# 10TH RESIDENTIAL COURSE ON CLINICAL PHARMACOLOGY OF ANTIRETROVIRALS

# Pharmacological Features of Liver Impairment

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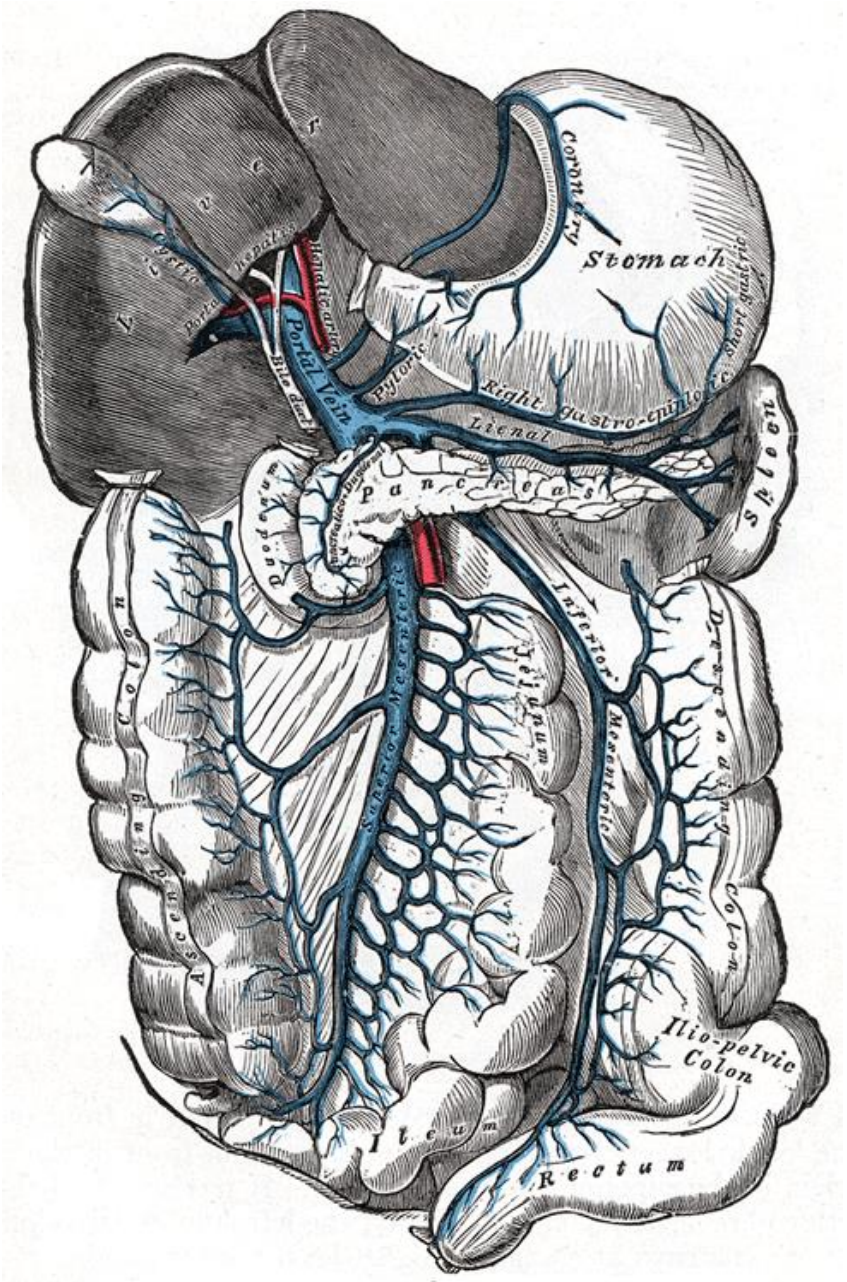
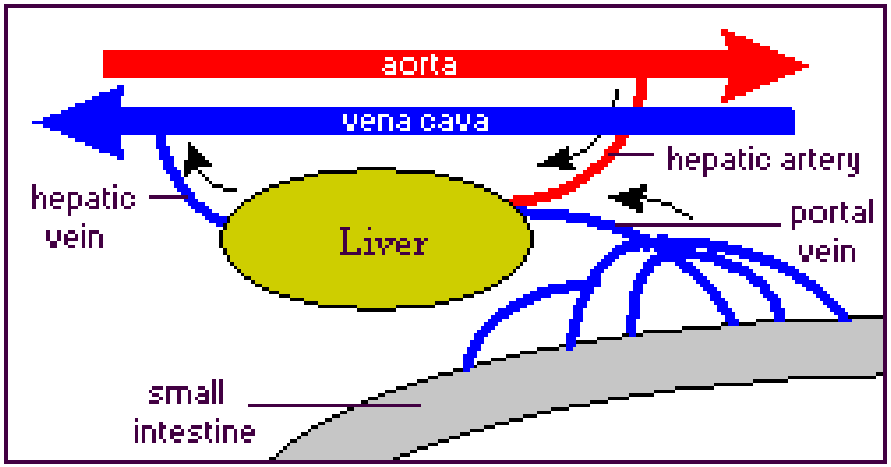
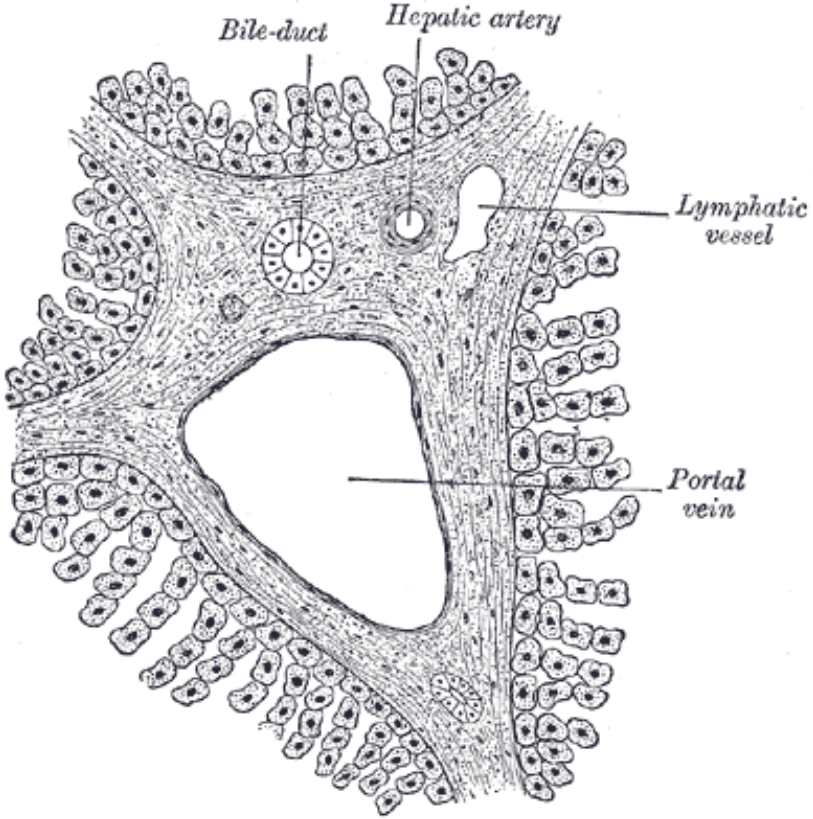

Stomach
Coronary
Portal Vein
Pylorus
Right gastro-epiploic
Lienal
Pancreas
Spleen
Duodenum
Inferior Mesenteric
Superior Mesenteric
Ascending Colon
Transverse Colon
Descending Colon
Ileum
Ilio-pelvic Colon
Rectum


