Medication use and patients co-infected with Human Immunodeficiency Virus and Hepatitis C Virus: quantifying the prevalence and identifying the predictors of clinically significant drug-drug interactions associated with therapy containing first generation non-structural 3A serine protease inhibitors

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Medication Use and Patients Co-Infected with Human Immunodeficiency Virus and Hepatitis C virus: Quantifying the Prevalence and Identifying the Predictors of Clinically Significant Drug-Drug Interactions associated with Therapy containing First Generation Non-Structural 3A Serine Protease Inhibitors

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ABSTRACT

This dissertation enhances our understanding of clinically significant drug-drug interactions (CSDDIs) and contraindicated drug interactions among patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection before and after the addition of HCV therapy including first generation non-structural (NS) 3A serine protease inhibitors. This is important to understand because the clinical sequelae of untreated chronic HCV infection are devastating yet drug-drug interactions greatly complicate treatment for these patients. The HIV/HCV coinfected population is a population that is particularly vulnerable because they are using a high volume of medications. Specifically, the standard of care for patients with HIV infection is the use of at least 3 antiretroviral agents. Many of the commonly used antiretroviral agents are processed by the cytochrome P450 (CYP450) isoenzyme system and are implicated in several drug interactions. Additionally, treatment of HCV infection involves the use of triple therapy including pegylated interferon, ribavirin and a direct acting antiviral (DAA) agent. Many DAAs are implicated in drug-drug interactions because they are also processed by the CYP450 isoenzyme system. Patients coinfected with HIV and HCV typically use at least 6 medications. Given the advances in treating HCV, this population is also developing age-related comorbidities which require medication-related intervention. This population is thus particularly vulnerable to CSDDIs.

Clinically significant drug-drug interactions have been implicated in a number of dangerous clinical outcomes and several medications have been removed from the market due to CSDDIs. Unfortunately, detection of CSDDIs is problematic because they
are not always intuitive to clinicians, who rely on drug interaction software programs to screen medication lists for CSDDIs. Unfortunately, a thorough evaluation of existing drug interaction software programs has not been performed to assess sensitivity and specificity.

This dissertation outlines three meaningful research questions regarding CSDDIs in this high-risk population. The first study quantifies the prevalence and identifies the predictors of CSDDIs after the addition of telaprevir-containing HCV therapy. This study identifies a high frequency of CSDDIs and contraindicated drug interactions before/after the addition of telaprevir-containing HCV therapy. Contraindicated interactions were predicted by various HIV medications, use of greater than or equal to ten non-HIV medications and dyslipidemia. The second study focuses on boceprevir-containing HCV therapy with respect to prevalence and predictors of CSDDIs. Similarly, a high prevalence of CSDDIs and contraindicated drug interactions were observed before/after the addition of boceprevir-containing HCV therapy. Contraindicated interactions were predicted by various HIV medications and the use of greater than or equal to eight non-HIV medications.

The third study quantifies the sensitivity and specificity of three commercially available software programs relative to a panel of clinical pharmacists serving as the gold standard. Overall, the point estimates for sensitivity and specificity did vary between products. These findings have important implications for clinicians considering therapeutic options for coinfected patients. We believe our findings shed light on the prediction and detection of drug interactions in this vulnerable population.
CHAPTER 1: BACKGROUND

Hepatitis C Virus

Viral characteristics

The hepatitis C virus (HCV) is among the most phylogenetically diverse viruses known to man and was first isolated in 1988.[1] This positive-strand ribonucleic acid (RNA) virus is a member of the Flaviviridae family.[2] Under electron microscopy, HCV is a small spherical-shaped, lipid-enveloped virus that is 50 nm in diameter.[2, 3] Two envelope proteins, E1 and E2, are incorporated in the lipid-envelope.[3]

Replication of HCV is a complex process that occurs in multiple steps.[4, 5] The primary site of HCV replication is within the hepatocytes.[4-6] Within the hepatocyte, the HCV genome is translated via a large open reading frame which encodes a polyprotein of ~3200 amino acids.[7] The polyprotein is cleaved by a series of proteases into 10 proteins.[7] Among these 10 proteins, 7 proteins are non-structural and the remaining are structural proteins.[2] Four viral enzymes are encoded by HCV in its non-structural region and are important as potential targets for medication therapy.[2, 8] These are non-structural (NS)2-3 cysteine autoprotease, NS3-4A serine protease, NS3 helicase, and NS5B RNA-dependent RNA polymerase.[2] The NS2-3 protease is responsible for cleavage the precursor viral polypeptide between non-structural proteins NS2 and NS3.[8] The NS3-4A protease is responsible for proteolytic cleavage of the HCV precursor protein at the following four sites: NS3/NS4A (self cleavage), NS4A/NS4B, NS4B/NS5A, and NS5A/NS5B.[8] The role of NS3 helicase is still unclear in
HCV replication.[9] Traditional helicases unwind a DNA double helix. However, there is no DNA in HCV replication. Several hypotheses exist about the potential function of NS3 helicase including unwinding of RNA when the HCV genome is replicated, smooth secondary RNA structures, remove RNA-binding proteins from viral RNA, assist translation, or process polyproteins.[9] The NS5B RNA-dependent RNA polymerase is responsible for RNA replication by producing a negative RNA strand intermediate.[7] This intermediate is important because it acts as the template for the positive RNA strand to be generated.[7] The newly generated RNA is packaged into new viral particles.[7] These new viral particles are released from the cytoplasm of the hepatocyte through the process of budding.[10]

Hepatitis C Virus Infection in Humans

Clinical Course: Acute Hepatitis C Virus

Acute HCV infection is rarely associated with clinically apparent symptoms. Among patients who experience symptoms, the most common symptoms include malaise, nausea and right upper quadrant pain.[11] These symptoms are usually followed by discolored urine and jaundice.[11] While these symptoms are non-specific, the incubation time of HCV is approximately is ~7 weeks and the onset of symptoms after specific exposures can distinguish between acute HCV from acute hepatitis A or hepatitis B infections.[12] Compared to acute hepatitis A or hepatitis B infection, the
severity of symptoms is diminished in acute HCV infection. The presence of HCV RNA in the blood can be observed as little as a few days after infection. However, elevations in liver function enzymes like alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are delayed. Extrahepatic symptoms do not commonly occur in acute HCV infection. Between 50% and 85% of individuals who are acutely infected with HCV will develop chronic HCV.

Clinical Course: Chronic Hepatitis C Virus Infection

Individuals who are chronically infected with HCV usually only have a few non-specific symptoms related to HCV. These symptoms include malaise and fatigue. Because of the insidiousness of the onset of these symptoms, individuals with chronic HCV infection are sometimes unaware that they are experiencing fatigue or malaise. The most useful laboratory values associated with chronic HCV infection are ALT and HCV RNA. Throughout the course of chronic HCV infection, ALT values will fluctuate; these fluctuations occur independently of the disease processes. Similarly, the extent of hepatic inflammation is not constant over time. Conversely, HCV RNA is typically continuous throughout the course of chronic HCV infection. Nonetheless, liver histology is the best marker of disease stage and liver damage. In some individuals, fibrosis may develop. This primarily occurs in the portal triads and may extend to other triads or central veins. If severe enough, fibrosis may lead to cirrhosis. Among patients who experience cirrhosis, approximately one fifth will experience some of the sequelae
related to hepatic decompensation.[1] These sequelae include esophageal varices, ascites, coagulopathy, encephalopathy and hepatocellular carcinoma.[1] The development of serious consequences of HCV infection like encephalopathy, hepatocellular carcinoma (HCC) and necessity for liver transplantation usually occur after a period of ~20 years in individuals with HCV monoinfection.[14, 15] This timeline is often accelerated in patients who are co-infected with HIV and HCC may be observed in as little as 5 years from diagnosis.[14, 16-18]
Extrahepatic Manifestations

While HCV primarily affects the liver, there are several extrahepatic manifestations that are associated with HCV infection. Extrahepatic organ systems that are affected by HCV infection include skin, eyes, joints, immune system, nervous system and kidneys.[1, 19] Approximately 70% of patients with HCV infection will experience at least one extrahepatic manifestation.[1]

Nephrotic Syndrome & Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate and clump together when blood is at colder temperatures.[20] Among HCV infected patients, cryoglobulins are problematic because they form immune complexes made by the HCV antigen, anti-HCV IgG antibodies, and a rheumatoid factor, which is an IgM kappa.[21] These immune complexes can deposit themselves on small & medium sized vessels and result in diminished blood flow to various areas of the body.[21] There are multiple types of cryoglobulins and are categorized into 3 types.[22] The categorization is based on clonality of the involved immunoglobulins. Type I cryoprecipitate is usually made up of a monoclonal immunoglobulin like IgM or IgG and most likely to be involved in lymphoproliferative disease.[22] Type II is mixed and the precipitate is made up of polyclonal immunoglobulins, primarily IgG, in addition to monoclonal immunoglobulins (IgA, IgG, and IgM).[22] The cryoprecipitate for Type III is also mixed and is made up of polyclonal IgG and polyclonal IgM. For HCV-infected patients, these immune complexes,
mainly Types II and III, deposit most frequently on the glomerulus of the kidney. As a result, patients develop proteinuria and hematuria and lead to nephrotic and nephritic syndromes in HCV-infected patients. In extreme cases, mixed cryoglobulinemia can develop into a florid B-cell malignancy. These syndromes with rapid deterioration of renal function occur in approximately 20-25% patients. Often times, cryoglobulinemia results in a number of extra-renal manifestations. The most common extra-renal manifestations include purpura, arthralgia, and peripheral neuropathy. There are three main strategies employed to treat HCV-related glomerulonephritis. These strategies include i) symptomatic therapy, ii) anti-HCV therapy, and iii) immunosuppressive therapy. The approach to treatment should stratify patients based on the severity of proteinuria and rapidity of renal disease progression. Symptomatic therapy and anti-HCV therapy for at least 12 months with interferon and ribavirin (with or without an erythropoietin stimulating agent) should be used in patients with moderate proteinuria and non-rapid progressive renal failure. The dose of ribavirin should be adjusted based on the patient’s renal function. Patients who have proteinuria indicative of nephrosis and/or progressive renal failure should receive symptomatic therapy, 3L of plasma exchange administered thrice weekly for 2-3 weeks, immunosuppressive therapy with either rituximab for 4 weeks or cyclophosphamide for 2-4 months, 3-day pulse dosing of methylprednisolone, and anti-HCV therapy. Symptomatic therapy for these patients should include furosemide, angiotensin converting enzyme (ACE) inhibitor alone or used in combination with an angiotensin receptor antagonist.
**Sjögren (sicca) syndrome**

There is an association between symptoms of Sjögren syndrome and HCV infection.[19] The etiology of Sjögren syndrome among HCV-infected individuals is unclear.[25] Specifically, it is unclear if HCV activates rheumatic factors that lead to an autoimmune response or if the virus directly causes symptoms.[26] Furthermore, it is unclear if the symptoms associated with Sjögren syndrome are influenced by genetics.[27] The syndrome is characterized by dryness of the mouth and eyes. As a result, Sjögren syndrome can affect multiple extra-ocular and extra-oral body sites including nose, vagina, and skin.[19] In more extreme cases of Sjögren syndrome, the glands around the face and neck can become swollen and patients can feel fatigued. Severe cases include vasculitis, Raynaud’s phenomenon, autoimmune hepatitis, peripheral neuropathy, and arthritis.[19] The diagnosis of Sjögren syndrome involves a combination of blood tests, physical findings, and biopsy. The specific laboratory tests are anti-nuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, and Sjögren-specific markers like SS-a(Ro) and SS-B(La). Physical findings that support the diagnosis of Sjögren syndrome are Schirmer test for tear production, ocular surface exam to detect dry spots, and dental examination to measure salivary gland function and quantify the amount of saliva produced in a given period of time.[19] Patients who are most likely to develop Sjögren syndrome are between the ages of 45 – 55 years.[19, 26, 27] Women have a 10-fold higher risk of developing Sjögren syndrome than men. Patients with HCV infection and Sjögren syndrome, are typically older non-HCV infected
patients, have a lower prevalence of parotidomegaly and a higher prevalence of liver involvement.[19, 26, 27] Based on laboratory findings, patients with HCV and Sjögren syndrome, have a higher prevalence of anti-parietal cell gastric antibodies, antimitochondrial antibodies, cryoglobulinemia, hypocomplementemia, and a lower prevalence of anti-Ro/SS-A compared to Sjögren syndrome patients who do not have HCV infection.[26, 27] The treatment of Sjögren syndrome is symptomatic and involves specific approaches like the use of saline nose sprays, artificial tears and hydration to alleviate symptoms.[19] For more extreme cases of Sjögren syndrome, non-steroidal anti-inflammatory drugs (NSAIDS) or immunosuppressive agents may be utilized.[19]

**Porphyra cutanea tarda**

Porphyra cutanea tarda is the most common type of porphyra.[28] It is characterized by cutaneous lesions with bullae, vesicles, and erosions on the dorsum of the hand. The mechanism is not fully understood and includes both hereditary and acquired factors.[28] The pathogenesis involves hepatic iron loading and increased oxidative stress.[29] These events lead to a decreased production of hepcidin by hepatocytes and cause an increase in iron absorption from the stomach.[28] Pophrya cutanea tarda is most commonly seen among patients with excessive alcohol intake and chronic hepatitis C infection.[28]
Treatment of porphyra cutanea tarda is geared towards iron reduction.[19, 28] This can be done by phlebotomy. Some clinicians will aim to achieve a mild or subclinical state of decreased iron. Among patients without hemachromatosis or chronic HCV infection, low-dose antimalarials can be used as adjunctive or alternative therapy.[28]

**Neurologic Complications**

Neurologic complications associated with HCV infection can be central or peripheral in nature.[30] Neurologic complications affecting patients with HCV infection include mixed cryoglobulinemia, stroke, myelopathy, cognitive impairment and encephalopathy.[31] Given the pathogenesis of HCV infection, it is unclear if all of these neurologic complications are a direct effect of viremia or other factors/exposures associated with HCV infection that predisposes patients to these effects.[32, 33]

The most frequently reported complication is a mixed cryoglobulinemia. This results in a subacute, distal, symmetric, sensorimotor polyneuropathy. Strokes (ischemic and hemorrhagic strokes) have been described but are limited within the literature.[32] Emerging reports describe transverse myelopathy and cognitive impairment associated with HCV infection.[32] In scenarios involving more advanced cases of HCV infection, encephalomyelitis can occur.[32] Currently, there are no treatment guidelines for any of these neurologic conditions that are specific to HCV infected patients. However, immunomodulating agents and antiviral therapy, geared towards mitigating HCV infection, are associated with positive clinical outcomes.[30, 32, 34]
Hepatic Manifestations – Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a group of cancers that are responsible for significant morbidity and mortality amongst men and women in the United States.[35] Nearly 50% of cases of hepatocellular carcinoma in the United States are thought to be attributable to chronic HCV infection.[36] In 2010, liver and bile duct cancers were reported as the fifth leading cause of cancer mortality in men and ninth leading cause in women in the United States.[35] In 2010, there were 24,120 reported new cases of this malignancy.[35] There has been an increasing trend in incidence and mortality since the early 1990’s.[35] The National Comprehensive Cancer Network (NCCN) guidelines for hepatobiliary cancers recommend screening for patients that are at risk. These recommended screenings include testing an alfafetoprotein (AFP) level and ultrasound every 6-12 months as clinically indicated. The benefits of screening and improving survival are fairly limited. However, current NCCN guidelines and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening at risk patients, like those with chronic HCV infection, every 6 months.[37] These recommendations are based on limited data described from a surveillance study implementing every 6 month screening with an AFP and ultrasound.[37] This investigation revealed a 37% mortality reduction in Chinese patients where screening adherence was poor at 60%.[38] An additional study in China revealed that combined AFP testing and ultrasound yields a higher detection rate.[39] The combination of these investigations suggests a benefit but no further studies have been completed in the
United States and other various regions where the incidence and mortality of HCC are rising.

One of the most alarming features of HCC is its prognosis. Five-year survival of HCC is 4.1% in patients that present with metastatic disease and the early detection, improvement of treatment options, and prognosis implications are at upmost importance to have a meaningful survival impact on patients.[40] The treatment of HCC involves the use of transcatheater arterial chemoembolization (TACE).[41, 42] This procedure involves cannulating the hepatic artery, which feeds to the tumor, and delivering high local doses of chemotherapy, including doxorubicin, cisplatin, or mitomycin C. The effectiveness of TACE is unclear and some data suggest that TACE does not affect clinical outcomes.[43] Among patients with highly progressed hepatic cirrhosis or hepatic decompensation, TACE is contraindicated because the ischemic damage that TACE would induce could lead to marked declines in liver function, encephalopathy, ascites and possibly death. Systemic chemotherapy has been used in patients with HCC, but is rarely responsive. Doxorubicin seems to have the most robust effect with response rates of ~20%. There appears to be little to no impact on survival.[44, 45] Oral therapy with sorafenib has been evaluated. Sorafenib appears to be somewhat promising for HCV infected individuals because it targets the RAF1 enzyme which is upregulated in patients with HCV infection.[46] Clinical trial data seems to demonstrate that sorafenib significantly improves survival (hazard ratio for all-cause mortality: 0.69, p=0.0006).[47] Sorafenib was also associated with an increased time to disease progression (5.5 mo vs 2.8 mo) and disease control rate (43% vs 32%).[48]
Whether a difference in disease progression of 2.5 months is clinically meaningful has yet to be determined. Clinical outcomes associated with HCC are usually grim and over one third of patients die within a year of diagnosis.

Among patients with HCV infection, treatment with interferon based therapy is protective against HCC (RR = 0.7).[49] With the availability of NS3/4A inhibitors, this protective effect is likely to be more pronounced since a higher proportion of patients are achieving a sustained virologic response.
Epidemiology of Hepatitis C Virus Infection

Case Definition and Diagnostic Criteria for Chronic Hepatitis C Virus Infection

The case definition of chronic HCV is one that is laboratory-confirmed and does not satisfy the case definition for acute HCV infection.[50] There are no clinical symptoms required to make the diagnosis of chronic HCV infection because most individuals are asymptomatic. In patients with chronic HCV infection, the degree of liver damage varies and patients who present with symptoms will range in severity.

The laboratory diagnosis of HCV infection includes at least one of the following [51, 52]:

1. Anti–HCV positive (repeatedly reactive) by enzyme immunoassay (EIA) verified by at least one additional more specific assay, or
2. HCV RIBA (recombinant immunoblot assay) positive, or
3. Nucleic Acid Test (NAT) positive for HCV RNA (including genotype), or
4. Antibodies to hepatitis C virus (anti-HCV) screening-test-positive with a signal to cut-off ratio predictive of a true positive as determined for the particular assay and posted by CDC.
Incidence of Acute Hepatitis C Virus Infection

Each year, there are approximately 850 cases of confirmed acute HCV infections reported each year. This corresponds to an incidence rate of 0.3 cases per 100,000 persons annually.[53] The Centers for Disease Control and Prevention (CDC) estimates that there are 2,800 acute cases and 17,000 total new HCV infections and that the low number of confirmed cases of acute HCV infection is likely to asymptomatic disease and significant underreporting.[53] The most common clinical characteristics that patients present with include jaundice (74.4%) or hospitalization related to HCV infection (57.5%). Among cases of acute HCV infection, case-fatality rate is extremely low (<1%). The most common risk exposures among patients with acute HCV infection are occupational and dialysis. The most common risk behaviors are multiple sex partners and injection drug use.[53]

Prevalence of Chronic Hepatitis C Virus Infection

There are approximately 3.2 million individuals living with chronic HCV infection in the United States. In 2010, there were 25,974 cases of laboratory-confirmed reports of chronic (past or present) HCV infection submitted to the National Notifiable Diseases Surveillance System.[53] The most commonly observed case criteria achieved were anti-HCV + signal to cutoff ratio (55.4%) or presence of HCVRNA (45.8%). Among enhanced viral hepatitis surveillance sites, the majority of these cases are male (62.8%).[53] The age groups of persons most likely to be diagnosed with chronic HCV infection are those born during 1945 – 1965. The majority of these infections occurred in the 1970s and 1980s, when rates of HCV were highest.[53]
Risk Factors for Transmission of Hepatitis C Virus Infection

Recreational Drug Use

Intravenous Drug Use

The use of intravenous drugs has been well-described in the literature as a common mode of transmission of the hepatitis C virus.[54] Intravenous drug users represent the largest risk group for acquiring HCV infection. These patients account for 30-40% of all identified HCV cases, and 50% of all new cases of HCV.[54] Hepatitis C infection among intravenous drug users (IDU) occurs at an alarming rate.[55] In retrospective studies quantifying the risk of HCV infection among injection drug users, nearly 80% of IDU will have a positive anti-HCV test result after 2 years of injecting.[55] In some settings where the population prevalence of HCV is higher, the risk of HCV acquisition approximates 100% among IDU.[55] It is important to note that these data are in the absence of syringe exchange programs that promote sterile injection practices. Successful syringe exchange programs can reduce the risk of HCV acquisition by nearly 500%.[56] Syringe exchange programs are not only beneficial for HCV transmission, but also help reduce transmission of other bloodborne pathogens including hepatitis B and human immunodeficiency virus.[56, 57] While needle exchange programs can reduce the transmission of HCV, a comprehensive approach that mitigates all of the ways HCV is transmitted is needed to lead to dramatic reductions in incident cases.[57]
**Intranasal Drug Use**

Emerging reports are starting to describe transmission of HCV via contaminated equipment used intranasal cocaine administration.[58] This has been particularly true among individuals with no other explainable risk factors for acquiring HCV infection. Among 38 self-reported intranasal drug users with active chronic HCV infection that provided nasal samples, trace amounts of blood in nasal secretions were detected in 74% of individuals.[59] There were five patients with quantifiable HCVRNA in their nasal secretions.[59] Both blood and HCV particles can be transferred onto equipment used for intranasal drug use (i.e. cocaine straws).[59] Other studies have demonstrated that HCV can remain viable on environmental surfaces for up to 16 hours. However, the actual quantity of virus required for transmission is not well understood.[59, 60]
Healthcare Transmission

**Hemodialysis**

Due to the percutaneous manipulation of the hemodialysis procedure, patients receiving dialysis treatment are particularly vulnerable to infection by bloodborne pathogens, including HCV.\[61, 62\] Additionally, patients receiving hemodialysis often require transfusions and this is another opportunity for HCV acquisition.\[62\] There have been a number of outbreaks of HCV infection among patients receiving hemodialysis. The low prevalence of HCV in the United States population and strict infection control practices has curbed HCV transmission in hemodialysis centers.\[62\] However, outbreaks have been reported in situations where infection control practices may have been compromised.\[62\]

In the developing world, the prevalence of HCV infection can be as high as 50%.\[63, 64\] The annual seroconversion in these settings is between 5-10% annually.\[64\] Understaffing of nurses in dialysis centers has been identified as a predictor of HCV transmission.\[65\] Specifically, high patient-to-nurse ratios have been associated with higher seroconversion in dialysis clinics.\[65\]

There are a number of strategies that can be employed to minimize the risk that the dialysis procedure places on patients. Among these strategies are application of universal precautions as recommended by the US Centers for Disease Control & Prevention, segregation of equipment, sufficient nursing staff available and separate
treatment rooms for patients with HCV infection. Employing these strategies can reduce the annual HCV seroconversion rate to 1% per year in hemodialysis centers.[65]

**Receipt of Blood or Blood Products**

Prior to the screening of blood products, there were early reports of transmission of non-A, non-B cases of viral hepatitis.[66, 67] The majority of these cases of viral hepatitis were later identified as hepatitis C infection.[66, 67] Given the percutaneous and permucosal patterns of transmission of HCV infection, it is unsurprising that this was a frequent mode of transmission. While tremendous strides have been made to screen blood that is used for blood transfusions, there are still opportunities for contamination and subsequent outbreaks. Serosurveys of blood donors have demonstrated that the frequency of HCV positivity among blood donors is low. This largely in part due to screening questionnaires that triage patients who may be at high risk for undiagnosed HCV infection and discourages them from donating blood altogether. In settings where HCV prevalence is high (>1%), like China, HCV seropositivity among blood donors is differs between first-time donors and repeat donors.[68] The rate of HCV positivity among first-time donors was 235 infections per 100,000 persons.[68] Among repeat donors, the rate of HCV positivity was 10 infections per 100,000 person-years.[68] Among blood donors that have been identified as being infected with HCV, over 50% have a traditional risk factor for HCV infection.[68] Among
patients with a discernible risk factor, blood transfusion was observed in one third of patients.[69] Since the development of a commercially available assay to test batches of blood, receipt of blood transfusions has been virtually eliminated as a potential source for transmission. Given that blood donors belong to an open population, it is important to continue to screen donors. In particular, it is important to identify patients who are at high risk for infections caused by bloodborne pathogens. Furthermore, samples of donated blood should continue to be routinely tested for HCV and blood provided by donors that contains HCV should be discarded and the donors should be prohibited from donating in the future. Collectively, these activities will continue to prevent iatrogenic transmission of HCV through the blood supply.
Multi-dose Vials

Reusable vials for medication administration have been linked to HCV transmission in a number of studies. This has been implicated as a source of HCV in outbreaks that occur in nosocomial settings. The majority of these transmissions have occurred in ambulatory hemodialysis units, interventional radiology wards and gastroenterology clinics performing invasive procedures like colonoscopies.[70-72] The contents of these vials have included normal saline, heparin and various medications used for general anesthesia.[73] Among the outbreaks involving multi-dose vials, two of them were highly publicized and occurred in the United States.[74-77] The first of these two outbreaks occurred in 2001 in New York City. A cluster of 4 patients treated at an outpatient gastroenterology center who developed acute hepatitis C virus infection were initially identified. Further investigation revealed additional cases of HCV and there were a total of 12 clinic-associated cases of HCV transmission.[74] The second outbreak occurred at a gastroenterology clinic performing endoscopies in Nevada whereby 8 cases of HCV infection were identified. There were two distinct quasi-species of the virus and implied that there were separate transmission events. In both transmission events, reuse of syringes on single patients in conjunction with use of single-use propofol vials for multiple patients was observed during normal clinic operations. As a result, 50,000 persons required notification and testing for HCV.[75]
Sexual Transmission

Transmission of HCV via sexual means is controversial within the literature. The major contributing factors to sexual transmission of HCV are the presence of HIV infection and sexual practices. Specifically, it appears that anal sex, fisting and other aggressive sex acts enhance the risk of HCV transmission through sexual means.

