AHRQ Grant Final Progress Report

Title of Project: Clinical Prediction of Hepatotoxicity & Comparative Hepatic Safety of Medications

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1. Structured Abstract
Purposes: (1) To evaluate the incidence and outcomes of drug-induced acute liver failure (ALF) in an integrated healthcare system; (2) develop and validate a highly sensitive model to identify patients with drug-induced liver injury who are at increased risk of ALF; and (3) compare the risk of severe acute liver injury and ALF associated with different medications to provide additional evidence on comparative hepatic safety.

Scope: Drug-induced hepatotoxicity is currently the second most frequent reason for withdrawal of marketed medications after release and one of the most common reasons for termination of therapeutic agents during pre-clinical studies.

Methods: This retrospective cohort study used 2004-2010 data from Kaiser Permanente Northern California, an integrated healthcare organization that provides inpatient and outpatient services, and 2004-2012 data from the Veterans Aging Cohort Study, which consists of electronic medical record data from HIV-infected patients at Veterans Affairs medical facilities across the United States.

Results: Drug-induced ALF is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes. A new risk prediction model with platelet count and total bilirubin identified patients with drug-induced liver injury at increased risk of ALF with high sensitivity and reasonable specificity. Additionally, risks of acute liver injury were low among fluconazole, ketoconazole, and itraconazole users, and pre-existing chronic liver disease was a strong risk factor. Acute liver injury occurred rarely within the first year of modern antiretroviral initiation, but protease inhibitor use was associated with a higher risk of aminotransferase elevations among hepatitis-coinfected patients.

Keywords: hepatotoxicity, acute liver failure, liver injury

2. Purpose
The purposes of this study were to (1) evaluate the incidence and outcomes of drug-induced acute liver failure (ALF) in an integrated healthcare system; (2) develop and externally validate a highly sensitive model to identify drug-induced liver injury patients at increased risk of ALF and compare its performance with that of Hy’s Law, which predicts severity of drug-induced liver injury based on levels of alanine aminotransferase or aspartate aminotransferase and total bilirubin; and (3) compare the risk of severe acute liver injury and ALF associated with different medications to provide additional evidence on the comparative hepatic safety of these medications. We sought to provide additional evidence on the hepatic safety of medications, informing decision making about the appropriate treatments for various clinical conditions and settings.

3. Scope
Background & Context
Drug-induced hepatotoxicity, defined as liver injury caused by exposure to a medication, is currently the second most frequent reason for withdrawal of marketed medications after release and one of the most common reasons for termination of otherwise promising therapeutic agents during pre-clinical studies. From a clinical standpoint, a missed diagnosis of severe drug-induced hepatotoxicity can lead to morbidity and mortality from liver failure, and it is now the leading cause of ALF among patients referred for liver transplantation. However, no population-based study has determined the incidence, etiologies, and outcomes of drug-induced ALF. Furthermore, few studies have examined the ability to predict the development of ALF among patients with suspected drug-induced liver injury. Moreover, few studies have examined the comparative risk of acute liver injury associated with drugs within classes. The determination of the comparative safety and effectiveness of medications is an area
of major importance in Comparative Effectiveness Research. Given the clinical and public health impact of drug-induced hepatotoxicity, the development of new methods to predict the likelihood of liver failure in the setting of hepatotoxicity and determination of the comparative risk of liver failure for medications within drug classes are crucial to understanding the comparative safety of drugs.

Currently, the most commonly employed method to predict the potential for a medication to lead to liver failure is “Hy’s Law,” created out of clinical impressions by Dr. Hyman Zimmerman at the Armed Forces Institute of Pathology. Hy’s Law, which uses elevations in both liver aminotransferases and total bilirubin for clinical prediction, has been invoked by the United States Food and Drug Administration (FDA) and pharmaceutical manufacturers as a key predictor of liver failure. Despite its extensive use, no studies have validated or sought to improve upon Hy’s Law to classify cases of drug-induced hepatotoxicity by risk of progression to liver failure, despite the enormous impact of this adverse event. Furthermore, almost no data have compared medications within drug classes for their risk of serious hepatotoxicity and liver failure. The results of such studies would enhance substantially the comparative safety of medications used for the treatment of any given condition.

Settings
This study used data from Kaiser Permanente Northern California (KPNC), an integrated healthcare organization that provides inpatient and outpatient services to Northern California residents, and the Veterans Aging Cohort Study, consisting of electronic medical record data from HIV-infected patients receiving care at Veterans Affairs (VA) medical facilities across the United States.

