organization (WHO), task shifting is defined as a “process whereby specific tasks are moved, where appropriate, to health workers with shorter training and fewer qualifications” (World Health
Applications of task shifting have been recognized by the WHO in HIV care for its lower costs and comparable efficiency to specialty care (Mdege, Chindove, & Ali, 2013).

The successful adoption of HIV care task shifting enticed the HCV field to replicate this model. Task shifting in HCV is based on shifting HCV care delivery from centralized tertiary services to accessible community-based primary care providers with technical support from specialists. The quality and effectiveness of task shifting in HIV were comparable between the two providers even in low resource primary care settings. In addition, HCV management task shifting is privileged over HIV by the natural history of the disease and the DAAs availability. First, the effectiveness of DAAs and shorter treatment duration in HCV ensure success and rapid patient turn. Second, HCV management especially at early stages of liver affection needs less intensive monitoring and consequently less need for advanced training for the primary providers and lower opportunity cost from their dedicated time to HCV management. Third, adherence rates are accepted to be higher for HCV DAAs due to lower adverse effects compared to HIV treatment. Fourth, the administration of a simple all-oral DAAs doesn’t require highly developed infrastructure nor modification for the existing primary care settings (Jayasekera, Arora, & Ahmed, 2016). Maximum benefit from HCV management task shifting can be achieved from delegation of primary providers who provide substance abuse services to HCV high risk population (Pawlotsky, Feld, Zeuzem, & Hoofnagle, 2015).

Preparedness and acceptance for task shifting among different types of providers is a key determinant for success of this model of care. A survey conducted among specialists and primary providers showed that referral is a barrier to DAAs effective management. About 77% of primary providers acknowledged loss of follow up of 24% of their referred patients to specialists, and 73% of specialists reported loss of follow up after the first visit and 15% non-adherence to the full treatment plan. Task shifting to primary providers was widely accepted by both types of providers and Managed Care Organizations’
pharmacy and medical directors. More than 73% of primary providers showed comfort with following the AASLD guidelines for HCV prescription and follow-up. On the other side, 98% of HCV specialists and 63% of Managed Care Organizations’ pharmacy and medical directors agreed that primary provider could efficiently prescribe HCV treatment following the AASLD guidelines (Levine-Wilkinson, Cummings, & Holman, 2014).

In Maryland, primary providers were surveyed and 12% reported treating HCV patients in the prior year. Basically, only 22% of respondents agreed that HCV treatment can be delivered by primary providers; however, 84% showed interest in HCV training. Interestingly, willingness to provide HCV treatment among providers was significantly associated with higher HCV patient interaction and availability of closely related services to HCV high risk patients including HIV treatment, and substance abuse and mental health services (Falade-Nwulia, McAdams-Mahmoud, et al., 2016). In Michigan, a survey showed only 9% of primary providers were comfortable with treating HCV patients (Thomson, Konerman, Choxi, & Lok, 2016).

Based on the success of the task shifting model, the integration of care strategy proposed by the national viral hepatitis action plan 2017-2020 recommended capacity development of primary care providers not only for screening and counseling but also to treatment of HCV patients. The action plan called for digital collaboration in training and technical assistance between specialists and primary providers in remote areas to enable these providers to deliver comprehensive care to HCV patients (DeSalvo et al., 2017).

The Infectious Diseases Society of America (IDSA) published a special position statement supporting the use of telehealth for timely, cost-effective specialty services in remote low-resource settings. The major concerns of IDSA revolve around ethical considerations in data management, licensure, and quality of services (Siddiqui et al., 2017).
In the same line with this guidance, the University of New Mexico medical center fostered the Project ECHO (Extension for Community Healthcare Outcomes) since 2003 to develop the capacities of primary providers in remote areas to manage underserved HCV patients. The training components of Project ECHO are; virtual learning platform using videoconference technology; and case-based learning. Training has been provided by the university medical center specialists to primary care providers in remote areas. In addition, mutual learning components of Project ECHO are: sharing best practices; and outcomes measurement. Project ECHO basic team is multidisciplinary including a physician; a nurse practitioner or a physician assistant; plus a nurse or a medical assistant; however, with the expansion of the project all types of health workers have been engaged. Moreover, Project ECHO provides a real-time multidisciplinary team medical assessment using videoconferencing to overcome the time and distance barriers for patients (Thornton et al., 2016).

Expansion of Project ECHO has been maximized at state, national, and international levels. At state level, Project ECHO have been collaborating with the New Mexico Corrections Department and the U.S. Indian Health Services (Thornton et al., 2016). Following New Mexico, several states have been applying the project for capacity development of primary providers to manage HCV cases. In Utah and Arizona, Project ECHO commenced in 2012 with support from the CDC and showed similar successful results to the original project (Mitruka et al., 2014). Since its establishment till 2016, Project ECHO provided care to more than 9,000 HCV patients (Thornton et al., 2016).

Models for reaching patients with specialists at community primary care settings showed promising results as well. An intervention applied a full-day outreach hepatology clinics in underserved areas primary care settings in California coupled with telephone based follow-up by a trained nurse and supportive medical assistant. Specialists followed the laboratory results and adverse effects remotely using supportive electronic health record system. Patients were able to reach out the specialist and the nurse via phone and
secure messaging through an electronic health record system. Results showed high adherence and cost-effectiveness (Jayasekera et al., 2017).

**Administrative Facilitators**

*Health Information Management.* The national viral hepatitis action plan 2017-2020 recommends developing a unified health record guidance associated with quality improvement activities to increase healthcare providers’ awareness of HCV testing and treatment recommendations for special patient groups e.g. PLWHIV. Additionally, health records should help improve screening and referral to DAAs based treatment (DeSalvo et al., 2017).

Data linkage can support identification of patients and help insure continuity of care. A study in Wisconsin investigated HCV care continuum till treatment initiation in PWIDs using three data sources: syringe exchange program surveillance data, the HepNet C survey results, and follow-up in person interviews. Results showed high degree of variability among these sources for HCV care continuum (Hochstatter et al., 2017).

*Prior Authorization Support.* To facilitate and speed up the PA process a study recruited three pharmacy students from June 2014 to March 2015 to assist the clinical pharmacist with the PA process. Students developed their own protocol after their training to help improve the PA process, ensure the efficiency of PA requests for approval, management of appeal denials, and guidance on documentation of the PA progress within an electronic medical record. The students spent 240 hours for developing their protocol and completing PA requests. Overall, the students completed 88 requests with 87.7% approval rate. One of the positive sides of the student work is the saving time for the clinical pharmacist spent to provide clinical services and conduct academic activities. Beside their PA role, the students provided awareness to patients on their insurance coverage and followed treatment delivery. Moreover, the students trained a new team of peer students to ensure sustainability of the program (Martin, Telebak, Taylor, & Volozhina, 2016).
IV- Influencing Factors on Access to Hepatitis C Directly Acting Antivirals in Kentucky

Hepatitis C Patients in Kentucky

The Commonwealth of Kentucky is among of the top regions suffering from HCV across the US. Between 2009 and 2013, Kentucky reported the highest increase of new HCV cases nationwide with a two and half fold jump (National Center for HIV/AIDS, Viral Hepatitis, STD, 2015). In 2012, the state had the highest number of HCV cases among young non-urban persons in the US with 85 cases (Suryaprasad et al., 2014). The Appalachian southeast Kentucky possesses the highest prevalence of HCV infection among the state regions. This prevalence is predominantly among young adults who inject drugs. In 2013, a study suggested that more than half (54.6%) the PWIDs in Appalachia are infected with HCV (Havens et al., 2013). Statewide, the number of patients who are diagnosed and eligible for HCV treatment is not available.

Kentucky Medicaid Program Prior Authorization Criteria

In 2014, Kentucky state government established its own Medicaid expansion program “Kynect” following the directions set forth in the Affordable Care Act (ACA). Kynect led to a reduction in the state uninsurance rate by one half in one year (from 16% in 2013 to 8% in 2014) (Artiga, Tolbert, & Rudowitz, 2016).

The Medicaid program in Kentucky is considered one of the most restrictive programs in its PA criteria. Approval of DAAs for Medicaid beneficiaries in Kentucky requires: proof of advanced liver disease documented by a Metavir fibrosis score of F3 or F4; absence of decompensated cirrhosis corresponding to a Child–Pugh score class B or C; prescription by or in consultation with a specialist; i.e. hepatologist, gastroenterologist, or infectious diseases or LT clinician; and a proof of six months abstinence from substance abuse including drugs and alcohol (Barua et al., 2015).
Geographical Access to Hepatitis C Treatment in Kentucky

Kentucky is Midwestern state covering an area of 39,728 square miles. In 2015, 1,835,685 Kentucky residents lived in rural areas out of total of 4,425,092 residents. The total number of hospitals in Kentucky is 103 of which 27 are Critical Access Hospitals. Kentucky has 109 Rural Health Clinics and 23 Federally Qualified Health Centers (Rural Health Information Hub, 2015).

In reference to the US Health Resources and Services Administration, underserved areas are those with a shortage in primary care providers, high infant mortality rates, high poverty rates, or a high elderly population. Following this definition, Kentucky is one of the medically underserved states with a total of 350 health professional shortage areas including 151 primary care shortage areas. Most of these shortage areas are located in the southeastern Appalachian region of the state. Within this shortage problem (figure 3), Kentucky patients infected with HCV, particularly those in southeast Kentucky, have limited choices for specialty care which are located either in central or northern Kentucky (Human Resources and Services Administration Data Warehouse, 2017).

Figure 3. Geographical distribution of health professional shortage areas in Kentucky [Source: (Human Resources and Services Administration Data Warehouse, 2017)]
Characteristics of Kentucky Clinic Hepatitis C Patients

In Kentucky Clinic, the Digestive Disease and Nutrition outpatient services had a total of 55,649 visits in the fiscal years 2010-2015; 10,214 (18.35%) of these visits were done by HCV infected patients. Out of total 13,943 new patients visited the clinic in these five years there were 3,149 new patients infected with HCV (Abdelwadoud, Racho, & Rosenau, 2017).

1- Sociodemographic Characteristics

Over the period 2010-2015, the absolute number and proportion of new HCV patients among the total new patients increased significantly from 421 (20.56%) in 2010-2011 to reach a peak of 1,071 new HCV patients (25.24%) in 2014-2015. The mean age of new HCV patients was 42.36 (Standard Deviation [SD] +/− 12.69). By age group, 1,889 (59.99%) new HCV patients were born after 1965 followed by 1,231 baby boomers (39.09%), and only 29 patients (0.92%) born before 1945. New male HCV patients were 1,683 (53.48%) while new female HCV patients were 1,465 (46.52%) (Abdelwadoud et al., 2017).

2- Insurance Coverage

Over the period 2010-2015, the new HCV patients who visited the Kentucky Clinic specialized Digestive Disease and Nutrition outpatient services were predominantly covered by Medicaid (1,582 patients corresponding to 50.24%) followed by 1,130 patients (35.88%) on private or other types of insurance plans, and 437 (13.88%) were covered by Medicare (Abdelwadoud et al., 2017).

3- Geographical Distribution

The geographical distribution of new patients with HCV infection who visited the Kentucky Clinic Digestive Disease and Nutrition outpatient services in central Kentucky demonstrated that patients residing in the same county as the clinic; i.e. Fayette county, were 716 (22.74%), while non-Fayette County residents comprised 2,421 (76.88%), and 12 (0.38%) had no residency data
(figure 4). Non-Fayette residents were predominantly from rural Appalachian counties in southeastern Kentucky (Abdelwadoud et al., 2017).

**Figure 4. Geographical distribution of the Kentucky Clinic new patients with hepatitis C virus across Kentucky state counties 2010-2015 [Source: (Abdelwadoud et al., 2017)]**

This distribution of cases is different from some northern states. In Massachusetts, a study that analyzed HCV surveillance data from 2002 to 2013 showed that reported HCV cases were highest in the most populous cities while smaller clusters were found around less population density cities and suburban areas (Goulart, n.d.).