aorta
vena cava
hepatic artery
hepatic vein
Liver
portal vein
small intestine

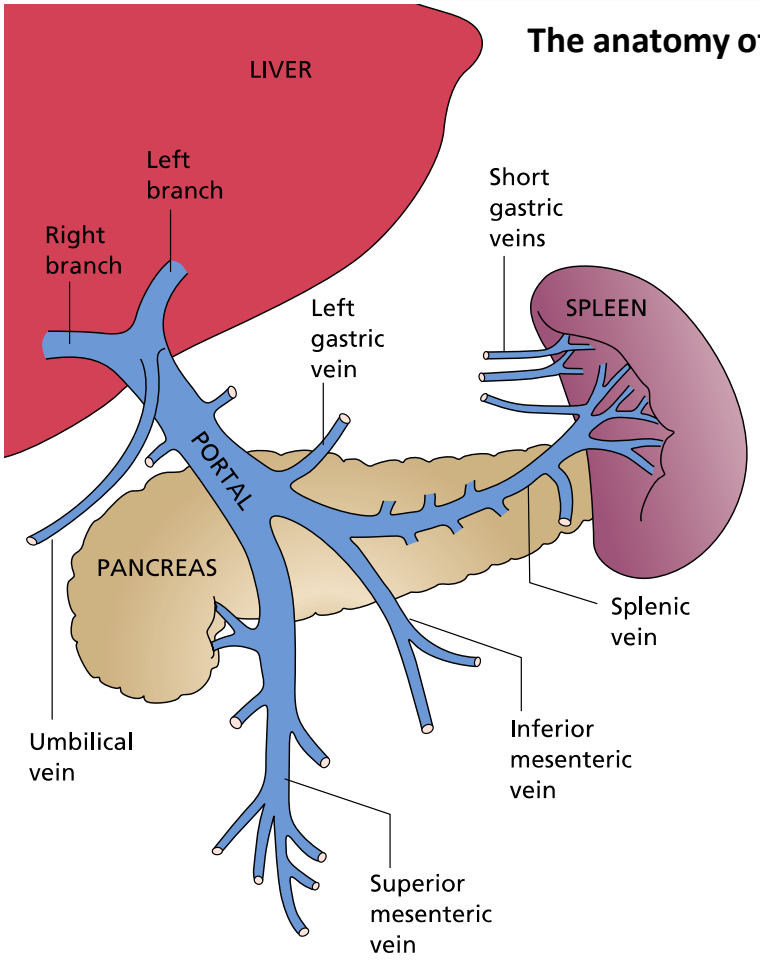

Bile-duct
Hepatic artery
Lymphatic vessel
Portal vein

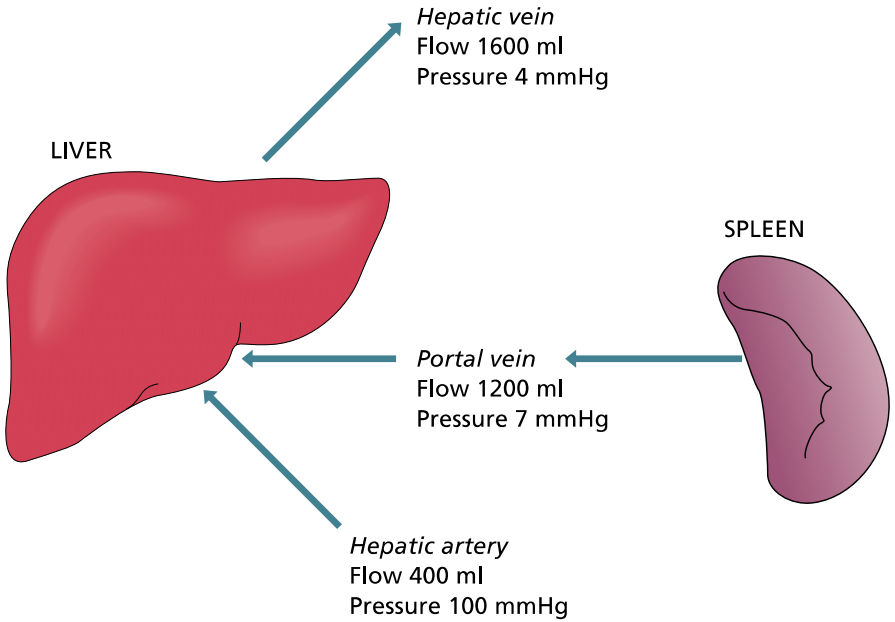
# The Hepatic Artery, Portal Venous System and Portal Hypertension: the Hepatic Veins and Liver in Circulatory Failure

*Sherlock's Diseases of the Liver and Biliary System*, Twelfth Edition. Edited by James S. Dooley, Anna S.F. Lok, Andrew K. Burroughs, E. Jenny Heathcote.

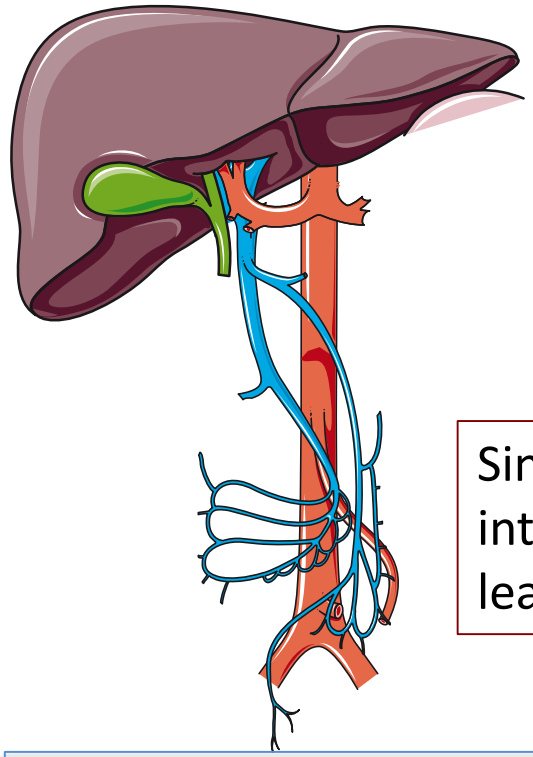

**Andrew K. Burroughs**
Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital and University College, London, UK

## The anatomy of the portal venous system



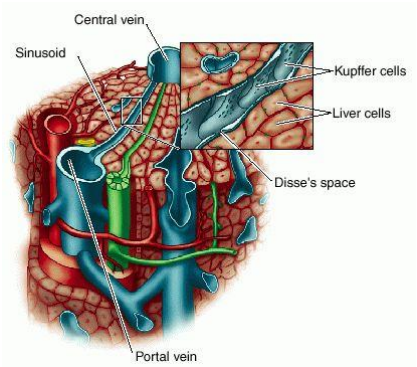




**The flow and pressure in the hepatic artery, portal vein and hepatic vein**



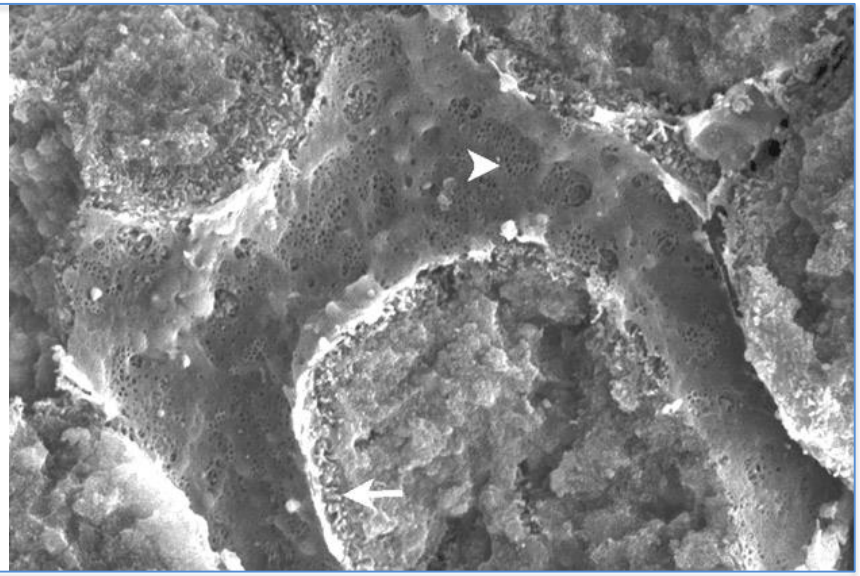
Dual blood supply consisting of 1500 - 1600 ml/min:

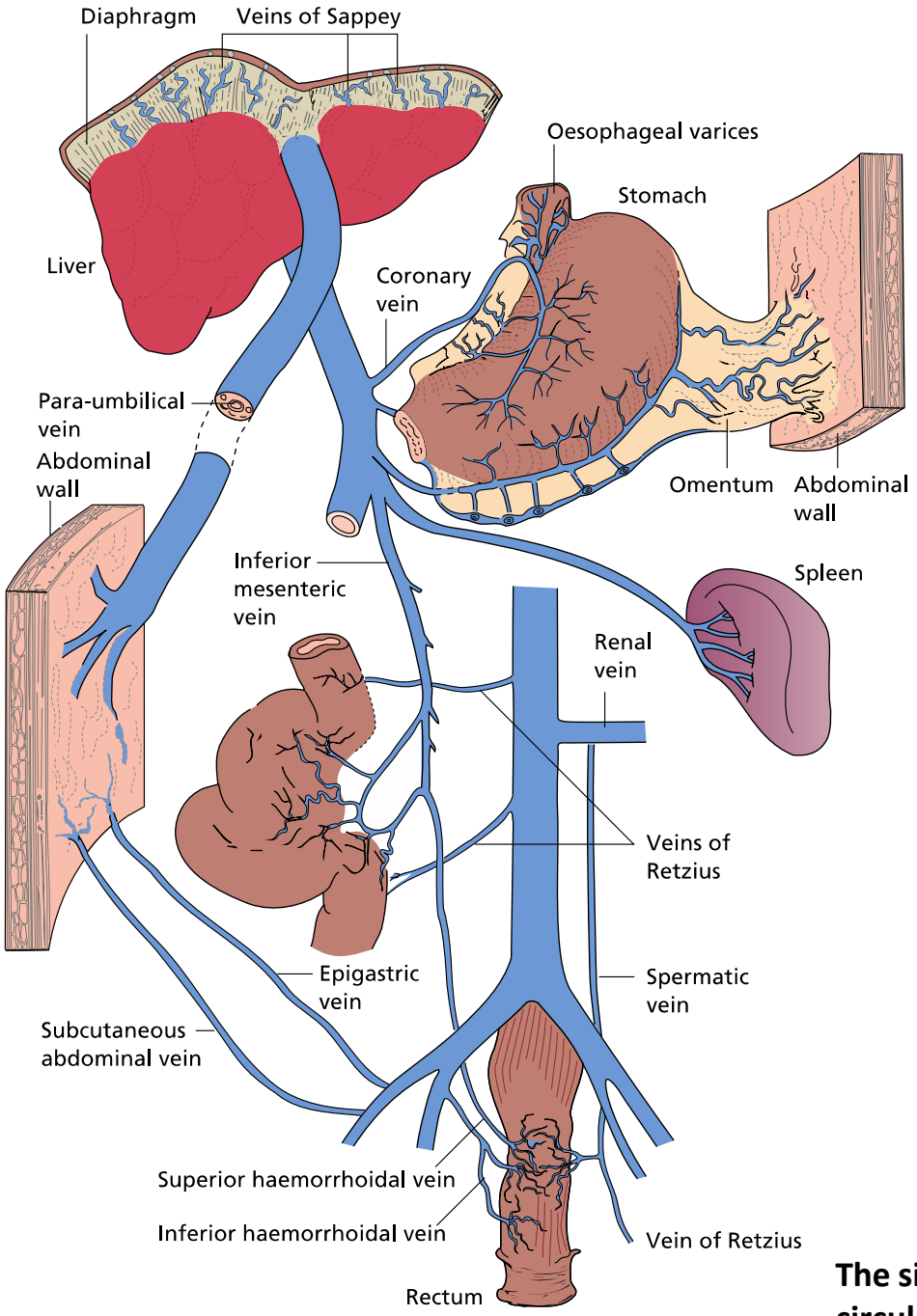
- Hepatic artery: 25%
- Portal Vein: 75%




Since only 25% of liver blood is of arterial origin, any intervening condition leading to further decrease in $pO_2$ might lead to hepatocellular hypoxia

The combination of open fenestrae, thin cytoplasm, and lack of an organized basement membrane reduces the distance required for oxygen diffusion and thereby facilitates oxygen delivery to the hepatocyte to compensate for the relatively low $pO_2$ in sinusoidal blood.



