Treatment Outcomes of Conventional Therapies for Hepatitis C in Federal Prisons and a Cost Analysis for Newer Therapies

BY

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Treatment Outcomes of Conventional Therapies for Hepatitis C in Federal Prisons and a Cost Analysis for Newer Therapies

APPROVED

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Education

MPH, Rollins School of Public Health, Emory University, Atlanta, GA, August 2012-Present, Prevention Science
Thesis Title: *Treatment Outcomes of Conventional Therapies for Hepatitis C in Federal Prisons and a Cost Analysis for Newer Therapies*
Advisor: Kathleen R. Miner, PhD, MPH, MCHES
Thesis Advisor: Anne Spaulding MD, MPH
Field Adviser: Michelle Williams, PharmD

MS, University of Georgia, Athens, GA, 2006, **Animal and Dairy Science**
Thesis title: *The Effect of the Immune Response in Broiler Chickens Challenged with Salmonella Heidelberg Following Use of Subtherapeutic and Therapeutic Antibiotics*
Advisor: Richard Barb, PhD

BS, University of Georgia, Athens, GA, 2001, Microbiology

BS, University of Georgia, Athens, GA, 1999, Cellular Biology

Research Experience

James A. Ferguson Emerging Infectious Diseases Fellowship Program, May-July 2013

Johns Hopkins Hospital, Kennedy Krieger Institute, and Center for Disease Control and Prevention, Baltimore, MD

- Department of Justice, Bureau of Prisons, under the direction of the Chief Pharmacist and Chief Physician, Washington, DC.
    - Research on the diagnosis and treatment of Hepatitis C,
    - Analyzed treatment outcomes of approved patients with dual therapy in the federal prisons from 2011
    - Present findings at the end of the program.
- Ryan White Foundation, Baltimore, MA
    - Research on Medicare plans, premiums, coverage and costs for the different parts (A-D).
    - Used findings to compare with the Ryan White Foundation plans and coverage for HIV/AIDS patients.
    - Comparisons were placed in brochures for patients to use as a comparison to make decisions of what type of coverage they will need.

Microbiological Laboratory Technician, **GS-0404-09**, September 2000-present
USDA-ARS, Bacterial-Epidemiology Antimicrobial Resistance Research Unit (BEAR), Athens, GA

- Staff member- Animal arm of the National Antimicrobial Resistance Monitoring System (NARMS) Program.
    - Co-Coordinated meetings and produced a working protocol for the *Salmonella* and *E.coli* NARMS working groups which includes CDC, USDA, Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), and FDA agencies from NARMS.
    - Oversee, supervise, and manage the susceptibility testing of over 6000 *Salmonella* and *E.*coli samples per year for the NARMS program and maintained log of all samples using notebooks, Excel and Access database to provide antibiotic resistance data upon request.
    - Collaborate with USDA-APHIS on NAHMS studies
    - Provide samples to scientists within the BEAR unit, other units, or universities for the purpose of their research.
    - Maintained and updated protocols for various microbial and molecular techniques and ensure equipment and instruments operated properly and were serviced
    - Prepared media to accommodate samples coming in on a weekly basis trained on preparing, receiving and shipping hazardous samples
    - Analyze data using programs such as Excel, Word, Access, and WHOnet, to formulate graphs and tables for future meetings, presentations, or publications.
    - Skilled in characterizing *Salmonella* by sequencing, serogrouping, serotyping, PCR for inc A/C genes, integrons 1-4, large plasmid preps, and beta-lactamase genes
    - Skilled in antimicrobial susceptibility testing of gram negative bacteria using the Sensititre broth microdilution system and the NARMS 96-well panel and customized panels used to test for ESBL, fluoraquinolone, and cefepime and cefquinone resistance.
    - Skilled in culturing bacterial samples such as *E.coli, Salmonella, Campylobacter, Enterococcus, Staphylococcus,* and *Clostridium* from environmental, fecal, and tissue samples.
    - Perform interagency quality control testing with the NARMS labs to ensure all methods are standardized. This includes isolate testing between the agencies and the WHO EQAS testing.
    - Supervised and managed college student employees and temporary full-time employees in the antimicrobial susceptibility testing.

Graduate Research: Department of Animal and Dairy Science-Reproduction and Physiology, University of Georgia, Athens, GA, January 2002-August 2006
Thesis title: *The Effect of the Immune Response in Broiler Chickens Challenged with Salmonella*

Heidelberg Following Use of Subtherapeutic and Therapeutic Antibiotics

- The purpose of the project was to determine type of immune response broiler chickens express following challenge with *Salmonella* and treatment with subtherapeutic and therapeutic antibiotics
- The serotype of *Salmonella* was Heidelberg
- The subtherapeutic and therapeutic antimicrobials were Chlortetracycline and Enrofloxacin,

- I tested for immune responses t cytokines IL-1β, IL-6, IL-8, MIP-1β and hormones IGF-I, T3, and T4 Cytokines were obtained by isolating and purifying RNA from tissue samples and measured using RT-PCR
- The hormones were obtained by isolating and purifying serum samples from radioimmunoassay (RIA) and measured using a gamma counter
- Antimicrobial susceptibility and PFGE testing was conducted using broth microdilution
- Plasmid preps were prepared using standard kits

Skills and Professional Development

- Experienced in PCR, Pulse Field Gel Electrophoresis (PFGE), bacterial culture and storage, and antimicrobial susceptibility testing.
- Skilled in Excel, Word, Access, WHOnet, and Powerpoint.
- Past experience in SAS
- Beginner experience in Grant writing
- Beginner experience in Community Needs Assessment
- Beginner experience in Cost effectiveness Analysis
- Beginner experience in Program Evaluation
- SkillPath Seminar for Continuing Education and Training Certifications, 2006
    - Mastering the Art of Negotiations
    - Business Writing Basics for Professionals
    - The Complete Guide to Poised and Powerful Public Speaking
    - Conflict Resolution and Confrontation Management
    - How to be a Better Communicator
- Information Technology Training Certifications
    - Fundamentals of Access XP, 2002
    - SAS Programming I: Essentials, 2003

Previous Work Experience

Classic City Cat and Dog Clinic, Athens, GA
Veterinarian Technician April 2006-December 2008
- Arranged appointments
- Collected payments
- Provided assistance for preparing vaccinations and culture test.
- Cared for animals outside office hours.

Lassiter Animal Hospital, Marietta, GA
Kennel Caregiver January 2000-August 2000
- Cared for the animals while in boarding by feeding, watering, walking, and bathing
- Provided medications for animals while in care if needed

Pet Boutique, Marietta, GA 1996-2001
Groomer

- Arranged appointments
- Collected payments
- Provided assistance in bathing and grooming of animals

Leadership and Service

- American Public Health Association Member, 2013
- Clarke County Mentorship Program, 2008-Present
    - Mentor Elementary children,
    - Presentations for Career days
    - Volunteer for field day and extracurricular activities
- Provide Scientific presentations to local Pre-schools, 2008-2010
    - Teach Pre-K the importance of germs and washing hands
- Provided help with Habitat for humanity, 1996
- Big sister in the University of Georgia Big Brother Big Sister program, 1996-1999
- Board member-Secretary for Homeowners Association in Whitehall Village, 2008-2013
- Board member-President of Homeowners Association in Whitehall Village, 2014- present

Awards

- Recipient of the Edith Hambie Excellence in Public Health Award-presented by the Dr. James A. Ferguson EID Fellowship Program, 2013
- USDA Merit Performance awards
    - Superior 2004-2006, 2008-2009, 2010-2012
    - Outstanding 2001-2002, 2006-2008

Oral presentation

Ball, Takiyah, Treatment Outcomes of Hepatitis C in Federal Prisons, Kennedy Krieger Institute, Baltimore, MD, July 2013.

Ball, Takiyah, The Effect of the Immune Response in Broiler Chickens Challenged with Salmonella Heidelberg Following Use of Subtherapeutic and Therapeutic Antibiotics, Russell Research, Athens, GA, August 2006.

Poster Presentations

Ball, Takiyah. Treatment Outcomes of Hepatitis C Genotype 1 in Federal Prisons. Emory University, Atlanta, GA, 2014.

PJ Fedorka-Cray, TA Ball, J Haro, SL House, ML Headrick. Antimicrobial Resistance among *Escherichia coli* Recovered From Athens, GA, Community Park Samples, Athens GA, 2002

PJ Fedorka-Cray, TA Ball, J Haro, ML Headrick. Antimicrobial Resistance in *Escherichia* coli Isolates from Broiler Carcass Rinsate Samples 2000-2002, Athens GA, 2002

Publications

Abstracts

Cray, P.J., Ball, T.A., Rose, M. 2006. In-vitro susceptibility of *Escherichia* coli isolated from

feces of us dairy cattle to cephalosporins. Third International Conference on Antimicrobial Agents in Veterinary Medicine. May 16 - 20, 2006. Orlando,FL.

