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Modeling Hepatitis C Treatment Policy

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Abstract

Chronic infection with Hepatitis C virus (HCV) results in cirrhosis, liver cancer and death. As the nation's largest provider of care for HCV, US Veterans Health Administration (VHA) invests extensive resources in the diagnosis and treatment of the disease. This report documents modeling and analysis of HCV treatment dynamics performed for the VHA aimed at improving service delivery efficiency. System dynamics modeling of disease treatment demonstrated the benefits of early detection and the role of comorbidities in disease progress and patient mortality. Preliminary modeling showed that adherence to rigorous treatment protocols is a primary determinant of treatment success. In depth meta-analysis revealed correlations of adherence and various psycho-social factors. This initial meta-analysis indicates areas where substantial improvement in patient outcomes can potentially result from VA programs which incorporate these factors into their design.

CONTENTS

FIGURES

TABLES

ACRONYMS AND ABBREVIATIONS

CASoS	Complex Adaptive System of Systems (concerning a specific system) or Complex Adaptive Systems of Systems (concerning the field of systems)
DAAs	Direct-acting antivirals
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Intravenous drug use
QALY	Quality adjusted life year
SD	System dynamics
Sandia	Sandia National Laboratories
SVR	Sustained viral response
US	United States
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

PREFACE

The United States (US) Veterans Health Administration (VHA) is engaged in a collaborative research program with the Complex Adaptive System of Systems (CASoS) Engineering group at Sandia National Laboratories (Sandia). This program continues the long-standing research partnership between the institutions aimed at applying advanced modeling and simulation methods to large-scale emerging problems in public health and healthcare management. This second year of the current research program has focused on leveraging the modeling capability developed in the first year to address policy issues of current interest to the Department of Veterans Affairs (VA) leadership.

Chronic infection with Hepatitis C virus (HCV) is a serious public health concern. HCV is currently the most prevalent blood-borne disease in the US, affecting almost four million Americans. HCV attacks a patient's liver and can cause cirrhosis, liver cancer and death. HCV has historically been difficult to treat because medication is expensive and adherence is very difficult. In addition, many patients are not eligible for treatment due to comorbidities or because they do not know they are infected.

This Hepatitis C Modeling effort will provide quantitative guidance for policies for effectively allocating scarce treatment resources to a growing population of US veterans with Hepatitis C. The treatments are expensive, rigorous and of variable efficacy. Modeling promises to allow different configurations for treatment factors now being deployed in VA facilities to be evaluated quantitatively.

The VHA is the largest provider of Hepatitis C care in the US. Improved screening, disease progression and treatment adherence models could improve the quality of VA care. Earlier this year, Sandia researchers and VA experts defined detailed conceptual models of HCV treatment in the VA. A computational model was built to model the disease progression in a cohort of VA patients. The disease progression model can be used to estimate the number of patients with each stage of the disease. It can also model the impact that policies such as improved screening or interventions would have on the patients.

While building the hepatitis disease progression model, we isolated HCV medication adherence as a critical component for a patient's successful treatment. We built an HCV treatment adherence model based upon a meta-analysis of prior studies identified through an exhaustive literature review. This model analyzes multiple factors that influence a patient's ability to successfully adhere to treatment, which has been shown to be necessary to obtain a sustained virological response. The model identifies factors that have the most potential for improving patient adherence. Finally, we conducted a sensitivity analysis on the model and gained several other insights.

Current work includes designing validation plans for both the treatment adherence model and disease progression model. Our VHA co-investigators are obtaining data sets relating treatment and screening practices to clinical outcomes for a range of VA facilities. These data will be particularly important to tuning the treatment adherence model, which was developed from non-VA datasets and studies.

1 OVERVIEW

The United States (US) Veterans Health Administration (VHA) is engaged in a collaborative research program with the Complex Adaptive System of Systems (CASoS) Engineering group at Sandia National Laboratories (Sandia). This program continues the long-standing research partnership between the institutions aimed at applying advanced modeling and simulation methods to large-scale emerging problems in public health and healthcare management. This second year of the current research program has focused on leveraging the modeling capability developed in the first year to address policy issues of current interest to the Department of Veterans Affairs (VA) leadership.

Chronic infection with Hepatitis C virus (HCV) is a serious public health problem in the United States. Estimates of the prevalence of HCV in the US range as high as 3.9 million, three to four times that of HIV, making it the most prevalent blood-borne infectious disease in the US (Chak, Talal, Sherman, Schiff, & Saab, 2011; Centers for Disease Control and Prevention [CDC], 2011). Left untreated, HCV can lead to hepatocellular carcinoma (HCC), advanced liver disease and death. In 2007, the number of deaths in the US attributable to HCV surpassed the number due to HIV (Ly et al., 2012).

While new cases of HCV are decreasing due to improved screening of the blood supply, chronic infection is a progressive disease that may require treatment for many who have been infected for decades. Hence, the number of patients who will require treatment for HCV is expected to increase dramatically over the next 20 years (Davis, Alter, El-Serag, Poynard, & Jennings, 2010). Antiviral treatment aimed at permanent cure of HCV –termed a sustained viral response (SVR)–can significantly reduce the risk of disease progression and death, but such therapy has historically had limited efficacy, substantial toxicity and high costs (Backus et al., 2011). The recent introduction of direct-acting antivirals (DAAs) has increased HCV cure rates, but regimens incorporating these new drugs are complex, difficult to incorporate into existing care models and more expensive than existing treatments.

The VHA is the largest provider of HCV care in the United States (US) with over 170,000 HCV patients in care in 2011 and an estimated prevalence rate of 4.0% among its population in care, three times that of the general US population (Dominitz et al., 2005; “VA Clinical Case Registry,” 2012). As new and more effective HCV treatments are developed and deployed within the VHA, there is considerable interest in developing new strategies to manage the complex care of these patients. Sandia researchers have teamed with Hepatitis C experts from the VHA to model several aspects of HCV treatment in the VHA in order to gain insight into policies that could improve HCV care. The VHA has the opportunity to lead the country in defining as well as delivering the most effective and efficient HCV care.

We have implemented two distinct models following an initial exploratory phase which involved background research and several high-level conceptual models. The first, our disease progression model, uses system dynamics (SD) to study the disease progression of a cohort of patients. Patients move through a series of stocks (compartments) and flows (transitions) representing different levels of liver scarring. Various policies are studied, such as the impact of reducing a cohort’s alcohol consumption to slow disease progression. The analysis will allow an alcohol use reduction policy to be optimized. These models will answer questions regarding the best time to treat patients and how care might be impacted if random screening is implemented.

We have additionally implemented a second treatment adherence model addressing HCV treatment adherence. Although treatment adherence has been shown to be critical for treatment success, the factors that influence adherence are not well understood. Therefore it is difficult to know if, for example, improving a patient's social support would have a greater or lesser impact on adherence than reducing stress. We conducted a literature review across multiple disciplines to compile a comprehensive list of adherence factors. We analyzed the model for critical features so that specific factors can be targeted to obtain the largest effect on the network. We find that highly connected factors and feedback loops are critically important to influencing adherence, meaning factors such as social support have a large potential to impact adherence. Our analysis also suggests that understanding the processes that cause factors to influence one another is also fundamentally important for improving adherence improvement strategies.