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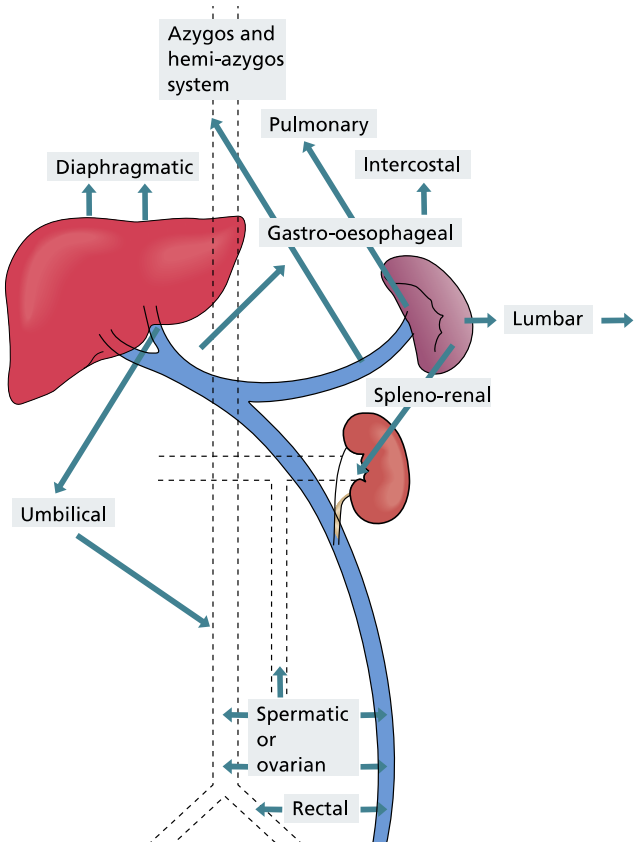


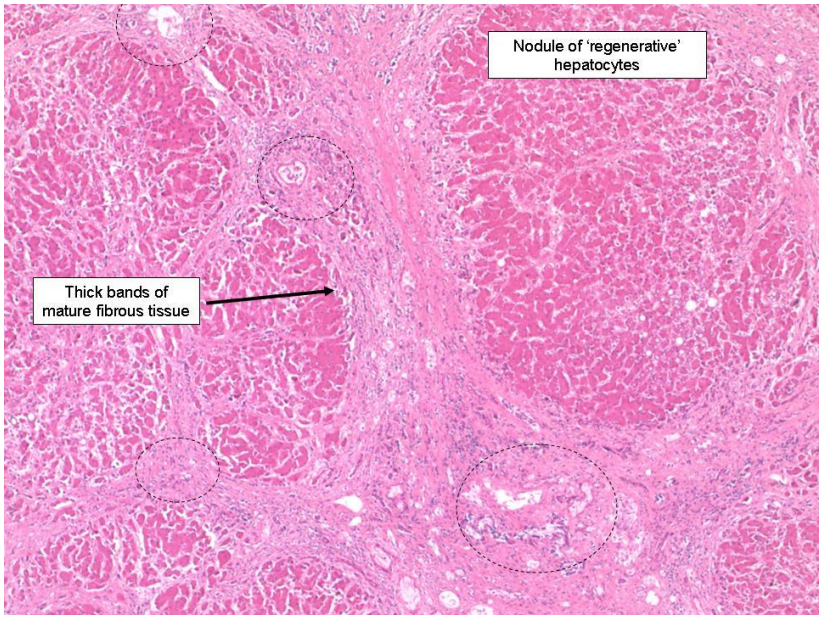

**....in the presence of intrahepatic portal vein obstruction**

**The sites of the portal-systemic collateral circulation in cirrhosis of the liver.....**

**CIRRHOSIS results in several pathophysiologic changes in the liver that may influence pharmacokinetics**

Histologically it consists of a diffuse process characterized by fibrosis and a conversion of normal organ architecture into structurally abnormal nodules

1. Reduction in liver blood flow
2. Intra- and extra-hepatic portal-systemic shunting
3. Reduction in the number and function of hepatocytes
4. Capillarization of the sinusoids




Loss of fenestration, thickening of the cytoplasm, and development of an organized basement membrane is called capillarization.

**Impaired synthesis of albumin** → **edema, ascites**

**reduced plasma binding of drugs**

- **Pathophysiology of Liver Disease and potential Pharmacokinetic impact**

  Absorption /Protein binding / Distribution / Metabolism /Excretion

- **Evaluation of Liver Function under a Pharmacological Perspective**

  Serum and clinical markers / histology / elastometry / dynamic function tests

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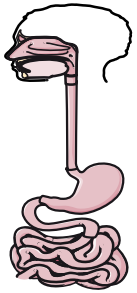
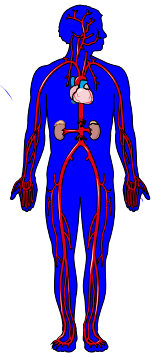
# Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption



- Protein Binding / Distribution



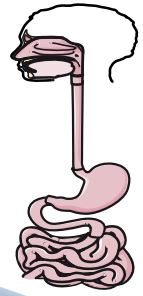
- Elimination

Metabolism → Biliary Excretion

Metabolism → Renal Excretion

# Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption



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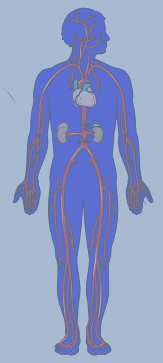

- Elimination

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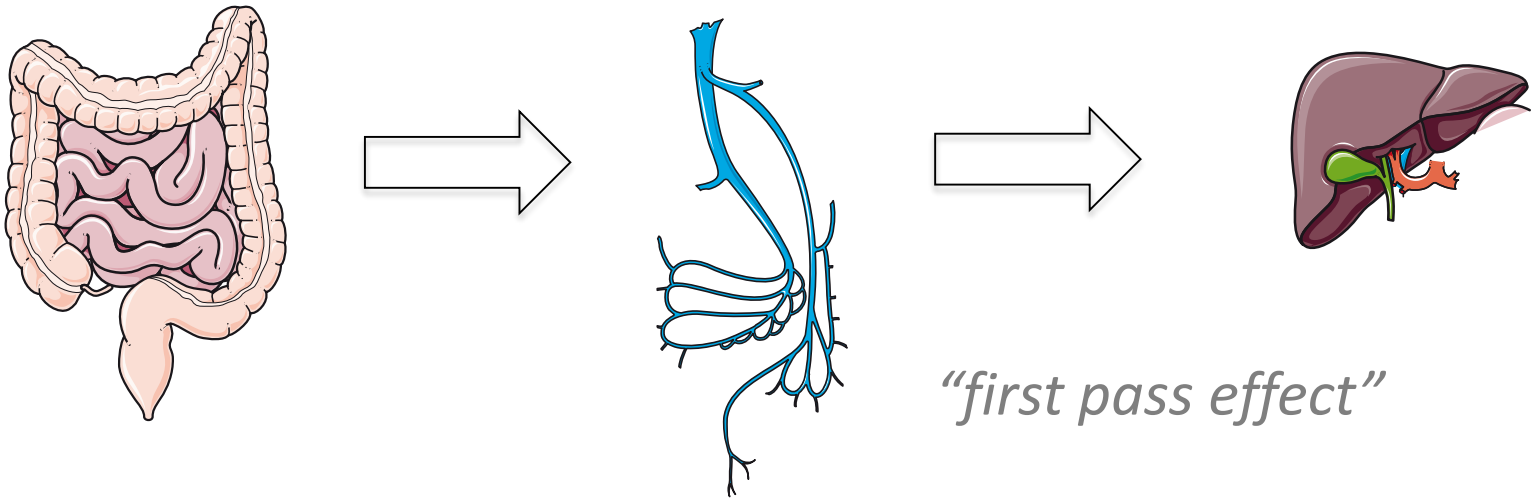
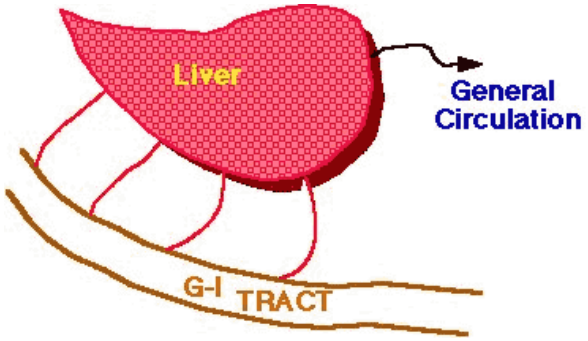
Metabolism → Renal Excretion

Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation



*"first pass effect"*

The effect of chronic liver disease on the bioavailability of orally administered drugs is mainly the result of reduced pre-systemic hepatic metabolism