**Summary**

This literature review serves as a guide for understanding the complexity of access to the DAAs-based therapy for HCV. The all-oral standardized treatment is a breakthrough cure for a challenging virus to control since its discovery. HCV special criteria renders it a major challenge for the US health system. The virus methods of transmission are associated with risky behaviors that informed its prevention strategies; however, these strategies are limited to reducing the risk of exposure due to the unavailability of a prophylactic vaccine.
The prevalence and incidence of HCV in the US emphasizes that it is the top priority blood-borne infection and its burden will remain pressing for the coming years even though a curative treatment has been discovered. Several studies supported the above conclusion, the clinical complication of HCV are obviously consuming the healthcare system with high cost services.

Various models for access to health services including general models, chronic diseases’ models, and HCV care models were employed in this review to guide its assessment of access to DAAs. The availability dimension of access revealed that the feasible diagnostic tools and the recently evolved highly effective and tolerable treatment open an opportunity for HCV elimination. Several studies showed the high effectiveness of DAAs in reducing morbidities and mortalities from HCV especially with early treatment. Collective evidence from different studies not only supports the curative role of the DAAs, but also their great potential to prevent transmission. On the other side, prescriber restrictions challenge mass provision of DAAs. Guidance from concerned organizations calls for utilizing and developing the expertise of different types of providers especially in underserved areas to fulfill the need for treatment. Moreover, almost all concerned organizations recommend expansion of screening for early treatment of HCV with DAAs. This expansion will drive a high demand represented by discovered and eligible patients for treatment. Consequently, this demand requires an equivalent responsive supply from a high acceptance and capacity health system.

Nevertheless, the treatment cascade and initiation rates at national level have shown insufficient response from the system especially in the last step from confirmation of diagnosis to treatment initiation. At organizational level, there is a large variability in treatment initiation rates suggesting that barriers are context specific and might be changing over time. Opposing these insufficient rates, ambitious projections anticipate a dramatic decrease in demand in the near future if the treatment would include all patients in need.
The concurrent characteristics of HCV patients in need for treatment shows that there are obvious changes compared the historical profile of HCV patients. Controversial results on patients’ characteristics among national and contextual studies invite an argument that these characteristics differ significantly across the US. The commonly accepted and representative studies point to Caucasian young non-urban Americans as the most affected by HCV, besides, the Caucasian patients have more likelihood to initiate treatment compared to other races. Substance abuse represents the key answer to the question what is the salient single character that predicts high HCV prevalence nowadays. While HCV and HIV have similar transmission methods, HCV prevalence is way higher among PWIDs. However, these disproportionately burdened high risk group is less favored in achieving HCV treatment initiation. In parallel, HIV/HCV co-infection patients possess low rates of treatment initiation.

The economic benefits of HCV treatment have been demonstrated by various studies. Cost-effectiveness in terms of QALYs favors strongly mass provision of DAAs. Several studies provided evidence on saving medical expenditure on future HCV complications in case of treating all patients in need. On the other hand, the national spending on DAAs increased tremendously over the past five years and peaked in the last two years. This spending is implemented under complex and different procedures in different health insurance organizations. While the sticker prices for DAAs are known, the key gap in this area is the unavailability of the final payed price by insurers to the pharmaceutical companies.

Moreover, patients are disproportionately prone to cost sharing for DAAs according to their type of insurance coverage. The most recent studies on patients’ distribution among insurers reflect the change of epidemic towards young PWIDs and showed that the greatest portion of HCV patients is currently covered by Medicaid. However, these patients are expected to fall under Medicare coverage in the near future with high probability of disease.
complications coupled with higher costs then. Another element to consider is the approval criteria set by different insurers for treatment initiation.

Commercial insurance attempts to avoid HCV patients’ treatment or enforce cost sharing on them. Medicare is more accepting HCV treatment coverage through its attached prescription drug plans with less strict criteria compared to Medicaid. Most Medicaid programs select patients who are at advanced liver disease stages; not on drug abuse or abstained for a relatively long time; could reach out to a specialist for prescription; and engaged in ART therapy in case of HIV coinfection. These discriminative criteria aim at ensuring that the limited allocated financial resources would be targeting the best positioned patients to achieve cure with minimal probability of resistance, relapse, or recurrence of infection. Several organizations oppose this approach and refuted it from a legal perspective and offered cost reduction solutions.

As a result of these restrictive criteria for inclusion, PA approval rates in Medicaid are insufficiently low and disproportionately accept different types of patients compared to other types of insurances according to various studies in different states. Another important evidence against these restrictions comes from the evidence of cost-effectiveness of full-access treatment expansion which is supported by cost-reduction evidence from preventing morbidity costs on the whole healthcare system even though these patients would be probably covered by Medicare when they develop these morbidities.

Most HCV specialized care is centralized in urban areas, this distribution opposes the distribution of patients within the increasing trend of HCV infection among rural residents. Evidence showed that geographical access to specialty HCV care can be singled out as the obstacle for treatment.

Adding to all these obstacles, stigma and providers’ negative attitudes towards high risk patients hinder access to treatment. Several studies have shown the potential effectiveness of increasing awareness and reassurance of patients to overcome patients fears and misunderstandings.
Recommendations and best practices for HCV care delivery conclude that patients’ needs are the best guide. Meeting the patients where they conventionally access healthcare and offering testing and linkage to care at these convenient points, especially for difficult to reach groups, have been highly supported by several interventions’ results.

Given the complex and often broken healthcare delivery system, patient navigators have been shown great results in ensuring continuity of care from testing to treatment initiation under several implementation models and depending on different personnel types.

The ultimate option for care delivery is integration of care, a patient centered approach offering all needed services under one umbrella is the best option. Integrating HCV treatment into primary care, as well as integration with other vertical programs e.g. substance abuse and HIV ART, have been proven effective especially among high risk PWIDs in remote underserved areas. Moreover, integration within a holistic social service model including housing showed promising results.

In support of the idea of integration, a primary care approach is a best match for HCV care. This approach requires task shifting from centralized specialty services to decentralized primary care proximal to the patients’ geographical and cultural needs. This approach is inspired by successful HIV models and with the effective and tolerable DAAs the results are expected to exceed those of HIV. However, task shifting is tied to capacity development of primary providers with technical support from specialty services. While some studies showed some hesitance among specialized and primary providers for assigning HCV treatment to the latter group, the success of Project ECHO and its expansion outweigh this hesitance if a well-established capacity development program was implemented. From another perspective, capacity development of HCV model of care should emphasize the administrative procedures. The two main support areas found useful are: maximizing the use of health information
system for linkage, continuity, and integration of care; and administrative support for the PA procedures with a specialized team.

In Kentucky, the burden and patients’ characteristics are alarming. First and foremost, the state ranks high in HCV prevalence and incidence among the US with special hot spot of infection in Appalachian southeastern Kentucky attributed to the substance abuse epidemic. In contrast to this need, the Kentucky Medicaid program, which covers the majority of HCV patients, is very restrictive in applying criteria to the highest need group of PWIDs living in remote rural areas with limited geographical access to specialists.

The Kentucky Clinic, this study setting, showed an escalating increase in utilization of specialized services by HCV patients from 2010 through 2015. The profile of these patients revealed that they are more commonly young males, Caucasians, and with Medicaid coverage. The geographic distribution of these patients demonstrated that more than three quarters were from outside the Clinic’s direct catchment area and predominantly from rural southeastern areas of Kentucky.

Taken together, the review offered a comprehensive insight to the influencing factors on the access to DAAs from both the demand and supply sides. The problem is that there appears to be a vast gap between the promise from DAAs benefits and treatment initiation. Nevertheless, this review indicates that one size does not fit all when addressing access to DAAs. This gap pertains to fact that influencing factors vary among different contexts given that every context has special demand and supply profiles. A contextual understanding of the demand and supply in Kentucky requires practice oriented research to identify the particular characteristics of HCV care and gaps in care that need to be filled.

VI- Empirical and Theoretical Basis for This Study

Given the high morbidity, mortality, and economic burdens of the HCV in Kentucky coupled with disparities in the potential for accessing the effective yet
costly DAA treatment, a study to investigate context specific barriers to treatment initiation is timely in order to address these barriers in Kentucky. Practice-oriented research directed at the current HCV treatment obstacles in Kentucky is lacking, in addition, previous studies in this context are scarce and did not offer practical clues to the interrelated barriers to HCV treatment in Kentucky. To our knowledge, this is the first practice-based study to investigate the barriers to DAA-based treatment initiation in Kentucky.

The interaction between HCV patients and the available model of care in Kentucky Clinic is specific to the Kentucky context. Accordingly, empirical exploratory research is highly valuable for addressing barriers to treatment initiation within this context. The conceptual model for this study, Figure 1, is adopted from several general and specific models to HCV care to capture all dimensions and possible factors influencing access to HCV treatment. The expected results from this study involve identifying the access barriers in the Kentucky clinic for HCV treatment initiation and proposing practice oriented feasible recommendations to overcome these barriers.
CHAPTER 3

METHODOLOGY

Chapter Overview

The first part of this chapter sets the methodological approach; design; study setting; and target population for this study. Subsequently, how this study was implemented is answered by the methodological techniques used including: procedures, instrumentation and measurements, and analytical strategies. Ethical considerations were addressed and the summary sets for how this methodology is aligned with the study aims.

I- Research Methodology

Study Design

Given that the supply and demand sides for access to health services do not exist in isolation, a mixed methods approach to comprehend the barriers for initiating HCV treatment among the Kentucky Clinic patients from both sides is required.

The qualitative part used a set of qualitative techniques to explore the current model of care provided to HCV patients in the Kentucky Clinic. For the quantitative part, since the objective was to estimate the risk of the outcome i.e. initiation of treatment over time; the study utilized longitudinal cross-sectional data. Accordingly, the quantitative part followed a retrospective cohort design.

The mixed results of these two parts were employed simultaneously to answer the research question of this study: what are the barriers for treatment initiation facing Kentucky Clinic HCV patients?

Since the qualitative part pursues a real life description of the current model of care provided to the target population of the study, the null hypothesis in this case anticipates that the model of care perfectly enables access, fulfilling
the needs of HCV patients, and offering no obstacles for treatment initiation. The null hypothesis for the quantitative part assumes no significant difference in the characteristics of the patients who initiated treatment and those who did not.

\( (H_{01}) = \) there are no barriers associated with the current model of care for DAAs-based treatment initiation in the Kentucky Clinic.

\( (H_{02}) = \) there is no difference between the characteristics of the patients who initiate the DAAs-based treatment and those who do not initiate the treatment in the Kentucky Clinic.

**Study Setting**

The study was conducted in the specialized HCV outpatient clinic affiliated with the Digestive Diseases and Nutrition Division at the Kentucky Clinic. The Division outpatient services are recognized as the largest across Kentucky for their variety and number of providers. The Kentucky Clinic is located in Fayette County, Lexington City, Central Kentucky and is the major outpatient services facility affiliated with the University of Kentucky. The outpatient facility provides a wide variety of primary, secondary, and tertiary services in more than twenty specialized clinics supported by specialized pharmacies, laboratory, and radiological facilities. Outpatient services of the Kentucky Clinic are provided by more than four hundred healthcare providers (University of Kentucky Healthcare, 2017).

**Study Population**

For the qualitative part of the study, key informants were the administrative and clinical staff working closely with HCV patients through their journey from referral to treatment initiation. In the qualitative analysis the study cohort comprised all chronic HCV patients who had their first visit to the Kentucky Clinic’s HCV clinic between July 1, 2014 and June 30, 2015.
Procedures

Data collection took place from October through December 2016. The purpose of the qualitative part was to explore the model of care including the administrative and clinical procedures in the Kentucky Clinic applied to the patients seeking HCV treatment. This model and its applied procedures begin with the patient’s referral to the Kentucky Clinic until the approval for treatment initiation is achieved. The quantitative part used data collected from the HCV clinic patients’ electronic medical records. The patients’ sociodemographic and clinical data are documented by the Kentucky Clinic administrative and clinical staff members during outpatient visits and maintained in a quality assured secure electronic medical records system.

