Community Knowledge and Attitudes Regarding Hepatitis C Disease, Testing, and Treatment in a High-risk Urban Population and a Review: HIV/HCV Coinfection

By
Brianna Norton

A Master’s Paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Public Health Leadership Program

Chapel Hill
2013

[Signature goes here]

______________________________
Advisor

Anthony Viera

______________________________
Date

[Signature goes here]

______________________________
Second Reader

Jason Stout

______________________________
Date
# Table of Contents

Community Knowledge and Attitudes Regarding Hepatitis C Disease, Testing, and Treatment in a High-risk Urban Population  

Page 3

HIV/HCV Coinfection: A review of the Literature  

Page 30
Abstract

Though hepatitis C virus (HCV) is the most common blood-borne infection in the United States, the epidemic has gone largely unnoticed, such that an estimated 75% of people living with HCV are undiagnosed. As a result, the Department of Health and Human Services (DHHS) has released a new Hepatitis Action Plan. This plan calls for a national commitment to educating high-risk communities about HCV and to testing, care and treatment within these communities to prevent HCV transmission and liver disease. The appropriate model for achieving these goals is unknown as is the acceptance of such interventions, particularly when many high-risk individuals may not have access to HCV specific medical treatment. We set out to assess attitudes about HCV screening and knowledge about HCV disease and treatment at several community-based testing sites that serve high-risk populations. This assessment was paired with a brief HCV educational intervention. Participants (N=140) were surveyed at five sites, including two homeless shelters, two drug rehabilitation centers, and a women’s “drop-in” center. Personal acceptance of HCV testing was almost unanimous, and 90% of participants reported that they would still want to be tested even if they were unable to receive HCV treatment. Baseline hepatitis C knowledge was poor; however, the brief educational intervention significantly improved knowledge and increased acceptability of testing when medical access issues were explicitly stated. Conclusion: Despite poor HCV knowledge and limited access to health care, hepatitis C screening was highly acceptable in this study population. As underscored by the DHHS action plan, this assessment supports HCV screening, education, and linkage to care in high-risk communities, even when access to HCV medical care may be difficult.
Introduction

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States (US), with an estimated 4 million persons chronically infected. It is the leading cause of end-stage liver disease and hepatocellular carcinoma, as well as the most common indication for liver transplantation. Until recently, this epidemic has gone largely unnoticed. Consequently, 75% of persons living with HCV are unaware of their infection and thus are at risk of developing sequelae such as cirrhosis and hepatocellular carcinoma, without an opportunity for treatment and appropriate disease management.

The burden of the HCV epidemic disproportionately affects certain US populations, resulting in significant healthcare disparities. Specifically, the prevalence of HCV is highest among persons with a history of intravenous drug use, incarcerated populations, homeless adults, and baby boomers (persons born between 1945-1965). African Americans are twice as likely to be infected when compared to the general US population. Furthermore, approximately one third of human immunodeficiency virus (HIV)-infected patients are co-infected with HCV, with HIV positive men who have sex with men becoming an increasingly recognized risk group. Many of these high-risk populations are hard-to-reach, and many do not have regular access to healthcare.

The magnitude of infection within the US population, and the extent to which HCV has been largely undiagnosed, has invigorated a national commitment to improve awareness, screening, and linkage to care for this disease. On May 12, 2011, the Department of Health and Human Services (DHHS) issued “Combating the Silent Epidemic of Viral Hepatitis: Action Plan for the
Prevention, Care and Treatment of Viral Hepatitis.” This action plan calls for a targeted HCV education strategy for high-risk communities, and also emphasizes outreach to priority populations to provide opportunities to get tested and seek care. The appropriate model for achieving these goals is unknown as is the acceptance of such interventions, particularly when many high-risk individuals may not have access to HCV specific medical treatment. We set out to assess attitudes surrounding HCV screening, as well as knowledge regarding HCV disease and treatment at several community-based testing sites that serve high-risk populations. This assessment was paired with a brief HCV educational intervention, followed by post-intervention assessment of changes in knowledge and attitudes.

Methods

Setting and Participants

Sites were chosen from a list of community based HIV/sexually transmitted diseases testing sites utilized by the local public health department (Wake County Human Services). A convenience sample of persons attending each of these settings was surveyed. The inclusion criteria were: 1) speak/understand English; 2) age 18 or older; (3) willingness to complete a pre and post-test survey instrument and participate in a short educational intervention. The survey was anonymous and clearly labeled as to its purpose (research study), and verbal consent was performed. No identifying information was obtained from subjects, and they were compensated for participation with a five dollar grocery store gift card. The study was exempted from institutional review board review by the Duke University Medical Center Institutional Review Board.
**Study Intervention**

An educational intervention was given as well as pre- and post-intervention surveys. Pre- and post-intervention survey instruments were administered verbally to participants to assess knowledge and attitudes surrounding hepatitis C disease, testing, and treatment.

The survey instrument assessed socio-demographic information, access to healthcare, knowledge of HCV, and attitudes toward community HCV screening. The survey was first piloted among patients in the Duke Infectious Diseases clinic to assess question comprehension, and revisions were made accordingly. To ensure full comprehension, study investigators verbally administered the survey instruments to all participants. The post-intervention survey consisted of a subset of the pre-intervention questions.

The educational intervention consisted of a brief (approximately 15 minute) standardized discussion of the epidemiology of HCV, clinical significance, care and treatment options, and preventative strategies, followed by a question/answer session. A spiral-bound flip-book with diagrams was used with the discussion. The intervention was designed with the assistance of professional health educators and was directed toward a fifth grade education level. The same investigator (B.N.) delivered the educational program at each site in order to maximize the consistency of the educational intervention across sites.

**Statistical Analysis**

The studied was powered on the primary objective: assessment of screening acceptability. We chose a sample size that would permit adequate assessment of whether a majority (i.e., >50%) of
participants felt that HCV screening would be acceptable in their community. Assuming that the true rate of HCV testing acceptance in the community was 60% in the underlying population, we needed 153 participants to exclude an acceptability rate of <50% with 80% power at a 5% type I error rate, using a one-sided significance test. The study was stopped early due to overwhelming acceptance of screening.

Continuous variables were summarized using medians/quartiles or means/standard deviations, as appropriate to the distribution. Categorical variables were summarized with frequency counts/proportions. Changes in knowledge and acceptance of HCV testing were assessed using the McNemar test to compare baseline and post-education responses. Answers of “not sure” were considered not correct (knowledge) or negative for acceptance. We created a composite knowledge score from 18 knowledge-related questions, assigning each correct answer one point. Bivariate associations between knowledge and pre-selected predictor variables were assessed using t-tests with categorical variables or Pearson correlations with continuous variables. All variables significantly associated with knowledge at an alpha of <0.05 were then entered into a multivariable linear regression model, centering the age variable in the model.

Results

Demographics

One hundred forty participants were surveyed at 5 sites, including 2 homeless shelters, 2 drug rehabilitation centers, and a women’s “drop-in” center. The majority of participants were male (66%) and African American (57%) (Table 1). The median age was 43 years old, with a range of 18 to 62 years. Participants varied in education levels, with 16% having stopped education
after elementary school. Most people had no health insurance (73%), and less than half stated they had a regular doctor (49%). Ninety-five percent of participants had heard of HCV, 56% said they knew someone with the disease, and 18% of participants stated that they had been diagnosed with HCV. Though all of these participants were surveyed at community centers serving high-risk individuals, 32% of participants still believed they were “not at all” likely to get HCV.

**Baseline Knowledge**

Baseline knowledge and attitudes regarding HCV and HCV screening are presented in Table 2. Baseline knowledge about HCV acquisition was variable. Although 90% of people knew that injecting drugs and getting a homemade tattoo are risk factors for HCV, 22% of people did not think sexual acquisition was possible, 17% thought HCV was transmitted from public toilets, and 28% thought HCV was transmitted from coughing or sneezing. Many people did not know what risk factors were associated with disease progression. Participants’ baseline knowledge concerning HCV treatment was also low. Seventy-six percent of participants believed that everyone diagnosed with HCV needed treatment, yet 65% either did not think HCV could be cured or did not know if it could be cured. Ninety-eight percent of participants said they would want treatment if they tested positive for HCV; however, 63% did not know about treatment side effects or thought that side effects of therapy were minimal.

**Baseline Attitudes**

Ninety-seven percent of participants stated they would get a free HCV test if it were offered, with 90% reporting that they would still want to be tested even if they were not able to receive
treatment. When told that, if positive, they would be offered free vaccines against hepatitis A and B, or lifestyle advice on how to stay healthy with HCV, more people wanted to be tested even if treatment was not accessible to them (95% and 96% respectively).

Almost all participants (99%) said that they wanted free HCV testing in their community, but participants were less positive when asked if other people in their community would want free HCV testing in the community (86%). Almost half (49%) thought that offering community-based screening without the availability of universal treatment would be problematic. Also, only 39% of participants believed that others in their community who tested positive for HCV would drink less alcohol. But most believed that HCV positive persons would get vaccinated against hepatitis A and hepatitis B (83%) or go to the doctor for treatment (76%).