Participants
The source population was an inception cohort, which is a defined sample of patients assembled for a study at a common point in their disease and followed up over time. The inception cohort included all patients in the data sources who did not have a diagnosis of chronic liver disease (defined by one or more of the following: hepatitis B, hepatitis C, autoimmune hepatitis, cirrhosis, hemochromatosis, hepatocellular carcinoma, and/or alcoholic liver disease) recorded within their initial year of enrollment. Additional inclusion/exclusion criteria differed according to the study aims.

Agency for Healthcare Research and Quality (AHRQ) Priority Populations
Our use of data from the VA system increases the proportion of patients from AHRQ priority populations, including patients who are minorities, live in inner cities, have low incomes, have disabilities, and need chronic or end-of-life care. Our use of data from KPNC also increases the proportion of patients from AHRQ priority populations, specifically women and elderly patients. Thus, use of these data sources ensures inclusion of AHRQ priority populations.

Incidence & Prevalence
A number of epidemiologic studies have evaluated the incidence of drug-induced hepatotoxicity, but results have varied. A retrospective study of 4,209 inpatients from Switzerland reported the incidence of drug-induced hepatotoxicity, defined as liver aminotransferase or direct bilirubin levels exceeding twice the upper limit of normal (ULN), to be 1.4%. In contrast, the incidence of hepatotoxicity among 160,000 Massachusetts outpatients was 0.04% per year using International Classification of Diseases, Ninth Revision (ICD-9) codes. Although these studies provide valuable data, their results are very different, potentially due to referral bias and definitely due to their use of markedly different definitions for drug-induced hepatotoxicity.
Epidemiologic studies have also evaluated the association between individual medications and/or drug classes and hepatotoxicity, typically defined by either elevations in liver aminotransferases or hospitalizations for acute hepatitis. One of these initial studies, led by Dr. Strom (a co-investigator on this study), used Medicaid data from Michigan and Florida between 1980 and 1987 to show that hospitalization for acute hepatitis was associated with use of erythromycin (odds ratio, 5.2; 95% confidence interval [CI], 1.1-26.6), sulfonamides (odds ratio, 11.4; 95% CI, 2.7-67.8), and tetracyclines (odds ratio, 3.6; 95% CI, 0.9-14.3). Many other studies have used data from clinical trials or population-based databases (e.g., United Kingdom’s General Practice Research Database, Kaiser Permanente, Ingenix) to evaluate hepatotoxicity due to such drug classes as nonsteroidal anti-inflammatory agents, thiazolidinediones, statins, antidepressants, antipsychotics, anti-tuberculosis agents, and antiretrovirals. Each used a different outcome. Many studied hospitalization for hepatic disease, an outcome of variable importance and subject to referral bias.

ALF is the most serious clinical outcome of drug-induced hepatotoxicity and is defined by the acute onset of hepatic encephalopathy and coagulopathy (international normalized ratio [INR] ≥1.5) within 26 weeks of illness onset in the absence of chronic liver disease. Few studies have examined liver failure from drug-induced hepatotoxicity. One case series from Sweden examined suspected cases of severe drug-associated hepatotoxicity from 1974-2004. Among 784 cases associated with a total bilirubin ≥2 times ULN, 72 (9%) either died from liver failure or underwent liver transplantation. A second study from Spain identified 446 cases of suspected drug-induced hepatotoxicity between 1994 and 2004. In total, 237 (53%) cases required hospitalization, and 18/237 (8%) developed liver failure. The incidence of liver transplantation or death was 12% in patients who presented to the hospital with both elevations in liver aminotransferases and jaundice. The United States Acute Liver Failure Study Group, a network of 23 centers examining the etiologies and outcomes of ALF since 1998, estimates that 58% of cases are due to drug-induced hepatotoxicity, particularly acetaminophen overdoses.

4. Methods

Study Design

We conducted a series of retrospective cohort studies to complete the study aims.

Data Sources & Collection

Data were from Kaiser Permanente Northern California (KPNC), an integrated healthcare organization that provides inpatient and outpatient services to Northern California residents, between January 1, 2004, and December 31, 2010. Data collected by KPNC included demographic information; outpatient and hospital diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9] codes); procedures; inpatient and outpatient laboratory results; emergency and referral services at non-Kaiser Permanente facilities; and dispensed medications. Diagnoses are assigned by clinicians and are not linked with compensation. Prescription drug benefits are used by >90% of members, and prior analyses have established the accuracy of pharmacy data. Mortality databases integrate death certificate data from the Social Security Administration Death Master File.

