Evaluating the Effect of Combining Treatment for Hepatitis C Virus and Intravenous Drug Use to Reduce Hepatitis C Virus Infection Rate

Amen Biru

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Doctor of Health Sciences

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Abstract

Hepatitis C is a virus on the liver that causes damage over several years due to its asymptomatic nature of the disease. HCV progresses from fibrosis to cirrhosis leading to liver damage/cancer. Although HCV affects the liver, it can also affect other organs, such as the digestive, central nervous system and, endocrine and immune systems. The effect of HCV is not only limited to close by organs as it also is responsible for cognitive impairment. Intravenous drug use (IVDU) has been identified as a significant risk factor for HCV infection. Therefore, this review aims to assess whether there is an additive advantage to combining HCV and IVDU treatment rather than providing treatment separately for HCV and IVDU.

Objectives: The primary purpose of this project is to examine and understand the efficacy of treating IVDU and HCV simultaneously to reduce the HCV infection rate in the U.S.

Methodology This systemic literature review used databases including Google Scholar, Scopus, Web of Science, Cochran Reviews, Pub Med, and Education Resources Information Center (ERIC). The research questions presented in this project were answered by following the patient/population, intervention/indicator, comparison, and outcome (PICO) format. Data analysis was conducted using the synthesis matrix system. Toronto & Remington's 2020 integrative review methodology and an appraisal tool, Joanna Briggs Institute (JBI), will be used. There was also a second reviewer to establish an agreement.

Results The findings emphasize the importance of integrating HCV prevention and treatment strategies into primary care settings, expanding access to direct-acting antiviral agents, implementing harm reduction interventions, and utilizing eHealth technologies. The studies highlight the effectiveness of combining HCV treatment with harm reduction programs, such as needle syringe programs and opioid substitution therapy, to reduce HCV transmission and

reinfection rates among IVDUs. The findings also underscore the need for comprehensive approaches that address social determinants and provide ongoing prevention efforts to reduce the burden of HCV infection.

Conclusions Overall, findings suggest that combining harm reduction strategies, HCV treatment, and support services can improve outcomes for IVDUs and reduce HCV transmission. The literature also highlights the importance of addressing barriers to treatment, preventing reinfection, and providing patient-centered care. However, there are gaps in the research, such as the need for long-term outcome studies and research in low-income countries.

Keywords: hepatitis c virus, intravenous drug use, opioid epidemic

Dedication

I dedicate this research project to my beloved father, Amb. Girma Birru, whose unwavering love, guidance, and support have shaped me into who I am today. You have been my pillar of strength, inspiration, and guiding light throughout my academic journey.

Your encouragement and belief in my abilities have driven my pursuit of knowledge and passion for research. You have always been there for me, providing endless support and guidance in every endeavor I undertake. Your wisdom, patience, and understanding have been invaluable, helping me navigate the challenges and obstacles I faced. Your sacrifices and dedication have shown me the true meaning of hard work. You have taught me to dream big, to never settle for mediocrity, and to always strive for excellence in everything I do.

This research project is a testament to the values and lessons you have taught me. Your influence has shaped my intellectual curiosity, determination, and commitment to making a difference through knowledge and innovation.

Thank you, Dad, for being my mentor, supporter, and role model. Your constant belief in me has given me the strength and confidence to overcome any obstacle. I am forever grateful for your love and guidance.

This project is dedicated to you, with all my love and appreciation, as a small token of gratitude for everything you have done and continue to do for me. Your presence in my life is a constant reminder of the power of love and the importance of family. May this research project reflect the values and principles you have instilled in me, and may it be a source of pride for both of us.

Acknowledgement

I would like to express my deepest gratitude and appreciation to the members of my committee for their invaluable guidance, support, and expertise throughout this research project. Their unwavering commitment and dedication have played a critical role in the successful completion of this study.

First and foremost, I would like to extend my heartfelt thanks to Dr. Allison-Jones, my committee chair. Your guidance, wisdom, and encouragement have been instrumental in shaping the direction and focus of this research. Your insightful feedback has greatly enriched the quality of this study. I am truly grateful for your mentorship and leadership. I would also like to extend my sincere appreciation to the members of my committee, Dr. Rubio and Dr. Willeman-Buckelew. Your expertise, constructive criticism, and thoughtful suggestions have significantly contributed to the development and improvement of this research. Your valuable insights and perspectives have broadened my understanding and enhanced the overall quality of this study.

In loving memory of my dear mother Lydia, who is no longer with us, she continues to guide me every day. This research project is a testament to her unwavering support, love, and the unforgettable mark she has left on my life. Your memory will forever reside in my heart, and I will continue to carry your legacy forward with all my ability. I miss you dearly, Mom!

I would like to take a moment to express my heartfelt gratitude and appreciation to my loving husband, Yonathan, and children, Lella, Liyat, and Leul, for their support, understanding, and encouragement throughout this journey. Zerihun, my beloved brother, I thank you dearly for your unwavering love, support, and friendship. You are a true blessing in my life, and I am grateful for every moment we share. To my entire family and friends, thank you for your constant support, understanding, and belief in me.

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List of Abbreviations

BLS …… Bureau of Labor Statistics

CDC…… Centers for Disease Control and Prevention

CMS ……... Centers for Medicare & Medicaid Services

COVID-19 ……...Coronavirus Disease 2019

ERIC ……... Education Resources Information Center

ETR ……. End-of-Treatment Response

HCV……. Hepatitis C Virus

HIV……... Human Immunodeficiency Virus

HRQoL ……..... Health-Related Quality of Life

ICER ……..... Incremental Cost-Effectiveness Ratio

IDF ……... International Diabetes Federation

IRB ……Institutional Review Board

IVDUs……... Intravenous Drug Users

JBI …… Joanna Briggs Institute

NCDAS …… National Center for Drug Abuse Statistics

NIDA …… National Institute on Drug Abuse

NIDDK……. National Institute of Diabetes and Digestive and Kidney Diseases

PCP……... Primary Care Physician

PRISMA ……... Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY ……... Quality-Adjusted Life Years

SVR ……... Sustained Virologic Response

USDHHS ……..... United States Department of Health and Human Services

USHHS ……. United States Health and Human Services

WHO……... World Health Organization

Chapter One

Introduction

Hepatitis C virus (HCV) is considered a silent killer because of the asymptomatic nature of the disease until it causes irreversible damage; as a result, only 19% of those infected globally and 40% in the United States (U.S.) are aware of their diagnosis (Khoja et al., 2021, United States Department of Health and Human Services (USDHHS), 2022). This project is a systemic literature review that aims to assess whether there is an additive advantage to combining HCV and intravenous drug use (IVDU) treatment rather than providing treatment separately for HCV and IVDU. Primarily, HCV is associated with substance abuse and mental health; thus, this review will assess the root cause of HCV prevalence and proposes an appropriate intervention that will focus on addressing an individual's physical, mental, and social well-being.

Background

Health is one of the most important assets we have as human beings. Often being healthy is habitually expressed as "the absence of disease or infirmity" (World Health Organization (WHO), 2022, para. 1). WHO defines being healthy as "a state of complete physical, mental, and social well-being" (WHO, 2022, para. 1). Every human being has a fundamental right to be able to attain and enjoy high standards of health. However, several factors, such as race, religion, socioeconomic status, and political beliefs, stand in the way. Developed countries, such as the U.S., spend significantly on healthcare, yet the population's overall health outcome is considered poor, which does not match the spending (Commonwealth Fund, 2020). Does having sufficient resources solely alleviate health burdens without addressing the root cause of the problem? The large number of funds invested into the U.S. healthcare economy may need to address the underlying causes contributing to poor health outcomes in the population.

The incidence of HCV can be used as an example, where the number of cases reported has continuously grown in the U.S. despite the funding allocated to battle the epidemic. According to the Centers for Disease Control and Prevention (CDC; 2021b), the estimated number of acute HCV infection cases grew from 24,700 in 2012 to 57,500 in 2019. Recent data reveals that the incidence rate of acute HCV infection has increased by 15% from 2019, totaling a 124% rise since 2013, thus making the number of infected individuals 66,700 in 2020 (CDC, 2022). Similarly, the national health expenditure in the U.S. was $4.1 trillion, a growth of 9.7% from 2019 -2020. In contrast, the cost associated with HCV infection is estimated to be $9.1 billion in 2024 (Centers for Medicare & Medicaid Services [CMS], 2021; CDC, 2022). Therefore, it is safe to indicate that sufficient funding is allocated to the healthcare system to reduce the incidence of HCV in the U.S. Although billions of dollars are being allocated to battle the HCV epidemic in the U.S., the infection rate continues to rise. Allocating a portion of the funds to tackle the root cause of the issue might be another avenue to explore for managing the escalating infection rate annually. The number one identified risk for HCV is being an IVDU, so shifting focus to treating IVDUs can potentially address the increasing rate of HCV infection from the root. The primary purpose of this research is to examine and understand the efficacy of addressing the root cause (IVDUs) behind the increasing rate of HCV infection to rising infection rate.

The liver is one of the most vital organs in the human body, and it supports metabolism, digestion, detoxification, and vitamin storage (Kalra et al., 2021). The function of the liver is critical because it plays a vital role in almost every organ system in the body. For instance, the liver interacts with the endocrine and gastrointestinal systems to facilitate digestion and metabolism. In addition, the liver aids by storing iron and copper while also metabolizing sex

hormones and producing proteins that are critical for reproduction (Kalra et al., 2021). Detoxification is another vital role the liver plays in maintaining the body's homeostasis. With detoxification, the liver removes toxic substances from the body by filtering through the sinusoid channels. Infections, autoimmune diseases, genetics, cancer, alcohol, and tobacco consumption can seriously damage the liver. Cirrhosis of the liver can be caused by injury and inflammation, which can lead to scarring, fibrosis, and necrosis. Alcoholism and chronic hepatitis B and C are the major causes of liver disease that start with inflammation and lead to necrosis (Kalra et al., 2021; Khatun & Ray, 2019).

HCV is a bloodborne infection transmitted from person to person through blood contact (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2020). HCV is a positive-stranded RNA virus in the Flaviviridae family (Khatun & Ray, 2019). HCV is classified into seven genotypes with several subtypes. It is spread through contact with an infected person's blood, which can occur by sharing drug needles, having tattoos or piercings done in unauthorized locations, getting an accidental needle stick, having unprotected sex, transmitting from mother to baby, having a history of blood transfusion or organ transplant before July 1992, being incarcerated, being infected with HIV, or any other circumstances that lead to exposure to an infected person's blood and other bodily fluids (CDC, 2020b). Often HCV tends to be asymptomatic, making early detection critical because chronic HCV can progress to liver fibrosis, cirrhosis, liver failure, and liver cancer (NIDDK, 2020).

Despite the significant advances in HCV research and treatment, acute and chronic infection rate has not been declining as expected (Bukh, 2016). The WHO (2021) estimates there are approximately 1.5 million new infections globally yearly, with an additional 58 million

chronic HCV infections. Only 15.2 million are aware of their diagnosis, and the remaining 43 million are undiagnosed.

In the U.S., it is estimated that 2.1–2.2 million individuals are chronically infected with HCV, with baby boomers (born between 1945–1965) accounting for most of the chronic infection (Litaker et al., 2021). However, the CDC (2021b) indicates a significant increase in acute HCV infection among persons aged 20–29 and 30–39 years, shifting the incidence of HCV infections from baby boomers to millennials (Rose et al., 2019). Recent evidence indicates that injecting drugs is the most common risk factor for acute HCV infection in the U.S. The millennial age group (20–39 years) is considered at high risk for injection drug initiation and potential overdose. Researchers believe that the surge in the opioid epidemic may contribute to this shift in demographics because the data reveals that millennials are more at risk for HCV infection than baby boomers.

Often, injection drug users are considered to have poorer overall health conditions when compared to the general population due to barriers resulting from socioeconomic issues such as discrimination, criminalization, and unstable housing (Muncan et al., 2020). Access to care plays a vital role in assisting the journey that has been started to battle the dual epidemic that the nation is facing. Recent data reveals that approximately 10% of those that were affected by alcohol and substance abuse disorder were able to receive treatment in substance abuse disorder treatment centers (National Institute on Drug Abuse [NIDA], 2021). Receiving treatment for substance use disorder requires ready access to care; however, injection drug users who most likely also suffer from mental health issues have difficulty receiving care because these individuals can be categorized as low-income (Lewis et al., 2020). Individuals infected with the HCV virus must

overcome several barriers to seek care; in addition, injection drug users account for most of those affected with HCV, thickening the layer of issues that need unraveling to address dual epidemics.

The opioid epidemic has been a national crisis in the U.S. since the 1990s; it is estimated that nearly 50,000 people have lost their lives due to opioid-related overdose (NIDA, 2021; CDC, 2021a). Misuse and addiction to opioid pain medications have led to an increase in neonatal abstinence syndrome and infectious diseases such as HIV and HCV (NIDA, 2021). Despite the several initiatives in place to combat the opioid crisis, the number of death due to opioid overdose, including prescription opioids, heroin, and illicitly synthetic opioid, fentanyl, continues to increase (CDC, 2021a). The peak in the opioid crisis and the HCV infection rates is a dual epidemic that calls for drug treatment and recovery services, testing, and preventative services for HCV and other infectious diseases such as HIV and Hepatitis B (CDC, 2017). Often stigma is considered one of the significant barriers that stand against injection drug users from seeking treatment; as a result, research reveals that stigma associated with drug use can severely impact mental and physical health (Muncan et al., 2020).

Purpose of the Research

This project aims to examine and understand the efficacy of treating IVDU and HCV simultaneously to reduce the HCV infection rate in the U.S. The researcher will conduct a synthesized literature review by critically evaluating the information presented in the articles, identifying gaps, and synthesizing the acquired knowledge on the subject matter.

Research Questions

The following research questions and related hypotheses aim to understand the efficacy of treating IVDU and HCV simultaneously to reduce the HCV infection rate.

RQ1: Is there more than an additive advantage to combining treatment for HCV and IVDU use to address the rise of the HCV infection rate?

H1a: Treating HCV and IVDU together has an additive advantage in addressing the rise of the HCV infection rate.

H10: Treating HCV and IVDU together has no additive advantage in addressing the rise of the HCV infection rate.

Organization of the Study

This proposal is organized into three chapters. This chapter introduces the topic, and the second chapter provides a literature review by combining various research ideas presented regarding the topic. The third chapter depicts a clear image of the data collection process used in this systemic literature review.

Chapter Two

Review of Literature

A literature review was performed to understand and evaluate the various perspectives/ideas presented regarding the core concepts of HCV and its relationship with injection drug users and the opioid epidemic. In searching for relevant articles, keywords that have been postulated in the research questions are Hepatitis C virus, injection drug users, and the opioid epidemic. In addition, the literature review included formative and summative research on how HCV affects different organs in the body, the relationship between HCV and the opioid epidemic, and its effect on individuals affected by substance abuse and mental health disorders. Below is a description of the research terms and search engines, along with the process and methodology used to extract relevant studies for this literature review.

Search Strategy

There are several steps involved in conducting an initial review of the literature. The first step involved a search on research engines such as Google Scholar, Pub Med, and Education Resources Information Center (ERIC). The inclusion criteria encompassed books and documents, clinical trials, meta-analyses, randomized control trials, peer-reviewed journals, reviews, systematic reviews, and English language. A time frame inclusion was also included in the search strategy, which is up-to-date articles from within the last seven years. The keywords used are Hepatitis C virus, injection drug users, behavioral theories, and opioid epidemic. In between the keywords AND was used individually and in between the key search words.

A total of 2,323 records were identified from the search engines. After screening the articles, 1900 were removed due to the topic's relevance. A total of 423 articles were left, and 300 were removed due to redundancy and lack of direct relation to the topic being searched. One-hundred

and twenty-three articles were left, and in the process of attempting to retrieve the documents, 84 were removed in the process of current and up-to-date research on the subject matter. A total of 39 articles were reviewed in this initial literature review.

