Drug-Induced Liver Injury (DILI)

Douglas T. Dieterich, M.D.
Professor of Medicine
Division of Liver Diseases
DILI Case

- 29yo female with no significant past history presents to the ER with fatigue and yellow eyes x 1 day.
- Admits to recent breakup with her boyfriend and feeling depressed
- States she took “some pills” over 24 hours ago
- No prior suicide attempts

- VS: sinus tachycardia, BP 110/80
- +Icteric sclerae, no spider angiomas, no shifting dullness or lower extremity dullness, +sleepy
DILI Case

- Labs: AST 4026, ALT 2502, Tbili 6, INR 2.5, Cr 0.7, pH 7.32, ALP 352, Plt 142
- Imaging: US with dopplers nonspecific heterogenous echotexture

*Acetaminophen level was 35*
Overview: DILI

• Epidemiology
• General principles of drug metabolism
• Mechanisms and risk factors
• Classification
• Common examples of drug hepatotoxicity
• DILINetwork
Epidemiology

• Relatively uncommon (1/10,000 to 1/100,000 subjects who take the drug)
• Leading cause of acute liver failure in the United States
• Single most common adverse drug reaction
• Mimics acute and chronic liver disease
• Most DILI resolves with drug discontinuation
• Prescription, herbal and over-the-counter dietary supplements and medications
• Difficult to identify high risk patients
Urgent news for people who took Rezulin

Many diabetes patients who took the drug Rezulin have experienced serious liver problems, including symptoms of jaundice (yellowing of skin or eyes) or dark urine. Some have developed liver failure and need liver transplants, while others have even died. If you or a family member used Rezulin and have had any of these problems, call us immediately, so we can evaluate your potential claim against the drug manufacturer.

Your legal rights have time deadlines, so call today (open 7 days/week) toll free from anywhere in the U.S. at 1-800-THE-EAGLE for a free consultation. We practice law only in Arizona, but associate with lawyers throughout the U.S. to help injured people across the country.

GOLDBERG & OSBORNE
The Injury Lawyers
1-800-THE-EAGLE
(1-800-843-3245)
Open 7 Days a Week
Offices in Phoenix & Tucson
Etiology of ALF in the USA Adult Registry (n=1,321)

More than half of all US ALF is drug-related

Since 1998

R. Todd Stravitz *Nature Reviews Gastroenterology & Hepatology* September 2009
Establishing Drug as Causative Agent

- Temporal profile
- Manifestation of liver toxicity has variable time course
- Liver enzymes abnormalities can persist for months
- Systematic literature search for each drug
- Rechallenge
- Exclude other diseases
- Extrahepatic features can point to immunoallergy
- Consider drug levels, liver biopsy
Drug Metabolism

- Drugs rendered hydrophilic by biochemical processes in the hepatocyte
- Hepatic biotransformation involves oxidative pathways, primarily by cytochrome P-450
- Hydrophilic product exported into plasma or bile by transport proteins located on the hepatocyte membrane
- Excreted by the kidney or the gastrointestinal tract
Hepatic Drug Metabolism

Phase I

Drug $\xrightarrow{\text{CYP}}$ Active Metabolite $\xrightarrow{\text{ROS}}$ Hepatic Injury

Phase II

Active Metabolite $\xrightarrow{\text{Transferases}}$ Conjugated Drug $\xrightarrow{\text{Excretion}}$
Classification of DILI

• Predictable vs. idiosyncratic hepatotoxins
• Direct toxins vs. immune mediated
• Allergic vs. Nonallergic
• Acute vs. chronic
• Liver test abnormalities:
  Hepatocellular vs. cholestatic vs. mixed
• Histologic features:
  granulomatous, steatotic, vascular
## Clinical Classification of DILI