Mc Dermott, P., Anandaraman, N., Haro, J.H., Ball, T.A., Hall-Robinson, E., Blickenstaff, K., Carter, P., Fedorka-Cray, P.J. 2008. Antimicrobial Resistant *E.*coli from Retail Chicken Breast and Slaughter Rinsates: NARMS 2002-2005. American Society for Microbiology Annual Meeting. CD-ROM. P-069.

Karlsson, M.S., Howie, R.L., Blickenstaff, K., Ball, T.A., Haro, J.H., Rickert, R., Folster, J., Zhao, S., Fedorka-Cray, P.J., Whichard, J. 2010. Cephalosporin Resistance Among Non-Typhi *Salmonella* from Humans, Retail Meats and Food Animals in the United States. Interscience Conference on Antimicrobial Agents and Chemotherapy Proceedings. Sept. 12-15. Boston, MA.

Peer Reviewed Publications

Sjolund-Karlsson, M., Howie, R.L., Blickenstaff, K., Boerlin, P., Ball, T.A., Chalmers, G., Duval, B., Haro, J., Rickert, R., Zhao, S., Cray, P.J., Whichard, J.M. 2013. Occurrence of ß-lactamase genes among non-Typhi Salmonella enterica isolated from humans, food animals, and retail meats in the United States and Canada. Microbial Drug Resistance. 19(3):191-197.humans, food animals, and retail meats in the United States and Canada

Karlsson, M.S., Joyce, K., Blickenstaff, K., Ball, T.A., Haro, J.H., Medalla, F., Ferdorka-Cray, P.J., Zhao, S., Crump, J., Whichard, J. 2011. Antimicrobial Susceptibility to Azithromycin among *Salmonella enterica* isolated in the United States. Antimicrobial Agents and Chemotherapy.

Karlsson, M.S., Howie, R.L., Rickert, R., Krueger, A., Tran., T., Zhao, S., Ball, T.A., Haro, J.H., Pecic, G., Joyce, K., Fedorka-Cray, P.J., Whichard, J., McDermott, P. 2010. Plasmid-Mediated Quinolone Resistance Among Non-Typhi *Salmonella enterica* isolates, USA. Emerging Infectious Diseases. 16(11):1789-1791

Karlsson, M.S., Howie, R.J., Blickstaff, K., Boerlin, P., Ball, T.A., Chalmers, G., Duval, B., Haro, J.H. , Rickert R., Zhao, S., Fedorka-Cray, P.J., Whichard, J. 2011. Occurrence of β-lactamases among *Salmonella enterica* isolated from Humans, Food Animals and Retail Meats in the United States and Canada. Microbial Drug Resistance.

Acknowledgements

I will like to extend my gratitude for everyone who has had a hand in this research project that I have been working on for the last 3 years. It all started with Dr. Harolyn Belcher giving me a chance when she offered me the James Ferguson Fellowship. With this fellowship, I was introduced to the world of Hepatitis C while interning with the Federal Bureau of Prisons in Washington, DC. There I was introduced to my field adviser, Dr. Michelle Williams, who taught me everything I know about HCV and its issues within the federal prison system. This internship allowed me to expand the project into a thesis, with the guidance of Dr. Anne Spaulding. Thanks for challenging me to the epidemiological side of the project and learning a whole new world of costs effectiveness.

I also want to express my thanks to my classmates and professors. Without the support, challenging minds, and lifelong friendships, I would have never gotten through this program. I really had a great time and look forward to future work together in the public health field.

Abstract

Objectives:

1. Examine treatment outcomes of using dual treatment of RBV-pegIFN for Hepatitis C in federal inmates in 2011.
2. Estimate the improvement of outcomes if LDV-SOF were given to these federal inmates from 2011 compared to RBV-pegIFN.
3. Estimate the incremental cost effectiveness ratio (ICER).

Design:

1. The first part of this study is a retrospective review of BOP Electronic Medical Records (BEMR) of inmates approved for treatment of Hepatitis C Genotype 1 in 2011, by Federal Bureau of Prisons. Demographic, antiviral therapy and dosage (peginterferon and ribavirin), viral loads at each stage of the treatment (4, 12, 24, and 48 weeks during treatment and 6 and 12 months post treatment completion), and reasons for stopped treatment or treatment failure data were collected.
2. Using a prospective strategy, this study provides a cost-effectiveness simulation using decision tree

Data Sources: Federal Bureau of Prisons, Center for Disease Control and Prevention, National Institutes for Health, Pharmaceutical companies

Target Population: Federal inmates approved for HCV GT 1 treatment in 2011

Time Horizon: One year

Perspective: Prison

Intervention: A prospective look at potential cost effectiveness of newer agents' LDV-SOF could have on Federal inmates approved for HCV treatment in 2011.

Outcome Measures: Number of SVR that could be achieved, QALYs, and ICER.

Results:

1. After gathering the data from BEMR, a total of 422 Hepatitis C positive patients were approved for treatment. Of the 422, there were 177 (41.9%) patients that had HCV genotype 1. 159 actually began treatment; eighteen patients never began treatment. After treatment 28.3% received SVR and 71.7% did not receive SVR.
2. After comparing the two interventions of RBV-pegIFN and LDV-SOF, we found with LDV-SOF the incremental cost effectiveness ratio was $742,020.00 per QALY.

Limitations: Medical labs and treatment response was not always obtained or recorded in timely manner causing gaps in data. Data was not complete in some cases due to lost to follow-up patients. The time horizon was not long enough to show the cost effectiveness of the newer agents.

Conclusion: Many patients with HCV genotype 1 in this study did not get cured. Data suggested that Black/African Americans and individuals with cirrhosis have lower odds of a cure and as age increases, the cure rate decreases. We saw in the study that the older the patients were, the less likely they were to finish treatment, which may have contributed to the lower odds of cure. Data also suggests that in the time frame that the study was conducted, newer agents were not cost effective, compared to the older regimens, in the first year of treatment. The horizon would have to be analyzed for the lifetime of the patient to see any cost effectiveness of the newer agents and we assume that LDV-SOF would be more cost effective than RBV-pegIFN.

Table of Contents

List of Tables and Figures

Figures

Tables

Chapter 1: Introduction

Hepatitis C virus (HCV) is a blood-borne pathogen seen in the general population in the United States, and even more so in the prisons (Vallabhaneni et al., 2006). In 2009, an estimated 16,000 persons had acute HCV and 3.2 million had chronic HCV (Division of Viral Hepatitis, 2009; Holmberg, Spradling, Moorman, & Denniston, 2013). Approximately 1.3% of the general population is sero-positive for the anti-HCV serum antibody, the seroprevalence in state prison population is even higher at 17% (Varan, Mercer, Stein, & Spaulding, 2014). The majority of the inmates who are HCV-infected contract the virus through drug use in the community. Tattoos and piercings are also very common, in this population (Spaulding et al., 2013).

Over the last 25 years, antiviral therapies have been developed to combat this infection. Ribavirin (RBV) and peginterferon (pegIFN) were some of the first therapies and had a cure rate of 66-80% in HCV gentoype 2 and 3, and a 45% cure rate in genotype 1 (Manns et al., 2001). In 2011, came the introduction of boceprevir and telaprevir which had a cure rate between 80-90%. These are no longer used because of adverse affects. Sofosbuvir and simeprevir, released in 2013, has a similar cure rate in genotoype 1 but with fewer side effects and an added advantage of decreased symptoms and duration of treatment (Feeney & Chung, 2014). Just recently (Oct 14, 2014), sofosbuvir-ledipasvir (LDV-SOF) was FDA approved as a new combination of agents treating HCV genotype 1 with cure rates greater than 95% (Spach & Kim, 2014). In December 2014, Viekira Pak was introduced from AbbVie a connotation of ombitasvir, paritaprevir, ritonavir, and dasabuvir; it has a cure rate of 95-100% for HCV patients (Pollack, 2014).

One third of US population infected with HCV pass through the jail or prison system every year (Spaulding et al., 2013). Although treatment is available in the prison system, most inmates have not had a long enough duration of stay to take the treatment and are released back into society. This poses a public health issue as they are released back into society still infected. The objectives for this project are to:

1. Examine treatment outcomes of using dual treatment of RBV plus pegIFN for chronic Hepatitis C in federal prisoners in 2011.
2. Estimate the improvement of outcomes if LDV-SOF were given to these federal inmates from 2011 compared to RBV plus pegIFN.
3. Estimate the incremental cost effectiveness ratio

The hypothesis is that newer treatments are tolerable and effective but are costly, and that over the lifetime of the patient newer therapies will be cost effective.

This paper will consist of a literature review of hepatitis, treatment, the methods of how present data were collected and analyzed, and findings of the analysis. This study will contribute to public health by providing a cost analysis of the new drugs from the federal prison sector.