For one aim, we also used data from the Veterans Aging Cohort Study (2004-2012), which consists of electronic medical record data from HIV-infected patients receiving care at VA medical facilities across the United States. Data included demographics, hospital and outpatient ICD-9 diagnoses, procedures, inpatient and outpatient laboratory results, and pharmacy data. Deaths were identified from the VA Vital Status file.
Interventions
There were no interventions with this study.

Measures
The primary outcome was ALF, defined based on American Association for the Study of Liver Diseases criteria. Using medical records, a definite diagnosis of ALF was confirmed if a patient had 1) no pre-existing liver disease, 2) coagulopathy (INR ≥1.5) without anticoagulation therapy, and either 3a) hepatic encephalopathy or 3b) liver transplant due to ALF. The ALF date was defined as the first of either the date that hepatic encephalopathy initially presented or the liver transplant date. A possible diagnosis of ALF was confirmed if a patient met criteria 1 and 2 (above) and had either 1) altered mentation in the absence of a recorded diagnosis of hepatic encephalopathy plus encephalopathy treatment (e.g., lactulose or rifaximin) with no other central nervous system abnormality or 2) liver transplant due to an unspecified etiology. For these patients, the ALF date was the first of either the date of initial encephalopathy treatment or the liver transplant date.

To determine the full spectrum of acute liver injury events, we also determined development of severe liver aminotransferase elevations, defined as an inpatient or outpatient alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >200 U/L (~5 times the ULN of the assays used, a threshold that represents clinically important hepatic injury, and ~10 times what has been considered normal liver aminotransferase levels for men [30 U/L] and women [19 U/L]). Next, we evaluated severe acute liver injury, defined by an inpatient or outpatient INR ≥1.5 and total bilirubin >2 times ULN within 30 days of each other. This definition indicates severe hepatic dysfunction and has been used by the FDA’s Mini-Sentinel initiative to assess serious drug-induced hepatotoxicity in the post-marketing setting.

Limitations
Our methods have several potential limitations. First, we used ICD-9 diagnoses to exclude patients with non-viral chronic liver disease, and there is the potential that some patients might have been misclassified as having underlying liver disease. Second, we restricted medical record review to patients with a peak total bilirubin ≥5.0 mg/dL, given the low likelihood of ALF developing without a peak total bilirubin reaching this value. There is the potential that we might have missed a very small number of patients with ALF who never obtained this total bilirubin level, in particular those with acetaminophen-induced ALF. However, even if the total incidence of drug-induced ALF was underestimated by as much as 25%, the incidence of drug-induced ALF would only increase to 2.57 cases per 1,000,000 person-years. Third, the data were reviewed retrospectively, and certain laboratory tests (e.g., hepatitis E serologies) were missing for some patients. Nevertheless, determination of the etiology of ALF was based on independent adjudication by at least two hepatologists. Additionally, there were no events deemed to be drug induced when a competing potential etiology was considered, yet not diagnosed, because of missing laboratory testing (e.g., a case when the diagnosis was deemed drug induced, but the patient lacked test results for other diagnoses, such as quantitative immunoglobulins for autoimmune hepatitis). Fourth, alcohol history was based on retrospective review of the medical record, which may have led to misclassification of chronic alcohol use. However, this limitation may also potentially exist in prospectively collected data if patients do not report alcohol use, and any misclassification would likely lead to under-recognition of chronic alcohol use and, thus, overestimation of true drug-induced ALF in the absence of chronic alcohol use. Fifth, the exact preparation and purchase location of the dietary/herbal supplements that led to ALF were not known.
5. Results

Principal Findings

- Electronic algorithms comprising relevant hospital diagnoses, laboratory evidence of liver dysfunction, and prescriptions for hepatic encephalopathy treatment had low positive predictive values (PPVs) for confirmed ALF events. Thus, studies evaluating ALF will need to rely on medical records to confirm this outcome.
- Drug-induced ALF is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes.
- A new risk prediction model (DrILTox ALF Score) with platelet count and total bilirubin identified patients with drug-induced hepatitis who are at increased risk of ALF with high sensitivity while retaining reasonable specificity.
- Risks of acute liver injury were similarly low among users of fluconazole, ketoconazole, and itraconazole. Pre-existing chronic liver disease was a strong risk factor for development of acute liver injury among azole users.
- Acute liver injury occurred rarely within the first year of modern ART initiation. Protease inhibitor use was associated with a higher risk of aminotransferase elevations among hepatitis-coinfected patients.