<table>
<thead>
<tr>
<th></th>
<th>Predictable Hepatotoxins</th>
<th>Idiosyncratic Hepatotoxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Dependent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reproducible in Other Species</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Incidence</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Latency to Injury</td>
<td>Short (hours)</td>
<td>Variable (weeks)</td>
</tr>
<tr>
<td>Extrahepatic involvement</td>
<td>Usually absent variable</td>
<td>May be present</td>
</tr>
<tr>
<td>Response to rechallenge</td>
<td>variable</td>
<td>Accelerated onset</td>
</tr>
</tbody>
</table>
Clinical Patterns of DILI

- Hepatocellular
- Cholestasis
- Granulomatous
- Microvesicular fat
- Steatohepatitis
- Autoimmune
- Fibrosis
- Vascular collapse
- Oncogenesis
- Mixed
Hepatocellular

- Marked elevations in serum aminotransferases

- Usually precedes increases in total bilirubin and modest increases in alkaline phosphatase

Acute hepatitis with hepatocellular swelling, inflammation and disarray of hepatic lobule
Hepatocellular

- Acarbose
- Acetaminophen
- Amiodarone
- Isoniazid
- Ketoconazole
- Rifampicin
- Tetracyclines
- Trazodone
- Methotrexate
- NSAIDs
- Statins

34yo with tylenol overdose- severe centrilobular necrosis with sparing of portal tracts and periportal hepatocytes
Cholestasis

- Increase in alkaline phosphatase
- Precedes or are relatively more prominent than increases in transaminases
- More prolonged jaundice after drug withdrawal

Bile stained hepatocyte, cellular swelling and minimal inflammation
Patterns of DILI

Table 3
Council for International Organizations of Medical Sciences (CIOMS) classification of drug-induced liver injury (DILI).

<table>
<thead>
<tr>
<th>Pattern</th>
<th>R Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular (ALT ↑ 3× ULN)</td>
<td>R ≥ 5</td>
</tr>
<tr>
<td>Mixed (ALT ↑ 3× ULN + AP ↑ 2× ULN)</td>
<td>5 &gt; R &gt; 2</td>
</tr>
<tr>
<td>Cholestatic (AP ↑ 3× ULN)</td>
<td>R ≤ 2</td>
</tr>
</tbody>
</table>

R = ratio = (ALT/ULN)/(AP/ULN)

ULN: upper limit of normal; AP: alkaline phosphatase; ALT: alanine aminotransferase

Table 6. Mortality Rates and Biochemical Injury Pattern Reported in Recent Reports

<table>
<thead>
<tr>
<th>Reference</th>
<th>Hepatocellular (%)</th>
<th>Cholestatic (%)</th>
<th>Mixed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Björnsson and Olsson²⁹</td>
<td>12.7</td>
<td>7.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Andrade et al²⁶</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Chalasani et al (current report)</td>
<td>7.5</td>
<td>14.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

J.M. Leitner et al. Pathomechanisms and Clinical Data Infection 2010
# Examples of DILI

<table>
<thead>
<tr>
<th>Signature disease</th>
<th>Drug(s) causing the feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>Acetaminophen, bromfenac, isoniazid, nevirapine, ritonavir, troglitazone</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Dantrolene, diclofenac, methyldopa, minocycline, nitrofurantoin</td>
</tr>
<tr>
<td>Acute cholestasis</td>
<td>ACE inhibitors, amoxicillin/clavulanic acid, chlorpromazine, erythromycins, sulindac</td>
</tr>
<tr>
<td>Mixed pattern or atypical hepatitis</td>
<td>Phenytoin, sulfonamides</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis</td>
<td>Amiodarone, tamoxifen</td>
</tr>
<tr>
<td>Fibrosis/cirrhosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
<td>NRTIs, valproic acid</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>Busulfan, cyclophosphamide</td>
</tr>
</tbody>
</table>

**NOTE.** ACE, angiotensin-converting enzyme; NRTI, nucleoside reverse-transcriptase inhibitor.
Hy’s Law

- Drugs causing acute hepatocellular injury and jaundice are associated with a mortality rate of approximately 10% (range of 5-50%)
- Validated by studies from Spain and Sweden