Chapter 2: Literature Review

Hepatitis C Virus

Hepatitis

Hepatitis is a virus that causes inflammation of the liver. There are six hepatitis viruses designated by letters such as hepatitis A, hepatitis B, all the way through hepatitis G (Davis, 2014). Hepatitis A, B, and C (HAV, HBV, and HCV) are the most common types in the US. HCV is the leading cause of liver disease and transplants (Division of Viral Hepatitis and National Center for HIV/AIDS, 2014).

The liver functions to purify the blood by changing harmful chemicals into useful chemicals, producing proteins, storage for sugars, fats, and vitamins, and build small chemicals into larger ones to use in the body. When the blood is infected with hepatitis virus, the virus multiplies within the liver and is dispersed into the blood stream throughout the body (Davis, 2014).

Genotypes

Hepatitis C is the liver disease caused by the HCV. HCV infection can range from mild to severe, lasting weeks or a lifetime (World Health Organization, 2012). HCV was originally named non-A and non-B hepatitis and it took over a decade to identify the etiological agent. HCV is a single-stranded, enveloped, RNA virus which is a part of the flaviviridae family. The virus is genetically heterogeneous and has multiple genotypes and subtypes. There are six major genotypes that have very distinct geographic distributions. These HCV genotypes are named genotypes 1-6, Genotype 1 is the most prevalent in the US (Simmonds et al., 2005).

Transmission

HCV is transmitted primarily through exposure to infected blood. The modes of transmission include the receiving of contaminated blood products, organ transplants, and transfusion; injections in health care settings with contaminated syringes; injection drug use; and being born to a mother infected with HCV (Shepard, Finelli, & Alter, 2005; Thomas et al., 1998). Rare modes of transmission of HCV, includes sexual contact (Terrault et al., 2013). HCV cannot be transmitted through exposure from sneezing, kissing, coughing, breast feeding, or sharing eating utensils (World Health Organization, 2012).

HCV pathogenesis occurs when the virus enters the host cell by attaching to receptors on the host cell. Through weak interactions, the virus releases its RNA into the host cell and undergoes replication and translation. The assembly of viral polyproteins are created on lipid droplets and released outside the host cell through a secretory pathway (Tang & Grise, 2009).

Symptoms and Diagnosis

The HCV incubation period lasts from two weeks to six months. Approximately 80% of those infected do not show signs of symptoms. If symptoms do exist, patients may exhibit vomiting, fever, nausea, jaundice, dark urine, abdominal pain, decreased appetite and joint pain (Division of Viral Hepatitis and National Center for HIV/AIDS, 2014; World Health Organization, 2012). Acute HCV is diagnosed when any of these symptoms are present if there is evidence of infection. Within eight weeks of infection the HCV RNA is detectable. At about four to 12 weeks after an acute HCV infection, alanine aminotransferase (ALT) levels increase. Anti-HCV antibodies can be detected in 90% of patients up to three months after infection. Few patients spontaneously clear the virus. To diagnose acute HCV, laboratory procedures include tests of elevated ALT levels which can reach seven times the normal limit, negative tests for

HAV and HBV, and a positive screening immunoassay on HCV either by enzyme immunoassay (EIA) or chemoluminescence immunoassay (CIA).

Chronic infection of HCV results in high levels of HCV RNA (10^5 to 10^7 international units IU/ml) in the blood. Most patients are asymptomatic and ALT levels may or may not be elevated. Chronic HCV is usually defined by the virus' presence in the blood more than six months (Federal Bureau of Prisons, 2009; World Health Organization, 2012). Chronic HCV can lead to fibrosis that can progress to cirrhosis of the liver. Factors that increase risk of cirrhosis include alcohol consumption, human immunodeficiency virus (HIV), and HBV. Once cirrhosis has developed, there is a one to four percent chance of developing hepatocellular carcinoma (HCC) per year (Federal Bureau of Prisons, 2009; World Health Organization, 2012).

HCV screening is recommended for people who have had a transfusion of blood products or had an organ transfusion; those who have been born to infected mothers, inject drugs, and have been incarcerated; and those who have abnormal lab tests, unexplained liver tests, and HIV. Recently, recommendations for the birth cohort between 1945 and 1965, to get screened have been issued, due to their higher risk for Hepatitis C (Rein et al., 2012).

Treatment

Antivirals

During the screening process for HCV, it is important to know which genotype is present. Each genotype may respond differently to antiviral treatments. The most common antiviral treatment regimen that has been used in the recent past is RBV and pegIFN. The pegIFN induces interferon-stimulated host genes and act as an inhibitor of HCV replication. These host genes also have antiviral functions. Ribavirin is used in combination with interferon α and is a

key component in the dual treatment regimen. The mode of action is still not fully understood, but the following lists what could be involved (Raymond T. Chung, 2009; Steven Flamm, 2014):

- Promoting interferon action
- The balance between pro-inflammatory (Th1-like) and anti-inflammatory (Th2-like) cytokines could be altered
- Inhibition of inosine monophosphate dehydrogenase causes a depletion of intracellular triphosphate (IMP)
- 5'-cap structure of viral mRNA is inhibited
- Viral-dependent RNA polymerases is inhibited
- Viral RNA mutagenesis

PegIFN mechanism of action involves inducing interferon-stimulated genes. These genes help establish an antiviral state within cells. Interferon-α acts by binding to cell surface receptors, which then activates a response cascade. Interferon-α may also lead to decreasing viral RNA stability. RBV and pegIFN are the standard for treatment up until 2011 was used for all strains of HCV.

The newest antivirals approved by FDA in 2014 are ledipasivir, a viral phosphoprotein that inhibits HCV NS5A, and sofosbuvir. Ledipasvir blocks viral replication, assembly, and secretion. Sofosbuvir is a viral polymerase nucleotide inhibitor that blocks the HCV NS5B polymerase needed for replication. Ledipasvir-sofosbuvir combination is used for HCV patients with genotype 1(Hepatitis C Online, 2014; Spach & Kim, 2014).

Side effects

Historically, one of the major issues for treating patients with HCV antivirals has been the side effects that can be sometimes unbearable to continue treatment. Sustained virologic response (SVR) depends on compliance with the therapy. Sometimes the dosage of treatment has to be reduced significantly or held altogether, because of adverse effects, which can also compromise the treatment outcome. For RBV and pegIFN, more than 80% of patients on this dual therapy encountered side effects. The side effects include anemia, neutropenia, thrombocytopenia, flu-like symptoms, neuropsychiatric side effects, respiratory symptoms, nausea, ophthalmologic disorders, glucose metabolism problems, autoimmune diseases, sarcoidosis, dermatologic complications, hair loss, thyroid dysfunction, migraines, and hearing loss. Using RBV before and during pregnancy can cause abortion and major birth defects (Kelleher TB, 2014). The most common side effects seen with the antivirals sofosbuvir and ledipasvir are headaches and fatigue (Afdhal et al., 2014). These are significantly more tolerable symptoms than those of previous antiviral regimens.

Cure rates

Over the recent year each new regimen has had improved efficacy in eradicating HCV. Other factors that can affect the cure rates are adverse reactions, co-morbidities, age, race, and incomplete treatments. RBV and pegIFN are older therapies that have been used together and have a cure rate of 66-80% in HCV gentoype 2 and 3, and a 45% cure rate in genotype 1 (Manns et al., 2001).

Hepatitis C in Federal Prisons

In the United States, there were a total of 210,961 inmates in the federal prisons as of December 30th, 2014. Eighty percent of these inmates are in facilities run by the Bureau of Prisons (BOP), 13% are in privately managed facilities, and 7% are in other facilities such as local jails or state prisons awaiting transfer. Of these inmates, dividing distribution of age in five year segments the 31-35 years old category represents 19%. Men represent 93% of inmates and non-Hispanic makes up 65.5% of the federal prison population. The race distribution include 1.5% Asian American, 1.9% Native American, 37.4% Black/African American, and 59.2% White (Federal Bureau of Prisons, 2014b).

Co-Morbidities

As mentioned previously, at least a third of the HCV positive inmates who come through the prison system acquired their infection through IDU (Spaulding et al., 2013). By using contaminated needles, HCV infection is only one of many other infections that can be transferred from one person to another. Problems that lie with treating injection drug users are the lack of screening, drug interactions for all treatments, and low treatment completion rates (Friedland, 2010). In contrast, one in every ten persons that contract HIV is through IDU in the community (World Health Oragnization, 2014b). Those persons with a co-infection of HIV/HCV have a higher progression of liver disease related to HCV. Lower response rates were seen with HIV/HCV co-infection treated with older agents. It is recommended to start treatment for HIV prior to HCV to stabilize the HIV disease and increase CD4 counts. Starting the HIV treatment first, avoids toxicity and ensure the HIV regimens are efficient and avoid developing resistance and optimize chance of obtaining a sustained viral response (SVR) (World Health Oragnization, 2014a). HCV and HBV co-infection can result in an accelerated disease driven by HCV

(Potthoff, Manns, & Wedemeyer, 2010). Both can be treated with antiviral therapy, but there is a chance of reoccurrence of HBV (Sulkowski, Mehta, Chaisson, Thomas, & Moore, 2004).