Modeling HCV disease progression and treatment provides insight into policies that can improve the quality, efficiency and cost-effectiveness of care provided by the VA. Data are being gathered to validate aspects of both models, allowing analysts to make more specific policy recommendations. As new data and research become available, modeling refinements will enable the VHA to further improve HCV patient treatment, continuing their record of providing the best possible care to veterans.

2 PROBLEM FORMULATION

Sandia researchers and HCV experts approached HCV modeling using a combination of a top-down and a bottom-up approach.

We conducted a high-level analysis to map resource flows and informational flows among entities such as pharmaceutical companies, insurance providers, the VHA, the Food and Drug Administration (FDA) and several others. Researchers used this high-level mapping in the development of a conceptual model to ensure all the relevant factors for a problem were taken into account.

Once we mapped the high-level influences, we proposed specific issues and categorized them into three areas: system-level factors, clinic-level factors and patient-level factors. System-level factors are issues that are constrained by the entire system or are system wide such as budgeting issues or screening protocols. Clinic-level factors can differ across regions and involve issues such as provider culture referrals and integrated care management. Lastly, patient-level factors affect the individual patients and include the health of the patient, social support and personal motivation.

In the next step we formulated the goals of this modeling. The goals act as a broad roadmap that keeps the modeling on track. After several initial brainstorming sessions the following goal-oriented questions emerged:

1. How good can HCV treatment get?
    a. How do we measure “good”? Quality adjusted life years (QALYs), additional years of life, cost of treatment?
2. What factors impact HCV care?
3. What are the relative impacts of factors?
4. How can we measure these factors?
5. How to we increase adherence?
6. How do we decrease uncertainty?

The following sections of this paper document the conceptual design and implementation of the two models we used to address these goals. We further show initial findings and indicate where additional data on systemic and facility characteristics can help increase the resolution and utility of the models.

3 DISEASE PROGRESSION MODEL

System dynamics (SD) is a modeling technique that uses stocks and flows governed by differential equations. In this modeling method, cohorts of entities in a given disease state are termed “stocks” and transitions between states are termed “flows.” We used SD methodology to model disease progression, mapping the progression of HCV for a VA cohort. HCV is a progressive disease, meaning the virus continuously attacks liver cells and the patient’s health deteriorates. HCV is often categorized into one of several stages. Initially, the patient is infected with the virus but the virus does not immediately attack the liver. The patient’s immune system may eradicate the virus automatically, in which case the patient will not be chronically infected. Alternatively, if the virus attacks the liver, the patient may begin to experience liver scarring. Mild scaring of the liver is categorized as Stage 1 fibrosis. This scarring can continue with escalating severity through Stage 2, 3 and 4 of fibrosis. The patient may also contract hepatocellular carcinoma (HCC) (liver cancer).
Categorization according to disease stage allows the disease progression to be represented in bins. In the literature, Markov models and SD implementations are frequently used to track the progression of disease through a population.

3.1 Model Implementation

We modeled HCV disease progression using Vensim®, an interactive SD modeling application. In our disease progression model, patients are introduced into the system are assigned a certain probability of advancing to the next stage of the disease over the course of one year (Figure 1). In later stages of the disease, death may occur with some yearly probability. Patients also have a probability of death from non-HCV causes at each stage in the disease. This death rate is 0.002 per year, corresponding to a rough estimate of a death rate for a middle-aged person in the US. Patients also have a risk of death from HCV related factors in Stage 3 fibrosis, cirrhosis and HCC.

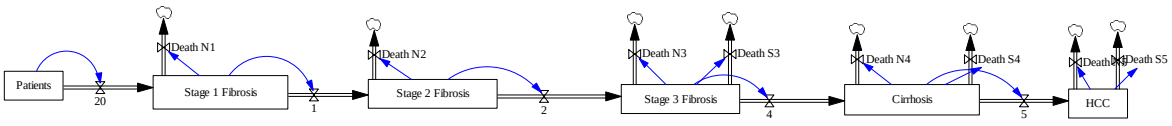

Figure 1: Diagram of Hepatitis C disease progression as structured in our model. Boxes denote disease stages and arrows denote changes between stages. The clouds denote patients leaving the system through death. Blue arrows denote changes in transition rates due to numbers of patients in a given stage.

We calculated our disease stage transition probabilities based on research describing a meta-analysis of a filtered set of 111 studies (Thein, Yi, Dore, & Krahn, 2008). The authors of the paper developed regression equations to estimate the disease progression rates as a function of several inputs, including duration of HCV infection, clinical/nonclinical trials, proportion of males, proportion of genotype 1, age at HCV acquisition, proportion with heavy alcohol use, and risk of HCV acquisition (Intravenous drug use (IDU) verses blood transfusion). There are issues with these equations, for example alcohol use only affects progression from Stages 1 to 3,

however the resulting progression rates provide a baseline estimate to serve as a starting point for our modeling.
Cohort characteristics are listed in Table 1. Disease progression rates are shown in Table 2. Model parameters are listed in Table 3.

Table 1: Cohort demographics

Variable	Value
Duration of HCV infection (years)	20
Clinical (1 for yes)	0
Male Proportion	0.8
Genotype 1 proportion	1
Age at HCV acquisition	25
Excess alcohol proportion	0
IDU Proportion	0.5
Blood Transfusion proportion	0.5

Table 2: Disease progression rates

Progression	Rate per year
Patients-Stage 1 Fibrosis	0.071271
Stage 1 Fibrosis– Stage 2 Fibrosis	0.062794
Stage 2 Fibrosis – Stage 3 Fibrosis	0.094269
Stage 3 Fibrosis – Cirrhosis	0.111995

Table 3: Model Parameters

Variable	Rate per year
Death from Stage 3 Fibrosis	0.01
Death from Cirrhosis	0.1
Death from HCC	0.75
Cirrhosis to HCC	0.03

We initialized our disease progression model with 160,000 patients (a rough estimation of the number of VA patients chronically infected with HCV) in Stage 0 and without any patients in other Stages. The model was run for 100 months. Patients' movement through the disease stages are shown in Figure 2. The number of patients with Stage 0 fibrosis decreases exponentially over time while the number of patients with later stages of the diseases peak sequentially. These results are consistent with other models in the literature (Davis et al., 2010).

