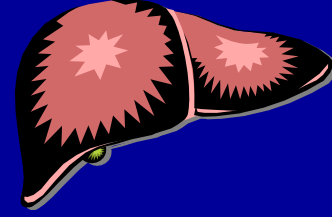

# Pre-existing liver disease and DILI: Putting it all together

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**University of Michigan Medical Center**

# Prior liver disease & DILI

- **Susceptibility**
  - Mechanism (s): Enzyme activity, inflammation, pharmacokinetic
  - Pro: Methotrexate, niacin, isoniazid
  - Con: Glitazones, statins
- **Outcomes**
  - Mechanism (s): ⇓ regeneration, ⇑ fibrogenesis
  - Pro: SOS in HCV, INH in chronic HBV
- **Approaches**
  - Retrospective case series
  - RCT in patients with liver disease
  - DILI in patients with and without liver dz

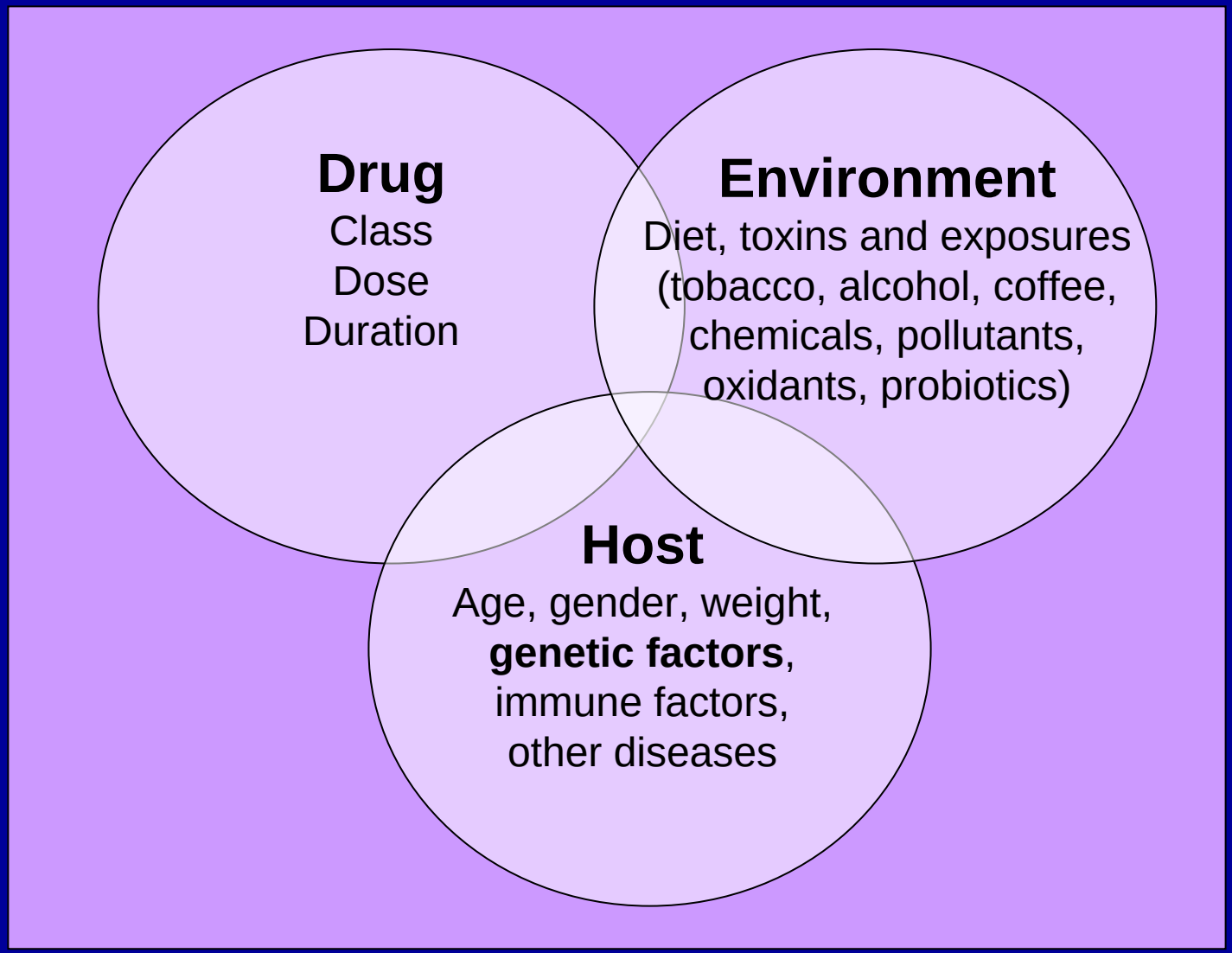
# “Idiosyncracy”