Outcomes

Evaluation of electronic algorithms for ALF. Identification of ALF is important for post-marketing surveillance of medications, but the validity of using ICD-9 diagnoses and laboratory data to identify these events within electronic health records is unknown. We examined PPVs of hospital ICD-9 diagnoses and laboratory tests of liver dysfunction for identifying ALF within a large, community-based, integrated care organization. We identified Kaiser Permanente Northern California health plan members (2004-2010) with a hospital discharge diagnosis suggesting ALF (ICD-9 570, 572.2, 572.4, 572.8, 573.3, 573.8, or V42.7) plus an inpatient international normalized ratio ≥1.5 (off warfarin) and total bilirubin ≥5.0 mg/dL. Hospital records were reviewed by hepatologists to adjudicate ALF events. PPVs for confirmed outcomes were determined for individual ICD-9 diagnoses, diagnoses plus prescriptions for hepatic encephalopathy treatment, and combinations of diagnoses in the setting of coagulopathy and hyperbilirubinemia.

Among 5,484,224 KPNC members between 2004 and 2010, 669 had inpatient diagnostic and laboratory criteria indicating potential ALF with no pre-existing liver disease. Chart review confirmed ALF in 62 (9%). Despite the presence of co-existing coagulopathy and hyperbilirubinemia, individual ICD-9 diagnoses had low PPVs (range, 5%-15%); requiring prescriptions for encephalopathy treatment did not increase PPVs of these diagnoses (range, 2%-23%). Hospital diagnoses of other liver disorder (ICD-9 573.8) plus hepatic coma (ICD-9 572.2) had high PPVs (67%; 95% CI, 9%-99%) but only identified two (3%) ALF events.

Algorithms comprising relevant hospital diagnoses, laboratory evidence of liver dysfunction, and prescriptions for hepatic encephalopathy treatment had low PPVs for confirmed ALF events. Studies of ALF will need to rely on medical records to confirm this outcome.

Incidence and outcomes of drug-induced ALF. Among 5,484,224 KPNC members between 2004 and 2010, 669 had inpatient diagnostic and laboratory criteria indicating potential ALF with no pre-existing liver disease. Chart review confirmed ALF in 62 (9%), and 32 (52%) of the 62 members categorized as having definite or possible ALF had a drug-induced etiology (27 definite, 5 possible). Acetaminophen was implicated in 18 events (56%); dietary/herbal supplements, in six (19%); antimicrobials, in two (6%); and miscellaneous medications, in six (19%). One patient with acetaminophen-induced ALF died (6%; 0.06 events/1,000,000 person-
years) compared with three patients who had non–acetaminophen-induced ALF (21%; 0.18/1,000,000 person-years). Overall, six patients (19%) underwent liver transplantation, and 22 patients (69%) were discharged without transplantation. The incidence rates of any definite drug-induced ALF and acetaminophen-induced ALF were 1.61 events/1,000,000 person-years (95% CI, 1.06-2.35) events and 1.02 events/1,000,000 person-years (95% CI, 0.59-1.63), respectively.

**Prediction of ALF among patients with drug-induced liver injury.** Hy’s Law biochemical criteria had high specificity (0.92) and negative predictive value (0.99) but low sensitivity (0.68) and PPV (0.02) for incident ALF. Prognostic models with AST, ALT, and total bilirubin alone had high discriminative ability (c-statistic range, 0.83-0.85). The model that had the highest discrimination (c-statistic, 0.87; 95% CI, 0.76-0.96) included platelet count and total bilirubin (DrILTox ALF Score = -0.00691292*platelet count [per 10^9/L] + 0.19091500*total bilirubin [per 1.0 mg/dL]), indicating that decreasing platelet count and increasing total bilirubin were strong predictors of incident ALF. This model closely predicted the actual observed numbers of patients with and without ALF (Hosmer-Lemeshow goodness-of-fit test p=0.29). A cutoff identifying high-risk patients had a sensitivity of 0.91 (95% CI, 0.71-0.99) and a specificity of 0.76 (95% CI, 0.75-0.77). There was little decrease in the model’s discriminative ability during internal validation.

We applied the Spanish drug-induced liver injury prognostic algorithm to our cohort of patients with suspected drug-induced liver injury within KPNC at the initial drug-induced liver injury diagnosis date. The specificity (99%) and negative predictive value (99%) of this algorithm were both very high, but the sensitivity was low (13%). Notably, with this algorithm’s focus on specificity, very few patients were identified as high risk, including only three of the 22 individuals who developed ALF. The PPV was 15%.