Table 1:

Research Terms and Search Engine Used in Initial Literature Review

# Of sear	First Search Term	Second Search Term	Third Search Term (If Applicable)	Data Base Searched	Results
1	Hepatitis C Virus			Pub Med	2500
2	Hepatitis C Virus	Demographics		Pub Med	156
3	Hepatitis C Virus	Substance Abuse		Pub Med	982
4	Hepatitis C Virus	Substance Abuse	Behavioral Theories	Pub Med	5
5	Hepatitis C Virus	Substance Abuse	Treatment	Pub Med	755
6	Hepatitis C Virus	Mental Health		Pub Med	295
7	Hepatitis C Virus	Mental Health	Behavioral Theories	Pub Med	1
8	Hepatitis C Virus	Mental Health	Treatment	Pub Med	243
9	Hepatitis C Virus	Reinfection		Pub Med	288
10	Hepatitis C Virus	Access to Care	United States	Pub Med	26
11	Substance Abuse	Access to Care		Pub Med	324
12	Opioid epidemic	Hepatitis C Virus		Pub Med	131
13	Opioid epidemic	Hepatitis C Virus	United States	Pub Med	3

Hepatitis C and its Effect on the Body

HCV was discovered in 1989 after evidence suggested that there was another virus other than Hepatitis A and B that caused damage to the liver (Houghton, 2019). The emergence of

HCV began in the mid-1970s; however, the complicated nature of the virus made it challenging to identify HCV for approximately 15 years. Subsequently, as knowledge of the replication cycle of HCV increased, effective treatments started emerging that improved quality of life.

Despite the emergence of more effective treatments, Houghton (2019) points out that infectious diseases like the HCV virus require the development of an effective vaccine to control the global pandemic. Nonetheless, the variability of the ribonucleic acid (RNA) in the virus has made it challenging to produce a safe and effective vaccine that can provide immunity/protection for the several genotypes and subtypes of the virus (Morozov & Lagaye, 2018). The genotypes of HCV are associated with a distinct geographic location and can vary based on the route of transmission (Schnell et al., 2018).

According to Morozov and Lagave (2018), genotype 1 is prevalent in North America, Japan, and Europe. In contrast, genotypes 3a and 1a are common among IVDUs, and genotype 1b is prevalent among people that have received a blood transfusion. The presence of several genotypes associated with subtypes has made it challenging to deliver an effective treatment that focuses on prevention (vaccine).

According to the CDC (2020a), people with human immunodeficiency virus (HIV) infection, healthcare workers, incarceration, children born to mothers with HCV infection, and people that have received blood transfusions are considered at risk for HCV. Mainly HCV is cogitated as a public health issue due to the progression of the disease from inflammation to cirrhosis and eventually to hepatocellular carcinoma (HCC; Morozov & Lagaye, 2018). HCV infection does not only cause liver damage; it is also known to instigate a series of extrahepatic effects on an individual's physical and mental well-being (Cheng et al., 2021; Barbosa et al., 2017). The burden of HCV infection surpasses the liver, and its effects are mainly noticed in the

digestive system, endocrine and immune system, and the central nervous system (Cooper et al., 2019).

The nature of the disease progression of HCV is to facilitate chronic inflammation along with causing a dysfunction in the endothelial which lays the platform for the development of cardiovascular disease (Badawi et al., 2018). Moreover, Adinolfi et al. (2018) mentioned that chronic hepatitis C significantly increases the risk of arteriosclerosis because HCV infection has close relations with metabolic disorders. However, the data indicating whether curing HCV improves arteriosclerosis conditions requires further analysis. Badawi et al. (2018) conducted a 10-year cross-sectional study to analyze the risk of cardiovascular disease in HCV-positive patients. The research revealed that the expansion of HCV-antiviral may have reduced cardiovascular-associated risk factors among HCV patients. Nonetheless, the data calls for further research to put forth a precise conclusion regarding the relationship between arteriosclerosis and HCV infection.

Chronic HCV infection manifests its adverse effects in several body organs in which the digestive system is another area that can be affected (Meissner, 2018). Liver fibrosis has been associated with high rates of dislocation of the bacteria in the gut, thus resulting in infection. Meissner (2018) indicates that the liver is one of the first areas that harbor dislocated bacteria from the gut, resulting in liver fibrosis, hepatic stellate cell activation, and the existing inflammation caused by the HCV infection. Often liver disease caused by HCV infection has been associated with changes in gut bacteria; however, the extent of the damage caused by the dislocation of bacteria in the gut will need further analysis even after the eradication of HCV to understand the relation of liver disease and gut microbiota fully (Honda et al., 2021). There is

inevitable evidence that suggests that HCV infection affects the digestive system by disrupting the gut bacteria.

The endocrine and the immune system are also affected by HCV infection due to the nature of the disease manifesting its negative effect on the regulation of glucose metabolism (Wensveen et al., 2019). Although the endocrine and the immune system carry out two different vital functions in the body, recent findings revealed that the roles of the two systems interact closely to support the body's healthy functioning. In addition to cirrhosis and hepatocellular carcinoma, research suggests that HCV infection is associated with several metabolic disorders, such as arteriosclerosis, diabetes, alteration in iron metabolic pathways, and lymphoproliferative disease (Chaudhari et al., 2021)

With metabolic disorders rising at an alarming rate, adding HCV infection into the pool as a significant factor contributing to the onset and progression of diseases, such as diabetes, requires immediate attention. According to the definition of metabolic syndrome from the International Diabetes Federation (IDF) and the National Cholesterol Education Program, the prevalence of metabolic syndrome in the United States is estimated to be around 22% (Moore et al., 2017). The co-occurrence of HCV infection and metabolic diseases, such as diabetes, dramatically increases the progression of fibrosis and hepatocellular carcinoma. Given that both the prevalence of HCV and metabolic disorders are rapidly growing, it can weigh heavily on the economy, the healthcare system, and the population's overall well-being (Chaudhari et al., 2021).

The harm caused due to HCV infection is not limited to organs closely related to the liver; it is also associated with causing cognitive impairment as well as mood disorders (Barbosa et al., 2017). Approximately 30% of patients who have not yet developed liver cirrhosis show symptoms related to depression and cognitive impairment. The main reason behind the

development of neuropsychiatric syndrome is the release of pro-inflammatory cytokines causing the HCV infection to be introduced to the central nervous system through the "Trojan horse" mechanism (Barbosa et al., 2017). However, there is scarce data regarding the relation of the viral load with the severity of cognitive impairment nor the successful reversal of the cognitive impairment after eradicating HCV from the body. Similarly, Barreira et al. (2019) reiterate that HCV infection presents a wide range of extrahepatic symptoms and emphasizes the importance of analyzing social and emotional factors better to understand the effects of the virus throughout the body while enhancing treatment adherence. In addition to physical health, HCV infection also affects an individual's emotional and social well-being; therefore, several researchers suggest the implementation of an integrated type of care that is focused on both physical and mental health while also bearing in mind the burden of the social aspect of an individual's health.

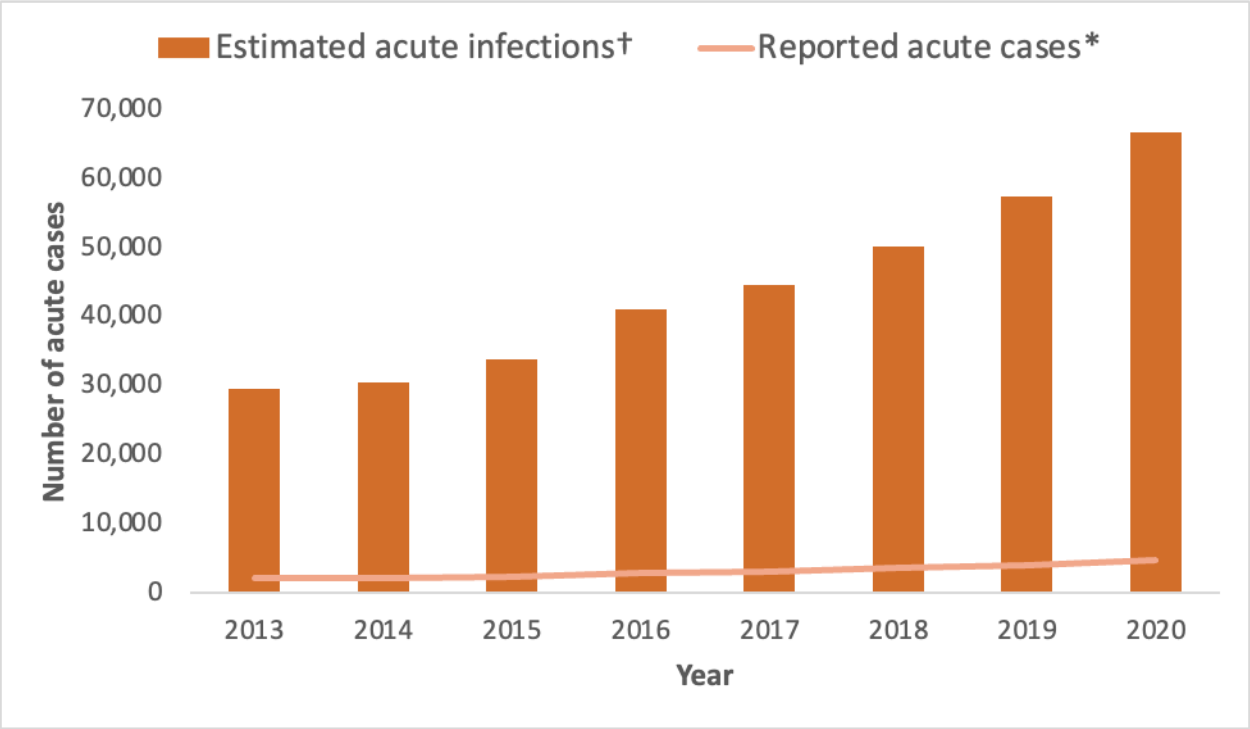
Factors Contributing to the Incidence of HCV

Acute and chronic HCV infection has been increasing over the last decade. Figure 1 indicates that the incidence rate of acute HCV infection has increased by two folds among injection drug users since 2013, with a surge of 124% (CDC, 2022). This incidence is more significant in males aged 20–39 (Figure 2). Several risk factors can be associated with HCV, such as from mother to baby, being an injection drug user, being a baby boomer, having a history of incarceration, and getting tattoos and piercings in an unregulated place (CDC, 2020a; Table 1). Nowadays, the most common method of transmission is through injection drug use, in which several factors, such as the opioid epidemic and lack of accessibility to mental health care services, have exasperated the infection rate. The demographics for acute HCV infection have revealed a shift from baby boomers to persons aged 20–39 who often use injection drugs;

however, chronic HCV infection affects both persons aged 20–39 and baby boomers (CDC, 2022; Figure 2). Table 2 identifies injection drug use as the most reported mode of transmission.

Figure 1

Number of reported cases of acute hepatitis C virus infection and estimated infections† United States, 2013–2020*



Reported confirmed cases. For the case definition, see https://ndc.services.cdc.gov/conditions/hepatitis-c-acute/

† The number of estimated viral hepatitis infections was determined by multiplying the number of reported cases that met the classification criteria for a confirmed case by a factor that adjusted for underascertainment and underreporting. The 95% bootstrap confidence intervals for the estimated number of infections are displayed in the Appendix.

Source: CDC, National Notifiable Diseases Surveillance System.
Reference: Klevens RM, Liu, S, Roberts H, et al. Estimating acute viral hepatitis infections from nationally reported cases. Am J Public Health 2014; 104:482. PMC3953761.
Centers for Disease Control and Prevention. Viral Hepatitis Surveillance Report – United States, 2020. https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm.
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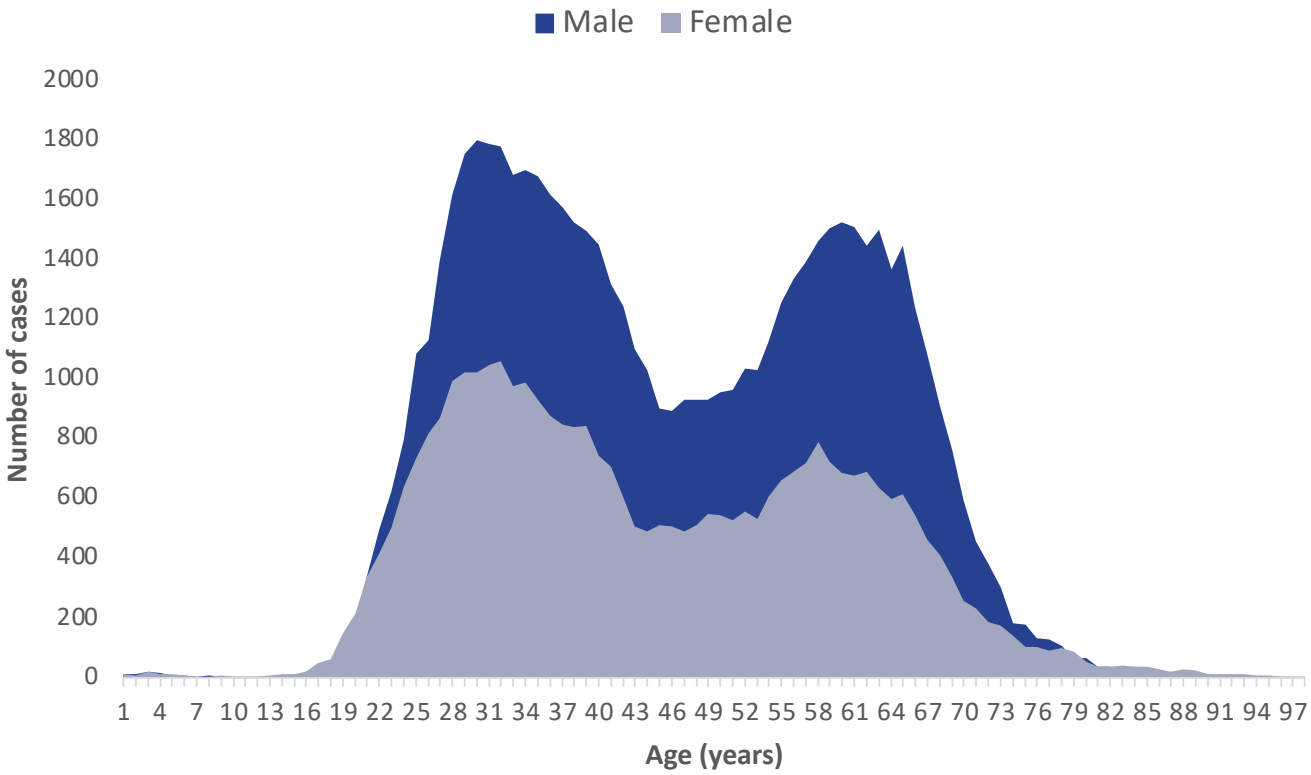
Figure 2

Number of newly reported chronic hepatitis C virus infection cases† by sex and age United States, 2020*



* During 2020, cases of chronic hepatitis C were either not reportable by law, statute, or regulation; not reported; or otherwise, unavailable to CDC from Arizona, Delaware, District of Columbia, Hawaii, Indiana, Kentucky, Nevada, North Carolina, Rhode Island, and Texas.
† Only confirmed, newly diagnosed, chronic hepatitis C cases are included. For the complete case definition, see https://ndc.services.cdc.gov/conditions/hepatitis-c-chronic/.

Source: CDC, National Notifiable Diseases Surveillance System.
Centers for Disease Control and Prevention. Viral Hepatitis Surveillance Report – United States, 2020. https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm.
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Table 2

Reported risk behaviors or exposures among reported cases of acute hepatitis C virus infection United States, 2020*

Risk behaviors/exposures†	Risk identified	No risk identified	Risk data missing
Injection drug use	1,017	523	3,258
Multiple sexual partners	167	352	4,279
Surgery	142	713	3,942
Sexual contact§	83	336	4,379
Needlestick	64	706	4,028
Men who have sex with men¶	44	258	2,803
Household contact (nonsexual)§	17	402	4,379
Dialysis patient	69	964	3,765
Occupational	9	923	3,866
Transfusion	1	885	3,912

* Reported confirmed cases. For the case definition, see https://ndc.services.cdc.gov/conditions/hepatitis-c-acute/. Reported cases may include more than one risk behavior/exposure. Case reports with at least one of the following risk behaviors/ exposures reported 6 weeks to 6 months prior to symptom onset or documented seroconversion if asymptomatic: 1) injection drug use; 2) multiple sexual partners; 3) underwent surgery; 4) men who have sex with men; 5) sexual contact with suspected/confirmed hepatitis C case; 6) sustained a percutaneous injury; 7) household contact with suspected/confirmed hepatitis C case; 8) occupational exposure to blood; 9) dialysis; and 10) transfusion.