Instrumentation

A- Qualitative Analysis:

The qualitative analysis developed a real life administrative and clinical flowchart describing the current model of care provided for HCV patients in the Kentucky Clinic and identifying the obstacles to treatment initiation. In order to ensure data quality, qualitative measures to explore the model of care used different techniques for triangulation. Combining techniques aimed at increasing visibility about the treatment initiation process and ensuring comprehensiveness of the results. To achieve these purposes, the study investigator conducted:

1- Field observations through attending the HCV clinic to observe and document the administrative and clinical procedures in practice;

2- Semi structured in-depth interviews with healthcare personnel providing administrative and clinical services to hepatitis C patients in order to better understand these procedures and related barriers to treatment initiation. To ensure comprehensiveness, one provider from each provider categories was interviewed. Interviewees included: hepatology specialist, specialty clinical pharmacist, registered nurse, physician assistant, clinical
services technician, the clinic administrator, and the patient access manager. The topic guide for these interviews included three main inquiries: each interviewee’s roles and responsibilities relevant to the treatment initiation procedures, the barriers he/she found hindering patients from treatment initiation, and his/her suggestions for overcoming these barriers.

3- Administrative forms collection from the interviewees to better understand the process and ensure the quality of data.

B- Quantitative Analysis:

1- Outcome Variable

Given the primary outcome of this analysis is treatment initiation, the outcome variable is defined as the initiation of all-oral treatment for chronic HCV either using a single DAA or a combination of DAAs, with or without RBV medication. To determine the predictive factors for DAAs treatment initiation, all patients were followed with an observation time calculated from the first visit of the patient to the Kentucky Clinic until treatment initiation or the last day of observation; i.e. November 30, 2016. For measurement, we constructed a treatment initiation binary variable (initiated treatment=1, did not initiate treatment=0).

2- Explanatory variables

Explanatory variables of interest in this analysis to assess the predictors for DAAs treatment initiation are:

Sociodemographic Variables:

1. Age: a discrete variable for patients’ completed years of age.

2. Age group: we constructed the age group variable from the patients’ documented date of birth. This variable divides the study subjects into three age groups according to the year of birth: before 1945, 1945-1965
(baby boomers with a historical high exposure to hepatitis C infection), and after 1965.

3. Health insurance coverage: the patients’ insurance coverage was constructed from the patients’ current primary payer into three classes: Medicare, Medicaid, and private or other types of insurance.

4. Gender: binary variable of the patient’s genotypic gender defined as:
   male=1 and female=0.

5. Race: the race variable has four categories: African-American, Asian, Caucasian, and Other races.

6. County of residence: the medical records document the patient county of residence as a nominal variable. We constructed a simplified variable for the multivariate analysis with two classes: Fayette (the county where Kentucky Clinic is located-) and non-Fayette.

7. Primary provider: although we consider the primary provider at the first visit less likely to influence the characteristics of the patient, we constructed a binary primary provider variable for statistical control purpose using a random provider assigned as 1 and all other providers in a reference class assigned as 0.

8. Referring provider: the referring provider was created as a binary variable for the purpose of controlling the multivariate model.

Clinical Variables

9. Genotype: a dichotomous variable constructed into two levels; patients with a single HCV genotype and those with a combination of two or more genotypes (known to have some resistance for SVR that could alter the clinical or insurance decision for treatment initiation).

10. Liver disease condition: a dichotomous variable constructed to classify the patients’ liver condition into two levels. Mild liver disease refers to patients
with F0-F2 score by METAVIR fibroscan; while advanced liver disease refers to patients with F3 score or above, or evidence of cirrhosis by another diagnostic tool.

11. Follow-up: binary variable to differentiate patients who had at least one follow-up visit after their initial visit to the clinic (assigned as 1) and those without any follow-up history (assigned as 0).

Behavioral Variable:

12. Substance abuse: a binary variable classifying patients into those with history of drug abuse (assigned as 1) and those without (assigned as 0).

Analysis Strategy

Qualitative Analysis:

Data collected from the field observation notes, in-depth interviews, and administrative forms’ review were gathered to describe the current model of care covering the administrative and clinical procedures for treatment initiation.

Quantitative Analysis:

Using the Statistical Analysis Software (SAS) 9.4 package (SAS Institute Inc., Cary, North Carolina), quantitative analysis was conducted in two stages:

1- Descriptive Analysis:

A descriptive analysis was performed to tabulate the frequencies and percentages of patients’ explanatory variables comparing those who initiated treatment to those who did not. In this analysis we used frequencies and percentages for the categorical explanatory variables. For the only discrete variable, age, we used means, standard deviations, and the student’s t-test to assess significance.

2- Time to Treatment Analysis:
Cumulative incidence of treatment initiation was calculated over the study period and Kaplan–Meier time to treatment analysis was used to construct time to treatment curves estimating the proportion of patients who initiated treatment at different time points comparing each explanatory variable levels.

Cox Proportional Hazards Regression analysis was conducted to identify predictive independent variables for treatment initiation over time using the relative risk estimate hazard ratio (HR) and 95% confidence intervals. Dummy variables for every explanatory variable were constructed to include them in the model with a reference first class for comparison.

The Cox regression analysis aimed at fitting all explanatory covariates including: age group, gender, race, health insurance coverage, county of residence, primary provider, referring provider, genotype, liver disease condition, follow-up, and substance abuse. We employed interaction terms assuming that the age group, insurance coverage, and liver disease condition are interrelated based on the fact that the majority of Medicare patients are older and probably experienced HCV for a long period of time, they are probably more susceptible for advanced liver disease reference to the natural history of HCV. Moreover, the PA approval for treatment initiation mandates advanced liver disease for Medicaid patients. Accordingly, the final model fitted all covariates of the first model while interaction terms were applied for the assumed interrelated covariates.

All tests were 2-tailed with a significance level of 0.05; i.e. a p-value less than 0.05 (two-tailed) was considered to be statistically significant.

II- Ethical Statement

The work described was approved by the Institutional Review Board of the University of Kentucky Office of Research Integrity.
III- Summary

Using mixed methods in this study aimed at improving the depth and the breadth of the analysis for comprehensive understanding of HCV treatment initiation barriers. The qualitative part of the study should reveal insights into how the model of care may hinder the outcome of the study. Simultaneously, the quantitative part compares the characteristics of patients who achieved and who did not achieve the outcome in addition to assessing the predictors among these characteristics for outcome achievement. Collective results from both analyses would help propose a comprehensive model of care enabling HCV patients access treatment based on the needs identified from the current model of care and patients’ characteristics.
CHAPTER 4

RESULTS

Chapter Overview

This chapter presents the study results in two sections: qualitative and quantitative analyses. A joint interpretation of these results then follows in order to simultaneously understand the barriers that hinder the Kentucky Clinic HCV patients from initiating DAA-based treatment.

I- Qualitative Results

Results of the data collected from the field observation notes, in-depth interviews, and administrative forms’ review reveal that the current model of care provided for HCV patients is linear (figure 5). The patient’s journey begins when the referring provider, in most cases the patient’s primary provider, issues a referral for HCV assessment by a HCV specialist clinician. The first administrative procedure occurs at the University of Kentucky Patient Access Center located nearly five miles from the Kentucky Clinic.

The Patient Access Center is responsible for receiving the referral calls from the referring facility and scheduling patients for a specialist appointment at the hepatitis C clinic either at the Kentucky Clinic or at the University of Kentucky Good Samaritan Hospital. While the Good Samaritan Hospital offers specialized HCV services, patients are referred after the first appointment for follow-up at the Kentucky Clinic due to the availability of the HCV specialist pharmacy. The obvious barrier at this initial step is the clinical information gap. Accordingly, incomplete clinical data leads to potential inaccurate prioritization of patients in scheduling.

The first appointment for HCV assessment is given to the patient based on the first available appointment either with a mid-level HCV specialist or a higher level attending physician at either clinic. The total number of specialists at the
time of this study was twelve, only one of them accepts HCV patients in her outpatient services, while the others accept patients in their specialized half day HCV clinic. Due to the limited availability of appointments with either level of specialists, the average waiting time for the first appointment at the Kentucky Clinic ranges from three to six months. Occasionally, a special note from the referring provider recommending an appointment with an attending physician results in a longer waiting time due to the limited number of appointments offered by the attending physicians. On the other hand, a priority note for an urgent clinical condition allows the Patient Access Center to find an earlier appointment.

Ensuring patient compliance with the scheduled appointment is jeopardized by several factors including: no response to the scheduling call from the Patient Access Center, change of phone number, lack of transportation on the day of the appointment, and more predominantly the patient’s perception that the appointment and the HCV treatment in general are of low importance. On the other hand, appointment cancellation by the specialist is a potential hazard. In this case, rescheduling takes up to six weeks after the initially scheduled appointment.

In almost all cases the patient is not prepared by his/her referring provider for the administrative and clinical procedures he/she will follow at the Kentucky Clinic for treatment approval. During the first appointment, the specialist assesses the patient referral papers and previous laboratory and radiological investigations if available. Clinical assessment includes questions about: history of HCV transmission methods with special emphasis on substance abuse practices, onset of HCV infection discovery, comorbidities and general clinical assessment, results of previous laboratory and radiological investigations, and whether there are missing investigations in the patient’s records. A common challenge at this point is the non-availability of laboratory or radiological results especially those done outside the Kentucky Clinic. Moreover, results requested by the clinic from other facilities are received by fax causing a delay.
Due to lack of awareness among the majority of patients about HCV, the specialist offers a standard awareness message about HCV methods of transmission, measures for prevention, and how to protect the patient’s close contacts. Finally, the specialist provides a general message on the current clinical status; the next plan including the required clinical, laboratory, and radiological assessments; possible prognosis; and an emphasis on the importance of compliance.

After the appointment, the specialist clinician orders laboratory and radiological investigations with two objectives: full clinical assessment and compliance with the PA requirements. Given the second objective, this order is completed in consultation with the HCV specialist pharmacist in the clinic. In few cases, patients with urgent clinical conditions; e.g., urgent follow-up appointments are requested for individuals with liver decompensation.

After the first appointment, follow-ups are scheduled by the patient. The second appointment, which may occur up to two months after the first appointment, aims at finalizing the administrative and clinical procedures required to comply with the treatment PA requirements. In most cases, the specialist clinician assesses the ordered laboratory and radiological investigations and conducts or orders a fibroscan procedure if not previously done. A potential challenge is identifying advanced liver disease in Medicaid patients since the fibroscan assessment for the F3 level has no clear cuts and inconsistency occurs among the clinicians conducting it. Besides, other evidence; e.g., cirrhosis in the liver biopsy, can waive this fibrosis level. Most clinicians employ supplementary investigations plus their clinical assessment to make the final decision on the stage of liver disease.

In parallel, the specialist pharmacist reviews the patient’s full record including illicit drug laboratory results and communicates with clinical and administrative personnel as necessary to ensure compliance with the PA requirements of the patient’s specific insurer. These requirements vary among different insurers and the insurer’s case-to-case flexibility is variable as well. The
chosen DAA protocol is assigned to the patient according to his/her clinical profile and usually this choice does not impact the PA decision.

When the patient’s PA file is completed, the specialist pharmacist administers the PA procedures with the insurer on behalf of the patient (appendices 1 and 2). Time to PA decision varies according to the type of insurer. In case of PA disapproval, the specialist pharmacist conducts an appeal (appendix 3) supported by laboratory and radiological investigations in consultation with the specialist clinician. The appeal process takes from one to two months on average.

Once the PA is approved, the specialist pharmacist works jointly with the clinical services technician; i.e. case manager, on implementing the DAAs treatment protocol (appendices 4 and 5). The first step is informing the patient about the approval, followed by patient education sessions supported by handouts about: the natural history of HCV and its prognosis, general precautions for liver protection, goals of treatment and its effectiveness, the potential side effects of the DAAs, and the treatment plan with special emphasis on the importance of compliance to achieve cure (appendix 6).

The treatment administrative plan is standardized for all patients and follows the DAAs twelve-week protocol (appendix 7). After the initial DAAs visit, there is a two-week laboratory assessment for which the patient has the option to take the laboratory tests at a proximal facility for geographical convenience. The specialist pharmacist or the case manager calls the patient on the day of the laboratory assessment to ensure compliance and offers support or modification the plan if the patient is not able to take the tests. In the fourth week, the patient visits the clinic for clinical follow-up and to ensure compliance. In the eighth week, the patient undergoes a laboratory assessment similar to the second week with another call from the specialist pharmacist or the case manager. At the end of treatment, the twelfth week, the patient visits the clinic for the final treatment and compliance follow-up.
These five follow-up visits are documented in a special pre-organized patient follow-up and outcomes Microsoft Office Excel® spreadsheet (Appendix 8) including all administrative and clinical follow-up data. In parallel, the specialist pharmacist conducts a follow-up clinical assessment survey with the patient focusing mainly on the patient reported clinical outcomes during each follow-up visit or phone call. In case of the patient’s failure to comply, there are three phone call reminders followed by a certified letter to the patient’s physical mailing address. While these well-established personalized follow-up procedures can ensure compliance, the integration of care with other services; e.g. primary care services and substance abuse programs is a major concern.