Changes in Knowledge and Attitudes Post-Intervention

The brief educational intervention significantly improved knowledge about HCV (Table 3). Eighty-one (81%) percent of participants understood that treatment was not necessary for everyone with HCV, as compared to 10% pre-education (p<0.0001). Ninety percent (90%) of participants gave correct responses regarding HCV cure rates after the educational intervention, as opposed to 33% pre-education (p<0.0001). After learning about the deleterious effects of alcohol in patients with HCV, significantly more participants believed that people in the community who tested positive for HCV would drink less alcohol (p=0.003). Attitudes toward personal acceptance of HCV testing did not change after education since almost all participants wanted to be tested on the pre-intervention survey. However, the participants’ perceived acceptability of HCV screening among other members of the community did increase after
education. Importantly, participants were significantly less likely after education to believe that offering community-based HCV screening without guarantee of universal treatment would be problematic (49% pre-intervention believed this would be problematic vs. 35% post-education, p=0.02).

**Knowledge Score and Associations**

The mean baseline knowledge score was 9.9 (SD 3.3), ranging from 0-18. Characteristics associated with greater knowledge were male gender, white race, younger age, and knowing someone with HCV (Table 4). Interestingly, participants who did not want to be tested for HCV if they were not guaranteed treatment had significantly lower knowledge scores than people who wanted to know their HCV status despite availability of treatment (p=0.003). When dichotomizing age based on the CDC screening recommendations, participants greater than 45 years old (baby boomer generation) had mean knowledge scores that were lower than younger participants (9.5 vs. 10.4, p=0.08). In multivariable analysis, white race, male gender, knowing a person with HCV, and wanting HCV testing even if treatment could not be offered remained associated with higher knowledge scores (Table 5).

**Discussion**

Community-based screening programs have the potential to reach persons at significant risk for HCV who do not normally access healthcare 12,13; however, it is important to understand the acceptability of HCV testing in a group that may have limited access to treatment. This issue is particularly important when the agency providing screening (the public health department) has
no resources to provide treatment, and therefore limited control over whether persons who test positive are engaged in treatment. In this study, we found that people who access community-based, non-traditional testing sites were highly accepting of integrating HCV-testing into community-wide screening programs. On the other hand, high-risk individuals had relatively rather poor knowledge about HCV. Nonetheless, a relatively easy on-site educational intervention significantly improved HCV knowledge and also increased acceptability of testing.

HCV testing of high-risk groups is cost-effective[14-16], yet early diagnosis continues to be inadequate[17,18]. Community-based testing may be able to identify persons living with HCV who do not regularly access healthcare but who are along some of the highest-risk populations[4,19,20]. Early HCV detection provides an opportunity for low-cost interventions that can decrease the risk of liver disease including alcohol reduction counseling, HIV testing, and immunization against hepatitis A and B. Furthermore, earlier identification can result in access to therapies at an earlier stage of liver disease which is associated with an improved treatment response rate (19) and less risk of long term complications including cirrhosis, end-stage liver disease, hepatocellular carcinoma and need for transplant. As newer medical therapies with improved efficacy and side effect profiles become increasingly available, early identification of disease by HCV screening will have greater potential to reduce poor outcomes.

Although community-based screening offers a number of opportunities for improved intervention, testing vulnerable populations who may not have full access to treatment raises the potential for misunderstanding and mistrust in these communities. To our knowledge, this is the first study to directly assess acceptability rates of community based HCV screening when access
issues were explicitly stated. We found that acceptability of screening was almost universal in this population, and remained high even when participants were told that they would not be able to receive treatment. Ninety seven percent of participants said that they would personally obtain a free HCV test, and 99% stated they would want free HCV testing in their community. Even when told they would not be able to receive treatment, 90% of participants said they would still want to know their HCV status. When told that free hepatitis A/B vaccination or advice on harm reduction (e.g. abstinence from alcohol), but no antiviral treatment, could be offered, almost all participants again wanted to be tested regardless of availability of medical therapy. This is important because the public health department often can provide free vaccinations and counseling as part of a community-based screening program.

In contrast to the high rates of acceptance of HCV screening, knowledge regarding HCV was relatively poor. This lack of knowledge was surprising given over half of participants reported knowing someone with HCV and 18% of participants endorsed personal infection with HCV. Our work supports prior investigations that have shown significant gaps in HCV knowledge in high-risk groups, such as persons living with HIV and intravenous drug users \(^{21,23}\). Similar to these studies, we found that lack of knowledge was associated with African American race and older age, two groups that are disproportionately afflicted by this disease. Participants demonstrated poor knowledge about HCV acquisition, which may impact a person’s ability to make choices that protect themselves and prevent transmission to others in their community. We also found a large percentage of people who did not know that alcohol or HIV could worsen HCV disease progression, and even fewer knew that obesity has a negative effect on liver health. This dearth of information makes it difficult for HCV positive people to make healthy lifestyle
choices when living with HCV. There were also significant misconceptions in understanding HCV therapy, as most people believed all HCV positive persons needed to be treated. Finally, a majority of participants were unsure or did not think that HCV could be cured, and over half carried erroneous beliefs regarding HCV treatment side effects. This hinders the ability of HCV positive persons to appropriately interpret their disease and lessens their ability to access care and treatment.\textsuperscript{24}

Fortunately, a brief educational intervention significantly improved HCV knowledge among the participants. Almost all areas of HCV knowledge improved post-intervention, with the greatest changes occurring in understanding of treatment. Notably, improvement in HCV knowledge has been shown to improve compliance with linkage to HCV care.\textsuperscript{25}

By increasing knowledge, our educational tool also increased acceptance rates for HCV testing. Although personal screening was highly accepted, some participants expressed concern regarding the community’s desire for screening if access to treatment was not universal. That said, those who were concerned about community acceptance demonstrated significantly more positive attitudes toward of HCV screening after education was provided. Furthermore, the small minority of individuals hesitant to be personally tested without a guarantee of treatment demonstrated lower HCV knowledge scores, even when adjusted for other variables. These findings underscore the importance of continued community education to enhance both knowledge of HCV and acceptance of community-based HCV screening.

This study has several limitations. Our population consisted of a convenience sample of high-risk individuals that access non-traditional testing sites of an urban health department in the
southern United States. Many of the participants were in drug/alcohol rehabilitation programs, and may have been more motivated to provide positive responses to survey questions than others in their communities. Our results therefore may not be generalizable to the entire at-risk population. Second, we assessed the impact of the educational intervention immediately following the discussion, so we cannot comment as to whether the improvement in knowledge was durable. Verbal administration of the surveys may have also biased the participants to provide more positive responses than a written instrument. Finally, since a member of the study team verbally administered the education intervention, its reproducibility cannot be guaranteed.

**Conclusion**

In this population of individuals at high risk for HCV acceptance of community-based HCV screening, even without guarantees of access to treatment, were very high. Despite inconsistencies in availability of HCV treatment and poor knowledge regarding HCV, high-risk patients are ready to know their HCV status. A comprehensive screening strategy that implements brief on-site education can aid in improving HCV knowledge, and encourage testing. The impact of such a program on change in behavior and engagement in care is yet to be determined, but community based screening programs in high-risk populations are the right place to start.
REFERENCES


7. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver international : official journal of the International


Table 1: Patient Demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>% (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66% (92)</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>46 (33,54)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>37% (52)</td>
</tr>
<tr>
<td>Black</td>
<td>57% (80)</td>
</tr>
<tr>
<td>Other</td>
<td>6% (8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>16% (22)</td>
</tr>
<tr>
<td>High School</td>
<td>39% (55)</td>
</tr>
<tr>
<td>Some College</td>
<td>31% (43)</td>
</tr>
<tr>
<td>Finished College</td>
<td>14% (20)</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>73% (102)</td>
</tr>
<tr>
<td>Medicaid/Medicare</td>
<td>12% (17)</td>
</tr>
<tr>
<td>Private</td>
<td>6% (9)</td>
</tr>
<tr>
<td>VA/Other</td>
<td>9% (12)</td>
</tr>
<tr>
<td>Has Regular Doctor</td>
<td>49% (68)</td>
</tr>
<tr>
<td>Questions</td>
<td>Yes</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Have you heard of HCV?</td>
<td>95% (133)</td>
</tr>
<tr>
<td>Do you know anyone who has HCV?</td>
<td>56% (79)</td>
</tr>
<tr>
<td>Have you been told you have HCV?</td>
<td>18% (25)</td>
</tr>
<tr>
<td>How likely do you think you are to get HCV?</td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>32% (42)</td>
</tr>
<tr>
<td>Somewhat</td>
<td>28% (36)</td>
</tr>
<tr>
<td>Very</td>
<td>16% (21)</td>
</tr>
<tr>
<td>Not sure</td>
<td>24% (31)</td>
</tr>
<tr>
<td>How do you think people get HCV infection?*</td>
<td></td>
</tr>
<tr>
<td>Having Sex?</td>
<td>56% (78)</td>
</tr>
<tr>
<td>Shooting up (injecting) drugs?</td>
<td>90% (126)</td>
</tr>
<tr>
<td>Using public toilets?</td>
<td>17% (24)</td>
</tr>
<tr>
<td>Sharing supplies for snorting drugs?</td>
<td>54% (75)</td>
</tr>
<tr>
<td>Coughing/sneezing on someone?</td>
<td>28% (39)</td>
</tr>
<tr>
<td>Getting a homemade tattoo?</td>
<td>90% (125)</td>
</tr>
<tr>
<td>Which of the following problems can HCV cause</td>
<td></td>
</tr>
<tr>
<td>to your body?*</td>
<td></td>
</tr>
<tr>
<td>Stroke?</td>
<td>11% (16)</td>
</tr>
<tr>
<td>Cirrhosis/Liver Failure?</td>
<td>81% (114)</td>
</tr>
<tr>
<td>Blindness?</td>
<td>38% (53)</td>
</tr>
<tr>
<td>Liver Cancer?</td>
<td>62% (87)</td>
</tr>
</tbody>
</table>
Heart Attack? 18% (25) 33% (47) 49% (68)
Death? 79% (111) 3% (4) 18% (25)