§ Cases with more than one type of contact reported were categorized according to a hierarchy: (1) sexual contact; (2) household contact (nonsexual).

Source: CDC, National Notifiable Diseases Surveillance System.

Centers for Disease Control and Prevention. Viral Hepatitis Surveillance Report – United States, 2020. https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm. Published September 2022.

Opioids Epidemic

Increased prescription of opioid pain medication in the late 1990s is considered the onset of the opioid epidemic after pharmaceutical companies assured both prescribers and patients that dependence/ addiction to the opioid was unlikely (U.S. Health and Human Services (HHS),

2021). As a result, increased usage of both prescribed and non-prescribed opioid medication resulted in a policy change that focused on limiting the use of opioids. At this point, individuals unable to acquire opioid pain medication through their providers resorted to illegal ways to satisfy their needs. In the U.S., approximately 10.1 million people over 12 have misused opioids in the past year (HHS, 2021). The number of deaths has been increasing yearly, and it is estimated that more than 760,000 people have lost their lives due to drug overdose since 1999. Although there was a slight decrease in the number of overdose-related death from 2017 to 2018, there was a significant increase in 2019 due to the illicitly manufactured drug fentanyl (Haley & Saitz, 2020).

The U.S. has suffered from a three-wave epidemic of opioids: prescription opioids, heroin, and synthetic opioids (Ciccarone, 2019). The first wave occurred in the 1990s when there was an increased prescription of opioids. As a result, the number of patients losing their lives due to opioid overdose started rising in the early 2000s. The misuse of the prescription of opioids has led patients to develop a dependency that eventually has turned into an addiction, which can have the characteristics of a mental disorder. In their defense, prescribers mention the role of relieving their patients from pain in delivering quality care (Dineen & DuBois, 2016).

The second wave of the epidemic has close ties with the first one due to the nature of the epidemic. Ciccarone (2019) states that the second wave is known for heroin overdose because patients prescribed opioids are now expected to cut back due to their increased dependence. Patients are now quickly transitioning to heroin because the effort to decrease opioid prescribing has led to the scarce availability of prescription painkillers. The third wave of the opioid epidemic is an extension of the second wave but in a more advanced and dangerous manner, involving synthetic opioids such as fentanyl. Fentanyl, manufactured by pharmaceutical

companies, is a synthetic opioid used to relieve severe pain in a controlled environment, mainly used to treat cancer-related pain. It is considered a Schedule II substance due to its nature to cause high dependency (Tabarra et al., 2019).

When analyzing the three waves of the opioid epidemic, health issues due to drug use seem to get more potent and more dangerous as time passes. When an individual becomes addicted to a substance, it is most common to search for a substance that creates an even better euphoria. As a result, opioid users are seen to resort to heroin, then to synthetic opioids like fentanyl. Recently, it has been noted that new, emerging psychoactive drugs are sold for purposes other than human consumption, with serious fatalities recorded. Although the surge in fentanyl-related cases started in 2006 in the U.S., the number of deaths related to fentanyl overdose continued to rise in the U.S., Canada, and Australia (Han et al., 2019).

In addition to the ongoing opioid epidemic, the emergence of the coronavirus disease 2019 (COVID-19) has caused a more severe strain and burden in society. Nonetheless, the emergence of the COVID-19 pandemic was expected to cause a significantly higher number than projected. However, the absence of real-time reporting due to the pandemic being more urgent can cause a limitation in confirming the suspected surge (Haley & Saitz, 2020). The COVID-19 pandemic has caused a strain on how individuals' function because it required several adjustments to control the spread of the virus. Several healthcare services have been closed or serve only emergent cases; this can profoundly affect people who use opioids because it creates the environment to deal with their disorder on their own rather than by the guidance of professionals (Galarneau et al., 2021).

Coronavirus Disease (COVID-19)

Meanwhile, the COVID-19 pandemic has created a positive result regarding opioid overdose due to the changes that favor access to care for low-income and vulnerable populations and Medicaid users (Haley & Saitz, 2020). Expansion of telemedicine for opioid users and emergency services while reducing the treatment barrier for naloxone, along with easing restrictions on the use of methadone, were some of the changes implemented to expand coverage using the COVID-19 pandemic. During the COVID-19 pandemic, opioid use continued to increase despite the policy changes implemented; however, additional actions from the states are necessary to benefit individuals that use Medicaid and commercial insurance similarly to Medicaid insurance users (Pessar et al., 2021).

Substance Abuse

In the U.S., approximately 37 million people are current illegal drug users, and 59 million individuals aged 12 and over have misused prescription drugs within the last year, making the issue of substance abuse a significant public health concern (National Center for Drug Abuse Statistics [NCDAS], 2023). The number of people affected by substance abuse continues to rise, responsible for millions of deaths yearly. McLellan (2017) describes substance abuse as using any psychoactive compound that can cause health and social problems; the substances may be legal, illegal, or controlled by a licensed physician. Seven classes categorize substances based on their effects: nicotine, alcohol, cannabinoids, opioids, depressants, stimulants, and hallucinogens. The number of annual deaths has been increasing by approximately 4%, accounting for over 70,000 deaths yearly (NCDAS, 2022). The burden of substance abuse extends beyond causing harm to human lives; it also has a significant financial impact and affects the workforce, education, and social system (McLellan, 2017). According to the NCDAS (2022), the U.S.

spends $272 billion yearly on drug abuse, including healthcare needs, crime, lost work productivity, and social impacts. Persons between the age of 18–25 and 26–29, 39% and 34%, respectively, are affected the most. The data reveals a high likelihood that individuals who attempt an illegal drug before the age of 13 will develop substance abuse disorder within the upcoming years (NCDAS, 2022).

Treatment of HCV

According to the World Health Organization (WHO), approximately 71 million people live with HCV infection, averaging about 1.5 million new infections yearly (World Health Organization, 2022b). HCV infection continues to be a global health burden in which most infected patients develop chronic hepatitis, eventually developing end-stage liver disease.

The evolution of HCV treatment has undergone several phases, starting in 2011 with the introduction of the first DAAs (telaprevir and boceprevir) used in combination with PegINF- α and ribavirin for the treatment HCV GT1 (Basyte-Bacevice & Kupcinskas, 2020). Although the clinical trial was promising in eradicating the virus, adverse side effects and complications affected patients severely. The need to continue intensive clinical trials searching for a well-tolerated medication was inevitable; therefore, year after year, FDA-regulated treatment plans were developed that addressed the eradication of the virus and less severe adverse side effects.

The treatment cost was another aspect that needed reevaluation because the original cost was over $150,000 (Oancea et al., 2020). Although the cost of treatment has significantly decreased, several other barriers hinder the eradication of HCV from the world, such as access to care, lack of providing comprehensive care, mistrust in the healthcare system, and fear of stigma (Mera et al., 2019; Barbosa et al., 2017; Paisi et al., 2022).

The CDC has set out guidelines recommending once-in-a-lifetime testing for all adults over the age of 18 and testing during every pregnancy for women, and regular testing for at-risk populations (CDC, 2020b). The CDC's recommendation addresses the primary tier in identifying infected individuals; however, the barriers to access and linkage to care makes the hope of eradicating HCV nearly impossible.

One of the first barriers to treating HCV is the asymptomatic nature of the virus; one-third of the infections resolve on their own, and the remaining two-thirds require access to care for testing to get a proper diagnosis (Chaudhari et al., 2021). Another major factor in treating HCV infection is access to care. The state's rules and regulations affect patients living in different geographic locations to receive life-saving treatment. Mera et al. (2019) provides an example in which an individual living in New Mexico will be able to receive immediate treatment; in contrast, an HCV-infected individual residing in Montana can only receive treatment that can be determined based on the eligibility for advanced liver fibrosis, sobriety, and compliance with other medications required to maintain one's health.

In addition, to state rules and regulations serving as a barrier to slowing the prevalence of HCV infection, the lack of substance use disorder programs exasperates the current issue. Tenner et al. (2019) delineates barriers that restrict patients in Texas from receiving treatment: the high cost of treatment medication not covered by private and government insurance, lack of specialist providers that treat HCV infection, and lack of substance abuse programs in the area. Treating HCV infection requires several tiers of barriers to be tackled, especially among the at-risk population; without addressing the walls between testing and linkage to care, it can be challenging to reduce the prevalence.

The epidemiology, incidence, and treatment issues associated with HCV combine to make it a prevalent healthcare issue. The Biopsychosocial (BPS) Model can be used to explore these factors.

The Biopsychosocial Model

George L. Engel proposed the biopsychosocial model in the mid-20th century to promote an understanding of the interconnection between biology, psychology, and social factors (Babalola et al., 2017). The model examines the effect of an individual's biology, mental well-being, and social attributes. However, evidence suggests that biopsychosocial has been around since the 1950s. Roy Grinker, a neurologist and psychiatrist, mainly emphasized biological factors as a significant contributor to mental illness (Ghaemi, 2009).

The biopsychosocial model was considered an improved change from the biomedical model due to the concept that focuses mainly close interaction of the mind-body (Babalola et al., 2017). The biomedical model focuses on the concept that the absence of illness defines health; therefore, illnesses can be diagnosed through biochemical markers that can be treated using physical interventions. On the contrary, the biopsychosocial model conceptualizes the significant effect biology, psychology, and social interaction can bear on an individual's health. Each dynamic possesses an interactive force that can contribute to an individual's well-being. According to this model, reducing an individual's illness to any one of the dynamics (biology, psychology, or social) can alter or reduce the quality of care rendered to a patient.

The biopsychosocial model can be applied to diseases like chronic HCV infection, which cause physical change and emotional and social impact on an individual's quality of life (Barreira et al., 2019). The biological dynamics of the biopsychosocial model deal with aspects of biology that bear significant leverage on the functionality of an individual's health that

resonate with the primary illness (Lehman et al., 2017). For instance, HCV is known for causing extrahepatic complications and neuropsychiatric disorders. As a result, several conflicting findings link HCV infection with schizophrenia (Cheng et al., 2021).

Cheng et al. (2021) investigated several populations diagnosed with schizophrenia to understand its precise correlation with HCV infection. Although the prevalence of schizophrenia was higher among some of the populations investigated in the study, such as veterans and individuals at risk for HCV infection, there was no clear explanation why the same scenario was not true amongst others. Therefore, the study conducted by Cheng et al. (2021) concluded that HCV was considered a significant risk factor for schizophrenia, in which treatment for HCV infection can reduce the severity of neuropsychiatric disorders such as schizophrenia. Referring to the biological dynamics of the biopsychosocial model, the biological change due to HCV infection can potentially influence an individual's mental state. An individual that has been affected by the malfunctioning of the liver along with the effects of a mental/emotional change will need an intervention that addresses both the "bio" and "psycho" dynamics of the biopsychosocial model.

Support for the biopsychosocial model is found in a study conducted by Youssef et al. (2017), where the study validates and emphasizes the importance of incorporating patients' mental and social support when planning care for HCV-infected individuals receiving treatment. The study aimed to assess health-related quality of life (HRQoL) among patients receiving treatment for HCV by comparing their mental state before and after initiating a treatment plan. In addition, Faccioli et al. (2021) also mention the importance of assessing and providing ongoing support for HCV-infected individuals even after eradication of the virus because the disease can affect several aspects of a patient's life.

In another study supporting the use of the biopsychosocial model, Kusnanto et al. (2018) conducted a hermeneutic review regarding the implementation of a biopsychosocial model in a primary care setting, resulting in an improved clinical outcome for managing chronic illnesses. Despite these findings, Kusnanti et al. (2018) identified setbacks associated with implementing a biopsychosocial model in a primary care setting, including the tremendous addition of workload due to the need to conduct a thorough evaluation of psychological, behavioral, and social dynamics. In addition, some diseases can be resolved using the biomedical approach alone, such as a fracture or a laceration. During these types of incidences, the use of the biopsychosocial model can potentially lead to the provision of unnecessary services that result in the wastage of time and resources.

Some argue that the biopsychosocial model is an idea that is far from reality because it can be challenging to integrate the mind, body, and social environment while also maintaining cost, efficiency, and quality (Kusnanto et al., 2018). The existing shortage of healthcare professionals in the U.S. can be an extenuating factor in implementing the biopsychological model. The Bureau of Labor Statistics (BLS) predicts that there will be a 13% increase in the demand for physicians from 2016–2026 (Zhang et al., 2020). In a recent study, the Health Resources and Service Administration reported an existing shortage of primary physicians, and this deficiency increased significantly from 2011–2020 (Zhang et al., 2020). The shortage of healthcare professionals confounds the implementation of the biopsychosocial model in primary care settings. However, Kusnanato et al. (2018) stress that the importance of synchronizing mind-body to address every aspect of an individual's health cannot be reiterated enough.

In a primary care setting, patients seek care for several conditions, including chronic disorders and functional disorders, are some of the conditions. In the U.S. and globally, chronic

disorders have been the major driving factors behind the increasing healthcare cost. In the U.S. alone, 75% of healthcare spending is consumed by treatments and hospitalization due to chronic diseases (Raghupathi & Raghupathi, 2018). Chronic disorders are defined as a condition that affects or restricts the functionality of an individual's mental and physical health, lasting for more than a year (Raghupathi & Raghupathi, 2018). Diabetes, heart disease, cancer, obesity, liver disease, respiratory diseases, and many others are categorized as chronic conditions that affect an individual's life quality. Chronic liver disease and cirrhosis are among the chronic conditions that are considered as one the major causes of death both globally and in the U.S. According to the report generated by the CDC in 2017, approximately 1.8% of the adult population in the U.S. had chronic liver disease and cirrhosis (Sharma & Nagalli, 2022). So far, chronic disorders have been addressed mainly through a biomedical approach due to several debilitating within the system, such as deficiency of healthcare professionals, cost, and lengthy time to address the three dynamics (biology, psychology, and social; Kusnanto et al., 2018).

Generally, the biopsychosocial model offers a broader approach to addressing diseases like HCV by focusing on mind-body interaction. The HCV virus has been around for the last few decades, and discovering effective treatment has been challenging; however, due to the relentless work of researchers, the cure rate has increased tremendously. The complicated nature of HCV enables it to affect several organs other than the liver, which calls for an approach that focuses on several dynamics of an individual's life to increase the quality of life. A biopsychosocial model is an approach that focuses on mind-body interaction rather than addressing an individual's physical illness. Substance abuse and mental health disorder are often associated with HCV because of these populations' chosen lifestyles. Therefore, addressing HCV infection without providing a treatment plan that focuses on the “bio,” “psycho,” and “social” aspects of an

individual's life can be considered an incomplete treatment because the risk factor has not been addressed from the root. The methodology for this study is described in the next chapter.

Chapter Three

Methodology

This section provides a clear guideline on the process and methods used to collect data. This project utilized several steps to make the information valid and reliable, such as identifying a study design, a target population, and a step-by-step data collection and analysis guide. The methodology section serves as a guideline for the steps taken in this project to collect and analyze the data by setting boundaries.

Study Design

The research design utilized in this project is a systemic literature review that aimed to bring together various perspectives on the topic to understand the subject matter deeply. Several works of literature were assessed and synthesized to understand the topic better while also identifying areas that require future research. This study did not require Institutional Review Board (IRB) approval because the reviewed data was acquired from a public database, and the articles reviewed have received IRB approval previously (Sataloff et al., 2021). This methodology aimed to answer the below research question by following the patient/population, intervention/indicator, comparison, and outcome (PICO) format (Higgins et al., 2019).

RQ1. In adults 18 years old and older (P), is there an additive effect of treating for HCV and IVDU in combination (I) compared with treating for HCV or IVDU alone (C) on the rise of HCV infection rate (O)?

The anticipated outcome from the systemic literature review will reveal evidence suggesting that combining treatment for HCV and IVDU will have a positive impact in reducing HCV's infection rate.

Target Population

The target population in this systemic literature review included individuals in the U.S. who are 18 years old or older, HCV positive, and IVDUs. The databases used in this review are Google Scholar, Scopus, Web of Science, Cochran Reviews, Pub Med, and Education Resources Information Center (ERIC). The main reason for using these databases is to include a wide range of perspectives that describe the topic and integrate novel research in progress. This systemic literature also included statistics regarding the prevalence and impact of the HCV globally and in the United States; however, the review mainly focused on the data from the United States.

Inclusion

As portrayed in Table 3, this review's inclusion criteria focused on articles published within the last five to seven years, published after 2015. In addition, peer-reviewed quantitative journal articles, academic books, professional journals, and data containing statistics from government websites were included in the review. The studies that were included mainly focused on comparing the efficacy of treating HCV and IVDU simultaneously with treating HCV and IVDU separately.