The post-treatment assessment of SVR is based on quantitative HCV RNA test conducted on the fourth, twelfth, and twenty-fourth weeks after end of treatment. The last SVR test is accompanied by an in-clinic visit for clinical assessment.
Figure 5. The current model of care and its administrative and clinical procedures applied to Hepatitis C patients seeking the DDA-based treatment at the Kentucky Clinic

<table>
<thead>
<tr>
<th>Step</th>
<th>Provider</th>
<th>Procedures</th>
<th>Potential Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral</td>
<td>Patient's Primary Provider</td>
<td>- Phone Call</td>
<td>- Lack of adequate clinical information.</td>
</tr>
<tr>
<td>Scheduling</td>
<td>Scheduler</td>
<td>- Electronic Scheduling</td>
<td>- Lack of communication coupled with the geographical isolation of the Patient Access Center from the Kentucky Clinic.</td>
</tr>
<tr>
<td>First Visit to the HCV Clinic (3-6 months)</td>
<td>HCV Specialist (+ Specialty Pharmacist)</td>
<td>- Clinical assessment + awareness message. - Ordering complementary lab. &amp; rad. investigations.</td>
<td>- Long waiting time (3-6 months).</td>
</tr>
<tr>
<td>Kentucky Clinic / Good Samaritan Hospital</td>
<td></td>
<td></td>
<td>- Patient incompatibility to the scheduled appointment.</td>
</tr>
<tr>
<td>Second Visit to the HCV Clinic (1-2 months)</td>
<td>HCV Specialist + Specialty Pharmacist</td>
<td>- Assessment of Lab. &amp; Rad. Investigations (+/- fibroscan). - Reviewing patient's clinical results against his/her insurer PA requirements.</td>
<td>- Appointment cancellation by the HCV specialist (+ 6 weeks).</td>
</tr>
<tr>
<td>Kentucky Clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Authorization (PA)</td>
<td>Specially Pharmacist (on behalf of the patient) + Patient’s Insurer</td>
<td>- Filing and revision of the patient administrative and clinical data in the PA form of his/her insurer. - Submission of the patient’s PA form.</td>
<td>- Lack of both referring provider and patient awareness about the HCV treatment administrative and clinical procedures.</td>
</tr>
<tr>
<td>PA Approval</td>
<td></td>
<td></td>
<td>- Unavailability and/or long time required for receiving previous lab. &amp; rad. investigations’ results.</td>
</tr>
<tr>
<td>PA Disapproval</td>
<td></td>
<td></td>
<td>- Unclear demarcation of advanced liver disease requires additional clinical procedures.</td>
</tr>
<tr>
<td>PA Appeal (1-2 months)</td>
<td></td>
<td></td>
<td>- Long waiting time between visits.</td>
</tr>
<tr>
<td>PA Decline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Initiation</td>
<td>HCV Specialist + Specialty Pharmacist + Case Manager</td>
<td>- Twelve-weeks treatment plan - Twenty-four weeks post-treatment SVR assessment</td>
<td>- Variability in the insurers’ PA requirements and their case-to-case flexibility.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Long time of the appeal process.</td>
</tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lack of integration of care with other services e.g. primary care services and substance abuse programs.</td>
</tr>
</tbody>
</table>
II- Quantitative Results

1- Descriptive Analysis:

A total of 880 HCV patients visited the HCV clinic at the Kentucky Clinic between July 1, 2014 and June 30, 2015. Descriptive analysis (table 1) revealed that only 195 (22.16%) patients initiated the DAAs treatment during the observation period; i.e. until November 30, 2016, while 685 (77.84%) patients did not initiate treatment. The mean age of all patients was 43.04 years (Standard Deviation [SD] +/- 12.36). The mean age of the patients who initiated treatment was significantly higher (51.55 years +/-10.4) compared to the mean age of the patients who did not initiate treatment (40.62 years +/-11.79), p-value < 0.0001.

When stratified according to year of birth categories, the age group of the baby boomers who initiated treatment comprised the highest proportion (66.67%) followed by those born after 1965 (32.31%) followed by the oldest group; i.e. those born before 1945 (1.03%). This distribution contrasted the fact that those born after 1965 represented the highest proportion (63.86%) of the entire study cohort.

The insurance type distribution showed that the 645 Medicaid patients, representing 73.30% of the whole study cohort, comprised less than half (47.18%) of the patients who initiated treatment followed by Medicare patients (28.72%) then private and other insurance patients (24.10%). The initiation rate among Medicaid patients was the lowest (14.26%) compared to Medicare (49.56%), and private and other types of insurance patients (38.52%).

Male patients comprised nearly two thirds (63.08%) of the patients who initiated treatment while females comprised nearly one third (36.92%). Racial group distribution of the study participants reflected the predominant Caucasian population in Kentucky. However, only 20.66% of the Caucasian participants initiated treatment compared to 44.45% of the African American participants. This distribution should not be mixed with the distribution of patients who initiated treatment showing that Caucasians were the most prevalent (86.67%) followed
by African Americans (12.28%) while only one patient (0.15%) was from the Asian and the unreported race group.

About three quarters of the patients who initiated treatment resided outside the Fayette county (73.85%) while nearly one quarter (26.15%) resided in the Fayette county.

The patients who initiated treatment with a single genotype represented 97.74% while those with combined genotype represented 2.06% (42 patients from the whole cohort did not have a reported genotype in their records, only one of them was among the patients who initiated treatment).

Although the patients with mild liver disease comprised 63.75% of the whole cohort, they represented only 29.74% of the patients who initiated treatment compared to the patients who initiated treatment and were at an advanced liver disease stage (70.26%). Only two patients (1.03%) did not have any follow-up visits and could not initiate treatment. The majority of the study cohort had a history of substance abuse (72.95%) and represented the highest proportion of the patients who initiated treatment (62.05%). However, the proportion for the patients without history of substance abuse who initiated treatment is lower (18.85% of the substance abuse participants) compared to those who had no history of substance abuse (31.1% of the participants with no history of substance abuse).
Table 1: Frequency distribution and percentages of the characteristics of the Kentucky Clinic hepatitis C patients who initiated vs. who did not initiate hepatitis directly acting antiviral therapy (July 2014 - November 2016)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Levels of Measurement</th>
<th>Initiated Treatment Frequency (Percentage per total initiated, Percentage per measure level)</th>
<th>Did not Initiate Treatment Frequency (Percentage per total did not initiate, Percentage per measure level)</th>
<th>Total Frequency (Percentage per measure group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td>(+/- Standard Deviation)</td>
<td>51.55 (+/-10.4)*</td>
<td>40.62 (+/-11.79)</td>
<td>43.04 (+/-12.36)</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td>Birth before 1945: 2 (1.03%, 50%)</td>
<td>2 (0.29%, 50%)</td>
<td>4 (0.45%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth 1945-1965: 130 (66.67%, 41.40%)</td>
<td>184 (26.86%, 58.60%)</td>
<td>314 (35.68%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth after 1965: 63 (32.31%, 11.21%)</td>
<td>499 (72.85%, 88.79%)</td>
<td>562 (63.86%)</td>
</tr>
<tr>
<td>Insurance Coverage</td>
<td></td>
<td>Medicare: 56 (28.72%, 49.56%)</td>
<td>57 (8.32%, 50.44%)</td>
<td>113 (12.84%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medicaid: 92 (47.18%, 14.26%)</td>
<td>553 (80.73%, 85.73%)</td>
<td>645 (73.30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Private and other types of insurance: 47 (24.10%, 38.52%)</td>
<td>75 (10.95%, 61.48%)</td>
<td>122 (13.86%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Females: 72 (36.92%, 17.43%)</td>
<td>341 (49.78%, 82.57%)</td>
<td>413 (46.93%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males: 123 (63.08%, 26.34%)</td>
<td>344 (50.22%, 73.66%)</td>
<td>467 (53.07%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>African American: 25 (12.82%, 45.45%)</td>
<td>30 (4.38%, 54.55%)</td>
<td>55 (6.25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caucasian: 169 (86.67%, 20.66%)</td>
<td>649 (94.74%, 79.34%)</td>
<td>818 (92.95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian and unreported: 1 (0.51%, 14.29%)</td>
<td>6 (0.88%, 85.71%)</td>
<td>7 (0.80%)</td>
</tr>
<tr>
<td>County of Residence</td>
<td></td>
<td>Non-Fayette: 144 (73.85%, 21.18%)</td>
<td>536 (78.25%, 78.82%)</td>
<td>680 (77.27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fayette: 51 (26.15%, 25.50%)</td>
<td>149 (21.75%, 74.50%)</td>
<td>200 (22.73%)</td>
</tr>
<tr>
<td>Primary Provider</td>
<td></td>
<td>Chosen: 42 (21.54%, 20.59%)</td>
<td>162 (23.65%, 79.41%)</td>
<td>204 (23.18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: 153 (78.46%, 22.63%)</td>
<td>523 (76.35%, 77.37%)</td>
<td>676 (76.82%)</td>
</tr>
<tr>
<td>Referring Provider</td>
<td></td>
<td>Unknown: 8 (4.10%, 14.55%)</td>
<td>47 (6.86%, 85.45%)</td>
<td>55 (6.25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: 187 (95.90%, 22.67%)</td>
<td>638 (93.14%, 77.33%)</td>
<td>825 (93.75%)</td>
</tr>
<tr>
<td>Clinical Variables</td>
<td></td>
<td>Single: 190 (97.94%, 23.11%)</td>
<td>632 (98.14%, 76.89%)</td>
<td>822 (98.09%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combined: 4 (2.06%, 25%)</td>
<td>12 (1.86%, 75%)</td>
<td>16 (1.91%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild liver disease: 58 (29.74%, 10.34%)</td>
<td>503 (73.43%, 89.66%)</td>
<td>561 (63.75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advanced liver disease: 137 (70.26%, 42.95%)</td>
<td>182 (26.57%, 57.05%)</td>
<td>319 (36.25%)</td>
</tr>
</tbody>
</table>
Table 1: Frequency distribution and percentages of the characteristics of the Kentucky Clinic hepatitis C patients who initiated vs. who did not initiate hepatitis directly acting antiviral therapy (July 2014 - November 2016) Continued

<table>
<thead>
<tr>
<th>Measure</th>
<th>Levels of Measurement</th>
<th>Initiated Treatment Frequency (Percentage per total initiated, Percentage per measure level)</th>
<th>Did not Initiate Treatment Frequency (Percentage per total did not initiate, Percentage per measure level)</th>
<th>Total Frequency (Percentage per measure group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow Up</td>
<td>No follow-up</td>
<td>2 (1.03%, 0.62%)</td>
<td>322 (47.01%, 99.38%)</td>
<td>324 (36.82%)</td>
</tr>
<tr>
<td></td>
<td>Follow-up at least once</td>
<td>193 (98.97%, 34.71%)</td>
<td>363 (52.99%, 65.29%)</td>
<td>556 (63.18%)</td>
</tr>
<tr>
<td>Behavioral Variable</td>
<td>Substance Abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No history of substance abuse</td>
<td>74 (37.95%, 31.09%)</td>
<td>164 (23.94%, 68.91%)</td>
<td>238 (27.05%)</td>
</tr>
<tr>
<td></td>
<td>History of substance abuse</td>
<td>121 (62.05%, 18.85%)</td>
<td>521 (76.06%, 81.15%)</td>
<td>642 (72.95%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>195 (22.16%)</td>
<td>685 (77.84%)</td>
<td>880 (100%)</td>
</tr>
</tbody>
</table>

*The difference between the mean age of patients who initiated and who did not initiate treatment is statistically significant (p-value=<0.0001)

**The number of patients whose genotype was missing = 42.

2- Time to Treatment Analysis

The average number of days to initiate treatment starting from the patient’s first visit to the Kentucky Clinic was 263.57 days with a minimum of 30 days and a maximum 793 days to initiate treatment. The cumulative incidence showed that the probability for DAAs treatment initiation at 203 days or less was 50%; i.e. the median number of days to treatment, then this probability accumulated at slower rate (figure 6).
The Kaplan–Meier time to treatment curves estimated the proportion of patients who initiated treatment at different time points (figures 7-16). Significant results from these curves demonstrated that gender, race, follow-up, substance abuse, and age group affected the likelihood of treatment initiation over time. At different time points, earlier treatment initiation times were found among: males compared to females (log rank p-value = 0.0016); African Americans followed by Caucasians then Asians and patients with unreported race (log rank p-value = < 0.0001); patients who had at least one follow-up visit compared to those who declined follow-up (log rank p-value = < 0.0001); patients with no history of substance abuse compared to those who had history of substance abuse (log rank p-value = < 0.0001).