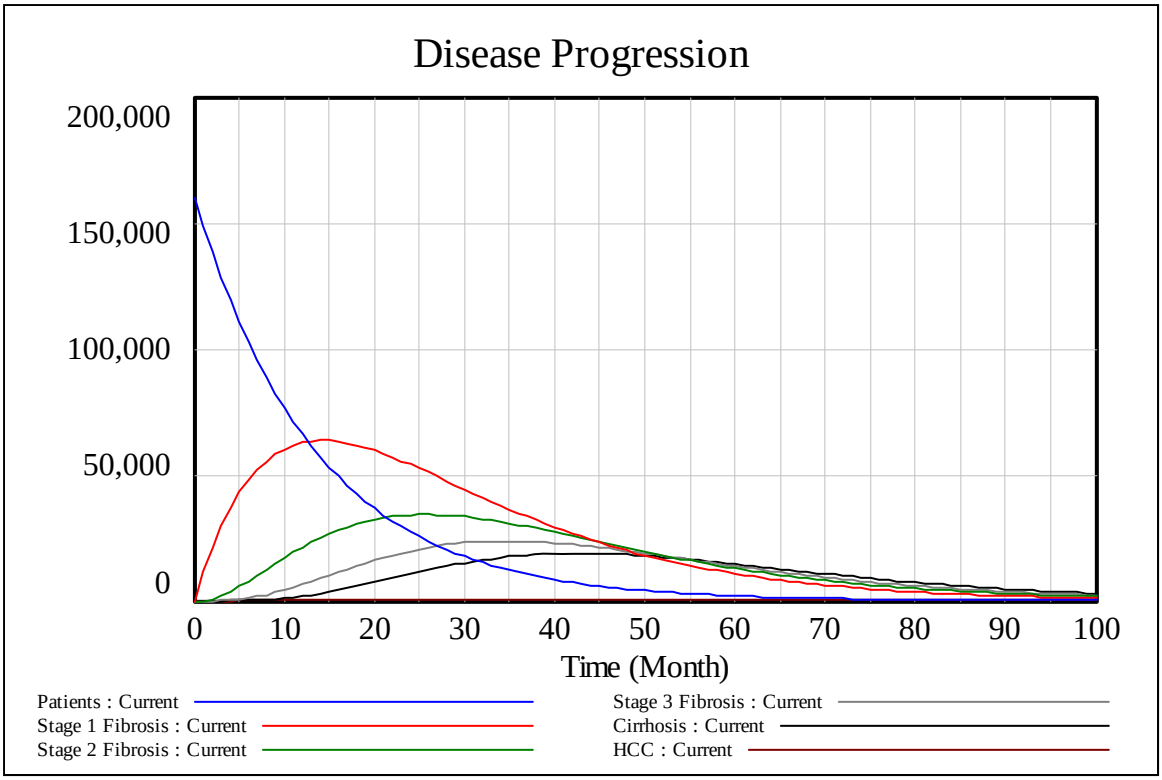

Figure 2: Graphic illustration of cohort movement through disease stages over a 100 month period. Note that the number of patients infected peaks sequentially for each disease Stage.

3.1.1 Metrics

We used a quality adjusted life year (QALY) metric to quantify the economic effects of model runs. At each time interval, we tallied the number of patients in each Stage (bin) and multiplied that number by the relevant weighting factor (obtained from Liu, Cipriano, Holodniy, Owens, & Goldhaber-Fiebert, 2012) shown in Table 4. For example, for 100 people in Stage 2, 90 would be added to the QALY value.

Table 4: QALY weights

Bin	Weight
Patient	1
Stage 1 Fibrosis	0.98
Stage 2 Fibrosis	0.9
Stage 3 Fibrosis	0.8
Cirrhosis	0.7
HCC	0.7

3.2 Effect of Alcohol Use on Disease Progression

Alcohol use is known to increase the disease progression rates for patients with chronic HCV (Thein et al., 2008). Investment in programs that reduce the number of patients using alcohol could have a large impact on the cohort's disease progression and the total QALYs. To investigate the effectiveness of an alcohol-use reduction program, we expanded the disease progression model to include two progression tracks. The first track is for a cohort with low-alcohol use while the second track is for a cohort with heavy alcohol use. The disease progression rates for the high-alcohol-use cohort are higher than the low-alcohol-use cohort.

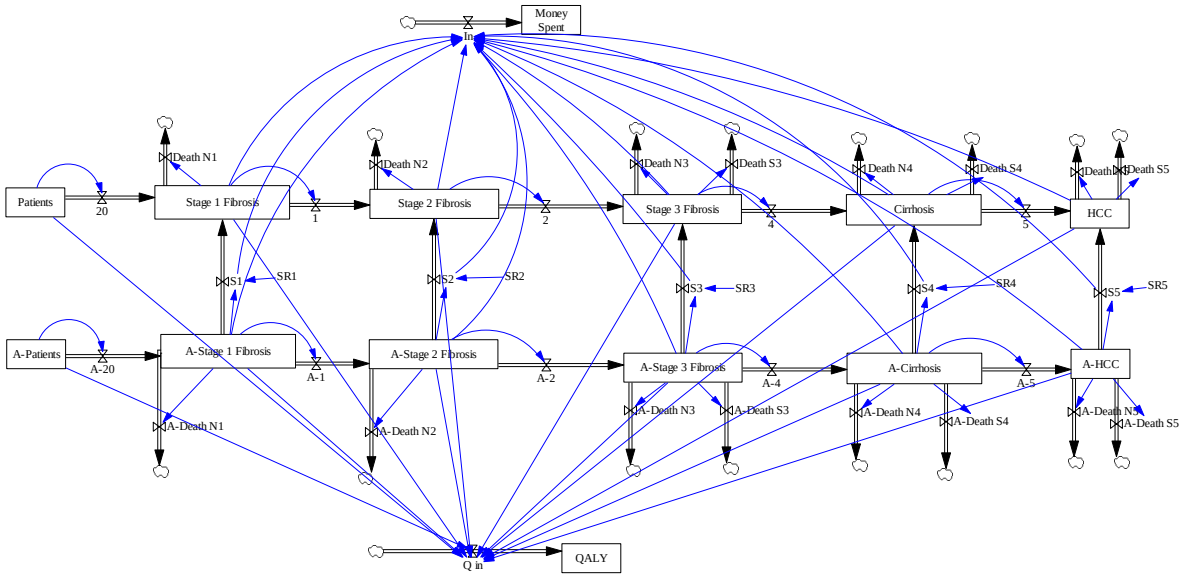

Figure 3: Disease progression model showing the effect of alcohol-use-reduction programs. The low-alcohol-use cohort (top) and high-alcohol-use cohort (bottom) have different disease progression rates.

The disease progression rates for the two tracks are shown in Table 5.

Table 5: Disease progression rates for high-alcohol-use and low-alcohol-use cohorts

Progression	Rate per year (Low Alcohol Use)	Rate per year (High Alcohol Use)
F0-F1	0.071271	0.071271
F1-F2	0.062794	0.139764
F2-F3	0.094269	0.148421
F3-F4	0.111995	0.111995

The model run allowed no transition between the two tracks. Patients remained in either the high-alcohol-use track or the low-alcohol-use track for the duration of the simulation. We initialized the disease progression model with 80,000 patients in each track. Figure 4 shows how the peak infection times for each stage differ for the two groups.

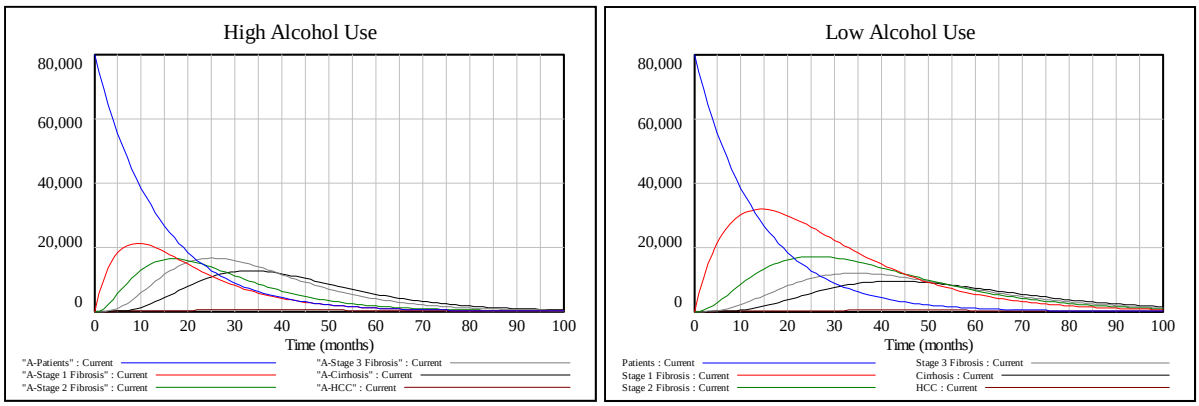

Figure 4: Number of infected patients in each stage for both high-alcohol-use and low-alcohol-use cohorts. Note that the maximum number of patients infected occurs earlier and is lower in magnitude for the high-alcohol-use cohort.