Exclusion

This review's exclusion criteria were focused on studies that did not concentrate on treatment for HCV and IVDU separately and treatments that combined HCV and IVDU. In addition, articles published before 2015 were not included in anticipation of using current and up-to-date data. This review also excluded meta-analysis, systemic reviews, and literature reviews to avoid redundancy/ describing articles multiple times.

Table 3

Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria		
	Inclusion	Exclusion
Population (P)	All races, and sexes and individuals 18 years and older, HCV positive, and are IVDU.	Patients without HCV, non-IVDU, younger than 18 years of age
Indications (I)	Combined treatment for HCV and IVDU	No treatment for HCV or IVDU
Comparison (C)	HCV treatment alone IVDU treatment alone	No treatment for HCV and IVDU
Outcome (O)	HCV infection rate	No impact on HCV rate
Study Design	Peer-reviewed journal articles, quantitative research, academic books, professional journals, and data containing sources from government websites	Meta analysis, systemic and literature review
Publication Language	English	Any other language
Time Frame	2015–2023	Before 2015
Sample Population Size	Any	None

Data Collection

The search technique used in this systemic literature review followed the PICO format to shape the data collection process. As portrayed in Appendix A., the data extraction process commenced by identifying the study design, authors, dates of the data reviewed, population (P), indication (I), comparison (C), and outcome (O). The PICO model is often used to develop research questions to address relevant components of the topic under review (Eriksen & Frandsen, 2018). In a systemic review, the PICO model plays a significant role in evidence synthesis by focusing on formulating a well-defined question. Keywords used in databases were identified using the PICO format (Table 4); as a result, (*n = 166*) articles were identified and removed (*n = 40*) due to irrelevance to the research. The first assessment that was used to determine eligibility is by scanning the title (*n = 126*). For example, if the title was not focused on the hepatitis c virus, IVDUs, HCV treatment, IVDU treatment, or combined treatment for HCV and IVDU, then it was excluded (*n = 45*). After screening the article titles, those that do not have a direct relation to the topic searched were removed. An abstract review was then conducted to ensure further relevance (*n = 81*) and to screen out redundancy (*n = 45*). This process aided in removing articles that were redundant and irrelevant to the topic. Each article was reviewed to compare and utilize the newer research presented in the database because the two subject matters discussed in this review—HCV and the opioid crisis—are both epidemics. Then the final number of articles (*n = 36*) was recorded into a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Appendix A). The PRISMA flow chart is a widely used tool that allows the researcher to report the data collection process by following a set of guidelines, thus, increasing the researcher's validity (Page et al., 2021).

Table 4 *Search Strategy Based in PICO & Boolean Operators*

	Search Strategy Based in PICO & Boolean Operators.						
	Population/ Problem		Intervention/ Indicator		Comparison		Outcome
Question 1	Adults in the U.S 18 years and older who are HCV positive and are IVDU OR American adults with HCV and IVDU	A N D	HCV and IVDU treatment OR HCV and illicit drug use treatment OR HCV and injection drug use treatment	A N D	HCV treatment OR IV drug use treatment OR Injection drug use treatment OR injection drug treatment OR illicit drug treatment	A N D	HCV infection rate

Data Analysis

The data collected in this project was analyzed using the synthesis matrix system. The synthesis matrix system allows the creation of a chart. It organizes the data collected to provide a visual presentation of the main ideas presented in each literature (data) that was used in this project. This review used Toronto & Remington's 2020 integrative review methodology and an appraisal tool, Joanna Briggs Institute (JBI; Santos et al., 2018; Appendix B). The average JBI checklist score is 76%, indicating a relatively good level of adherence to the methodological quality and reporting standards outlined in the JBI Checklist. This score suggests that the assessed study has addressed most of the items on the checklist, indicating a comprehensive and well-conducted research process. The JBI checklist consists of several criteria that evaluate different aspects of a research study, such as the clarity of the research question, eligibility

criteria, data collection methods, statistical analysis, and the overall validity of the results. Each criterion carries a specific weight or score; the total score is calculated by summing the scores achieved for each criterion. In addition, there was a second reviewer to establish an agreement. Both researchers used the data extraction table (Appendix C) to establish an agreement. Both researchers read the articles and completed the data extraction table separately. The results completed by both researchers were compared and checked for similarity. If the results of both researchers were not similar, then the article was reviewed again until both researchers agreed, and Cohen's kappa calculation was performed to further establish agreement.

Cohen's kappa is a statistical measure used to assess the level of agreement between two raters (McHugh, 2012). It considers the agreement that could occur by chance alone and provides a stronger evaluation of inter-rater agreement rather than simple percent agreement. It provides a value between -1 and 1, with different ranges corresponding to different levels of agreement. A kappa value less than 0 indicates agreement worse than chance, while values between 0 and 0.20 suggest slight agreement. Kappa values ranging from 0.21 to 0.40 represent fair agreement, while values from 0.41 to 0.60 indicate moderate agreement. Kappa values ranging from 0.61 to 0.80 suggest substantial agreement, and values from 0.81 to 1 indicate almost perfect agreement. These ranges provide a guideline for interpreting the strength of agreement based on the kappa coefficient (McHugh, 2012).

Researcher A	Researcher B		
		YES	NO
	YES	20	0
	NO	6	10

P_o is the proportion of observed agreement.

P_e is the proportion of agreement expected by chance.

$P_o = (20+10)/36$

$= 0.833$

kappa = (Po - Pe) / (1 - Pe)

P_e is calculated as the total number of times Researcher 1 said "Yes" divided by the total number of articles, multiplied by the total number of times that Researcher 2 said "Yes" divided by the total number of articles, added to the total number of times that Researcher 1 said "No" multiplied by the total number of times that Researcher 2 said "No."

Yes = [(20+0)/36] * [(20+6)/36] = 0.401

No = [(6+10)/36] *[(0+10)/36 = 0.44 * 0.277 = 0.123

$P_e = 0.401 + 0.123 = 0.524$

$k = (p_o – p_e) / (1 – p_e)$

$k = (0.88-0.524)/ (1-0.524)$

$= 0.356/0.476$

$= 0.747$

According to the interpretation of Cohen's kappa coefficient ranges, a value of 0.61 to 0.80 corresponds to substantial agreement (McHugh, 2012). A kappa result of 0.747 indicates substantial agreement between the two researchers. This indicates that there is a remarkable level of agreement beyond what would be expected by chance alone.

Project Summary

This systemic literature review investigated several risk factors associated with HCV. This study will seek to evaluate and understand if addressing/treating HCV and IVDU jointly can

impact the rapidly increasing HCV infection rate. This review will contribute to the understanding that the two epidemics, HCV and IVDU, are intertwined, and it requires an approach aimed at addressing both collectively rather than individually. Chapter four provides the review results, while chapter five provides discussion and implications.

Chapter Four

Results

HCV infection is a significant global health concern, particularly among individuals who engage in IVDU. There is growing recognition of the need for effective interventions targeting HCV treatment and harm reduction strategies in this population. The primary focus of this review was to assess whether there is an additive advantage in combining HCV and IVDU treatment. By synthesizing the findings from diverse studies, this review aimed to contribute to understanding the effectiveness and potential benefits of integrated interventions targeting HCV and IVDU. The insights gained from this review will inform future research, policy development, and the implementation of evidence-based strategies to address the complex challenges associated with HCV infection and injection drug use.

An overview of the included studies is provided in Appendix A, detailing their study design, authors, date, duration, location, population, indication, comparisons, and outcome. A total of 36 articles were selected for inclusion following the methods described in Chapter Three. This review consists of prospective cohort studies (n = 5), longitudinal prospective experimental studies (n = 1), qualitative studies (n = 3), retrospective cohort studies (n = 6), case studies (n = 1), cohort studies (n = 6), comparative study (n = 1), cross-sectional study (n = 1), decision-tree analysis (n = 1),), modeling or simulation studies (n = 4), observational study (n = 2), quantitative study (n = 1), and randomized controlled clinical trials (n = 5). Among the included articles, four discussed HCV treatment alone, and twelve explored the benefits of IVDU in individuals infected with HCV, and 21 focused on the combined treatment for HCV and IVDU. The target population in 36 articles comprised adults over 18 years of age who were infected with HCV and engaged in injection drug use. In this review, the literature findings covered a

wide range of geographic locations; Australia (n = 1), Austria (n = 1), Bangladesh (n = 1),) Canada (n = 5), Czech Republic (n = 1), Tanzania (n = 1), France (n = 1), Italy (n = 1, Norway (n = 2), Spain (n = 2), Sweden (n = 1), Switzerland (n = 1), Taiwan (n = 1), U.S. (n = 17). The main aspect of this review focused on finding if there is an additive advantage in combining HCV and IVDU treatment.

Measured Outcome

HCV treatment

The four articles that focused on HCV treatment alone collectively emphasized the importance of integrating HCV prevention and treatment strategies into primary care settings, expanding access to direct-acting antiviral agents, implementing harm reduction interventions, and utilizing eHealth technologies to enhance screening, diagnosis, and management of HCV infection among IVDU. Artenie et al. (2015) conducted a study to explore the relationship between HCV seroconversion and the frequency of primary care physician visits among IVDUs. Among the 226 participants in the study, 79 individuals experienced HCV seroconversion, leading to an incidence rate of 17.6 per 100 person-years (95% CI: 14.0–21.8), as opposed to the rate of 20.8 per 100 person-years (95% CI: 15.9–26.7) observed in IVDUs who didn't report visiting a primary care physician. Integrating management of HCV infection into primary care is considered an essential strategy for achieving HCV elimination goals as it expands access to care, facilitates early diagnosis and treatment, and provides comprehensive and continuous care for individuals with HCV, leading to improved outcomes and reduced HCV transmission rates in the population (Artenie et al., 2015). Although integrating HCV treatment in a primary care setting reveals promising results, addressing barriers to access treatment is also a significant piece that needs to be solved.

Groesssi et al. (2017) conducted a study to evaluate the cost-effectiveness of the HCV self-management program compared to standard care for individuals with HCV infection. The program demonstrates positive effects on health outcomes by improving patient self-efficacy, treatment adherence, and health-related quality of life. Integrating self-management programs into HCV care has the potential to enhance patient outcomes and reduce healthcare costs. As a result, the study highlights the importance of integrated care models that combine HCV treatment with harm reduction strategies such as access to clean needles and syringes, opioid substitution therapy, and other supportive services. The article also underlines the remarkable advances made in HCV treatment with the introduction of direct-acting antiviral therapy because, historically, IVDUs faced barriers to accessing HCV treatment due to concerns about reinfection and adherence to therapy. Introducing the new direct-acting antiviral therapy demonstrated high cure rates across different populations, including IVDUs. Reducing the infection rate of HCV is achievable; however, interventions and treatment plans will need to be tailored toward the population's needs.

Similarly, Yi et al. (2019) conducted a study that sheds light on the high prevalence of HCV infection among IVDUs in Cambodia and emphasizes the urgent need for targeted interventions to address this public health issue. The study included 286 IVDUs and found that the prevalence of HCV was 30.4% where 28.3% of participants tested positive for HCV. The study also highlighted a lack of knowledge about HCV and low access to prevention and treatment services among the participants. Evidence suggests that HCV treatment must be coupled with harm reduction programs to address the two prominent conditions, IVDU and HCV. Although introducing direct-acting antiviral agents has revolutionized HCV treatment by offering highly effective and well-tolerated options, the therapy does not stop reinfection.

Selfridge et al. (2019) states that direct-acting antiviral treatment for HCV is highly effective in achieving sustained virologic response among individuals attending an inner-city community health center in Victoria, Canada. The study also suggests that successful direct-acting antiviral treatment is associated with lower rates of HCV reinfection and improved survival outcomes. These findings emphasize the importance of providing accessible HCV treatment to vulnerable populations, such as IVDUs, to improve health outcomes and reduce HCV-related mortality. As a result, studies conducted by Selfridge et al. (2019) and Yi et al. (2019) highlight that combining individualized care and tailored approaches are crucial to optimizing treatment outcomes among IVDUs. Collaboration between healthcare providers, harm reduction programs, and substance use treatment services is crucial in providing comprehensive care and support for this population.

Additionally, the study by Groessi et al. (2017) highlights the cost-effectiveness of interventions focused on self-management programs in improving health outcomes for individuals with HCV infection. Generally, the findings of the articles highlight the importance of primary healthcare engagement, targeted interventions, harm reduction strategies, comprehensive HCV care, and self-management programs in the prevention, detection, and treatment of HCV among IVDUs. These findings contribute to the growing body of knowledge on effective approaches to address HCV in this vulnerable population.

IVDU Treatment

The literature regarding the outcome of IVDU treatment reveals that opioid substitution therapy or opioid agonist therapy should be paired with a needle syringe program, mental health counseling, or direct-acting antiviral therapy to achieve successful results. Ijioma et al. (2021) conducted a hypothetical simulation where the effectiveness of a syringe service program alone,

medication for opioid use disorder alone, and combining syringe service program and medication for opioid use disorder was assessed to understand the transmission rate among IVDUs. The study revealed that the combination of a syringe service program and medication for opioid use disorder was the most effective, along with a syringe service program, in preventing HCV transmission among IVDUs. The implementation of syringe service programs resulted in cost savings compared to no intervention (the syringe service program alone saved $363,821 incremental cost per 100 IVDUs). Combination programs that integrated syringe service programs and medication for opioid use disorder were the most cost-effective strategy for HCV harm reduction among IVDUs ($347,573 incremental cost saving achieved per 100 HCV cases per 100 IVDUs).

Similarly, HCV reinfection rate was assessed where individuals received opioid agonist therapy with or without a needle syringe program (Carson et al., 2018). The result revealed that reinfection after treatment was still prevalent when the needle exchange program was not included in the treatment plan because active/ongoing drug use continues to be an issue. Grebely et al. (2022) examined reinfection rates and risky behaviors among individuals receiving opioid agonist therapy after completing direct-acting antiviral therapy. The results of the study revealed that ongoing drug use was reported among 59% of the total participants (296 total participants), and a higher reinfection rate was noticed among recent IV drug use (1.9 [95% CI, 0.5 to 4.8] per 100 person-years; 212 person-years). Active/ongoing drug use is common among IVDUs therefore, it is crucial to pair direct-acting antiviral therapies with needle syringe programs and opioid substitution therapy programs to achieve a successful result (Grebely et al., 2022; Akiyama et al.,2020b; Islam, 2017; Selfridge et al., 2021).

Although reinfection is prevalent, the new direct-acting antiviral therapy has enabled successful outcomes even among IVDUs involved with ongoing drug use (Macías et al., 2019). The study investigated the response to direct-acting antiviral therapy in individuals who participate in an ongoing IVDU or receive opioid substitution therapy. The study findings indicate that direct-acting antiviral therapy is highly effective in achieving a sustained virological response in this population. The sustained virologic response rates were comparable to those observed in individuals who do not use drugs or receive opioid substitution therapy. Additionally, the study found that adherence to direct-acting antiviral treatment was crucial for achieving optimal outcomes, emphasizing the importance of comprehensive support programs for individuals with ongoing drug use or opioid substitution therapy. The results of this study suggest that direct-acting antiviral therapy can successfully treat HCV in this population, highlighting the potential for expanding access to treatment and improving outcomes for individuals with HCV who use drugs or are on opioid substitution therapy.

Treatment plans that address reinfection are a critical part of the puzzle that can aid in eliminating HCV from the world. Islam et al. (2017) examined the incidence, risk factors, and prevention of HCV reinfection. The study's findings indicate that reinfection with HCV is a significant concern among individuals who participate in an ongoing drug use or have previously cleared the infection use. The reinfection incidence was high, particularly among individuals who continued high-risk behaviors, such as IVDUs. The study also highlights the importance of prevention strategies to reduce the risk of reinfection. Access to harm reduction services, such as needle exchange programs and opioid substitution therapy, was associated with a reduced risk of reinfection.