Criteria for treatment

Historically, in order to treat for HCV, the provider needed to ensure that the patient was an appropriate candidate. FBOP has strict guidelines that have to be followed to ensure patients receive the appropriate treatment and optimize likelihood of positive treatment outcomes. According to the FBOP Clinical Practice Guidelines in 2009, there were ten steps for detecting, evaluating, and treating chronic Hepatitis C using the antivirals RBV plus peg FN, which are listed below (Federal Bureau of Prisons, 2009):

1. "Appropriately screen inmates for hepatitis C
2. Provide initial medical follow-up for anti-HCV positive inmates
3. a) Determine if hepatitis C treatment is not recommended and b) Monitor HCV-infected inmates who are not on treatment
4. Obtain HCV RNA assay and HCV genotype
5. Assess liver fibrosis and need for a liver biopsy
6. Determine if treatment should be initiated
7. Conduct a pre-treatment evaluation
8. Determine appropriate treatment and obtain informed consent
9. Manage side effects and monitor treatment response
10. Assess for sustained viral response (SVR)"

Since 2011, there have been four new FDA approved medications to directly act against HCV (Simeprevir, Sofosbuvir, Harvoni, and Veikira Pak). The FBOP has released interim guidance

(January, 2015) for treating inmates with a more urgent need for treatment. Treatment is considered on a case-by-case basis. There are four scenarios that should be prioritized involving those with chronic HCV and they include:

1. "Advanced hepatic fibrosis/cirrhosis
2. Liver transplant recipients
3. Co-morbid medical conditions associated with HCV (e.g. cryoglobulinemia with renal disease or vasculitis, lymphomas/hematologic malignancies)
4. Continuity of care for newly incarcerated inmates who are being treated at the time of incarceration"

Measuring the degree of fibrosis can be done in several ways which include evaluating an aspartate aminotransferase (AST)-to-platelet ratio (APRI) score. An APRI score ≥ 1.0, or if the patient has low albumin or platelets or elevated bilirubin and an APRI score of 0.7-1.0, they will generally be considered for treatment at higher priority. Liver biopsies are no longer required but past biopsies can still be used to meet the criteria. Those who are pregnant (RBV is teratogenic), in general, will not be considered for treatment of HCV with RBV containing regimen. In summer 2014, the recommended treatment regimen for genotype 1, in most cases, was a 12 week course of treatment of SOF + RBV + IFN (Federal Bureau of Prisons, 2014a).

Updated guidelines have not been published on monitoring the newest medication regimens, but the following general statements have been made (Federal Bureau of Prisons, 2014a):

1. "Prior to using simeprevir based regimen (without sofosbuvir); the NS3 Q80K polymorphism should be tested (for drug resistance).

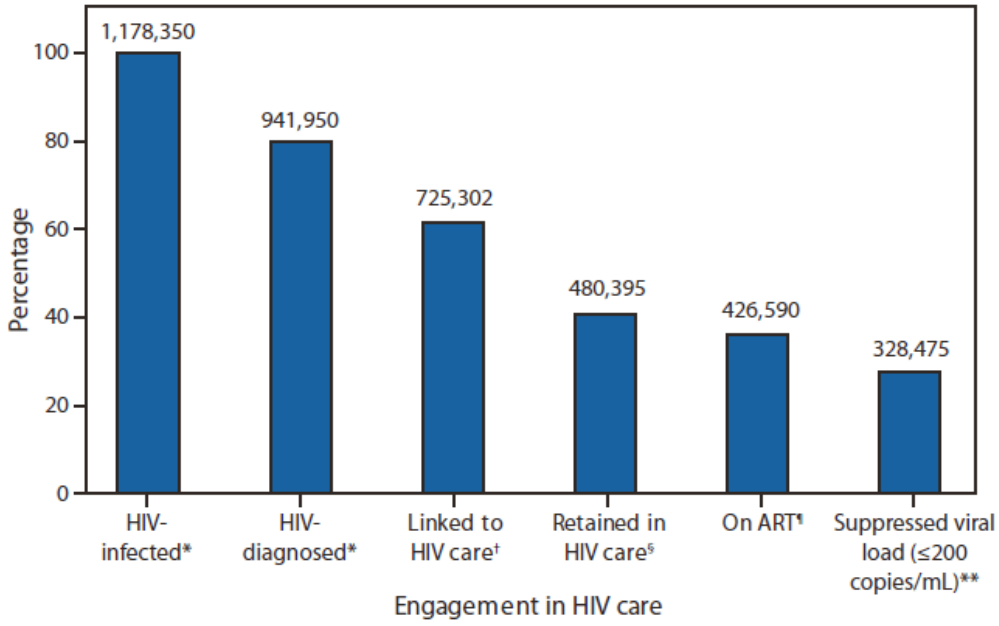
2. Pregnancy test should be given prior to and periodically during and after treatment for those women of childbearing potential on ribavirin based regimens.
3. Viral loads for sofosbuvir based regimens should be collected prior to treatment, 4 weeks into treatment, at the end of treatment, and 12 or 24 weeks after completion of treatment."

Since the inception of new direct acting antiviral agents such as LDV-SOF and Viekira Pak, new guidelines are being put into place for treatment of HCV.

Hepatitis C and HIV Care Continuum

In 2011, the Center for Disease Control and Prevention (CDC) released a Morbidity and Mortality Weekly report (MMWR) on the HIV prevention through care and treatment from 2008. In this report, CDC was able to build a cascade of care and treatment that gives estimates of U.S. HIV testing and prevalence, the percentage of HIV-positive adults who receive care, achieved suppression of the virus, and received preventative counseling. The estimates used were from three surveillance datasets which included the National HIV Surveillance System, Behavioral Risk Factor Surveillance System, and Medical Monitoring Project. Figure 1 represents their findings of continuum care for HIV in the U.S. (Center for Disease Control and Prevention, 2011).

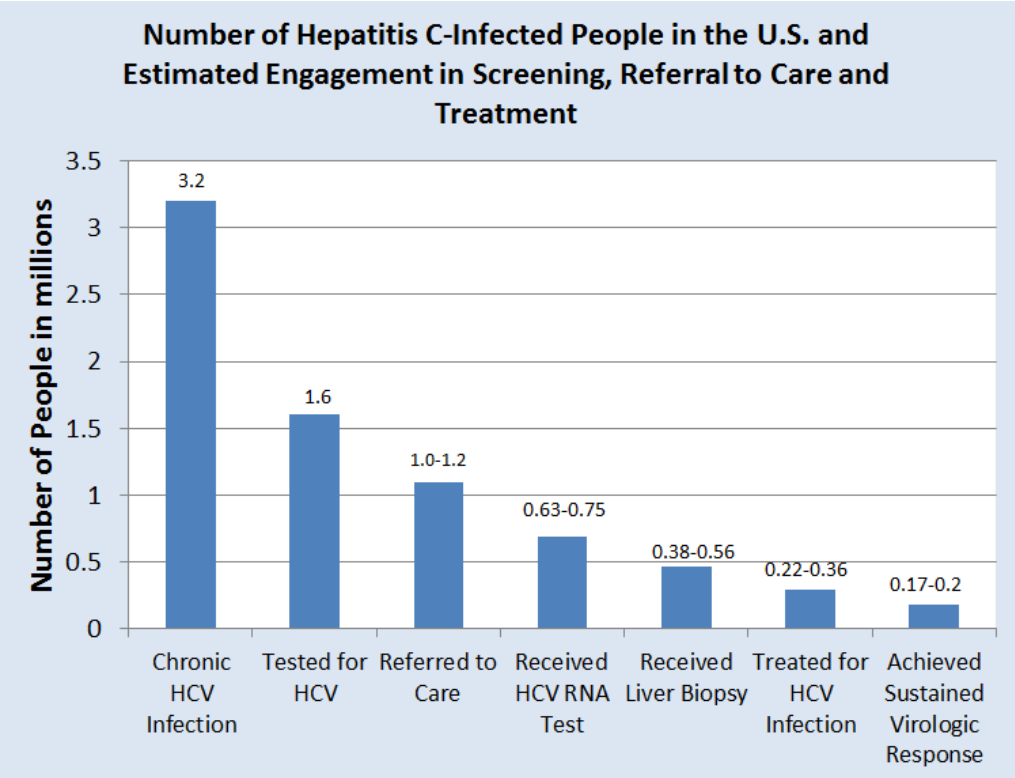
Figure 1: Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care — United States



Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6047a4.htm?s_cid=mm6047a4_w

For hepatitis C, as in HIV, the public health system needs to maintain and engage those infected with HCV within the continuum of care (National Institute of Drug Abuse, 2013). Figure 2 displays the continuum care for HCV in the US. Like HIV, this information provides a framework that will help to improve management and reduce transmission with continuous clinical care of diagnosis, linkage to medical care, prevention interventions, and the appropriate antiviral therapy (Center for Disease Control and Prevention, 2011) .