The fraction ($F_H$) of an absorbed oral dose escaping first-pass clearance:

Hepatic blood flow

Unbound drug

Intrinsic clearance of unbound drug

$$F_H = 1 - f_H \times E_H = \frac{Q_H + f_u \times CL_{int}\,(1 - f_H)}{Q_H + f_u \times CL_{int}}$$

Fraction of the mesenteric blood flow passing through the liver

Hepatic extraction ratio

**Drugs can be categorized according to the efficiency of the liver in their removal from the circulation:**

## High Hepatic Extration Ratio ($E_H > 0.7$)

Blood flow limited: rather insensitive to changes in protein binding or enzyme/ transporter activity. Significant impact may result from decrease in blood flow and porto-systemic shunting

## Intermediate Hepatic Extration Ratio ($0.3 < E_H < 0.7$)

May be influenced by changes in either one of its 3 primary determinants (e.g. hepatic blood flow [$Q_H$], intrinsic clearance of unbound drug [$CL_{int}$] and the fraction of unbound drug [$f_u$])

## Low Hepatic Extration Ratio ($E_H < 0.3$)

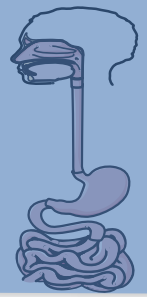
Mainly influenced by changes in protein binding and in the intrinsic hepatic clearance ($CL_{int}$). Enzyme/transporter capacity-limited

| DRUG | Normal Oral Bioavailability | CIRRHOSIS | Fold Increase |
|---|---|---|---|
| Carvedilol | 0.19 | 0.83 | 4.4 |
| Chlormethiazole | 01. | 1.16 | 11.6 |
| Labetalol | 0.33 | 0.63 | 1.9 |
| Meperidine | 0.48 | 0.87 | 1.8 |
| Metoprolol | 0.50 | 0.84 | 1.7 |
| Midazolam | 0.38 | 0.76 | 2.0 |
| Morphine | 0.47 | 1.01 | 2.1 |
| Nifedipine | 0.51 | 0.91 | 1.8 |
| Nisoldipine | 0.04 | 0.15 | 3.8 |
| Pentazocine | 0.18 | 0.68 | 3.8 |
| Propranolol | 0.36 | 0.60 | 1.7 |
| Verapamil | 0.10 | 0.16 | 1.6 |

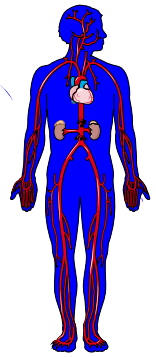
*Verbeeck RK. Eur J Clin Pharmacol 2008; 64: 1147-61*

# Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption



- Protein Binding / Distribution



- Elimination

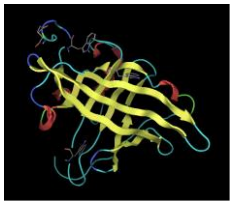
Metabolism → Biliary Excretion

Metabolism → Renal Excretion

# CIRRHOSIS also results in changes in protein binding and distribution:


1. Reduced albumin and $\alpha 1$ – acid glycoprotein (AAG)

2. Increase in endogenous compounds (e.g. bilirubin) inhibiting plasma protein binding of several drugs



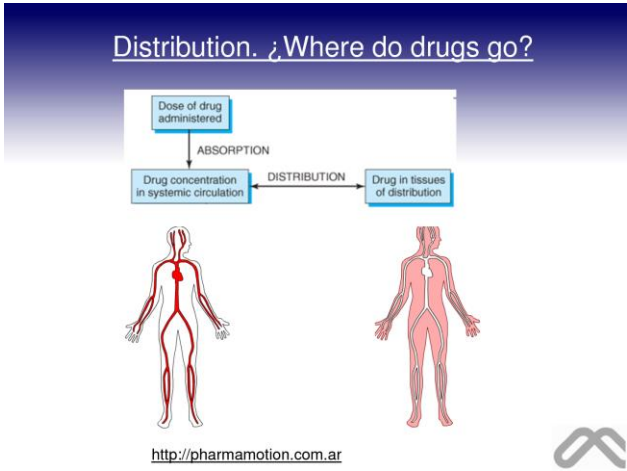
3. Qualitative changes in albumin and AAG