**Hippocrates, ~400 B.C.**

- **(idios) - one’s own, self**
- **(syn) - together**
- **(crasis) - a mixing, mixture**

**A person’s own mixture of characteristics, factors, nature and nurture, uniquely**

# DILI pathogenesis



# DILI susceptibility
## Liver disease rationale

- Altered bioactivation pathways
  - ⇑ CYP2E1 in ALD, NAFLD
- Reduced detoxification pathways
  - ⇓ GSH in ALD, advanced cirrhosis
- Altered immune reactivity
  - APAP in mice
  - ? Chronic HBV and isoniazid
- Impaired clearance of parent drug/ metabolite
  - ⇓ Blood flow, binding, metabolism

(Patel Am J Gastroenterol 2002; 97)

# Pharmacokinetics & DILI

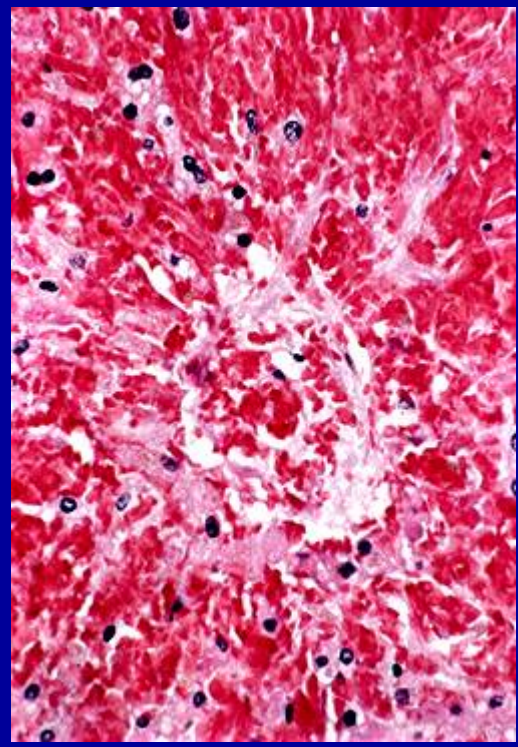
| Drug | Risk factor |
|---|---|
| Acetaminophen | Total dose |
| Tetracycline | Total dose (renal fcn) |
| Methotrexate * | Total dose, alcohol, DM, liver dz |
| Pehexilene | Total dose, slow hydoxylator |
| Amiodarone | Dose over time |
| Cyclophosphamide | Total dose |
| Valproic acid | Total dose, young age |
| Oral contraceptives | Total dose (Adenomas) |
| Aspirin | Dose |
| Niacin * | Total dose |
| Bromfenac | Total dose |

**Liver disease alters clearance of drug/ toxic early metabolite or reduces protein binding in serum**

(Schenker J Hepatology 1999; 31)

# Sinusoidal Obstruction Syndrome

- 30- 40% of BMT recipients
- Independent predictors (355)
  - Abnormal AST
  - Prior liver disease
    - HCV (+) OR: 9
  - Abdominal XRT
  - Donor/ recipient mismatch



Altered drug pK vs endothelial cells (↑ ICAM)

(Strasser Hepatology 1999; 29)

# Isoniazid in chronic HBV

## Vietnamese immigrants in the US

| | sAg +/ eAg + N=22 | sAg +/ eAg – N=33 | sAg – N=103 |
|---|---|---|---|
| Completed INH | 38% * | 81% | 88% |
| ⇑ ALT | 48% * | 7% | 3% |
| INH hepatitis | 13% * | 0% | 0% |

* P < 0.05 vs eAg – and sAg -.