What makes HCV worse for the people that have it?*
Drinking coffee? 4% (5) 56% (78) 41% (57)
Drinking Alcohol? 82% (115) 6% (9) 11% (16)
HIV infection? 82% (115) 3% (4) 15% (21)
Being obese? 34% (47) 26% (36) 41% (57)
Does everyone who has HCV need treatment?* 76% (107) 10% (14) 14% (19)

How many people who get treated for HCV, get cured?*
All 3% (4)
Some 33% (46)
None 29% (40)
Not sure 36% (50)

Do you think that the side effects of HCV treatment are very bad?
Yes 21% (29)
Somewhat 17% (24)
No 14% (19)
Not Sure 49% (68)

Would you get a free blood test for HCV? 97% (136) 2% (3) 1% (1)
Would you want to get treated for HCV if you 98% (137) 1% (1) 1% (2)
tested positive?

Would you want to be tested for HCV, if when you tested positive you could get free treatment?  
99% (139) 0% (0) 1% (1)

Would you still want to be tested, if you were told you could not be offered treatment?  
90% (126) 10% (14) 0% (0)

Would you still want to be tested if you were told you could not be offered treatment, but you could get free vaccines against HAV/HBV?  
95% (133) 5% (7) 0% (0)

Would you still want to be tested if you were told you could not be offered treatment, but you could get lifestyle advice on how to stay healthy with HCV?  
96% (134) 4% (5) 1% (1)

Do you want free HCV testing in your community?  
99% (139) 0% (0) 1% (1)

Do you think other people would want free HCV testing?  
86% (121) 1% (1) 13% (18)

If people in the community tested positive for HCV, do you think they would do the following things if they were told it would help them?

Drink less alcohol?  
39% (55) 24% (33) 37% (52)

Get a shot against HAV/HBV?  
83% (116) 2% (3) 15% (21)

Go to the doctor for treatment?  
76% (107) 1% (92) 22% (31)

Do you think it will be a problem if we tested for
HCV in your community but might not be able to offer treatment to everyone who’s positive?

*Questions that were used in composite knowledge score
### Table 3: Analysis of Pre and Posttest Changes of Answers

<table>
<thead>
<tr>
<th>Knowledge Related Questions</th>
<th>Pre-Test</th>
<th>Post-Test</th>
<th>p-value (McNemar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How do you think people get HCV?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having Sex?</td>
<td>56%</td>
<td>84%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shooting up (injecting) drugs?</td>
<td>90%</td>
<td>98%</td>
<td>0.001</td>
</tr>
<tr>
<td>Using public toilets?</td>
<td>60%</td>
<td>95%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sharing supplies for snorting drugs?</td>
<td>54%</td>
<td>85%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coughing/sneezing on someone?</td>
<td>52%</td>
<td>94%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Getting a homemade tattoo?</td>
<td>89%</td>
<td>97%</td>
<td>0.0074</td>
</tr>
</tbody>
</table>

What makes HCV worse for the people who have it?

<table>
<thead>
<tr>
<th>What makes HCV worse for the people who have it?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking coffee?</td>
<td>45%</td>
<td>86%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drinking Alcohol?</td>
<td>82%</td>
<td>96%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV infection?</td>
<td>82%</td>
<td>89%</td>
<td>0.121</td>
</tr>
<tr>
<td>Being obese?</td>
<td>33%</td>
<td>80%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Does everyone who has HCV need treatment?                   | 10%      | 81%       | <0.0001           |

How many people who get treated for HCV get cured?          | 33%      | 90%       | <0.0001           |
<table>
<thead>
<tr>
<th>Attitude Related Questions</th>
<th>Pre-Test %</th>
<th>Post-test %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would you want to be tested for HCV, if when you tested positive you could get free treatment?</td>
<td>99%</td>
<td>100%</td>
<td>1.0</td>
</tr>
<tr>
<td>Would you still want to be tested, if you were told you could not be offered treatment?</td>
<td>90%</td>
<td>90%</td>
<td>1.0</td>
</tr>
<tr>
<td>Would you still want to be tested if you were told you could not be offered treatment, but you could get free vaccines against HAV/HBV?</td>
<td>95%</td>
<td>96%</td>
<td>.727</td>
</tr>
<tr>
<td>Would you still want to be tested if you were told you could not be offered treatment, but you could get lifestyle advice on how to stay healthy with HCV?</td>
<td>96%</td>
<td>95%</td>
<td>1.0</td>
</tr>
<tr>
<td>Do you want free HCV testing in your community?</td>
<td>99%</td>
<td>97%</td>
<td>0.25</td>
</tr>
<tr>
<td>Do you think other people would want free HCV testing?</td>
<td>86%</td>
<td>92%</td>
<td>0.077</td>
</tr>
<tr>
<td>Do you think it will be a problem if we tested for HCV in your community but might not be able to offer treatment to everyone who’s positive?</td>
<td>49%</td>
<td>35%</td>
<td>0.019</td>
</tr>
<tr>
<td>If people tested positive for HCV, do you think people would do the following if they were told</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
it would help them?

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drink less alcohol?</td>
<td>39%</td>
<td>54%</td>
<td>0.003</td>
</tr>
<tr>
<td>Get a shot against HAV/HBV?</td>
<td>83%</td>
<td>86%</td>
<td>.383</td>
</tr>
<tr>
<td>Go to the doctor for treatment?</td>
<td>76%</td>
<td>79%</td>
<td>.524</td>
</tr>
</tbody>
</table>
**Table 4: Bivariate Analysis of Knowledge Score**

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>Mean (SD) Knowledge Score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9.9 (3.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (140) r=-0.17</strong></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (92)</td>
<td>10.4 (.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female (48)</td>
<td>9.1 (.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (52)</td>
<td>10.8 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Non-White (88)</td>
<td>9.4 (3.5)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Regular Doctor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (68)</td>
<td>9.8 (3.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>No (72)</td>
<td>10.1 (3.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary (22)</td>
<td>9.4 (3.6)</td>
<td></td>
</tr>
<tr>
<td>High School (55)</td>
<td>9.5 (3.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>Some College</td>
<td>10.1 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Finished College</td>
<td>11.5 (2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (102)</td>
<td>10.0 (3.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>No (38)</td>
<td>9.8 (2.7)</td>
<td></td>
</tr>
</tbody>
</table>

Do you know anyone with
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV?</strong></td>
<td>10.5 (3.1)</td>
<td>9.3 (3.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Yes (79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Do you have HCV?</strong></td>
<td>10.6 (3.8)</td>
<td>9.8 (3.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Yes (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (112)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Would you still want to be tested if you could not get treatment?</strong></td>
<td>10.2 (3.1)</td>
<td>7.5 (3.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Yes (126)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 5: Multivariable Analysis of Characteristics Associated with Knowledge Score

<table>
<thead>
<tr>
<th>Characteristics*</th>
<th>Adjusted Mean</th>
<th>p-value</th>
<th>Beta coefficient (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>0.271</td>
<td>-.026 (.024)</td>
</tr>
<tr>
<td>31 years (-1SD below mean)</td>
<td>10.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56 years (+1SD above mean)</td>
<td>9.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10.60</td>
<td>0.002</td>
<td>-1.76 (.566)</td>
</tr>
<tr>
<td>Female</td>
<td>8.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10.70</td>
<td>0.065</td>
<td>-1.13 (.605)</td>
</tr>
<tr>
<td>Non-White</td>
<td>9.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you know someone with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV?</td>
<td>9.28</td>
<td>0.025</td>
<td>1.22 (.540)</td>
</tr>
<tr>
<td>No</td>
<td>10.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would want to be tested even if</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>can’t be offered treatment?</td>
<td>0.005</td>
<td>2.53 (.890)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Referent group placed first under each category
HCV and HIV Coinfection: A Review of the literature