↓

Increase of the unbound fraction (fu) in blood

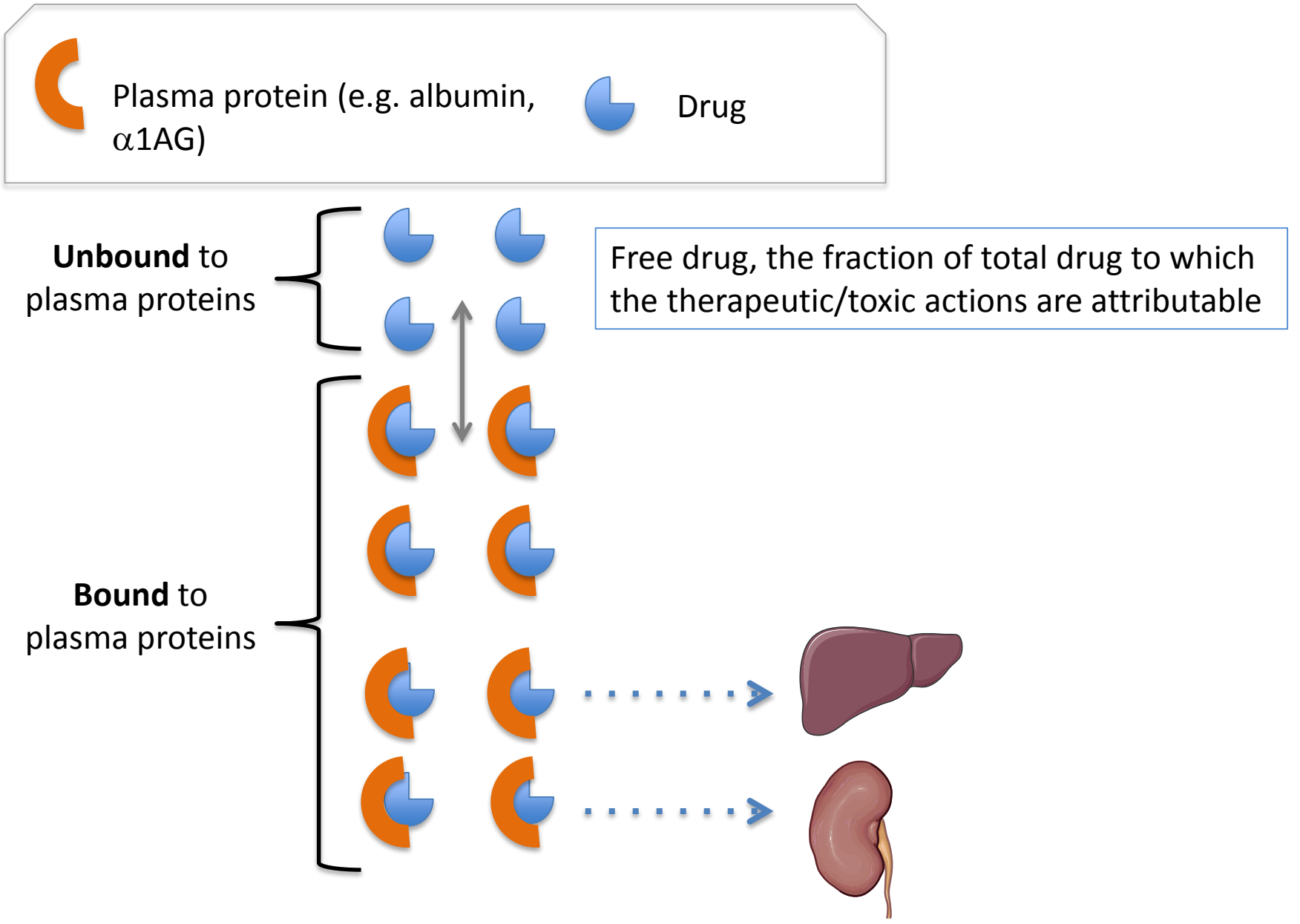
↓

Increase in volume of distribution



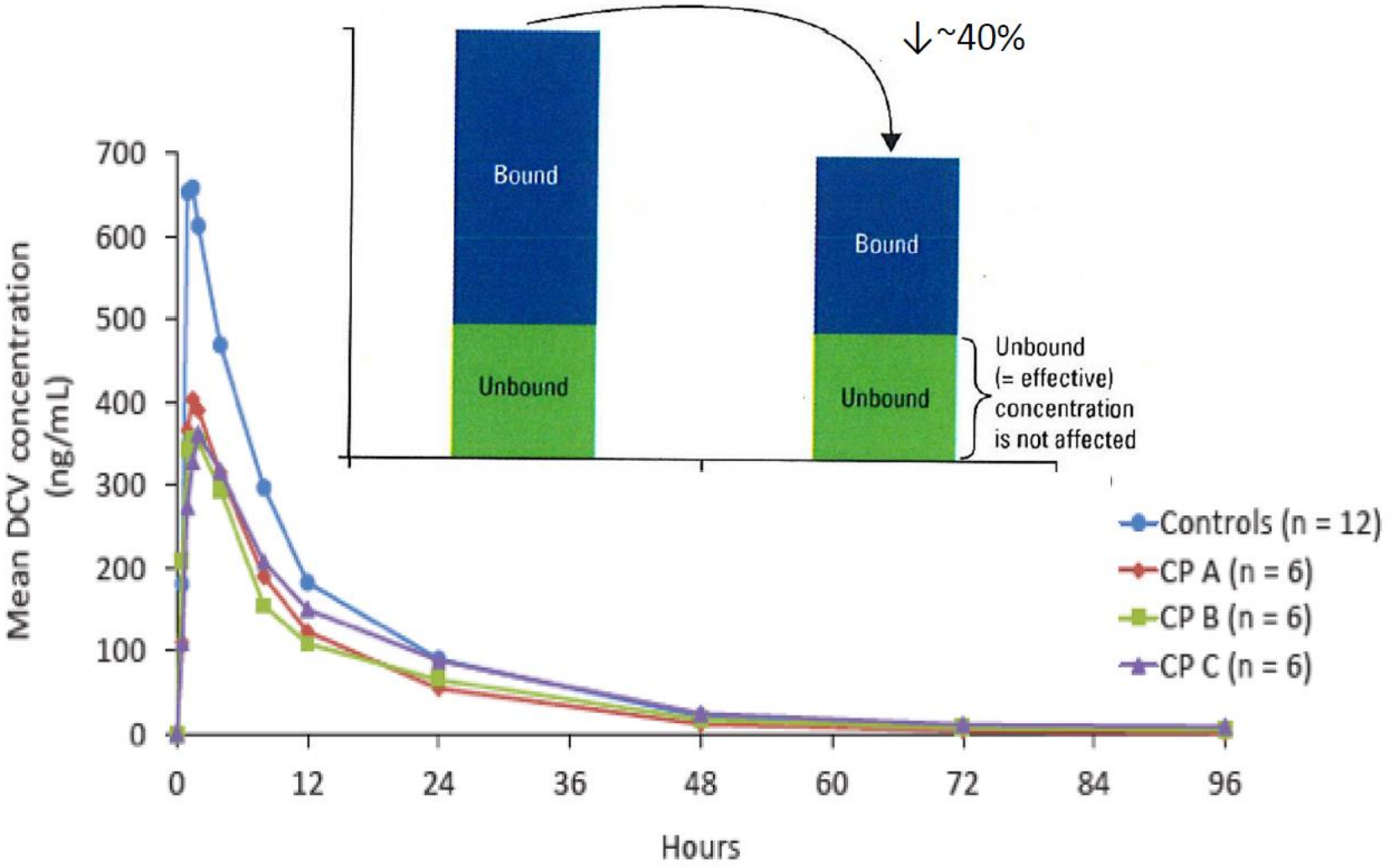
# Systemic Clearance and Oral Clearance:

| EPATIC EXTRACTION RATIO ($E_H$) | SYSTEMIC CLEARANCE ($Cl_{syst}$) | ORAL CLEARANCE ($CL_{or}$) |
|---|---|---|
| $E_H < 0.3$ | $f_u \times CL_{int}$ | $f_u \times CL_{int}$ |
| $0.3 < E_H < 0.7$ | $CL_H = Q_H \times \frac{f_u \times CL_{int}}{Q_H + f_u \times CL_{int}}$ | $f_u \times CL_{int}$ |
| $E_H > 0.7$ | $Q_H$ | $f_u \times CL_{int}$ |


Plasma protein (e.g. albumin, α1AG)
Drug
Unbound to plasma proteins
Bound to plasma proteins
Free drug, the fraction of total drug to which the therapeutic/toxic actions are attributable

# Daclatasvir Unbound Concentrations Unchanged in Hepatic Impairment

‡

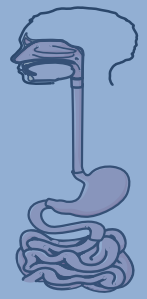



Total concentrations appear lower, but free amount is unchanged.

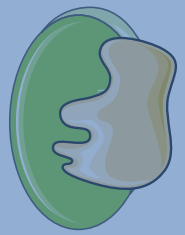
Bifano, M. 62nd AASLD 2011

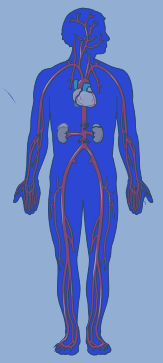
# Pathophysiology of Hepatic Dysfunction and Pharmacokinetic Consequences

- Absorption



- Protein Binding / Distribution





- Elimination

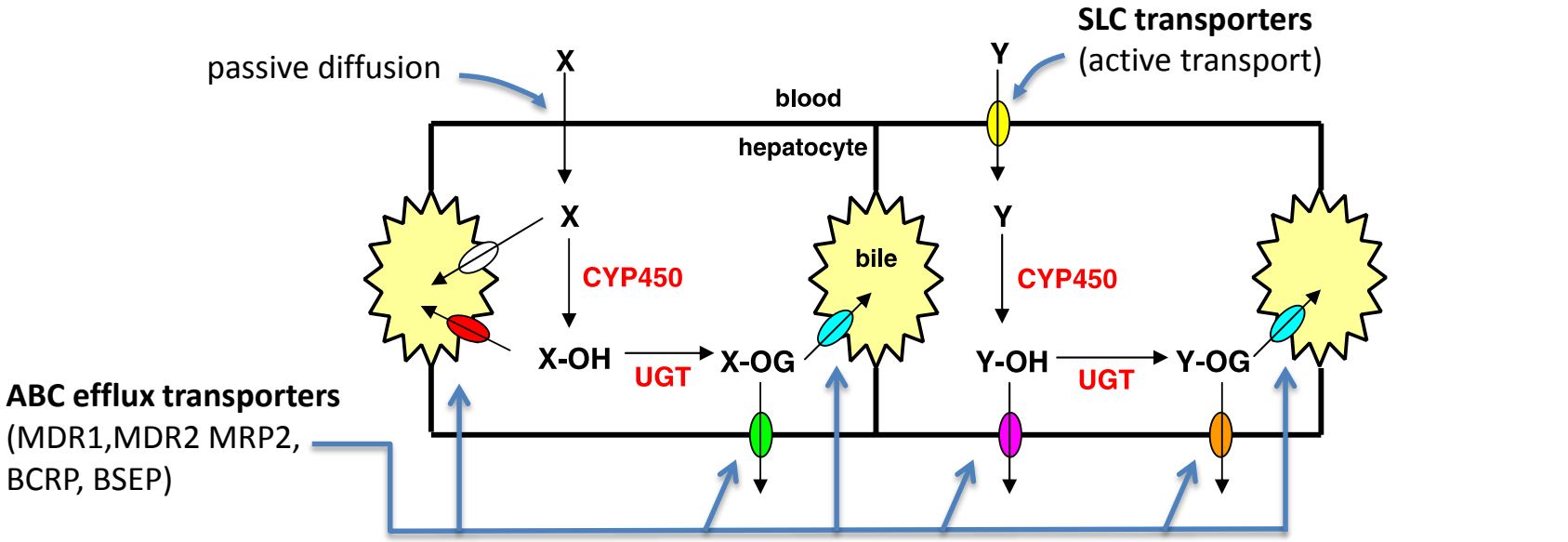
Metabolism → Biliary Excretion

Metabolism → Renal Excretion

The hepatic intrinsic clearance (**CLint**) represents the capacity of the liver to clear unbound drugs from the blood when there are no limitations in liver blood flow

**CLint** depends on:

- metabolic enzyme activity
- activity of sinusoidal and canalicular transporters




- In chronic liver disease, a reduction in absolute liver cell mass or a decrease in enzyme activity due to alteration in the function of surviving cells may lead to impaired drug metabolism.
- Reduction in drugs & oxygen uptake (sinusoidal capillarization) might also contribute to reduced hepatic metabolism

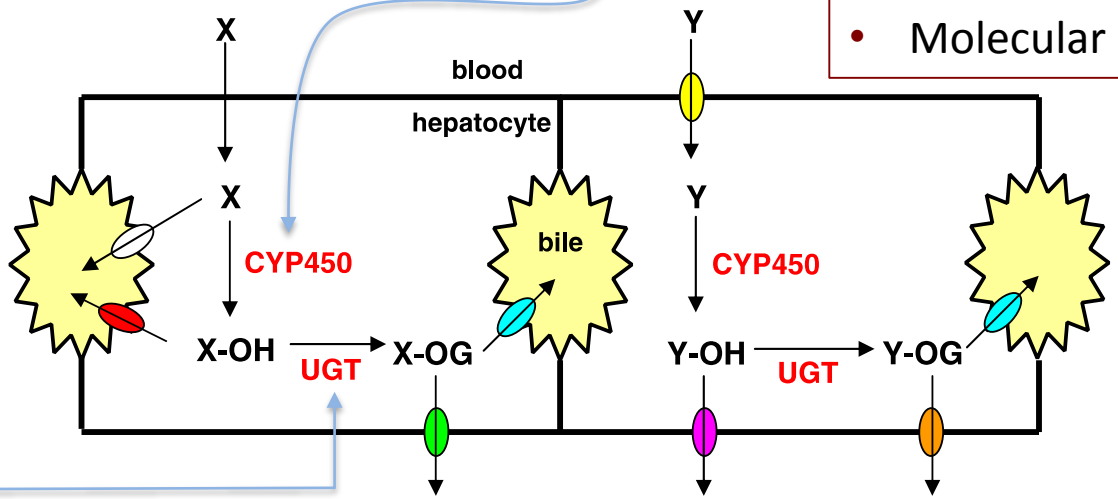
The microsomal mixed-function oxydase system (located in the SER of hepatocytes) is responsible for phase I oxydative metabolism.