Figure 2: Number and percentage of HCV-infected persons engaged in selected stages of the continuum of HIV care — United States



Source: http://www.drugabuse.gov/about-nida/noras-blog/2013/07/world-hepatitis-day

Comparing the two cascades, it is seen that HCV has higher incidence and prevalence diagnosed infections than HIV. In recent years, HCV has trumped HIV as a cause of deaths in the United States, resulting in over 15,000 deaths in 2007, compared to 12,700 deaths from HIV (Horn, 2012; National Medical Association, 2014). These data showed that HCV has been an emerging infection. With the rapid changing and success of treatment, HCV may be controlled and become a rare disease (Kabiri, Jazwinski, Roberts, Schaefer, & Chhatwal, 2014).

Cost Analysis of Hepatitis C

One prescribing issue with treating patients for hepatitis C is the costs for treatment. Although the newer treatments have been successful in increasing the cure rates, the prices of

those treatments is high. For example, the cost to treat HCV patients with sofosbuvir in North America and Europe are $94,500 (Gilead) US dollars for a single 12 week regimen. This is $1000 per pill according to the manufacturer (Gilead Science). Simeprevir is estimated to cost $66,000 US dollars for a 12 week regimen used in the US and Canada according to the manufacturer (Janssen Pharmaceuticals) (World Health Oragnization, 2014a). With the newly approved agents, LDV-SOF, the wholesale costs of one pill is $1125. The cost for a course of therapy ranges from $63,000-189,000 (Hepatitis C Online, 2014; Spach & Kim, 2014). This is compared to the dual regimen of RBV plus pegIFN costing $9000-$12,000 in US dollars for a 24-48 week course (Solomon et al., 2011).

The estimated direct medical cost to treat HCV is over $750 billion per year in the US. Indirect medical cost range between $4-5 billion a year (United HealthCare Services, 2011). There are over 8 million hospital stays a year related to HCV treatment. The high economic burden of HCV is due to the management of its long-term consequences, such as cirrhosis, liver transplantation, and liver cancer.

Recently, attention has been growing in the cost effectiveness of treatments for hepatitis C, particularly for genotype 1. Having a cost-effectiveness analysis (CEA) allows for an examination of both health outcomes and costs of alternative intervention strategies (Center for Disease Control and Prevention, 2014; Hadix, Teutsch, & Corso, 2003). A CEA is used generally to assess the consequences of the expansion of existing programs and to compare a common health outcome with an alternative program. This examination will allow decision-makers to decide resource allocations. When looking at treating HCV, a CEA is appropriate to know if the newer treatments are more cost effective and have the best health outcomes (Hadix et al., 2003).

Summary

Overall, HCV is an emerging infectious disease that can be prevented and cured if the appropriate education and antiviral therapy is delivered. Data shows that with dual therapy of RBV plus pegIFN, there is a cure rate of 40%-50% in HCV genotype 1 patients. This data mostly represents the US population and state prison system. There is little to no data published that represents the federal prison population. This study will provide data from the federal aspect, filling in missing gaps for a full representation of all those infected with HCV by examining the treatment outcomes of the dual therapy RBV plus pegIFN and estimate the incremental cost effectiveness ratio (ICER) if LDV-SOF were given to the federal inmates from 2011 compared to RBV plus pegIFN.

Chapter 3: Treatment Outcomes of Using Dual Treatment of Ribavirin and Peginterferon for Hepatitis C in Federal Inmate Cohort 2011: And an Analysis of the Costs of Treating Patients with Newer Direct Acting Agents

Introduction

Hepatitis C Virus (HCV) is a blood borne virus that results in inflammation of the liver and is the leading cause of liver disease and transplants (Davis, 2014; Division of Viral Hepatitis and National Center for HIV/AIDS, 2014). There are six major genotypes (GT 1-6), and GT 1 is the most prevalent in the US (Simmonds et al., 2005). Modes of transmission are through contaminated blood products, organ transplants, injection drug use, and tattoos (Shepard et al., 2005; Thomas et al., 1998). Eighty percent of infected persons have no symptoms. If symptoms exist, they may include vomiting, rash, fever, nausea, dark urine, abdominal pain, joint pain, and jaundice (Division of Viral Hepatitis and National Center for HIV/AIDS, 2014). Treatment includes using antiviral agents usually in combination. Peginterferon (pegIFN) was the first antiviral used followed by ribavirin (RBV) which was used in combination. Several other antivirals have been developed in the last five years and these include telaprevir, boceprevir, sofosbuvir (SOF), simeprevir, and ledipasvir (LDV). The side effects of treatment have decreased as newer agents are developed. Eighty percent of the patients receiving RBV-pegIFN treatment encounter side effects. With newer agents such as LDV-SOF, the side effects are more tolerable (Kelleher TB, 2014; Spach & Kim, 2014). The cure rates have also increased with the development of newer agents ranging from 45% (RBV-pegIFN) to over 95% (LDV-SOF) (Manns et al., 2001; Spach & Kim, 2014).

The leading issue with HCV is the cost of treatment. The US spends over $750 billion per year on direct medical costs for treating HCV patients. Cost has increased from $9000-12,000 (RBV-pegIFN) to $63,000-$189,000 (LDV-SOF) (Solomon et al., 2011; Spach & Kim, 2014).

Although HCV is an emerging infectious disease, the virus can be prevented and cured if the education and antiviral agents are given appropriately. There is very little data on federal inmates with HCV and this study will provide information examining the treatment outcomes of the dual therapy of RBV-pegIFN, and estimating the incremental costs effectiveness ratio (ICER) if LDV-SOF were given to the federal inmates from 2011 in comparison to RBV-pegIFN.

Methods

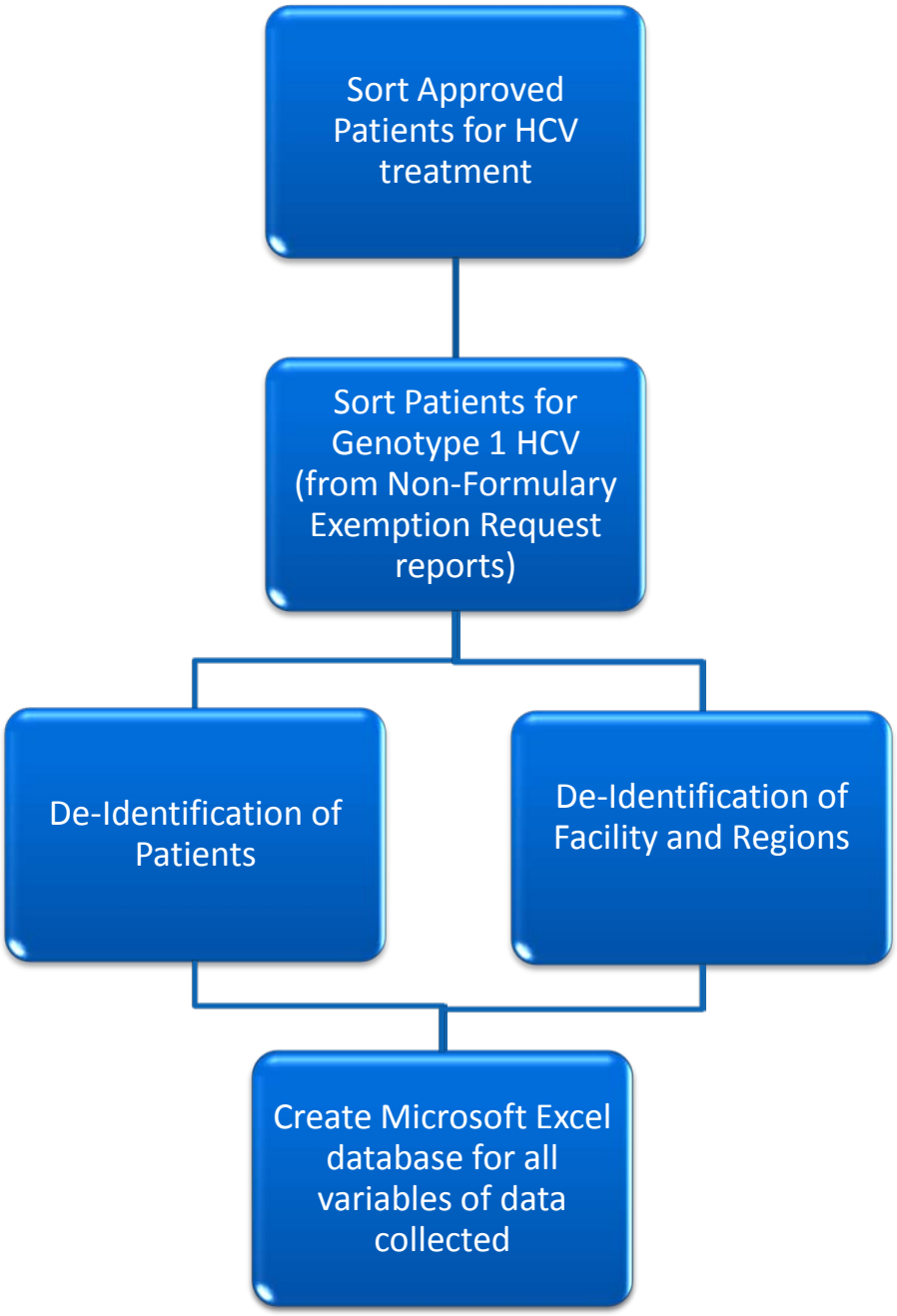
Subjects

Federal Bureau of Prisons had approximately over 210,000 inmates in the year 2011. The average length of stay is 5-10 years and the majority are male inmates (94%). Inmates are tested for HCV based on risk factors, if clinically indicated, or upon request.