In addition to the direct-acting antiviral therapy, a study conducted by Gustafsson et al. (2016) showed promising results when medication-assisted treatment for opioid dependence is paired with a smartphone innovation called A-CHESS. The study randomly assigned 440 participants to receive medication-assisted treatment alone or medication-assisted treatment and A-CHESS; the results suggested bundling this intervention (medication-assisted treatment and A-CHESS) increased effectiveness and access to treatment for opioid dependence and HCV. Needle syringe programs and opioid substitution therapy have effectively prevented HCV transmission among IVDUs. A modeling study conducted in Tanzania assessed the impact of HIV and HCV prevention and treatment interventions among IVDUs in Dar es Salaam (Fraser et al., 2021). The study revealed that a scaled-up harm reduction intervention could be expected to reduce HCV incidence by 81.4% over the next decade. The results suggested that scaling up harm reduction interventions, including needle and syringe programs and opioid substitution therapy, could substantially reduce HIV and HCV transmission among this population.

Minoyan et al. (2020) conducted a study within an ongoing community cohort, interviewing and testing IVDUs undergoing opioid agonist therapy for HCV. The results demonstrated a 77% decrease in HCV acquisition among those receiving opioid agonist therapy compared to non-recipients. Additionally, the study highlighted that opioid substitution therapy was associated with a lowered risk of HCV infection for both injecting and non-injecting drug users. This suggests that opioid substitution therapy reduces HCV transmission among individuals with a history of drug use (Wang et al., 2020; Akiyama et al., 2020b). Wang el. (2020) also investigated the risk of HCV infection among individuals receiving opioid substitution therapy, both injecting and noninjecting drug users. The study emphasizes the elevated risk of HCV infection among individuals receiving opioid substitution therapy,

particularly among IVDUS. It underscores the need for effective preventive measures and interventions to reduce HCV transmission in this population, including harm reduction initiatives, education on safer drug use practices, and testing and treatment programs for HCV. In addition, opioid substitution therapy was associated with increased HCV testing, treatment uptake, and improved treatment outcomes, emphasizing its beneficial role in HCV management.

Harm reduction strategies are crucial in preventing new infections and improving public health. Generally, the findings emphasize the effectiveness of harm reduction strategies, such as needle syringe programs, opioid substitution therapy, and access to direct-acting antiviral therapy, in preventing HCV transmission among IVDUs. Bota et al. (2021) highlight the importance of comprehensive approaches that combine prevention, treatment, and support services, such as mental health counseling to reduce the burden of HCV. While direct-acting antiviral therapy for HCV infection has been highly effective, there is a significant risk of reinfection, mainly among IVDUs. However, incorporating harm reduction strategies such as needle syringe programs and opioid agonist therapy can help reduce reinfection rates, as well as improve testing, treatment uptake, and outcomes. Comprehensive approaches that address social determinants, such as access to care and ongoing prevention efforts, are crucial for reducing the HCV infection rate. The main findings of the articles that focused on IVDU treatment emphasized that treating IVDU alone without combining it with harm reduction strategies results in a high reinfection rate.

HCV and IVDU treatment

Each study reviewed in this section contributes to the broader understanding of HCV treatment and prevention among IVDUS. The collective evidence can be used for the development and implementation of comprehensive and effective interventions that can be used

to address the increasing HCV infection rate. The retrieved articles covered various features of HCV treatment and prevention among IVDUs. The findings suggest that integrated and patient-centered approaches effectively improve the treatment uptake, management, and outcomes of HCV infection among IVDUs. These approaches include combining HCV treatment with harm reduction programs, increasing screening and diagnosis rates, increasing linkage to care, and utilizing telemedicine to expand access. The studies highlight the importance of integrated treatment protocols that address the unique needs of IVDUs (Fadness et al., 2019; Talal et al., 2019; Rosenthal et al., 2020). In an observational trial at a harm reduction organization's drop-in-center in Washington, D.C. in the U.S., 100 patients infected with HCV that have opioid disorders with ongoing drug use issues were receiving treatment for HCV and IVDU (Rosenthal et al., 2020). The study assessed sustained virologic response (SVR) and uptake and retention in opioid agonist therapy; 88% achieved a sustained virologic response, and by week 24, 68% were receiving opioid agonist therapy. The findings of the study by Rosenthal et al. (2020) suggested the feasibility and benefits of integrating both treatments to improve health outcomes. In addition, a study conducted in Sweden by Ydrebor et al., 2023 examined the linkage to HCV treatment among individuals receiving opioid substitution therapy in two units. The results revealed that out of 225 participants, 29 were referred to the model of care (testing for HCV and treatment for HCV RNA-positive patients on site), and 17 patients received treatment in which 100% of those treated reached sustained virologic response. A randomized controlled trial is being conducted by Fadness et al. (2019) to evaluate the efficacy of an integrated treatment approach for IVDU infected by HCV.

Often, individuals infected with HCV face several barriers, such as access to care to stigma (Tofighni et al., 2020). A study conducted by Assoumou et al. (2021) explored patient

perspectives on increasing treatment uptake and identified strategies to enhance engagement. The study's findings identify active substance use as a significant barrier to HCV treatment uptake and suggest using an integrative approach that treats HCV and substance use concurrently. Telemedicine was found to be a promising approach to addressing barriers to providing HCV treatment within opioid treatment programs, with patients reporting positive reactions to this mode of care delivery (Telal et al., 2019). The findings indicated positive patient experiences and acceptance of telemedicine to enhance HCV care and access.

Additionally, studies conducted in Italy and Bangladesh reported increased HCV screening, diagnosis, and linkage to care rates among IVDUs through patient-centered programs. A retrospective study conducted in Bangladesh by Rahman et al. (2019) investigated HCV treatment outcomes among IVDUs receiving harm reduction services in Bangladesh; 87% of the participants achieved a sustained virologic response, and 75% were adherent to HCV therapy. The study states that additional interventions, such as opioid substitution therapy, mental health counseling, and follow-up, alongside HCV treatment, will need to be provided concurrently to achieve a fulfilling result. Meanwhile, the study by Mangia et al. (2021) focused on implementing a patient-centered program in Italy to improve HCV-related outcomes among IVDUs. Considering this population's unique needs and challenges, the program adopted a comprehensive approach. Mangia et al. (2021) assessed the impact of a patient-centered program on HCV screening, diagnosis, and linkage to care rates among HCV-infected IVDUs. The results indicated increased screening rates, improved diagnosis rates, and enhanced linkage to care; 98% of the participants completed HCV treatment without reinfection.

Modeling studies underline the importance of combining HCV treatment and prevention strategies among IVDUs (Zelenev et al., 2021; Fraser et al., 2018). Zelenev et al. (2021)

conducted a modeling analysis suggesting that implementing HCV treatment, harm reduction strategies, and targeted interventions could significantly reduce HCV transmission and prevalence among IVDUs in the United States. These findings support the importance of comprehensive approaches integrating multiple interventions to effectively control HCV among this high-risk population, such as IVDUs. Similarly, Fraser et al. (2018) used a mathematical modeling approach to simulate the spread of HCV in rural areas and evaluate the potential impact of scaling up interventions. They incorporated data on HCV prevalence, transmission risk behaviors, and the effectiveness of interventions such as HCV testing, linkage to care, and treatment. The model also considered factors such as the availability of healthcare resources, treatment capacity, and the impact of scaling up interventions over time. The results demonstrated that scaling up HCV prevention and treatment interventions could substantially impact tackling the increasing HCV epidemic. HCV incidence and prevalence reduced significantly (90% reduction) in 2030 and scaled-up medication-assisted treatment and syringe service program treatment rates can be reduced by half (89 per 1000 annually or 15%) compared to those without scaled-up medication-assisted treatment and syringe service program (159 per 1000 or 25%; Fraser et al., 2018). Investing in HCV interventions for IVDU can yield cost savings in the long run.

Cousein et al. (2018), Schackman et al. (2018) and Barbosa et al. (2019) conducted a study that collectively emphasize the effectiveness and cost-effectiveness of interventions targeting harm reduction and the cascade of care for HCV among IVDUs. The studies highlight the importance of implementing comprehensive strategies to address HCV transmission and improve health outcomes among this population. Cousien et al. (2018) employed a mathematical modeling approach to simulate the impact of various interventions on HCV transmission and

disease progression among IVDUs. The findings indicated that when scaled-up interventions were combined with harm reduction improvements, there was a reduction of 37% in new infections with an incremental cost-effectiveness ratio (ICER) of €5300/QALY, translating to a life expectancy of 16.694 quality-adjusted life years (QALY). In contrast, without these improvements, the reduction in new infections was 41% with an ICER of €105600/QALY, resulting in a life expectancy of 16.701 QALYs. Expanding the cascade of care by increasing HCV testing, treatment initiation, and adherence was cost-effective in improving health outcomes and reducing the long-term burden of HCV. Similarly, in the U.S., Schackman et al. (2018) used a mathematical model to simulate the outcomes and costs associated with implementing the intervention (screening and linkage to care) compared to the standard of care. The result revealed that 35% of the participants in the control were linked to care, achieving 31% sustained virologic response; on the contrary, the intervention group resulted in 60% linkage to care, with 54% achieving sustained virologic response with a monetary saving of $511,00–$975,600. Barbosa et al. (2019) assessed the cost-effectiveness of scaling up HCV prevention and treatment among IVDUs. The study emphasizes that expanding HCV prevention measures, such as needle exchange programs and providing access to affordable treatment, can lead to substantial reductions in HCV-related morbidity, mortality, and healthcare costs.

The issue of reinfection after successful treatment was also examined, with a study from Switzerland exploring reinfection rates among IVDUs attending a multidisciplinary treatment center (Falcato et al., 2021). The study showed that reinfection with HCV after successful treatment with direct-acting antiviral was relatively common among IVDUs. Out of the total number of participants (n = 153) included in the study, a significant proportion (approximately 58%) experienced reinfection within 346 person-years following their successful treatment. The

findings emphasize the ongoing challenges IVUDs face in maintaining sustained virologic response status even after successful treatment. The high rates of reinfection emphasize the need for comprehensive and integrated interventions beyond antiviral therapy alone. The study emphasizes the importance of harm reduction strategies, such as education on safer injection practices, needle exchange programs, and access to opioid substitution therapy, to effectively reduce the risk of HCV reinfection among this vulnerable population. HCV reinfection is a significant concern, particularly among high-risk populations such as IVDU and individuals with a history of HCV infection.

Understanding the dynamics and implications of HCV reinfection is crucial for effective prevention and management strategies. The study conducted by Akiyama et al. (2020a) investigated transmission, relapse, and reinfection patterns of HCV among IVDUs receiving opioid agonist therapy. The findings of this study highlight the complex dynamics of HCV transmission, relapse, and reinfection among IVDUs receiving opioid agonist therapy. Identifying transmission networks and reinfection events emphasizes the ongoing risk of HCV acquisition within this population, even during opioid agonist treatment. Akiyama et al. (2020a) underline the need for comprehensive interventions that address initial HCV infection and the risk of reinfection and relapse. Strategies such as harm reduction programs, increased access to opioid agonist therapy, and ongoing monitoring and support for IVDUs can reduce HCV transmission and reinfection rates. A study conducted by Corona-Mata et al. (2023) assessed the efficacy of a comprehensive strategy for detecting and treating HCV infection in a population attending addiction centers. The study implemented a strategy focused on screening, comprehensive evaluation (screening for advanced liver disease), and treatment of HCV infection. As a result, three aspects were assessed: treatment uptake, end-of-treatment response

(ETR), and sustained virologic response rate. A high treatment uptake of 90.9% was observed; of the 33 participants, 93.3% reached ETR, and 78.8% achieved a sustained virologic response. The findings suggest that the comprehensive strategy implemented in the addiction center population effectively detected HCV infection, facilitated treatment initiation, and achieved favorable treatment outcomes. The high rates of treatment completion and sustained virologic response indicate this population's successful control and management of HCV infection.

Similarly, another study discussed the potential for HCV treatment in low-threshold programs and projected the impact of scaling up prevention and treatment interventions (Midgard et al., 2021). The study demonstrated high rates of treatment initiation (363 out of 488 participants) and virologic response (94.7%) among individuals undergoing HCV treatment. However, high reinfection cases (3.74 per 100 person-year) were detected, particularly among younger individuals engaged in ongoing IVDU. This indicates the need for ongoing surveillance and comprehensive harm reduction strategies to prevent reinfection and support successful retreatment in this population.

Ongoing surveillance efforts and comprehensive harm reduction strategies collaborate to improve each stage of the HCV care cascade for IVDU populations. Identifying new infections, facilitating diagnosis and linkage to care, and supporting treatment initiation and adherence contribute to reducing the HCV infection rate and improving outcomes among individuals who inject drugs. Marshal et al. (2022) examined the HCV care cascade from the perspective of IVDUs infected with HCV in the interferon-free direct-acting antiviral treatment era. The findings highlight the complex and multi-layered nature of the care cascade, with various barriers and facilitators influencing engagement at each stage. Person-centered care, characterized by respectful and supportive relationships between clients and healthcare providers, enhances

engagement. Peer support programs are valuable in navigating the cascade and providing emotional support. Ongoing support after receiving direct-acting antiviral treatment, including monitoring for reinfection, and addressing long-term effects of HCV, is critical to the care cascade. Overall, the study emphasized the importance of comprehensive, patient-centered approaches and support services in addressing the challenges of HCV care and optimizing maximum outcomes.

Similarly, a study by William et al. (2019) explored the impact of direct-acting antiviral treatment on the lives of IVDUs infected by HCV. The study aimed to understand how receiving direct-acting antiviral treatment can bring positive changes and transformations in participants' lives, such as physical and mental well-being, social connections, self-perception, and personal growth. An in-depth interview was conducted with a sample of 27 participants receiving direct-acting antiviral therapy, where one group was receiving opioid agonist therapy, and the other was participating in a needle syringe program. Both groups reported engaging in life projects such as pursuing education, employment, and strengthening family relationships after receiving direct-acting antiviral treatment. The study's result supported the need to implement comprehensive support services and address social determinants of health to maximize the positive impact of HCV treatment on the lives of IVDUs.

Several pieces of literature support the significance of addressing the specific needs and experiences of IVDU in the context of HCV treatment to optimize outcomes. A study conducted in the Czech Republic by Krekulová & Vavrinčíková (2021) focused on understanding the perspectives and challenges faced by IVDU during the HCV treatment process. The study's findings indicate that most participants expressed a desire to undergo HCV treatment due to concerns about their health and the potential for transmission to others. Moreover, integrating

HCV treatment into the existing methadone program was deemed beneficial, as it facilitated access to treatment and enhanced adherence. These studies highlight the importance of tailored interventions, integrated care, harm reduction strategies, and ongoing support services in improving HCV treatment and prevention outcomes among IVDUs. Overall, this review examined the literature on the effectiveness and benefits of combining HCV and injection drug use IVDU treatment. Thirty-six articles were included, employing various research methods, and covering various geographic locations.

Among the articles, 20 focused on combined HCV and IVDU treatment, four discussed HCV treatment alone, and twelve explored the benefits of IVDU in HCV-infected individuals. The findings highlighted the importance of integrating HCV prevention and treatment strategies into primary care settings, expanding access to direct-acting antiviral, implementing harm reduction interventions, and utilizing eHealth technologies. Combining HCV and IVDU treatment improved outcomes and reduced HCV transmission rates. Harm reduction strategies, such as needle syringe exchange programs and opioid substitution therapy, effectively prevented HCV transmission among IVDUs. The studies emphasized the need for comprehensive approaches that address social determinants, access to care, ongoing prevention efforts, and tailored treatment plans to optimize outcomes among IVDUs. Telemedicine and patient-centered programs were also identified as promising approaches to enhance HCV care and access. The findings contribute to understanding the effectiveness and potential benefits of integrated interventions targeting HCV and IVDU, with implications for research, policy development, and implementation of evidence-based strategies to address these health concerns. A discussion of findings and related impactions will be provided in Chapter Five.

Chapter Five

Discussion

The primary purpose of this project was to investigate and evaluate the effectiveness of concurrently treating IVDUs infected with HCV as a strategy to reduce the HCV infection rate in the United States. IVDU is a significant risk factor for HCV transmission and the prevalence of HCV infection among IVDUs is disproportionately high (Shayan et al., 2021). Traditional approaches to HCV treatment have often overlooked this population due to various challenges, including ongoing drug use and limited access to healthcare (Biondi & Feld, 2020).

This project aimed to address IVDUs' challenges in accessing care by exploring the feasibility and impact of providing integrated care, which involves simultaneous treatment for opioid use disorder and HCV infection. By offering both opioid substitution therapy and direct-acting antiviral treatment for HCV, this approach can potentially improve outcomes for IVDUs and reduce the HCV transmission rate.