The system consists of two enzymes:

- Cytochrome P450
- NADPH-dependent P450 reductase

These enzymes require two additional components to function:

- NADPH
- Molecular oxygen ($O_2$)

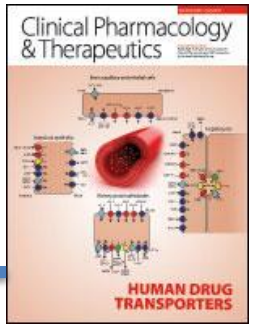



As a consequence, CYP450 enzymes are generally more sensitive than **phase II conjugating enzymes** in case of reduced $O_2$ as a result of shunting, sinusoidal capillarization and reduced liver flow

Chronic liver diseases are associated with variable reductions in CYP450 activities, but these were found to be non uniform and unrelated to reductions in hepatic blood flow.

# Liver disease selectively modulates cytochrome P450–mediated metabolism

Reginald F. Frye, et al. Clin Pharm Ther 2006; 80: 235-45.



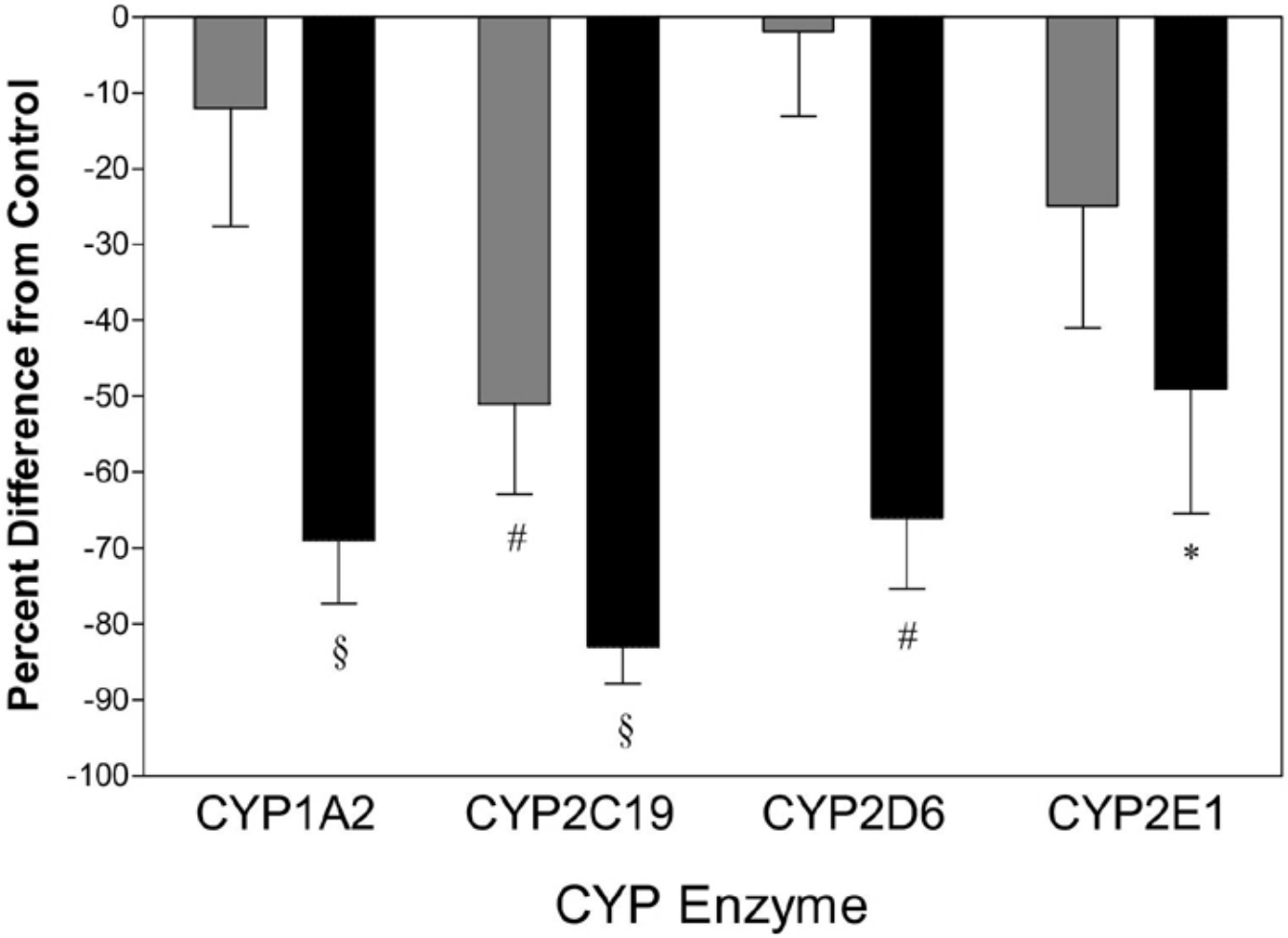

- 20 patients with different etiologies and severity of liver disease
- 20 age-, sex-, and weight-matched healthy volunteers
- Liver disease severity was categorized by use of the Child-Pugh score
- All participants received a cocktail of 4 oral drugs simultaneously:

✓ Caffeine (CYP1A2)
✓ Mephenytoin (CYP2C19)
✓ debrisoquin (INN, debrisoquine / CYP2D6))
✓ Chlorzoxazone (CYP2E1)

- The primary end points were measurements of specific CYP metabolism indexes for each enzyme.

**Liver disease selectively modulates cytochrome P450–mediated metabolism**

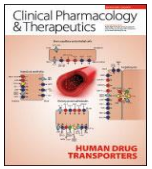
Reginald F. Frye, et al. Clin Pharm Ther 2006; 80: 235-45.




Mean (SE) percentage difference in index of drug metabolism from control group for caffeine, mephenytoin, debrisoquin, and chlorzoxazone in same cohort of patients with compensated (*black bars*, n = 8) or decompensated (*gray bars*, n = 12) liver disease. *Section mark*, $P < .001$ in comparison with control subjects; *pound sign*, $P < .01$ in comparison with control subjects; *asterisk*, $P < .05$ in comparison with control subjects.

Proposed interpretation by the Authors:

**Liver disease selectively modulates cytochrome P450–mediated metabolism**
Reginald F. Frye, et al. Clin Pharm Ther 2006; 80: 235-45.




**"sequential progressive model of hepatic dysfunction"**

As an alternative to:

a. The sick cell theory
b. The intact hepatocyte theory

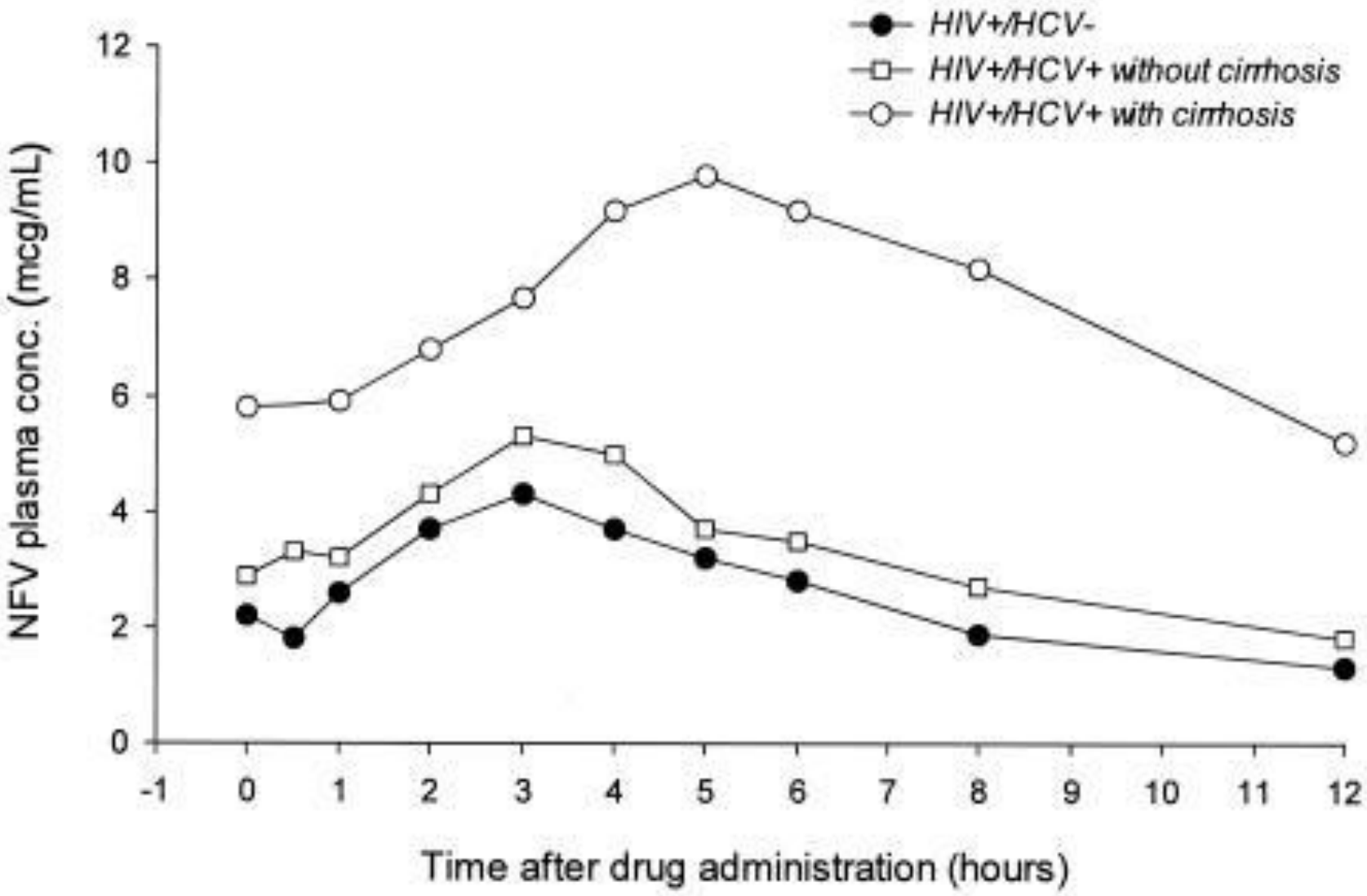
Different aspects of hepatic function are modified in the presence of liver disease, and the order of progression of alteration of each function follows a defined sequence:

| EARLY STAGE | | INTERMEDIATE STAGE | | END STAGE | |
|---|---|---|---|---|---|
| CYP2C19 | ↓ | CYP2C19 | ↓ | CYP2C19 | ↓ |
| CYP1A2 | ↕ | CYP1A2 | ↓ | CYP1A2 | ↓ |
| CyP2D6 | ↕ | CyP2D6 | ↕ | CyP2D6 | ↓ |
| CYP 2E1 | ↕ | CYP 2E1 | ↕ | CYP 2E1 | ↓ |