We measured the total QALYs gained at the end of the 100 months to analyze the difference between the two runs. The number of QALYs increases about 5% when half of the patients are on the low-alcohol-use track compared to the run where all patients were on the high-alcohol-use track. The improvement in QALYs can also be studied for various ratios of patients in the two tracks.

In addition, the model was configured to enable patients to shift from the fast disease progression track to the slow disease progression track. This scenario represents the implementation of alcohol use reduction programs at a facility. Additional simulations were run to study what intervention programs are most effective.

3.3 Modeling Treatment

Various treatment strategies were studied using the disease progression model. The treatment model adds an additional track where patients can be cured, resulting in a higher QALY value and no disease progression. Only low-alcohol-use patients can enter treatment. Treated patients are either cured or experience a failed treatment with a certain probability. If treatment fails, they enter a new disease progression with slower transition rates due to the benefits from treatment. Patients in treatment have a base-rate QALY for their disease Stage minus an additional deficit of .165 due to treatment [40]. Cured patients have a QALY of 1.

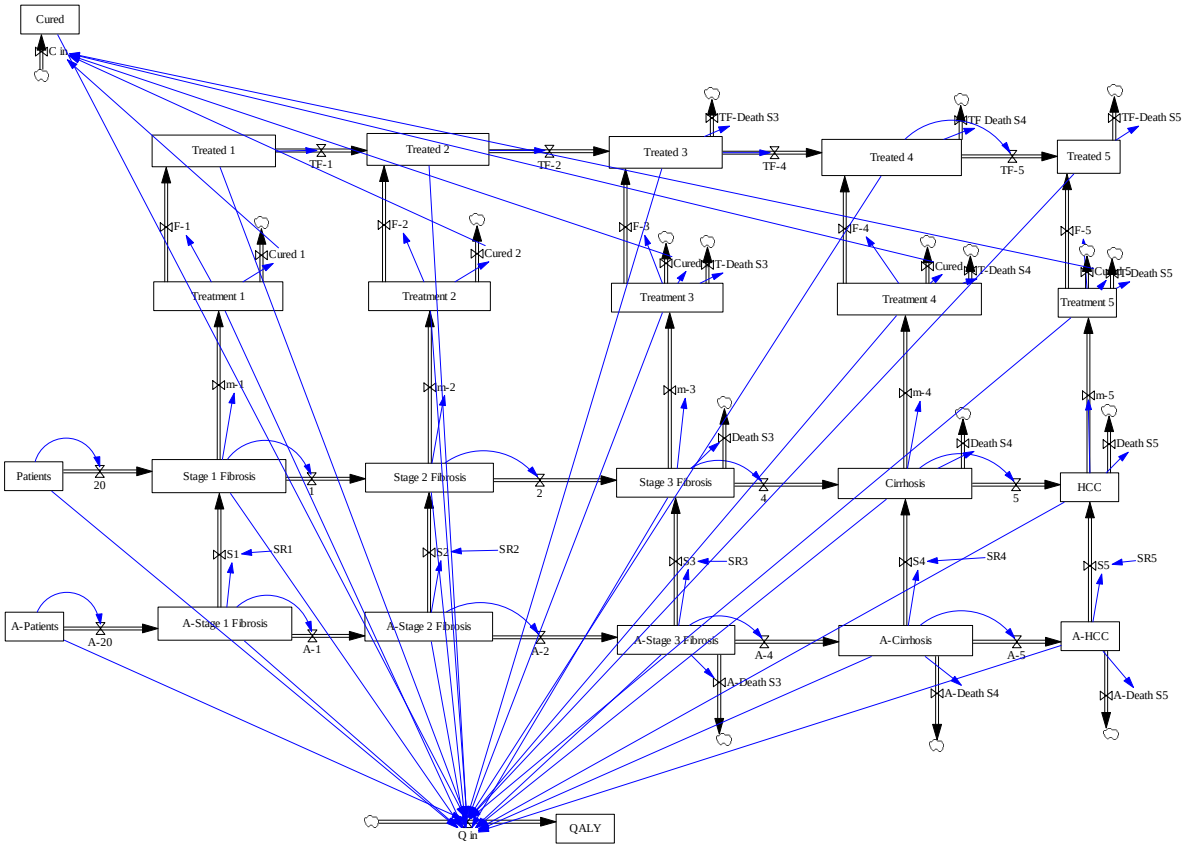

Figure 5: Diagram of disease progression model showing components, transitions and rates for the treatment track (top), low-alcohol-use track (middle) and high-alcohol-use track (bottom).

We tested various parameters and recorded their effect on metrics such as total death and QALYs. Modeling results suggest that relatively small treatment rates (such as 5% of Stage 1 fibrosis patients) can result in relatively large improvements in QALYs (up to 22%). However, most of these improvements are long term and do not impact the total QALY values until late in the simulation runs.

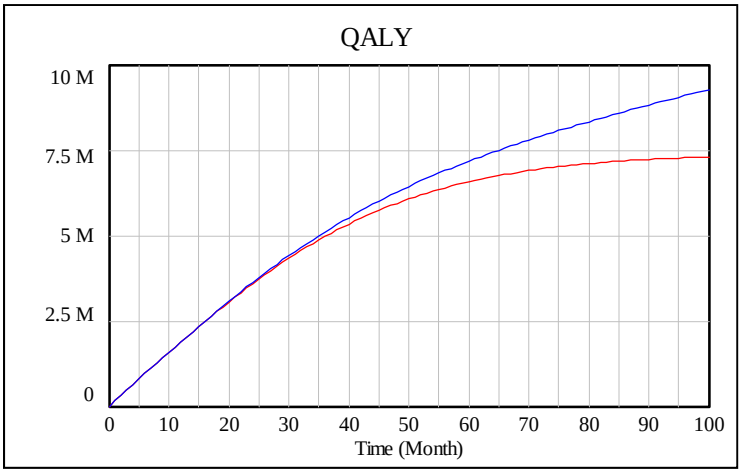

Figure 6: Graph illustrating comparison QALYs over a 100-month period for patients with Stage 1 fibrosis with no treatment (red line) and those with 5% treatment (blue line).

Figure Note: significant improvements due to 5% treatment do not begin until month 35.

Costs were also be implemented into the model to compare several policies. Table 6 shows some example costs per year for patients in various stages of the disease (Liu et al., 2012).

Table 6: Sample treatment costs per year for patients in various stages of HCV.