**Comparative hepatic safety of azole antifungals.** Among 195,334 azole initiators (178,879 fluconazole; 14,296 ketoconazole; 1,653 itraconazole; 478 voriconazole; 28 posaconazole), incidence rates (events/1,000 person-years [95% CIs]) of liver aminotransferases >200 U/L were similarly low with fluconazole (13.0 [11.4-14.6]), ketoconazole (19.3 [13.8-26.3]), and itraconazole (24.5 [10.6-48.2]). Rates were higher with voriconazole (181.9 [112.6-278.0]) and posaconazole (191.1 [23.1-690.4]) but comparable. Severe acute liver injury was uncommon with fluconazole (2.0 [1.4-2.7]), ketoconazole (2.9 [1.1-6.3]), and itraconazole (0.0 [0.0-11.2]) but more frequent with voriconazole (16.7 [2.0-60.2]) and posaconazole (93.4 [2.4-520.6]). Only one patient developed ALF due to ketoconazole. Pre-existing chronic liver disease increased risks of aminotransferases >200 U/L (hazard ratio, 4.68 [95% CI, 3.68-5.94]) and severe acute liver injury (hazard ratio, 5.62 [95% CI, 2.56-12.35]).

**Risk of acute liver injury with modern antiretroviral therapy (ART).** Liver aminotransferases >200 U/L developed in 206 (2%) people, and rates were higher for viral hepatitis-coinfected versus HIV-monoinfected people (116.1 versus 20.7 events/1,000 person-years; p<0.001). The risk of this outcome was similar between initiators of abacavir/lamivudine and tenofovir/emtricitabine in hepatitis-coinfected (hazard ratio, 0.68 [0.29-1.57]) and in HIV-monoinfected (hazard ratio, 1.19 [0.47-2.97]) groups. Coinfected patients had a higher risk of aminotransferases >200 U/L after ART initiation with a protease inhibitor than with a non-nucleoside reverse transcriptase inhibitor (hazard ratio, 2.01 [1.36-2.96]). Severe acute liver injury developed in 30 patients (0.3%) and was more frequent with hepatitis coinfection (15.9 versus 3.1 events/1,000 person-years; p<0.001) but was too uncommon to evaluate in adjusted analyses.
Discussion

Our development and evaluation of the performance of electronic algorithms to identify ALF based on relevant hospital diagnoses, laboratory evidence of severe liver injury, and treatment for hepatic encephalopathy sought to improve upon prior analyses that exclusively focused on diagnosis codes.\textsuperscript{66} The algorithms we developed yielded PPVs that were higher than previously reported,\textsuperscript{62,67} but they remained too low to be acceptable for use within observational studies. There are several reasons that sufficiently high PPVs might not have been observed. First, ALF is a diagnosis that occurs very rarely.\textsuperscript{68} Consequently, the low prevalence of ALF likely resulted in the low PPVs of the electronic algorithms we developed. Second, there is no ICD-9 diagnosis code that specifically indicates ALF. Although the ICD-9 diagnoses we selected focused on liver injury,\textsuperscript{67,69} they did not exclusively indicate ALF. Hepatic failure is included as a specific diagnosis in the ICD-10 coding system (K72), but these diagnoses have not yet been in wide use within the US, and the validity of this diagnosis code for ALF is unknown. Furthermore, hepatic failure is not a specific clinical diagnosis, so it might not result in increased PPVs. Third, many patients had pre-existing liver or biliary disease that was not electronically detected by our selected clinical, serologic, or virologic diagnoses. Common causes of false-positive classifications in our study were hepatic ischemia, alcoholic liver disease, and cancer in the liver. We attempted to exclude patients with alcoholic liver disease, but this was incomplete without review of medical records. Hepatic ischemia was often a consequence of septic or cardiogenic shock on admission; consequently, it was not possible to exclude these patients based on pre-hospitalization diagnoses. Modest improvement in the PPV of the algorithm might be possible by exclusion of patients with a cancer that could potentially metastasize to the liver prior to the hospitalization, but this would not be sufficient to obviate the need for chart review. Finally, the complexities of the ALF definition,\textsuperscript{59,70} particularly with regard to the challenge of confirming hepatic encephalopathy in clinical practice,\textsuperscript{71} could have led to inaccurate coding of these diagnoses.