Among HCV-serodiscordant heterosexual couples, the risk of sexually-acquired HCV is very low. A cross-sectional study of HCV-infected patients and their partners was performed to estimate the risk for HCV infection among their monogamous heterosexual partners. This study included 500 anti-HCV-positive, HIV-negative index subjects and their long-term heterosexual partners. Overall, HCV prevalence among partners was 4% (n=20). Among these couples, there were nine couples who had concordant HCV genotype/serotype. In three couples (0.6%), viral isolates were highly related. This denotes that transmission of HCV most likely occurred within the couple. Based on over 8000 person-years of follow-up, the maximum incidence rate of HCV transmission by sex was 1 case per 190,000 sexual contacts. Within the study, no specific sexual practices were related to HCV acquisition among couples.[78]

There are a growing number of reports from Europe and the United States describing sexual transmission of HCV among HIV-infected men who have sex with men (MSM).[79-81] Additionally, the incidence of re-infection with HCV in this population is high in individuals who have received treatment and achieved a sustained virologic response.[82, 83] A number of studies have attempted to identify sexual acts that
promote HCV transmission. The most common behaviors that enhance the risk of HCV transmission are fisting, multiple partners, use of sex toys, unprotected anal intercourse and co-infection with a sexually transmitted infection.[80, 81, 84-86] Many of these infections occur in the absence of injection drug use. A unique finding is that clusters of phylogenetically-linked cases are being identified. This may be suggestive of overlapping sexual networks.[87]
Incarceration

Individuals in correctional facilities often originate from other high-risk environments and may engage in high-risk behaviors.[88] As a result, individuals in correctional facilities are at high risk for HCV acquisition. Epidemiologic data estimate that over a third of the 1.8 million inmates in the United States may be infected with HCV.[89] While many of the individuals were infected prior to incarceration, the risk of transmission within a correctional facility remains, particularly if these individuals are engaging in high-risk activities like unprotected aggressive anal intercourse and sharing of drug paraphernalia. In some settings, as much as 50% of prisoners have a history of injection drug use prior to incarceration and continue to do so while in prison.[88, 90] Best available data demonstrate a low rate of HCV seroconversion of 1.1 per 100 person-years while incarcerated.[91, 92] Within the Department of Corrections, there is high turnover. Many individuals after incarceration will return to previous high-risk environments and behaviors that transmission of HCV.[89] Additionally, these individuals have a higher probability of being re-incarcerated and have a longer cumulative lifetime history of exposure to HCV-related activities.[91, 92]
**Vertical Transmission**

The seroprevalence of HCV infection among pregnant is low and occurs in approximately 2% of pregnant women.[93-95] Pregnant women with HCV infection usually have at least one risk factor for HCV acquisition. Factors associated with HCV seropositivity among pregnant women include IV drug use, a history of sexually transmitted infections, hepatitis B infection, history of transfusion, and three or more different lifetime sexual partners or a sexual partner who used IV drugs.[93, 96] The overall risk of perinatal HCV infection also appears to be variable, yet small, and averages 4.7% (range: 0 – 15%).[94-105] The United States Public Health Service (USPHS) estimates that the probability of perinatal HCV transmission is 5-6%.[96] Vertical transmission is influenced by the trimester of exposure.[106] There have been no reports of vertical transmission of HCV when the mother is acutely infected before the 3rd trimester.[106] Transmission is more likely to occur among women who are chronically infected with HCV or acutely infected in the 3rd trimester.[106] Factors that contribute to the probability of perinatal HCV infection include: high levels of HCV RNA among infected mothers and HIV coinfection. [96, 107-111] The probability of vertical transmission of HCV is higher among women with a high anti-HCV (>1:20,000) and HCV RNA (10^7 - 10^{10} copies).[109, 112, 113] The median maternal HCV RNA is usually ¼ - ½ log higher among women whose children acquire HCV than women whose children did not acquire HCV infection.[110] The risk of perinatal HCV transmission is higher among women with HIV/HCV coinfection.[101, 102, 104, 107, 108, 114-117] In an Italian cohort of 23 HIV-1 infected children born to 22 HIV/HCV coinfected mothers, the prevalence of
persistent anti-HCV antibodies and circulating HCV RNA was 8.7%.\textsuperscript{107} In another cohort of 70 mother-child pairs, HCV RNA was detected in 14 (20%) children.\textsuperscript{114} There was heterogeneity of transmission risk by coinfection status.\textsuperscript{114} Among the 17 mothers that were HCV-monoinfected, HCV RNA was detected in 2 (12%) children.\textsuperscript{114} Conversely, HCV RNA was detected in 12 (23%) children born to the 53 HIV/HCV coinfected mothers.\textsuperscript{114} While HCV can be found in breastmilk, breastfeeding is not contraindicated.\textsuperscript{118} There have not been any studies demonstrating an association between breastfeeding and an increased risk of HCV transmission.\textsuperscript{119}

Pregnancies among women who are HCV carriers may be more complex and associated with worse outcomes relative to the uninfected pregnant population.\textsuperscript{120} Specifically, HCV carriers have a higher likelihood of preterm deliveries (<37 weeks gestation), premature rupture of membranes, placental abruption, induced labor induction and deliveries via Caesarean section.\textsuperscript{120} Compared to infants born to mothers without hepatitis, infants born to mothers with HCV infection have slightly higher frequencies of mortality, congenital malformations and low birth weight (<2500 kg).\textsuperscript{120} In children born to women with HCV infection, there are three clinical patters of HCV infection.\textsuperscript{114} The first is a transient viremia and occurs infrequently.\textsuperscript{114} The second is an acute pattern of HCV infection and does not occur often.\textsuperscript{114} The third is a chronic pattern of HCV and is the most common presentation for children perinatally infected with HCV.\textsuperscript{114} Children who perinatally acquire both HCV and HIV, almost exclusively present with the chronic pattern of HCV infection.\textsuperscript{114} Children born to HIV/HCV coinfected mothers may have disease sequelae associated with HCV and HIV.
infections like chronically-evolving liver disease and autoimmune thrombocytopenia.[107] Among infants infected with HCV at birth, the infection is usually persistent and develops into chronic HCV infection.[97] Additionally, children infected with HCV usually have abnormal alanine aminotransferase.[97] The irregularities in alanine aminotransferase can be transient or persistent and vary.[97, 121] In a Swedish cohort of fourteen women with chronic HCV infection and their 21 children, there were only two children that developed long-standing elevations in ALT.[121]
Tattooing

The data surrounding tattooing as a potential risk factor for HCV infection are conflicting.[122-124] Some studies have observed an increased frequency of HCV infection among tattoo recipients whereas others have not. In a cohort study of 106 tattoo recipients and 106 non-recipients that presented to an emergency room in Michigan, presence of HCV RNA was detected in 6.6% of tattoo recipients and 2.8% of non-recipients, \( p = 0.82. \)[125] While there were no significant differences in the proportion of patients with HCV RNA by tattoo status, individuals with tattoos were more likely to have a body piercing and this may be a potential source of HCV infection.[125] Another study demonstrated that there was no association between multiple tattoos and HBV or HCV seroprevalence.[123]

Despite these data, other studies have identified the presence of a tattoo as a potential risk factor for HCV infection. This is particularly true among patients who are non-IDU.[124, 126-128] In a cohort of healthy, non-IDU men that did not engage in multiple sexual activity, there was a significantly higher proportion of anti-HCV positivity among individuals with a tattoo versus those without a tattoo. A relationship between number of tattoo sites and HCV risk was also observed. Additionally, the risk of HCV infection was higher if the tattoo was done by a non-professional friend rather than a professional.[127] Similarly, the setting in which a tattoo is administered appears to be associated with HCV infection. Among 642 prisoners, there were 449 prisoners who had ever been tattooed. Nearly half (42%) of prisoners with tattoos had received their tattoo
in a correctional facility. Prisoners who were HCV antibody positive were more likely to have acquired a tattoo in prison than prisoners who were HCV antibody negative.[129]

Among the risk factors for HCV infection, tattoo application is an intermittent cause and is responsible for ~0.6 – 4% of all HCV cases.[130-132] In a cross-sectional study evaluating the prevalence of HCV antibodies among 1537 pregnant women, the most common risk factors for transmission were IDU, past/present sexual partner that used was an IDU, having a tattoo and being incarcerated. The only variables to remain in the multivariate model were IDU (odds ratio [OR], 50.1; P < 0.001), and having a tattoo (OR, 3.5; P = 0.07).[133]
Effect of HIV Coinfection among Persons with underlying HCV Infection

Coinfection with HIV and HCV occurs commonly among patients with underlying HIV infection or whose mode of infection was through the use of intravenous drugs. Among individuals that are HIV-infected, the prevalence of chronic HCV infection is ~25%.\[80, 81, 134, 135\] Coinfection with HIV/HCV is particularly concerning because patients are at an increased risk for a number of deleterious outcomes.\[14, 16-18\] First, mortality is hastened among patients with HIV/HCV coinfection relative to patients with HIV monoinfection or HCV monoinfection.\[14, 16-18, 136\] Second the probability of developing hepatocellular carcinoma is significantly higher among patients with HIV/HCV coinfection than patients with either monoinfection. The time to development of cirrhosis, hepatic decompensation, fibrosis, hepatocellular carcinoma and need for liver transplant can occur much faster in the context of HIV/HCV coinfection than monoinfection.\[14, 16-18\] In patients that are HCV monoinfected, development of hepatocellular carcinoma or need for liver transplant usually occurs after an average of 15-20 years after initial infection. These data are highly variable because the index date of HCV infection is generally not known, particularly in patients that have continued to engage in high risk behaviors over long periods of time. Often times, patients with HCV monoinfection die of other causes before they ever need a liver transplant or develop hepatocellular carcinoma. In patients with HIV/HCV coinfection, these outcomes can happen in as little as 5-10 years.\[14, 16-18\] The use of combination antiretroviral therapy has had a dramatic impact on this timing and the timing may be less dramatic in
the era of widespread antiretroviral use. Nonetheless, there is still an increased risk of
the occurrence of these outcomes altogether.

Another issue is the management of HIV infection. Coinfection with HIV/HCV
complicates the management and control of patient’s HIV disease. Patients with
HIV/HCV coinfection are two times as likely to develop an AIDS-defining illness.[137] The
presence of HCV infection among individuals with underlying HIV disease appears to
cause an increase in T-cell activation. Consistent T-cell activation will lead to immune
dysfunction and enhanced HIV and HCV replication.[138] Many of the medications that
are used to treat HIV infection are hepatotoxic and may increase fibrosis through
cumulative hepatotoxicity.[139-141] The presence of coinfection enhances the risk of
hepatotoxicity and may limit the number and types of ART that a coinfected patient may
utilize.

The goal of HCV treatment is to achieve a sustained virologic response (SVR).
This is defined as an undetectable HCV viral load (HCV RNA) 24 weeks after completing
HCV therapy. Therapies used to treat HCV infection have historically only been mildly
effective in patients with HIV/HCV coinfection.[142-145] The approval of the novel class
of NS3A protease inhibitors has significantly improved the probability of achieving a
SVR. For coinfected patients, achieving a SVR is particularly important as it is
independently associated with a mortality benefit. Additionally, coinfected patients that
achieve a SVR are less likely to progress to end-stage liver disease (ESLD), require liver
transplantation or develop hepatocellular carcinoma.[49]
One of the issues surrounding the treatment of HCV infection among patients with HIV/HCV coinfection is the presence of drug-drug interactions. Several clinicians have deferred treatment in their coinfected patients in anticipation of newer medications with a more favorable drug-drug interaction profile.
Pharmacotherapy of HCV Infection

Prior to 2011, the standard of care for patients with HCV infection has been the use of interferon (IFN) in combination with ribavirin (RBV).[146] A polyethylene glycol (peg) molecule was added to IFN to prolong its half-life. The advantage of PegIFN was that it could be administered less frequently than traditional IFN.[147] In April 2011, the United States Food and Drug Administration (FDA) approved boceprevir and telaprevir for the treatment of HCV genotype 1 infection to be used in combination with pegIFN and RBV. The 2011 iteration of the HCV treatment guidelines recommended either the use of telaprevir or boceprevir as the NS3/4A serine protease inhibitor of choice.[148] In December 2013, simeprevir and sofosbuvir were licensed by the FDA. In February 2013, the treatment guidelines for were updated and incorporate the use of sofosbuvir and simeprevir.[149]

Interferon-based therapies

Interferon-alpha 2a

Interferons are endogenous glycoproteins and are otherwise known as cytokines. Among mammals there have been 10 unique interferons identified and there are over 25 different subtypes. Interferon alpha 2a represents only one of the subtypes. More generally, interferon is made by host cells in response to invasion by pathogens. These pathogens can be infectious (bacteria, viruses, etc.) or non-infectious (tumor cells) in nature. Interferon has a number of in vivo functions. However, the primary
functions of interferon are to i) activate natural killer cells and macrophages and ii) increase recognition of infection or tumor cells through enhanced regulation of T-cells.[150]

Interferon alpha 2a is a recombinant interferon. The recombinant form of interferon alpha 2a behaves similarly to the endogenous interferon alpha that is created in vivo in response to infection or tumor cells. While the exact mechanism of interferon alpha 2a is not fully understood, it is believed to bind to the cell surface and activate tyrosine kinase. In turn, this activates a number of interferon-related enzymes that are thought to exert biologic pleitropic effects of interferon such as antiviral, antiproliferative and immunomodulatory effects.[150]

One of the disadvantages of interferon alpha 2a is that it is administered subcutaneously. In individuals without any underlying health conditions, the half-life of interferon alpha 2a ranges from 3.7 – 8.5 hours. The major pathway of elimination is filtration through the glomeruli and proteolysis in the renal tubules during reabsorption.[150]

Interferon alpha 2a has demonstrated activity against a number of viruses including HCV, HIV, human papillomavirus (HPV), human T-lymphotropic virus type I (HTLV-I), poliovirus, varicella-zoster virus, and variola virus (smallpox). Interferon alpha 2a carries the United States Food and Drug Administration indication for hepatitis C virus infection. It also has effects on tumor cells and has been used in the treatment of AIDS-related Kaposi’s sarcoma, induction and maintenance of remission of hairy-cell
leukemia, non-Hodgkins lymphoma and chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (CML) in patients who are within 1 year of diagnosis and minimally pretreated.[150]

When pegylated interferon alpha 2a became commercially available, clinicians were moving away from monotherapy and using pegylated interferon alpha 2a in combination with ribavirin.[151] Some of the interferon-related toxicities that were observed became more pronounced in the presence of ribavirin. Primarily, the main toxicities that became more pronounced were the blood dyscrasias like anemia and neutropenia. Some of these blood dyscrasias make patients more vulnerable to infections and serious infectious diseases have been reported among patients receiving interferon-based therapy. Complete blood counts on these patients should be monitored frequently as well as signs and symptoms associated with anemia, neutropenia and thrombocytopenia.

As a class, interferons are known to cause constitutional symptoms shortly after administration. Patients will often experience flu-like symptoms in the 24-48 hours after administration. These effects persist for approximately 1-2 days.[152] Some patients will experience alopecia. While this is rare, it is a permanent effect of interferon-based therapy. One unique, and highly publicized, side effect of all interferon therapies is its psychiatric effects. Specifically, patients initiating interferon therapy should be warned about depression, homicidal and suicidal thoughts. Patients with uncontrolled depressive disorders should not initiate therapy with interferons. Patients with
uncontrolled diabetes mellitus are at risk for retinal adverse events on interferon and periodic ocular exams are recommended to diabetic patients initiating interferon.

Interferon therapy does have an effect on thyroid stimulating hormone (TSH). Patients whose TSH cannot be adequately maintained should not be treated.[153]

Roche was the primary manufacturer of interferon alpha 2a. In 2007, Roche announced that the production of interferon alpha 2a would cease due to a business decision and the widespread uptake and availability of pegylated interferon alpha 2a. All prefilled syringes of interferon alpha 2a were expected to be depleted by December of 2007.[150]

Pegylated interferon alpha 2a

Pegylated interferon alpha 2a is a recombinant version of interferon alpha 2a that is covalently conjugated to bis-monomethoxy polyethylene glycol (PEG).[154] The impetus for conjugating interferon alpha 2a with PEG was to prolong the half-life and decrease the clearance of the drug. As a result, pegylated interferon alpha 2a can be dosed less frequently than interferon alpha 2a. The safety of pegylated interferon alpha 2a is comparable to interferon alpha 2a.[151] However, the tolerability of pegylated interferon alpha 2a is improved which may enhance patient preference.[151] Historical data comparing monotherapy with pegylated interferon alpha 2a versus interferon alpha 2a demonstrated a higher frequency of virologic response at 48 weeks (69% and 28%, respectively).[155]
Similar to interferon alpha 2a, pegylated interferon alpha 2a is administered subcutaneously. While this has been an undesirable characteristic of all interferon products, there is greater popularity for pegylated interferon alpha 2a since it needs to be administered less frequently than interferon alpha 2a. The mean half-life of peglylated interferon alfa-2a is 80 hours (range 50—140 hours) as compared with 5.1 hours (range 3.7—8.5 hours) for interferon alfa-2a. Unlike interferon alpha 2a, pegylated interferon alpha 2a does have a reduced clearance in patients with a creatinine clearance < 30 mL/minute and those patients on hemodialysis. Patients with a creatinine clearance < 30 mL/min or on hemodialysis who are using conventional doses of pegylated interferon alpha 2a (180 mcg weekly) are likely to have elevated exposures. As a result, patients with a creatinine clearance < 30 mL/min should reduce the dose of pegylated interferon alpha 2a to 135 mcg weekly and monitor for signs and symptoms of toxicity.

**Pegylated interferon alpha 2b**

Pegylated interferon alpha 2b is a conjugate of interferon alpha 2b covalently bound to PEG. Pegylated interferon alpha 2b carries the FDA indication for chronic HCV infection and melanoma. Analogous to pegylated interferon alpha 2a, pegylation allows the half-life to be prolonged and decreases clearance. By doing this, pegylated interferon alpha 2b can be administered less frequently than its non-pegylated counterpart. The frequency of adverse reactions are similar between
interferon alpha 2b and pegylated interferon alpha 2b with one exception. Pegylated interferon alpha 2b is more likely to cause bone marrow suppression than interferon alpha 2b.[156] The efficacy of pegylated interferon alpha 2b has been compared with pegylated interferon alpha 2a when used in combination with ribavirin 800-1400mg/day. Sustained virologic response appeared to be similar for pegylated interferon alpha 2b (40%) and pegylated interferon alpha 2a (38%). While virologic response did not differ between the formulations, there was a lower frequency of relapse among patients using pegylated interferon alpha 2b (20-24%) compared to patients receiving pegylated interferon alpha 2a (32%).[157]

Ribavirin

Ribavirin is an antiviral agent that has activity against several RNA and DNA viruses. Ribavirin is a synthetic guanosine anologue.[158] Ribavirin has been used to treat herpes zoster, herpes genitalis, varicella and respiratory syncytial virus.[158] For chronic hepatitis C, ribavirin is ineffective as monotherapy and must be combined with either interferon alpha or pegylated interferon alpha to exert its effects.

In vivo, ribavirin undergoes a series of phosphorylation steps. Once fully phosphorylated, ribavirin causes a decrease in guanosine triphosphate through inhibition of inosine monophosphate dehydrogenase. It is hypothesized that ribavirin behaves like a potent RNA virus mutagen and increases the mutation rate of RNA
viruses well above the mutation rate that occurs through natural replication. As a result, virion production cannot occur efficiently and lead to 'error catastrophe.'[159]

Ribavirin, when used for the treatment of chronic HCV infection, is orally administered.[158] Ribavirin rapidly absorbed after ingestion. Once in plasma, ribavirin does not bind to plasma proteins and has a large volume of distribution. There is considerable transport of ribavirin into erythrocytes and occurs over a period of 4 days after the ingestion of one orally administered dose. As concentrations of ribavirin in the erythrocytes ascends, plasma concentrations of ribavirin descend. Ribavirin is metabolized by a process of deoxyribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Because of the non-plasma process of elimination, the plasma half-life of ribavirin appears to be prolonged and is ~300 hours when ribavirin is administered at conventional doses of 600mg twice daily.[158]

The labeled indications of ribavirin are chronic hepatitis C when used in combination with interferon alpha or pegylated interferon alpha. Ribavirin also has the labeled indication for respiratory syncytial virus. The dose of ribavirin is dependent upon a patient’s body weight. For individuals weighing > 75kg, the dose is 600mg administered orally twice daily. For individuals weighing less than 75 kg, the dose is 400mg in the morning and 600mg in the evening. Because of the strong effects on erythrocytes, ribavirin is contraindicated in patients with hemoglobinopathy, sickle cell disease and thalassemia. Patients who develop cirrhosis or fulminant hepatitis on ribavirin should discontinue therapy.[158]
The primary toxicity of ribavirin is anemia and occurs in 10-20% of patients. Ribavirin-associated anemia usually occurs within the first 1-2 weeks of initiating therapy. Fatal and non-fatal myocardial infarction and difficulty breathing have been reported in patients with ribavirin-induced anemia. The management strategy of anemia among patients taking ribavirin is to reduce the dose. Leukopenia, neutropenia, lymphopenia and thrombocytopenia are the next most common set of adverse reactions that occur with ribavirin. Their frequency varies and is usually most pronounced in patients that are on full dose ribavirin therapy that is used for prolonged durations.[158]

Direct Acting Antiviral Agents

There has been a renewed interest in developing effective therapies for patients with chronic HCV infection. Currently, there are over 17 compounds in pre-clinical and clinical development. In April 2011, two new agents, telaprevir and boceprevir, were approved for the treatment of genotype 1 HCV infection by the United States Food and Drug Administration. In December 2013, simeprevir and sofosbuvir were approved.