Stage	Cost Per Year
Treatment	$40,000
Stage 1 Fibrosis	$1,404
Stage 2	$1,404
Stage 3	$1,404
Cirrhosis	$4,194
HCC	$44,224
Cured	$406

3.4 Screening

Efficient screening of patients for HCV is important. Patients can be infected for decades without displaying symptoms and fibrosis can develop without being noticed for several years. Screening enables earlier diagnosis, providing treatment options and the potential for lifestyle changes that reduce the speed of HCV disease progression.

The disease progression model can simulate screening programs by implementing two disease progression tracks, analogously to the alcohol use analysis described above. Patients are not eligible to enter treatment unless they have been diagnosed, so the core model structure is identical.

A significant proportion of HCV-infected patients are unaware that they are infected. We tested various policies with the SD model, such as random screening and high risk screening.

4 TREATMENT ADHERENCE MODEL

4.1 Background

Antiviral therapy for HCV currently consists of administration of injected and oral drugs several times a week for 6 to 12 months with frequent visits for clinical and laboratory monitoring and to address the near-universal occurrence of significant side effects such as anemia, disabling fatigue and drug-induced depression. In some cases, patients have become sufficiently depressed to attempt suicide. Adherence to prescribed antiviral therapy in the face of these challenges is a critical determinant of whether HCV can be treated for a long enough period of time to develop a sustained virologic response (SVR) (Lo Re et al., 2011).

The likelihood of adherence is a central factor in a provider's decision about patient eligibility for antiviral therapy. In other words, how likely is it that a given patient at a given facility will be able to adhere to a complex medication regimen that has challenging physical and neuropsychiatric side effects given the patient's comorbidities and personal and environmental factors? While there is ample evidence, in both VA and non-VA settings, that points to successful treatment of patients with a range of comorbidities by committing resources to address these conditions, there are many system-level and patient-level factors that influence outcomes (Kramer, Kanwal, Richardson, Mei, & El-Serag, 2012).

The VA's policy and operational initiatives to increase antiviral treatment rates in HCV patients require that both eligibility criteria and resource issues are addressed. Current eligibility criteria prevent many patients from obtaining treatment, primarily due to provider concerns about adherence (Muir & Provenzale, 2002; Bini et al., 2005; Rowan, Tabasi, Abdul-latif, Kunik, & El-Serag, 2004; Kramer et al., 2012). The most common reasons for treatment ineligibility are active alcohol use, substance use disorders and depression, all of which affect adherence. Medical contraindications usually account for less than 10% of treatment ineligibility cases. There is good evidence that common eligibility contraindications (such as alcohol abuse, psychiatric diagnosis and depression) should not be firm exclusionary guidelines, but rather patients should be evaluated on a case-by-case basis (Seeff & Hoofnagle, 2002). An expert panel of VA providers recently published HCV treatment guidelines which note that while uncontrolled depression or active suicidal ideation are absolute contraindications to antiviral treatment, patients with stabilized psychiatric conditions should be considered for treatment (Yee et al., 2012). Further, they recommend that patients with alcohol and illicit drug use should also be considered for treatment on a case-by-case basis. There is evidence to suggest that providers are both overly cautious in treating HCV patients and especially inaccurate in predicting adherence. One study showed that 40% of patients whom providers predicted would fail to adhere were able to successfully complete treatment (Paterson et al., 2000).

4.2 Formulation

Understanding the factors influencing patient adherence–and the interactions between such factors–is critically important to optimizing systems of care for patients with HCV as well as for patients with other chronic conditions. This is a challenging situation for many providers who may lack the time and resources to thoroughly analyze and understand a patient's projected ability to adhere or the system-level factors that might affect adherence. The development of new tools, such as our treatment adherence model, affords the potential to aid providers in making more accurate decisions about referrals to treatment and providing necessary support for patients

prior to and during the treatment process. Even more importantly, such a model could provide significant support for the design and implementation of micro- and macro-system-level changes to improve HCV treatment rates.

Unfortunately, the current research in HCV therapy adherence is poor. Studies are fragmented and incomplete. Psychologists, hepatologists and epidemiologists each focus on a subset of adherence factors in most studies (such as psychological factors or health factors) instead of considering all adherence factors. Even within a single discipline, studies do not consistently report the same factors, measure the same variables or use the same terminology. Other challenges, such as differing survey measures for factors like social support or stress, are frequently present. As a result, the reported correlations for factors drastically fluctuate (Ammassari et al., 2002). We used a meta-analysis methodology to minimize these issues.

We conducted a literature review to obtain papers with adherence correlation values and identified a representative sample of 14 papers (Wagner et al., 2011; Holzemer et al., 1999; Gifford et al., 2000; Carrico et al., 2011; Schneider, Kaplan, Greenfield, Li, & Wilson, 2004; Ammassari et al., 2001; Simoni, Frick, & Huang, 2006; Bottonari, Safren, McQuaid, Hsiao, & Roberts, 2010; Grant et al., 2004; Johnson, Elliott, Neilands, Morin, & Chesney, 2006; Wu, Moser, Chung, & Lennie, 2008; Maeda, Shen, Schwartz, Farrell, & Mallon, 2012; Hansen et al., 2009; Stawski, Silwinski, Almeida, & Smyth, 2008). We reserved a statistically rigorous meta-analysis for later studies. We used data from patient adherence to highly-active antiretroviral treatment (HAART) for HIV infection where HCV treatment data were not available, based on the similarity in epidemiology between HIV and HCV patients, especially with regard to behavioral factors and regimen complexity and toxicity. We did not limit the treatment adherence model to factors directly affecting adherence. As illustrated in Figure 7, most studies obtain correlation values between contributing factors (such as social support and drug use) and adherence but do not consider correlations between contributing factors themselves. Since our model takes these higher-order effects into account and represents these links, it should provide a more accurate model of adherence and second- and third-order effects can be propagated throughout the model.

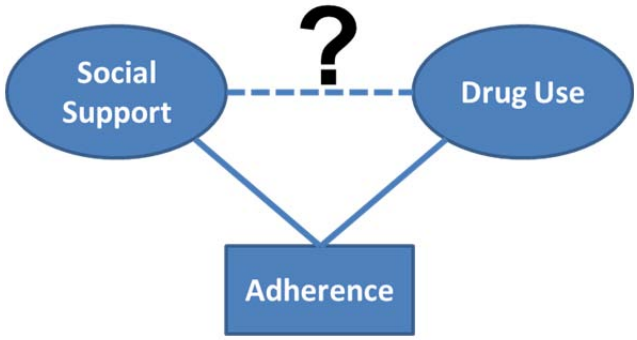

Figure 7: Diagram showing that possible correlations between contributing factors are often ignored in the literature.

We converted all data to correlation values using the methodology proposed by Hasselblad and Hedges (1995). If multiple correlations existed for the same link, the data were combined into a single value using a random effect model and by weighting each correlation by sample size. Causality between factors was also hypothesized. For example, it is clear that medication

complexity affects adherence, but adherence does not affect medication complexity. Other factors, such as depression and stress, are likely bi-directional. Figure 8 illustrates currently modeled factors, linkages and influence flows (as shown by arrow directionality) we obtained from the literature review. It is likely that more factors and connections than modeled here exist but have not yet been studied.