Nearly 50% of Americans take one or more prescription medications every month,\textsuperscript{72} 15% consume over-the-counter analgesics daily,\textsuperscript{73} and almost 20% use dietary or herbal supplements regularly.\textsuperscript{74} Untoward effects of medication and supplement use are an important public health concern, particularly as the population ages and medication usage increases. In our study evaluating the incidence of drug-induced ALF,\textsuperscript{75} we reported an incidence of definite drug-induced ALF of 1.61 per million person-years in an integrated healthcare system that approximates a population-based cohort, with the overwhelming majority related to over-the-counter medications or products. These data provide a better understanding of the true population-representative incidence of drug-induced ALF, the most severe form of drug-induced hepatotoxicity, and its associated morbidity and mortality in an integrated healthcare organization.

An important observation was the role of over-the-counter medications and supplements. Dietary/herbal supplements were implicated in 18.8% of drug-induced ALF cases. Combined with acetaminophen, 75% of drug-induced ALF cases in this study were attributed to over-the-counter products, with over one half of the acetaminophen overdoses being unintentional. Such results stand in stark contrast to data from countries where acetaminophen is infrequently combined with other painkillers and is not a cause of ALF (e.g., no cases of acetaminophen-induced ALF reported in a 6.5-year period in Argentina\textsuperscript{76}). Stricter regulation of co-formulation of acetaminophen with other painkillers or limiting the number of acetaminophen tablets available for over-the-counter purchase might help decrease the number of acetaminophen-related ALF cases. Additionally, although acetaminophen has proven health benefits, most dietary/herbal supplements do not have demonstrated efficacy for the treatment or prevention of particular diseases, and these products currently do not undergo pre-marketing safety assessments by the FDA.\textsuperscript{77} These data suggest that standard prescription medications are a rare source of ALF; although, there is an ongoing need for continued vigilant reporting
and prospective studies of hepatotoxicity and ALF among users of these products, consideration should also be given to additional pre-marketing regulatory oversight of dietary supplements and herbal products as well as to additional post-marketing efforts to identify drug-, herbal-, and dietary supplement-induced liver injury. Furthermore, given that over one half of cases of acetaminophen-induced ALF were from unintentional overdoses, consideration should be given to laws that limit the size of packs of acetaminophen and/or require acetaminophen packages to use blister packs. Such legislation enacted in the United Kingdom in 1998 resulted in a significant reduction in cases of ALF from acetaminophen.76

Hy’s Law has been the most commonly used method to identify potential signals of severe hepatotoxicity within clinical trials.12,14-17 The high specificity of Hy’s Law biochemical criteria observed in our analysis confirms their value as a marker of severe hepatotoxicity. However, the low sensitivity of Hy’s Law criteria indicates that, in clinical practice, it is unable to identify a sizable proportion of patients with drug-induced hepatitis who are at high risk for progression to ALF. Few studies have evaluated, or sought to improve upon, the ability of Hy’s Law biochemical criteria, determined at recognition of drug-induced hepatitis, to predict incident ALF. A recent analysis of 771 patients with drug-induced hepatitis (32 of whom developed ALF) included in the Spanish Drug-Induced Liver Injury registry between 1994 and 2012 found that an algorithm based on AST >17.3 times ULN, total bilirubin >6.6 times ULN, and AST:ALT ratio >1.5 identified patients who developed ALF with 80% sensitivity and 82% specificity.65

Our development of the DrILTox ALF Score had high sensitivity (91%) and negative predictive value (99%), demonstrating that very few patients with drug-induced hepatitis who develop ALF will be missed while triaging more than 75% of the patients into a low-risk group with little likelihood of developing ALF (<1 in 3,500).79 The PPV of this cutoff was low (1%), which is not surprising given the low incidence of ALF.80 However, the incidence of ALF in the high-risk group identified by the DrILTox ALF Score (1 case/100 people) is 1,000 times higher than the incidence of drug-induced ALF in the general population (5.5 cases/1,000,000 people80) and more than 30 times higher than that in people categorized as low risk by the DrILTox ALF Score.

Platelet count and total bilirubin are both credible as predictors of ALF. Platelet count can be affected by ALF-induced inflammation and hepatic function.81 A recent analysis found that larger declines in platelet count are associated with greater severity of ALF from any etiology and may predict the development of multi-organ system failure and poor outcomes.82 In addition, total bilirubin reflects whole-liver functional capacity, and increasing total bilirubin can be a marker of hepatic dysfunction.