(Patel Am J Gastroenterol 2002)

# Isoniazid in chronic HBV

| | HBsAg + INH rx N=43 | HBsAg – INH rx N=276 | HBsAg + No INH N=86 |
|---|---|---|---|
| Age | 44.9 | 45.8 | 44.9 |
| % eAg + | 21% | | 20% |
| % abnormal BL ALT | 23% | 6% | 17% |
| % Hepatotoxicity * | 35% ^ | 9% | 8% |
| % Hepatotoxicity ** | 23% ^ | 9% | 2% |
| % Hospitalized | 18% ^ | 6% | 0% |

^ $p < 0.05$

* ALT > 1.5 x BL ** anti-HBe conv/ ⇑ BL ALT removed

- Age and HBsAg + independent predictors of hepatotoxicity
- Most episodes of hepatotoxicity associated with ⇑ HBV DNA

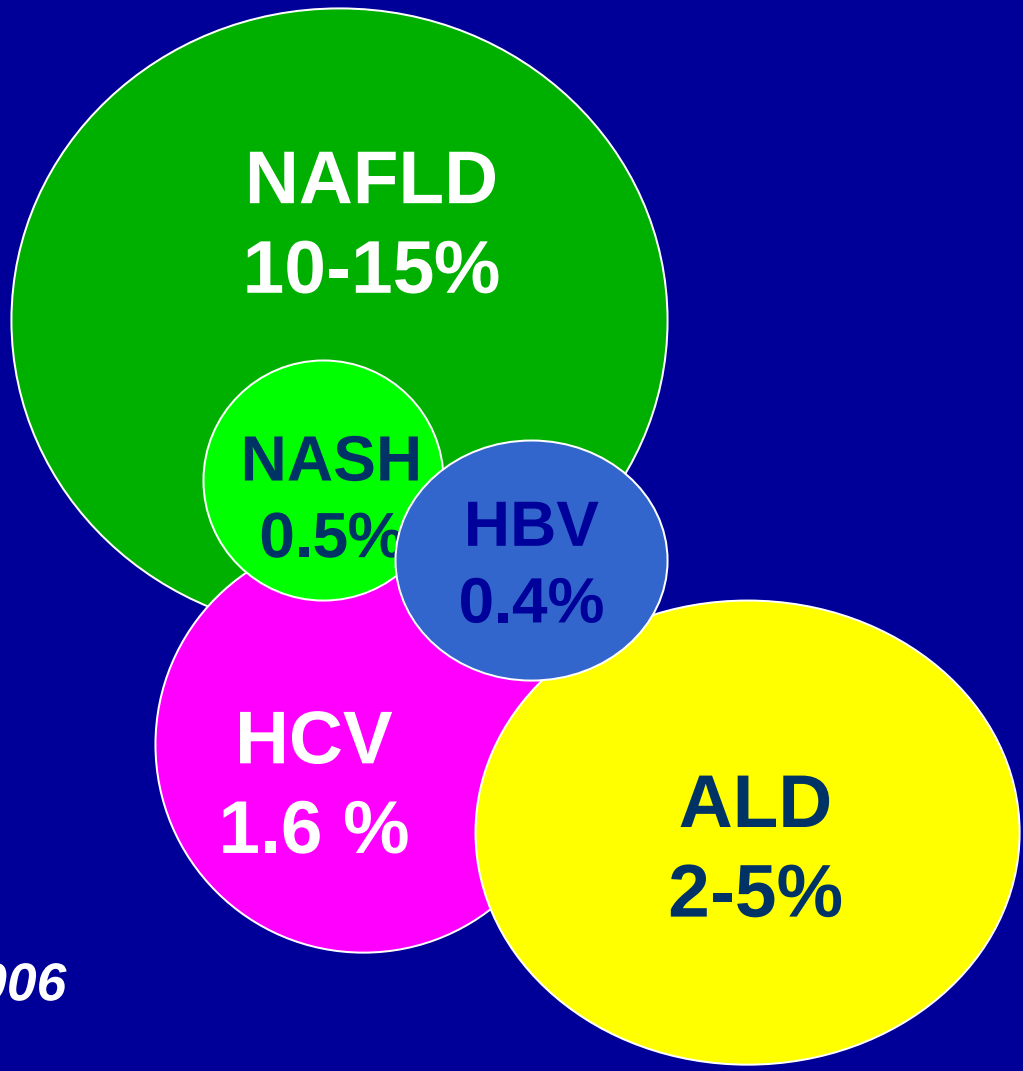
(Wong Hepatology 2000; 31)