Percentage of patients with DILI progressing to liver transplantation and/or death

(Andrade Gastroenterology 2005;129)
Six Mechanisms of DILI

- Cell membrane rupture
- Cholestasis
- Drug adducts (2)
- Apoptosis
- Mitochondrial function

Susceptibility Factors

Drug
- Dose
- Class
- Duration
- Reactive metabolite
- Mitochondrial effects

Genetic Factors
- Drug Metabolism
- Detoxification
- Transport
- Others

Environment
- Age
- Gender
- ETOH
- Other drugs
- Underlying disease

Kaplowitz  Clinic Infect Disease 2004
Risk Factors for DILI

- Age (i.e. INH toxicity > 40, Reye’s syndrome < 3)
- Female gender
- Nutritional status- obesity and malnutrition
- Genetic factors (i.e. halothane)
- Concomitant medications
- History of drug reactions
- Alcohol consumption
- Underlying liver disease and co-morbidities
# Examples of Drug Hepatotoxicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose related</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Metabolic idiosyncrasy</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Immunoallergy</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Chronic hepatitis/Fibrosis</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Vascular/VOD</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Chronic w/autoantibodies</td>
<td>Hydralazine</td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
</tbody>
</table>
Dose dependent toxicity: Acetaminophen

- Minimal hepatotoxic dose 7.5g in adults
- Severe toxicity/fatal doses >15g
- Biochemical signs of liver damage in 24 to 48 hours
- Centrilobular necrosis
- Risk of toxicity correlates with plasma acetaminophen level (after 4 hours) and time after ingestion
- Late presentation or treatment (>12 hrs) associated with poor outcome
ACM cases as % of all ALF/yr

Total ALF cases:

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>85</td>
<td>94</td>
<td>99</td>
<td>123</td>
<td>134</td>
<td>148</td>
<td>152</td>
<td>147</td>
</tr>
<tr>
<td>%</td>
<td>32%</td>
<td>42%</td>
<td>44%</td>
<td>39%</td>
<td>49%</td>
<td>51%</td>
<td>53%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Data from ALFSG from AASLD meeting
Mechanism of Acetaminophen-Induced Liver Toxicity: The Basis for “The Therapeutic Misadventure”

1. Patients with acetaminophen toxicity related to accidental misuse had higher rates of morbidity/mortality than those who attempted suicide (Schiodt et al. NEJM, 1997)

2. Presence of acetaminophen-cysteine adducts in serum may signify unrecognized instances of acetaminophen toxicity (Davern TJ et al., Gastroenterology, 2006)
Acetaminophen Toxicity: Treatment

• Activated charcoal within 4 hours of ingestion
• Administer NAC within 8 hours post ingestion
• Oral N-Acetylcysteine
  140mg/kg loading followed by
  70mg/kg q 4hrs x 72 hrs
• IV NAC
  150 mg/kg loading x 1 followed by
  12.5 mg/kg/hr over 4 hrs
  6.25 mg/kg/hr over 16 hrs
• Supportive care/transplant for cases of FHF
Isoniazid

- Mechanism: metabolic idiosyncrasy
- **High frequency**: 6-21 per 1000 of exposed persons
- Mortality 5-10%
- Increased risk/severity with
  - age > 35 or <5
  - alcohol
  - In combination (rifampicin, pyrazinamide, APAP)
- Hepatitis B/C
- Pregnancy
- Malnutrition
- Genetic variations
Isoniazid

- ALT abnormalities:
  - 10-36% in the first 10 weeks
  - typically resolve spontaneously
  - okay to continue INH if LFT’s < 5x normal
- Hepatitis develops after latency period
  - 1 week-6 mo.
- Prodrome symptoms of fatigue, malaise, n/v
- Cases associated w/fatal outcome
  - longer duration of therapy
  - continued intake after onset of symptoms
- Most deaths from INH are preventable
- LFT monitoring - watch for clinical symptoms
Dilantin