By age group, the patients who were born before 1945 and baby boomers initiated treatment earlier than those born after 1965 (log rank p-value = < 0.0001). By insurance type, the patients who were on Medicare initiated
treatment the earliest followed by private or other types of insurance patients then those on Medicaid (log rank p-value = < 0.0001). Liver disease condition curves demonstrated that patients with advanced liver conditions initiated treatment earlier than patients with mild liver disease (log rank p-value = < 0.0001).

On stratifying the patients’ insurance type by their liver disease condition, the Kaplan–Meier time to treatment curves showed that patients’ covered by private or other insurance types with advanced liver disease were the earliest to initiate treatment, while Medicaid patients with mild liver disease were the latest to initiate treatment.

Figure 7. Kaplan-Meier estimates for DAAs treatment initiation by gender with 95% Hall-Wellner confidence bands
Figure 8. Kaplan-Meier estimates for DAAs treatment initiation by race with 95% Hall-Wellner confidence bands

Figure 9. Kaplan-Meier estimates for DAAs treatment initiation by county of residence with 95% Hall-Wellner confidence bands
Figure 10. Kaplan-Meier estimates for DAAs treatment initiation by genotype with 95% Hall-Wellner confidence bands

Log rank p-value = 0.8648

Figure 11. Kaplan-Meier estimates for DAAs treatment initiation by follow-up with 95% Hall-Wellner confidence bands

Log rank p-value = <0.0001
Figure 12. Kaplan-Meier estimates for DAAs treatment initiation by history of substance abuse with 95% Hall-Wellner confidence bands

Long rank p-value = <0.0001

No History of Substance Abuse

History of Substance Abuse

Figure 13. Kaplan-Meier estimates for DAAs treatment initiation by year of birth with 95% Hall-Wellner confidence bands

Log rank p-value = <0.0001

Born Before 1945

Born Between 1945 and 1965

Born After 1965
Figure 14. Kaplan-Meier estimates for DAAs treatment initiation by insurance type with 95% Hall-Wellner confidence bands

Figure 15. Kaplan-Meier estimates for DAAs treatment initiation by liver disease condition with 95% Hall-Wellner confidence bands
In the Cox proportional hazards regression analysis, we included the hypothesized interaction terms of age, insurance type, and liver disease condition plus all other covariates. To fit the best model, we followed a backward elimination strategy to include the significant interactions only, we also excluded the age group of patients born before 1945 where only two patients initiated treatment. The final model (table 2a and 2b) fit statistics showed that Akaike’s Information Criterion (AIC) for intercept and covariates is lower (AIC = 2193.189) than the initial model (AIC = 2221.310).
Tables 2a and 2b. Estimates from the final Cox proportional hazards regression model for the characteristics of the Kentucky Clinic hepatitis C patients

2a

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>P-Value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Substance Abuse</td>
<td>1</td>
<td>-0.00807</td>
<td>0.15545</td>
<td>0.0027</td>
<td>0.9586</td>
<td>0.992</td>
<td>0.731 1.345</td>
<td>No history of substance abuse</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>0.03615</td>
<td>0.15631</td>
<td>0.0535</td>
<td>0.8171</td>
<td>1.037</td>
<td>0.763 1.408</td>
<td>Female</td>
</tr>
<tr>
<td>Follow-up at least one visit</td>
<td>1</td>
<td>3.97326</td>
<td>0.71312</td>
<td>31.0435</td>
<td>&lt;.0001</td>
<td>53.157</td>
<td>13.139 215.066</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Fayette County Residency</td>
<td>1</td>
<td>0.09086</td>
<td>0.19298</td>
<td>0.2217</td>
<td>0.6377</td>
<td>1.095</td>
<td>0.750 1.599</td>
<td>Non-Fayette county residency</td>
</tr>
<tr>
<td>African American</td>
<td>1</td>
<td>0.26653</td>
<td>0.25386</td>
<td>1.1023</td>
<td>0.2938</td>
<td>1.305</td>
<td>0.794 2.147</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Asian or Unreported Race</td>
<td>1</td>
<td>0.07336</td>
<td>1.01640</td>
<td>0.0052</td>
<td>0.9425</td>
<td>1.076</td>
<td>0.147 7.889</td>
<td>Caucasian</td>
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<tr>
<td>Combined Genotype</td>
<td>1</td>
<td>0.00175</td>
<td>0.52416</td>
<td>0.0000</td>
<td>0.9973</td>
<td>1.002</td>
<td>0.359 2.799</td>
<td>Single genotype</td>
</tr>
<tr>
<td>Chosen Primary Provider</td>
<td>1</td>
<td>-0.07425</td>
<td>0.18038</td>
<td>0.1695</td>
<td>0.6806</td>
<td>0.928</td>
<td>0.652 1.322</td>
<td>All other primary providers</td>
</tr>
<tr>
<td>Unknown Referring Provider</td>
<td>1</td>
<td>-0.19755</td>
<td>0.37543</td>
<td>0.2769</td>
<td>0.5987</td>
<td>0.821</td>
<td>0.393 1.713</td>
<td>All other referring providers</td>
</tr>
</tbody>
</table>

*Significant values at alpha level of 0.05 and Confidence Limits not including the null value i.e. 1, are in bold.*
### Hazard Ratios for Insurance Types vs. Age Groups at Advanced Liver Disease Stage

<table>
<thead>
<tr>
<th>Description</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare vs. Medicaid baby boomers (born 1945-1965)</td>
<td>1.703</td>
<td>1.079 - 2.688</td>
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<tr>
<td>Medicare vs. Private and Other Insurance baby boomers (born 1945-1965)</td>
<td>0.727</td>
<td>0.432 - 1.223</td>
</tr>
<tr>
<td>Medicaid vs. Private and Other Insurance baby boomers (born 1945-1965)</td>
<td>0.427</td>
<td>0.267 - 0.682</td>
</tr>
<tr>
<td>Medicare vs. Medicaid patients born after 1965</td>
<td>5.055</td>
<td>2.356 - 10.846</td>
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<tr>
<td>Medicare vs. Private and Other Insurance patients born after 1965</td>
<td>1.384</td>
<td>0.588 - 3.258</td>
</tr>
<tr>
<td>Medicaid vs. Private and Other Insurance patients born after 1965</td>
<td>0.274</td>
<td>0.131 - 0.573</td>
</tr>
</tbody>
</table>

### Hazard Ratios for Insurance Types vs. Age Groups at Mild Liver Disease Stage

<table>
<thead>
<tr>
<th>Description</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare vs. Private and Other Insurance baby boomers (born 1945-1965)</td>
<td>1.709</td>
<td>0.740 - 3.944</td>
</tr>
<tr>
<td>Medicaid vs. Private and Other Insurance baby boomers (born 1945-1965)</td>
<td>0.380</td>
<td>0.164 - 0.881</td>
</tr>
<tr>
<td>Medicare vs. Private and Other Insurance patients born after 1965</td>
<td>3.252</td>
<td>1.349 - 7.843</td>
</tr>
<tr>
<td>Medicaid vs. Private and Other Insurance patients born after 1965</td>
<td>0.243</td>
<td>0.117 - 0.508</td>
</tr>
</tbody>
</table>

*Significant values at alpha level of 0.05 and Confidence Limits not including the null value i.e. 1, are in bold.

Adjusting for other covariates, significant Hazard ratio results from the final model (tables 2a and 2b) demonstrated that:

The likelihood of treatment initiation over time at the advanced liver disease stage for the baby boomers (born between 1945 and 1965) on Medicare is 1.7 times that of their age group counterparts on Medicaid (CI 95%, 1.079 - 2.688). Within the same age group and at the same liver disease stage, Medicaid patients possess 0.43 times the likelihood of private and other types of insurance patients (CI 95%, 0.267 - 0.682). For the younger patients born after 1965 and at advanced liver disease stage, the Medicare patients' likelihood for treatment
initiation is 5.06 times those on Medicaid coverage (CI 95% 2.356 - 10.846) who have only 0.27 times the likelihood of private and other insurance patients to initiate treatment (CI 95% 0.131 - 0.573)

On the other hand, the mild liver disease patients' treatment initiation likelihood over time results revealed that baby boomers on Medicare are 4.5 times as likely as Medicaid baby boomers to initiate treatment (CI 95%, 1.079 - 2.688) while Medicaid patients have only 0.38 times the likelihood of private and other types of insurance patients (CI 95%, 0.164 - 0.881). The Medicare patients born after 1965 and at mild liver disease stage have 13.36 times the likelihood of those on Medicaid coverage (CI 95% 6.203 - 28.770) and 3.25 those on private and other types of insurance patients (CI 95% 1.349 - 7.843). These Medicaid patients, at mild liver disease stage and born after 1965, have only 0.24 times the likelihood of private and other insurance patients to initiate treatment (CI 95% 0.117 - 0.508)

The results showed no significant difference in the treatment initiation likelihood over time between Medicare versus private and other types of insurance at any stage of liver disease except the aforementioned likelihood of mild liver disease patients born after 1965.

III- Summary

Multiple interrelated difficulties in accessing the DAAs treatment were found of relevance to the current model of care and patients' characteristics. The treatment initiation journey is long and hindered by complicated stepwise administrative and clinical procedures. Lack of proper communication between the referring facility, the scheduling center, and the HCV clinic is obvious. Moreover, lack of awareness among the patients and their referring provider concerning the treatment initiation procedures add to the difficulty in communication. The administrative and clinical procedures are centered around the PA requirements. Medicaid applied restrictive criteria favoring advanced liver
disease patients which requires a clinical proof difficult to achieve in border line cases between the mild and advanced liver disease stages.

Under the current restrictive PA requirements, the overall rate and characteristics of the patients who initiate treatment are not satisfactory. Disproportionate access to treatment is found among Medicaid patients, younger patients born after 1965, and those with mild liver disease. The time to treatment analysis is consistent with these findings.
CHAPTER 5

IMPLICATIONS FOR PUBLIC HEALTH

I- Discussion

Several barriers to HCV treatment initiation have been identified in the current model of care. Referral and scheduling are strictly administrative in nature lacking adequate clinical information, reflecting the patient’s needs, leading to a potential inadequate preparation before the first visit to the Kentucky Clinic HCV services.

Moreover, there is an obvious inadequate communication between the Patient Access Center and the Kentucky Clinic during the scheduling process compounded by the geographical distance between the two facilities. In addition, the waiting time for the first visit at the Kentucky Clinic is long. From the patient side, several factors favor non-compliance with the scheduled appointment plus the possibility of cancellation by the HCV specialist.

On the patient first visit at the HCV clinic, lack of patient awareness about the disease and the DAAs treatment clinical and administrative procedures are major obstacles. This barrier was underscored elsewhere as one of the major barriers to treatment (Grebely, Oser, Taylor, & Dore, 2013). Moreover, the referring provider in most cases is not aware of these procedures at the Kentucky Clinic adding to the inadequate preparation problem. The San Francisco safety net healthcare system experience offers an opportunity to overcome this obstacle through mandatory educational training for the patients prior to the clinical assessment for the DAAs treatment initiation (Lubega, Agbim, Surjadi, Mahoney, & Khalili, 2013).

Deficient linkage to care and patient education have been addressed collectively in several contexts through a patient navigation system (Ford, Johnson, Desai, Rude, & Laraque, 2016) which is lacking in the Kentucky Clinic.
although the specialist pharmacist and the case manager offer navigation roles in a limited part of the patient journey particularly inside the clinic.