Telaprevir, simeprevir and boceprevir represent medications from a novel family of medications known as direct acting agents (DAA). Specifically, boceprevir and telaprevir belong to the NS3/4A serine protease inhibitor class of medications. Since the approval of these agents, the treatment approach for patients with HCV infection includes the use of pegylated interferon alpha, ribavirin and one of the two recently
approved NS3/4A serine protease inhibitors.[160, 161] The addition of the NS3/4A serine protease inhibitor to pegylated interferon alpha and ribavirin has been met with a dramatic improvement in the probability of achieving a SVR.

While these agents are a welcome addition to the armamentarium of drugs used to treat HCV infection, the use of triple drug therapy regimens is complex. Patients require intensive follow-up to determine the timing of when to initiate/discontinue certain medications in the regimen. For HCV-monoinfected patients, response-guided therapy (RGT) is utilized to determine the duration of therapy. The use of RGT involves obtaining HCVRNA at week 4 and 12 (telaprevir) or week 8 and 24 (boceprevir) to determine how long a patient will remain on therapy.[160, 161] The use of boceprevir and telaprevir are associated with a considerable number of adverse events and require appropriate detection and management strategies so that patients can finish the entire course of therapy. Both boceprevir and telaprevir require highly specific timing (every 7-9 hours) of drug administration and this can be problematic for patients with hectic lifestyles.[160, 161] Consumption of meals with at least 20 grams of fat further complicates drug administration for patients on telaprevir-based regimens.[161] Pill burden serves as another barrier to taking boceprevir and telaprevir-based antiviral regimens.[160, 161] Boceprevir requires ingestion of 12 capsules per day whereas telaprevir requires 6 tablets per day. Boceprevir and telaprevir are potent inhibitors of CYP3A4. As a result, there are several drug-drug interactions that are likely to occur with these DAAs. An important sub-group of individuals with HCV infection are those with HIV coinfection. Many of the DAAs interact with several ART agents. Patients with
HIV/HCV coinfection may need their ART regimens modified while receiving HCV therapy with a DAA.

**Boceprevir**

Boceprevir is indicated for the treatment of genotype 1 HCV infection in adult patients with compensated liver disease who are either treatment-naïve or partial/non-responders to interferon-based therapy. Boceprevir blocks the proteolytic activity of NS3/4A serine protease and prevents the conversion of HCV-encoded polyproteins to functional viral proteins.[160] The mechanism of resistance to boceprevir involves amino acid substitutions. These substitutions are associated with a 2 - >50 fold decrease in boceprevir activity against HCV in cell cultures. Among patients enrolled in the registrational studies who failed to achieve a sustained virologic response, amino acid substitutions that emerged on therapy were detected in 53% of these patients. These amino acid substitutions confer cross-resistance to other NS3/4A serine protease inhibitors, but no cross-resistance to interferon or ribavirin.[160]

Boceprevir for oral administration is mixture of two diastereomers, SCH534128 (active) and SCH534129 (inactive).[160] Administration of boceprevir with food is recommended to improve tolerability. However, the coadministration of boceprevir with food does not change the pharmacokinetic profile of boceprevir. Within the plasma, SCH534129 rapidly converted to an active metabolite. After absorption from
the intestines, the majority of boceprevir is bound plasma proteins. The elimination of boceprevir primarily involves metabolism by aldoketoreductase. It also undergoes slight metabolism by CYP3A4/5 and is a substrate for p-glycoprotein. Once metabolized, boceprevir is excreted primarily by the feces (79%). Less than 10% is excreted via the urine. The half-life for boceprevir is 3.4 hours.[160]

Because of the plasma half-life, boceprevir needs to be administered every 7-9 hours.[160] Boceprevir must be given in combination with pegylated interferon alpha and ribavirin. Boceprevir has a low genetic barrier to resistance and monotherapy with boceprevir is not recommended. Treatment regimens that include boceprevir for genotype 1 HCV infection depend on a patient’s previous history with HCV therapy. For patients without cirrhosis and are either treatment-naïve or previous partial response/relapse, a 4-week lead-in period with pegylated interferon alpha and ribavirin should precede therapy with boceprevir. After the 4-week lead-in period, boceprevir is added to the regimen and triple drug therapy should be taken. The duration of therapy varies as a function of the patient’s HCVRNA on weeks 8 and 24. For patients with an undetectable HCVRNA at both weeks 8 and 24, therapy can be discontinued at week 36 (4 weeks of lead-in, followed by 32 weeks of triple therapy). If HCVRNA is detectable at week 8 and undetectable at week 24, triple drug therapy should continue until week 36 and dual drug therapy with pegylated interferon alpha and ribavirin should be continued until week 48. Among patients with cirrhosis or non-cirrhotic patients who were a previous null responder to HCV therapy, a 4-week lead-in period with pegylated interferon alpha and ribavirin should precede triple therapy with boceprevir, pegylated
interferon alpha and ribavirin for 44 weeks. The total treatment duration for these individuals is 48 weeks.[160]

The most common adverse reactions associated with boceprevir therapy are hematologic and include anemia, neutropenia and thrombocytopenia. Other side effects of boceprevir are nausea, vomiting, diarrhea, dysgeusia, anorexia, and xerostomia. While constitutional symptoms have been reported, these are most likely a function of combination therapy with pegylated interferon alpha. The most important monitoring parameters for boceprevir include HCVRNA and complete blood count with differential.[160]

**Telaprevir**

Telaprevir is indicated for the treatment of genotype 1 HCV infection in adult patients with compensated liver disease who are either treatment-naïve or previous inadequate response to interferon-based therapy.[161] Telaprevir blocks the proteolytic activity of NS3/4A serine protease and prevents the conversion of HCV-encoded polyproteins to functional viral proteins (NS4A, NS4B, NS5A and NS5B). The mechanism of resistance to telaprevir is similar to boceprevir and involves amino acid substitutions on the NS3 domain. Among patients enrolled in the registrational studies who failed to achieve a sustained virologic response, amino acid substitutions that emerged on therapy were detected in 100% of these patients.[161]
After oral administration of telaprevir, 59—76% of telaprevir is absorbed into systemic circulation.[161] For optimal absorption, telaprevir should be coadministered with at least 20 grams of fat per dose. Telaprevir binds to protein in a concentration-dependent fashion. Protein binding is inversely related to telaprevir concentrations; protein binding decreases as telaprevir concentrations increase. The main proteins that telaprevir is bound to are alpha 1-acid glycoprotein and albumin. Telaprevir is eliminated through a series of reactions involving hydrolysis, oxidation, and reduction. All of these reactions occur in the liver. The primary hepatic enzyme involved metabolism of telaprevir is CYP3A4. Subsequent to metabolism in the liver, telaprevir is excreted through the feces (82%). Other minor routes of elimination include exhaled air (9%) and through the urine (1%). The steady-state half-life of telaprevir is 9-11 hours.[161]

Telaprevir must be given in combination with pegylated interferon alpha and ribavirin.[161] Telaprevir has a low genetic barrier to resistance and monotherapy with telaprevir is not recommended. Treatment regimens that include telaprevir for genotype 1 HCV infection depend on a patient’s previous history with HCV therapy. The HCVRNA results at weeks 4 and 12 are important for determine the duration of therapy. Among patients who do not have cirrhosis and are either treatment-naïve or a previous relapse on interferon alpha/ribavirin therapy, therapy with telaprevir, pegylated interferon alpha, and ribavirin should be administered for 12 weeks. If the HCVRNA at week 4 and 12 are undetectable, patients can discontinue telaprevir and use pegylated interferon alpha and ribavirin for an additional 12 weeks (total treatment duration of 24
weeks). If the week 4 and 12 HCVRNA are detectable but < 1000 IU/mL, patients can discontinue telaprevir and use pegylated interferon alpha and ribavirin for an additional 36 weeks (total treatment duration of 48 weeks). If the HCVRNA is > 1000 IU/mL at weeks 4 and 12, therapy should be discontinued. In patients without cirrhosis and are either previous partial or null responders, triple therapy with telaprevir, pegylated interferon alpha and ribavirin should be administered for 12 weeks, followed by 36 weeks of pegylated interferon alpha and ribavirin (48 weeks total). The same course of therapy should be administered in patients with cirrhosis.[161]

The most common adverse reactions associated with telaprevir are rash, which can occur in up to 50% of patients receiving telaprevir. Rashes were generally mild to moderate in nature and serious rashes were observed infrequently. Anemia is another toxicity of telaprevir and occurs in approximately one third of patients. Other hematologic reactions that occur with telaprevir are lymphopenia and leukopenia. A unique set of adverse reactions associated with telaprevir are anorectal reactions including itching, burning and discomfort. Nausea, vomiting, diarrhea and dysgeusia occur more frequently in patients receiving HCV treatment regimens that include telaprevir than in patients receiving HCV treatment regimens of pegylated interferon and ribavirin alone. The most important monitoring parameters for telaprevir include HCVRNA and complete blood count with differential.[161]
Combination therapy with pegylated interferon, ribavirin and NS3/4A protease inhibitors

There have been 5 studies evaluating the efficacy of NS3/4A protease inhibitors, telaprevir and boceprevir, in combination with pegylated interferon alpha-2a and ribavirin.[162-164] These studies have been performed in adult patients who are HCV-monoinfected. Studies examining the use of pegylated interferon, ribavirin and NS3/4A protease inhibitors among patients with HIV/HCV coinfection are still on-going and continue to be open to enrollment.

Treatment-Naïve Studies:

ADVANCE Trial

The purpose of the ADVANCE trial was to evaluate the safety and efficacy of response-guided telaprevir therapy.[162] The study design was a phase 3, randomized, double-blind, placebo-controlled trial among chronically infected HCV patients receiving. The study included patients with chronic genotype 1 HCV mono-infection, that were 18 – 70 years of age and had an absolute neutrophil count > 1500 cells/mm$^3$, platelets > 90,000 cells/mm$^3$, and hemoglobin ≥ 12 g/dL (males) and ≥ 13 g/dL (females). This study did not include patients with HIV or hepatitis B coinfection or patients with decompensated liver disease, liver disease from other causes and hepatocellular carcinoma. Block randomization was performed and stratified based on genotype (1a, 1b or unknown) and baseline viral load (HCVRNA < 800,000 IU/mL or HCVRNA ≥ 800,000 IU/mL). Patients
were randomized to one of three study arms: i) pegylated interferon alfa-2a and ribavirin for 48 weeks (PR), ii) telaprevir in combination with pegylated interferon alfa-2a and ribavirin for 12 weeks, followed by pegylated interferon alfa-2a and ribavirin alone for an additional 12 weeks if the patient’s week 4 and 12 HCVRNA was undetectable or an additional 36 weeks if the patient’s week 4 or 12 HCVRNA was detectable (T12PR), ii) telaprevir for 8 weeks followed by 4 weeks of placebo in combination with pegylated interferon alfa-2a and ribavirin (T8PR). Similar to the T12PR arm, pegylated interferon alfa-2a and ribavirin were continued for 12 or 36 weeks depending on the patient’s HCVRNA at week 4 and 12 of therapy. The primary endpoint of this study was sustained virologic response (SVR).[162]

More patients in the T12PR or T8PR group compared with the PR group had achieved a SVR (75% and 69%, respectively, vs. 44%; P<0.001 comparing T12PR or T8PR group with the PR group). Anemia, gastrointestinal side effects, and skin rashes occurred more frequently among patients randomized to receive telaprevir-based therapy than among those receiving peginterferon-ribavirin.[162]

**ILLUMINATE Study**

The ILLUMINATE study was an international, multicenter, phase III randomized non-inferiority trial to evaluate the utility with response-guided therapy (RGT) among patients receiving combination therapy with pegylated interferon alfa 2a (PegIFN), ribavirin (RBV) and telaprevir.[163] All patients received 12 weeks of triple combination
therapy, followed by 8 weeks of PegIFN and RBV. After 20 weeks of therapy, patients were divided into two groups, those that achieved an extended rapid virologic response (eRVR) and those that did not achieve an eRVR. Patients who did not achieve an eRVR continued therapy with PegIFN and RBV through 48 weeks of therapy. Patients who did achieve an eRVR were randomized, stratified by genotype 1 subtype and race, to continue therapy with PegIFN and ribavirin through 24 weeks of therapy or 48 weeks of therapy. The dose of PegIFN was 180 mcg/week. The dose of 1000-1200 mg/day.

Telaprevir was discontinued if the HCV RNA > 1000 IU/mL at week 4. Therapy with PegIFN and RBV was discontinued if the decline in HCV RNA from baseline was < 2 log_{10} at week 12 or if HCV RNA was detectable (≥ 10 IU/mL) between weeks 24 and 36.

Overall, the proportion of patients that achieved SVR was high and was achieved in 72% of study patients. Among patients that did not achieve eRVR (n = 118), SVR was observed in 64% of individuals. Among patients that achieved eRVR, SVR was similar between patients that completed 24 (n = 162) and 48 (n = 160) weeks of combination antiviral therapy, 92% versus 88%, respectively. A series of stratified analyses were performed among patients that achieved eRVR. There was no substantial heterogeneity by genotype (1a versus 1b), race (Caucasian, black and Asian/other) and liver histology (bridging fibrosis/cirrhosis versus none/minimal/portal fibrosis). Patients that had diabetes did appear to have slightly lower frequencies of SVR compared to patients without diabetes. Specifically, SVR was achieved in 75% and 80% of patients with diabetes that received therapy for 24 and 48 weeks, respectively. Among patients that without diabetes, SVR was achieved in 93% of patients that received therapy for 24 and
88% of patients that received therapy for 48 weeks. There was also a low frequency of relapse among randomized patients. Virologic failure was uncommon among patients that achieved an eRVR. Telaprevir-resistant variants were observed primarily in patients that did not achieve an undetectable HCV RNA. Among patients with telaprevir-resistant variants at the time of treatment failure, over half of these patients did not have these variants after a median of 43 weeks of follow-up.[163]

**SPRINT-2**

The SPRINT-2 study was an international, randomized, placebo-controlled, phase III clinical trial evaluating boceprevir in combination with PegIFN and ribavirin among treatment-naïve patients with genotype 1 chronic HCV infection.[164] Patients were stratified based on baseline HCV RNA and genotype subtype. Patients were randomized to one of three treatment arms: i) 4-week lead-in period with PegIFN and ribavirin, followed by 44 weeks of PegIFN, ribavirin and placebo (PR48), ii) 4-week lead-in period with PegIFN and ribavirin, followed by 44 weeks of PegIFN, ribavirin and boceprevir (B44PR48) and iii) response-guided therapy (RGT) arm. The RGT arm consisted of a 4-week lead-in period with PegIFN and ribavirin, followed by 24 weeks of PegIFN, ribavirin and boceprevir. If the HCVRNA was undetectable at week 8 and week 24 of therapy, RGT therapy was complete. If the HCVRNA was detectable at or after week 8 and undetectable at week 24, therapy with PegIFN and ribavirin was continued for an additional 24 weeks. The dose of PegIFN alfa 2b was 1.5 mcg/kg administered subcutaneously once weekly. Ribavirin was weight based between 600 – 1400 mg once
daily by mouth. The primary outcome of the study was sustained virologic response (SVR) at 24 weeks post-completion of therapy. The stopping rule for study therapy was detectable HCVRNA at week 24 of therapy and all treatment was stopped. Boceprevir was discontinued and PegIFN/ribavirin was continued through week 48 in cases of virologic breakthrough or incomplete virologic response and rebound. Virologic breakthrough was defined as HCV RNA undetectable during treatment, followed by HCV RNA > 1000 IU/mL. Incomplete virologic response and rebound was an HCV RNA increase ≥ 1 log_{10} IU/mL above nadir HCV RNA, with HCV RNA > 1000 IU/mL.

The results of the study were stratified by black race. In the intention-to-treat (ITT) analysis among the non-black cohort, the proportion of patients achieving SVR was significantly higher in the boceprevir-containing arms compared to the PR48 arm (p < 0.05). The frequency of SVR was 67%, 68%, and 40% among patients in the RGT (n = 316), B44PR48 (n = 311) and PR48 (n = 311), arms respectively. In the non-black cohort, heterogeneity was observed when the results were stratified by week 4 HCV RNA. In patients that achieved an undetectable HCV RNA at week 4, SVR response frequencies were 89%, 90% and 96% in patients in the RGT, B44PR48 and PR48 arms, respectively. Conversely, in patients that did not achieve an undetectable HCV RNA at week 4 of therapy, SVR was observed in 68%, 69% and 36% of patients in the RGT, B44PR48 and PR48 arms, respectively. In the intention-to-treat (ITT) analysis among the black cohort, the frequency of SVR was 42%, 53%, and 23% among patients in the RGT (n = 52), B44PR48 (n = 55) and PR48 (n = 52), arms respectively. In the black cohort, heterogeneity was observed when the results were stratified by week 4 HCV RNA. In
patients that achieved an undetectable HCV RNA at week 4, SVR response frequencies were 100%, 0% and 100% in patients in the RGT, B44PR48 and PR48 arms, respectively. Conversely, in patients that did not achieve an undetectable HCV RNA at week 4 of therapy, SVR was observed in 45%, 52% and 22% of patients in the RGT, B44PR48 and PR48 arms, respectively.

Among both black and non-black cohorts, 22% of patients in RGT arm had a detectable HCV RNA between weeks 8 and 24 and were assigned to receive 48 total weeks of therapy. The frequency of SVR in this subgroup that received 24 weeks of boceprevir and 48 weeks of PegIFN/RBV was comparable to group that received 44 weeks of boceprevir and 48 weeks of PegIFN/RBV (74% vs 74%). Overall, SVR rates were numerically higher with boceprevir-containing regimens versus PegIFN/RBV control arms across various subgroups.[164]

**Treatment-Experienced Studies**

**REALIZE**

The REALIZE study was an international, multicenter, randomized, double-blind, placebo-controlled phase III trial to evaluate the use of telaprevir in combination with PegIFN/RBV for patients who are treatment-experienced and previously failed therapy with PegIFN/RBV.[165] Patients were randomized in a 2:2:1 fashion and stratified by previous response and HCVRNA. The three arms of the study were: 1) telaprevir + PegIFN + RBV for 12 weeks, followed by 4 weeks of placebo + PegIFN/RBV and then 24
weeks of therapy with PegIFN and RBV (T12PR48 with lead-in), 2) Placebo + PegIFN/RBV for 4 weeks, followed by 12 weeks of therapy with telaprevir + PegIFN/RBV and then 24 weeks of PegIFN/RBV (T12PR48 with no lead-in) and 3) Placebo + PegIFN/RBV for 24 weeks, followed by 24 weeks of PegIFN/RBV (PR48). The outcome of interest was SVR.

Telaprevir therapy was discontinued (PegIFN/RBV continued through 48 weeks of therapy) if HCVRNA was > 100 IU/mL at weeks 4, 6, and 8 for patients in the no lead-in arm and at weeks 8, 10 and 12 for patients in the lead-in arm. Patients who stopped telaprevir therapy were considered to have virologic failure. PegIFN and RBV were discontinued if there was < 2-log decline in HCVRNA at completion of the telaprevir treatment phase (week 12 for patients in the no lead-in group and week 16 for patients in the lead-in group). Additionally, PegIFN/RBV were discontinued if HCVRNA was detectable at week 24 or 36 in any arm of the study. Patients with previous relapse and previous nonresponse who received telaprevir-containing regimens demonstrated early, robust virologic suppression that persisted through completion of treatment and 24-wk follow-up. The frequency of SVR was significantly higher with telaprevir-containing regimens compared to PegIFN/RBV across all treatment-failure populations and is displayed in Table 1. SVR rates with telaprevir-containing regimens higher among previous relapsers than nonresponders. PegIFN/RBV lead-in phase prior to telaprevir did not influence SVR frequencies in any patient group.[165]
The RESPOND-2 study was an international, multicenter, randomized, double-blind, placebo-controlled phase III trial among treatment-experienced HCV-infected patients. All patients were genotype 1 and previously failed therapy with PegIFN and RBV. The randomization procedure was stratified by HCV subtype and previous response. Eligible patients were randomized in a 2:2:1 fashion to one of three study arms: 1) 4-week lead-in period with PegIFN + RBV, followed by 44 weeks of PegIFN + RBV + placebo (PR48); 2) 4-week lead-in period with PegIFN + RBV, followed by 44 weeks of PegIFN + RBV + boceprevir 800 mg by mouth every 8 hours (B44PR48); and 3) response-guided therapy (BPR-RGT). The BPR-RGT study arm consisted of 4-week lead-in period with PegIFN + RBV, followed by therapy with PegIFN + RBV + boceprevir 800 mg by mouth every 8 hours. Patients’ HCV RNA values were assessed at week 8 (week 4 of triple therapy) and week 12 (week 8 of triple therapy). If HCV RNA was undetectable at weeks 8 and 12, therapy was discontinued at week 36 (week 32 of triple therapy). If the HCV RNA was detectable at week 8 and undetectable at week 12, therapy was continued until week 48 (week 44 of triple therapy). If the HCV RNA was detectable at weeks 8 and 12, the patient was considered a treatment failure and all treatment was stopped. Boceprevir was discontinued and PegIFN/RBV was continued through week 48 in cases of virologic breakthrough or incomplete virologic response and rebound. Virologic breakthrough was defined as an HCV RNA undetectable during treatment, followed by HCV RNA > 1000 IU/mL. Incomplete virologic response and rebound was
defined as an HCV RNA increase by $\geq 1 \log_{10} \text{IU/mL}$ above nadir, with HCV RNA $> 1000$ IU/mL.

Overall, the frequency of SVR was significantly higher among patients receiving boceprevir-containing regimens (59% for BPR-RGT and 66% for B44PR48) relative to patients in the PegIFN/RBV control arm (21%). These findings were independent of previous response. Proportions of SVR were higher among individuals who previously failed PegIFN/RBV therapy because of relapse versus patients who were previous non-responders. Response ($\geq 1 \log_{10} \text{IU/mL}$ decline in HCV RNA) to PegIFN/RBV during the lead-in period was 3-fold more frequent among patients receiving boceprevir-containing regimens than the control arm. Approximately 50% of patients receiving boceprevir-containing regimens received achieved an undetectable HCV RNA at week 8. Achievement of an undetectable HCV RNA was associated with a high rate of SVR among patients in all three study arms.

In all subgroups analyzed, proportions of SVR were numerically higher among recipients of boceprevir-containing regimens than patients in the control arm. The subgroups that were assessed were: race (black versus non-black); HCV subtype (1a versus 1b); HCV RNA ($\leq 800,000$ IU/mL versus $> 800,000$ IU/mL); and liver histology (no/minimal/portal fibrosis versus bridging fibrosis/cirrhosis versus cirrhosis). End of treatment response was markedly higher among patients that received boceprevir-containing regimens compared to PR48, 70% (BPR-RGT) vs 77% (B44PR48) vs 31% (PR48). Relapse was observed more frequently in the PR48 group (32%) than in the BPR-RGT (15%) and B44PR48 (12%). Virologic breakthrough or incomplete virologic response
was infrequent and observed in less than 10% of each study arms. In an exploratory, post-hoc analysis, slight differences in the frequencies of an undetectable HCV RNA at week 8 between the two boceprevir-containing regimens were driven by the presence of cirrhosis. Among patients with cirrhosis, undetectable HCV RNA at week 8 was observed in 18% of BPR RGT patients and 73% of B44PR48 patients. Among patients without cirrhosis, undetectable HCV RNA at week was observed in 50% of BPR RGT patients and 49% of B44PR48 patients.

Among the 98 patients receiving a boceprevir-containing regimen that did not achieve a SVR, boceprevir-resistance variants were identified in 44% of patients and were more common among patients who had a poor initial response to the PegIFN/RBV lead-in period (28-34%) versus patients with a robust response (6-9%). The PR48 group had the highest proportion of patients meeting the virologic criteria for stopping therapy at week 12, followed by BPR-RGT and B44PR48, 61%, 22% and 18%, respectively.