# Hepatic steatosis and liver injury

- Oxidative stress may ↑ susceptibility to mitochondrial toxins
  - Tamoxifen: DM, hyperlipidemia (OR:3.6) [1]
- **Methotrexate:** Obesity, diabetes, alcohol, & liver dz [2]
- **US ALFSG:** Obese had greater txp/ death (OR: 1.63) [3]
- **LDLT:** Post-op cholestasis, delayed graft fcn ~ steatosis [4,5]

(Bruno BMJ 2005)
(Langman J Gastroenterol Hepatol 2001; 16)
(Rutherford Clin Gastro Hep 2006)
( Hayashi Trans Proc 1998)
(Lo Liver Transpl 2003; 9)

# US Liver Disease




**Diabetes**
70-80% NAFLD

**Obese**
30-50% NAFLD

*NHANES IV, 2006*

# Contraindicated in Liver Disease*

Methotrexate
Pemoline
Tolcapone
Valproate
Dantrolene
Clonazepam
Felbamate
Tacrine
Estrogens

Metformin
Niacin
Gemfibrozil
Lovastatin & others

* Package Insert

# LFT monitoring recommended

Amiodarone
Flutamide
Tretinoin
Fluconazole
Pemoline
Labetalol
Disulfiram
Methyldopa
Diclofenac
Carbamazapine

Valproic acid
Methotrexate
Nitrofurantoin
Allopurinol
Cyclosporine
Mercaptopurine
Ritonavir
Pyrazinamide
Isoniazid
Mirtazapine
Clonazepam
Ketaconazole

Nicotinic Acid
Gemfibrozil
Statins
Fenofibrate
Pioglitazone
Rosiglitazone
Tamoxifen

* Per package insert

# Hepatotoxicity of thiazolidindiones

| | Drug<br>ALT > 3X | Placebo<br>ALT > 3 X |
|---|---|---|
| Troglitazone | 1.9% | 0.6% |
| Pioglitazone | 0.26% | 0.25% |
| Rosiglitazone | 0.25% | 0.18% |

# Rosiglitazone in diabetics

| | Abnormal BL ALT * n=210 | Normal ALT N=628 | p |
|---|---|---|---|
| % chronic HBV/ HCV | 4.5% | 2% | |
| Peak ALT < 10 X ULN | 10% | 6.6% | 0.2 |
| Peak ALT > 10 X ULN | 0.9% | 0.6% | 0.9 |
| Bili > 3.0 | 0% | 0.3% | 0.9 |
| Discontinuation over 12 months | 8.6% | 8.1% | 1.0 |

* 61% normal ALT at 12 mon vs 51% in untreated liver controls p=0.02

(Chalasani Am J Gastro 2005; 100)

# Statin hepatotoxicity

| | Normal ALT N=1437 | Abn ALT * N=342 | Liver dz N=2245 |
|---|---|---|---|
| Age | 57 + 12 | 54 + 12 | 48 + 18 |
| Weight | 201 + 51 | 205 + 53 | 196 + 60 |
| Base AST | 22 + 7 | 55 + 37 | 57 + 49 |
| Base ALT | 20 + 8 | 43 + 23 | 61 + 47 |
| Chol (mg/dl) | 245 + 44 | 240 + 82 | 213 + 51 |
| Atorvastatin | 47% | 43% | |
| Simvastatin | 50% | 55% | |
| Fluvastatin | 3% | 2% | |