The findings from this project contribute to the existing evidence regarding the efficacy of simultaneous treatment for IVDU and HCV. It provides valuable insights into this integrated approach's feasibility, suitability, and effectiveness and its potential impact on reducing the HCV infection rate among IVDUs.

Discussion of the Results

The results and findings discussed in this review provide a valuable understanding of the effectiveness and potential benefits of integrated interventions targeting HCV and IVDU. The reviewed studies shed light on the importance of combining HCV treatment with harm reduction strategies and addressing the specific needs of individuals who engage in IVDU.

Regarding HCV treatment alone, the collected literature emphasized the significance of integrating HCV prevention and treatment strategies into primary care settings (Artenie et al., 2015). The findings highlighted the importance of expanding access to direct-acting antiviral agents, implementing harm-reduction interventions, and utilizing eHealth technologies for screening, diagnosis, and management of HCV infection among IVDUs (Yi et al., 2019; Grossei et al., 2017). Integrating the management of HCV infection into primary care was deemed essential for achieving HCV elimination goals, as it facilitates early diagnosis, treatment, and comprehensive care for individuals with HCV. The studies also emphasized the need to address barriers to accessing treatment to ensure remarkable outcomes (Grossei et al., 2017; Artenie et al., 2015)

The introduction of direct-acting antiviral therapy was identified as a significant advancement in HCV treatment by overcoming historical barriers faced by IVDUs in accessing treatment (Grossei et al., 2017). The therapy demonstrated high cure rates across different populations, including IVDUs (Selfridge et al., 2019). The studies underlined the importance of reducing the infection rate of HCV through tailored interventions and treatment plans that consider the population's unique needs (Yi et al., 2019; Grossei et al., 2017; Selfridge et al., 2019). Collaboration between healthcare providers, harm reduction programs, and substance use treatment services was emphasized as crucial for providing comprehensive care and support to IVDUs (Selfridge et al., 2019; Yi et al., 2019).

The literature collected regarding IVDU treatment collectively provides valuable insights into the effectiveness of various interventions for preventing and treating HCV among IVDUs. The findings highlight the importance of combining harm reduction strategies, such as needle syringe programs and opioid substitution therapy, with other interventions to achieve successful

outcomes (Carson et al., 2018; Grebely et al., 2022; Akiyama et al.,2020b; Islam, 2017; Selfridge et al., 2021).

A study by Ijioma et al. (2021) demonstrated that combining a syringe service program and medication for opioid use disorder is a more practical approach to preventing HCV transmission among IVDUs. This combination also leads to cost savings compared to no intervention. Similarly, Carson et al. (2018) and Grebely et al. (2022) highlight the significance of needle syringe programs in reducing reinfection rates and risky behaviors among IVDUs.

Direct-acting antiviral therapy has also shown promising results in treating HCV among IVDUs, even those with ongoing drug use (Macías et al., 2019). The study revealed that direct-acting antiviral therapy is highly effective in achieving a sustained virological response in this population. Adherence to treatment and comprehensive support programs also play a crucial factor in achieving the desired outcome (Macías et al., 2019; Bota et al., 2021).

The prevention of reinfection is a critical aspect of HCV treatment, as highlighted by Islam et al. (2017). Access to harm reduction services, such as needle exchange programs and opioid substitution therapy, can significantly reduce the risk of reinfection (Ijioma et al., 2021; Islam et al., 2017; Fraser et al., 2021). Combining medication-assisted treatment for opioid dependence with innovative approaches, such as smartphone interventions like A-CHESS, has shown promise in improving treatment effectiveness and access for opioid dependence and HCV (Gustafsson et al., 2016).

In addition, harm reduction strategies, including needle syringe programs and opioid substitution therapy, have consistently shown effectiveness in preventing HCV transmission among IVDUs (Ijioma et al., 2021; Carson et al., 2018; Fraser et al., 2021; Grebely et al., 2022; Akiyama et al.,2020b; Islam, 2017; Selfridge et al., 2021). The findings emphasize the

substantial impact of scaled-up harm reduction interventions in reducing HCV transmission among this population. The studies also emphasize the role of opioid substitution therapy in reducing HCV transmission among individuals with a history of drug use (Minoyan et al., 2020; Wang et al., 2020). Opioid substitution therapy reduces the risk of HCV infection and increases HCV testing, treatment uptake, and improved treatment outcomes (Minoyan et al., 2020). Overall, the findings support implementing comprehensive harm reduction strategies that combine prevention, treatment, and support services to address HCV among IVDUs effectively. These strategies should include needle syringe programs, opioid substitution therapy, access to direct-acting antiviral therapy, and ongoing prevention efforts. A comprehensive approach that addresses social determinants and ensures access to care is crucial for reducing HCV transmission rates and improving public health outcomes (Bota et al., 2021).

In the context of combined HCV and IVDU treatment, the collected evidence supports developing and implementing comprehensive interventions to address this population's increasing HCV infection rates. The findings highlight the effectiveness of integrated and patient-centered approaches in improving treatment uptake, management, and outcomes of HCV infection among IVDUs.

One of the key findings is the positive impact of combining HCV treatment with harm reduction programs. Studies conducted in Washington, D.C., U.S., Sweden, Italy, and Bangladesh demonstrate the effectiveness of harm reduction strategies, such as opioid substitution therapy, needle exchange programs, and mental health counseling, alongside HCV treatment in improving health outcomes and reducing reinfection rates (Rosenthal et al., 2020; Ydrebor et al., 2023; Rahman et al., 2019; Mangia et al., 2021). These integrated approaches resulted in high rates of sustained virologic response and treatment completion among IVDUs.

The use of telemedicine is another promising approach identified in the literature. Studies suggest telemedicine can help overcome barriers to accessing HCV treatment within opioid treatment programs (Telal et al., 2019; Assoumou et al., 2021). Patients reported positive experiences and acceptance of telemedicine, which can enhance HCV care and improve access to IVDUs.

Mathematical modeling studies emphasize the benefits of combining HCV treatment and prevention strategies to reduce HCV transmission and prevalence among IVDUs (Zelenev et al., 2021; Fraser et al., 2018; Cousien et al., 2018). These studies highlight the potential impact of scaling up interventions such as HCV testing, linkage to care, harm reduction strategies, and medication-assisted treatment. In addition, the findings demonstrate that comprehensive approaches integrating multiple interventions can substantially reduce HCV incidence and prevalence among IVDUs (Zelenev et al., 2021; Fraser et al., 2018).

The cost-effectiveness of interventions targeting harm reduction and the cascade of care for HCV among IVDUs is also highlighted (Cousein et al., 2018; Schackman et al.,2018; Barbosa et al., 2019). Mathematical modeling studies and cost-effectiveness analyses support implementing comprehensive strategies, including harm reduction improvements, scaling up HCV prevention, and treatment interventions (Zelenev et al., 2021; Fraser et al., 2018; Cousien et al., 2018; Schackman et al.,2018). These interventions not only improve health outcomes but also yield long-term cost savings.

Reinfection after successful treatment is a significant concern among IVDUs (Falcato et al., 2021). Studies from Switzerland and Italy highlight the relatively high rates of reinfection among this population (Falcato et al., 2021; Krekulová & Vavrinčíková, 2021). Comprehensive harm reduction strategies, ongoing surveillance, and support services are essential in reducing

the risk of reinfection and addressing the challenges of maintaining sustained virologic response status (Falcato et al., 2021; Akiyama et al., 2020a; Corona-Mata et al., 2023; Midgard et al., 2021; Marshal et al., 2022). The literature emphasizes the need for person-centered care, peer support programs, and ongoing monitoring and support for IVDUs throughout the HCV care cascade. Studies show that respectful and supportive relationships between patients, healthcare providers, and peer support groups can enhance engagement and improve health outcomes (William et al., 2019; Marshall et al., 2022). Furthermore, comprehensive support services addressing social determinants of health can maximize the positive impact of HCV treatment on the lives of IVDUs (William et al., 2019; Krekulová & Vavrinčíková, 2021)

Overall, the reviewed studies regarding the combination of HCV and IVDU treatment highlight the understanding of the effectiveness and benefits of integrated interventions targeting HCV and IVDU. The literature supports the implementation of comprehensive strategies that address the specific needs and experiences of IVDUs, integrate HCV treatment into existing programs, and provide ongoing support services.

Relationship of the Findings to Prior Research

The findings discussed in this review build upon prior research in HCV and IVDU. The findings regarding the effectiveness of HCV treatment confirm and extend previous research on the effectiveness of direct-acting antiviral therapy for HCV treatment. Prior studies have demonstrated these therapies' high cure rates and efficacy across different populations, including individuals who engage in IVDU (Manns & von Hahn, 2013). The current findings reinforce this evidence and emphasize the importance of expanding access to HCV treatment to achieve HCV elimination goals (Artenie et al., 2015; Macías et al., 2019; Gustafsson et al., 2016; Bota et al., 2021).

Another aspect discussed in this review is the integration of HCV and harm reduction strategies, in which previous research has highlighted the importance of integrating HCV prevention and treatment strategies with harm reduction approaches (Willenbring, 2005). The current findings align with this literature, emphasizing the need for comprehensive interventions that combine HCV treatment, harm reduction programs (such as needle syringe programs and opioid substitution therapy), and support services (Grossei et al.,2017; Fraser et al., 2021; Bota et al., 2021). Integrating these strategies is crucial for addressing the specific needs and challenges IVDUs face. In addition, prior studies have highlighted the risk of reinfection due to ongoing drug use, and the limitation of receiving treatment was emphasized (Hellard et al., 2009). The current findings reinforce these concepts, emphasizing the need for comprehensive support programs that combine harm reduction measures with HCV treatment to minimize reinfection risk and the ability of the new antiviral medication to successfully treat IVUD involved with ongoing drug use (Selfridge et al., 2019; Macías et al., 2019; Isalm et al., 2017)

The importance of patient-centered care for individuals affected by HCV and IVDU cannot be reiterated enough. The current findings highlight the significance of tailored interventions that consider the unique needs and circumstances of IVDUs (Selfridge et al., 2019; Yi et al., 2019). Integrating HCV treatment, harm reduction programs, and support services within a patient-centered framework is essential for improving treatment uptake, adherence, and overall health outcomes (Rahman et al., 2019; Mangia et al., 2021). Addressing barriers to receiving adequate treatment is a concept that has been an important topic when it comes to addressing HCV infection among IVDUs (Artenie et al., 2015; Tofighni et al., 2020). Prior research has identified stigma, limited healthcare access, and ongoing drug use as barriers to HCV treatment (Manns & von Hahn, 2013). The current findings emphasize the need to address

these barriers through innovative approaches, such as eHealth technologies, expanded primary care involvement, and collaborative care models involving multiple stakeholders (Artenie et al., 2015; Groessi et al., 2017; Telal et al., 2019).

Generally, the relationship of the current findings to prior research lies in their alignment with the extension of existing knowledge regarding the effectiveness of HCV treatment, the integration of harm reduction strategies, the identification of barriers to treatment, the prevention of reinfection, and the importance of patient-centered care.

Gaps in the Literature

While the reviewed literature provides valuable insights into integrating HCV and IVDU treatment, a few gaps exist in the current research. Many of the studies reviewed focused on short-term outcomes such as HCV treatment uptake, sustained virologic response, and reduced HCV transmission rates (Wang et al., 2020; Assoumou et al., 2021; Corona-Mata et al., 2023). There is a need for more research that examines the long-term outcomes of integrated interventions, including the durability of treatment response, reinfection rates, and overall health outcomes among IVDUs.

In addition, most of the studies included in the review were conducted in high-income countries, particularly in North America and Europe. There is a need for research that includes a more diverse range of populations and settings, such as low- and middle-income countries and regions with high rates of HCV and IVDU. This would provide a more comprehensive understanding of the effectiveness and challenges of integrated interventions in different contexts.

While some qualitative studies were included in the review, there is a need for more qualitative research to explore the experiences, perspectives, and barriers faced by IVDUs in

accessing and adhering to integrated treatment programs (Assoumou et al., 2021; Tofighi et al., 2018; William et al., 2019). Qualitative research can provide valuable insights into the social, cultural, and structural factors influencing treatment outcomes and help develop tailored interventions (Renjith et al., 2021).

Many individuals who engage in IVDU may have comorbidities or co-infections, such as HIV or mental health disorders (Cooper et al., 2019). The reviewed literature had limited focus on the integration of HCV treatment with the management of these comorbidities. Future research should explore integrating care for multiple conditions to ensure comprehensive care for IVDUs. Addressing these gaps in the literature would contribute to a more comprehensive understanding of the challenges and opportunities in integrating HCV and IVDU treatment. It would also inform the development of evidence-based interventions that can effectively address the complex needs of this population and contribute to efforts to eliminate HCV not only in the United States, but globally as well.

Implications for Future Practice, Research, and Policy

The implications for future practice, research, and policy in integrating HCV and IVDU treatment are multi-layered. Addressing implications can help improve the outcomes and well-being of IVDUs affected by HCV. Healthcare providers must aim to integrate HCV treatment with existing harm reduction and substance use disorder treatment services (Day et al., 2019). This includes providing HCV testing, education, counseling, and treatment within harm reduction programs, needle exchange programs, and drug treatment centers. Collaboration between healthcare providers, addiction specialists, social workers, and mental health professionals is essential to address the complex needs of IVDU infected with HCV (Grebely et al., 2017). Coordinated care can improve treatment adherence and overall health outcomes. In

addition, peer support programs that involve individuals who have walked similar paths and experiences can play a significant role in engaging and supporting IVDUs in HCV treatment (Jugnarain et al., 2022). Incorporating peer navigators or community health workers can help bridge gaps and enhance communication between healthcare providers and IVDU populations.

Moreover, research should explore the impact of integrating HCV and IVDU treatment on health disparities and equity (Goodyear et al., 2021). This includes investigating whether integrated interventions effectively reach and address the needs of underserved populations, such as racial and ethnic minorities, people experiencing homelessness, and individuals with a history of incarceration. Further research must examine the factors that facilitate or hinder the successful implementation of integrated interventions among these vulnerable populations, such as access to care, religious beliefs, social norms, stigma, and low-literacy level. This includes identifying barriers and facilitators at the individual, organizational, and systemic levels and developing strategies to overcome implementation challenges (Schaeffer & Khalili, 2015).

Often addressing the needs of the underserved population requires the dedication of policymakers and healthcare professionals to make an impact (Anderman & CLEAR Collaboration, 2016; Laraque & Varma,2017). Policymakers should ensure that funding and reimbursement structures support integrating HCV and IVDU treatment (Trickey et al., 2019). Adequate resources should be allocated to sustain integrated interventions, including funding for testing, treatment medications, harm reduction services, and support programs. In addition, policies should be revised to reduce barriers to HCV treatment for individuals, i.e., IVDUs, homeless individuals, and low-income families. This includes eliminating restrictions to received treatments. Policies should be evidence-based and focused on harm reduction principles.

Policymakers should promote collaboration and coordination among healthcare providers, harm reduction programs, and substance use disorder treatment services.

By addressing these implications, future practice, research, and policy can contribute to improving the integration of HCV and IVDU treatment, enhancing access to care, reducing health disparities, and ultimately working towards eliminating HCV as a public health threat.

Summary

The review explored the effectiveness of combining HCV and IVDU treatment. It included thirty-six articles from diverse settings and populations. The findings highlighted the importance of integrated care to improve HCV treatment uptake, management, and outcomes among IVDUs. The studies on HCV treatment alone emphasized integrating HCV prevention and treatment strategies into primary care settings. Access to direct-acting antiviral agents, harm reduction interventions, and eHealth technologies were identified as essential elements in this integration.

Research on IVDU treatment showed that opioid substitution therapy should be combined with harm reduction strategies, such as needle syringe programs, mental health counseling, and direct-acting antiviral therapy. Combining these interventions reduced HCV transmission rates and improved treatment outcomes, especially when addressing ongoing drug use among IVDUs.In addition, the findings emphasized the significance of addressing HCV reinfection, as it remains a concern even after successful treatment. Comprehensive harm reduction strategies, access to care, and ongoing support services are crucial in preventing reinfection and supporting successful retreatment. The collective evidence highlights the importance of integrated and patient-centered approaches to improve HCV treatment and prevention outcomes in this high-risk population. Integrated treatment protocols that consider the unique needs of IVDUs have been shown to improve health outcomes effectively. Patient-centered programs in Italy and Bangladesh have successfully increased HCV screening, diagnosis, and linkage to care rates among IVDUs. Mathematical modeling studies emphasize the significance of combining HCV treatment and harm reduction strategies to reduce HCV transmission in this vulnerable group.