Adverse events were common across all treatment arms and occurred in over 95% of patients. The most common adverse events were anemia, dysguesia, dry skin, and rash. Each of these adverse events occurred at statistically significant frequencies among patients on boceprevir-containing regimens than patients in the control arm. Serious adverse events occurred more frequently among patients receiving boceprevir-containing regimens. There were a statistically higher proportion of patients in the B44PR48 arm that experienced serious adverse events than patients in the PR48 arm, 14% compared to 5%, p < 0.05, respectively. Similarly, adverse events leading to
discontinuation of study drugs was statistically higher among B44PR48 (12%) patients than PR48 patients (2%). Both boceprevir-containing regimens were associated with a higher frequency of adverse events leading to dose modification than patients in the PR48 arm.[166]
Drug Interactions

Adverse events are an important aspect of morbidity and mortality in the United States. Adverse events affect over 700,000 hospitalized patients each year.[167] At the individual level, adverse drug events are an important contributor to emergency department visits and hospitalizations. Among hospitalized individuals, patients who experience adverse drug events are hospitalized 8 – 12 days longer than patients who do not suffer adverse drug events, resulting in an excess cost of $16,000 – $24,000 per hospitalization.[168] Additionally, the risk of death is nearly twice as high among hospitalized patients that experience adverse drug events.

The use of > 4 medications is associated with an increased risk of adverse drug events. Among the most overlooked types of adverse drug events are drug-drug interactions. Within the hospital setting, drug-drug interactions can be observed in up to 37% of patients.[169] Over $5 billion is estimated to be spent on the management of drug-drug interactions in hospitalized settings.[170] Many of these drug-drug interactions are either preventable or manageable. In the outpatient setting, drug-drug interactions are more ubiquitous and may be associated with higher costs.[171] A common reason why drug-drug interactions are overlooked is that they are not obvious or easily identifiable.

Drug interactions can be categorized as either pharmacokinetic or pharmacodynamic.[172] Pharmacodynamic interactions are drug interactions that result
in an effect on the body.[172] Sometimes, synergy may be involved and the risk of these effects may be more pronounced than the risks present if either of the agents involved in the interaction are used individually. Conversely, pharmacodynamics drug-drug interactions can be antagonistic in nature where the effect of one medication is blunted by the presence of another medication. Other types of pharmacodynamics interactions include altered cellular transport and additivity. Pharmacokinetic drug-drug interactions involve the presence of one medication can result in changes in absorption, distribution, metabolism or excretion of another agent. Pharmacokinetic interactions are generally associated with a change in drug exposure-profile (concentration, area under the curve, etc.) within the body. Often times, these interactions intensify exposure to drugs that traditionally were not perceived to be toxic at lower concentrations. Changing the exposure-profile distorts the known distribution of toxicities.

The majority of pharmacokinetic drug-drug interactions occur at the point of metabolism. The liver is implicated in the metabolism of several medications. After uptake of orally administered from the gastrointestinal tract, medications enter the systemic circulation via the small intestine and portal vein. Many medications are passed through the portal circulatory system and to the liver. Within the liver, medications can take on one of two fates. They are either passed through the liver and back into systemic circulation (first pass effect) and will be metabolized by the liver upon second pass or excreted via non-hepatic means. Alternatively, drugs that do not undergo the first pass effect may undergo metabolism in the liver. This is where the majority of drug metabolism occurs.
Within the liver, medications can undergo phase I and/or phase II metabolic reactions to be metabolized into smaller particles that can be excreted from the body. Phase I metabolic reactions are those that involve reduction, oxidation or hydrolysis. Phase II metabolic reactions include sulfation, methylation, acetylation, conjugation and glucuronidation.

A common way that medications are metabolized is through the cytochrome (CYP) P450 isoenzyme system. The cytochrome P450 isoenzymes is a super-family of isoenzymes in the liver and small intestines. There have been 17 families of CYP enzymes with approximately 50 isoforms that have been identified in the human genome. The CYP isoenzyme system plays an important role in the metabolism of several chemicals that may either be endogenous or exogenous. Nearly 75% of commercially-available medications rely on CYP isoenzymes for metabolism and subsequent excretion. After being metabolized by the CYP450 isoenzymes, the medications and metabolites are excreted via the fecal-biliary route or by renal means. Mammalian CYP450 are bound to the endoplasmic reticulum and are membrane bound. The most common mammalian CYP isoenzymes are CYP3, CYP2C11 and CYP2E1.

In terms of metabolism of medications, the majority of medications that are processed by the CYP450 isoenzymes utilize CYP3A and CYP2D6. Medications can take on multiple roles within the CYP450 isoenzyme system. Some medications are substrates. This means that the medication will bind to the CYP450 isoenzyme. Other medications are CYP450 inhibitors. Medications that are CYP450 inhibitors block the
actions of CYP450 isoenzymes from exerting their effects. Medication substrates that are used in the presence of a CYP450 inhibitor are vulnerable to delayed or non-functional metabolism. As a result, the in vivo exposure to the substrate will be enhanced and there may be a subsequent pharmacodynamics effect where changes in medication effects (toxicity or pharmacologic action) can be observed. An example of a common inhibitor of CYP450 is ritonavir. When used in combination with an HIV protease inhibitor like lopinavir (substrate), ritonavir prevents CYP450 isoenzymes from metabolizing lopinavir and allows lopinavir concentrations to remain high for prolonged periods of time. This is a beneficial interaction that permits less frequent dosing of lopinavir when coadministered with ritonavir. Medications can also induce the CYP450 isoenzyme system. Medications that are CYP450 inducers hyperstimulate CYP450 isoenzymes to metabolize drugs with greater efficiency. When CYP450 inducers are used in the presence of a CYP450 substrates, the substrate may be vulnerable to diminished drug effect. This could be consequential when the substrate-bound medication is used for conditions that require a sufficient amount of drug exposure to exert a pharmacodynamics effect. A common example of a CYP450 inducer is the antimycobacterial drug rifampin. When rifampin is used in combination with an HIV protease inhibitor like atazanavir (CYP450 substrate), concentrations of atazanavir are decreased to the point where they are below the genetic barrier to HIV resistance. Prolonged use of atazanavir and rifampin can result in virologic failure and emergence of atazanavir-resistant strains of HIV.
Drug Interactions involving Boceprevir

The metabolism of boceprevir occurs via aldo-ketoreductase (AKR). Boceprevir has inhibitory effects on p-glycoprotein the cytochrome P450 (CYP) series of isoenzymes. Specifically, boceprevir is a strong inhibitor of CYP3A4/5. However, boceprevir is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Based on in vitro data, boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1.[160]

There are several medications that should not be coadministered with boceprevir. Medications that are contraindicated when coadministered with boceprevir are described in Table 2 and include medications from the following drug classes: alpha 1-adrenoreceptor antagonists, anticonvulsants, antimycobacterial agents, ergot derivatives, gastrointestinal motility agents, herbal products, select HMG-CoA reductase inhibitors, oral contraceptives, phosphodiesterase type 5 inhibitors used for pulmonary hypertension, neuroleptic agents, and sedative/hypnotic agents.[160]
**Drug Interactions involving Telaprevir**

Telaprevir is a strong inhibitor of the cytochrome P450 isoenzyme system. Specifically, it is a strong inhibitor of CYP3A. Additionally, telaprevir has inhibitory effects on p-glycoprotein, organic anion transporter (OAT) 1B1 and OAT2B1. Telaprevir is a substrate of CYP3A and p-glycoprotein.[161]

Due to its inhibitory properties on CYP3A, telaprevir is expected to increase the concentrations of several drugs that are substrates of the CYP3A isoenzymes and prevent their metabolism. As a result, patients may be at risk for adverse effects secondary to increased exposure to CYP3A substrates. Table 2 displays medications that should not be coadministered with telaprevir. Among these classes are alpha 1-adrenoreceptor antagonists, antimycobacterial agents, ergot derivatives, gastrointestinal motility agents, herbal products, select HMG-CoA reductase inhibitors (lovastatin & simvastatin), neuroleptic agents, phosphodiesterase type 5 inhibitors used for pulmonary hypertension, and sedative/hypnotic agents.[161]
Research Question and Specific Aims

The purpose of this dissertation is to evaluate the distribution of medication use among patients infected with HCV/HIV coinfection, quantify the prevalence of clinically significant drug-drug interactions and identify patients at greatest risk of experiencing a CSDDI. The aims and objectives of this dissertation are as follows:

Research Paper 1: Prevalence and predictors of important telaprevir drug Interactions among patients co-infected with hepatitis C and human immunodeficiency virus

Research Questions:

1) What is the prevalence of clinically significant drug-drug interactions (CSDDI) among HIV/HCV-coinfected patients upon initiation of PegIFN/RBV/telaprevir?

2) Which antiretroviral therapies are associated with the lowest risk of CSDDI involving PegIFN/RBV/telaprevir?

3) What are the risk factors for experiencing a contraindicated drug-drug interaction involving PegIFN/RBV/telaprevir?

Specific Aims:

Aim #1: Quantify the prevalence of CSDDI involving PegIFN/RBV/telaprevir among HIV/HCV-coinfected patients.

Aim #2: Determine predictors of developing a CSDDI when PegIFN/RBV/telaprevir are added to a patient’s medication profile.
**Aim #3:** Among patients receiving antiretroviral therapy, determine which classes of antiretroviral therapies are associated with the lowest risk of contraindicated drug-drug interactions involving PegIFN/RBV/telaprevir.

- **Hypotheses:** The prevalence of CSDDI in this population is high. Identifiable predictors of CSDDI exist. Patients using integrase strand transfer inhibitors have the lowest risk of CSDDI.
**Research Paper 2:** Prevalence and risk factors for clinically significant drug-drug interactions involving boceprevir-based hepatitis C therapy among Veterans’ Affairs patients co-infected with hepatitis C and human immunodeficiency virus

**Research Questions:**

1) How frequently do clinically-significant drug-drug interactions involving PegIFN/RBV/boceprevir occur among HIV/HCV coinfected Veterans’ Affairs patients?

2) What are the risk factors of clinically significant drug-drug interactions involving PegIFN/RBV/boceprevir among HIV/HCV coinfected Veterans’ Affairs patients?

**Specific Aims:**

- **Aim #1:** Quantify the prevalence of CSDDI involving PegIFN/RBV/boceprevir among HIV/HCV-coinfected Veterans’ Affairs patients.

- **Aim #2:** Identify predictors of contraindicated drug-drug interactions involving therapy with PegIFN/RBV/boceprevir among HIV/HCV coinfected Veterans’ Affairs patients.

- **Hypothesis:** The prevalence of CSDDI involving PegIFN/RBV/boceprevir is high among HIV/HCV coinfected patients. Identifiable predictors of CSDDI involving PegIFN/RBV/boceprevir exist.
Research Paper 3: Comprehensiveness of Drug Interaction Software Programs: A
Comparative Analysis of Programs to Identify Clinically Significant Drug-Drug
Interactions among HIV/HCV coinfected patients eligible to initiate Pegylated Interferon,
Ribavirin and Telaprevir

Research Question 3: Does the identification of clinically significant drug-drug
interactions involving PegIFN/RBV/telaprevir among HIV/HCV coinfected patients differ
between Lexi-Interact, Micromedex and Clinical Pharmacology software programs?

Specific Aims:

Aim #1: Evaluate the distribution of clinically significant drug-drug interactions
(CSDDI) detected by Lexi-Interact, Micromedex and Clinical Pharmacology software
programs.

Aim #2: Compare the sensitivity and specific of each drug interaction software
program.

Aim #3: Determine if any drug interaction software program independently is
associated with an increased probability of failing to capture a CSDDI.

Hypothesis: The distribution of CSDDI does not differ between various software
programs. Sensitivity and specific of each software program is not
heterogeneous. None of the software programs are independently associated
with an increased probability of failing to detect a CSDDI.
Research Questions and Resulting Manuscripts

Each research question will result in an original publication capable of being published in a peer-reviewed medical journal. All three manuscripts of the dissertation will evaluate HIV/HCV-coinfected patients that received care either at the Upstate Medical University or Veterans’ Affairs Medical Center in the Upstate New York Veterans’ Affairs Healthcare Administration (VISN-2) between January 1, 2000 and July 31, 2012.

The first manuscript will quantify the prevalence of clinically-significant drug-drug interactions (CSDDI) involving PegIFN/RBV/telaprevir therapy among HIV/HCV-coinfected patients. Additionally, the study will identify antiretroviral therapy (ART) regimens associated with the lowest risk of drug-drug interactions with PegIFN/RBV/telaprevir. This will provide important data for clinicians who are considering prescribing telaprevir therapy and determine if a given patient is at high risk for a clinical significant drug-drug interaction.

The second manuscript will focus on the use of boceprevir-containing HCV treatment regimens. This manuscript will determine the frequency of CSDDI involving boceprevir. Recently, the hepatitis C treatment guidelines were updated and advocate the use of sofosbuvir and simeprevir. Despite the availability of simeprevir and sofosbuvir, their availability and uptake into foreign markets will be a slow transition. Patients with HIV/HCV infection seeking care in developing countries may still rely on treatment with boceprevir.
The third manuscript will compare the ability of three commercially available software programs used to comprehensively identify clinically-significant drug-drug interactions involving telaprevir-containing therapy. Drug interaction software is highly utilized in a variety of healthcare settings by clinicians. Each piece of software differs significantly in their subscription price and computer search algorithm to identify clinically significant drug-drug interactions. The sensitivity/specificity of each program has not been quantified and it is unclear which software program is most robust for the HIV/HCV co-infected population, particularly among those initiating HCV therapy. The manuscript will have the greatest impact on healthcare institutions with a high census of HIV/HCV coinfected patients initiating HCV therapy.
CHAPTER 2: METHODS

Project #1

Title

Prevalence and predictors of important telaprevir drug interactions among patients co-infected with hepatitis C and human immunodeficiency virus

Introduction

Direct acting treatment modalities for chronic hepatitis C have dramatically increased the rate of sustain virologic response (SVR).[162-164, 166, 173-175] Non-structural protein 3/4 (NS3/4A) serine protease inhibitors represent the first available class of direct acting hepatitis C virus (HCV) agents and treatment guidelines have incorporated these therapies into the standard HCV treatment regimen among patients infected with genotype 1 virus.[148]

Despite the availability of direct acting agents, use of these medications introduces increased drug toxicity risks and drug cost.[176] Drug-drug interactions represent another important concern since the currently available NS3/4A protease inhibitors boceprevir, telaprevir, and simeprevir affect cytochrome P450 metabolism and p-glycoprotein transporters.[177] Numerous proven and theoretical pharmacokinetic drug interactions have been associated with these agents and careful consideration for drug interaction presence and management is necessary.[178]
Patients co-infected with Human Immunodeficiency Virus (HIV) and HCV are likely to have an even greater risk for drug-drug interactions when receiving therapy with NS3/4A protease inhibitors. HIV/HCV co-infected patients must remain on antiretroviral therapy during HCV treatment to optimize HCV treatment outcomes and sustain HIV virologic suppression. Numerous drug interactions have been documented between antiretrovirals and NS3/4A protease inhibitors.[179] Despite this information, there are currently limited data to describe the prevalence, risk factors, and feasibility of co-administration of NS3/4A protease inhibitors with antiretroviral agents in HIV/HCV co-infected patients.

Given this gap in the literature, the primary objective of this study was to quantify the prevalence of clinically significant drug-drug interactions (CSDDI) in HIV/HCV co-infected patients if HCV therapy that includes telaprevir is added to patients’ medication regimens. As a secondary objective, we were interested in identifying which ART regimens are associated with the lowest risk of CSDDI involving telaprevir. Given the increased use of non-ART medications for other comorbidities among HIV patients, we also wanted to determine the clinical risk factors that are associated with a higher probability of a contraindicated medication combination involving telaprevir.

For this study, we chose to focus on telaprevir over boceprevir and simeprevir because of clear contradictions to co-administration with primary ART agents.[160, 161, 180] Based on these data, telaprevir appears to be among the more viable NS3/4A
protease inhibitor for treating patients who are HIV/HCV coinfected and receiving concomitant antiretroviral therapy to manage their HIV infection.

Research Design and Methods

Study Design and Population

A cross-sectional study of patients coinfected with HCV and HIV was performed at the Upstate New York Veterans’ Healthcare Administration (VISN-2) and Upstate University Hospital (Syracuse, NY). Patients receiving care between at these institutions between January 1, 2000 and July 31, 2012 and infected with both HCV and HIV were eligible for inclusion. Inclusion criteria were: 1) age ≥ 18 years 2) documented HIV infection and 3) laboratory-confirmed diagnosis of HCV infection. Patients with less than 45 progress notes and no medication history were excluded from the analyses.

Data Collection

Trained reviewers extracted information from the patients’ medical records on demographics, comorbidities, social history and medication lists. Demographic covariates included age, year of HCV and HIV diagnosis, sex, race, height, and weight. Episodic illnesses such as oropharangeal candidiasis, pneumonia, and various other opportunistic infections were not considered comorbid conditions.
Laboratory data included the most recent CD4 cell count, HIV-RNA and HCV-RNA. Because of the non-parametric distributions of HIV-RNA and HCV-RNA, both of these variables were log-transformed to assess them as a continuous variable. For patients with an undetectable HIV-RNA or HCV-RNA, the next digit below the threshold of detection was imputed before log-transformation to a continuous variable. For instance, a value of 49 would be imputed for a patient with an undetectable HIV RNA (< 50 copies/mL).

The drug name, dose, strength and frequency were abstracted from the most recent outpatient medication list.

**Outcome**

The primary outcome of this study was the prevalence of CSDDIs between the medications in the patient’s profile and the addition of telaprevir-based HCV therapy. Telaprevir-based HCV therapy was defined as telaprevir, pegylated interferon alpha (PegIFN) and ribavirin.

For each patient, CSDDI were identified by entering all medications into Lexi-Interact drug interaction software. Once their medication profile was added, the number and nature of CSDDI were recorded. Subsequently, telaprevir-based HCV therapy was added to the medication profile in Lexi-Interact to assess the potential for a CSDDI and the number and nature of CSDDI were recorded. For the purposes of these analyses, CSDDI were those that Lexi-Interact ranked as D- (interactions requiring
enhanced monitoring or dosage modification) or X-rated (contra
ingicated interactions).\[181\]

For both outcomes (D/X-rated and X-rated interactions), the output from Lexi-
Interact was cross-matched with the current prescribing information for telaprevir
(Incivek\textsuperscript{\textregistered}).\[161\] If new drug-drug interaction data emerged during the study period,
these data were included in the drug interaction analysis.

\textbf{Data Analysis Plan}

Categorical variables were compared by the $\chi^2$ or Fisher’s exact test. Continuous
variables were evaluated using the Student’s T or Mann-Whitney U test. McNemar’s test
was used to assess the frequency of drug-drug interactions because the data is
inherently matched (before/after adding telaprevir therapy). Breakpoints in the
distribution of continuous variables were determined using classification and regression
tree (CART) analysis.\[182\]

All variables associated with the outcomes of interest in the bivariate analysis
($p<0.2$) were considered for inclusion in the multivariate regression model.
Multiplicative effect measure modification was assessed through the use of interaction
terms. Due to the high proportion ($>10\%$) of patients who were expected to achieve the
outcome, a log-binomial regression with robust variance estimates was utilized.\[183\] A
backwards stepwise approach was used to derive the most parsimonious model. Variables remained in the final model if the associated p-value was less than 0.05. All calculations were computed using SPSS version 11.5 (SPSS Inc., Chicago, IL), SAS version 9.3 (SAS Institute, Cary, NC) and CART software (Salford Systems, San Diego, CA).

**Sample Size Justification**

Assuming a type I error frequency of 5% and 80% power, a minimum of 234 patients were required to detect an effect size of 20% for the specified outcome.
Project #2

Title

Predicting the probability of experiencing clinically significant drug-drug interactions involving boceprevir-containing hepatitis C therapy among patients co-infected with hepatitis C and human immunodeficiency virus

Introduction

Worldwide, there are 150 million individuals infected with chronic hepatitis C (HCV) infection.[184] Among these individuals, a significant proportion are also co-infected with human immunodeficiency virus (HIV). Co-infection with HIV is problematic for HCV-infected patients because of accelerated liver disease progression and early mortality.[185] The landscape of medication used to treat HCV infection is evolving rapidly. Prior to 2011, the standard of care was the use of pegylated interferon (PegIFN) and ribavirin (RBV), had only been marginally effective and only a third of HIV/HCV coinfected patients treated with PegIFN and RBV are able to achieve an undetectable HCV viral load 6 months after discontinuation of therapy (sustained virologic response, SVR).[142, 144] The availability of first-generation non-structural protein 3/4A (NS3/4A) serine protease inhibitors, such as boceprevir, significantly enhanced the probability of achieving a SVR when used in combination with PegIFN and RBV.[160] Nearly two thirds of HCV-infected patients were able to achieve a SVR on therapy that includes a NS3/4A protease inhibitor.[164] Achieving a SVR is of critical importance in patients with HIV/HCV co-infection and can prevent several deleterious outcomes (death,
hepatocellular carcinoma, need for liver transplant, etc) associated with HCV infection. Most recently, simeprevir and sofosbuvir became available and were incorporated into the treatment guidelines. Despite the availability of simeprevir and sofosbuvir, their availability and uptake into foreign markets will be a slow transition. Patients with HIV/HCV infection seeking care in developing countries may still rely on treatment with boceprevir.

Despite the availability of NS3/4A protease inhibitors, like boceprevir and telaprevir, their use has been hampered by cost/reimbursement, toxicity and risk of drug-drug interactions. Of the three, the perceived potential for drug-drug interactions has been a major deterrent for avoiding using NS3/4A protease inhibitors among co-infected patients. While drug-drug interactions are a significant concern, the risk depends on multiple clinical factors like polypharmacy, and usage and type of ART regimens patients are receiving. An understanding of these factors on the probability of drug-drug interactions will help clinicians identify which patients require more intensive medication management.

The objectives of this study were two-fold. The first objective was to quantify the prevalence of clinically significant drug-drug interactions (CSDDI) when boceprevir-containing HCV therapy is added to patients’ medication profiles. The second objective of this study was to determine the clinical risk factors associated with an increased probability of contraindicated drug-drug interactions. Our study focused on boceprevir over telaprevir and simeprevir because it has gained licensure in a significant number of developing countries where HCV infection is problematic.
Research Methods

A cross-sectional study was performed among Veterans’ Affairs Medical Center (VAMC) patients between January 1, 2000 and July 31, 2011. Patients from the VAMC that were included in this study were from the Upstate New York Veterans’ Healthcare Administration (VISN-2). Inclusion criteria for this study were: 1) age ≥ 18 years, 2) documented HIV-infection and 3) laboratory-confirmed diagnosis of HCV infection. Patients with no medication history were excluded.

Data Collection

Data that were extracted from the patients’ medical records included demographics, comorbidities, social history and medications lists. Age, year of HCV diagnosis, year of HIV diagnosis, sex, race, height, and weight were the demographic characteristics that were collected. The patient’s entire list of comorbidities was documented. Transient conditions such as thrush, pneumonia, and other opportunistic infections were not considered as comorbid conditions.

Where available, the most recent CD4 cell count, HIVRNA and HCVRNA were obtained from the laboratory reports. To assess HIV-RNA and HCV-RNA as a continuous variable, these variables were log-transformed.
The latest medication list from the patient’s medical records was utilized in this study. The drug name, dose, strength and frequency were collected. In situations where the patient’s most recent medication list was during an inpatient admission, the most recent outpatient medication list was utilized.

**Outcome**

The outcomes of interest in this study were the presence of i) clinically-significant drug-drug interactions (CSDDI) and ii) contraindicated drug-drug interactions. Drug-drug interactions were identified by Lexi-Interact drug interaction software. The rating system in Lexi-Interact was used to define which drug-drug interactions were considered clinically-significant and contraindicated. Interactions rated by Lexi-interact with a level D- or X- severity rating were considered clinically significant. Drug-drug interactions rated by Lexi-Interact as X-rated were considered contraindicated drug-drug interactions.

The patients’ medication lists were entered into Lexi-Interact and D- and X-rated interactions were documented. To determine the effect of boceprevir-containing HCV therapy on the excess risk of CSDDI and contraindicated drug-drug interactions, boceprevir, pegylated interferon alpha and ribavirin were added to the patients’ medications lists in Lexi-Interact and reanalyzed. All D- and X-rated interactions were documented.