In fact, several questions for a successful and context specific patient navigation system require answers. First, when and how to start this system, should it be at the point of referral or earlier at the point of discovery which can be driven by an active screening program? A comprehensive navigation system using mobile clinics for screening, linkage, and continuation of care throughout the journey to treatment initiation showed successful results in answering this question (Trooskin et al., 2015). Mobile clinics were proven effective in discovering patients in high prevalence remote areas and linking them to standardized DAAs treatment (Morano et al., 2014).

Second, who should be assigned this role? Social workers and community health workers has been assigned patient navigation roles where the latter were chosen from local communities to ensure cultural acceptance (Ford et al., 2016; Ramirez et al., 2016). In some models of patient navigation, this role is assigned to a counseling psychologist to accommodate patients practicing risky behaviors; e.g., IDU, or those incarcerated (Allison et al., 2016; Seña et al., 2016).

Third, what should these navigators offer? Comprehensive services based on the patients’ needs and including a fundamental educational component is appropriate, but its implementation requires personalization of these services. A patient needs assessment has been utilized as the first tool in the navigation process and showed successful results in elevating treatment initiation rates (Glick, Armstrong, Tobin, & Allgood, 2016). In general terms, the more comprehensive the navigation model is, the better the results (Linas et al., 2014).

Adding to the improper education and preparation obstacles, laboratory and radiological investigations performed outside the Kentucky Clinic requires time for retrieval in order to reach the patient’s record. In parallel, clinical procedures to prepare the patient are complex especially for proving a condition
of advanced liver disease in order to comply with Medicaid PA requirements. The second visit of the patient, which is intended to finalize the PA requirements, is usually scheduled far from the first visit, one important cause of this delay is the time needed for completion of laboratory and radiological investigations. Insurers have variable approval requirements; the Medicaid program is the most demanding and restrictive. However, even within Medicaid, insurers are variable in their flexibility and acceptance of advanced liver disease evidence. In case the PA request is disapproved, another lengthy appeal process adds to the patient’s delay in initiating treatment.

The health information system within the Kentucky Clinic is well established and efficient; however, data linkage to other healthcare facilities including the referral facilities could offer greater support to the linkage and continuity of care needs and overcome the delay in arrival or inability to retrieve the laboratory and radiological studies done outside the Clinic. Data linkage offered successful results in this area connecting substance abuse programs with specialized HCV services (Hochstatter et al., 2017). Speeding up the PA process and the possible appeal process at the Kentucky Clinic should benchmark with the pharmacy students-based model that offered excellent support to the specialist pharmacists and improved the PA process overall (Martin, Telebak, Taylor, & Volozhina, 2016).

In addition to the within model of care obstacles, integration with other services is not provided. Integration of services is a cornerstone for a successful and comprehensive model of care and is based on the patient centered health services principle. The ideal integration approach is holistic in nature including HCV supportive services; e.g., the patient navigation system and educational programs, in addition to other services outside the HCV services based on the patient’s needs (Allison et al., 2016; US Department of Health and Human Services, 2011). Best practices evidence expanded the integrated services to involve other social services as well (Maier, Ross, Chartier, Belperio, & Backus, 2016). To implement this approach, a multidisciplinary team of providers was
employed in several contexts including HCV, HIV, and substance abuse providers (Bruggmann & Litwin, 2013; Butner et al., 2017). The best setting to initiate and coordinate this integrated approach is at the place where the patient accesses his/her health services and the most accessible facility for him/her; e.g., a primary care or substance abuse management facility (Akyar et al., 2016; Bruggmann & Litwin, 2013; Jayasekera et al., 2017; Zeremski et al., 2013).

Similar to this integration approach, the task shifting principle should be implemented for improvement of treatment initiation rates in Kentucky. This answers a potential question: who should coordinate the integrated services and manage HCV using the DAAs? The primary provider is the most convenient and is best positioned to offer the HCV DAAs-based therapy (Pawlotsky, Feld, Zeuzem, & Hoofnagle, 2015; Thornton et al., 2016).

The quantitative results revealed that less than one quarter (22.16%) of the patients in this study cohort initiated treatment during the observation period after referral. This proportion is comparable to the estimates for the proportion of patients who initiated treatment among those referred to care at the national level which ranged from 18.33% to 30% (Holmberg, Spradling, Moorman, & Denniston, 2013). However, the Kentucky Clinic initiation rates are lower than another national treatment initiation estimate pointing to a percentage between those who were prescribed treatment (58.35%) and those who achieved SVR (34.30%) out of the total patients with a confirmed HCV RNA test (Yehia, Schranz, Umscheid, & Lo Re, 2014). Chhatwal et al. (2016) estimated that the 2015 the national treatment initiation rate was about 33.34% of those theoretically prepared for referral, given their HCV status awareness and insurance coverage. This lower estimate is still higher than our study results. Moreover, our results are lower than the 2013 VHA results which determined that 24.5% of the patients linked to care initiated treatment; probably IFN-based therapy (Meyer et al., 2015) and was close to the homeless veterans’ initiation rate (22.9%) (Noska, Belperio, Loomis, O’Toole, & Backus, 2017). Check hep-C
2012-2013 multicenter initiation rates are higher than our results as well (29.8%) (Ford et al., 2017).

Racial groups distribution in this study’s participants reflects the predominant Caucasian population in Kentucky. However, only 20.66% of the Caucasians initiated treatment compared to 45.45% of the African American participants. This result is the inverse of the initiation rate favoring Caucasians in other studies (Kanwal et al., 2016; Vutien, Hoang, Brooks, Nguyen, & Nguyen, 2016).

Our study results demonstrated a predominance of young HCV patients; 63.86% of all participants were born after 1965. This finding is higher than the New York City Check HepC Program distribution which showed only 55% born after 1965 (Ford et al., 2017).

The insurance coverage distribution of our study participants showed that Medicaid had the highest proportion (73.3%), which contrasts with the 2015 finding that revealed that Medicaid patients who had HCV infection represented 24% of all insurance types (Chhatwal et al., 2016). Moreover, the initiation rate among the current study Medicaid patients is obviously low (14.26%) compared to Medicare (49.55%), and private and other types of insurance patients (38.52%).

The distribution of age group, insurance type, and liver disease condition characteristics of the whole study cohort showed an obvious discrepancy from the characteristics of the patients who initiated treatment. The youngest group of patients, born after 1965, comprised almost two thirds of the whole cohort but only one third of those who initiated treatment. The Medicaid patients who comprised three quarters of the cohort represented less than half of the patients who initiated treatment. Similar to the age group pattern, mild liver disease patients represented two third of the whole cohort, but less than one third of the treatment initiation patients.
Consistent distribution of the entire cohort and the patients who initiated treatment characteristics were found. Higher proportions of treatment initiation were found in males, non-Fayette residents, patients with a single genotype of HCV, and patients with history of substance abuse.

Given the high proportion of patients with history of substance abuse among the study participants (72.95%), their higher initiation rate does not reflect greater privilege for treatment initiation since their proportion compared to their group total is only 18.85%, whereas those without a history of substance abuse who initiated treatment represented 31.1% of the group total. The same concept applies to the patients who reside far from the Kentucky Clinic and reflects the predominance of HCV in the Appalachian Mountains in southeast Kentucky.

Time to treatment initiation results are consistent with the long waiting time found in the model of care results. The average time to treatment initiation is 263.57 days. The cumulative incidence of treatment initiation showed a higher rate in the first half of the incidence curve compared to the second half. Univariate analysis using Kaplan-Meier time to treatment initiation estimates showed significant earlier treatment among males, African Americans, patients who followed-up at least once, and patients without a history of substance abuse. The disproportionate treatment initiation achievement among the patients born before 1965 was inconsistent under Medicaid coverage and with mild liver disease; patients showed significantly later treatment initiation at different points of time. Bivariate analysis of insurance and liver disease condition showed that Medicaid patients with mild liver disease had the lowest chance for treatment initiation at different time points compared to other groups.

The cox model significance results confirmed the previous results on age group, insurance type, and liver disease condition. Medicare baby boomers have almost double and more than quadruple the likelihood of Medicaid baby boomers to initiate treatment at advanced and mild liver disease stages respectively. This likelihood jumps to five and thirteen times respectively on comparing patients born after 1965 with the same characteristics. Likewise, Medicaid baby boomers
have less than half the likelihood of private and other insurance patients to initiate treatment at either disease stages. In parallel, the Medicaid patients born after 1965 have nearly quarter the likelihood of private and other insurance patients to initiate treatment at either disease stage. The only significant likelihood difference between Medicare and private and other types of insurance was found among mild liver disease patients born after 1965 where the former group are three times as likely as the latter group to initiate treatment.

II- Conclusion

This study provides a comprehensive view and analysis of the interrelated barriers to the DAAs treatment initiation at the Kentucky Clinic. These barriers do not exist neither in isolation from each other nor from their influencing factors. The main current model of care obstacles include: lack of proper preparation of patients for the DAAs treatment administrative and clinical processes; lack of communication between the three facilities: the referring, the scheduling, and the HCV treatment facility; including long waiting times and lengthy processes. In general, the HCV treatment services are broken and not properly connected with other services needed by HCV patients.

Collectively from the quantitative results, the current profile of the least privileged patients reveals that accessing the DAAs treatment is poor among patients: on Medicaid, born after 1965, with mild liver disease condition, with a history of substance abuse, and those residing in remote areas.

Accordingly, we reject both null hypotheses since the current model of care possess different barriers hindering treatment initiation and the characteristics of the patients who initiate treatment are significantly different from the patients who do not.

To this end, addressing the identified barriers is important for readjusting the current model of care in order to accommodate the needs of the Kentucky Clinic patients.
III- Recommendations

The study results emphasize the need for collective actions to improve access to DAAs treatment in Kentucky. All such efforts must be situated within a patient centered comprehensive model of care (figure 17).

The cornerstone for effective linkage to care is a well-established patient navigation system. This proposed system should engage the patients at the earliest stage of the disease and where he/she lives. Screening and linkage to care should be active rather than the most common accidental discovery. Using mobile clinics to access difficult to reach populations with a high HCV prevalence rate in the Appalachian Mountains could provide a solution for linking geographically disadvantaged patients to the standardized DAAs treatment. However, the expected driven demand should be met by a responsive and well prepared supply side.

A fundamental point is that the navigation system works by improving linkage and continuity of care in a comprehensive manner. The patient navigator could be a social worker, community health worker, or a counseling psychologist based on the patient’s geographical, cultural, and behavioral needs. The navigation should commence with a patient needs assessment to ensure success. The role of the patient navigator is crucial in providing necessary education to patients about the disease and the treatment processes. In parallel, understanding how patients perceive the value and procedures of HCV treatment is necessary to tailor a Kentucky specific educational curriculum for the patients. In addition, these navigators could play an important role in increasing awareness among the referral facilities about the administrative and clinical procedures required for the DAAs treatment approval. Training health services providers at all possible points for the discovery of HCV with special focus on the referring providers in Kentucky should be the ultimate goal.
Figure 17. Proposed patient centered comprehensive model of care to improve access to hepatitis C virus directly acting antivirals treatment in the Kentucky Clinic
There is potential to build an integrated healthcare model centered on the patient’s needs. Basically, this model should include all services required by the patient; e.g., primary care and substance abuse services. The starting point should be the most convenient and the natural access point for the patients. The multidisciplinary team engaged in initiating treatment should act together; however, the primary provider is positioned best to carry out the coordinating role. Moreover, the primary care services in an ideal model to provide HCV treatment by applying the task shifting approach. Finally, social services; e.g., housing and transportation, could be woven into the integrated model to ensure success.

Administrative support for the HCV clinic at the Kentucky Clinic should employ a data linkage information system with other facilities to ensure continuity of care and to speed up the treatment initiation process. Special support for the PA process can be provided by pharmacy students to speed it up and help improve the PA approval rates.

HCV treatment services should prioritize the least privileged patients to initiate treatment. Allocation of resources and efforts should focus on: young HCV patients living in Kentucky’s southeastern Appalachian Mountains, Medicaid patients, patients with mild liver disease, and those involved in substance abuse.