- Severe acute drug hepatitis: 1 in 10,000
- Onset: 1-8 weeks
- Mortality rate: 10-40%

- Clinical features (pseudomononucleosis syndrome):
  - fever
  - rash (exfoliative dermatitis)
  - internal organs (kidney, lung, liver) involved
  - leukocytosis, eosinophilia
  - lymphadenopathy
Amoxicillin/Clavulanic Acid

- Most frequently reported antibiotic associated with DILI
- Estimated risk of symptomatic hepatitis: 1 in 100,000
- Clavulanic acid component probably responsible
- Typically produces a cholestatic hepatitis
- Delayed symptom onset: 1 to 8 weeks
- Strong association with HLA haplotype DRB1*1501-DRB5*0101-DQB1*602, suggesting immunologic idiosyncrasy
Augmentin DILI: Prognosis

- 69 patients with Amoxicillin-Clavulanate Hepatotoxicity, Spanish registry
- Half of cases presented after cessation of therapy (mean 15, range 2-55 days)
- 2.9% overall rate of severe outcome (death/liver transplant)

- 55
  - 1 death
  - 1 OLT
  - 4 persistent abnormal liver tests (8.5 month follow-up)
  - 49 Normalization of liver tests: mean 77 days
Other antibiotics

- Cephalosporins
  - few reports of hepatotoxicity
  - biliary sludge associated with ceftriaxone

- Quinolones
  - relatively safe, with exception of trovafloxacin

- Sulfonamides
  - immunoallergic toxicity (rash, fever, eosinophilia)
  - cholestatic hepatitis

- Macrolides (erythromycin, azithromycin, clarithromycin)
  - cholestatic hepatitis, rash/eosinophilia
  - acute liver failure with telithromycin (Ketek)

- Antifungals
  - most common with ketoconazole
  - asymptomatic LFT elevations frequent

- Minocycline, nitrofurantoin
  - autoimmune hepatitis/SLE-like syndrome
Drug Induced Fibrosis: Methotrexate

- Dose dependent promoter of hepatic fibrosis
- Avoidance of daily dosing, limitation of weekly doses to 5-15 mg decreases risk
- Increased risk with ETOH, DM, obesity
- Monitor LFT’s; however fibrosis can develop in absence of LFT abnormalities
- Consider liver biopsy after 4g of MTX or 2 years of treatment Or Fibroscan
Veno-occlusive Disease

• Hepatic venous outflow obstruction from nonthrombotic occlusion of terminal hepatic venules and small intrahepatic veins due to endothelial damage
• BMT patients- alkylating chemotherapy
• Onset 2-10 weeks after starting therapy
• Sx’s: abdominal pain, hepatomegaly, progression to acute liver failure
• Resembles Budd Chiari except for patency of large hepatic veins on imaging
• No specific treatment, prognosis poor
Peliosis Hepatis

- Dilation and disruption of reticulin framework around sinusoids, resulting in blood filled cavities
- Causative drugs: androgens, estrogens, azathioprine, tamoxifen
- Can present as shock and abdominal pain from spontaneous rupture of the liver
- Liver biopsy contraindicated in suspected cases
- Arteriography, CTA, MRI may be diagnostic
Antiretroviral-associated liver injury