* Alcohol, HCV, HBV excluded

*(Chalasani Gastroenterology 2004)*

# Statin hepatotoxicity

| | Normal ALT | Abn. ALT | Liver dz |
|---|---|---|---|
| Statin duration (yr) | 0.48±0.08 | 0.48±0.08 | |
| Statin discontinue | 10.7% | 11.1% | |
| ↑ AST/ALT | 1.7% | 4.7% | 6.4% |
| 1-10 xULN | p=0.002 | | p=0.2 |
| ↑ AST/ALT | 0.2% | 0.6% | 0.4% |
| >10 xULN | p=0.6 | | p=0.6 |

*(Chalasani Gastroenterology 2004)*

# RCT of pravastatin in patients with liver disease

- **Inclusion**
  - LDL > 100 mg/dl
  - Chronic liver dz: 64% NAFLD 24% HCV 12% other

| | Pravastatin (n=160) | Placebo (n=160) |
|---|---|---|
| % ⇓ T cholesterol | 20%* | 3% |
| % ⇓ LDL | 31% * | 3% |
| % ⇑ ALT > 2X BL | 7.5% | 12.5% |

Time to ALT ⇑ and cumulative % at week 36 similar

(#446 Lewis DDW 2006)

# Prospective Entry Criteria

- Children ≥ 2 years and adults
- Within 6 months of liver injury onset
  - AST or ALT > 5 ULN or BL
  - Alk Phos > 2 ULN or BL
  - Bilirubin ≥ 2.5 mg/dl

- Prior HCV, HBV, NAFLD encouraged
  - **Exclude:** Liver txp, known AIH, PSC, PBC

# Prospective study

- **35** of 215 (**16%**) cases had prior liver dz
  - **15** of 99 (**15%**) adjudicated cases had prior liver dz
    - 15 adjudicated similar to other 18
- PMH liver disease (n=15)
  - 8 chronic HCV
  - 5 abnormal LFT's
  - 1 chronic HBV
  - 3 NAFLD
  - 1 ALD
  - 1 PBC

(Unpublished DILIN Jan 5, 2007)

# Adjudicated cases

| | Prior Liv dz n=15 | No Liv dz N=84 |
|---|---|---|
| Female | 67% | 58% |
| Caucasian | 80% | 80% |
| Age at onset | 53 + 10 | 46 + 19 |
| Prior drug allergies | 27% | 54% |
| Single Rx drug * | 46.7% | 72.6% |
| Single CAM | 6.7% | 4.8% |
| Multiple drug/CAM | 46.7% | 22.6% |

* Antibiotics most common (50% and 37%)