Finally, investment in patient centered applied research to identify other barriers not covered in this study, with special consideration to the patients’ acceptance and geographical access dimensions is important. The overall picture can help fill in pieces that are arguably missing in the study results.

IV- Summary

HCV chronic infection is a major public health problem in Kentucky with particular relevance to the drug abuse epidemic in the Appalachian Mountains.

In parallel, there is an unprecedented advancement in the history of HCV control with the availability of highly effective DAAs. On condition that an effective
access to the DAAs can be reached, HCV infection is almost a curable disease. Additionally, the curative solution offered by the DAAs for HCV chronic infection is a real benefit to the public’s health by preventing further infections and reducing the risk of the negative health and economic outcomes from liver disease. DAAs treatment initiation is not only a major public health problem in Kentucky, but also a health equity and social justice issue.

However, access to treatment in the Kentucky Clinic is hindered by a variety of barriers revolving mainly around the model of care, which is greatly influenced by the insurance system. In addition, chronic HCV is strongly stigmatized by both the society and the healthcare system. This stigma is reflected in the restrictive PA requirements particularly for the patients who are involved in injection drug use.

In conclusion, access to DAAs’ treatment initiation is too complex to be solved by reducing their prices alone; structural adjustment for the model of care and prioritizing the disproportionately affected groups of patients by HCV infection is needed as well. Therefore, timely treatment with DAAs addressing the current model of care barriers and patients’ characteristics based restrictions should be a priority to improve the public’s health in Kentucky. This study makes suggestions to improve access to HCV treatment initiation by proposing a patient centered comprehensive model of care.
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https://doi.org/10.3748/wjg.v19.i44.7846
APPENDIX 1
Hepatitis C Treatment Prior Authorization Request Form 1

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<td>Patient's Phone Number:</td>
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<table>
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<th>Medication Information</th>
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<tbody>
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<tbody>
<tr>
<td>Medication &amp; Strength:</td>
</tr>
<tr>
<td>Directions:</td>
</tr>
<tr>
<td>Quantity:</td>
</tr>
<tr>
<td>Refills:</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Medication Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication &amp; Strength:</td>
</tr>
<tr>
<td>Directions:</td>
</tr>
<tr>
<td>Quantity:</td>
</tr>
<tr>
<td>Refills:</td>
</tr>
</tbody>
</table>

Physician Signature*: ___________________________ Date: __________

*By signing above the physician is providing a prescription that can be used to facilitate dispensing and/or coordination of delivery for the requested medication.

Clinical Information: Documentation from the medical record including test results, lab reports, medication history must be submitted to support answers below. The genotype report, fibrosis level report and negative urine toxicology screen(s) MUST be provided or the prior authorization cannot be processed.

1. Does the patient have a diagnosis of chronic hepatitis C? [ ] Yes [ ] No

2. What genotype does the patient have? (Submit lab results from the past 6 months with PA Request) 1 2 3 4 5 6

3. If a subtype was detected please note here (e.g. a,b,c): __________

4. Is the medication prescribed by a specialist (i.e. gastroenterologist, hepatologist, or infectious disease)? [ ] Yes [ ] No

5. Is the patient treatment naive? (If yes, skip to question 11) [ ] Yes [ ] No [ ] Unsure

6. Is this a request to extend or continue therapy from another plan? [ ] Yes [ ] No

7. Has the patient been previously treated with a sofosbuvir-based regimen (Sovaldi, Harvoni)? [ ] Yes [ ] No

8. Has the patient been previously treated with an oral protease inhibitor (Incivek, Victrelis, or Olysio)? [ ] Yes [ ] No
APPENDIX 2

Hepatitis C Treatment Prior Authorization Request Form 2

**Passport Health Plan Prior Authorization**

**Hepatitis C Therapy**

*Note: Form must be completed in full. An incomplete form may be returned.*

*Information on this form is protected health information and subject to all privacy and security regulations under HIPAA*

<table>
<thead>
<tr>
<th>Patient Last Name:</th>
<th>Patient First Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatitis C co-infected:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If YES, HIV Viral Load:</td>
<td>IU/mL</td>
<td>or Copies/mL</td>
</tr>
<tr>
<td>Lab Date:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the member at least 18 years old?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation?</td>
<td>Not indicated</td>
<td>Yes</td>
</tr>
<tr>
<td>If yes, please specify regimen and duration:</td>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Did member complete previous treatment?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>If no, please provide documentation why therapy was discontinued or not completed:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the member currently receiving therapy with any of the following (check all that apply):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>LowaLi</td>
</tr>
</tbody>
</table>

**Does member have chronic HCV with cirrhosis?**

| Yes | No |
| Compensated | Decompensated |

**Does the member have hepatocellular carcinoma?**

| Yes | No |
| METAVIR Score: |

**Please provide documentation (attached to request) of liver biopsy result OR at least 2 of the following:**

- Ultrasound based transient elastography score: Date: 
- Fibroscan score: Date: 
- Other tests for fibrosis: Date: 
- Genotyping results: Date: 
- Other documentation: Date: 

**Does member have chronic HCV with cirrhosis?**

| Yes | No |
| Compensated | Decompensated |

**Does the member have hepatocellular carcinoma?**

| Yes | No |
| METAVIR Score: |

**Please provide documentation (attached to request) of liver biopsy result OR at least 2 of the following:**

- Ultrasound based transient elastography score: Date: 
- Fibroscan score: Date: 
- Other tests for fibrosis: Date: 
- Genotyping results: Date: 
- Other documentation: Date: 

**Member has been evaluated for current history of substance abuse and alcohol:**

- AUDIT C | Yes | No |
- GAGE | Yes | No |
- NDAX drug screening tool | Yes | No |
- Other: | Yes | No |

**Member has history of substance abuse and alcohol abuse within past 6 months:**

| Yes | No |
| If history within past 6 months, member has completed/lip participating in: |
| Recovery Program | Counseling Services |

**Name of program/service specialist:**

**Is member committed to continuing to abstain from use of alcohol and illicit drugs during HCV treatment?**

| Yes | No |
| Urine/laboratory toxicology screen results (attach with request): |

**For continuation of therapy beyond week 12, HCV RNA titer from treatment week 4 must be submitted and prescriber must attest to substance abuse criteria (see box #19) for renewal of therapy. If indicated for treatment duration beyond 12 weeks, HCV RNA titers must be submitted every 8 weeks for continuation of treatment.**

**PHYSICIAN’S SIGNATURE:**

**PHYSICIAN’S SPECIALTY:**

**DATE:**
APPENDIX 3

Hepatitis C Treatment Prior Authorization Appeal Form

Appeals Department
RE: Request for Appeal of Case ID ______________________

Date: ______________________

To Whom It May Concern:

I, ______________________ (DOB ______________________),

ID# ______________________) give my prescriber,

______________________________, permission to represent me in the prior
authorization appeals process for ______________________, which was
originally denied on ______________________. Please contact the prescriber’s office at
859.218.1885 or fax them at 859.257.3089 with any questions, and thank you for your
consideration.

Regards,

X ______________________ (pt signature)
# APPENDIX 4

## Hepatitis C Treatment Order

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prescription Orders (28 day supply)</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daklinza 60mg (Daclatasvir)</td>
<td>□ Take 60mg PO QD</td>
<td>QS</td>
</tr>
<tr>
<td>Epclusa (Sofosbuvir/Velpatasvir)</td>
<td>□ Take 400/100 mg (1 tablet) daily with or without food</td>
<td>QS</td>
</tr>
<tr>
<td>Resistance Test for GT3 cirrhosis</td>
<td>□ No resistance found □ Resistance</td>
<td></td>
</tr>
<tr>
<td>Harvoni (Sofosbuvir/Ledipasvir)</td>
<td>□ Take 400mg/90mg (1 tablet) QD with or without food</td>
<td>QS</td>
</tr>
<tr>
<td>Ribavirin 200mg</td>
<td>□ Take ___ mg QAM and ___ mg QPM □ Weight based □ Reduced Dose D/T</td>
<td>QS</td>
</tr>
<tr>
<td>Sovaldi 400mg (Sofosbuvir)</td>
<td>□ Take 400mg PO QD with or without food</td>
<td>QS</td>
</tr>
<tr>
<td>Viekira Pak (Grazoprevir/Pibrentasvir/Foxivic/Asunaprevir)</td>
<td>□ Take 25/150/100 mg (2 tablets) PO QAM and 250mg BID with food</td>
<td>QS</td>
</tr>
<tr>
<td>Zepatier (elbasvir/grazoprevir)</td>
<td>□ Take 50mg/100mg (1 tablet) QD with or without food</td>
<td>QS</td>
</tr>
<tr>
<td>Resistance Test for GT1a</td>
<td>□ No resistance found □ Resistance</td>
<td></td>
</tr>
</tbody>
</table>

## Clinical Information

<table>
<thead>
<tr>
<th>Diagnosis: □ B18.2 Chronic HCV □ No HIV Co-infection</th>
<th>Pregnancy Factors:</th>
<th>Diagnosis Date:</th>
<th>1. UDS/UAS? □ Yes □ No Date: Result:</th>
<th>2. UDS/UAS? □ Yes □ No Date: Result:</th>
<th>3. UDS/UAS? □ Yes □ No Date: Result:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Viral Load: Hemoglobin: Platelets: ALT: AST:</td>
<td>Results date:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously treated? □ Yes □ No Previous TX utilized:</td>
<td>Response:</td>
<td>Dates of Tx:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis Test #1 □ Yes □ No Date:</td>
<td>Fibrosis Score: Cirrhosis? □ Yes □ No</td>
<td>Decompensated DSX? □ Yes □ No</td>
<td>Genotype: CTP Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis Test #2 □ Yes □ No Date:</td>
<td>Fibrosis Score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height: Weight: Wt in Kg: Tranplant? □ Pre □ Post □ N/A If yes, Date:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Insurance Information

<table>
<thead>
<tr>
<th>Primary Insurance:</th>
<th>Secondary Insurance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy:</td>
<td>Group:</td>
</tr>
<tr>
<td>Phone:</td>
<td>BIN:</td>
</tr>
</tbody>
</table>

DDIs with HCV tx? □ Yes □ No Pharm Initial _______ Med list updated and accurate? □ Yes □ No Patient Initial: _______ PPI Use: Dose: _______ Reason: _______ Able to decrease to omeprazole 20 mg or d/c? □ Yes □ No If TX Denied, Appeal? □ Yes □ No Additional Pertinent Information:
APPENDIX 5
Hepatitis C Treatment Initiation Form

HEPATITIS C TREATMENT

PATIENT: _______________________
MIN: _______________________

PROVIDER: _______________________
THERAPY START DATE: _______________________

LENGTH OF TREATMENT: ___________ weeks PRESENT DURING TEACHING: □ Patient □ Significant Other □ Family □ Other

TREATMENT INITIATION CHECKLIST:

☐ Patient Education and Support Materials Provided

☐ Potential Side Effects
  • Fatigue – Drink plenty of water
  • Headache – Can take up to 2000mg of Tylenol daily
  • Nausea – Take food with meds
  • Skin reactions – dry, itchy skin, rash, redness
  • Trouble sleeping

☐ Pregnancy and Contraception
  • Monthly negative pregnancy test

  • 2 forms of contraception (not hormonal birth control)
  • Female partners of male patients
  • Pregnancy Registry: 1-800-526-6367

☐ Labs and Follow-up Appointments
  • Appointment dates
  • Lab dates and appointment calendar provided

☐ Lab Location: ___________________________________________________________

☐ Take Medication to hospital if admitted.

TREATMENT MEDICATIONS:

☐ Daklinza (Daclatasvir)
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • One tablet taken once daily with or without food

☐ Epclusa (Sofosbuvir/Velpatasvir)
  • Dose #1 ________________________ AM/PM
    • One tablet taken once daily with or without food

☐ Harvoni (Ledipasvir and Sofosbuvir)
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • One tablet taken once daily with or without food

☐ Ribavirin
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • Take __________ tablets daily in the morning
  • Dose #2 ________________________ AM/PM
    • Take __________ tablets daily in the evening

☐ Sovaldi (Sofosbuvir)
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • One tablet taken once daily with or without food

☐ Technivie
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • Two tablets with food

☐ Viekira Pak
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • Two pink and one brown tablet daily in the morning with food (3 tablets total)
  • Dose #2 ________________________ AM/PM
    • One brown tablet daily in the evening with food

☐ Zepatier (Vibasvir/Grazoprevir)
  • Store at room temperature 77 F
  • Dose #1 ________________________ AM/PM
    • One tablet taken once daily with or without food

I have read, understand, and have been provided with a copy of this form.