Introduction

Chronic hepatitis C is a global health problem, with an estimated 170 million persons infected worldwide\(^{26}\). In industrialized countries, HCV is the leading cause of end-stage liver disease and hepatocellular carcinoma, as well as the most common indication for liver transplantation \(^{2,3}\). Due to shared routes of acquisition, many persons with HIV are also chronically infected with Hepatitis C. Of the 33 million persons living with HIV globally, it is estimated that 30% are dually infected with HCV\(^{27}\). Liver-related mortality, associated with HCV, has been found to be a leading cause of death for HIV patients in the era of highly active antiretroviral treatment. The burden of HCV in the US is predicted to peak in 2030, resulting in significant increases in rates of cirrhosis, end-stage-liver disease, and hepatocellular carcinoma\(^{28}\). This clinical and financial burden will be greatest among HIV-infected individuals given the more rapid disease progression and thus requires immediate attention. HIV/HCV co-infected patients use more health care than either their HCV or HIV mono-infected counterparts, and this is reflected in the increased outpatient visits, emergency department visits, and hospital admissions\(^{29}\). Although historically HIV-infection was a baseline risk factor for poorer response to therapy, this no longer appears to be true with newer HCV medications. Thus, consideration of HCV treatment is recommended in all HIV/HCV co-infected patients. Here I will review the latest developments in epidemiology, transmission, and therapeutics and will provide a roadmap for the management of the co-infected patient.
**Transmission**

The transmission of HCV is most efficient through blood-to-blood contact, thus risk factors associated with parenteral exposure to both HIV and HCV viruses influence the risk of co-infection. Prior to 1992, exposure to HCV through contaminated blood products was common, and many hemophiliacs were infected with both HIV and HCV via blood transfusions. Since the availability of routine screening of blood products, this mode of transmission has significantly reduced. Currently, IVDU remains the primary mode of transmission in industrialized countries, such that the prevalence of HIV/HCV co-infection is as high as 77% in this population.

**Sexual Transmission of HCV**

Sexual transmission of HCV is believed to be inefficient, although there may be host factors that can influence the risk. Biological plausibility for sexual transmission is supported by the isolation of HCV in both semen and vaginal secretions. However, early cross sectional studies of partners of HCV mono-infected heterosexual hemophiliac men showed almost negligible risk of sexual transmission, and partners that were HCV positive all had other risk factors for HCV. A prospective study of heterosexual serodiscordant partners consisted of 529 person-years of follow up with more than 40,000 vaginal or anal penetrations, with no transmission of HCV between partners. This was further supported by a prospective study of 895 heterosexual monogamous couples who were HCV serodiscordant and did not use condoms. After 10 years of follow-up there was no evidence of sexual transmission of HCV between partners. Studies involving HCV mono-infected MSM also showed very low risk of sexual transmission, even when participants engaged in unprotected anal sex.
Although sexual transmission in the setting of HCV mono-infection is rare, there is good argument that active HIV-infection may increase host susceptibility to HCV sexual transmission. The presence of active HIV infection has been associated with an increased risk of sexual acquisition of HCV even in early studies of heterosexual partners. An early cross sectional study of 231 heterosexual hemophiliacs found that HIV was almost four times more likely to be transmitted than HCV to a female partner, and that in all cases of HCV transmission the partner was also infected with HIV. Three percent of female sexual partners of HIV/HCV co-infected hemophiliacs became infected with HCV, compared to zero of the female partners of HIV-negative/HCV positive hemophiliacs. Furthermore, the large Women’s Interagency HIV Study found that, even after controlling for IVDU, HIV infected women were almost two times as likely to have HCV as HIV-negative women. Many studies report increased sexual risk behaviors and the presence of pre-existing STDs, as well as HIV positivity, to account for the increase risk of HCV heterosexual transmission.

HIV positive MSM may have the greatest risk of sexual transmission of HCV. Over the last decade there have been increasing reports of acute HCV outbreaks among HIV-positive MSM in Europe, Australia, and the United States. Phylogenetic analysis has revealed an MSM-specific strain of HCV in HIV positive cohorts in the Netherlands, France, and the UK. In Amsterdam a large prospective study of 1836 MSM were studied over the course of almost 2 decades, 1984-2003. Phylogenetic analysis found that 83% of the MSM infected after 2000 had a strain similar to another participant, typical of a common source of infection. These strains differed significantly from the strains found in IVDUs, suggesting needle sharing was an unlikely source of infection. The lack of clustering prior to 2000 supports recent transmission and a growing epidemic among HIV positive MSM. An international phylogenetic study then
attempted to associate these distinct outbreaks throughout Europe. A large study conducted in England, The Netherlands, France, Germany, and Australia found 11 strongly supported monophyletic transmission clusters of MSM specific strains of HCV. Overall, 84% of participants were infected with an HCV strain that was most similar to a strain in another study participant. The participants from Australia, of which half were IDU rather than MSM, also clustered together but did not overlap with the individuals from Europe. Molecular clock analysis suggested that the majority of these transmissions occurred after 1996. This study is evidence of an emerging international network of HCV transmission among the HIV positive MSM community, and similar sexual networks of transmission have been identified in NYC. 54. The fact that phylogenetic has identified numerous strains of HCV that are representative of HCV transmission clusters refutes the notion that this epidemic is related to the virus, and instead supports host related factors. Co-infections are recognized risk factors for viral transmission, HSV and HIV being excellent examples, yet how HIV might increase HCV sexual transmission is not fully understood. There is evidence that specific behaviors can increase risk of HCV infection. Several well designed cohort studies support a relationship between high-risk sexual practices such as unprotected anal sex, group sex, use of sex toys, and fisting and acquisition of HCV. With increasing reports of acute HCV infection among the HIV-infected MSM, the overall prevalence of HCV among HIV-infected MSM is increasing. In one study in Amsterdam the prevalence of HCV among HIV positive MSM increased from 1-4% before 2000, to 21% in 2008. This is compared with an estimated prevalence of 0.4% among HIV negative MSM 55.
Natural History and Progression of Disease

HIV on HCV

With the advent of highly active antiretroviral therapy, patients with HIV are living longer and are less frequently dying from AIDS related complications. As a result, there is growing emergence of morbidity and mortality from HCV among HIV positive persons. In fact, liver-related deaths were noted to be the primary cause of non-AIDS related mortality among one large cohort of HIV-infected individuals\textsuperscript{56}, and HCV related mortality is responsible for up to 11.5\% of overall mortality in cohorts of HIV positive individuals\textsuperscript{57}. In general, HIV/HCV co-infected individuals have higher mortality than HIV monoinfected individuals, and almost half of all deaths among the co-infected are found to be due to liver-related causes\textsuperscript{58}.

HIV infection can increase HCV viremia by 2-to-8 fold, resulting in significant decrease in spontaneous clearance of acute HCV as compared to mono-infected individuals\textsuperscript{59}, resulting in most HIV positive individuals going on to develop chronic infection. Individuals with chronic Hepatitis C develop varying degrees of fibrosis of the liver, over varying degrees of time. This fibrosis can ultimately lead to cirrhosis, producing liver failure, hepatocellular carcinoma, or death. Progression to cirrhosis is more common among HIV/HCV co-infected individuals. In one meta-analysis, HIV/HCV co-infected individuals were found to be twice as likely to develop cirrhosis, and 6 times as likely to develop decompensated liver disease as compared to their HCV mono-infected counterparts\textsuperscript{60}.

Risk factors for progression to liver fibrosis are similar to HCV mono-infected and include fibrosis stage, older age, duration of infection, alcohol consumption, male sex, high BMI, diabetes, and steatosis\textsuperscript{61}. HIV co-infection has also been shown to be an independent predictor of liver progression, with various factors believed to be the cause. The rate of cirrhosis is 2 to 5
fold higher among HIV/HCV. Certainly weaker immune status has been proposed, and many studies have shown that lower CD4 counts, both current and nadir, do lead HCV persistence, more rapid liver fibrosis, and poor interferon treatment response. In HIV-infected patients with compensated liver cirrhosis, mortality was high and associated with older age, CD4 counts <200, and detectable HIV viral loads.

As HAART has become more widely available, there have been mixed reports as to whether co-infection is indeed still a risk for worsened HCV liver disease among patients on effective HAART therapy. In general, studies have overwhelmingly shown that HAART and HIV viral suppression independently reduce liver fibrosis among HIV/HCV co-infected individuals. It is plausible that suppressed viral load itself can reduce liver damage through reduced HIV replication in fibrosis promoting stellate cells, and reduce proinflammatory cytokines. Reduced HCV exposure to the HIV gp120 protein has been shown to decrease HCV viral replication, and thus may be another mechanism of slower fibrosis among patients with HIV viral suppression. HAART, even in individuals with CD4 counts above 350, appears to significantly reduce necroinflammatory activity of the liver in HIV/HCV co-infected individuals. One study found that HIV/HCV coinfected patients had the same fibrosis progression rate as the mono-infected HCV patients if their HIV viral load was suppressed to undetectable. In a study of 26,641 veterans, HIV/HCV co-infection was only an increased risk factor for cirrhosis when compared to HCV monoinfection during the pre-HAART era, but not among HIV/HCV co-infected patients on HAART. Antiviral therapy has also shown to not only decrease fibrosis in HIV/HCV co-infected but also liver-related mortality. In other studies, results were not as promising. One meta-analysis of studies conducted in the HAART era, determined that HIV/HCV coinfected patients continue to have higher rates of cirrhosis than HCV mono-infected...
patients. The HIV/HCV coinfected patients receiving HAART did have less cirrhosis, but did not fully decrease to the level of the HCV mono-infected\textsuperscript{70}. One large study of over 12,000 patients, found that HCV infection still increased mortality among HIV infected patients who were on HAART\textsuperscript{71}. These data support the rapid initiation of HAART in patients with HCV co-infection in order to reduce fibrosis progression, though these patients are likely to still be at higher risk of clinical outcome than their mono-infected counterparts. As in mono-infected patients, fibrosis stage is strongly associated with risk of cirrhosis, decompensated liver disease, HCC, or death\textsuperscript{72}. Importantly, treatment with ART and higher CD4 counts are associated with significantly lower risk of poor clinical outcomes.