Furthermore, the research underscores the cost-effectiveness of interventions targeting harm reduction and the cascade of care for HCV among IVDUs. However, the issue of HCV reinfection after successful treatment remains a concern, highlighting the necessity for comprehensive harm reduction strategies. Overall, a tailored, patient-centered approach and ongoing support services are crucial for enhancing engagement in the care cascade and optimizing outcomes for IVDUs in the context of HCV treatment and prevention efforts.

Conclusion

The battle against HCV has seen remarkable progress in recent years due to the development of advanced treatment options and preventive strategies. Among the high-risk populations vulnerable to HCV infection, IVDUs have been a focus of concern due to their increased susceptibility to transmission. Combining HCV treatment and prevention efforts among IVDUs has emerged as a promising approach to address the rising infection rates and improve health outcomes within this group.

The body of research reviewed in this study demonstrates the vital importance and undeniable benefits of combining HCV treatment with interventions targeted at individuals who are IVDUs. The evidence overwhelmingly supports the implementation of integrated and patient-centered approaches that address the unique needs of this high-risk population. Comprehensive and effective interventions can be developed and implemented by merging HCV treatment with harm reduction programs, increasing screening and diagnosis rates, enhancing linkage to care, and utilizing telemedicine. These efforts have proven to significantly improve treatment uptake, management, and outcomes of HCV infection among IVDUs. As we continue our fight against HCV, embracing this integrated approach is not merely essential, but also serves as a guiding light leading us towards a future where the burden of HCV is alleviated and the health and well-being of those affected will be safeguarded.

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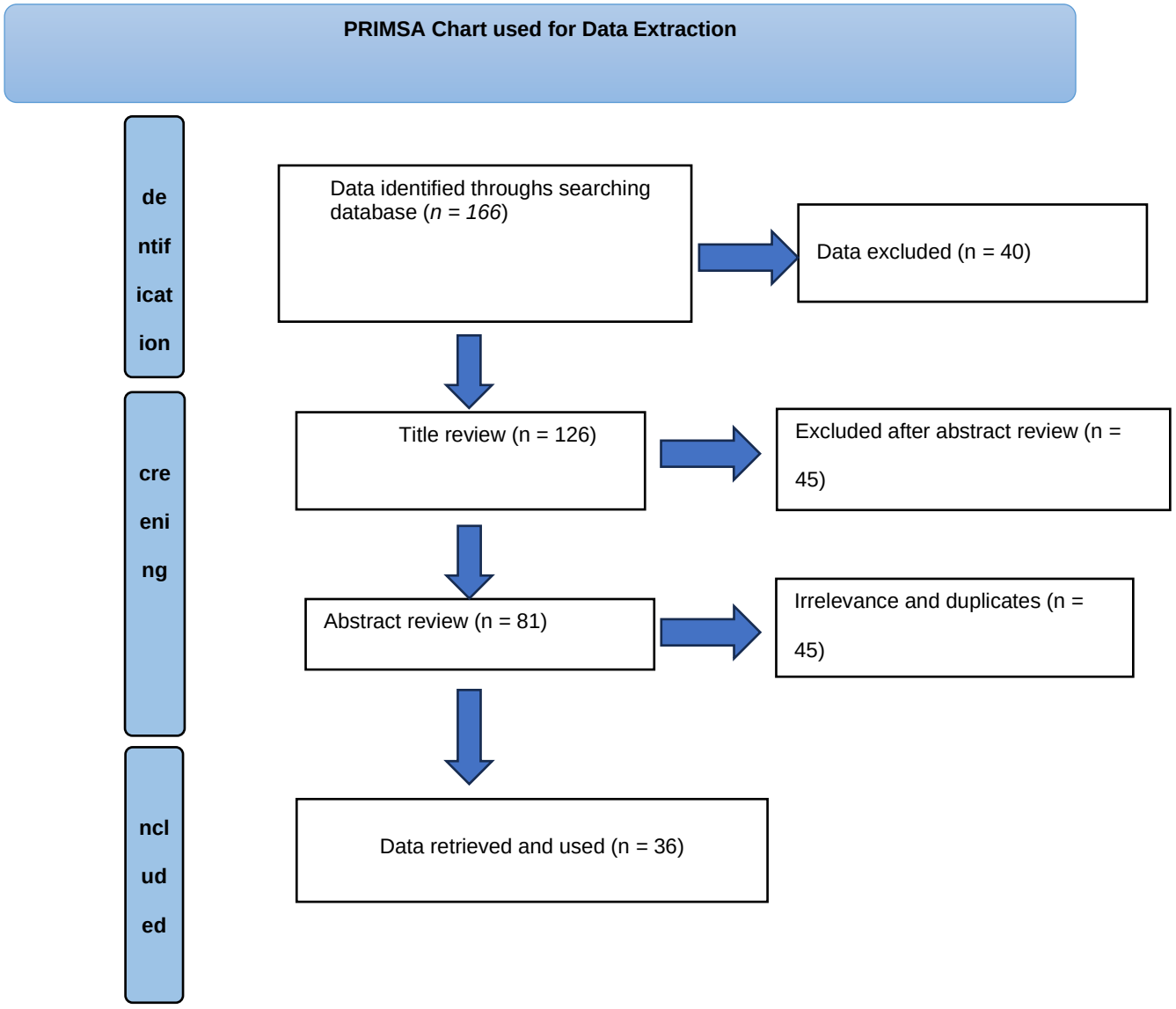
Appendices

Appendix A: PRISMA Chart for Data Extraction



Appendix B: JBI Checklist

JBI Checklist Questions	Authors					
	Akiyama et al., 2020a	Akiyama et al., 2020b	Artenie et al., 2015	Assoumou et al., 2021	Barbosa et al., 2019	Bota et al., 2021
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria for appraising studies appropriate?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes No ✓ Unclear Not Applicable	Yes No ✓ Unclear Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
7. Were there methods to minimize errors in data extraction?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
9. Was the likelihood of publication bias assessed?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
10. Were recommendations for policy and/or practice	Yes ✓ No	Yes ✓ No	Yes ✓ No	Yes ✓ No	Yes ✓ No	Yes ✓ No

supported by the reported data?	Unclear Not Applicable	Unclear Not Applicable	Unclear Not Applicable	Unclear Not Applicable	Unclear Not Applicable	Unclear Not Applicable
11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	9/11 = 82%	9/11 = 82%

JBI Checklist Questions	Authors					
	Carson et al., 2018	Corona-Mata et al, 2023	Cousien et al., 2018	Fadness et al., 2021	Falcato et al., 2021	Fraser et al., 2018
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria for appraising studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
7. Were there methods to minimize errors in	Yes ✓ No Unclear	Yes ✓ No Unclear	Yes ✓ No Unclear	Yes ✓ No Unclear	Yes ✓ No Unclear	Yes ✓ No Unclear

data extraction?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
9. Was the likelihood of publication bias assessed?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
10. Were recommendations for policy and/or practice supported by the reported data?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	10/11 = 91%	9/11 = 82%	9/11 = 82%	9/11 = 82%	9/11 = 82%	9/11 = 82%

JBI Checklist Questions	Authors					
	Fraser et al., 2021	Grebely et al., 2022	Groessi et al., 2017	Gustafson et al., 2016	Ijioma et al., 2021	Islam et al., 2017
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria	Yes	Yes	Yes	Yes	Yes	Yes

for appraising studies appropriate?	No Unclear ✓ Not Applicable	No Unclear ✓ Not Applicable	No Unclear ✓ Not Applicable	No✓ Unclear Not Applicable	No✓ Unclear Not Applicable	No✓ R1 Unclear ✓ R2 Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
7. Were there methods to minimize errors in data extraction?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
9. Was the likelihood of publication bias assessed?	Yes No Unclear✓ Not Applicable	Yes No Unclear✓ Not Applicable	Yes No Unclear✓ Not Applicable	Yes No Unclear✓ Not Applicable	Yes No Unclear✓ Not Applicable	Yes No Unclear✓ Not Applicable
10. Were recommendations for policy and/or practice supported by the reported data?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	9/11 = 82%	8/11 = 73%

JBI Checklist Questions	Authors					
	Krekulová & Vavrinčíková 2021	Macías et al., 2019	Mangia et al., 2021	Marshall et al., 2022	Midgard et al., 2021	Minoyan et al., 2020
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not	Yes ✓ No Unclear Not	Yes ✓ No Unclear Not	Yes ✓ No Unclear Not	Yes ✓ No Unclear Not	Yes ✓ No Unclear Not Applicable

	Applicable	Applicable	Applicable	Applicable	Applicable	
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria for appraising studies appropriate?	Yes No✓ R1 Unclear ✓ R2 Not Applicable	Yes No✓ R1 Unclear ✓ R2 Not Applicable	Yes No✓ R1 Unclear ✓ R2 Not Applicable	Yes No✓ R1 Unclear ✓ R2 Not Applicable	Yes No✓ R1 Unclear ✓ R2 Not Applicable	Yes No Unclear ✓ Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
7. Were there methods to minimize errors in data extraction?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
9. Was the likelihood of publication bias assessed?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
10. Were recommendations for policy and/or practice supported by the reported data?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%

JBI Checklist Questions	Authors

	Rahman et al., 2019	Rosentahal et al., 2020	Schackman et al., 2018	Selfridge et al., 2019	Selfridge et al., 2021	Talal et al., 2019
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria for appraising studies appropriate?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
7. Were there methods to minimize errors in data extraction?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
9. Was the likelihood of publication bias assessed?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
10. Were recommendations for policy and/or practice supported by the reported data?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable

11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%

JBI Checklist Questions	Authors					
	Tofighi et al., 2018	Wang et al., 2020	William et al., 2019	Ydreborg et al., 2023	Yi et al., 2019	Zelenev et al., 2021
1. Is the review question clearly and explicitly stated?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
2. Were the inclusion criteria appropriate for the review question?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
3. Was the search strategy appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
4. Were the sources and resources used to search for studies adequate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
5. Were the criteria for appraising studies appropriate?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
6. Was critical appraisal conducted by two or more reviewers independently?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
7. Were there methods to minimize errors in data extraction?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
8. Were the methods used to combine studies appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable

9. Was the likelihood of publication bias assessed?	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable	Yes No Unclear ✓ Not Applicable
10. Were recommendations for policy and/or practice supported by the reported data?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
11. Were the specific directives for new research appropriate?	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable	Yes ✓ No Unclear Not Applicable
Score	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%	8/11 = 73%

Appendix C: Data Extraction Table

Study	Authors	Date,	Population (P)	Indication (I)	Comparison	Comparison	Outcome

Design		Duration, and Location	Adults 18 years old or older who are IVDU and are infected with HCV	IVDU and HCV treatment	(C) HCV treatment	(C) IVDU treatment	(O) HCV infection rate
Randomized control trial	Akiyama et al., 2020a	Bronx, New York 3 OAT location in Bronx	Adult (18 and over), HCV infected and IVDU Participants (n = 141)			Investigate the rate of HCV reinfection among IVDUs receiving (OAT) after achieving SVR through DAA therapy	The study demonstrates a low rate of HCV reinfection among IVDUs on OAT who had achieved SVR through DAA therapy. The findings highlight the importance of OAT as a protective factor and the need for comprehensive harm reduction strategies to reduce reinfection risk. The risk factors associated with the high reinfection rate are homelessness and association with other IVDUs
Randomized control trial	Akiyama et al., 2020b	Bronx, New York	Adult (18 and over), HCV infected and IVDU Participants (n = 150 IVDU) from 3 OAT clinics	Evaluate the change that can be brought by using next-generation sequencing (NSG) to differentiate reinfection from treatment failures. Moreover,			The results suggest that HCV transmission, relapse, and reinfection are complex processes influenced by multiple factors,

				identifying transmission linkages along with risk factors associated with HCV transmission among IVDU		including drug use behaviors, treatment adherence, and social networks among IVDUs. The findings underscore the importance of integrated approaches that combine HCV treatment with harm reduction measures, such as access to sterile syringes and opioid agonist therapy, to effectively prevent new infections and reinfections.
Prospective Cohort Study	Artenie et al., 2015	2004-2013 Montreal, Canada	Adult (18 and over), HCV infected and IVDU Participants (n = 226), attending NEP through community programs		Investigated the potential role of primary healthcare in a combined approach to HCV prevention, specifically in relation to HCV seroconversio n among IVDUs	The study highlights the potential role of primary healthcare, specifically regular visits to a primary care physician, in preventing HCV seroconversi on among IVDUs. Integrating primary healthcare into a combined approach

						with harm reduction measures can contribute to the prevention and control of HCV among IVDUs.
Qualitative study	Assoumou et al., 2021	Nov 2018-Aug 2019. Boston Treatment Center, USA (drug detoxification center)	Adult (18 and over), HCV infected and IVDU	Aimed to gather insights from patients (in-depth interview) in receiving treatment for drug addiction at a detoxification center on strategies to enhance the uptake of hepatitis C treatment.		The findings emphasize the importance of raising awareness, integrating care, addressing treatment barriers, providing peer support, and counseling, and streamlining access and navigation processes.
Retrospective cohort Study	Barbosa et al., 2019	Rural Perry County, Kentucky (PC), and urban San Francisco, California (SF), U.S. 1998-2015	Adult (18 and over), HCV infected and IVDU Two models were used stratified by age or injection duration, intervention status and risk behavior	Evaluating the cost-effectiveness of scaled-up medication-assisted treatment (MAT) and SSP with HCV treatment and direct-acting anti-viral treatment (DAA) in both rural and urban areas.		Combining scaled-up MAT and SSP programs and HCV treatment for IVDUs has been revealed to be a practical approach to reducing the HCV infection rate. The findings suggest that expanding HCV prevention and treatment programs

						tailored to people are IVDUs can be a cost-effective strategy for addressing the HCV burden.
Retrospective study	Bota et al., 2021	2014-2019 Hepatology outpatient clinic, Austria	Adult (18 and over), HCV infected and IVDU Participants (n = 431)		Addresses the challenges associated with achieving HCV elimination even with the availability of highly effective antiviral agents. The study focuses on patients with and without a history of intravenous drug use, highlighting the specific barriers and complexities in each group. Compared HCV's reinfection rate and adherence to treatment among IVDUs vs non-IVDUs	The on-going risk factor for reinfection of HCV among IVDUs requires a better strategy to be put in place because treating HCV alone does not eliminate the on-going risk factor among IVDUs. The study It emphasizes the need for comprehensive strategies that address treatment accessibility, engagement in care, reinfection risk, and the reduction of stigma and discrimination.
Cohort Study	Carson et al., 2018	Australia 2014-2019	Adult (18 and over), HCV infected, incarcerated and IVDU. Incarcerated within the four prisons and have received		Investigated the occurrence of HCV reinfection among individuals in Australia prison after receiving	The study reveals that reinfection after treatment was prevalent even after receiving OAT. NSPs

			DAA therapy for HCV infection. Participants (n = 388)		DAA treatment.	have a significant impact on reducing reinfection. The findings emphasize the need for comprehensive strategies that address both HCV treatment and prevention, including harm reduction measures, for individuals both during incarceration and after release. These findings have important implications for developing effective interventions and policies to reduce HCV transmission and reinfection rates in prison populations and the broader community.
Longitudinal prospective experimental study	Corona-Mata et al, 2023	2019-2020 Andalusia, Spain	Adult (18 and over), HCV infected and IVDU Participants (n = 556)	Investigates the effectiveness of a comprehensive strategy for detecting and treating hepatitis HCV infection in a		The study demonstrates the efficacy of a comprehensive strategy for detecting and treating HCV infection in

				population attending addiction centers. The research aims to assess the impact of an integrated approach that combines testing, linkage to care, and DAAs on HCV detection and treatment outcomes.	a population attending addiction centers. The findings support the integration of HCV screening, linkage to care, and treatment initiation with DAAs in addiction care settings. The comprehensive approach improves HCV detection, linkage to care, treatment uptake, and treatment completion rates, ultimately leading to a high rate of sustained virologic response. It requires a multilayer approach ranging from education to access to care to address HCV-infected individuals that are also IVDUs.
Modelling	Cousien et al., 2018	France	Adults (18 and over), HCV infected, IVDUs	Examined the effectiveness and cost-effectiveness of interventions targeting harm	The study suggests that harm reduction interventions, such as NSPs and

		reduction and the HCV cascade of care among IVDUs in France	OST, as well as cascade of care intervention s targeting HCV testing, linkage to care, and antiviral treatment, are effective in reducing HCV transmission and improving health outcomes among IVDUs in France. In addition, the findings underscore the importance of comprehensi ve strategies that address both harm reduction and the HCV cascade of care for effective HCV prevention and treatment in this population.