Data Collection

Federal Bureau of Prisons data collection: The diagram below shows the flow of how data was collected from BEMR and imported for data analysis.

Figure 3: Flow Chart of How Data Collection was Sorted and Imported



For each approved HCV genotype 1 patient, information for data analysis were collected from medical records. The methods for collection of demographic and treatment data of each patient are listed below:

- From the list of approved patients, each patient's medical record was obtained through BEMR and de-identified.
- From the patient profile: age, birth year, gender, and ethnicity was obtained
- From prescription file: the dosage for each week of treatment for RBV-pegIFN was obtained
- From the non-formulary request form, inmate health summary and document manager: treatment start date, co-infection information, cirrhosis, baseline information (viral loads and regimen dosage), 4-48 week information (viral load and regimen dosage, reasons for stop treatment, adverse affects, treatment response status: Rapid Viral Response (RVR), Early Viral Response (EVR), End of Treatment Response (ETR), and Sustained Viral Response, (SVR), previous treatment status, outcomes, and notes were all collected for data analysis.
- Request for missing information was submitted to the facility health services staff to retrieve.
- All information that could not be retrieved was left blank and noted in the notes section as reasons for incomplete data.

Antiviral Interventions

The antiviral intervention of RBV-pegIFN was given to the HCV positive inmates approved for treatment in the year 2011. In this study we want to use a prospective strategy to estimate the cost effectiveness if LDV-SOF were available to these patients. Observed cure rates for RBV-pegIFN range between 40-50% (Manns et al., 2001); whereas, LDV-SOF averages over 95% cure rates (Highleyman, 2013). We estimate that using the new direct acting agents (LDV-

SOF) would have been more cost effective had they been available in 2011. The prevalence of SVR is also estimated to be higher with the new direct acting agents in these patients.

Medical Costs

The treatment regimen of RBV-pegIFN for HCV genotype 1 is taken in a course of 48 weeks costing an estimated $12,080 (Solomon et al., 2011). Since new antiviral therapies have become available, although the cure rates have doubled, the prices have almost tripled. One pill of LDV-SOF is approximately $1125 and this is taken on a daily basis, averaging $94,500 over a 12 week course (Spach & Kim, 2014). Even though there is a large price increase of the new direct acting agents, we estimate that the LDV-SOF regimen will still be more cost effective throughout the life of the patient.

Utility losses

To calculate the ICER using the quality adjusted life years (QALYs), we used the prevalence of the SVR within the study cohort of Federal inmates in 2011. The QALY values were collected from studies collected by Eckman et al (McLernon, Dillon, & Donnan, 2008; Thein, Krahn, Kaldor, & Dore, 2005). The QALYs is basically quality of life a person where they have utility range from 0 which is death to 1 which is perfect. This number is mostly estimated by surveys and studies on the population of interest. A decision tree was used to calculate the ICER using these prevalence and QALY values.

The ICER is how much it costs to add one QALY and is calculated by dividing the change in costs by the changes in QALYs. An ICER value over $50,000 is considered not to be effective and below $50,000 is cost effective.

Data Sources

All data was extracted from the Bureau's Electronic Medical Records (BEMR) by FBOP staff/interns. All medical records provided time frames and treatments of the inmates. Costs of agents and probabilities of health outcomes were obtained from data sources such as literature reviews, CDC, pharmaceutical companies, and National Institute for Health (NIH).

Results

After gathering the data from BEMR, a total of 422 Hepatitis C positive patients were approved for treatment. There were 177 (41.9%) patients that had HCV genotype 1, with 159 that actually began treatment. As seen below in Table 1, of the 159 patients with GT 1 that received treatment, the majority of participants were male (n=150; 94.3%) and White (n=87; 54.7%). The average age was 50 (STDV=2.12). Patients having co-morbidity infections included HCV mixed genotype (HCV genotype 1 and 2) =3 (1.9%), HIV=4 (2.5%), Hepatitis B=2 (1.3%). There were 25 (15.7%) patients diagnosed with cirrhosis.

Table 1: Demographics of the Federal Bureau of Prisons Approved Inmates Distribution with HCV GT 1, 2011 (N=159)

Demographics	N (%)
Race/Ethnicity	
White	87 (54.7)
Black/African American	45 (28.3)
Hispanic	25 (15.7)
American Indian	1 (0.6)
Asian/Pacific Islander	1 (0.6)
Gender	
Male	150 (94.3)
Co-Infection	
HIV	4 (2.5)
HCV Genotype 2	3 (1.9)
HBV	2 (1.3)
Cirrhosis	25 (15.75)

The viral loads were collected at 4, 12, 24, and 48 weeks of treatment and 24 weeks post treatment. At each of these weeks the prevalence of treatment response was recorded. Treatment response stages included Rapid Viral Response (RVR) =5.7% (no detection after 4 weeks), Early Viral Response (EVR) =29.6% (no detection after 12 weeks), End of Treatment Response (ETR) =33.3% (no detection after 48 weeks) and Sustained Viral Response (SVR) =28.3% (no detection 6 months post-treatment) (Table 2).

Table 2: Viral Response for Each Treatment Stage (N=159)

Response by Treatment Stages	N (%)
Rapid Viral Response	9 (5.7)
Early Viral Response	47 (29.6)
End of Treatment Response	53 (33.3)
Sustained Viral Response	44 (28.3)
Viral Loads	
Greater than 1 million	127 (79.9)
Cured	34 (26.8)
Less than 1 million	36 (22.6)
Cured	11 (32.4)

Using STATA, all collected data from the Microsoft Excel file was imported to calculate the unadjusted odds ratio of age, race/ethnicity, and cirrhosis. A logistic regression analysis was performed to collect this information. The odds ratio for age was 0.93 with a 95% confidence interval of 0.89 to 0.97. The odds ratio for African Americans was 0.38 with a confidence interval of 0.16 to 0.94. The odds ratio of those patients with cirrhosis was 0.31 with a confidences interval of 0.09 to 1.09 (Table 3).

Table 3: Unadjusted Odds Ratios by Age, Race, Cirrhosis Diagnosis (N=159)

	Cured	
	Odds Ratio	**95%CI**
Age	0.93*	(0.89, 0.97)
Race (African American)	0.38*	(0.16, 0.94)
Cirrhosis	0.31	(0.09, 1.09)

*$p<0.05$, statistically significant

Throughout the study there were many patients who discontinued treatment recommended by physician due to adverse effects, refusal due to adverse effects of treatment, null treatment response, or relapse of the virus. As mentioned above there were 177 patients approved for treatment and of those 159 began treatment. Eighteen patients turned down therapy due to potential side effects or awaiting new therapies. Of the 159 who began with the treatment, 45 received an SVR; whereas, 114 did not receive an SVR. Table 4 below demonstrates the treatment outcome categories we collected throughout the study. The SVR (28.3%) represents all of those who continued treatment and were successful. A little over 15 % of the patients demonstrated adverse effects including anemia, mental health issues, neutropenia, rash, thrombocytopenia, and other reactions. The relapsed patients (5.03%) had viral loads that rebounded post treatment. Those who discontinued treatment were in the category of null responders, partial responders, those that refused treatment during the treatment and those that were lost to follow-up. The null responders (23.9%) discontinued treatment due to viral load not decreasing by 2 log or viral rebound. Partial responders (6.92%) were successful at the

beginning of the treatment (2 log drop in viral load at treatment week 12) but either never achieved undetectable viral load or had a viral load rebound on treatment. Patients that refused treatment (8.18%) did so due to the way the treatments made them feel. Those who were lost to follow-up were granted early release and were either not able to finish treatment or were unable to obtain viral loads to evaluate for ETR or SVR.