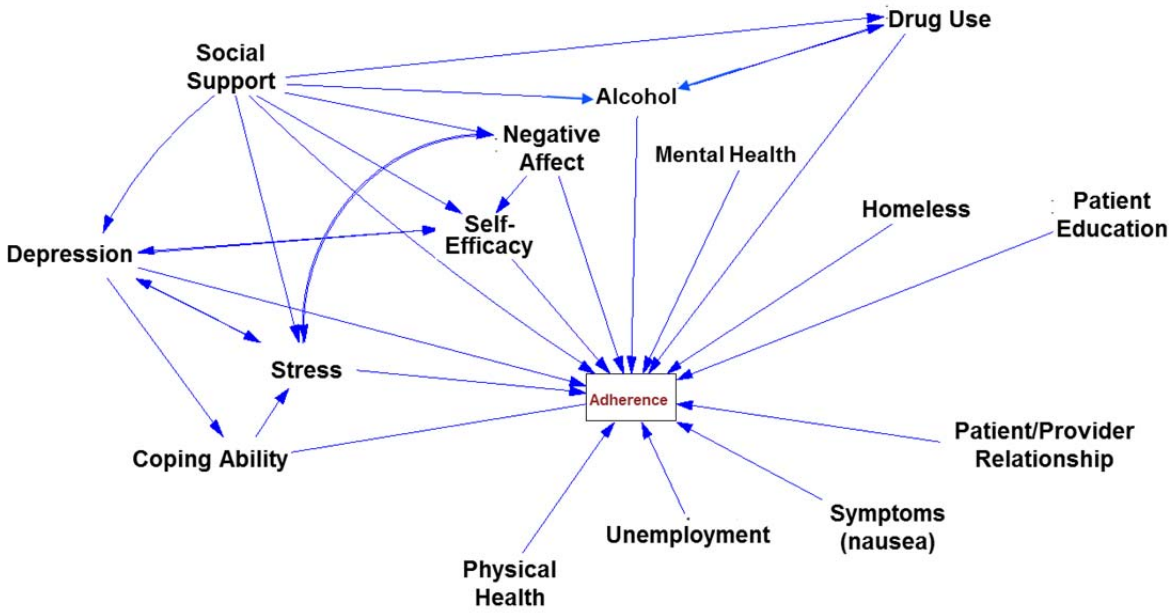

Figure 8: Diagram of relationships among components in the current treatment adherence model initialized with data obtained from the literature review.

Figure Note: Arrows represent causality from one factor to another.

4.2.1 Data Compilation

In order to create a comprehensive factor map, we conducted a literature review using Google Scholar. We searched for terms such as ”adherence,” “correlation” and “odds ratio” paired with the factors we are interested in such as ”social support,” “depression” and “alcohol.” Once we isolated germane articles, we collected relevant data and parameter values.
While many literature reviews on treatment adherence exist, most limit their analysis to categorical reviews: the number of studies finding some correlation are reported but the papers do not include quantitative analysis of the reported correlation strength (Huckans, Loftis, Blackwell, Linke, & Hauser, 2007; Simoni et al., 2006; Bottonari et al., 2010).
Our literature review is not on par with a meta-analysis of the literature. For reasons outlined below, including vast discrepancies in reported correlations, differing terminology, differing populations, different diseases and different medications, we did not think a meta-analysis would be justified at this time. Instead, we compiled a representative selection of papers that would allow us to test a methodology.

4.2.2 Data Conversion

To combine correlation values from various sources, we first converted all data into R correlation values.
Most frequently we converted data from odds ratio to correlation. Odds ratio describes the strength of association between two binary data values. It is commonly used in logistic regression studies that have categorical response variables. In regression analysis where the response variable is quantitative, a Pearson's r is a common measure of the strength and direction of the linear relationship between two variables. In order to combine the results from different sources we used a common meta-analysis conversion from odds ratio into correlation coefficient. Hasselblad and Hedges originally proposed this method in their paper (1995). First, we converted the natural logarithm of the odds ratio to the standardized mean difference using the following conversion:

$$d = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$$

Once all the odds ratio values are expressed as mean difference, we computed a conversion into correlation coefficient using the following equation:

$$r = \frac{d}{\sqrt{d^2 + a}}$$

where *a* is a correlation factor for cases where $n_1 \neq n_2$, where n_1 and n_2 are the population sizes of the two studies, respectively. For n_1, we took a raw average of all the sample sizes and converted all the values to a common sample size.

$$a = \frac{(n_1 + n_2)^2}{n_1 n_2}$$

The correlation factor *a* depends on the ratio of n_1 to n_2, rather than the absolute values of these numbers. If n_2 was not known precisely, then we used $n_1 = n_2$ and the previous formula yields *a* = 4 (Borenstein, Hedges, Higgins, & Rothstein, 2009).
Once the all the data was in the same format, we combined correlations reported by multiple sources. When combining these studies, we weighted the effects based off each studies expected precision, instead of taking an arithmetic mean. There are two general approaches in meta-analysis to weighting the combined effect: fixed-effect models and random-effect models.
In the fixed-effect model it is assumed there is one true effect size that all studies have in common. This is often an unrealistic assumption. Most meta-analyses are based on the random-effect model where there is not one true effect size for all studies.
We did not assume that the characteristics and methods were the same for all the studies we used. The inherent differences between studies introduce the concept of heterogeneity among the effect sizes. To account for this heterogeneity in computing the summary correlation, we used the inverse variance method for pooling the correlations, and we used the DerSimonian-Laird method to estimate the heterogeneity variance among studies (Jackson, Bowden, & Baker, 2009). Under the DerSimonian-Lair method let *Yi* be the treatment effect of the *i*th study where

$Yi|\mu \sim N(\mu i, \sigma_i^2)$ where μi is the true treatment effect of the *i*th study and σ_i^2 is within-study variance. The random-effect model further assumes that $\mu i \sim N(\mu, \tau^2)$, where μ and τ^2 are the overall treatment effect and between-study variance. We conducted the computations in the R programming language using DerSimonian-Lair estimate of τ^2 for the random-effect model.

4.2.3 Data

The data we used to initialize the treatment adherence model are given below.

Table 7: Table of adherence factors obtained from application of the DerSomian-Laird method to literature values

7A: Single Variables

Reference	Factor 1	Factor 2	Correlation Coefficient	Population Size
Holzemer et al., 1999	Symptoms (mental/physical)	Adherence	0.41	420
Carrico et al. 2011	Homeless	Adherence	-0.52	227
Carrico et al. 2011	Alcohol Use Disorder	Adherence	-0.11	227
Schneider et al., 2004	Physical health	Adherence	0.12	554
Schneider et al., 2004	Mental health	Adherence	0.20	554
Ammassari et al., 2001	Drug use	Adherence	-0.01	358
Ammassari et al., 2001	Unemployment	Adherence	0.05	358
Simoni et al., 2006	Social Support	Negative affect	-0.42	136
Simoni et al., 2006	Negative affect	Self-efficacy	-0.35	136
Simoni et al., 2006	Negative affect	Adherence	-0.20	136
Bottonari et al., 2010	Avoidant Coping	Adherence	-0.27	87
Bottonari et al., 2010	Avoidant Coping	Stress	0.18	87
Bottonari et al., 2010	Avoidant Coping	Depression	0.01	87
Johnson et al., 2006	Social Support	Stress	-0.42	540
Wu et al., 2008	Patient provider relationship	Adherence	0.04	134
Maeda et al., 2012	Self-efficacy	Depression	-0.30	252
Hansen et al., 2009	Alcohol Use Disorder	Drug use (cocaine)	0.34	268
Hansen et al., 2009	Social support	Alcohol	-0.18	268
Hansen et al., 2009	Social support	Drug use (cocaine)	-0.20	268
Stawski et al., 2008	Stress Scale	Negative affect	0.36	116