Interactions were evaluated by a clinical pharmacist and categorized according to their management strategies: 1) contraindicated drug-drug interactions or
medications that should never be coadministered, 2) interactions requiring dosage adjustment of one or both agents and 3) interactions requiring no intervention or increased clinical/laboratory monitoring.

Data Analysis Plan

For the bivariate analyses comparing each clinical covariate with CSDDI and contraindicated drug-drug interactions, categorical variables were compared by the Chi-squared or Fisher’s exact test. Continuous variables were evaluated using the Student’s T or Mann-Whitney U test. Classification and regression tree (CART) analysis was used to identify breakpoints in continuous variables. For the comparison of frequency of CSDDI or contraindicated drug-drug interactions before and after addition of boceprevir-containing HCV therapy, McNemar’s test was used. Variables in the bivariate analyses that were associated (p < 0.2) with contraindicated drug-drug interactions were considered for inclusion in the hierarchically well-defined explanatory multivariate regression model. Interaction terms were used to assess multiplicativity. Because a high proportion (> 10%) of patients were expected to have contraindicated drug-drug interactions, this study utilized log-binomial regression with robust variance estimates.[183] The most parsimonious model was derived by a backwards stepwise approach. The only variables that were retained in the final model were those with a p-value less than 0.05. All calculations were computed using SPSS version 11.5 (SPSS inc., Chicago, IL), SAS version 9.3 (Cary, NC) and CART software (Salford Systems, San Diego, CA).
Sample Size

Assuming a type I error frequency of 5% and 80% power, a minimum of 234 patients were required to detect an effect size of 20% in the primary outcome (difference in proportion of subjects with a CSDDI between any two predictor variables).
Introduction

Adverse events are an important aspect of morbidity and mortality in the United States.[188] At the individual level, adverse drug events are an important contributor to emergency department visits and hospitalizations.[189, 190] The use of > 4 medications is associated with an increased risk of adverse drug events.[191] Among the most overlooked types of adverse drug events are drug-drug interactions.[192, 193] Within the hospital setting, drug-drug interactions can be observed in up to 37% of patients.[194] Many of these drug-drug interactions are either preventable or manageable. In the outpatient setting, drug-drug interactions are more ubiquitous and may be associated with higher costs.[195] A common reason why drug-drug interactions may be overlooked is that they are not obvious or easily identifiable.

The availability of computer software programs to screen patients’ medication profiles has significantly improved the ability to detect drug-drug interactions. However, there are several commercially-available software programs available to screen drug-drug interactions. These characteristics of these software programs vary considerably.[196] Most notably, each software program uses its own search algorithm
and ranks the severity of drug-drug interactions differently. These variations can cause one software program to flag coadministration of two drugs as dangerous whereas another program may not even identify coadministration of the same two drugs as problematic. This is important for patient safety because clinicians rely on these software programs to identify clinically significant drug-drug interactions.

One population that is particularly vulnerable to drug-drug interactions are patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection and considering initiating HCV therapy. Drug-drug interactions are most likely to occur when new medications are added to patients’ medication profiles. For patients with HIV/HCV co-infection, one treatment modality includes the use of pegylated interferon alpha, ribavirin and telaprevir. Telaprevir is strong inhibitor of CYP3A and associated with a significant number of drug-drug interactions. Patients with HIV infection are already at an increased risk of drug-drug interactions because of the metabolic pathways of antiretroviral therapy (ART) used to manage HIV disease and the high numbers of other medications to control other comorbidities.

The goal of our study was to compare commercially available software programs used to screen patients’ medication profiles for drug-drug interactions among HIV/HCV coinfected patients if they were to initiate telaprevir-based HCV therapy. The objectives of this study were to i) compare the distribution of clinically significant drug-drug interactions (CSDDI) detected by Lexi-Interact, Micromedex and Clinical Pharmacology software programs, ii) quantify the sensitivity and specificity of each software program,
and iii) determine if any of the software programs are independently associated with an increased probability of failing to capture a CSDDI or “near misses”.

Research Design and Methods

Data were obtained from a cross-sectional performed among patients coinfected with HIV and HCV receiving care between January 1, 2000 and July 31, 2011. Patients were derived from two sources: i) Veterans’ Affairs patients and ii) patients from Upstate Medical University. Inclusion criteria are: 1) age ≥ 18 years, 2) laboratory-confirmed diagnosis of HCV infection and 3) documented HIV infection.

Data Collection

The following data elements were recorded from the patients’ medical records: demographics, list of comorbidities, targeted laboratory values (most recent CD4 count, HIV RNA and HCV RNA), and medication list. The most recent outpatient medication list from the patient’s medical records was utilized in these analyses. The drug name, dose, strength and frequency were recorded for each medication in the medication profile.

Identification of Drug-Drug Interactions and Outcomes

The exposure of interest in this study was each of the commercially-available software programs used to identify drug-drug interactions among patients with HIV/HCV coinfection initiating therapy with telaprevir-containing HCV treatment
regimen. The three specific drug interaction software programs that were compared were i) Lexi-Interact, ii) Micromedex and iii) Clinical Pharmacology.

The outcome of interest in this study was the occurrence of clinically significant drug-drug interactions (CSDDI). For each patient, medication lists plus telaprevir-containing HCV therapy were entered into each of the software programs and CSDDI were recorded. Telaprevir-containing HCV therapy was defined as pegylated interferon alpha, ribavirin and telaprevir. The purpose of adding telaprevir-containing HCV therapy to the patients’ medication profile was to simulate the type of pharmacist decision making that would occur when new medications are initiated in patients at high risk for experiencing the effects of a clinically-significant drug-drug interaction. For Lexi-Interact, clinical significance was defined as drug-drug interactions that were classified as either D- or X-rated. For Micromedex, clinical significance was defined as drug-drug interactions that were ranked as “Major” or “Contraindicated.” For Clinical Pharmacology, clinical significance was defined as drug-drug interactions that were ranked as “1” or “2”.

The CSDDI identified by the three software programs were cross-matched with the current prescribing information for telaprevir (Incivek®). If new drug-drug interaction data became available, these data were also included in the analyses of CSDDI.
Adjudication of Drug-Drug Interactions by an Expert Panel of Clinical Pharmacists

An expert panel of 3 clinical pharmacists was assembled to adjudicate drug-drug interactions. All clinical pharmacists had completed residency training and had significant and diverse clinical experience working with patient populations at high risk for polypharmacy and drug-drug interactions.

For each patient, the panelists were provided a 1) medication list and 2) list and nature of CSDDI identified by the three software programs. The panelists were blinded to the software programs from which the lists of interactions were derived. Panelists were asked to identify which interactions they considered clinically-significant. Among the interactions deemed clinically-significant, panelists were asked to describe the intensity of clinical intervention. Clinical interventions were categorized as: 1) avoid medication coadministration, 2) alter dosage of at least one medication and 3) increased clinical or laboratory monitoring. In situations where there was discordance, majority was used to determine whether a specific interaction was clinically-significant. If there was disagreement between panelists on the intensity of clinical intervention, the panelists were reconvened to achieve consensus.

This study also examined if any of the software programs were associated with an increased probability of failing to capture a CSDDI, otherwise known as near misses. Near misses were defined as CSDDI that were captured by the expert panel but not identified by any one of the software programs.
Data Analysis Plan

Descriptive statistics were used to evaluate the distribution of CSDDI. The occurrence and distribution of drug-drug interactions between the three software programs were compared using the paired T-test and Wilcoxon signed rank test.

For each software program, sensitivity and specificity was computed and the interactions identified by the expert panel was considered the gold standard. Sensitivity was defined as the number of CSDDI that were correctly identified by both the software program and expert panel divided by the number of CSDDI identified by the expert panel. Specificity was defined as the number non-interactions that were correctly classified by both the software program and expert panel divided by the total number of non-interactions identified by the expert panel. Sensitivity and specificity were compared using McNemar’s test.

Bivariate analyses comparing the clinical covariates associated with failure to capture a CSDDI (near misses) were performed using Chi-square or Fisher’s exact test for categorical variables and Student’s T or Mann Whitney U test for continuous variables. Conditional multivariate regression analyses were performed to determine if any of the software programs was independently associated with near misses. All variables associated (p < 0.2) with near misses and present in ≥ 5% of the study population was entered into the multivariate regression model and considered as a potential confounder. If the resulting conditional odds ratio for software program did not change more than 10%, the variable was removed from the model and not considered a potential confounder. The process was repeated until all potential confounders had
been assessed and the most parsimonious model with a sufficient subset of confounders had been identified. Multiplicativity was evaluated in the regression model through the use of interaction terms.

CHAPTER 3: MANUSCRIPT #1

Prevalence and predictors of important telaprevir drug interactions among patients co-infected with hepatitis C and human immunodeficiency virus

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Presentation: Data not presented elsewhere.
ABSTRACT

Background:
Among patients with HIV and hepatitis C (HCV) co-infection, drug-drug interactions involving non-structural protein 3/4 (NS3/4A) serine protease inhibitors for HCV infection are an important concern because these drugs affect cytochrome P450 metabolism and p-glycoprotein transporters.

Objectives:
The primary objective was to determine the prevalence of clinically significant drug-drug interactions (CSDDI) in HIV/HCV co-infected patients if telaprevir-based HCV therapy is added to patients’ medication regimens. Secondary objectives were to identify antiretroviral therapy (ART) regimens associated with the lowest risk of CSDDI and determine the clinical risk factors.

Methods:
A cross-sectional study was performed among adult HIV/HCV co-infected patients. Demographics, comorbidities, social history and medication lists were extracted from medical records. For each patient, CSDDI were identified by entering all medications and pegylated interferon, ribavirin and telaprevir into Lexi-Interact drug interaction software. The number and nature of CSDDI were recorded before and after addition of telaprevir-based therapy.
Results:

There were 335 patients included. Prior to the addition of telaprevir-based HCV therapy, there was a high frequency (82.1%) of any CSDDI. After the addition of telaprevir-based HCV therapy, the frequency of any CSDDI increased to 97% (p < 0.001). Contraindicated interactions rose from 20.0% to 38.2% patients after addition of telaprevir-based therapy. Use of ≥ 10 non-HIV medications, dyslipidemia and protease inhibitors were independently associated with the occurrence of a contraindicated interactions.

Conclusions:

Clinicians considering initiating telaprevir in HIV/HCV co-infected patients should be vigilant of drug-drug interactions, particularly among patients with dyslipidemia, those using ≥ 10 non-HIV medications, and those using protease inhibitors.
INTRODUCTION

Direct acting treatment modalities for chronic hepatitis C have dramatically increased the frequency of sustained virologic response (SVR).[162-164, 166, 173-175] Non-structural protein 3/4 (NS3/4A) serine protease inhibitors represent the first available class of direct acting hepatitis C virus (HCV) agents and treatment guidelines have incorporated these therapies into the standard HCV treatment regimen among patients infected with genotype 1 virus.[148]

Despite the availability of direct acting agents, use of these medications introduces increased drug toxicity risks and drug cost.[176] Drug-drug interactions represent another important concern since the currently available NS3/4A protease inhibitors, boceprevir, telaprevir, and simeprevir, affect cytochrome P450 metabolism and p-glycoprotein transporters.[177] Numerous proven and theoretical pharmacokinetic drug interactions have been associated with these agents and careful consideration for drug interaction presence and management is necessary.[178]

Patients co-infected with Human Immunodeficiency Virus (HIV) and HCV are likely to have an even greater risk for drug-drug interactions when receiving therapy with NS3/44A protease inhibitors. HIV/HCV co-infected patients must remain on antiretroviral therapy during HCV treatment to optimize HCV treatment outcomes and sustain HIV virologic suppression. Numerous drug interactions have been documented between antiretrovirals and NS3/4A protease inhibitors and there are only a select number of antiretrovirals that can be coadministered with these agents.[179] Despite this information, there are currently limited data to describe the prevalence, risk
factors, and feasibility of co-administration of NS3/4A protease inhibitors with antiretroviral agents in HIV/HCV co-infected patients.

Given this gap in the literature, the primary objective of this study was to determine the prevalence of clinically significant drug-drug interactions (CSDDI) in HIV/HCV co-infected patients if telaprevir-based HCV therapy is added to patients’ medication regimens. As a secondary objective, we were interested in quantifying which ART regimens are associated with the lowest risk of CSDDI involving telaprevir. Giving the increased use of non-ART medications for other comorbidities among HIV patients, we also wanted to determine the clinical risk factors that are associated with a higher probability of a contraindicated medication combination involving telaprevir.

For this study, we chose to focus on telaprevir over boceprevir and simeprevir because of clear contradictions to co-administration with primary ART agents.[160, 161, 180] Based on these data, telaprevir appears to be among the more viable NS3/4A protease inhibitor for treating patients who are HIV/HCV co-infected and receiving concomitant antiretroviral therapy to manage their HIV infection.
METHODS

Study Design and Population

A cross-sectional study of patients co-infected with HCV and HIV was performed at the Upstate New York Veterans’ Healthcare Administration (VISN-2) and Upstate University Hospital (Syracuse, NY). Patients receiving care at these institutions between January 1, 2000 and July 31, 2012 and infected with both HCV and HIV were eligible for inclusion. Inclusion criteria were: 1) age ≥ 18 years 2) documented HIV infection and 3) laboratory-confirmed diagnosis of HCV infection. Patients with no medication history were excluded from the analyses.

Data Collection:

Trained reviewers extracted information from the patients’ medical records on demographics, comorbidities, social history and medication lists. Demographic covariates included age, year of HCV and HIV diagnosis, sex, race, height, and weight. Episodic illnesses such as oropharangeal candidiasis, pneumonia, and various other opportunistic infections were not considered comorbid conditions.

Laboratory data included the most recent CD4 cell count, HIV-RNA and HCV-RNA. Because of the non-parametric distributions of HIV-RNA and HCV-RNA, both of these variables were log-transformed to assess them as a continuous variable. For patients with an undetectable HIV-RNA or HCV-RNA, the next digit below the threshold of detection was imputed before log-transformation to a continuous variable. For instance,
a value of 49 would be imputed for a patient with an undetectable HIV RNA (< 50 copies/mL).

The drug name, dose, strength and frequency were abstracted from the most recent outpatient medication list.

**Outcome Assessment**

The primary outcome of this study was the prevalence of CSDDIs between the medications in the patient’s profile and the addition of telaprevir-based HCV therapy. Telaprevir-based HCV therapy was defined as telaprevir, pegylated interferon alpha (PegIFN) and ribavirin.

For each patient, CSDDI were identified by entering all medications into Lexi-Interact drug interaction software. Once their medication profile was added, the number and nature of CSDDI were recorded. Subsequently, telaprevir-based HCV therapy was added to the medication profile in Lexi-Interact to assess the potential for a CSDDI and the number and nature of CSDDI were recorded. For the purposes of these analyses, CSDDI were those that Lexi-Interact ranked as D- (interactions requiring enhanced monitoring or dosage modification) or X-rated (contraindicated interactions).[181]

For both outcomes (D/X-rated and X-rated interactions), the output from Lexi-Interact was cross-matched with the current prescribing information for telaprevir
(Incivek®).[161] If new drug-drug interaction data emerged during the study period, these data were included in the drug interaction analysis.

Statistical Analyses

Categorical variables were compared by the $X^2$ or Fisher’s exact test. Continuous variables were evaluated using the Student’s T or Mann-Whitney U test. McNemar’s test was used to assess the frequency of drug-drug interactions because the data is inherently matched (before/after adding telaprevir therapy). Breakpoints in the distribution of continuous variables were determined using classification tree (CART) analysis.[182]

All variables associated with the outcomes of interest in the bivariate analysis ($p<0.2$) were considered for inclusion in the multivariate regression model. Multiplicative effect measure modification was assessed through the use of interaction terms. Due to the high proportion (> 10%) of patients who were expected to achieve the outcome, a log-binomial regression with robust variance estimates was utilized.[183] A backwards stepwise approach was used to derive the most parsimonious model. Variables remained in the final model if the associated p-value was less than 0.05. Once the final model was derived, potential confounders were put back into the model and only retained if their presence changed the resulting prevalence ratios by more than 10%. All calculations were computed using SPSS version 11.5 (SPSS Inc., Chicago, IL), SAS version 9.3 (SAS Institute, Cary, NC) and CART software (Salford Systems, San Diego, CA).
Sample Size Justification

Assuming a type I error frequency of 5% and 80% power, a minimum of 234 patients were required to detect an effect size of 20% for the specified outcome.

Ethics

This study was approved by Institutional Review Boards at the Stratton Veterans’ Affairs Medical Center (Albany, NY) and Upstate University Hospital (Syracuse, NY).

Given the retrospective nature of the study, a waiver of consent was obtained.
RESULTS

There were 4,794 adult Veterans’ Affairs patients with laboratory-confirmed HCV during the study period. Of these, only 250 patients were coinfected with HIV/HCV. Among these patients, 6 did not have medication histories available and were excluded, leaving 244 patients from the VAMC eligible for analysis. An additional 91 patients from Upstate Medical University satisfied inclusion criteria. The final analysis included a total of 335 HIV/HCV coinfected patients.

The majority of patients were male (87.2%), and disproportionately distributed by study site: 239 (98.0%) males from the VAMC study site and 53 (58.2%) males from Upstate University Hospital, p < 0.001. The mean (SD) age of patients was 55.6 (7.3) years. The median (IQR) durations of HIV and HCV infections for these patients were 18 (13 – 23) and 13 (10 – 17) years, respectively. The patients had a median (IQR) of 8 (6 – 12) underlying comorbidities. The patients were using a mean (SD) of 11.2 (4.9) medications. There were 306 (91.3%) patients receiving combination antiretroviral therapy (ART). The most commonly used ART regimen types were comprised of 2 nucleoside reverse transcriptase inhibitors (NRTI) plus a: non-nucleoside reverse transcriptase inhibitor (NNRTI) (39.9%), protease inhibitor (PI) (38.6%), mixed/multiple class ART regimen (17.0%) and integrase strand transfer inhibitor (ISTI) (4.6%). Antidepressants (30.7%) and central nervous system (CNS) depressants (47.8%) were the most frequently used non-HIV drug classes.

The distribution and nature of CSDDIs are displayed in Figure 1a. The addition of telaprevir-based HCV therapy resulted in a statistically significant increase in the
frequency of each type of CSDDI. Prior to the addition of telaprevir-based HCV therapy, there was a high frequency (82.1%) of any CSDDI (D- or X-rated interactions). After the addition of telaprevir-based HCV therapy to the patients’ medication regimens, the frequency of any CSDDI increased to 97% (p < 0.001). Drug-drug interactions requiring a dose change of at least one medication occurred in 88 (26.3%) patients prior to the addition of telaprevir-based HCV therapy. This increased to 120 (35.8%) patients after the addition of telaprevir-based HCV therapy. The prevalence of contraindicated (X-rated) drug-drug interactions increased significantly from 20% to 38.2% after the addition of telaprevir-based HCV therapy (p < 0.001).

Interactions involving ART occurred frequently and significantly increased with the addition of telaprevir-based HCV therapy. Contraindicated interactions involving ART occurred in 95 (28.4%) patients after addition of telaprevir-based HCV therapy. The prevalence of contraindicated drug-drug interactions before and after addition of telaprevir-based hepatitis C therapy, stratified by type of ART regimen, is displayed in Figure 1b. There was no difference in the frequency (14.3%) of contraindicated drug-drug interactions before or after addition of telaprevir-based HCV therapy for patients receiving integrase strand transfer inhibitor (ISTI)-based ART regimens to patients’ medication profiles (p = 1.00). The probability of contraindicated drug-drug interactions for recipients of NNRTI-based ART regimens did not significantly differ before (17.2%) and after (26.2%) addition of telaprevir-based HCV therapy (p = 0.08). For patients receiving protease inhibitor (PI)-based regimens and mixed class ART regimens, there
was a statistically significant 2-fold increased frequency of contraindicated drug-drug interactions after the addition of telaprevir-based HCV therapy.

The bivariate analyses comparing the clinical covariates and occurrence of a contraindicated drug-drug interaction are displayed in Table 1. The CART-derived breakpoints were identified for age (≥ 52 years), duration of HIV infection (≥ 21 years), total number of medications (≥ 14) and total number of non-HIV medications (≥ 10). The probability of contraindicated drug-drug interactions was significantly higher for patients above these thresholds. The proportion of patients receiving ART was higher among patients with a contraindicated drug-drug interaction than those without and the distributions of ART regimen types varied. Among patients with a contraindicated drug-drug interaction, PI-based ART was the most common regimen. Classes of medications that significantly different between patients with and without a contraindicated drug-drug interaction were calcium channel blockers, corticosteroids, erectile dysfunction drugs and HMG Co-A reductase inhibitors. Comorbidities that differed between patients with and without contraindicated drug-drug interactions were depression, substance abuse, dyslipidemia and neuropathy.

The results of the multivariate regression analyses are displayed in Table 2. The use of at least 10 non-HIV medications and protease inhibitors were independently associated with the occurrence of a contraindicated drug-drug interaction involving telaprevir-based HCV therapy. Additionally, dyslipidemia was the only comorbidity that was associated with a contraindicated drug-drug interaction. In a separate model, use of protease inhibitors was removed from the model and replaced with each of the
individual protease inhibitors. Use of darunavir, fosamprenavir and lopinavir were the only protease inhibitors to remain in the final model and continued to be independently associated with a contraindicated drug-drug interaction.
DISCUSSION

There were several notable findings from this investigation. First, we observed a high frequency of CSDDI (82.1%) prior to the addition of telaprevir-based HCV therapy to patients’ medication profiles. Consistent with the literature, this is a population of patients that are already at high risk for CSDDI.[181, 198] The use of multiple medications, polypharmacy, is common among patients with HIV and will continue to become problematic as this population continues to age.[199] After the addition of telaprevir-based HCV therapy, almost all patients (97%) had a CSDDI. This finding is important because drug-drug interactions can lead to harmful, yet preventable, patient outcomes including drug toxicity or inadequate clinical response. Our results demonstrate that nearly all coinfected individuals considering telaprevir-based therapy are vulnerable. Given their similarities in drug metabolism, comparable findings are likely with boceprevir and simeprevir-based HCV therapies.

The majority of drug-drug interactions observed after the addition of telaprevir-based HCV therapy involved antiretroviral therapy. While the treatment guidelines recommend reviewing ART prior to the addition of HCV agents, this study illustrates that a high proportion of patients would require alterations to their ART regimens. It is important to note that the risk of contraindicated drug-drug interactions varied between and within different classes of ART regimens when telaprevir-based HCV therapy is added. In this study, PI-based ART was the most problematic and independently associated with the occurrence of a contraindicated drug-drug interaction. To refine this risk assessment, we replaced the use of PIs with the individual
PI agents; the only protease inhibitors to remain in the model and continue to be independently associated with a contraindicated drug-drug interaction were darunavir, lopinavir and fosamprenavir.

In addition to considering the ART, the risk of contraindicated drug-drug interactions was dependent on the full complement of medications received. Unsurprising, polypharmacy was an important predictor and use of ≥ 10 non-HIV medications was independently associated with an increase probability of contraindicated drug-drug interactions. This underscores the obvious risk of contraindicated drug-drug interactions among populations in which polypharmacy is crucial to optimizing management of comorbidities, especially as life expectancy increases and more drugs are utilized.

Dyslipidemia was also an independent predictor of CSDDIs. Dyslipidemia may have been a proxy for medication use patterns among the patients studied. Treatment of dyslipidemia is most often with an HMG CoA reductase inhibitor and many drugs in this class are known to interact with telaprevir.