# Changes in Nelfinavir PK with Cirrhosis

CYP2C19 is exquisitely sensitive to the presence of liver disease

*Branch, R. A. 1998. Drugs in liver disease. Clin. Pharmacol. Ther. 64:462– 464.*




*Regazzi M et al. Antimicrob Agents Chemother. 2005; 49: 643*

**Conjugation reactions** are thought to be less affected than CYP450 reactions in patients with chronic liver disease:

Oxazepam
Lorazepam
Temazepam
} mainly cleared by glucuronidation

mainly cleared by phase I reactions } Diazepam, Midazolam

NOT reduced in liver cirrhosis ⇕ **CLEARANCE** ↓ Reduced in liver cirrhosis

*Pentikainen PJ, et al. J Clin Pharmacol 1989; 29: 272-77 Chalasani N, et al. Hepatology 2001; 34: 1103-08 Hoyumpa AM, et al. Hepatology 1991; 13: 786-95 Shull HJ, et al. Ann Intern Med 1976; 84: 420-25 Kraus JW, et al. Clin Pharmacol Therap 1978; 24: 411-19 Ghabrial H, et al. Eur J Clin Pharmacol 1986; 30: 93- 7 Klotz U, et al. Clin Pharmacol Therap 1977; 21: 430-6*

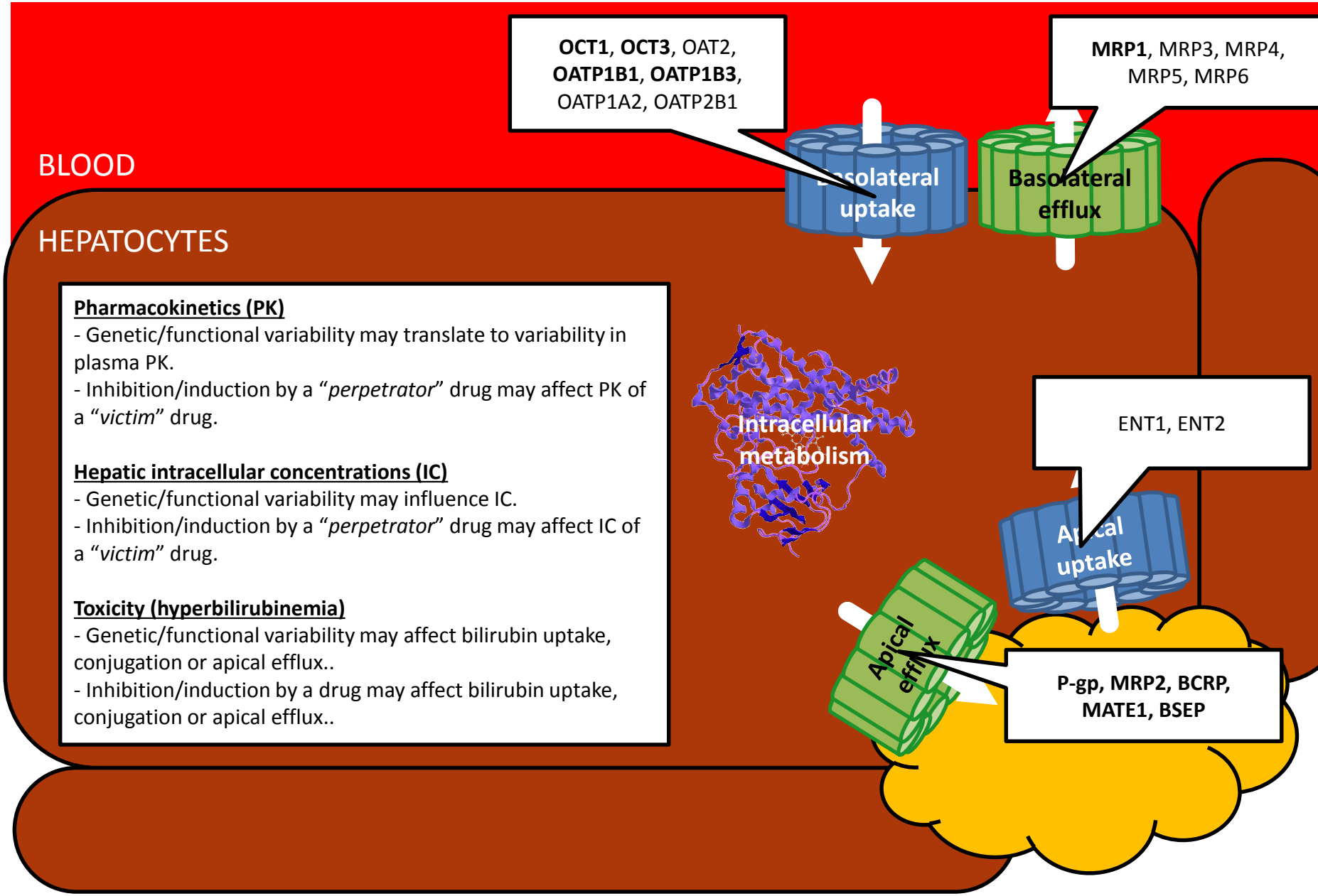
Activation of latent UDP-glucuronyltransferase (UGT) enzymes in liver injury
*Hoyumpa AM, et al. Hepatology 1991; 13: 786-95, Debinsky HS, et al. Gastroenterology 1995; 108: 1464-69*

Increased extra-hepatic metabolism in cirrhosis (e.g. morphine)
*Mazoit JX, et al. Clin Pharmacol Therap 1990; 48: 613-18*

In subsequent studies, carried out on patients with **more advanced liver disease**, impaired glucuronidation was found for drugs like morphine, diflunisal, lormetazepam, oxazepam, lamotrigine, zidovudine and mycophenolate mofetil

*Hasselstrom J, et al. Br J Clin Pharmacol 1990; 29: 289-97 Crotty B, et al. Eur J Clin Pharmacol 1989; 36: 501-6 Mcdonald JI, et al. Eur J Clin Pharmacol 1992; 42: 471-4 Hildebrand M, et al. Eur J Drug Metab Pharmacokinet 1990; 15: 19-26 Sonne J, et al. Hepatology 1990; 11: 951-6 Marcellin P, e al. Br J Clin Pharm 2001; 51: 410-14 Taburet AM, et al. Clin Pharmacol Therap 1990; 47: 731-9 Parker G, et al. J Clin Pharmacol 1996; 36: 332-344*

# Mechanisms for hepatic residence and clearance of drugs



# HCV, liver disease and transporters

Pharmacological Reports
2012, 64, 927–939
ISSN 1734-1140



Drug Metab. Pharmacokinet. 25 (2): 190–199 (2010).

**Regular Article**

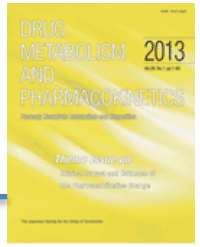
## Hepatitis C Virus-related Cirrhosis is a Major Determinant of the Expression Levels of Hepatic Drug Transporters

| | mRNA levels (amol/μg total RNA) HCV (−), LC (−) | HCV (+), LC (−) | HCV (−), LC (+) | HCV (+), LC (+) | Ratio [(+), (+)/(−), (−)] |
|---|---|---|---|---|---|
| OCT1 | 16.63 ± 8.91 | 13.64 ± 9.23 | 10.70 ± 4.60 | 8.87 ± 5.56*** | 0.53 |
| OCTN2 | 0.70 ± 0.32 | 0.83 ± 0.47 | 0.55 ± 0.24 | 0.75 ± 0.39 | 1.07 |
| OAT2 | 11.86 ± 7.36 | 13.37 ± 8.62 | 10.06 ± 4.03 | 10.27 ± 5.66 | 0.87 |
| OAT7 | 0.62 ± 0.33 | 0.56 ± 0.30 | 0.47 ± 0.19 | 0.47 ± 0.20 | 0.76 |
| OATP1B1 | 10.55 ± 6.71 | 8.04 ± 4.78 | 6.72 ± 2.95 | 5.91 ± 2.89*** | 0.56 |
| OATP1B3 | 3.83 ± 2.27 | 2.91 ± 1.95 | 2.80 ± 1.54 | 1.98 ± 1.15** | 0.52 |
| OATP2B1 | 31.20 ± 13.72 | 32.50 ± 20.18 | 24.13 ± 10.17 | 24.36 ± 10.91 | 0.78 |
| MATE1 | 3.14 ± 2.04 | 2.13 ± 1.27 | 2.04 ± 0.93 | 1.34 ± 0.68*** | 0.43 |
| PEPT1 | 1.01 ± 0.55 | 1.24 ± 0.66 | 0.81 ± 0.39 | 0.94 ± 0.32 | 0.93 |
| MDR1 | 1.15 ± 0.52 | 1.56 ± 0.87 | 1.07 ± 0.35 | 1.40 ± 0.43* | 1.22 |
| MRP1 | 0.25 ± 0.14 | 0.40 ± 0.26 | 0.27 ± 0.17 | 0.51 ± 0.53* | 2.04 |
| MRP2 | 2.96 ± 1.77 | 2.44 ± 1.66 | 1.45 ± 0.68 | 1.45 ± 0.54*** | 0.49 |
| MRP3 | 2.58 ± 1.31 | 2.64 ± 1.34 | 1.68 ± 0.55 | 2.18 ± 1.09 | 0.85 |
| MRP4 | 0.09 ± 0.05 | 0.16 ± 0.14 | 0.11 ± 0.05 | 0.18 ± 0.13*** | 2.06 |
| MRP5 | 0.07 ± 0.04 | 0.10 ± 0.06 | 0.06 ± 0.02 | 0.11 ± 0.08 | 1.49 |
| MRP6 | 3.41 ± 2.16 | 3.13 ± 1.76 | 2.50 ± 1.28 | 2.33 ± 1.15 | 0.68 |
| BCRP | 0.57 ± 0.33 | 0.45 ± 0.25 | 0.33 ± 0.17 | 0.31 ± 0.22*** | 0.53 |