- Determining the incidence of DILI is difficult due to combination therapy
- Incidence is influenced by presence of host risk factors (HBV, HCV, alcohol)
- Elevated LFT’s in HIV infected patients may reflect other etiologies besides drug hepatotoxicity
- All classes of antiretrovirals have been associated with hepatic injury
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Severe ALT Elevation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Lamivudine(^{15})</td>
<td>3.7–3.8</td>
</tr>
<tr>
<td></td>
<td>Tenofovir(^{16})</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Zidovudine(^{17})</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine(^{18})</td>
<td>2–5</td>
</tr>
<tr>
<td></td>
<td>Abacavir(^{19})</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Didanosine(^{20})</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Stavudine(^{21})</td>
<td>6–13</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Rilpivirine(^{22})</td>
<td>&lt;1–2</td>
</tr>
<tr>
<td></td>
<td>Etravirine(^{23})</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Delavirdine(^{24})</td>
<td>4.1–5.1</td>
</tr>
<tr>
<td></td>
<td>Efavirenz(^{25})</td>
<td>2–8</td>
</tr>
<tr>
<td></td>
<td>Nevirapine(^{26})</td>
<td>5.3–14</td>
</tr>
<tr>
<td>PI</td>
<td>Nelfinavir(^{27})</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>Indinavir(^{28})</td>
<td>2.6–4.9</td>
</tr>
<tr>
<td></td>
<td>Darunavir/ritonavir(^{29})</td>
<td>5.6–6.9</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir/ritonavir(^{30})</td>
<td>4–8</td>
</tr>
<tr>
<td></td>
<td>Ritonavir(^{31})</td>
<td>5.3–8.5</td>
</tr>
<tr>
<td></td>
<td>Atazanavir/ritonavir(^{32})</td>
<td>3–9</td>
</tr>
<tr>
<td></td>
<td>Tipranavir/ritonavir(^{33})</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir(^{34})</td>
<td>3–11</td>
</tr>
<tr>
<td>CCR5 blocker</td>
<td>Maraviroc(^{35})</td>
<td>2.4</td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td>Raltegravir(^{36})</td>
<td>4</td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>Enfuvirtide(^{37})</td>
<td>5.4–6.2</td>
</tr>
</tbody>
</table>
Genetic Associations and ARTs

• Association between HLA-DRB1*01 and nevirapine-associated hypersensitivity
  – Occurs within first 6 weeks of treatment

• HLA-B*5701 associated with hypersensitivity reactions with abacavir
  – negative predictive value of 100%
  – resulted in a dramatic decrease in the incidence of this toxicity

• CYP2B6 genotype strong predictor of higher plasma levels of efavirenz
Protease Inhibitors

• Hepatotoxicity with ritonavir
  – Low dose (<200mg BID) less hepatotoxic than previously used higher/boosted doses

• Unconjugated hyperbilirubinemia
  – Indinavir (Crixivan) and atazanavir (Reyataz)

• Severe hepatotoxicity
  – Tipranavir (Aptivus)
Nucleoside Reverse Transcriptase Inhibitors (NRTI)

- May be associated with lactic acidosis and microvesicular hepatic steatosis
- Mechanism: mitochondrial toxicity
- Early NRTI’s (AZT, ddI, d4T)
  - mostly asymptomatic LFT abnormalities
  - 5% rate of serious hepatotoxicity
- Newer NRTI’s (lamivudine, abacavir, tenofovir) associated with much lower incidence (<1%) of hepatotoxicity
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Nevirapine (Viramune), efavirenz (Sustiva), delavirdine (rescriptor)

- Nevirapine:
  - rash associated hypersensitivity
  - rare cases of hepatotoxicity reported
  - increased risk with HBV/HCV coinfection
  - and higher CD4 counts/post exposure prophylaxis regimens
HAART Considerations in Patients with Liver Disease

- HCV: didanosine-ribavirin: lactic acidosis zidovudine-ribavirin: anemia

- HBV: HBV flares following discontinuation of emtricitabine, lamivudine, tenofovir

- Liver transplant: PI/NNRTI’s induce P450-> lower FK dose requirement watch for sudden decrease in FK level after stopping HAART avoid use of certain NRTI’s (ddC, ddI, d4T)
Treatment Options for HIV/HCV Genotype 1 Patients

Preliminary recommendations on use of boceprevir or telaprevir in HIV/HCV genotype 1 coinfected patients[1]