While this study is the first to quantify the prevalence of interactions involving telaprevir, several limitations should be considered. First, the exposure variable, telaprevir-based HCV therapy, was theoretical. None of the patients in the study actually received telaprevir therapy. Rather, the data were meant to quantify the magnitude of interactions that would occur had these patients initiated telaprevir-based HCV therapy. The theoretical design is also an asset. It is statistically more efficient to study theoretical risk, and from a bioethical perspective, we did not wait for drug interactions
to occur before studying them. Second, we used an automated software program, Lexi-
Interact, to define the presence of CSDDI and contraindicated drug-drug interactions.
The gold standard would have been to convene an expert panel. However, in practice,
most pharmacists rely on automated programs to screen for drug-drug interactions and
use clinical judgment to determine the existence of a truly clinically significant drug-drug
interaction. The use of Lexi-Interact to define our outcome is objective, reproducible,
and not vulnerable to inter-pharmacist variability. In a survey of hospital pharmacists, it
was also the most preferred program by pharmacists on the basis of database quality
and performance.[196] Third, our two outcomes (CSDDI and contraindicated drug-drug
interactions) were limited to interactions that Lexi-Interact considered D- or X-rated. We
limited our outcomes to these interactions because they are the more serious potential
drug-drug interactions. However, we recognize that pharmacists’ opinions on the
importance of C-rated interactions may vary and some require pharmacotherapeutic
intervention. From a statistical perspective, perfect specificity and imperfect sensitivity
that is non-differentially distributed will lead to unbiased prevalence ratios. We
anticipate that our prevalence estimates of CSDDI are conservative and more
interactions, of lesser severity, may indeed exist. Fourth, we included all HIV/HCV
coinfected patients and did not restrict to patients with solely genotype 1 HCV infection.
Genotype was documented in the medical charts of only 92 patients. Furthermore,
there is no biologically plausible reason to expect patients with non-genotype 1 HCV
infection to have different medication use patterns than patients with genotype 1 HCV
infection. Because there is no heterogeneity expected, the interactions identified are
still pertinent and preserve statistical efficiency. Finally, our data does not provide any comparative context on the frequency of CSDDI or contraindicated interactions that would occur with other NS3/4A serine protease inhibitors to treat HCV infection like boceprevir or simeprevir. Although only telaprevir was used in this analysis, similar drug interaction concerns are likely with the other available NS3/4A protease inhibitors. With the rapid approval of several other agents from different medications classes on the horizon, it is unclear what the population-based risk of drug-drug interactions would be and similar studies would need to be performed upon market entry. Since neither of these agents are recommended for co-administration with any available first-line HIV protease inhibitors or non-nucleoside reverse transcriptase inhibitors, drug interaction management is likely to be even more challenging for HIV/HCV co-infected patients.[160, 180] A similar analysis with boceprevir and simeprevir might be equally valuable to compare to the current results, as well as with other drugs from other classes like sofosbuvir. An understanding of the drug interaction potential with these drugs will aid in the selection of safe and appropriate drug therapy.

In summary, the availability of telaprevir-based HCV therapy is changing the therapeutic landscape for patients with HIV/HCV coinfection. Clinicians considering initiating HCV therapy with telaprevir for HIV/HCV coinfected patients should be vigilant of drug-drug interactions, particularly among patients with dyslipidemia, those using ≥ 10 non-HIV medications, and those using a protease inhibitor. Pharmacists can help prevent adverse events associated with drug-drug interactions. Future research should
evaluate strategies to avoid drug-drug interactions, such as switching ART regimens and minimizing polypharmacy.

ACKNOWLEDGEMENTS

This material is based upon work partially supported by the Office of Research and Development, Department of Veterans Affairs. This article has greatly benefited from the thoughtful editing of Thomas Lodise and Allison Krug. Vertex Pharmaceuticals provided support only to complete the project and was not involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation and review of the final manuscript.
Figure 1a: Distribution of drug-drug interactions before and after addition of telaprevir-based hepatitis C therapy
Figure 1b: Prevalence of contraindicated drug-drug interactions before and after addition of telaprevir-based Hepatitis C therapy, stratified by type of antiretroviral therapy regimen.
Table 1: Bivariate analyses of clinical covariates associated with contraindicated drug-drug interactions involving telaprevir-based HCV therapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No contraindicated drug-drug interaction (N = 206)</th>
<th>Contraindicated interaction present (n = 129)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>55.0 ± 7.8</td>
<td>56.6 ± 6.3</td>
<td>0.04</td>
</tr>
<tr>
<td>• Age ≥ 52 years*</td>
<td>146 (70.9)</td>
<td>106 (82.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male Sex</td>
<td>175 (85.0)</td>
<td>117 (90.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>• African American</td>
<td>111 (54.4)</td>
<td>85 (66.4)</td>
<td></td>
</tr>
<tr>
<td>• Hispanic</td>
<td>27 (13.2)</td>
<td>18 (14.1)</td>
<td></td>
</tr>
<tr>
<td>• White</td>
<td>60 (29.4)</td>
<td>24 (18.8)</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>6 (2.9)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Weight, mean ± SD</td>
<td>80.8 ± 18.6</td>
<td>78.3 ± 15.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Duration of HIV infection, median (IQR)</td>
<td>17 (11 – 22)</td>
<td>19 (15 – 24)</td>
<td>0.009</td>
</tr>
<tr>
<td>• Duration of HIV ≥ 21 years*</td>
<td>60 (29.1)</td>
<td>54 (41.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of HCV infection, median (IQR)</td>
<td>13 (8 – 16)</td>
<td>15 (11 – 19)</td>
<td>0.002</td>
</tr>
<tr>
<td>Parameter</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Most recent CD4 count</td>
<td>511 (288 – 688)</td>
<td>380 (187 – 542)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Most recent log-transformed HIVRNA</td>
<td>2.3 ± 1.1</td>
<td>2.4 ± 1.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Most recent log-transformed HCV RNA</td>
<td>5.0 ± 1.8</td>
<td>5.4 ± 1.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Antiretroviral Therapy Treatment experienced</td>
<td>191 (92.7)</td>
<td>124 (96.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Receiving Antiretroviral Therapy</td>
<td>182 (88.3)</td>
<td>124 (96.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Antiretroviral Regimen Type</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Non-nucleoside reverse transcriptase inhibitor</td>
<td>90 (49.5)</td>
<td>32 (25.8)</td>
<td></td>
</tr>
<tr>
<td>• Protease inhibitor</td>
<td>53 (29.1)</td>
<td>66 (53.2)</td>
<td></td>
</tr>
<tr>
<td>• Integrase strand transfer inhibitor</td>
<td>12 (6.6)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>• Other/Mixed class regimen</td>
<td>27 (14.8)</td>
<td>24 (19.4)</td>
<td></td>
</tr>
<tr>
<td>• None</td>
<td>24 (11.6)</td>
<td>5 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Use of Nucleoside reverse transcriptase inhibitors</td>
<td>176 (85.4)</td>
<td>107 (82.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>• Zidovudine</td>
<td>45 (21.8)</td>
<td>20 (15.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>• Lamivudine</td>
<td>77 (37.4)</td>
<td>38 (29.5)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Count 1</td>
<td>Count 2</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>89 (43.2)</td>
<td>53 (41.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>90 (43.7)</td>
<td>62 (48.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Abacavir</td>
<td>26 (12.6)</td>
<td>15 (11.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Didanosine</td>
<td>6 (2.9)</td>
<td>10 (7.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Stavudine</td>
<td>23 (11.2)</td>
<td>11 (8.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Use of non-nucleoside reverse transcriptase inhibitor</td>
<td>104 (50.5)</td>
<td>43 (33.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>81 (39.3)</td>
<td>31 (24.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>20 (9.7)</td>
<td>4 (3.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>3 (1.5)</td>
<td>2 (1.6)</td>
<td>0.95</td>
</tr>
<tr>
<td>Etravirine</td>
<td>0 (0.0)</td>
<td>6 (4.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Use of Protease Inhibitor</td>
<td>63 (30.6)</td>
<td>87 (67.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>43 (20.9)</td>
<td>14 (10.9)</td>
<td>0.02</td>
</tr>
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<td>Darunavir</td>
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<td>20 (15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>0 (0.0)</td>
<td>6 (4.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>0 (0.0)</td>
<td>46 (35.7)</td>
<td>&lt;0.001</td>
</tr>
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<td>Saquinavir</td>
<td>3 (1.5)</td>
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<td>0.95</td>
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<td>Indinavir</td>
<td>4 (1.9)</td>
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<td>0.30</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>13 (6.3)</td>
<td>2 (1.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>36 (17.5)</td>
<td>80 (62.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Non-HIV Medication Usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td>22 (10.7)</td>
<td>17 (13.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>- Raltegravir</td>
<td>20 (9.7)</td>
<td>17 (13.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>- Elvitegravir</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>1 (0.5)</td>
<td>1 (0.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Non-HIV Medication Usage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Number of Medications, median (IQR)</strong></td>
<td>10 (7 – 13)</td>
<td>13 (10 – 16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Use of ≥ 14 medications*</td>
<td>39 (18.9)</td>
<td>57 (44.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number of Non-HIV medications, median (IQR)</strong></td>
<td>7 (4 – 9)</td>
<td>9 (6 – 13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Use of ≥ 10 non-HIV medications*</td>
<td>50 (24.3)</td>
<td>60 (46.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>43 (20.9)</td>
<td>25 (19.4)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>12 (5.8)</td>
<td>8 (6.2)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>58 (28.2)</td>
<td>45 (34.9)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Azole antifungals</strong></td>
<td>7 (3.4)</td>
<td>7 (5.4)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>12 (5.8)</td>
<td>26 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>21 (10.2)</td>
<td>29 (22.5)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Central nervous system depressants</strong></td>
<td>94 (45.6)</td>
<td>66 (51.2)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Erectile dysfunction drugs</strong></td>
<td>9 (4.4)</td>
<td>49 (38.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Count 1</td>
<td>Count 2</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>28 (13.6)</td>
<td>28 (21.7)</td>
<td>0.05</td>
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<tr>
<td>Alcoholism</td>
<td>65 (31.6)</td>
<td>53 (41.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17 (8.3)</td>
<td>18 (14.0)</td>
<td>0.10</td>
</tr>
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<td>Asthma</td>
<td>10 (4.9)</td>
<td>3 (2.3)</td>
<td>0.38</td>
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<tr>
<td>Bipolar/mood/personality disorder</td>
<td>28 (13.6)</td>
<td>10 (7.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>17 (8.3)</td>
<td>14 (10.4)</td>
<td>0.42</td>
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<tr>
<td>Chronic kidney disease</td>
<td>11 (5.3)</td>
<td>11 (8.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>20 (9.7)</td>
<td>14 (10.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Depression</td>
<td>72 (35.0)</td>
<td>64 (49.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (12.6)</td>
<td>21 (16.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (11.2)</td>
<td>31 (24.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Epilepsy/seizures</td>
<td>11 (5.3)</td>
<td>7 (5.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>25 (12.1)</td>
<td>15 (11.6)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td>13 (6.3)</td>
<td>14 (10.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>History of cancer</td>
<td>17 (8.3)</td>
<td>14 (10.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>117 (56.8)</td>
<td>88 (68.2)</td>
<td>0.04</td>
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<tr>
<td>Hypertension</td>
<td>70 (34.0)</td>
<td>52 (40.3)</td>
<td>0.24</td>
</tr>
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<td>Insomnia</td>
<td>13 (6.3)</td>
<td>13 (10.1)</td>
<td>0.21</td>
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<tr>
<td>Neuropathy</td>
<td>15 (7.3)</td>
<td>19 (14.7)</td>
<td>0.03</td>
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<tr>
<td>Condition</td>
<td>Count</td>
<td>Count</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>Osteoporosis/osteoarthritis/osteopenia</td>
<td>20 (9.7)</td>
<td>14 (10.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
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<td>22 (17.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prostate disease</td>
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<td>15 (11.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Schizophrenia/psychosis</td>
<td>17 (8.3)</td>
<td>12 (9.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>21 (10.2)</td>
<td>22 (17.1)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

All data presented as n(%), mean (standard deviation) or median (interquartile range), unless noted otherwise. *CART-derived breakpoint
Table 2: Clinical covariates independently associated with presence of contraindicated drug-drug interactions after addition of telaprevir-based HCV therapy to patients’ medication regimens

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Prevalence Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model #1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of a protease-inhibitor</td>
<td>2.49</td>
<td>1.87 – 3.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of ≥ 10 non-HIV medications</td>
<td>1.74</td>
<td>1.36 – 2.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.53</td>
<td>1.17 – 1.99</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Model #2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>4.36</td>
<td>3.26 – 5.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>4.15</td>
<td>3.14 – 5.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>3.96</td>
<td>3.11 – 5.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of ≥ 10 non-HIV medications</td>
<td>1.80</td>
<td>1.44 – 2.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.62</td>
<td>1.26 – 2.08</td>
<td>0.002</td>
</tr>
</tbody>
</table>
CHAPTER 4: MANUSCRIPT #2

Predicting the probability of experiencing clinically significant drug-drug interactions involving boceprevir-containing hepatitis C therapy among patients co-infected with hepatitis C and human immunodeficiency virus

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Key words: hepatitis C, HIV, antiretroviral, drug interaction

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INTRODUCTION:

Worldwide, 150 million individuals are infected with chronic hepatitis C virus (HCV) infection and a significant proportion of these individuals are also co-infected with human immunodeficiency virus (HIV). Co-infection with HIV is problematic for HCV-infected patients because of accelerated liver disease progression and early mortality. The landscape of medication used to treat HCV infection is evolving rapidly. Prior to 2011, the standard of care was pegylated interferon (PegIFN) and ribavirin (RBV), but this combination is only marginally effective. Approximately one in three HIV/HCV coinfected patients treated with PegIFN and RBV are able to achieve an undetectable HCV viral load 6 months after discontinuation of therapy (sustained virologic response, SVR).

The recent addition of first-generation non-structural protein 3/4A (NS3/4A) serine protease inhibitors, such as boceprevir, has significantly enhanced the probability of achieving a SVR when used in combination with PegIFN and RBV. Nearly two thirds of HCV-infected patients are able to achieve SVR on therapy that includes a NS3/4A protease inhibitor. Achieving a SVR is of critical importance in patients with HIV/HCV co-infection and can prevent several deleterious outcomes (hepatocellular carcinoma, need for liver transplant, mortality, etc.) associated with HCV infection. Most recently, simeprevir and sofosbuvir have been incorporated into treatment guidelines, but availability and uptake in foreign markets is a long process. Thus, patients with HIV/HCV infection in developing countries may still rely on treatment with boceprevir.
Despite the availability of NS3/4A protease inhibitors, like boceprevir and telaprevir, their uptake has been limited by concerns about cost/reimbursement, toxicity and the risk of drug-drug interactions. Of these, the latter has been the chief concern limiting the use of NS3/4A protease inhibitors among coinfected patients. While drug-drug interactions are possible and should be considered in the treatment decision matrix, the risk depends on multiple clinical factors, such as polypharmacy, dosage, and the type of ART regimen the patient is on. An understanding of these factors on the probability of drug-drug interactions will help clinicians identify which patients require more intensive medication management.

This study has two objectives. The first is to quantify the prevalence of clinically significant drug-drug interactions (CSDDI) when boceprevir-containing HCV therapy is added to a patient’s medication profile. The second is to determine the clinical risk factors associated with an increased probability of contraindicated drug-drug interactions. Our study focused on boceprevir over telaprevir and simeprevir because it has gained licensure in a significant number of developing countries where HCV coinfection is a concern.
METHODS:

A cross-sectional study was performed among Veterans’ Affairs Medical Center (VAMC) patients served by the Upstate New York Veterans’ Healthcare Administration (VISN-2) between January 1, 2000 and July 31, 2011. Inclusion criteria for this study were: 1) age ≥ 18 years, 2) documented HIV infection and 3) laboratory-confirmed HCV infection. Patients with no medication history were excluded.

Assuming a type I error frequency of 5% and 80% power, a minimum of 234 patients were required to detect an effect size of 20% in the primary outcome (difference in proportion of subjects with a CSDDI between any two predictor variables). Based on a preliminary electronic record review, it was likely enough study subjects would meet our inclusion criteria.

From the patients’ medical records we extracted social history, demographics (age, sex, race, height, and weight), and clinical data (years of HCV and HIV diagnosis, CD4 cell counts, comorbidities, and medication lists). Transient conditions such as thrush, pneumonia, and other opportunistic infections were not considered as comorbid conditions. Where available, the most recent CD4 cell count, HIV-RNA and HCV-RNA were obtained from the laboratory reports; HIV-RNA and HCV-RNA were log-transformed for assessment as continuous variables.

The drug name, dose, strength and frequency were collected from the patient’s most recent medication list. When the most recent medication list was created during an inpatient admission, the most recent outpatient medication list was utilized instead.
Outcomes of Interest

The outcomes of interest in this study were the presence of 1) clinically-significant drug-drug interactions (CSDDI) and 2) contraindicated drug-drug interactions. Drug-drug interactions were identified by Lexi-Interact drug interaction software. The rating system in Lexi-Interact was used to define which drug-drug interactions were considered clinically significant vs. contraindicated. Interactions rated by Lexi-interact with a level D or X severity rating were considered clinically significant; those rated X were also considered contraindicated drug-drug interactions.

To determine the effect of boceprevir-containing HCV therapy on the excess risk of CSDDI and contraindicated drug-drug interactions, boceprevir, pegylated interferon alpha and ribavirin were added to the patients’ medications lists in Lexi-Interact and reanalyzed. All D- and X-rated interactions were documented and categorized by a clinical pharmacist according to their management strategies as follows: 1) interactions requiring no intervention or increased clinical/laboratory monitoring; 2) clinically significant interactions requiring dosage adjustment of one or both agents; and 3) contraindicated drug-drug interactions (i.e., medications that should never be coadministered).

Data Analysis

For the bivariate analyses comparing each clinical covariate with CSDDI and contraindicated drug-drug interactions, categorical variables were compared by the Chi-squared or Fisher’s exact test. Continuous variables were evaluated using the Student’s
T or Mann-Whitney U test. Classification and regression tree (CART) analysis was used to identify breakpoints in continuous variables. McNemar’s test was used to compare the frequency of CSDDI or contraindicated drug-drug interactions before and after the addition of boceprevir-containing HCV therapy.

Variables in the bivariate analyses that were associated (p < 0.2) with contraindicated drug-drug interactions were considered for inclusion in the hierarchically well-defined explanatory multivariate regression model. Because a high proportion (> 10%) of patients were expected to have contraindicated drug-drug interactions, this study utilized log-binomial regression with robust variance estimates.[183] The most parsimonious model was derived by a backwards stepwise approach. The only variables that were retained in the final model were those with a p-value for the prevalence ratio of less than 0.05. Interaction terms were used to assess effect modification. Potential confounders were included in the final model for evaluation and only retained if their presence changed the resulting prevalence ratios by more than 10%. All calculations were computed using SPSS version 11.5 (SPSS Inc., Chicago, IL), SAS version 9.3 (Cary, NC), and CART software (Salford Systems, San Diego, CA).

RESULTS

The mean (standard deviation, SD) age of the 244 study patients was 57.4 (6.1). The median (interquartile range, IQR) durations of HIV and HCV infections were 19 (15 –
and 15 (12 – 19) years, respectively. Alcoholism, depression and history of substance abuse were the most frequently observed comorbidities. Most (n= 222, 91.0%) of the patients were on antiretroviral therapy (ART). The most common ART regimen types were non-nucleoside reverse transcriptase inhibitors (NNRTIs) (37.7%) and protease inhibitors (PIs) (36.9%). The median (IQR) number of non-HIV medications was 8 (5 - 11). The most commonly used classes of non-HIV medications were central nervous system (CNS) depressants, antidepressants, and erectile dysfunction drugs.

The frequency of clinically significant drug-drug interactions (D- and X-rated interactions) significantly increased after the addition of boceprevir-containing HCV therapy from 85.7% to 97.5%, p < 0.001. Similarly, the prevalence of contraindicated drug-drug interactions (X-rated interactions) increased from 20.9% to 73.9%, p < 0.001, after the addition of boceprevir-containing therapy. Clinically significant drug-drug interactions involving ART increased from 74.6% to 84.8%, p < 0.001 and contraindicated drug-drug interactions involving ART changed from 6.6% to 77.9%, p < 0.001, after the addition of boceprevir-containing HCV therapy. In a restricted analysis of patients only receiving ART, the addition of boceprevir-containing HCV therapy would have resulted in statistically and clinically significant increases in contraindicated drug-drug interactions for mixed class ART regimens (18.9% to 67.6%), NNRTI (17.4% to 84.8%) and PI (25.6% to 83.3%).

The bivariate analyses of demographic and clinical characteristics associated with a contraindicated drug-drug interaction after the addition of boceprevir-containing HCV therapy are described in Table 1. The variables associated with a contraindicated drug-
drug interaction were CD4 count, treatment-experience, use of ART, ART regimen type, use of nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, PIs, total number of medications and total number of comorbidities. Specific medications that were associated with a contraindicated drug-drug interaction after addition of boceprevir-containing HCV therapy were lamivudine, emtricitabine, tenofovir, efavirenz, nevirapine, atazanavir, darunavir, lopinavir, indinavir, nelfinavir, ritonavir and erectile dysfunction drugs. Dyslipidemia was the only specific comorbidity that was associated with a contraindicated drug-drug interaction. There were four continuous variables with breakpoints identified by CART: age ≥ 71 years, duration of HIV infection ≥ 8 years, total medications ≥ 8 and comorbidities ≥ 11. Above these breakpoints, the prevalence of contraindicated drug-drug interactions was significantly higher.

The results of the multivariate regression analyses are displayed in Table 2. The only variables that were independently associated with contraindicated drug-drug interactions were atazanavir, darunavir, lopinavir, efavirenz and use of ≥ 8 medications.
DISCUSSION:

We observed a number of interesting findings in this study. First, the HIV/HCV coinfected population is highly vulnerable to drug-drug interactions. This risk increased significantly when boceprevir-containing HCV therapy was added to the medication regimen. Second, the two most important drivers of contraindicated drug-drug interactions were polypharmacy (use of at least 8 medications) and four specific ART medications (efavirenz, lopinavir, atazanavir and darunavir).

Regarding polypharmacy, treatment of HIV infection alone requires the use of at least three medications, and possibly more for patients with significant treatment experience. Additionally, as the population of patients with HIV infection ages they develop comorbidities that also require medication therapy management.[200] Given these factors, it is not uncommon to find HIV/HCV coinfected patients prescribed ≥ 8 medications. Efforts should be made to proactively manage the patient’s regimen to reduce the probability of experiencing a drug-drug interaction involving boceprevir-containing HCV therapy.

With respect to the four specific ART medications likely to increase the risk of contraindicated drug interactions, three are considered the preferred ART drugs (atazanavir, darunavir and efavirenz).[199] These drugs should be avoided in patients for whom boceprevir-containing HCV therapy is recommended, and substituted by other preferred ART medications.[160] However, such substitution may be problematic in the developing world where access to some of the newer ART agents may be limited.
Some limitations to this analysis should be noted. First, the hepatitis C guidelines have recently been updated to reflect the risks identified here and no longer advocate the use of boceprevir or telaprevir. However, these drugs are still available and will likely to be relegated to resource-limited areas where there is a need for administration of prompt HCV therapy. In this situation, patients may not be receiving contemporary ART medications and drug-drug interactions become a safety issue. Second, we used Lexi-Interact to define the presence of clinically significant drug-drug interactions. Other commercially-available software programs exist and it is unclear if the same results would be obtained if a different program were utilized. We chose this program because it is highly accessible, contains drug-interaction data on medications used outside of the United States and has been used in other studies of a similar nature. Third, patients in the study did not receive boceprevir and this exposure of interest was theoretical. However, the intent was to capture the population-based risk of experiencing clinically-significant drug-drug interactions involving boceprevir-containing therapy and identify predictors of such interactions. The theoretical design allowed us to complete the study faster than if we were to wait for the same number of HCV patients to initiate boceprevir-containing therapy in clinical practice. This study design is an important contribution to pharmacy practice and institution policy because it can estimate the population-based risk of an outcome. In other words, statistical modeling allows us to estimate the number of patients who would need to have their ART regimens modified and inform a discussion about whether an agent is safe to add to the formulary based on medication use patterns in the institution. Finally, we recognize that boceprevir is
only indicated for patients with genotype 1 HCV infection. We did not use genotype as an entry criterion in this study because genotype was largely unavailable (documented in less than a third of the medical charts). However, based on population-based surveillance, the majority of patients would be expected to have genotype 1 infection. Additionally, the information bias that non-genotype 1 patients would introduce would be negligible because there is no inherent reason to anticipate heterogeneity of patterns of medication use or clinical characteristics by HCV genotype.