This comparison of scoring systems illustrates the inherent trade-offs of focusing on different parameters (sensitivity for the DrILTox ALF Score versus specificity for the Spanish drug-induced liver injury algorithm). The focus on specificity of the Spanish drug-induced liver injury algorithm results in few patients being classified as high risk but misses 86% (19/22) of the ALF events. In contrast, the DrILTox ALF Score’s focus on sensitivity identified far more patients as high risk but captured over 90% of the ALF events. We believe that, in the context of current clinical practice, clinicians would be unlikely to embrace a prognostic score that leads to a high rate of missed incident ALF events, because the costs of the missed ALF events far outweigh the costs of periodically evaluating liver function tests among patients identified as high risk for ALF by the DrILTox ALF Score.

In our study evaluating the comparative hepatic safety of azole antifungals,83 the absolute risks and rates of both liver aminotransferase levels >200 U/L and severe acute liver injury (manifested by hepatic dysfunction) were similar among fluconazole, ketoconazole, and itraconazole users. Furthermore, among the 187,703 azole users without chronic liver disease, ALF, the most severe form of acute liver injury, was confirmed in only one patient, a user of ketoconazole, highlighting the rarity of this event. The findings from this population-based study using liver-associated laboratory tests to define acute liver injury contradict the
analyses by the FDA and European Medicines Agency that suggested that ketoconazole use was associated with a higher risk of acute liver injury than other azole antifungals. However, these agencies’ decisions were based primarily on spontaneous adverse event reports and prior analyses of acute liver injury diagnosis codes.

In our study of the risk of acute liver injury associated with antiretroviral drugs, classes, and regimens among HIV-infected patients initiating ART within two integrated healthcare systems, we found low absolute risks and rates of acute liver injury within the first year of ART. Incident liver aminotransferases >200 U/L occurred in 2% of the 10,083 HIV-infected patients in the cohort. Severe acute liver injury, manifested by coagulopathy and hyperbilirubinemia, occurred in <1%, and no ALF events were identified among patients without hepatitis coinfection. These results highlight the rarity of antiretroviral-associated acute liver injury with modern ART and provide evidence for the hepatic safety of these regimens. Rates of acute liver injury were higher for hepatitis-coinfected patients. Among these individuals, initiation of protease inhibitor-based ART was associated with a higher risk of aminotransferases >200 U/L compared with initiation of non-nucleoside reverse transcriptase inhibitors (NRTI)-based ART. The risk was significantly higher for coinfected initiators of darunavir/ritonavir plus tenofovir/emtricitabine, atazanavir/ritonavir plus tenofovir/emtricitabine, and lopinavir/ritonavir plus zidovudine/lamivudine compared with those initiating efavirenz plus tenofovir/emtricitabine. However, among HIV-monoinfected patients, no differences in the risk of this outcome were found among different NRTI combinations; protease inhibitor, integrase strand transfer inhibitors, or non-NRTI classes; or commonly used ART regimens.

Conclusions

Electronic algorithms comprising relevant hospital diagnoses, laboratory evidence of liver dysfunction, and prescriptions for hepatic encephalopathy treatment had low PPVs for confirmed ALF events. Until an electronic algorithm for ALF is developed that has sufficiently high PPV, studies evaluating ALF will need to rely on medical records to confirm this outcome.

Drug-induced ALF is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes. We found that the incidence of drug-induced ALF was 1.61 per million person-years in adults in a population-representative cohort, and acetaminophen and dietary/herbal supplements were implicated in three quarters of cases.

Hy’s Law has low sensitivity but high specificity for ALF. The DrILTox ALF Score, based on platelet count and total bilirubin, discriminated the risk of developing ALF among patients with suspected drug-induced hepatitis with high sensitivity. Hy’s Law biochemical criteria at diagnosis of drug-induced hepatitis had high specificity and negative predictive value, but low sensitivity and PPV, for incident ALF. A new risk prediction model with platelet count and total bilirubin identified patients with drug-induced hepatitis who are at increased risk of ALF with high sensitivity while retaining reasonable specificity. This model is based on simple laboratory variables, has internal validity, and demonstrated superior sensitivity to the most commonly used existing tool (Hy’s Law). Future studies should evaluate the classification performance of the DrILTox ALF Score in other populations and determine if its use improves outcomes.

Risks of acute liver injury were similarly low among users of fluconazole, ketoconazole, and itraconazole. In the subgroup without chronic liver disease, rates of liver aminotransferases >200 U/L were increased with itraconazole, voriconazole, and posaconazole. The risk of acute liver injury was higher with voriconazole than fluconazole, but results were based on few users and events. Pre-existing chronic liver disease was a strong risk factor for development of acute liver injury among azole users, and, if confirmed, should lead to recommendations for screening liver function testing in these patients prior to use.