HAART can result in direct hepatotoxicity and worsen HCV liver disease. Most liver related toxicity to HAART, however, is reversible with discontinuation of the drug. Severe steatosis with lactic acidosis has occurred with the NRTI’s such as didanosine and stavudine, and these medications should be avoided in patients with HCV\textsuperscript{73}.

\textit{HCV on HIV}

While the effect of HIV on HCV natural history is clearly detrimental, the effect of HCV on HIV disease is not as well understood. Although there are two large cohorts reporting an association between HCV positivity and increased AIDS related clinical events in HIV/HCV infected individuals as compared to HIV monoinfected patients, there are several weaknesses of the study design. Use of HCV antibody may simply serve as a marker of other baseline risk factors, such as substance use and psychiatric disease, which increase the risk of poor adherence to ARVs and thus poor HIV control\textsuperscript{74,75}. Most studies show no association between HIV related outcomes or virologic suppression and HCV status\textsuperscript{76-79}. In one large cohort with almost 6000 patients, no
association with HCV positivity and increased AIDS-related events in the adjusted analysis, but instead an increased in liver related deaths\textsuperscript{79}. The impact of HCV on immune recovery in HIV infected patients taking HAART is also controversial. The large cohort study mentioned above did not identify a difference in immune reconstitution in co-infected as compared to HIV-monoinfected patients\textsuperscript{79}. Initial data from the Swiss HIV Cohort Study reported that HCV positivity was associated with a lesser CD4 count recovery\textsuperscript{75}; however, with extended follow-up (4 years) this association was lost\textsuperscript{80}. A meta-analysis reported CD4 cell count response in HIV/HCV co-infected individuals was on average 33.4 cells/mm\textsuperscript{3} lower at 48 weeks as compared to the HIV monoinfected group (54). This meta-analysis did not report longer term results. Thus while short term CD4 reconstitution may be blunted, this does not appear the case beyond 48 weeks. Furthermore, discordance between absolute CD4 counts and CD4 percentages has been noted in patients with more advanced liver disease, due to possible splenic sequestration\textsuperscript{81,82}. Clinicians should assess CD4 percentage in addition to the absolute count when evaluating response to HAART in patients with HCV and sequelae of liver disease.

**Management**

The increased risk of liver disease progression and associated mortality, and the burden of healthcare utilization associated with this patient population argue for increased attention to evaluate and manage liver disease in all HIV/HCV co-infected patients. Such management considerations include harm reduction counseling, vaccination against other hepatitides, assessment of liver disease stage/severity, and evaluation for medical treatment.
**Harm reduction**

Education remains a key intervention for HIV/HCV infected patients. Emphasis on approaches to reduce transmission in patients with ongoing risk factors is especially important. It is reported that the prevalence of HCV infection is as high as 77% in HIV-infected IV drug users. Use of needle exchange programs and engagement in substance abuse treatment programs are proven interventions to decrease rates of transmission and to maintain sobriety. As we have become increasingly aware of HCV sexual transmission among HIV positive MSM, education on condom use and safer sexual practices is highly encouraged. In particular, clarification of issues related to serosorting (HIV positive men choosing to have unsafe sex with other HIV positive men) in the HIV-infected MSM community is critical due to the risk behaviors reported in this group of patients.

Alcohol use should also be addressed so as to reduce the progression to liver disease. Alcohol abuse is frequent among HCV carriers, and in one study up to 40% of persons with chronic HCV were considered problem drinkers. Alcohol consumption is known to cause accelerated progression of liver fibrosis, higher frequency of cirrhosis, and increased incidence of hepatocellular carcinoma. Patients with alcohol abuse and concomitant HCV are known to have worsened survival than for either disease alone. Furthermore, alcohol use causes reduced interferon responsiveness and worsen treatment outcomes for patients that will eventually go on to obtain HCV medical therapy. Though some studies suggest that only moderate to heavy alcohol consumption (greater than 40g per day) affects progression to cirrhosis, many other studies have shown a dose response association with alcohol intake and worsened liver fibrosis even in patients who were minimal drinkers. HIV/HCV co-infected patients should be
encouraged to maintain complete abstinence of alcohol. Studies have shown that HCV persons aware of their diagnosis will reduce their alcohol intake\textsuperscript{19}.

Vaccinations against hepatitis A and B should be performed in all patients that do not show immunity to chronic infection. An isolated Hepatitis B core antibody is more frequent in HIV positive and Hepatitis C positive persons and should not be associated with immunity\textsuperscript{94}. One study found that these patients have a good immune response to vaccine, with a 74\% response rate, and therefore HIV positive patients with only HepBcAb should also be immunized. In general, HIV positive patients have reduced immunogenicity to the standard three dose HBV vaccine series, with seroconversion between 17.5\% to 72\%\textsuperscript{95}. Some studies suggest that a lower CD4 count at the time of vaccination, particularly CD4<200, is associated with reduced protective immunity\textsuperscript{96,97}. Therefore, the recommendation is to delay vaccination until a patient’s CD4 count is higher than 200. Other factors such as HIV viral load and CD4 nadir also decrease immunogenicity to HBV immunization, regardless of CD4 count at the time of immunization, and enhanced vaccine strategies, such as double-dosing, can improve immunogenicity among all HIV positive persons. A large randomized controlled trial showed that HIV positive adults vaccinated with 4 double dose HBV vaccine series had a significantly greater response to vaccine than the persons receiving standard HBV immunization (82\% response versus 65\%). Immunogenicity can also be improved using double-dose of the combined HBV and HAV vaccine (Twinrix) using standard 3 dose scheduling series\textsuperscript{98}. Double-dosing of HBV vaccine should be considered in all HIV/HCV co-infected individuals in order to increase the chance of obtaining protective immunity in this group of at-risk patients.
**Fibrosis Staging**

Fibrosis is a wound healing response to liver injury. In the HIV/HCV co-infected patient there are multiple etiologies of liver injury including chronic hepatitis co-infection, antiretroviral drug toxicity, opportunistic infections, non-alcoholic fatty liver disease, and/or alcohol use.

Although current Food and Drug Administration (FDA) approved therapies offer improved response rates, the therapy remains complex, difficult to tolerate and not always effective. Current treatment guidelines only recommend treating patients that are at greatest risk for disease progression. This recommendation is inextricably tied to the fact that we haven’t had safe, tolerable, effective treatments for HCV and so the benefit of treatment has to be weighed with the risk of adverse events, and the likelihood that a person will eventually develop liver disease. Staging allows physicians to determine if deterring therapy is preferable for patients without significant disease. As therapies improve in both tolerability and efficacy, with all oral regimens and lower pill burdens, staging may become obsolete as we begin to treat all-comers with HCV infection. For now, staging all HIV/HCV co-infected patients is recommended.

Findings have been consistent in that there is little association between ALT or HCV RNA and the degree of histopathologic fibrosis. Almost 25% of HIV/HCV infected patients with normal liver enzymes have advanced fibrosis on liver biopsy. As a result, in patients without obvious signs of cirrhosis or liver disease, the gold standard for determining the degree of fibrosis is liver biopsy. Though the biopsy has great specificity, it is still prone to sampling error and interobserver variation, as only a small portion of the liver is taken for pathologic evaluation. As a result, we can only assert that the degree of liver fibrosis is at least as extensive as seen on biopsy. The biopsy assesses for both grade and stage of liver disease. METAVIR is a validated
scoring system that assesses liver damage through histological lesions. The grade(A0-A3) reflects the extent of necroinflammatory injury, while the stage(0-4) reflects the extent of fibrosis and whether cirrhosis is present.