Randomized control trial	Fadness et al., 2021	2017-2019; Norway Community care clinics and individuals receiving OAT in Bergen	Adult (18 and over), HCV infected and IVDU Participants (n = 298; n = 148 integrated care and n = 150 standard care) IVDUs recieiving follow up from OAT clinics/community care clinics, 18 years and older	Aimed to compare two different treatment approaches: integrated treatment combining OST and HCV treatment versus standard treatment where OST and HCV treatment are provided separately		The study findings highlight the efficacy and benefits of an integrated treatment approach for HCV infection among people who inject drugs. By addressing substance use and HCV infection concurrently, this model of care offers a comprehensive approach that improves treatment outcomes, reduces HCV transmission risks, and enhances overall engagement and retention in care.

Retrospective study	Falcato et al., 2021	Zurich, Switzerland 2015-2019	Adult (18 and over), HCV infected and IVDU Patients who achieved sustained viral response (SVR12) after HCV treatment with DAA Participants (n = 153)	Assessed the reinfection rate after patients complete HCV treatment and attend a low threshold access center for comprehensive addiction medicine.		Reinfection can remain low only if IVDU individuals continue to receive care for their addiction in a well-developed harm reduction program. The study highlights the occurrence of HCV reinfection among patients attending a multidisciplinary treatment center for people who use drugs in Zurich, Switzerland, following successful DAA therapy. The findings emphasize the need for targeted prevention and treatment strategies, including harm reduction approaches and comprehensive support services, to address the ongoing risk of reinfection in this

						population.
Modelling	Fraser et al., 2018	Scott County, Indiana	Adults (18 and over), IVDU and HCV infected Participants (n = 436)	Assess the impact of combining scaled-up programs in SSP, MAT, and HCV treatment on the infection rate for HCV in rural areas of the U. S		When treatment for HCV was combined with scaled-up MAT and SSP, promising results were recorded regarding reducing current and future HCV infection rates. The study projected the potential impact of scaling up HCV prevention and treatment interventions in rural areas of the U.S. The findings

						underlined the importance of expanding access to prevention measures and increasing treatment coverage to address the growing HCV epidemic.
Modelling	Fraser et al., 2021	Dar es Salaam Tanzania 2019	Adult (18 and over), HCV infected and IVDU		Assessing the impact of current and new scaled-up harm reduction interventions on the transmission of HCV.	The study highlighted the potential impact of implementing comprehensive HCV prevention and treatment interventions for IVDUs. By combining NSPs, OST, significant reductions in new infections and improved health outcomes could be achieved. Moreover, these interventions were found to be cost-effective, suggesting that investing these programs could yield long-term benefits for

						both individuals and the public health system.
Cohort Study	Grebely et al., 2022	U.S 2014-2015	Adult (18 and over), HCV infected, and IVDU Genotypes 1, 4, or 6 receiving stable OAT. Participants (n = 296)		Reinfection rate among IVDU who are receiving OAT	Reinfection rate was higher for those with ongoing IVD. OAT has shown a significant impact in improving IVDU related behaviors. The results highlight the occurrence of HCV reinfection and ongoing risk behaviors among individuals receiving OAT after achieving SVR following HCV treatment. The findings underscore the need for integrated approaches that address ongoing risk behaviors and provide comprehensive support to individuals to prevent reinfection and improve long-term outcomes.
Randomized control trial	Groessi et al., 2017	U.S. Data collected in	Adult (18 and over), HCV infected and	Assessed the impact of self-		Self-management programs

		2011 and analyzed in 2014	IVDU Participants (n = 134)	management interventions among individuals infected by HCV.		among HCV-infected individuals revealed improved quality of life and preparation for treatment as well as avoided transmission to others The study demonstrates the cost-effectiveness of the hepatitis C self-management program. It highlights the positive impact of the program on health outcomes and healthcare costs. The findings support the implementation of self-management programs as a valuable approach to HCV management, emphasizing the potential benefits for both individuals and healthcare systems.
Randomized control trial	Gustafson et al., 2016	Massachusetts and Wisconsin, U. S	Adult (18 and over), HCV infected and IVDU		Evaluating the effectiveness of MAT alone vs.	Combining MAT with A-CHESS has revealed promising

			Currently on MAT Participants (n = 440)	when it's combined with a smartphone innovation known as A-CHESS on HCV prevention.	evidence for increasing access, effectiveness, and treatment adherence.
Decision tree analysis	Ijioma et al., 2021	U.S	IVDU and HCV infected. Cost were standardized to use 2019 U.S. Dollars	Examined the cost-effectiveness of syringe service programs (SSPs), medications for opioid use disorder (MOUD), and combination programs.	The study indicates that SSPs, MOUD, and combination programs are cost-effective in reducing HCV transmission among IVDUs. SSPs provide access to sterile syringes, while MOUD helps individuals manage opioid addiction and reduce risky injection practices. The combination of both interventions offers the greatest cost-effectiveness in terms of reducing HCV transmission and related healthcare costs.

Cohort Study	Islam et al., 2017	Canada	Adult (18 and over), HCV infected and IVDU who has achieved SVR through treatment or spontaneous clearance. Participants (n-5915)		The effect of OST and mental health counseling on the reinfection of HCV was assessed.	HCV treatment combined with OST and mental health counseling revealed a significant impact in reducing the reinfection rate. The findings of the study contribute to the understandin g of HCV reinfection dynamics and provide valuable insights into the risk factors and prevention measures that can be implemente d to reduce reinfection rates.
Cohort study design	Krekulo vá & Vavrinč íková 2021	Czech Republic 2020	Adult (18 and over), HCV infected and IVDU Individuals that are in methadone program in 2020 (n = 24)	Explored the experiences of people who are IVDUs and participate in a methadone substitution treatment program with HCV treatment		The results of this study suggest that providing HCV treatment within a methadone substitution treatment program can be an effective and accessible approach for IVDUs. By integrating HCV care into existing programs, IVDUs can receive comprehensi

						ve support, address HCV-related health issues, and experience positive treatment outcomes.
Prospective multi cohort study	Macías et al., 2019	Spain (Time frame not mentioned)	Adult (18 and over), HCV infected and IVDU Participants (n = 1752) Recruited from 33 infectious disease unit		Assessed the response to DAA therapy among two groups: ongoing drug users and individuals receiving OST	The study found that both ongoing drug users and individuals receiving OST had favorable responses to DAA therapy for HCV infection. Despite the potential challenges associated with ongoing drug use and the use of OST, the effectiveness of DAA therapy in achieving HCV cure was demonstrated in both groups. The findings highlight the importance of providing access to DAA therapy for ongoing drug users and individuals receiving OST. The study

						suggests that these populations should not be excluded from HCV treatment based on their drug use status OST. Instead, they should be offered comprehensive care that includes access to effective antiviral therapy.
Cohort Study	Mangia et al., 2021	Italy 2019-2021	Adult (18 and over), HCV infected and IVDU Participants n = 1470 from 15 Services for Dependence (SERDs)	Evaluated the impact of a patient-centered program on HCV screening, diagnosis, and linkage to care rates among IVDUs in Italy		The findings of the study highlight the effectiveness of a patient-centered approach in engaging and addressing the needs of IVDU. By focusing on the individual and providing tailored care, the program achieved positive outcomes in terms of increased screening, diagnosis, and linkage to care rates

Case study	Marshall et al., 2022	Five case studies	Adult (18 and over), HCV infected and IVDU	Focused on understanding the hepatitis C care cascade from the perspective of clients in the era of interferon-free DAA treatment.		The care cascade has structural barriers when addressing HCV infection among IVDUs. Lack of access to care is the primary barrier. The findings underscore the importance of client-centered care, the complexities and barriers faced by clients, and the need for targeted strategies to improve the care cascade and promote equitable access to hepatitis C testing and treatment services.
Prospective observational study	Midgard et al., 2021	2013-2020 Oslo, Norway	Adult (18 and over), HCV infected and IVDU Participants (n = 768)	Aimed to examine the implementation of HCV treatment and reinfection surveillance in a low-threshold program for IVDUs in Oslo, Norway.		High HCV treatment uptake among IVDU and emphasizes on the importance of unrestricted DAA treatment access. In addition, the study calls for an improved effort to

					engage individuals that are IVDU in an OAT program to effectively eradicate the virus from the world. The study highlights the importance of accessible and comprehensive programs that address the unique needs of this population. It also emphasizes the need for ongoing surveillance and harm reduction strategies to minimize the risk of reinfection and improve treatment outcomes among IVDUs.
Prospective cohort study	Minoyan et al., 2020	2010-2017. Montreal, Canada	Adult (18 and over), HCV infected and IVDU Participants were from recruited through street-level strategies and community-based programs. 106 events were observed	Investigated the relationship between harm reduction coverage and HCV incidence among IVDU	The study highlights the positive impact of harm reduction coverage on reducing the incidence of HCV among IVDUs. Access to NSPs and participation in OAT were associated with

						decreased HCV transmission. Implementing comprehensive harm reduction strategies that include both NSPs and OAT is vital for effectively preventing HCV infection among IVDUs. Increasing the coverage and accessibility of harm reduction services is crucial to achieve significant reductions in HCV incidence within this population.
Prospective Study	Rahman et al., 2019	2016-2019 Bangladesh	Adult (18 and over), IVDUs either recent injecting drug use (within the previous two months) or a history of injecting drug use and are currently receiving OST. Participant (n = 200)	Assessed the viability of providing HCV treatment to IVDUs receiving harm reduction services.		Results revealed positive implications of providing HCV treatment to IVDUs receiving harm reduction services. However, OST and continued support is also needed to achieve meaningful results. The findings of

						the study provide insights into the challenges and opportunities associated with providing HCV treatment to people who inject drugs in Bangladesh.
Cohort study	Rosenthal et al., 2020	Harm reduction organization center, Washington, D.C.	Adult (18 and over), HCV infected and IVDU Participants (n = 100)	Examines the impact of concurrent initiation of HCV treatment and OAT		Concurrent initiation of OAT and HCV treatment can lead to successful eradication of the virus and reduced risk associated with drug use. The study highlights the benefits and effectiveness of concurrent initiation of HCV treatment and OAT among IVDUs. It emphasizes the importance of integrated care, multidisciplinary teams, and comprehensive support services to improve

						treatment outcomes and engagement in care.
Comparative study design	Schackman et al., 2018	(New York and San Francisco) U.S. 2008-2011	Adult (18 and over), HCV infected and IVDU Participants (n = 489) were randomized across both sites; 244 were assigned to the intervention group and 245 were assigned to the control group Location Methadone maintenance treatment	Evaluated the cost-effectiveness of HCV screening and linkage to care in a methadone maintenance treatment.		The results of this study suggest that implementing HCV screening and treatment linkage interventions in MMT programs is a cost-effective approach to addressing the HCV epidemic among individuals with opioid use disorder. By integrating HCV care into existing MMT

					programs, more individuals can be reached, diagnosed, and connected to appropriate treatment services, ultimately improving their health outcomes and reducing the overall burden of HCV.
Retrospective study	Selfridge et al., 2019	2014-2017 Victoria, Canada	Adult (18 and over), HCV infected and IVDU Participants (n = 270)	Assessed the effectivity of HCV treatment DAA along with reinfection and mortality rates among those attending community health center in Victoria, Canada.	HCV treatment (DAA) has proven to be effective; However, high mortality and reinfection were noticed among a marginalized population, thus emphasizing the need to address drug use as well while treating for HCV. The findings underscore the importance of comprehensive care, harm reduction strategies, and ongoing support services in achieving successful

						treatment outcomes and reducing the burden of HCV infection.
Observational Study	Selfridge et al., 2021	Victoria, Canada 2014-2019	Adult (18 and over), HCV infected, and IVDU Participants (n = 482) treated with DAA therapy between November 2014 and December 31, 2019		Aimed to investigate the occurrence of HCV reinfection among individuals who had achieved SVR following (DAA) therapy.	High reinfection rate of HCV recorded among IVDU. The findings highlight the need for targeted prevention strategies and comprehensive support to address the ongoing vulnerability of this population to reinfection. These findings have implications for the design and implementation of HCV prevention programs and underscore the importance of addressing social determinants of health to reduce reinfection rates.
Quantitative study	Talal et al., 2019	U.S. Participants (n-45)	Adults (18 and over), HCV infected and IVDU Participants (n-	Aimed to assess patient satisfaction, acceptability, and feasibility		The study found that patien clinical management of HC was deemed satisfactory, a convenience, and overcomi findings highlight the poten

			45) Interview questionnaire after the initial HCV telemedicine evaluation, when initiating HCV treatment, and 3 months post-HCV treatment completion	of telemedicine as a means of delivering HCV care to individuals receiving treatment for opioid use disorder.		delivering HCV manageme treatment for opioid use dis outcomes in HCV care.
Qualitative Study	Tofighi et al., 2018	Bellevue Hospital in New York City, U.S 2018	Adult (18 and over), HCV infected and IVDU Admitted to in-patient detoxification at Bellevue Hospital Participants n = 23	In-depth interviews with IVDUs infected with HCV regarding the factors influencing the care continuum and effective eradication of the virus.		The study emphasizes the importance of addressing the specific needs of people who use drugs to enhance their engagement in the Hepatitis C care continuum. By implementin g integrated care models and tailored intervention s, it is possible to improve HCV testing, treatment, and overall outcomes among this population.
Cross-sectional study	Wang et al., 2020	2012-2015. Southern Taiwan	Adult (18 and over), HCV infected and IVDU Participants 815 (IVDU) and 212 were non-IVDU		Aimed to assess the risk of HCV infection among IVDU and non-IVDUs receiving opioid substitution	OST alone does not play a factor in reducing the risk for HCV in IVDU. The study indicates the need for

					therapy (OST)	HCV assessment and treatment to be combined.
Qualitative study	William et al., 2019	2017-2018 U.S. Homeless clinic setting	Adult (18 and over), HCV infected and IVDU Participants (n = 27)	"Life projects" is a conceptual framework exploring social incentives among IVDUs being treated for HCV. Explored the benefit of HCV treatment among IVDU.		Understanding the social incentives using "Life projects" revealed a significant impact on treatment uptake and adherence among IVDUs infected by HCV. The findings emphasize the importance of comprehensive care models and policy changes to ensure equitable access to treatment and support services for HCV infected IVDUs.
Retrospective cohort study	Ydreborg et al., 2023	2017 Sahlgrenska University Hospital Gothenburg, Sweden	Adult (18 and over), HCV infected and IVDU Participants (n = 225)	Examined the linkage to HCV treatment among individuals receiving OST in two units in Gothenburg, Sweden. The research aims to assess the rates of linkage to HCV treatment and		A model of care based on DAA was introduced at an OST unit. The model encompassed assessment for HCV and liver disease. Integrating the model of care in an

				identify factors associated with successful linkage.		OST revealed success in linking patients to care. However, it is crucial to identify an intervention that can be tailored based on the individual's circumstance to successfully connect all patients with HCV to receive care that will end up in a complete follow-through.
Retrospective cohort study	Yi et al., 2019	Cambodia June – Dec 2017	Adult (18 and over), HCV infected and IVDU Participants (n = 286)		Assessed the prevalence of HCV infection rate among IVDU's in Cambodia	High prevalence of HCV infection and reinfection among IVDUs in Cambodia. The study calls for a tailored intervention to be implemented along with expanding screening, diagnosing, and using new DAA treatments. The findings underline the importance of implementing evidence-based harm

						reduction programs and improving access to HCV testing and treatment services to prevent and control HCV infection among IVDUs.
Modelling study	Zelenev et al., 2021	20013. Hartford, Connecticut	IVDU and HCV infected (n = 1574) IVDU network (based on respondent driven sampling)	Aimed to model and evaluate combination strategies for HCV treatment and prevention among IVDUs in the United States		The study indicates scaling up HCV treatment, integrating prevention interventions, targeting high-risk networks, and addressing reinfection risk are crucial for reducing HCV transmission