In countries with rapidly expanding economies, pharmacists have a particularly important role to play regarding the evaluation of new therapeutic agents for HCV against their country’s unique backdrop of disease epidemiology, reimbursement, and potential drug interactions. We found that the addition of boceprevir-containing HCV regiments to patients with HIV/HCV coinfection is associated with a high prevalence of important drug-drug interactions especially among patients on at least 8 medications or one of four ART medications (atazanavir, darunavir, efavirenz and lopinavir). Thus, boceprevir-containing HCV therapy remains a significant safety issue for HIV/HCV coinfected patients. Future research should investigate the population-based risk of drug-drug interactions among emerging HCV agents and whether these findings would be more pronounced in the developing world where boceprevir-containing HCV is most likely to be utilized.
Table 1: Bivariate analyses of clinical covariates associated with contraindicated drug-drug interactions involving boceprevir-containing HCV therapy.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No contraindicated drug-drug interaction (N = 64)</th>
<th>Contraindicated interaction present (n = 180)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>58.1 (7.0)</td>
<td>57.2 (5.8)</td>
<td>.32</td>
</tr>
<tr>
<td>Age ≥ 71 years*</td>
<td>4 (6.3)</td>
<td>0 (0)</td>
<td>.004</td>
</tr>
<tr>
<td>Male Sex</td>
<td>62 (96.9)</td>
<td>177 (98.3)</td>
<td>.61</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>.91</td>
</tr>
<tr>
<td>African American</td>
<td>44 (69.8)</td>
<td>117 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (9.5)</td>
<td>18 (10.0)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (19.0)</td>
<td>42 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.6)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>History of HIV and HCV infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HIV infection, median (IQR)</td>
<td>20 (15 – 25)</td>
<td>19 (14 – 24)</td>
<td>.39</td>
</tr>
<tr>
<td>Duration of HIV ≥ 8 years*</td>
<td>64 (100)</td>
<td>165 (91.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Duration of HCV infection, median</td>
<td>14 (13 – 19)</td>
<td>15 (12 – 19)</td>
<td>.88</td>
</tr>
<tr>
<td>(IQR)</td>
<td>Most recent CD4 count, median (IQR)</td>
<td>515 (328 – 690)</td>
<td>395 (187 – 621)</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>(IQR)</td>
<td>Most recent log-transformed HIVRNA, mean ± SD</td>
<td>2.65 (1.14)</td>
<td>2.46 (1.04)</td>
</tr>
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</table>

### Antiretroviral Medication Use

<table>
<thead>
<tr>
<th>Antiretroviral regimen type</th>
<th>Receiving antiretroviral therapy</th>
<th>43 (67.2)</th>
<th>179 (99.4)</th>
<th>&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td></td>
<td>14 (32.6)</td>
<td>78 (43.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td></td>
<td>15 (34.9)</td>
<td>75 (41.9)</td>
<td></td>
</tr>
<tr>
<td>Integrase strand transfer inhibitor</td>
<td></td>
<td>2 (4.7)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other/mixed class regimen</td>
<td></td>
<td>12 (27.9)</td>
<td>25 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Use of Nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td>41 (64.1)</td>
<td>162 (90.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td>17 (26.6)</td>
<td>35 (19.4)</td>
<td>.23</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td>33 (51.6)</td>
<td>66 (36.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td></td>
<td>6 (9.4)</td>
<td>78 (43.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>12 (18.8)</td>
<td>93 (51.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abacavir</td>
<td></td>
<td>5 (7.8)</td>
<td>22 (12.2)</td>
<td>.33</td>
</tr>
<tr>
<td>Medication</td>
<td>New York (N=316)</td>
<td>Nationwide (N=1908)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>2 (3.1)</td>
<td>11 (6.1)</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>12 (18.8)</td>
<td>19 (10.6)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Use of non-nucleoside reverse transcriptase inhibitor</td>
<td>17 (26.6)</td>
<td>89 (49.4)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0 (0)</td>
<td>83 (46.1)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>16 (25.0)</td>
<td>3 (1.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td>.26</td>
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</tr>
<tr>
<td>Etravirine</td>
<td>0 (0)</td>
<td>3 (1.7)</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>Use of protease inhibitor</td>
<td>18 (28.1)</td>
<td>93 (51.7)</td>
<td>.001</td>
<td></td>
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<tr>
<td>Atazanavir</td>
<td>0 (0)</td>
<td>33 (18.3)</td>
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<tr>
<td>Darunavir</td>
<td>0 (0)</td>
<td>13 (7.2)</td>
<td>.02</td>
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<tr>
<td>Fosamprenavir</td>
<td>0 (0)</td>
<td>5 (2.8)</td>
<td>.33</td>
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<tr>
<td>Lopinavir</td>
<td>0 (0)</td>
<td>40 (22.2)</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>Saquinavir</td>
<td>3 (4.7)</td>
<td>2 (1.1)</td>
<td>.12</td>
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<td>Indinavir</td>
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<td>.004</td>
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<td>Nelfinavir</td>
<td>11 (17.2)</td>
<td>3 (1.7)</td>
<td>&lt;.001</td>
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<tr>
<td>Ritonavir</td>
<td>2 (3.1)</td>
<td>82 (45.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>2 (3.1)</td>
<td>18 (10.0)</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>2 (3.1)</td>
<td>18 (10.0)</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>1.00</td>
<td></td>
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</tbody>
</table>

Non-HIV Medication Usage
<table>
<thead>
<tr>
<th></th>
<th>Total Number of Medications, median (IQR)</th>
<th>Use of ≥ 8 medications*</th>
<th>Number of Non-HIV medications, median (IQR)</th>
<th>Use of ≥ 8 medications*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 (6 – 13)</td>
<td>39 (60.9)</td>
<td>12 (9 – 15)</td>
<td>152 (84.4)</td>
</tr>
<tr>
<td>Use of ≥ 8 medications*</td>
<td>8 (5 – 10)</td>
<td>8 (6 – 12)</td>
<td>.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>16 (25.0)</td>
<td>4 (6.3)</td>
<td>8 (6 (5 – 10)</td>
<td>34 (18.9)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>17 (26.6)</td>
<td>3 (3.9)</td>
<td>.30</td>
<td>.49</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2 (3.1)</td>
<td>7 (3.9)</td>
<td>.25</td>
<td>1.00</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>3 (4.7)</td>
<td>22 (12.2)</td>
<td>.10</td>
<td>.10</td>
</tr>
<tr>
<td>Statins</td>
<td>31 (48.4)</td>
<td>95 (52.8)</td>
<td>.55</td>
<td>.55</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>6 (9.4)</td>
<td>35 (19.4)</td>
<td>.08</td>
<td>.08</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4 (6.3)</td>
<td>51 (28.3)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>depressants</td>
<td>3 (4.7)</td>
<td>3 (1.7)</td>
<td>.19</td>
<td>.19</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>11 (17.2)</td>
<td>33 (18.3)</td>
<td>.84</td>
<td>.84</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Median (IQR) number of comorbidities</td>
<td></td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>8 (6 – 11)</td>
<td>10 (7 – 13)</td>
<td>≥ 11 comorbidities</td>
<td>20 (31.3)</td>
</tr>
<tr>
<td></td>
<td>29 (45.3)</td>
<td>83 (46.1)</td>
<td>.91</td>
<td>.91</td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (4.7)</td>
<td>20 (11.1)</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Bipolar/mood/personality disorder</td>
<td>11 (17.2)</td>
<td>23 (12.8)</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>6 (9.4)</td>
<td>22 (12.2)</td>
<td>.54</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5 (7.8)</td>
<td>12 (6.7)</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>8 (12.5)</td>
<td>19 (10.6)</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>24 (37.5)</td>
<td>83 (46.1)</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (10.9)</td>
<td>31 (17.2)</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3 (4.7)</td>
<td>41 (22.8)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Epilepsy/seizures</td>
<td>3 (4.7)</td>
<td>9 (5.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>7 (10.9)</td>
<td>22 (12.2)</td>
<td>.79</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td>3 (4.7)</td>
<td>20 (11.1)</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>9 (14.1)</td>
<td>20 (11.1)</td>
<td>.53</td>
<td></td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>47 (73.4)</td>
<td>124 (68.9)</td>
<td>.50</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (43.8)</td>
<td>77 (42.8)</td>
<td>.89</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (7.8)</td>
<td>18 (10.0)</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>8 (12.5)</td>
<td>23 (12.8)</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis/osteoarthritis/osteo genesis</td>
<td>10 (15.6)</td>
<td>20 (11.1)</td>
<td>.35</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>12 (18.8)</td>
<td>31 (17.2)</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>n (%)</td>
<td>mean (SD)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Prostate disease</td>
<td>5 (7.8)</td>
<td>24 (13.3)</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia/psychosis</td>
<td>7 (10.9)</td>
<td>20 (11.1)</td>
<td>.97</td>
<td></td>
</tr>
</tbody>
</table>

All data presented as n (%), mean (standard deviation) or median (interquartile range), unless noted otherwise. *CART-derived breakpoint
Table 2: Clinical covariates independently associated with presence of contraindicated drug-drug interactions involving boceprevir-based HCV therapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Adjusted Prevalence</th>
<th>95% Confidence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>3.77</td>
<td>2.73 – 5.19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Darunavir</td>
<td>3.27</td>
<td>2.17 – 4.95</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>3.17</td>
<td>2.20 – 4.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>3.73</td>
<td>2.69 – 5.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of ≥ 8 medications</td>
<td>1.23</td>
<td>1.01 – 1.50</td>
<td>.04</td>
</tr>
</tbody>
</table>
CHAPTER 5: MANUSCRIPT #3

Quantifying the sensitivity and specificity of drug interaction software programs used to identify contraindicated drug-drug interactions among patients coinfected with human immunodeficiency virus and hepatitis C

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INTRODUCTION:

Drug-drug interactions are associated with considerable morbidity in the United States. Several drugs have been removed from the market because of adverse events that occurred because of clinically significant drug-drug interactions (CSDDI).

One population that is particularly vulnerable to CSDDI are patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection. Treatment of HIV infection alone requires the use of ≥ 3 fully active antiretroviral (ART) medications.[200] Treatment of HCV infection includes triple therapy with pegylated interferon alpha, ribavirin and a direct acting antiviral agent.[149] Many of these medications are processed through the cytochrome P450 isoenzyme system and involved in a high frequency of drug-drug interactions.[160, 161, 180, 187] To further contribute to the risk of CSDDI, patients with HIV/HCV coinfection may be using a high volume of non-HIV/HCV medications to treat other comorbidities. Collectively, this population is at risk for the effects of CSDDI and appropriate identification is important to preserve patient safety.

One reason why CSDDI may be overlooked is that it is impractical for clinicians to manually assess every drug-drug interaction without reference materials. The availability of computer software programs to screen patients’ medication profiles has significantly improved the ability to detect possible CSDDI and intervene. However, there are several commercially-available software programs available to screen drug-drug interactions.[201-203] Characteristics of these software programs vary
considerably. Most notably, each software program uses its own search algorithm and
ranks the severity of drug-drug interactions differently.[196] These variations can cause
one software program to flag co-administration of two drugs as dangerous whereas
another program may not even identify co-administration of the same two drugs as
problematic. This is important for patient safety because clinicians rely on these
software programs to identify CSDDI.

While several drug interaction software programs exist, their validity often has
been accepted at face value without a thorough assessment of their sensitivity and
specificity. Given the clinical importance of this void in the literature, the objective of
our study was to quantify the sensitivity and specificity of drug interaction software
programs against a panel of clinical pharmacists assessing medication profiles and rating
the clinical significance of drug interactions.
METHODS:

Study Design and Population

Data were obtained from a cross-sectional study performed among patients coinfected with HIV and HCV receiving care between January 1, 2000 and July 31, 2011. The full methods are described elsewhere. In summary, patients were from two sources: i) Upstate New York Veterans’ Healthcare Administration and ii) patients from Upstate Medical University. Inclusion criteria were: 1) age ≥ 18 years, 2) laboratory-confirmed diagnosis HCV infection and 3) HIV infection identified by ICD-9 code 042.

Data Collection

The following data elements were recorded from the patients’ medical records: demographics, list of comorbidities, targeted laboratory, and medication list. The most recent outpatient medication list from the patient’s medical records was utilized in these analyses. The drug name, dose, strength and frequency were recorded for each medication in the medication profile.

Drug Interactions

The outcome of interest in this study was the occurrence of contraindicated drug-drug interactions. The three commercially-available software programs used to identify drug-drug interactions assessed in this study were i) Lexi-Interact, ii) Micromedex and iii) Clinical Pharmacology.[201-203] For each patient, the medication list plus telaprevir-containing HCV therapy were entered into each of the software
programs and the clinically significant drug-drug interactions (CSDDI) were recorded. The rating system for each software program varies and is described in Table 1.

Interactions that were considered CSDDI were interactions that were, for all intents and purposes, either considered i) major, usually requiring some clinical intervention like alteration of therapy or ii) contraindicated coadministration of the drug-drug combination. While the outcome of interest in this study was contraindicated drug-drug interactions, interactions that were considered major were captured because contraindicated interactions are most likely to be misclassified into this category.

Telaprevir-containing therapy was defined as pegylated interferon alpha, ribavirin and telaprevir. The purpose of adding telaprevir-containing therapy to the patients’ medication profile was to simulate the type of pharmacist decision making that would occur when new medications are initiated in patients at high risk for experiencing the effects of a contraindicated drug-drug interaction.

Since newer drugs are more likely to have drug-drug interaction data that changes with time, the CSDDI identified by the three software programs were cross-matched with the current prescribing information for telaprevir (Incivek®).[161] If new drug-drug interaction data became available, these interactions were also included in the analyses.

Consensus Panel of Clinical Pharmacists to Adjudicate Drug Interactions
A panel of 5 clinical pharmacists was assembled to adjudicate drug-drug interactions identified. All clinical pharmacists had completed residency training and had significant and diverse clinical experience working with patient populations at high risk for polypharmacy and drug-drug interactions.

For each patient, the panelists were provided a 1) medication list and 2) list and nature of CSDDI identified by any of the three software programs. The panelists were blinded to the software programs from which the lists of interactions were derived. Panelists were asked to identify which CSDDI they perceived to be clinically significant enough to warrant intervention. Panelists were instructed to deem an interaction clinically significant if it was either i) major, requiring a clinical intervention or ii) contraindicated.

One of the purposes of the panel was to capture the decision process that the majority of pharmacists in practice would employ. Recognizing that there is heterogeneity in clinical practice, the most extreme panelists (the panelists that identified the most and least number of interactions) were removed and their data was not utilized in subsequent analyses. Because perfect consensus on each interaction was unlikely by all 3 remaining panelists, a modified Delphi method[204] was utilized in situations where there was discordance between the remaining panelists on whether a drug-drug combination should be contraindicated. Panelists were convened to achieve consensus on drug-drug combinations initially found to be discordant. If there were drug-drug combinations without complete agreement among the panelists after consensus conference, a majority vote was used to determine whether or not the drug-drug combination should be classified as a contraindicated drug-drug interaction. A sub-
analysis was performed among just the interactions that were perfectly concordant among the panelists.

For each software program, sensitivity and specificity was computed utilizing the panel of clinical pharmacists as the “gold” standard. Inter-rater reliability among the panelists was assessed using Fleiss’ kappa for multiple raters.[205] A series of stratified analyses were performed to assess if certain factors altered sensitivity/specificity of the software programs.
RESULTS:

There were 335 patients that satisfied inclusion criteria. The full description of clinical factors among the patients in this analysis are described elsewhere. In summary, patients were primarily male sex (87.2%) and the mean (standard deviation, SD) of the patients was 55.6 (7.3) years. The number of patients ≥ 50 and ≥ 65 years of age was 273 (81.5%) and 31 (9.3%), respectively. Polypharmacy was observed frequently and the median (IQR) number of medications was 11 (7 - 14). Over 90% of patients were receiving combination antiretroviral therapy (ART). Among patients on ART, the most common regimen types were: protease inhibitors (38.6%), non-nucleoside reverse transcriptase inhibitors (39.9%), mixed/multiple class regimens (17.0%) and integrase strand transfer inhibitors (4.6%).

A total of 927 unique CSDDI were identified by the 3 software programs. Among these interactions, 124 (13.0%) were considered contraindicated by ≥ 1 software programs. The panelists identified an additional 28 CSDDI that none of the programs had rated as a CSDDI and 2 were considered contraindicated interactions by the panel. The total number of interactions evaluated in this study was 955. The numbers of interactions identified by Clinical Pharmacology, Micromedex and Lexi-Comp were 558, 300 and 553, respectively. The proportion of interactions involving HIV and HCV therapy were 40% and 11.9%, respectively.

Prior to the consensus panel there were 772 (80.8%) interactions that all 3 panelists did not consider to be a contraindicated drug-drug interaction. Among the 183 interactions that at least one of the panel members felt was a contraindicated drug-drug
interaction, 39 had perfect agreement by all three panelists that the interaction should be considered contraindicated. The remaining 144 interactions with discordant panelist opinions on whether they were a contraindicated drug-drug interaction were discussed via consensus conference. After the consensus conference, complete agreement was achieved on 83 of the discordant interactions discussed. Among these 83 interactions where complete concordance was achieved, 22 interactions were considered contraindicated and the remainder were considered non-contraindicated interactions. Majority vote was used to determine contraindicated status for any remaining discordant interactions. A total of 86 drug-drug interactions were considered contraindicated by the panelists. Weighted Cohen's kappa was performed to determine if there was agreement between the panelists on whether they felt the drug-drug combinations should be contraindicated. There was high agreement between the panelists, $\kappa = 0.69 \pm 0.03$, $p < 0.001$.

The overall and stratified sensitivity and specificity of the three software programs is displayed in Table 2. The sensitivities and specificities of Clinical Pharmacology and Lexi-Interact were comparable. Micromedex had the highest overall specificity but lower sensitivity. Upon stratification by interactions involving HIV medications, there did not appear to be substantive heterogeneity and all programs had stratum-specific sensitivity/specificity values within 10% of the overall sensitivity/specificity value. In the stratified analyses of interactions that involved medications used to treat HCV infection, sensitivity of Lexi-Interact among interactions involving HCV medications was 90.9% and 62.5% for interactions not involving HCV.
medications. For Clinical Pharmacology, sensitivity was 81.3% for interactions not involving HCV medications and 45.5% for interactions involving HCV medications. In the stratified analyses examining interactions involving medications administered by oral and non-oral routes of administration, sensitivity was similar to the overall sensitivity computed. There were differences in specificity for interactions involving non-orally administered medications. Within this strata, specificity for Clinical Pharmacology and Lexi-Interact were 32% and 57%, respectively. The specificity for Micromedex did not differ from the overall specificity computed for Micromedex. In a subanalysis that only classified the interactions that were perfectly concordant as contraindicated interactions by panelists, the sensitivity of Clinical Pharmacology, Micromedex and Lexi-Interact were 68.9%, 59.0%, and 73.8%, respectively. The specificity of these programs were 42.3%, 70.5%, and 43.2%.

In an analysis to identify what types of drug interactions were missed by each program but classified as contraindicated by panelists, programs missed interactions either involved HIV or HCV medications. For Lexi-Interact, 10/16 (38.5%) of missed interactions involved HIV medications. For Clinical Pharmacology, 12/24 (50%) of missed interactions involved HCV medications. For Micromedex, 14/35 (40%) of missed interactions involved HIV medications. The absolute number of patients that would be affected by these missed interactions was also assessed. The absolute numbers of patients that would have been affected by these missed interactions for Clinical Pharmacology, Lexi-Interact and Micromedex were low and were 49, 27, and 28 patients, respectively.
DISCUSSION:

The availability of drug interaction software programs to assist clinicians in screening for drug-drug interactions has been a welcome advance in technology. Clinicians rely on these programs to provide accurate and complete drug interaction data. An ideal program would have a high sensitivity to capture all meaningful drug-drug interactions that may put a patient at risk for harm. Conversely, the ideal software program needs to be reasonably specific to avoid clinician fatigue of filtering through unimportant drug interactions or, worse, ignore interactions altogether. The intent of our study was to quantify the sensitivity and specificity of three popular software programs against a panel of clinical pharmacists as the “gold standard”. The study was exploratory and performed to screen a hypothesis. In our study, we found that all three software programs that sensitivities between 59% and 72%. This is lower than anticipated and there is significant room for improvement.