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not on ART</td>
<td>Use either boceprevir or telaprevir</td>
</tr>
<tr>
<td>Patients receiving RAL + 2 NRTIs</td>
<td>Use either boceprevir or telaprevir</td>
</tr>
<tr>
<td>Patients receiving ATV/r + 2 NRTIs</td>
<td>Use telaprevir at the standard dose. Do not use boceprevir.</td>
</tr>
<tr>
<td>Patients receiving EFV + 2 NRTIs</td>
<td>Use telaprevir at increased dose of 1125 mg every 7-9 hours. Do not use boceprevir.</td>
</tr>
</tbody>
</table>

*These recommendations may be modified as new drug interaction and clinical trial information become available.

Management Issues with Comedications
Statins

• Transient elevation of LFTs (< 3x normal) are common (~2%) within the first year
• Acute liver failure is rare 0.2 per 100,000
• Statins and DILI is likely a myth
• Scandanavian Simvastatin Survival study
• If there is a clear benefit, do not withhold in patients with underlying liver disease
## FDA: Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>2001</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>(2001) LFTs before and at 6 and 12 weeks after start or elevation of dose and semiannually</td>
<td>(2009) LFTs before initiation of therapy in those with history of liver disease or when indicated</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>(2000) LFTs before treatment and semiannually for first year or until 1 year after last elevation</td>
<td>(2008) LFTs before treatment and then when clinically indicated</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>(2001) LFTs before initiation of therapy, before elevation of dose, and when clinically indicated</td>
<td>(2007) LFTs before initiation of therapy and when indicated</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>(2001) LFTs before and at 12 weeks after the initiation of therapy and any elevation of dose</td>
<td>(2009) No change</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>(2001) LFTs before initiation of therapy, after elevation of dose, and semiannually</td>
<td>(2009) No change</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>(2003) LFTs before and at 12 weeks after initiation of therapy and any elevation of dose and periodically</td>
<td>(2009) No change</td>
</tr>
</tbody>
</table>
Herbal Medicine Use

• Prevalence
  – 18.9% of the US population
  – 21% of patients with liver disease

• Issues unique to herbal toxicity:
  – marketing as dietary supplements
  – variation in composition among products
  – often found as mixed preparations contamination with other toxins
  – many patients do not report use

Kennedy Clinical Therapeutics 2005
Strader Am J Gastro 2002
Herbal use and race

- Multiple Race
- Asian
- American Indian/Alaskan native
- White
- Black

Percent
Top 10 Herbal Products

- Echinacea 38%
- Ginseng 23%
- Gingko biloba 20%
- Garlic 18.6%
- Glucosamine 13.7%
- St. John’s wort 11.5%
- Peppermint 11.3%
- Fish oils 11.1%
- Ginger supplements 9.9%
- Soy supplements 9.1%
What Is DILIN?

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established the Drug-Induced Liver Injury Network (DILIN) to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal products and supplements. Currently, DILIN is conducting 2 registry studies:

- **Retrospective Study**, to establish a nationwide registry of people who have experienced liver injury within the past 10 years after using any of 7 specific drugs and one drug category (quinolone antibiotics).
- **Prospective Study**, to establish a nationwide registry of people who have experienced liver injury within the past 6 months after using certain drugs or alternative products.
DILIN Report 2008

- 300 patients enrolled, >100 different drugs
- At 6 months
  - 13.6% chronic DILI
  - 8% died (n=18)
    - Liver related death in 44% (n=8)
  - 2.1% liver transplant
- More than one agent implicated in ~20% of cases
- Antimicrobials represent the single largest class of agents
- Coexisting diabetes was an independent risk factor for more severe DILI
Conclusions

• DILI is the major cause for ALF in the US

• Idiosyncratic hepatoxicity are uncommon, but can be severe with continuation of drug

• Interplay of multiple genetic and environmental factors

• Challenge is to identify these factors to avoid the use of problematic drugs in the rare susceptible individual