_________________________________________________________ [patient signature]

_________________________________________________________ [healthcare provider signature]

_________________________________________________________ [date]
APPENDIX 6

Patient Hepatitis C Treatment Agreement Form

University of Kentucky GI Health Program
740 S. Limestone St, D268
Lexington, KY 40536
Phone: 859.323.0079 Fax: 859.257.0520

Member Treatment Agreement- Hepatitis C Medicine

I, ______________________________________, have talked to my provider about taking Hepatitis C medicine. I understand and agree to the following:

- I will take ______________ (drug) starting on __________ (date). I will take this medicine __________ (Sig) for ______ (§) weeks.
- If I do not treat Hepatitis C, it could get worse, and I could develop cirrhosis, liver cancer, or liver failure.
- There are risks and possible side effects linked to taking this medicine. I have talked to my provider about the risks and benefits. I agree to follow the therapy as instructed by my provider.
- I've had the chance to ask questions about Hepatitis C, other treatment options, and the risk of treatment. I have enough information to understand my treatment.
- There are no promises that this medicine will cure Hepatitis C.
- Received medicine counseling, education, and training. This includes discussion about medication interactions and medications that may worsen my condition. This will also include discussion about the importance of appropriate contraception during and for 6 months after treatment.

To help make my treatment a success, I agree to:

- Take my medicine as ordered unless my doctor stops the medicine.
- Go to all of my follow-up visits.
- Take any lab tests my doctor orders to see if the medicine is working.
- Take any alcohol or drug tests my doctor orders. I know that taking alcohol and drugs could make my treatment less effective and make my Hepatitis C worse.

By signing here, I agree to ALL of the bullet points on this page.

Signature: ____________________________

Date: ________________________________

Prescriber's signature: ____________________

Date: ________________________________
## APPENDIX 6

### Patient Appointments Schedule Form

**Appointments and Labs**

Your appointments will be with the following provider: ____________________________  
Please alert Tonia Carr, RN at (859) 323-0079 if you cannot keep any of your appointments.

<table>
<thead>
<tr>
<th>Days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>__</td>
<td></td>
</tr>
<tr>
<td>__</td>
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</tbody>
</table>

Please note the provider appointments and lab visits listed. These are very important dates and are chosen to coincide with crucial time points in your therapy. These are not optional! These labs let your provider know how you are doing on the inside, regardless of how you feel on the outside. Please post this calendar somewhere readily visible. You are responsible for getting your labs done on time and getting to your scheduled appointments!

### 2016

<table>
<thead>
<tr>
<th>January</th>
<th>February</th>
<th>March</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 S M T W F S</td>
<td>2 2 2 4 5 6</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>1 2 3 4 5 6 7</td>
<td>2 3 4 5 6 7</td>
<td>8 9 10 11 12 13 14</td>
</tr>
<tr>
<td>8 9 10 11 12 13 14</td>
<td>15 16 17 18 19 20 21</td>
<td>22 23 24 25 26 27 28</td>
</tr>
<tr>
<td>10 11 12 13 14 15 16</td>
<td>17 18 19 20 21 22 23</td>
<td>24 25 26 27 28 29 30</td>
</tr>
<tr>
<td>7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31</td>
<td></td>
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### April

<table>
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</tr>
<tr>
<td>15 16 17 18 19 20 21</td>
<td>22 23 24 25 26 27 28 29 30</td>
</tr>
<tr>
<td>23 24 25 26 27 28 29 30 31</td>
<td></td>
</tr>
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</table>

### July

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<tbody>
<tr>
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</tr>
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<td>15 16 17 18 19 20 21</td>
<td>22 23 24 25 26 27 28 29 30</td>
</tr>
<tr>
<td>23 24 25 26 27 28 29 30 31</td>
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</table>

### October

<table>
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<tbody>
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<td>8 9 10 11 12 13 14</td>
</tr>
<tr>
<td>15 16 17 18 19 20 21</td>
<td>22 23 24 25 26 27 28 29 30</td>
</tr>
<tr>
<td>23 24 25 26 27 28 29 30 31</td>
<td></td>
</tr>
</tbody>
</table>

**☐ Labs and Appointments at UK**  **☐ Labs Only (Can be done locally)**
**Hepatitis C Patient Follow-Up and Treatment Outcomes Spreadsheet**

<table>
<thead>
<tr>
<th>WEEK (scheduled)</th>
<th>Screen</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>16</th>
<th>20</th>
<th>32</th>
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<tbody>
<tr>
<td>DATE (scheduled)</td>
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<tr>
<td>WEEK (actual)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATE (actual)</td>
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<td></td>
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</tr>
</tbody>
</table>

| Harvoni          |        |          |   |   |   |   |   |   |    |    |    |

| HCV RNA          |        |          |   |   |   |   |   |   |    |    |    |
| WBC              |        |          |   |   |   |   |   |   |    |    |    |
| Hemoglobin       |        |          |   |   |   |   |   |   |    |    |    |
| Platelets        |        |          |   |   |   |   |   |   |    |    |    |
| AST              |        |          |   |   |   |   |   |   |    |    |    |
| ALT              |        |          |   |   |   |   |   |   |    |    |    |
| Alkaline Phosphatase |   |          |   |   |   |   |   |   |    |    |    |
| Bilirubin        |        |          |   |   |   |   |   |   |    |    |    |
| K                |        |          |   |   |   |   |   |   |    |    |    |
| Creat            |        |          |   |   |   |   |   |   |    |    |    |
| Asparate         |        |          |   |   |   |   |   |   |    |    |    |
| Albumin          |        |          |   |   |   |   |   |   |    |    |    |

| HCV RNA          |        |          |   |   |   |   |   |   |    |    |    |
| WBC              |        |          |   |   |   |   |   |   |    |    |    |
| Hemoglobin       |        |          |   |   |   |   |   |   |    |    |    |
| Platelets        |        |          |   |   |   |   |   |   |    |    |    |
| AST              |        |          |   |   |   |   |   |   |    |    |    |
| ALT              |        |          |   |   |   |   |   |   |    |    |    |
| Alkaline Phosphatase |   |          |   |   |   |   |   |   |    |    |    |
| Bilirubin        |        |          |   |   |   |   |   |   |    |    |    |
| K                |        |          |   |   |   |   |   |   |    |    |    |
| Creat            |        |          |   |   |   |   |   |   |    |    |    |
| Asparate         |        |          |   |   |   |   |   |   |    |    |    |
| Albumin          |        |          |   |   |   |   |   |   |    |    |    |

| Last Name        |        |          |   |   |   |   |   |   |    |    |    |
| First Name       |        |          |   |   |   |   |   |   |    |    |    |
| MRN              |        |          |   |   |   |   |   |   |    |    |    |
| DOB              |        |          |   |   |   |   |   |   |    |    |    |
| Gender           |        |          |   |   |   |   |   |   |    |    |    |
| Race             |        |          |   |   |   |   |   |   |    |    |    |
| Age              |        |          |   |   |   |   |   |   |    |    |    |
| Height           |        |          |   |   |   |   |   |   |    |    |    |
| BMI              |        |          |   |   |   |   |   |   |    |    |    |
| Patient Phone (1)|        |          |   |   |   |   |   |   |    |    |    |
| Patient Phone (2)|        |          |   |   |   |   |   |   |    |    |    |
| Genotype         |        |          |   |   |   |   |   |   |    |    |    |
| Subtype          |        |          |   |   |   |   |   |   |    |    |    |
| Baseline HCV RNA |        |          |   |   |   |   |   |   |    |    |    |
| HCV RNA          |        |          |   |   |   |   |   |   |    |    |    |
| WBC              |        |          |   |   |   |   |   |   |    |    |    |
| Hemoglobin       |        |          |   |   |   |   |   |   |    |    |    |
| Platelets        |        |          |   |   |   |   |   |   |    |    |    |
| AST              |        |          |   |   |   |   |   |   |    |    |    |
| ALT              |        |          |   |   |   |   |   |   |    |    |    |
| Alkaline Phosphatase |   |          |   |   |   |   |   |   |    |    |    |
| Bilirubin        |        |          |   |   |   |   |   |   |    |    |    |
| K                |        |          |   |   |   |   |   |   |    |    |    |
| Creat            |        |          |   |   |   |   |   |   |    |    |    |
| Asparate         |        |          |   |   |   |   |   |   |    |    |    |
| Albumin          |        |          |   |   |   |   |   |   |    |    |    |

| Fibrilosis Overall |    |          |   |   |   |   |   |   |    |    |    |
| AIP              |        |          |   |   |   |   |   |   |    |    |    |
| RBV              |        |          |   |   |   |   |   |   |    |    |    |
| Rib osure        |        |          |   |   |   |   |   |   |    |    |    |
| Fibroscan (GI)   |        |          |   |   |   |   |   |   |    |    |    |
| AIP (Radiology)  |        |          |   |   |   |   |   |   |    |    |    |
| MIB-assay        |        |          |   |   |   |   |   |   |    |    |    |
| Liver Biopsy     |        |          |   |   |   |   |   |   |    |    |    |
| Cirrhosis Imaging|        |          |   |   |   |   |   |   |    |    |    |
| BPD or portal hypertension | |          |   |   |   |   |   |   |    |    |    |
| Decompensation   |        |          |   |   |   |   |   |   |    |    |    |
| CTP Score        |        |          |   |   |   |   |   |   |    |    |    |
| MELD Score       |        |          |   |   |   |   |   |   |    |    |    |
| MD visit (date)  |        |          |   |   |   |   |   |   |    |    |    |
| Physical Exam    |        |          |   |   |   |   |   |   |    |    |    |
| RN contact (date)|        |          |   |   |   |   |   |   |    |    |    |
| Vital Signs (check) |    |          |   |   |   |   |   |   |    |    |    |
| Review Compliance (check) |   |          |   |   |   |   |   |   |    |    |    |
| Missed Dose(s)   |        |          |   |   |   |   |   |   |    |    |    |
| Review Adverse Events (check) |   |          |   |   |   |   |   |   |    |    |    |
| Review Medication (check) |    |          |   |   |   |   |   |   |    |    |    |
| Review Birth Control (check) |   |          |   |   |   |   |   |   |    |    |    |
| Comments         |        |          |   |   |   |   |   |   |    |    |    |

| Other            |        |          |   |   |   |   |   |   |    |    |    |
| Hepatic Encephalopathy |    |          |   |   |   |   |   |   |    |    |    |
| Ascites          |        |          |   |   |   |   |   |   |    |    |    |
| Varicose Bleeding|        |          |   |   |   |   |   |   |    |    |    |
| Treatment Experience |    |          |   |   |   |   |   |   |    |    |    |
| Previous Tx completed?|   |          |   |   |   |   |   |   |    |    |    |
| Interferon       |        |          |   |   |   |   |   |   |    |    |    |
| RBV              |        |          |   |   |   |   |   |   |    |    |    |
| Ribosure         |        |          |   |   |   |   |   |   |    |    |    |
| PolymeraseInhibitor |    |          |   |   |   |   |   |   |    |    |    |
| NS5A Inhibitor   |        |          |   |   |   |   |   |   |    |    |    |
| Protease Inhibitor|        |          |   |   |   |   |   |   |    |    |    |
| Other            |        |          |   |   |   |   |   |   |    |    |    |

| Lab Location     |        |          |   |   |   |   |   |   |    |    |    |
| Lab Phone        |        |          |   |   |   |   |   |   |    |    |    |
| Registration Fax |        |          |   |   |   |   |   |   |    |    |    |
| Lab Fax          |        |          |   |   |   |   |   |   |    |    |    |
| Provider         |        |          |   |   |   |   |   |   |    |    |    |
| Intended Tx Duration (weeks) | |          |   |   |   |   |   |   |    |    |    |
| Birth Control 1  |        |          |   |   |   |   |   |   |    |    |    |
| Birth Control 2  |        |          |   |   |   |   |   |   |    |    |    |
| CAD              |        |          |   |   |   |   |   |   |    |    |    |