7B: Redundant Variables

Reference	Factor 1	Factor 2	Correlation Coefficient	Population Size
Bottonari et al., 2010	Stress	Adherence	-0.29	87
Gifford et al., 2000	Stress	Adherence	-0.35	133
Gifford et al., 2000	Self-efficacy	Adherence	0.42	133
Maeda et al., 2012	Self-efficacy	Adherence	0.63	252
Simoni et al., 2006	Self-efficacy	Adherence	0.15	136
Johnson et al., 2006	Social Support	Depression	-0.45	540
Maeda et al., 2012	Social support	Depression	-0.24	252
Wu et al., 2008	Depression	Adherence	-0.26	134
Wagner et al., 2011	Depression	Adherence	-0.08	1365
Bottonari et al., 2010	Depression	Adherence	-0.58	87
Maeda et al., 2012	Depression	Adherence	-0.24	252
Maeda et al., 2012	Social Support	Adherence	0.24	252
Wu et al., 2008	Social support	Adherence	0.21	134
Simoni et al., 2006	Social Support	Adherence	0.13	136
Schneider et al., 2004	HIV-specific information	Adherence	0.15	554
Wu et al., 2008	Knowledge	Adherence	0.07	134
Simoni et al., 2006	Social Support	Self-efficacy	0.35	136
Maeda et al., 2012	Social Support	Self-efficacy	0.27	252
Bottonari et al., 2010	Depression	Stress	0.43	87
Johnson et al., 2006	Depression	Stress	0.65	540

7C: Combined Variables

Reference	Factor 1	Factor 2	Correlation Coefficient
Combined	Stress	Adherence	-0.33
Combined	Self-efficacy	Adherence	0.41
Combined	Social Support	Depression	-0.35
Combined	Depression	Adherence	-0.28
Combined	Social Support	Adherence	0.21
Combined	Knowledge	Adherence	0.13
Combined	Social Support	Self-efficacy	0.30
Combined	Stress	Depression	0.56

4.3 Analysis

We conducted a high-level analysis of the system after initializing the treatment adherence model. Exact values of the model inputs are unknown. Analysis of the relationships between input values and output results indicate which inputs are most important to determining output

values. Our model illustrates the importance of highly connected factors. A factor that affects eight other factors can produce more of an impact than a factor only affecting one other factor. The modeled data show that social support is an important factor due to its high connectivity. Social support influences many other factors (Figure 8) and therefore has the potential to create a much greater effect than could be surmised from its single line of direct impact on adherence. Highly connectedness of factors may be artifacts of data collection since mediating factors may cause double counting. For example, the effect of social support on adherence through negative affect may already be accounted for in the direct correlation between social support and adherence. This possibility for double counting factors indicates that our model likely overestimates the value of some highly connected factors.

The model contains a number of feedback loop structures that represent the influence of tightly-connected factors. For example, stress, depression and coping ability are interconnected in a feedback loop (Figure 9). Lower levels of depression result in an increased ability to cope, in turn causing lower stress and lowered depression. This positive feedback loop is important when developing interventions: if a patient's stress levels rise, the patient could enter a downward spiral from which it is difficult to recover. Conversely, lowering stress results in beneficial outcomes for all factors.

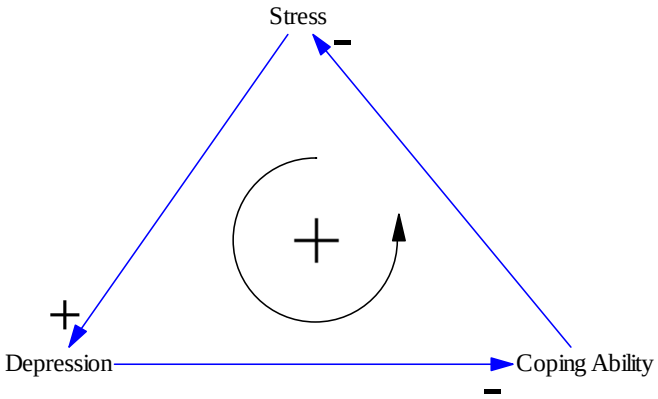

Figure 9: The positive feedback loop among stress, depression and coping ability.

Figure Note: The small positive and negative signs denote proportional or inverse relationships between the factors, respectively.

An organization managing HCV adherence has several options for engineering better patient outcomes. Policy options could address either improving a factor or improving a link between factors. Figure 10 illustrates the relationship between social support and adherence. Investing in the social support factor (1) increases a patient's support network by providing more friends and peers who can provide support. Investing in the link between social support and adherence (2) strengthens the relationship between social support and adherence. This involves understanding why social support influences adherence and enabling the patient's peers to be more effective at positively impacting patient adherence.

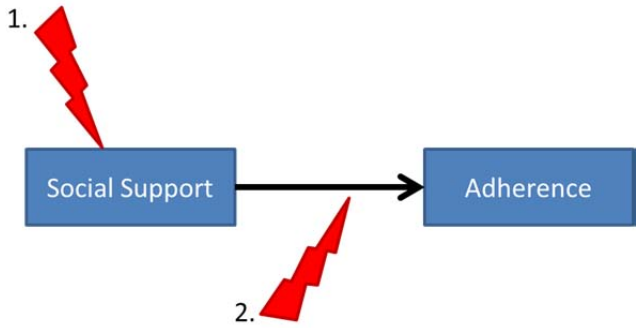

Figure 10: Diagram showing factor-based and link-based interventions.

Figure Note: Option 1 denotes an increase in social support of a patient. Option 2 denotes an increase in the correlation between the two factors.

Investing in adherence factors or links (causes for observed correlations) has different effects on adherence. Model results for the net change to adherence due to investment in different factors are illustrated in Figure 11. There is a linear increase in adherence when resource units are invested in various factors. Investing 0.5 resource units in social support results in exactly half of the benefit of investing 1 resource unit in social support, meaning there is a linear relationship between the investment and adherence. Additionally, we find that certain factors impact adherence more than others. For example, for a constant resource investment, social support has the largest impact on adherence of all the factors examined.