Though the biopsy is still the most accurate measure of liver fibrosis, it is invasive, expensive, and not without risk to patients such as pain, bleeding, or death\(^\text{101}\). As a result, non-invasive tests such as serum biomarkers and ultrasound elastography are being used as alternatives to biopsy. Many scoring indices have been developed and evaluated for possible replacement of the liver biopsy, such as the FibroTest, Forn Index, APRI score, Hepascore, Fibrometer, SHASTA, and Fib-4. These scoring systems include various combinations of biomarkers such as platelets, liver enzymes, alpha2macroglobulin, apolipoproteins, hyaluric acid, and other variables. In one study that evaluated and compared all non-invasive biomarker tests, Fibrometer was found to have the highest accuracy (71%) when compared to biopsy for classifying patients with higher fibrosis scores (greater than or equal to 2). All other biomarker indices had much lower accuracies. As a result, biomarkers may help to determine pre-test probability for extent of fibrosis but they are generally too inaccurate to facilitate treatment decisions.

Transient elastography (Fibroscan) is another noninvasive method of detecting liver fibrosis that has gained popularity and widespread use in Europe. This technology uses ultrasound vibrations to transmit an elastic shear wave through the liver. The velocity of this wave correlates with tissue stiffness, such that the faster the wave travels, the stiffer the liver. The diagnostic accuracy of transient elastography is not as good in HIV/HCV co-infected patients as compared to HCV mono-infected patients, but is most reliable at determining when a patient has cirrhosis\(^\text{102}\). For all Fibroscan studies of HIV/HCV co-infected individuals, liver stiffness has been significantly associated with extent of fibrosis, but the accuracy for determining exactly
which stage of fibrosis the patient lives has been only been reliable in cirrhotics\textsuperscript{103-105}. The elastography has been shown to be more accurate in predicting fibrosis than other serum biomarkers such as the Fib-4 or APRI score\textsuperscript{103}. When using a cut-off value of 12.3kPa, TE accurately identifies people with cirrhosis 83\% of the time\textsuperscript{102}. Most of the discordancy in results with Fibroscan is from an over estimation of fibrosis as compared to biopsy. In one study, a subsample of the patients with discordant results had biopsies from clinical work-ups prior to study participation. These biopsies were evaluated and almost half had more advanced fibrosis on previous biopsy than on study biopsy, leading us to believe that in at least some circumstances, biopsy may actually underestimate fibrosis. When using a cut off value of 14.6kPa, TE had a positive predictive value of 86\%, and a negative predictive value of 94\% for cirrhosis. Only 5\% of patient with an LS measurement of <14.6kPa had cirrhosis, and 17\% who had an LS measurement >14.6kPa did not have cirrhosis, though most had Stage 2 or greater\textsuperscript{104}. Defining cut off values for moderate or minimal fibrosis has proved more difficult and TE cannot be reliably used to determine these situations.

Many physicians would withhold or delay treatment if liver histology displays a fibrosis stage less than or equal 2, since these individuals are regarded as slowly progressive\textsuperscript{106,107}. Treatment should be deterred until more efficacious and tolerable therapies are available. Treatment is advised for those with more advanced fibrosis such as stage 3 or greater.

**Goals of Therapy**

Unlike HIV, it is possible to completely eradicate HCV from the human body and cure people of the disease. The current definition of cure is not a clinical outcome but rather a virologic surrogate typically defined as a sustained virologic response, or undetectable HCV viral load, 24 weeks post treatment. While most trials used SVR24 as their virologic endpoint, new data show
that SVR12 and SVR24 are highly concordant. In evaluating 3 large clinical trials with over 1500 patients, the concordance rate of SVR12 and SVR24 was over 98%\textsuperscript{108}. As a result, SVR12 is an acceptable primary endpoint in clinical trials and clinical practice, though follow-up HCV RNA should be obtained for the minority of individuals who are late relapsers.

Though the measurement of clinical cure is a surrogate marker, SVR has been shown to be associated with reduced clinical outcomes and improved mortality. In one large retrospective study of HIV/HCV co-infected individuals followed for approximately 20 months post-treatment, patients that reached an SVR had significantly less overall mortality, liver-related death, and liver decompensation\textsuperscript{109}. The difference in hepatocellular carcinoma was not significant perhaps due to small numbers; there was no person that developed HCC in the group that responded to treatment versus 9 persons in the group that did not achieve SVR. In a large prospective study of 22,942 patients all-cause mortality was substantially reduced in patients achieving an SVR, such that hazard ratios of 0.7, 0.64, and 0.51 were achieved for genotypes 1, 2, and 3 respectively\textsuperscript{110}.

**Treatment**

*Interferon and Ribavirin*

The current guidelines for treatment of HCV in an HIV infected patient consists of pegylated interferon-alpha once weekly with weight based ribavirin\textsuperscript{111}. Interferons are naturally occurring proteins that are known to play a role in the control and eradication of human viruses\textsuperscript{112}. Interferon-alpha was used as an early therapy for chronic HCV even prior to its distinct identification, when patients were thought to have non-A, non-B
hepatitis. Eventually, interferon-alpha was shown to have long standing eradication of the virus in a small sub-set of HCV mono-infected individuals and became the standard of treatment. A study of 80 HIV/HCV co-infected patients was published in 1996, and showed a sustained virologic response in 18% of patients taking interferon-alpha three times a week for one year\textsuperscript{113}. Though interferon showed promise in treating a subset of patients infected with HCV, the addition of ribavirin to the treatment regimen improved treatment outcomes substantially. Ribavirin is a guanosine analogue that has activity against many viruses, though its exact mechanism of action against HCV is unknown. Initial studies with ribavirin monotherapy showed minimal decrease in transaminases, and no decrease in viral levels or virologic elimination with prolonged therapy\textsuperscript{114}. Interestingly, when used in combination with interferon-alpha, clinical trials showed a decrease in the rate of relapse and greater success of SVR. Though interferon and ribavirin revolutionized the therapy for chronic HCV, efficacy still remained low and side effect profiles were poor. In an effort to decrease the number of injections (three times a week), and potentially increase efficacy, pegylated interferon was created. With the addition of a polyethylene glycol molecule, interferon-alpha showed a 70-fold increase in serum half-life, a 3-fold greater peak activity and other pharmokinetic improvements\textsuperscript{115}. Clinical trials in co-infected individuals showed increased efficacy with pegylated interferon as compared to standard interferons\textsuperscript{116-119}. The first pivotal trial to compare these crucial therapies in the HIV/HCV co-infected population was the APRICOT trial. This trial is the largest international trial to date to show treatment efficacy in people coinfected with HCV and HIV, and is the only trial to include a monotherapy arm\textsuperscript{116}. 868 co-infected persons were randomized to one of three regimens: peginterferon alfa-2a plus ribavirin, peginterferon alfa-2a plus placebo, or interferon alfa-2a plus ribavirin.
Participants were treatment-naïve and had compensated liver disease, including 16% of patients with bridging fibrosis or cirrhosis, and 85% were on anti-retroviral therapy. Due to concerns of drug-drug interactions with ART, a fixed-dose of ribavirin was used, regardless of participant weight. Overall, a greater number of patients achieved an SVR in the pegylated interferon and ribavirin arm than any other group. For patients with genotype 1, an SVR of 29%, 14%, and 7% were achieved for the pegylated interferon plus ribavirin group, pegylated interferon monotherapy, and standard interferon plus ribavirin group, respectively. The SVR for genotypes 2/3 were higher: 62%, 36%, and 20% respectively. Characteristics associated with greater response to therapy were non-genotype 1 virus and an initial viral load <800,000, variables similar to that of HCV mono-infected patients. Importantly, CD4 counts and use of ART were not associated with treatment response. Subsequently many other trials showed the superiority of pegylated interferon versus standard interferon in achieving an SVR among HIV/HCV coinfected patients, with SVR’s for genotype 1/4 ranging from 14-35%, and SVR’s of 44-73% for Genotypes 2/3.

It is clear that ribavirin plays a role in aiding and sustaining viral clearance. In a large study of 1311 patients with chronic hepatitis C mono-infection, higher doses of weight-based ribavirin rather than fixed-dose ribavirin led to greater SVR rates\(^\text{120}\). Two trials of HIV/HCV co-infected participants did use the higher, weight dose regimen and achieved SVR rates of 35-38% which was somewhat higher than in the APRICOT trial of fixed dose ribavirin. That said, the lack of direct comparison of fixed-dose versus weight-based ribavirin in trials of HIV/HCV co-infected patients, makes it impossible to state whether this regimen has greater efficacy for HIV/HCV co-infected patients. Because it is clear that weight based ribavirin has improved efficacy among HCV mono-infected patients, guidelines recommend weight based therapy for co-infected
patients as well, though there are no randomized controlled trials to support this recommendation.

Despite increased efficacy with pegylated interferon and ribavirin for HIV/HCV co-infected individuals, the rates of SVR are still less than that of mono-infected patients. There are many different possibilities for this lower response rate including, greater discontinuation due to side effects, higher baseline HCV viral loads, immunological defects that worsen viral clearance, and suboptimal doses of ribavirin. Even in a randomized controlled trial of 104 co-infected patients matched by age, sex, and genotype to HCV monoinfected cohort, the SVR rates were still lower among co-infected participants (27.3% vs. 56.4% for genotype 1, and 52% vs. 88% for genotype 2/3) despite all patients receiving peginterferon-alpha 2a and weight based ribavirin\textsuperscript{121}.