Table 4: Treatment Outcomes (N=159)

Treatment Outcomes	N (%)
SVR	45 (28.3)
ETR	17 (10.7)
Adverse effects	25 (15.72)
Relapse	8 (5.03)
Null Responders	38 (23.9)
Partial Responders	11 (6.92)
Refusals	13 (8.18)
Lost to Follow-up	2 (1.26)

The patients that discontinued treatment included those who had adverse effects, null responders, partial responders, refusals, and those lost to follow-up totaling 89 patients. Figures 4 and 5 demonstrate the distribution of patients that were approved for treatment and the prevalence of those who discontinued treatment by age and race/ethnicity, respectively.

Figure 4: Total Number of Patients Approved for Dual Therapy Treatment (N=159) and Discontinued Treatment by Age (N=89) in BOP 2011

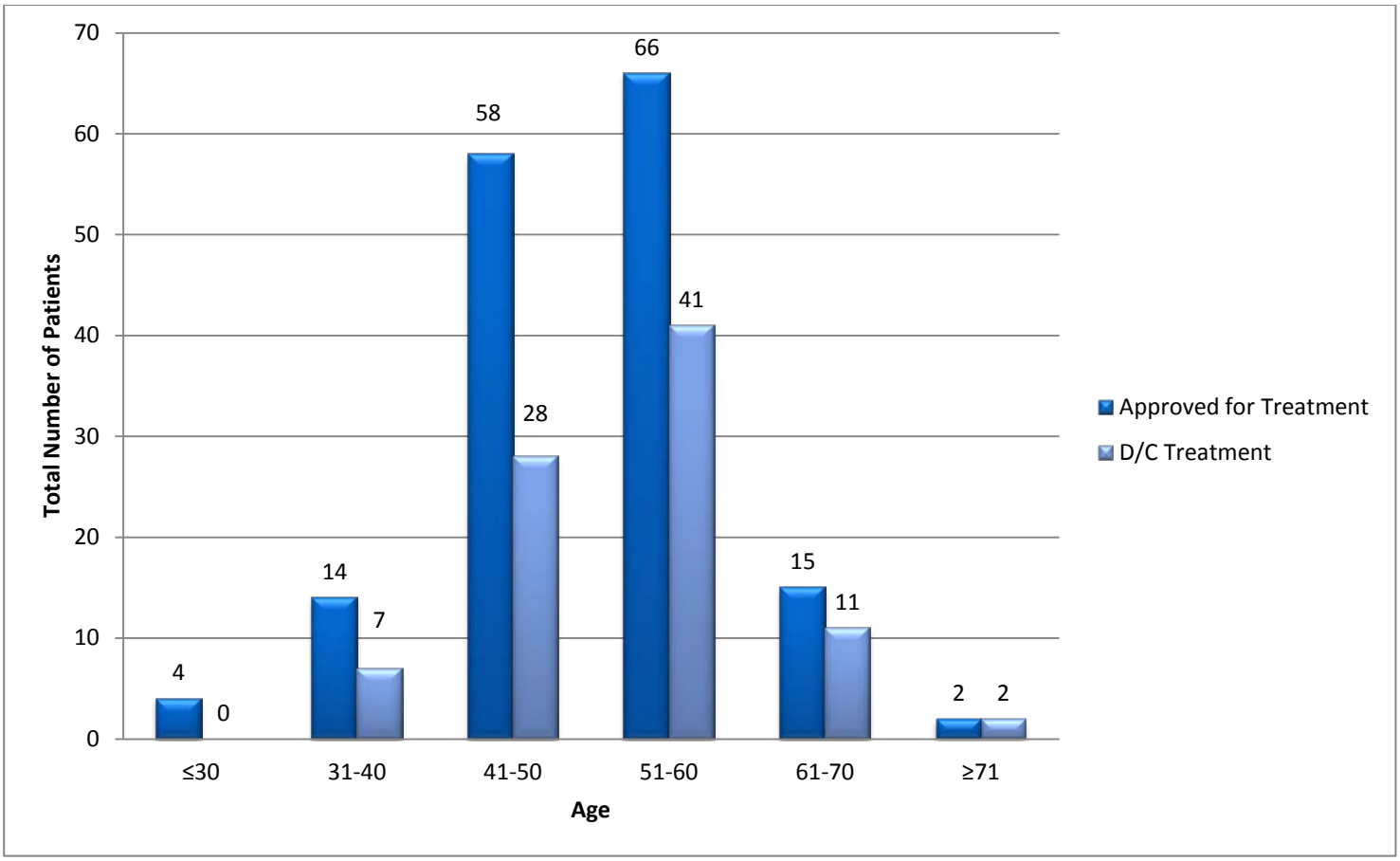
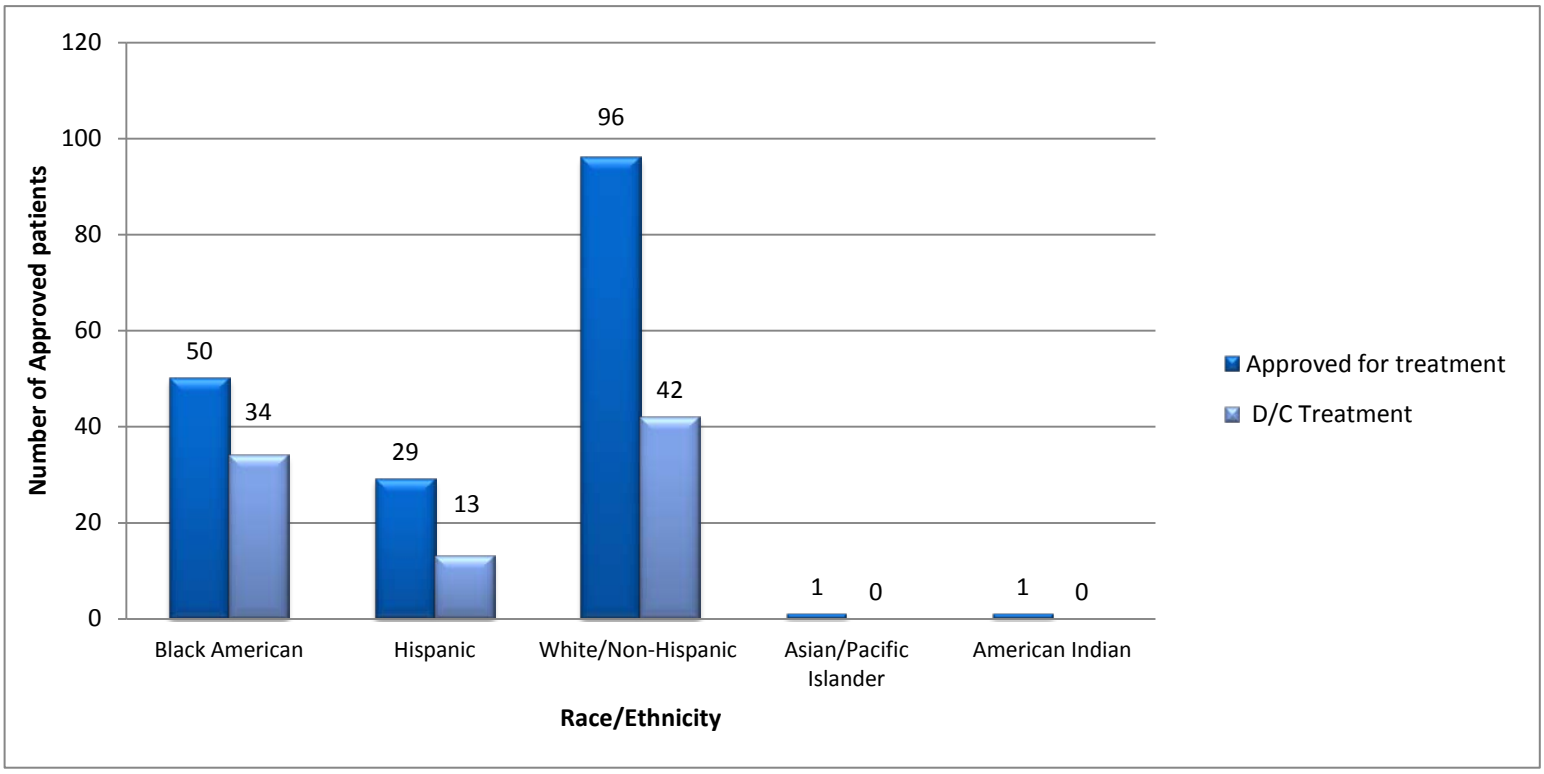


Figure 5: Number of Patients Approved for Dual Therapy Treatment (N=159) and Discontinued Treatment by Race/Ethnicity (N=89) in BOP 2011



CEA Study Results

In this study, we wanted to compare the cure rates or SVR of the older agents used in the patients in 2011 (RBV-pegIFN) with the possible SVR if new agents such as LDV-SOF were used. The model used for this CEA was a decision tree using QALY (Appendix A). The prevalence rates were calculated from the data collected from the 2011 cohort of inmates being treated with RBV-pegIFN. The SVR rates (95%) of LDV-SOF were estimated based on literature review for treatment. As mentioned in the introduction, the cost of RBV-pegIFN treatment for 48 weeks is estimated to be $12,040 and for a 12 week course of LDV-SOF the

estimated cost to treat is $94,500 (Solomon et al., 2011). The QALY values were obtained from literature (McLernon et al., 2008; Thein et al., 2005). Using these differences in these values and the incremental QALY the ICER of the 2011 cohort of inmates if treated with LDV-SOF was $742,020.00 per QALY saved when compared with the treatment given RBV-pegIFN (Table 5).