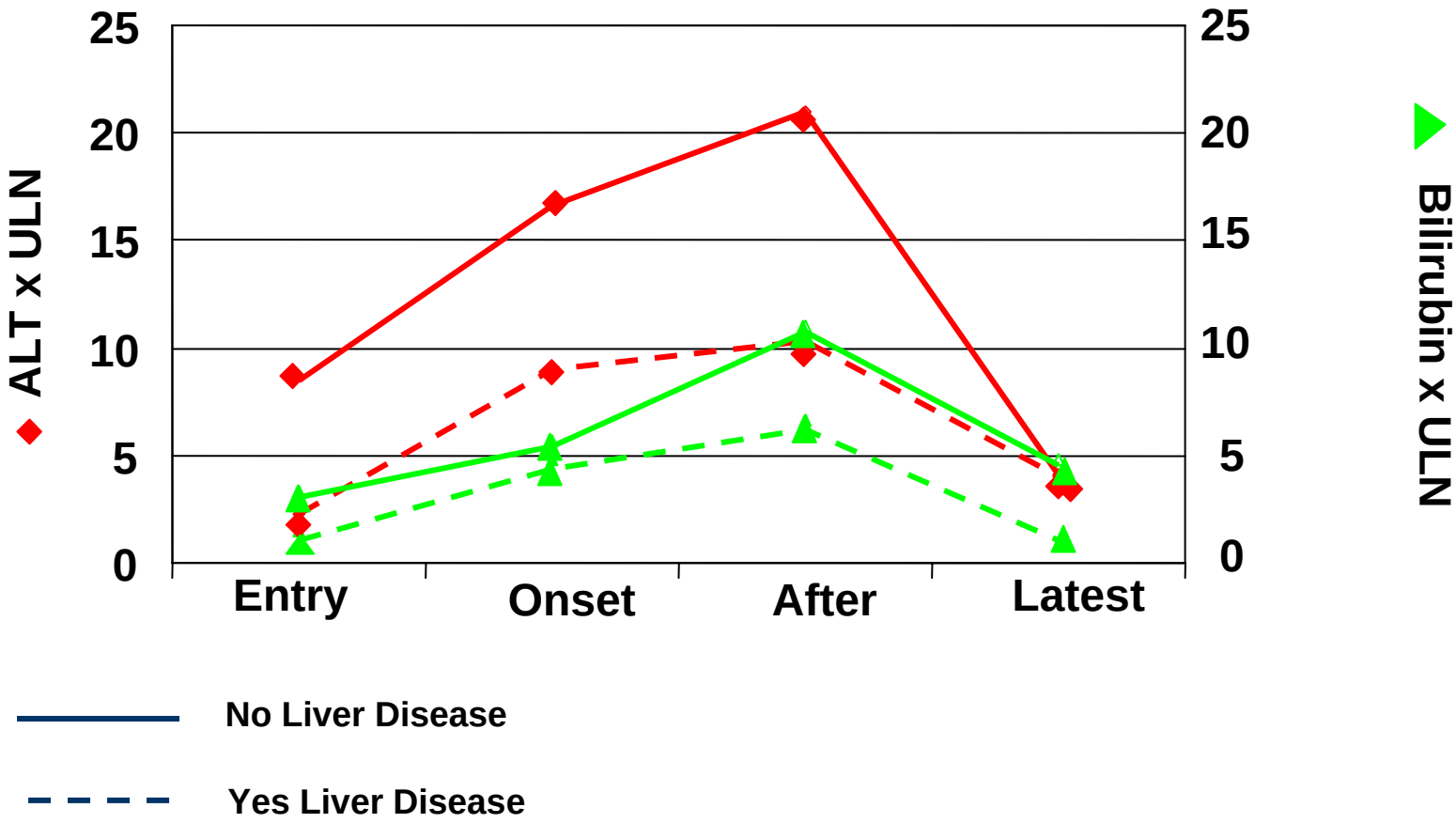
(Unpublished DILIN Jan 5, 2007)

# Adjudicated cases

| | Prior Liv dz n=15 | No Liv dz N=84 |
|---|---|---|
| Jaundice | 60% | 70% |
| Pruritis | 40% | 48% |
| Fever/ rash | 7%/ 20% | 37%/ 24% |
| Ascites | 0% | 11% |
| Liver biopsy | 47% | 44% |
| Hepatocellular/ mixed-cholestatic | 62%/ 38% | 56%/ 44% |
| Hospitalized | 47% | 70% |
| Steroids | 7% | 23% |
| Liver transplant | 0% | 1% |

(Unpublished DILIN Jan 5, 2007)

# Adjudicated cases




(Unpublished DILIN Jan 5, 2007)

# Causality assessment

**A panel of study hepatologists assess the strength of causal relationship between the implicated drug and liver injury**

| | Prior Liv dz n=15 | No Liv dz N=84 |
|---|---|---|
| Definite (> 95%) | 33.3% | 32.1% |
| Very Likely (75-95%) | 26.7% | 42.9% |
| Probable (50-75%) | 20.0% | 13.1% |
| Possible (25-50%) | 20.0% | 9.5% |
| Unlikely (< 25%) | 0% | 2.4% |

(Unpublished DILIN Jan 5, 2007)

# Idiosyncratic DILI

- **“The oft-cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact” [1]**

- **Beyond isoniazid “underlying hepatic disease appears to have no significant effect on most forms of hepatic injury ”**

**([1] Zimmerman Hepatotoxicity 1999)**