**Protease Inhibitors**

Though interferon and ribavirin were the first drug combination to show cure in a subset of HCV patients, the regimen is limited by its long treatment duration, difficult side effects, and overall poor response rates. As a result, new drugs are rapidly becoming available to improve these adversities and cure more HCV infected persons. Efforts to improve outcomes are focused on producing antivirals with activity directly against the hepatitis C virion, rather than the traditional immunomodulating agents on which we have previously depended.

2011 marked the approval of the first direct acting antiviral therapies against HCV and though they continue to be administered with peg-IFN and ribavirin, they have significantly increased the chance of cure among chronically infected HCV patients. Telaprevir and Boceprevir are new HCV therapies that act directly on HCV NS3/4A protease enzymes to inhibit viral replication. The NS3 is a viral protein that, with its cofactor NS4a, produces HCV protease activity\textsuperscript{122}. This
HCV NS3/4a complex catalyzes cleavage of the single HCV polypeptide into its functional components and is essential for viral replication. These (DAA’s) direct acting antivirals have significantly increased the rate of SVR achieved in the HCV mono-infected population, increasing the number of patients appropriate for treatment and revolutionizing the care of chronically infected HCV patients.

Initial studies showed that despite a high potency for reducing viral load, these medications had a low barrier to resistance and thus would still need to be given with an anti-viral “backbone.” Telaprevir monotherapy was given for 14 days and resulted in a 5 log reduction in HCV viral load. Unfortunately there was significant viral breakthrough, and a majority of these patients had resistance mutations. Even in the patients that experienced complete viral suppression at 14 days, there was emergence of a virus that contained low level resistance mutations. All patients with virologic failure in the phase 2 trials for boceprevir emerged with resistance mutations.

Fortunately, HCV appears to convert back to wild type virus with time and some studies have shown that retreatment with a protease inhibitor is possible in previously exposed patients. That said, combination therapy to reduce the emergence of resistance is necessary.

**Telaprevir**

In the pivotal phase III trial ADVANCE, triple therapy of telaprevir, peginterferon, and ribavirin obtained SVR rates of 75% as compared to 44% percent in the standard of care arm. Patients taking telaprevir who achieved an eRVR (HCV RNA<25IU/ml at both 4 and 12 weeks) stopped therapy at 24 weeks, while those that did not stopped therapy at the typical 48 week mark. All patients were treatment naïve and telaprevir was given TID for 12 weeks in combination with peginterferon alpha-2a and weight-based ribavirin, followed by additional peginterferon and ribavirin for a total treatment course of 24 or 48 weeks. The patients receiving telaprevir for
12 weeks, achieved SVR rates of 75% as compared to only 44% in persons receiving standard of care (peginterferon and ribavirin.) The ILLUMINATE trial again proved that a shorter duration of therapy was as effective for patients who achieved eRVR. Among patients who achieved an eRVR, the SVR rate in the 24-week treatment arm (92 percent) was noninferior to the SVR rate in the 48-week treatment arm (88 percent). Telaprevir was also shown to be effective in patients that had previously failed interferon/RBV HCV therapy. The overall SVR rates in the telaprevir arm were 64% compared to 17% in the patients that received peginterferon and ribavirin only. Among the patients that had cirrhosis, the SVR rates were 49% in the telaprevir arm versus only 8% in the standard of care arm. The primary side effects of telaprevir were rash and worsened anemia.

Boceprevir showed similar improvements in SVR rates. In the Phase III SPRINT-2 trial, treatment naïve patients with genotype 1 were randomized to receive either standard of care versus response guided boceprevir treatment versus boceprevir treatment for the full treatment duration of 48 weeks. All patients received peginterferon and ribavirin for a 4 week lead in phase followed by triple drug therapy. Patients were analyzed separately based on race. For nonblack patients, patients who received response guided treatment had SVR rates of 67%, and black patients who received response guided therapy had response rates of 42%, and for patients receiving full 48 week course 53%. The SVR rates for patients who achieved an eRVR were 97% for whites and 87% for blacks. Boceprevir was also shown to improve cure rates for previous non-responders, though null responders were not studied. Prior non-responders who received full 48 week triple therapy had SVR rates of 52%, and prior relapsers had SVR rates of 75%. Anemia is the most common and problematic side effect of boceprevir, and over 40% of patients on boceprevir needed erythropoietin in most trials.
The protease inhibitors have not been approved for patients with HIV/HCV co-infection, though initial data show promising results and many people are treating patients off-label. The results of the phase II trial for telaprevir use in HIV/HCV co-infected patients with HCV genotype 1 have been announced\textsuperscript{129}. This study consisted of two groups: 1) 13 HIV/HCV co-infected patients with CD4 counts greater than 500 without need for ART’s and 2) 47 co-infected participants with stable HIV suppression on either efavirenz plus truvada or boosted atazanavir plus either lamivudine or emtricitabine. Patients were randomized to receive telaprevir (12 weeks) or placebo plus interferon alpha-2a plus fixed-dose ribavirin for a total of 48 weeks. Telaprevir dose was increased to 1125mg TID for patients on efavirenz due to a known drug-drug interaction leading to reduced telaprevir levels. Overall, 74\% of patients on telaprevir reached an SVR compared to an SVR rate of 45\% in the standard of care arm. Participants experienced more side effects on telaprevir, specifically rash, pruritus, nausea, and dizziness. Though anemia was equally as common in both arms (18\%), participants were more likely to receive blood transfusions and erythropoietin-stimulating agents in the telaprevir group. Finally, there was no HIV virologic breakthrough in either arm, and though absolute CD4 counts dropped as total wbc decreased, the CD4 cell percentage remained stable.

Results of the phase IIb trial for boceprevir showed similarly encouraging results for HIV/HCV coinfected patients. This study enrolled 100 previously untreated HIV/HCV coinfected patients with genotype 1 virus and randomized them to either boceprevir 800mg TID or placebo plus weight-based pegylated interferon alpha-2 and weight-based ribavirin for a total of 48 weeks of therapy\textsuperscript{130}. As done in mono-infected trials, there was a 4-week lead in phase in which the participants received only interferon and ribavirin followed by either placebo or boceprevir for 12 weeks, completing 48 weeks of treatment with interferon ribavirin. All patients had
undetectable HIV viral loads on ART, and most patients were on boosted protease inhibitors with 2NRTI’s, though there were a total of 15 patients on raltegravir. The SVR rate was 60.7% in the boceprevir group as compared to 26.5% in the standard of care arm. 20% of participants discontinued therapy due to adverse events in the Boceprevir group as compared to only 9% in the placebo arm. Overall, there were more reported side effects in the boceprevir group, with anemia being the most numerous complaint, noted in 41% of patients on boceprevir. There were a few patients that had HIV virologic break through near the end of therapy, though this number was not different between groups (3 vs. 4 patients in boceprevir vs. control group).

Current trials of telaprevir and boceprevir are in Phase III and are evaluating response guided therapy.

**Drug-drug interactions with Protease Inhibitors**

It is important to note that HCV protease inhibitors are metabolized by the cytochrome P450 system, and therefore have potential for significant drug-drug interactions, particularly for HIV/HCV co-infected patients on NNRTI’s or HIV protease inhibitor therapies. There are several noted drug-drug interactions between ART and the HCV protease inhibitors. Important drug-drug interactions were found in an open-label drug interaction study of boceprevir and several protease inhibitors. Coadministration of boceprevir and boosted lopinavir and darunavir significantly lowered the AUC of boceprevir, raising concern over potential HCV treatment failure when these drugs are given in combination. Data that attempt to determine the association between various boceprevir levels and SVR rates are unclear, making this drug-drug interaction difficult to interpret. Particularly worrisome is the fact that boceprevir lowered the trough concentrations of atazanavir, lopinavir, and darunavir by 49, 43%, and 59% respectively. These data raise concerns about provoking HIV virologic breakthrough in patients.
on these regimens. Though there was no evidence of increased HIV virologic breakthrough in phase 2 trials of boceprevir when these combinations were used, it is currently not recommended to combine these drugs. A similar study evaluating co-administration of raltegravir and boceprevir did not show any significant effects on exposure of either of the drugs. A raltegravir based HIV regimen is currently the best choice when treating HIV/HCV coinfected patients with boceprevir.

Investigational Drugs

The expectation for new drug development will be to create combination therapies that have better cure rates, less side effects, require decreased duration of treatments, and can be used without interferon.

Newer Protease Inhibitors

Current protease inhibitors are given three times daily, have significant side effect profiles such as pruritic rash and anemia, and easily develop resistance. The new protease inhibitors have been developed in order to reduce the dosing schedule from thrice daily to once daily, with the hopes of better side effect profiles and greater efficacy. Two of the newest protease inhibitors that are currently in phase III development are Simeprevir (TMC435) and Faldaprevir (BI 2010335). In HCV mono-infected patients taking once daily simeprevir plus peginterferon/ribavirin, SVR rates were achieved in 86% of patients. Of note, patients received response guided therapy such that patients with undetectable HCV viral loads at week 4 received 24 weeks of therapy, while all others received 48. Unlike current protease inhibitors, SVR rates were similar for both genotype 1a and 1b. Simeprevir will likely be used in
HIV/HCV co-infected individuals and has been evaluated with ARTs. Simperevir is not recommended with efavirenz due to reduce levels of simeprevir, but appears to be safe with raltegravir, rilpivirine, and tenofovir\textsuperscript{134}.