Acute liver injury events were rare among HIV-infected people initiating ART. Patients with viral hepatitis coinfection had higher rates of acute liver injury events with modern ART regimens than did those with HIV alone. Among viral hepatitis-coinfected patients, initiation of
protease inhibitor-based ART, particularly with darunavir/ritonavir, atazanavir/ritonavir, and lopinavir/ritonavir, was associated with a higher risk of liver aminotransferase elevations versus with non-NRTI-based ART. However, hepatic dysfunction was uncommon in these patients, highlighting the safety of all potent ART regimens and emphasizing that providers should not be reluctant to initiate protease inhibitors in viral hepatitis-coinfected patients.

**Significance & Implications**

Until an electronic algorithm for ALF is developed that has sufficiently high PPV, studies evaluating ALF will need to rely on medical records to confirm this outcome. Our results have improved understanding of the incidence, etiology, and outcomes of ALF in a community-based population. These data highlight the rarity of this outcome and provide estimates of the true risk of ALF resulting from medications, herals, and/or dietary supplements. Furthermore, such events are rarely due to prescription medications. Although continued vigilance for acute liver injury from prescription medications remains important, these data suggest that closer attention to the hepatotoxicity of over-the-counter medications, particularly dietary and herbal supplements, is needed.

The DrILTox ALF Score that we created provides an increased ability to identify patients with suspected drug-induced liver injury who are at high risk of ALF. The score is relatively easy to compute and could be used by providers in clinical practice. Strategies to manage complications of drug-induced hepatitis could therefore be directed toward high-risk patients. Such patients could undergo more intensive monitoring of liver-related laboratory tests to detect evolving hepatic dysfunction earlier in the course of drug-induced hepatitis, which might improve prognosis. Likewise, patients with high-risk scores could be referred to hepatology specialty care earlier, which might improve outcomes. High-risk patients might also be considered for earlier transfer to a liver transplant center and for treatment with N-acetylcysteine, which improves outcomes in acetaminophen- and non-acetaminophen-induced liver injury. Economic modeling would be needed to determine how use of the DrILTox ALF Score to guide care would impact cost-effectiveness.

The findings from our population-based study evaluating acute liver injury among azole antifungal initiators contradict analyses by the FDA and European Medicine Agency that suggested that ketoconazole use was associated with a higher risk of acute liver injury than other azole antifungals. However, these agencies’ decisions were based primarily on spontaneous adverse event reports and prior analyses of acute liver injury diagnosis codes. Pre-existing chronic liver disease was a strong risk factor for development of acute liver injury among azole users, and, if confirmed, should lead to recommendations for screening liver function testing in these patients prior to use.

Our results also highlight the rarity of antiretroviral-associated acute liver injury with modern ART and provide evidence for the hepatic safety of these regimens. Importantly, although the risk of aminotransferase elevations after protease inhibitor-based ART initiation was increased in coinfected patients, there were very few severe acute liver injury events among these individuals. Thus, providers should not be reluctant to initiate protease inhibitors in coinfected patients. This study identified several factors, including hepatitis coinfection, heart failure, older age, and higher pre-ART HIV RNA levels, that might increase acute liver injury risk. Hepatitis and heart failure can independently lead to hepatic fibrosis and dysfunction, which could impair the liver’s ability to tolerate acute insults from drug-induced acute liver injury. Older HIV-infected patients are more likely to have other comorbidities and polypharmacy, which could increase exposure to hepatotoxic medications or drug-drug interactions. Finally, patients with higher HIV RNA levels at ART initiation might have more vigorous immune reconstitution after ART initiation. Patients with these characteristics might benefit from closer monitoring of liver aminotransferases after ART initiation.
6. List of Publications and Products

Products
No products were created in conjunction with this grant.

Publications
The following is a listing of manuscripts that were published during this grant period:


The following is a listing of manuscripts that are yet to be published:


The following is a listing of abstracts accepted during this grant period:


Byrne DD, Tate JP, Forde KA, Kostman JR, Roy JA, Lo Re V 3rd: The risk of acute liver injury with statin use in chronic hepatitis C virus infection. ID Week 2016, New Orleans, LA. October 2016. Poster presentation [Abstract 6009].


7. Literature Cited


82. Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lee WM. Thrombocytopenia in acute liver failure (ALF): A marker of multi-organ system failure and poor prognosis. 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC [Abstract 110].