Table 5: ICERs Calculation from Societal Perspective

Intervention Strategy	Costs	Incremental Cost	QALY	Incremental QALY	ICER ($ per QALY)
RBV-IFN	**$10,848**		**0.83**		**-**
LDV-SOF	**$85,050**	**$74,202**	**0.93**	**0.1**	**$742,020.00**

Discussion

Based on the results from this 2011 study, the majority were male patients (94.3%). We found that a large proportion of the federal inmates treated for HCV genotype 1 were represented by the white, non-Hispanic population at 54.7%, followed by African Americans at 28.3% within the HCV population. We looked at the viral responses of the inmates throughout their treatment to get an idea of how the response of the treatment was portrayed throughout the 48 week regimen. During these stages of viral load assessments, other labs and clinical evaluations conducted were used to determine any adverse effects of the patients and the treatment would be adjusted as necessary. To reach rapid viral response, HCV RNA will be undetected after four weeks of treatment, early viral response HCV RNA is undetected after 12 weeks of treatment or

reduced by 2 logs, end of treatment response HCV RNA is undetected after treatment has ended, and sustain viral response HCV RNA is undetected 12 or 24 weeks after end of treatment (Ghany, Nelson, Strader, Thomas, & Seeff, 2011; Ghany, Strader, Thomas, & Seeff, 2009). As seen in this study few had an RVR (5.7%). The viral response was better in most patients at later treatment stages, with EVR and ETR at 29% and 33.3%, respectively. We saw that the SVR was 28.3% which was a decrease from the ETR. The average SVR with these inmates is lower than the US average of 40-50% cure rates with the RBV-pegIFN regimen. The reasons for the low cure rates in these patients include adverse affects such as neutropenia, anemia, thrombocytopenia, mental health issues, lost to follow up, and partial and null responders. Other reasons could include more advanced liver disease (Metavir Stage $\geq$2) of all BOP patients that were treated compared with the U.S. general population treated.

There were very limited studies with demographic distributions on just HCV genotype 1. What we did see is that age plays a major role in the HCV prevalence and treatment outcome. CDC estimates that the majority of persons infected with HCV were born between the years of 1945 and 1965. With the average age of 50 in the federal inmates treated for HCV genotype 1, the patients fall within this category. We also found that age was statistically significant with those of not reaching SVR through treatment for HCV using RBV-pegIFN regimen. Those of older ages were also more likely to discontinue treatment which could be the reason for lower cure rates in the older patients. There are limited studies in patients over the age of 60 and their ability to handle the treatment and adverse affects of RBV-pegIFN. Reasons for limited studies are due to other health issues that older adults are faced with such as other co-morbidities and age related risk factors. In the few studies that were performed, it was found that there was little significant difference in HCV treatment compared to younger HCV patients (Mindikoglu &

Miller, 2009). In this study, we found that the odds ratio of age was 0.93 with a confidence interval of 0.89-0.97. The odds of being cured of HCV were 7% less for each year of age. If we look at those over the age of 60, the main reasons for such a low probability of cure was due to adverse affects. Such affects included neutropenia, anemia, and thrombocytopenia. Other reasons were partial and null responders.

Like age, race played an important role in treatment outcomes of HCV in the federal inmates. HCV cure rate by race has a significant health disparity pattern. The odds of cure were significantly lower for African Americans compared to other races. In fact, odds of clinical "cure" were 62% less for African American compared to other races. The reasons for low response rates to RBV-pegIFN are not fully understood. There have been recent studies that mention a known factor, interleukin 28B (IL28B), that is a natural part of our immune system and may be the reason for low response to the regimen of RBV-pegIFN (Franciscus, 2013). IL28B is responsible for triggering our bodies to make more lambda interferon. The genotype for IL28B is called CC genotype which increases the chance of producing a stronger immune response. The CC genotype has been known to help with ridding the body of HCV, but has not been seen in African Americans.

Successful treatment of those patients with cirrhosis had an odds ratio of 0.31 with a confidence interval of 0.9 to 1.09. The odds of cure for individuals with cirrhosis were lower than those without at 69%.

Other information that we obtained when examining the disparities age and race has on this dual regimen given to the inmates included an account of those who may have dropped out of the treatment intervention. Out of all patients approved for treatment, approximately 50% of

the patients discontinued due to adverse effects. Within that percentage the majority (46%) was in the age range of 51-60 and was either white non-Hispanic (47%) or black/African American (38%). The data also concluded that 38% of the patients were null responders and 8% went into relapse during the treatment intervention. The age range for both the null and relapse responders were between ages 51-60. The distribution of race/ethnicity for the null responders was seen at the highest (45%) in the black/African American population, whereas in the relapse responders the highest (63%) was seen in the white non-Hispanic population. The high percentage in the black/African American population for a null response could be due to the genetic mutation of IL28B as mentioned earlier.

Over the last four years, the treatment and cure rates of HCV have improved markedly. The prison setting permits consistent treatment and follow-up at no cost to the patients. Many studies have proved that the new direct acting agents have been more cost effective in the US population, irrespective of the increased price of the treatments (Rein et al., 2012). In this study, we also have been able to predict that having the new agents would have cured more patients and been effective saving $742,020.00 per QALY. This data was calculated using an analytical horizon of one year. Because of the short horizon the data shows that it is not cost effective within this one year for using the new directing agents LDV-SOF. As mentioned earlier an ICER over $50,000 is not considered cost effective. The study would have to be extended using an analytical horizon of lifetime to estimate the cost effectiveness of the new agents. It is assumed that over the lifetime of patients with HCV (which ranges around 30 years), their QALY would be higher and in the long run, the new agents would be cost effective.

Limitations

The overall limitations were distinguishing the different METAVIR fibrosis stages. FBOP data only presented patients with stages two and above including those that were cirrhotic (Stage 4). The fibrosis stages two and three were not distinguishable for this study to analyze. Patients were screened for HCV on a risk basis, so these patients may not be representative of all HCV infected persons within BOP. Other limitations included limited generalizability, missing determinants of SVR, and few were lost to follow up due to a patient transfer or released during treatment. As the data was analyzed all data gaps were recorded and those providers were contacted to get the missing information such as SVR viral loads, if possible. With the viral loads not being collected at the appropriate times according to the FBOP guidelines, providers were contacted to address the incidences. Although the guidelines, in general, require inmates to have sufficient time to complete treatment while still incarcerated at BOP, to be approved for treatment, there were still a few patients that were released earlier than anticipated. There were also patients that were transferred to other facilities, which postponed treatment or were lost to follow-up. Because the treatment was interrupted there stood an increased possibility of relapse or null response.

These limitations also had an impact on conducting the CEA for this study group. The data with the exact probabilities of patients that had HCC, decompensated cirrhosis, or liver transplants were limited due to length of sentencing remaining at end of treatment. The probabilities used were taken from the average ranges from previous studies within the US population. There were also limitations on the resources to do an extended decision tree to cover all health outcomes and have a very thorough cost effective analysis for comparing LDV-SOF and RBV-pegIFN.

Chapter 5: Conclusion and Public Health Significance

In conclusion, our data suggest that Black/African Americans and individuals with cirrhosis had lower odds of a cure using conventional therapies of RBV plus peg IFN. The data also suggested that as age increased the cure rates decreased especially in older (40-60 years of age) patients. Since this study was done in 2011, newer and more effective therapies have been introduced for HCV patients. The newer regimens are known to decrease the length of treatment, adverse effects and increase cure rates of HCV. Although the newer regimens of LDV-SOF did not show cost effectiveness within one year of this study, we assume it would have been more cost effective throughout the lifetime of the patient. These newer agents would have also provided better results to African Americans because of the lack of success with RBV-pegIFN due to the ILB28B gene. Now that the newer agents are available and inmates are now being treated with LDV-SOF, it will be interesting to see actual cure rates with the new agents. For future research, a more robust model for the CEA will be used to look at a lifetime horizon and each health outcome throughout the life of the disease.

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Appendices

Appendix A: CEA Decision Tree