Faldeprevir, once daily, plus peginterferon/ribavirin for 24 weeks led to SVR rates of 83% in HCV mono-infected patients, and side effects were similar to those of interferon and ribavirin therapy\textsuperscript{135}. This protease inhibitor is currently in phase III development and being studied with BI’s polymerase inhibitor BI 207127 and ribavirin to create an interferon-free, all oral regimen. Results of the phase II trial showed a 43–50% SVR12 in genotype 1a and 57–80% in genotype 1b for patients with compensated liver cirrhosis, who took 12 weeks of triple oral therapy\textsuperscript{136}.

The NS5A inhibitors

NS5a is a metalloprotein that is part of the HCV replication complex, a membranous web of nonstructural proteins essential for viral replication. Though the exact mechanism of NS5A replication regulation is unclear, inhibitors of the protein in replicon assays has been potent\textsuperscript{122}. These drugs are active against all genotypes and have potent viral suppression but have a low barrier to resistance. They are mostly being used in combination therapy with other oral therapies so as to create interferon-free regimens. Daclatasvir (BMS-790052), a new NS5A inhibitor is currently being evaluated in Phase III trials for both mono-infected and HIV/HCV co-infected individuals.

Drug-drug interactions between common ARTs and daclatasvir have been studied. Daclatasvir appears to have no effect on the drug levels of tenofovir, efavirenz, or boosted atazanavir\textsuperscript{137}. These ARTs do exhibit some change in exposure to the NS5A inhibitor, but adjusting daclatasvir dosing up when combined with efavirenz, and decreasing the dose when given with boosted
atazanavir can overcome this, and all trials are using dose-adjusted combinations of daclatasvir for co-infected individuals.

**NS5B Polymerase Inhibitors**

These drugs can be divided into two classes, the nucleotide inhibitors and the non-nucleoside inhibitors. The non-nucleotide inhibitors bind to one of three allosteric binding sites outside of the enzymatic region, creating conformational change at the active site which induces polymerase inhibition. These drugs are genotype 1 specific, have a low barrier to resistance, and are not as far along in development as other classes. That said, they may be helpful in building drug combinations that act on different parts of the HCV virus, creating more potent oral combination regimens.

The nucleotide polymerase inhibitors bind directly to the NS5B active polymerase site. They have shown extreme potency and high barrier to resistance, and are currently being considered the therapeutic backbone of interferon free regimens. Sofosbuvir (GS-7977) is the furthest along in production. It has activity against all genotypes, is extremely potent, with a good side effect profile, and once daily oral dosing.

Results from the ELECTRON study showed extremely promising interim results for interferon-free therapy. After 12 weeks of GS-7977 in combination with ribavirin for patients with HCV genotype 2/3, 100% of participants reached an SVR\textsuperscript{138}. Of the 25 treatment naive HCV genotype 1 patients treated with Sofosbuvir (GS-7977) and ribavirin for 12 weeks, 84% achieved an SVR24. Side effects were minimal in all studies and there were no discontinuations due to adverse events.

Sofosbuvir showed similarly potent viral kinetics in HIV/HCV co-infected individuals in a phase 1b trial, with a $>1.5\text{log}_{10}$ HCV viral reduction in 24 hours\textsuperscript{139}. Sofosbuvir combined with
ribavirin is already being studied in HIV/HCV co-infected patients with HCV genotypes 2/3, and a shortened duration of therapy (12 weeks) is being evaluated. There have been no clinically significant interactions between sofosbuvir and efavirenz, rilpivirine, boosted darunavir, raltegravir, tenofovir, and emtricitabine in healthy volunteers\textsuperscript{140}. Drug interactions may be different in persons infected with HIV and hepatitis C as compared to healthy controls and therefore careful monitoring must take place in Phase III clinical trials.

One of the most exciting studies of 2012, was the combination of Sofosbuvir (GS-7977) and daclatasvir (BMS-790052) with and without ribavirin\textsuperscript{141}. 88 patients with genotypes 1, 2, and 3 received 24 weeks of therapy. The SVR4 rate was 100% in genotype 1 and over 85% in genotype 2/3, regardless of ribavirin use. Ribavirin was associated with anemia, but all other side effects were mild including fatigue, nausea, and headache. Importantly, there was no association between SVR and IL28 genotype, ribavirin use, or viral subtype, of which most were the difficult to treat 1a. A current trial is evaluating the same treatment but for only 12 weeks treatment duration. Gilead will not pursue additional phase III trials with BMS using daclatasvir in this drug combination, but instead has its own NS5A inhibitor in which they are conducting trials. Certainly, when daclatasvir (BMS-790052) and Sofosbuvir (GS-7977) become FDA approved, clinicians will be able to use them as they feel will most benefit their patients.

\textit{Gilead’s NS5A inhibitor (GS-5885)}

Data from the ELECTRON 4 trial are promising in Genotype 1 patients. Treatment naïve patients and prior null responders were randomized into 4 arms where patients were given Sofosbuvir plus ribavirin with/without Gilead’s NS5a inhibitor. 100% of participants in the triple therapy arm were cured, including 4 of 9 null responders who were available for evaluation at the end of the study. This compared with 84% in the dual therapy arm for treatment naïve
patients, and only 10% in the prior null responders. Anemia was associated with ribavirin use, but all other side effects were minor. Gilead has announced the phase III ION-I study evaluating a fixed-dose combination of sofosbuvir and their NS5A inhibitor alone or with ribavirin for 12 and 24 weeks. These results will be eagerly awaited to see if they are as effective as the daclatasvir/sofosbuvir data. Certainly these fixed dose combinations, if shown to have good efficacy, will be tried in the HIV/HCV co-infected populations.

**Liver Transplant in the HIV/HCV Co-infected Patient**

Despite advancement’s in HCV therapies, many HCV/HIV co-infected individuals will develop end-stage liver disease, leaving liver transplant as their only choice of therapy. Furthermore, some patients with compensated cirrhosis will develop acute de-compensation while being treated for HCV with interferon containing regimens. In one of the largest trials of HCV/HIV co-infected patients (APRICOT trial), 7.5% of the cirrhotic patients treated with interferon developed persistent decompensated cirrhosis or died due to hepatic de-compensation while on treatment\(^{142}\). Many of these patients were on didanosine, an antiretroviral now known to be associated with hepatic dysfunction in HCV/HIV coinfected individuals and therefore currently contraindicated in such patients. That said, due to the increased risk of de-compensation, it is imperative to have liver transplant available to HIV/HCV co-infected cirrhotic patients if they are to be treated with interferon.

Prior to HAART, HIV was considered an absolute contraindication to transplant due to immunosuppression and poor long-term survival of HIV infected individuals\(^ {143}\). With the introduction of more effective antiretroviral therapies, early transplant outcomes for HIV infected individuals were shown to be similar to their uninfected counterparts\(^ {144-146}\).
Unfortunately, HCV infection was a risk factor for worsened survival after liver transplantation. Two recent prospective cohort studies conducted in the United States and Spain showed worsened patient and graft survival for HIV/HCV co-infected patients as compared to HCV monoinfected controls\(^\text{147,148}\). The multicenter US study found a 3-year patient and graft survival rate of 60% and 53% respectively for HCV/HIV coinfected individuals, compared to 79% and 74% for the HCV monoinfected. Five year survival rate in the Spanish study was 71% in the monoinfected and 54% in the HIV/HCV coinfected. Importantly, multiple studies have found specific risk factors particularly associated with poor outcomes among the HIV infected cohort\(^\text{147-149}\). Patient predictors of poor outcome consist of HCV genotype 1, higher pre-transplant MELD score, BMI <21, and combined kidney-liver transplantation. Other variables associated with worse outcomes are older donor age, anti-HCV-positive donor, and centers that perform less than 1 liver transplant per year in HIV positive patients. When evaluating the subset of patients that do not meet these poor risk criteria, all studies show that this more favorable subset of HIV/HCV coinfected individuals have the same survival and outcomes as the HCV monoinfected. These data suggest that liver transplantation can indeed prolong survival for HCV patients coinfected with HIV, but appropriate risk stratification should be performed before this option is considered. That said, developing effective HCV therapy that would obviate the need for transplantation would be most beneficial for the long-term survival of the HCV/HIV co-infected population.
59. Vallet-Pichard A, Pol S. Natural history and predictors of severity of chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection. J Hepatol 2006;44:S28-34.


141. Sulkowski M, Gardiner DF, Rodriguez-Torres M, et al. High Rate of Sustained Virologic Response with the All-oral Combination of Daclatasvir Plus Sofosbuvir, with or without Ribavirin, in Treatment Naïve Patients Chronically Infected with HCV Genotype 1,2,3. In: 63rd Annual Meeting of the AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES Boston, USA; 2012.