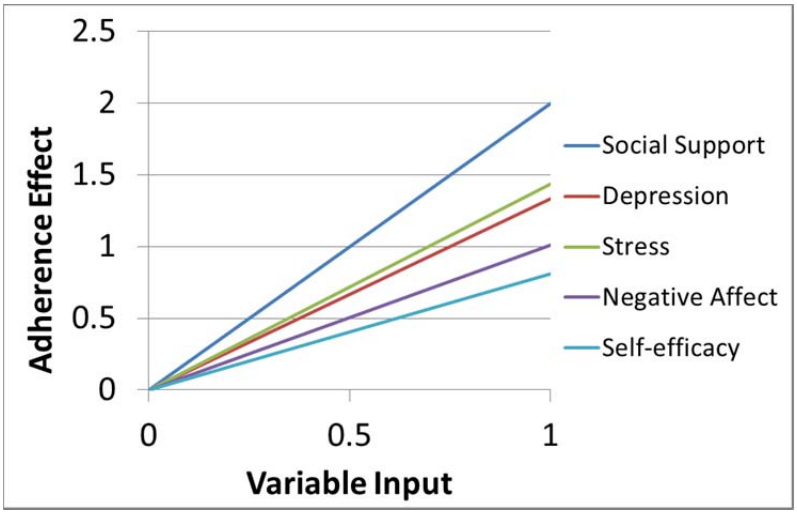

Figure 11: Diagram illustrating the effects of investments in various adherence factors.

When links that are part of feedback loops are varied, there is a fundamental change in behavior. Figure 12 illustrates the variation in correlation between stress and depression, which results in a nonlinear effect on adherence due to the feedback loop structure.

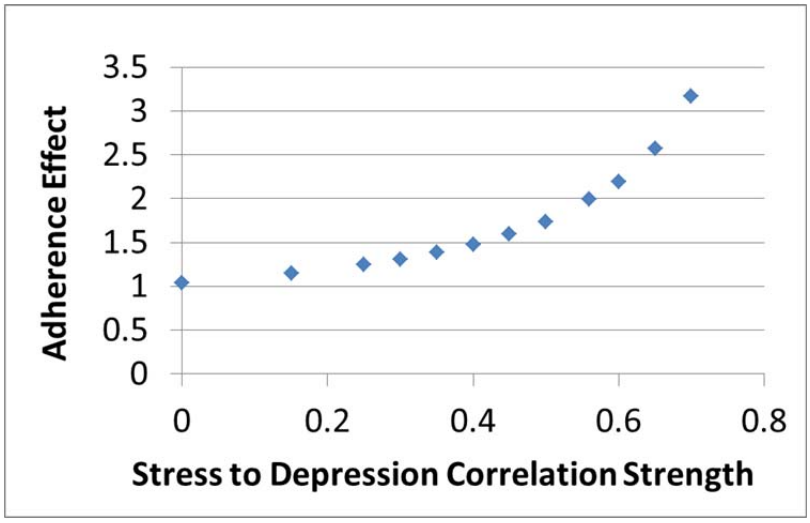

Figure 12: Graph showing the changing strength of correlations: as the strength of the correlation between stress and depression is increased, adherence is affected.

The nonlinearity is due to loops in the model. Figure 13 diagrams one such loop in which depression and stress are correlated to each other and are in turn both correlated with adherence.

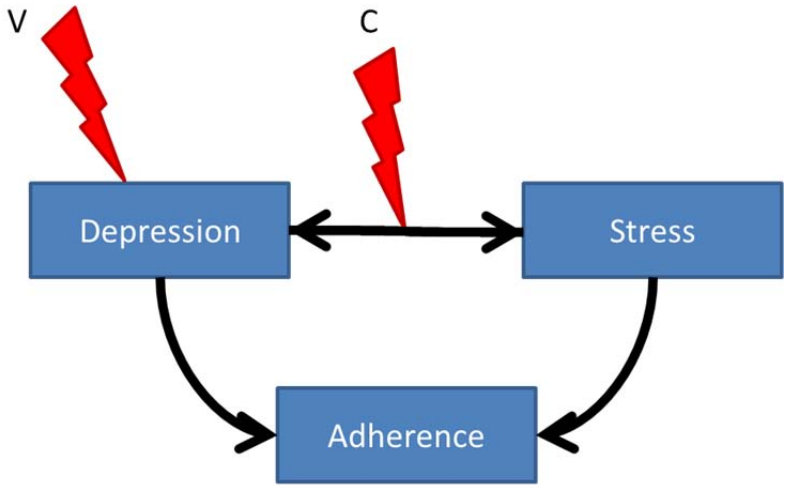

Figure 13: An example of a looped factor relationship.

Figure Note: The correlation between depression and stress is represented as C; an investment in a factor is represented as V.

If we consider a situation in which *V* is the input to a factor, *C* represents the correlation between two factors with dual causality and both factors are connected to adherence with correlations of 1, then the final effect on adherence is:

$$Adherence = V * C + V * C^2 + V * C^3 + V * C^4 + \cdots$$
$$Adherence = V * (C + C^2 + C^3 + C^4 + \cdots)$$

which is simply *V* multiplied by an infinite geometric series, expressible as:

$$Adherence = V * \sum_{n=1}^{\infty} C^n$$

The geometric series converges for $C < 1$ and is expressible as:

$$Adherence = V * \frac{1}{1 - C}$$

Keeping *C* constant and varying *V* results in a linear function. Keeping *V* constant and varying *C* results in a nonlinear function. Therefore, the form of the treatment adherence model encourages investing in links rather than factors. In other words, understanding the causes for observed correlations (or why a factor influences adherence) results in a greater ability to effectively influence factors' potential effects.

4.4 Conclusions

As the VA works to improve treatment rates, adherence-related factors such as alcohol use, drug abuse and mental health disorders must be evaluated in the context of adherence. Understanding adherence is critical to effective patient treatment. Adherence factor maps can aid providers in understanding patients' ability to adhere to antiviral therapy and can guide the design and implementation of policy and operational changes aimed at improving care.

Current research on adherence to HCV therapy is sparse and frequently conflicting. In this work, we constructed a detailed adherence map and analyzed it for robust recommendations. We find that highly connected factors and feedback loops identify the most important influences affecting treatment success. The factors we identified should be targeted for interventions at both the patient and system levels. Furthermore, our model formulation indicates that link-based interventions should be more effective than factor-based interventions provided the links are part of feedback loops. Interventions targeted at links can generate nonlinear returns, while interventions based solely on factors result in linear returns.

More research is needed to understand the casual relationships between adherence factors. Historically, adherence research focuses on correlations between factors while the mechanisms that connect them remain unknown. Our work shows that understanding these mechanisms and how to influence them is critical to the design of successful policy.

Several limitations to our work exist. First, the source data were not derived from a rigorous meta-analysis due to the relatively low number of literature citations for adherence. Some of the available cases of adherence studies are characterized by mediating factors, divergent terminology and sparseness. The derived factor map may omit significant but unknown factors. Our work shows significant variability between correlations which could be due to variability in populations. If this is the case, the identification of new latent factors that could classify patients into one of several unique adherence factor maps would be useful for individualizing an adherence evaluation.

Effective application of factors could result in more patients being treated and cured of HCV. More work is needed in this area. New data and research on adherence could help VA improve HCV patient treatment and continue to provide the best possible care to veterans.

5 NEXT STEPS

The disease progression model and the treatment adherence model could be developed further. Obtaining data to verify parameter values in the models, such as disease progression rates or adherence factor correlations, would enable a more quantitatively precise analysis.
VA data from the Clinical Case Registry and facility surveys could be used to calibrate and verify these models. New surveys could be undertaken to generate facility level data capturing changes in operating policy and medical practice since the widespread use of triple therapy.
These computational models can also be used to conduct case studies on various VA facilities. By comparing the data and structure from different facilities, the benefits of certain policies (such as integrated care) might be obtained.

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