From our previous publication, a high proportion of patients are at risk for a contraindicated drug-drug interaction if they were to initiate telaprevir-based HCV therapy. Newer therapies with a safer interaction profile are emerging for the treatment of chronic HCV infection and this study could have been performed using any alternate types of HCV therapy to the patients’ medication profiles. However, the fundamental issue is still the software programs that are used and merits attention because comprehensively and correctly classifying drug interactions will continue to be an important concern. The method of detection is important to ensure that all interactions are captured and adequately assessed.
Some considerations should be taken into account to appropriately interpret these data. First, our data does not encourage/discourage the use of any one program. The goal of our study was not to compare these programs against one another. Rather, the objective of this study was to quantify the sensitivity and specificity of three commercially available software programs against a panel of clinical pharmacists. Second, we used a panel of clinical pharmacists as a gold standard. This is likely to be a contentious issue because a true “gold standard” for these programs does not exist. We adopted this methodology from the literature which frequently uses panels to define the presence or absence of a condition.[204, 206, 207] We also limited the influence of outliers by removing the two panelists who identified the most and least number of interactions to capture the experience of most clinical pharmacists who would be involved in initiating these medications. While the pharmacists in our study were highly trained, none were true drug-drug interaction experts. Future studies should investigate the level of expertise in these consensus panels to determine if differences in adjudicating interactions actually exist. Third, one problem with consensus panels is they are imperfect. Using an imperfect measurement tool as the gold standard will lead to biased estimates of sensitivity and specificity.[208-210] One reason why specificity is underestimated in this study is because we only captured interactions that were considered clinically significant (rated major or contraindicated). We did not collect information on less severe interactions. The purpose of assessing only CSDDI that were non-contraindicated (eg D-rated by Lexi-Interact, 2 by Clinical Pharmacology and “Major” by Micromedex) was to classify interactions that the software programs may
not have deemed a contraindicated interaction but the panelists would have considered to be a medication combination that should be avoided. These types of interactions are the likely place for there to be misclassification of contraindicated status. Interactions with lower severity (eg A/B/C for Lexi-Interact, 3 or 4 for Clinical Pharmacology and minor/unknown for Micromedex) are less likely to be categorized as contraindicated by panel members. Non-inclusion of interactions of lesser severity led to underestimates of specificity. In a post-hoc analysis, we estimated that there were approximately 1500-2000 interactions of lower severity that we did not have panelists assess for clinical significance. However, it was not practical to have clinical pharmacists adjudicate this volume of interactions. Recalculating specificity with these extra 1500-2000 interactions would have resulted in specificity being approximately 79%, 89% and 79% for Clinical Pharmacology, Micromedex, and Lexi-Interact, respectively. Fourth, this study was done among the medications being used by patients with HIV/HCV coinfection. It is unclear if the sensitivity/specificity of these programs would be the same in other therapeutic domains and thus the generalizability is limited to this population until future studies are performed.[211]

In summary, identification of drug interactions is an important safety issue affecting patients with HIV/HCV coinfection. Clinicians rely on software programs to screen patients’ medications for drug interactions. All three software programs that were evaluated had sensitivities in excess of 55% and opportunities to improve exist. Given the safety implications, a rigorous approach to assessing validity of these programs needs to be embraced by the medical community.
Table 1: Categorization of drug interaction severity by Lexi-Interact, Clinical Pharmacology and Micromedex

<table>
<thead>
<tr>
<th>Rating system</th>
<th>Lexi-Interact</th>
<th>Clinical Pharmacology</th>
<th>Micromedex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: no interaction</td>
<td>4: no action required</td>
<td>1: contraindicated</td>
<td>Unknown</td>
</tr>
<tr>
<td>B: no action required</td>
<td>3: monitor therapy</td>
<td>2: alter therapy</td>
<td>Minor</td>
</tr>
<tr>
<td>C: monitor therapy</td>
<td>2: alter therapy</td>
<td>1: contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>D: alter therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X: contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant drug-drug interactions</td>
<td>D: alter therapy</td>
<td>2: alter therapy</td>
<td>Major</td>
</tr>
<tr>
<td></td>
<td>X: contraindicated</td>
<td>1: contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
Table 2: Sensitivities and specificities of drug interaction software programs, stratified by type of medication, interaction and route of administration

<table>
<thead>
<tr>
<th></th>
<th>Clinical Pharmacology</th>
<th>Micromedex</th>
<th>Lexi-Interact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>72.1 (61.2-81.0)</td>
<td>59.3 (48.1-69.6)</td>
<td>69.8 (58.8-78.9)</td>
</tr>
<tr>
<td>Specificity</td>
<td>42.9 (39.6-46.3)</td>
<td>71.4 (68.1-74.3)</td>
<td>43.3 (39.6-46.6)</td>
</tr>
<tr>
<td><strong>Interactions involving non-HIV medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>66.7 (51.5-79.2)</td>
<td>56.3 (41.3-70.2)</td>
<td>66.7 (51.5-79.2)</td>
</tr>
<tr>
<td>Specificity</td>
<td>41.0 (36.7-45.5)</td>
<td>64.4 (60.1-68.5)</td>
<td>50.7 (46.3-55.0)</td>
</tr>
<tr>
<td><strong>Interactions involving HIV medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>78.9 (62.2-89.9)</td>
<td>63.2 (46.0-77.7)</td>
<td>73.7 (56.6-86.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>45.9 (40.6-51.4)</td>
<td>82.0 (77.5-85.9)</td>
<td>32.0 (27.1-37.2)</td>
</tr>
<tr>
<td><strong>Interactions involving non-HCV medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81.3 (69.2-89.5)</td>
<td>59.4 (46.4-71.2)</td>
<td>62.5 (49.5-</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td></td>
<td>70.8 (67.4-84.1)</td>
<td>42.7 (39.2-46.3)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>45.4 (41.9-48.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interactions involving HCV medications**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>59.1 (36.7-78.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>45.5 (25.1-67.3)</td>
<td></td>
<td>90.9 (69.4-98.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76.1 (65.9-84.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>40.2 (30.3-51.0)</td>
<td></td>
<td>47.8 (37.4-58.4)</td>
</tr>
</tbody>
</table>

All data presented as percent (95% confidence interval)
CHAPTER 6: CONCLUSIONS

Overview

The purpose of the dissertation was to gain a stronger understanding of clinically significant drug-drug interactions (CSDDI) involving patients with HIV/HCV infection and for whom treatment with a first generation NS3A serine protease inhibitor might be a consideration. Tremendous advances have been made in developing newer medications to treat chronic hepatitis C infection. Prior to the approval of the first-generation NS3 serine protease inhibitors telaprevir and boceprevir in 2011, the likelihood of achieving a functional cure for chronic HCV infection was poor.[146] In the past three years, 4 medications have been approved for the treatment of chronic hepatitis C to be used in combination with pegylated interferon and ribavirin.[160, 161, 180, 187]

The probability of achieving a SVR, the goal of HCV therapy, is approximately 80% with newer HCV medications.[140, 141, 164] However, the use of these newer medications is not benign. Telaprevir and boceprevir need to be taken for approximately 24 weeks in combination with pegylated interferon and ribavirin.[160, 161] Telaprevir can be administered either twice or thrice daily but with at least 20 grams of fat per dose[161]; boceprevir needs to be administered three times per day[160]. Collectively, these administration issues are concerning from the perspective of medication adherence. Both telaprevir and boceprevir have a low genetic barrier to resistance and adherence is critical to ensure a high probability of achieving a SVR. Another critical safety issue concerning these drugs is the metabolic pathway. Both drugs are metabolized by the cytochrome P450 isoenzyme system.[160, 161] This isoenzyme
system metabolizes hundreds of other medications and the metabolic pathway can be grossly affected. When medications compete for substrate binding, the metabolism can be enhanced (induction) or prolonged (inhibition). For patients who have HIV/HCV infection, this isoenzyme system is important for the metabolism of several medications used to treat HIV infection, especially the non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[181]

Polypharmacy, the use of multiple medications concomitantly, becomes problematic for the HIV/HCV coinfected population because the standard of care for HIV infection involves the use of ≥ 3 antiretroviral medications and HCV therapy includes 3 medications (pegylated interferon, ribavirin and a direct acting antiviral agent).[149, 200] These patients are using a minimum of 6 medications in addition to any other medications prescribed for comorbid conditions. Given that most patients with HCV infection are currently between 50-70 years[53], they either have or will soon develop age-related comorbidities that require medications. Thus, patients with HIV/HCV infection are very vulnerable to clinically significant drug-drug interactions (CSDDI) and deleterious clinical consequences could occur in the absence of an intervention by a healthcare professional.

Drug interactions are an unrecognized and underappreciated safety concern because they are often difficult to discern. Often, patients are clinically or socially unstable, and other comorbidities can complicate the medical profile. Additionally, a drug interaction may not immediately cause a deleterious effect but may exert its influence only after prolonged therapy or high-intensity exposure. Finally, drug
interactions are not always intuitive to prescribing/dispensing clinicians. With thousands of drug products on the market, it is difficult for the clinician to memorize every possible drug interaction. The advent of computer programs designed to screen medication profiles for drug interactions has been an important advance in pharmacy informatics. The three most popular drug interaction screening programs are Lexi-Interact, Micromedex and Clinical Pharmacology.[201-203] As a medical community, clinicians have adopted these programs at face value without a thorough evaluation of their comprehensiveness. It is not clear if these programs are equally sensitive nor whether they are specific enough to avoid clinician fatigue in filtering through unimportant drug interactions. In practice, there is no gold standard measure to define drug interactions. The development of a valid and reliable tool is an unmet need.

Prior to the work presented here, no studies had been performed examining the population-based risk and predictors of CSDDIs involving newer HCV therapies in the HIV/HCV coinfected population. Such knowledge is critical to ensuring patient safety. Additionally, very little was known about the comprehensiveness of the software programs commonly used to identify drug-drug interactions. To address these gaps in the literature, we sought to answer three research questions. Our first specific aim was to identify the prevalence and predictors of CSDDIs when telaprevir-based HCV therapy is added to the medication regimen for those with HIV/HCV coinfection. Our hypothesis was that the prevalence of CSDDIs would be high (>50%) and that discernable predictors existed, such as polypharmacy and use of high risk medications. Our second specific aim focused on the same issue but with boceprevir-based HCV therapy. Similarly, we
hypothesized that CSDDIs would be high (>50%) and that polypharmacy and high risk medications, like antiretroviral therapy, would predict which patients would develop a CSDDI. Our third specific aim concerned the software programs used to identify CSDDIs. The goal was to quantify the sensitivity and specificity of three commercially available software programs against a gold standard panel of clinical pharmacists. Our hypothesis was that sensitivity for each program would be high (>70%) and specificity would be low (<50%). Each of these aims resulted in a manuscript suitable for publication in a peer-reviewed medical journal. The first and third manuscripts were among HIV/HCV coinfected patients who received care at either Upstate University Hospital (Syracuse, NY) or the New York Veterans Administration (VA) Health Care Network, or Veterans Integrated Service Network 2 (VISN-2) between 2000 and 2011. The second manuscript only included HIV/HCV coinfected patients from VISN-2.

**Pertinent Findings**

In each of the studies, we observed a number of interesting findings that contribute to the body of knowledge surrounding CSDDIs among HIV/HCV infected patients who might initiate therapy with telaprevir or boceprevir-containing therapy. In the first study concerning telaprevir, we observed an alarming prevalence of CSDDIs and contraindicated interactions among HIV/HCV patients. Perhaps more concerning, the prevalence of CSDDIs and contraindicated interactions was high even before the addition of telaprevir-containing therapy, and the prevalence increased significantly after a telaprevir-containing agent was added.
Given the importance of ART for the management of HIV infection, we also evaluated which types of ART were associated with the lowest risk of contraindicated interactions. The ART regimen type with the lowest risk of a contraindicated interaction after the addition of telaprevir-containing therapy were the integrase strand transfer inhibitors (ISTIs). Given the time period of our study, the most frequently used ISTI was raltegravir. We were not able to delineate, with sufficient power, if heterogeneity in risk existed for the other ISTIs. Conversely, protease inhibitor ART regimens had the highest risk of a contraindicated interaction after the addition of telaprevir-containing therapy. This is important because switching patients to ISTI-based ART may be a potential mechanism to avoid contraindicated interactions in this population when considering the addition of HCV therapy. The predictors of contraindicated interactions were dyslipidemia, administration of protease inhibitors, and use of ≥ 10 non-HIV medications. To add some granularity to our multivariate prediction models, we replaced the use of protease inhibitors with the individual protease inhibitors and the only agents to remain significant were darunavir, lopinavir and fosamprenavir.

In the boceprevir study examining the prevalence and predictors of CSDDIs and contraindicated interactions among HIV/HCV patients, we observed similar findings. Even before the addition of boceprevir-containing HCV therapy, we observed a high frequency of CSDDIs and contraindicated interactions. After the addition of boceprevir, the frequency of these outcomes increased significantly. The prevalence of CSDDIs after boceprevir therapy approached 100%, indicating that nearly all patients are at risk. Once again, ISTI regimens were associated with the lowest risk of contraindicated interactions.
after the addition of boceprevir-containing therapy. Significant increases in the probability of a contraindicated interaction were observed among patients using non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and mixed/multiple class ART regimens. This finding diverges from the telaprevir paper in that we did not find a statistically significant increase in the frequency of contraindicated interactions. We surmise this was primarily because there is a direct interaction between boceprevir and efavirenz, the most popular NNRTI. In the multivariate model, important predictors were atazanavir, lopinavir, efavirenz, darunavir and use of ≥ 8 medications.

In the third paper which quantified the sensitivity and specificity of drug interaction software programs, we observed tremendous variance between products. Specifically, Micromedex had lower point estimates of sensitivity than Clinical Pharmacology and Lexi-Interact. However, specificity was highest for Micromedex, and sensitivity was highest for Clinical Pharmacology and Lexi-Interact. In a stratified analysis of HCV and non-HCV medications containing interactions, differences did persist. Specifically, among interactions involving HCV medications, sensitivity was highest for Lexi-Interact relative to the other programs. In this strata, specificity was highest for Micromedex relative to the other programs. Among interactions with non-HCV medications (in other words, medications the patients were already on before addition of telaprevir-based therapy), the exact point estimates of sensitivity did vary. However, we did not have enough power to observe significant differences in these point
estimates. Specificity was significantly higher for Micromedex compared to the other programs.

**Limitations**

Several considerations should be taken into account before interpreting these data. Each of these studies were cross-sectional in nature and several attendant limitations should be noted. These issues are i) temporal ambiguity and ii) lead-time bias. Specifically, temporal ambiguity is not likely to be an issue because exposure to telaprevir- or boceprevir-containing HCV therapy was entirely theoretical. Lead-time bias may be an issue because patients who have been living with HIV/HCV coinfection longer may be using more medications as a function of duration of illness and may not be representative of patients who are newly diagnosed. We attempted to control for this by adjusting for the duration of HIV and HCV infections. In both the bivariate and multivariate analyses, this did not appear to be an important covariate and was not associated with any particular medication use patterns.

Another concern is the data were retrospectively obtained. While this certainly affects studies involving participant recall, we limited the amount of bias that could be introduced by only using data that was objectively defined in the patients’ medical records. Medication lists were obtained from the patients’ dispensing records. All clinical and demographic information were items that were documented in the medical records. Any potential or residual information biases are non-differentially distributed between exposure groups because we examined the same individual under different exposure conditions. The biases are also likely to be non-differentially distributed by
outcome status and the overall measure of association is downwardly biased towards to the null, if at all.

Additionally, the exposure in this study was completely hypothetical. None of the patients in these studies received telaprevir- or boceprevir-containing HCV therapy. When designing an epidemiologic study, one of the goals is to achieve a design that mimics the counterfactual as closely as possible. In all three studies, each patient was evaluated for CSDDIs and contraindicated interactions under different exposure conditions (e.g., before/after addition of telaprevir- or boceprevir-containing therapy). This approach is also attractive from a bioethical perspective. We did not need to wait for more than 330 patients to initiate therapy with both of these agents to evaluate the drug-drug interaction risk. We were able to answer this question without exposing patients to harm and will hopefully prevent harm by alerting clinicians to the risks.

From a practical standpoint, both telaprevir and boceprevir are being replaced by newer agents, such as simeprevir and sofosbuvir. Thus, the relevance of the drugs studied here may diminish, but they are unlikely to be rendered inconsequential. Rather, telaprevir and boceprevir will likely be deployed in developing countries where the prevalence of HCV is high and resources are scarce. Another important political issue that may prolong the lifespan of these drugs is pricing. Simeprevir and sofosbuvir are priced much higher than the established agents. As the third generation of direct-acting antiviral drugs for the treatment of chronic HCV infection become available, the price war is likely to become competitive and third party payers will influence clinical use.
Finally, for the drug interaction software study, our methodology is novel for this inquiry. Our study was exploratory and serves as a means to screen hypotheses. To our knowledge, no evaluation has yet been undertaken to estimate the sensitivity and specificity of popular software programs to capture CSDDIs and contraindicated interactions relative to a panel of clinical pharmacists. No gold standard for these software programs exists and one needs to be established. If a panel is to be employed as the gold standard, the ideal composition of this panel needs to be determined in subsequent studies. In our study, we devised a consensus panel of 5 clinical pharmacists to serve as the experts. However, humans are imperfect and inconsistencies can lead to biased point estimates of sensitivity and specificity. We attempted to reduce bias by removing the most extreme pharmacists from the panel: the panelists identifying the most and least CSDDIs. This also increased the probability of achieving perfect consensus on adjudicated interactions among the remaining three panel members. Collectively, these findings suggest that the software programs should be tested more thoroughly to capture important feedback regarding which are most clinically meaningful in practice.

**Future Directions**

The findings from the dissertation have important implications for subsequent research and the ongoing clinical care of HCV-infected patients. The telaprevir and boceprevir papers demonstrated that patients with HIV/HCV coinfection use a high volume of medications. Even before the addition of HCV therapy, these patients had a high frequency of CSDDIs and contraindicated interactions. However, the clinical
outcomes associated with these interactions remains unclear. Future studies should consider assessing the relationship between CSDDIs and meaningful clinical endpoints, such as death and hospitalizations. Currently, CSDDIs are largely under-recognized and underappreciated. Data describing the relationship between CSDDIs and mortality and hospitalization will elucidate this issue.

Our study was performed in a very select group of patients. Patients with HIV/HCV coinfection are a small proportion of all patients with HCV coinfection. A larger population of patients, those with HCV monoinfection, are likely to have many of the same medication-related issues as patients with HIV/HCV coinfection. The literature is also fairly limited regarding the typical medication profile among patients with HCV monoinfection. It is not known whether these patients have a high frequency of underlying CSDDIs and contraindicated drug interactions. It would be helpful to describe predictors of CSDDIs in this population as well.

Newer drugs are emerging for the treatment of chronic HCV infection. Telaprevir and boceprevir are the first generation direct-acting antiviral drugs used to treat chronic HCV infection. They are being replaced with the second generation direct-acting antiviral drugs, simeprevir and sofosbuvir. Simeprevir is a NS3 serine protease inhibitor and has a high number of drug-drug interactions. Sofosbuvir is a polymerase inhibitor and does not appear to have as many drug-drug interactions, however, the exact population-based frequency is not known. Furthermore, the predictors of CSDDIs and contraindicated interactions involving simeprevir and sofosbuvir are not yet described in the literature. While the current focus is on simeprevir and sofosbuvir, third generation
direct-acting regimens of HCV therapy are on the horizon and these studies will need to be replicated for patients with HCV monoinfection as well as those with HIV/HCV coinfection.

Finally, software programs used to identify CSDDIs and contraindicated interactions would benefit from modifications to improve sensitivity and specificity. Given the absence of a “gold standard” for these programs, future research should focus on defining the gold standard. If an expert panel is appropriate, the ideal composition of this panel should also be defined. For instance, it is unclear what the ideal number of panelists should be or the level of expertise among the panel members. There may also be other methodologically sound means to quantify the sensitivity and specificity of these software programs. Such studies should also include patients with comorbid health conditions to ascertain whether our findings are generalizable to other subspecialties.

In conclusion, these studies collectively underscore the importance of identifying predictors of important drug-drug interactions, both for existing drugs as well as those in development. The detection of these drug-drug interactions hinges on the development of robust software packages which take into consideration the demographic characteristics of the population (such as age and concomitant medications outside the treated condition). While advances have been made on both fronts—prediction and detection—it is important to continue this work because medication-related issues are among the most inexorable patient safety problems, particularly in vulnerable populations with high medication use.
REFERENCES


96. Dienstag JL. Sexual and perinatal transmission of hepatitis C. *Hepatology* 1997, **26**:66S-70S.


Increased vertical transmission of human immunodeficiency virus from hepatitis 
C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis* 

111. Jamieson DJ, Skunodom N, Chaowanachan T, Roongpisuthipong A, Bower WA, 
Chotpitayasunondh T, et al. Infection with hepatitis C virus among HIV-infected 

infant transmission of hepatitis C virus: rate of infection and assessment of viral 

Hepatitis C--role of perinatal transmission. *Aust N Z J Obstet Gynaecol* 

Perinatal transmission and manifestation of hepatitis C virus infection in a high 

*al.* Perinatal transmission of hepatitis C virus from human immunodeficiency 
virus type 1-infected mothers. Women and Infants Transmission Study. *J Infect 

transmission of the hepatitis C virus to infants of anti-human immunodeficiency


Table 1: Clinical Outcomes of Patients Enrolled in the REALIZE Study, Stratified by Previous Failure Type

<table>
<thead>
<tr>
<th>SVR, %</th>
<th>T12PR48 No Lead-in</th>
<th>T12PR48 With Lead-in</th>
<th>PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 266)</td>
<td>(n = 264)</td>
<td>(n = 132)</td>
</tr>
<tr>
<td>Previous relapsers</td>
<td>83*</td>
<td>88*</td>
<td>24</td>
</tr>
<tr>
<td>Previous nonresponders</td>
<td>41*</td>
<td>41*</td>
<td>9</td>
</tr>
<tr>
<td>- Previous partial responder</td>
<td>59*</td>
<td>54*</td>
<td>15</td>
</tr>
<tr>
<td>- Previous null responder</td>
<td>29*</td>
<td>33*</td>
<td>5</td>
</tr>
</tbody>
</table>

*P < .001 vs pegIFN/RBV control arm.
Table 2: Medications that are Contraindicated when Coadministered with Boceprevir or Telaprevir

<table>
<thead>
<tr>
<th>Drugs Within Class that are Contraindicated With VICTRELIS</th>
<th>Clinical effects</th>
<th>Drugs within Class that are Contraindicated with INCIVEK</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>Increased alfuzosin concentrations can result in hypotension</td>
<td>Alfuzosin</td>
<td>Potential for hypotension or cardiac arrhythmia</td>
</tr>
<tr>
<td>Carbamazepine, phenobarbital, Phenytoin</td>
<td>May lead to loss of virologic response to VICTRELIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>Potential for cardiac arrhythmias.</td>
<td>Cisapride</td>
<td>Potential for cardiac arrhythmias</td>
</tr>
<tr>
<td>Dihydroergotamine,</td>
<td>Potential for acute</td>
<td>Dihydroergotamine,</td>
<td>Potential for acute</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Ergotamine, Ergonovine, Methylergonovine</th>
<th>Ergot Toxicity Characterized by Peripheral Vasospasm and Ischemia of the Extremities and Other Tissues.</th>
<th>Ergonovine, Ergotamine, Methylergonovine</th>
<th>Ergot Toxicity Characterized by Peripheral Vasospasm or Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drospirenone</td>
<td>Potential for Hyperkalemia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>May Lead to Loss of Virologic Response to VICTRELIS.</td>
<td>Rifampin</td>
<td>Rifampin Significantly Reduces Telaprevir Plasma Concentrations</td>
</tr>
<tr>
<td>St. John’s Wort (Hypericum perforatum)</td>
<td>May Lead to Loss of Virologic Response to Boceprevir</td>
<td>St. John’s Wort (Hypericum perforatum)</td>
<td>Plasma Concentrations of Telaprevir Can Be Reduced by Concomitant Use of the Herbal Preparation St.</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Potential for Adverse Events</td>
<td>Potential for Adverse Events</td>
<td>Potential for Adverse Events</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Lovastatin, simvastatin</td>
<td>Potential for myopathy, including rhabdomyolysis</td>
<td>Lovastatin, simvastatin</td>
<td>Potential for myopathy including rhabdomyolysis</td>
</tr>
<tr>
<td>REVATIO® (sildenafil) or ADCIRCA®</td>
<td>Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.</td>
<td>Sildenafil (Revatio®) or tadalafil (Adcirca®) [for treatment of pulmonary arterial hypertension]</td>
<td>Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Potential for cardiac arrhythmias</td>
<td>Pimozide</td>
<td>Potential for serious and/or life-threatening adverse reactions</td>
</tr>
</tbody>
</table>

*Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.*
<table>
<thead>
<tr>
<th>Triazolam; orally administered midazolam†</th>
<th>Prolonged or increased sedation or respiratory depression</th>
<th>Orally administered midazolam, triazolam</th>
<th>Prolonged or increased sedation or respiratory depression</th>
<th>such as cardiac arrhythmias</th>
</tr>
</thead>
</table>

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APPENDICES

Appendix A: Data collection forms for Manuscript #1 and Manuscript #2

Age: ______  Gender: M  F
Race: AA  Hisp  Cauc  Other  Weight: ______ kg  lbs

Height ______ cm  inch

HIV dx date: ___________ Latest CD4 count ___________ Latest HIV RNA

HCV dx date: ___________ HCV genotype ______ Latest HCV viral load

Tx Hx: Experienced or Naïve  Regimen Type: NNRTI-  PI-

INSTI-

Number of NRTIs:  2  3  4  5  Total number of antiretrovirals: ______

Current medications:

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Drug Resistance (drugs only, not mutations):

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</tbody>
</table>
Co-morbidities:

Drug Interaction results info:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

*Medication regimen as listed above*

Total drug interactions present: ____________

Clinically significant interactions present: ____________

Number of dose-changing interactions: ____________

Number of contraindicated/extreme precaution interactions: ____________

197
**BOCEPREVIR**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication regimen as listed above PLUS PegIFN + ribavirin + boceprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total drug interactions present: _____________

Clinically significant interactions present: _____________

Number of dose-changing interactions: _____________

Number of contraindicated/extreme precaution interactions: _____________
**TELAPREVIR**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

*Medication regimen as listed above PLUS PegIFN + ribavirin + telaprevir*

Total drug interactions present: ____________

Clinically significant interactions present: ____________

Number of dose-changing interactions: ____________

Number of contraindicated/extreme precaution interactions: ____________
Appendix B: Data collection form for Manuscript #3

Drug Interaction results info: Lexi-Comp: Severities: A, B, C, D, & X (Clinically Significant: D & X)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Severity</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

Total drug interactions present: __________

Clinically significant interactions present: __________

Number of dose-changing interactions: __________

Number of contraindicated/extreme precaution interactions: __________
Drug Interaction results info: Micromedex: Severities Unknown, Minor, Moderate, Major, CI

(Clinically Significant: Major & CI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Severity</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

Total drug interactions present: ____________

Clinically significant interactions present: ____________

Number of dose-changing interactions: ____________

Number of contraindicated/extreme precaution interactions: ____________
Drug Interaction results info: Clinical Pharmacology Severities: 1-4, Clinically Significant: 1 & 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Severity</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Total drug interactions present: ____________
Clinically significant interactions present: ____________
Number of dose-changing interactions: ____________
Number of contraindicated/extreme precaution interactions: ____________