GSTA1 SULT1A1 SULT2A1 UGT1A1 UGT1A4 UGT1A6 ABCB1 ABCC2 ABCC3 ABCC4 ABCG2

**Hepatitis C Virus-related Cirrhosis is a Major Determinant of the Expression Levels of Hepatic Drug Transporters.**

Ogasawara K, et al. Drug Metab Pharmacokinet 2010; 25: 190-99




**Fibrosis stage proportional Decreases in mRNA levels of OCT1 and OATP1B1 in cirrhotic patients**

*….may prevent the accumulation of endogenous and exogenous toxic compounds in damaged hepatocytes…*

**Upregulation of MRP4 mRNA in patients with HCV-associated cirrhosis**
(Also reported in
- ✓ PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS,
- ✓ PRIMARY BILIARY CIRRHOSIS
- ✓ ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE)

*…may serve to prevent further damage to hepatocytes through the increased efflux of potentially toxic compounds, like bile acids…….*

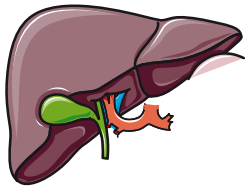
**Both support the general hypothesis of activation of multiple detoxifying mechanisms**

## Biliary Excretion

- Reduced formation or secretion of bile into the duodenum leads to a decreased clearance of both endogenous and exogenous substances that are eliminated by biliary excretion (e.g. ampicillin, piperacillin, several cephalosporins, clindamycin, ciprofloxacin)

- Hepatocellular damage from biliary obstruction (e.g. changes in the membrane and cytoskeleton of biliary canaliculi) and resulting impairment of metabolic drug clearance

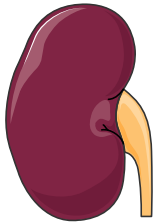
- Role of transporters (up-regulation of efflux pumps suggesting a compensatory mechanism limiting hepatocellular accumulation of toxic biliary constituents)



## Renal Excretion

- Advanced liver disease is often complicated by impaired renal function – **hepatorenal syndrome**, such as unexplained progressive renal failure occurring in patients with chronic liver disease without other causes of renal failure

- Conventional creatinine-based GFR measurements often inadequate:
  - Reduced muscle mass
  - Impaired metabolism of creatine to creatinine
  - Increased fractional tubular secretion of creatinine



- **Pathophysiology of Liver Disease and potential Pharmacokinetic impact**

  Absorption /Protein binding / Distribution / Metabolism /Excretion

- **Evaluation of Liver Function under a Pharmacological Perspective**

  Serum and clinical markers / histology / elastometry / dynamic function tests

# Child-Pugh classification and scoring of liver diseases

| Clinical/Biochemical Indicator | 1 point | 2 points | 3 points |
|---|---|---|---|
| Serum bilirubin (mg/dL) | < 2 | 2 - 3 | > 3 |
| Serum albumin (g/dL) | > 3.5 | 2.8 – 3.5 | < 2.8 |
| Prothrombine time (s > control) | < 4 | 4 - 6 | > 6 |
| Encephalopathy (grade) | none | 1 or 2 | 3 or 4 |
| Ascites | absent | slight | moderate |

Points are summed, and the total score is classified according to severity as follows:

**GROUP A** (mild) = 5 – 6 points

**GROUP B** (moderate) = 7 – 9 points

**GROUP C** (severe) = 10 – 15 points

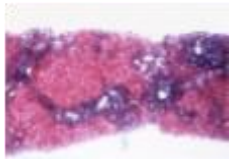
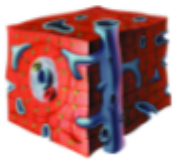
Verbeeck RK. Eur J Clin Pharmacol 2008; 64: 1147-1161

# Staging of fibrosis in chronic viral hepatitis

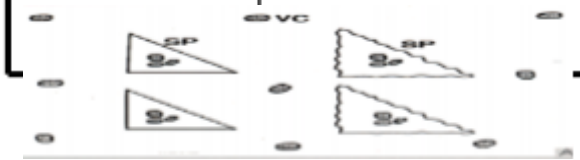
| Definition | No Fibrosis | Fibrous Portal Expansion | Few Bridges or Septa | Numerous Bridges or Septa | Cirrhosis |
|---|---|---|---|---|---|
| IASL | No Fibrosis | Mild Fibrosis | Moderate Fibrosis | Severe Fibrosis | Cirrhosis |
| Metavir | F0 | F1 | F2 | F3 | F4 |

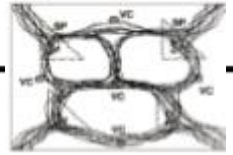






Goodman Z et al. J Hepatol 2007;47:598-607

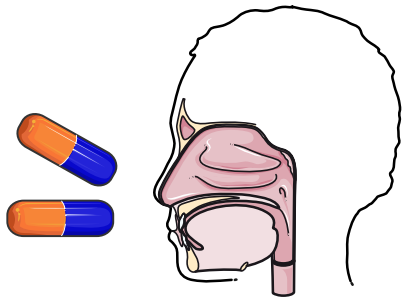
# Metavir score by liver stiffness assessed with transient elastography (Fibroscan®)

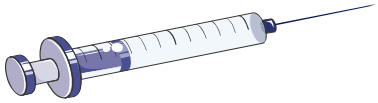
| Metavir score | Liver stiffness (kPa) |
|---|---|
| F0 | < 5.0 |
| F1 | 5.1-7 |
| F2 | 7.1- 9.5 |
| F3 | 9.6- 12.5 |
| F4 | >12.5 |

*Castéra L. et al. Gastroenterology 2005; 128: 343-350*

# DYNAMIC LIVER FUNCTION TESTS (1)

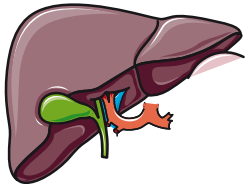
In order to better predict individual drug handling in patients with hepatic dysfunction





Oral or IV administration

Exogenous substance mostly or exclusively eliminated by the liver



**Determination of:**

**a) the plasma disappearance of the probe**
or
**b) the appearance of a metabolite**

- PLASMA
- URINE
- EXPIRED AIR (Breath Test)

Exogenous substances used as model substrates can be classified as:

1. **Blood-flow-limited** (high extraction ratio)
2. **Capacity-limited** (low-extraction ratio)

# DYNAMIC LIVER FUNCTION TESTS (2)

Based on test principles, the measurement of hepatic extraction of **blood-flow dependent probes** (e.g. indocyanine green and sorbitol) will give an estimate of the *degree of sinusoidal and vascular shunting*.

It is not clear how concurrent alteration of hepatic-uptake mechanisms might affect the hepatic clearance of these high extraction ratio molecules

**LIDOCAINE** ($E_H > 0.7$) transformation into MONOETHYLGLYCINEXYLIDIDE (MEGX) CYP3A AND CYP1A2. The test was shown to correlate with Child-Pugh scores

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*Metabolic dysfunction of liver cells* can be assessed by **low extraction ratio substances**, whose clearance should be minimally dependent upon alterations in hepatic blood flow and the presence of portal-systemic shunts

**ANTIPYRINE**: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP3A4

**CAFFEINE**: CYP1A2
Ratios of PARAXANTHINE (a caffeine metabolite) to CAFFEINE are reduced in patients with liver disease and correlate linearly with Child-Pugh scores

**MIDAZOLAM**: CYP3A4
In order to by-pass intestinal CYP3A4 activity and thus using it as a marker for hepatic CYP3A4 MIDAZOLAM should be administer IV – Midazolam is not a Pgp substrate

# DYNAMIC LIVER FUNCTION TESTS (3)

**$^{14}CO_2$ BREATH TESTS:**

**AMINOPYRINE** (CYP2D6, CYP2C9, CYP2C19, CYP1A2)

**ERYTHROMYCIN** (CYP3A probe, Pgp substrate)

**CAFFEINE** (CYP1A2)

**Low hepatic extraction ratio ($E_H < 0.3$)**

No demonstration has been so far provided on the superiority of these dynamic liver function tests over Child-Pugh classification

In addition, several studies found a significant correlation in the same group of patients between tests using a low-extraction drug and tests using a high-extraction drug

Clinicians rely more on the Child-Pugh score which is more easily available and consists of parameters to which they are more accustomed

*…just some anti-HCV drugs…*

## Sofosbuvir PK Fact Sheet

UNIVERSITY OF LIVERPOOL

*Hepatic Impairment*

No dose adjustment of sofosbuvir is warranted in mild, moderate or severe hepatic impairment. The safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.

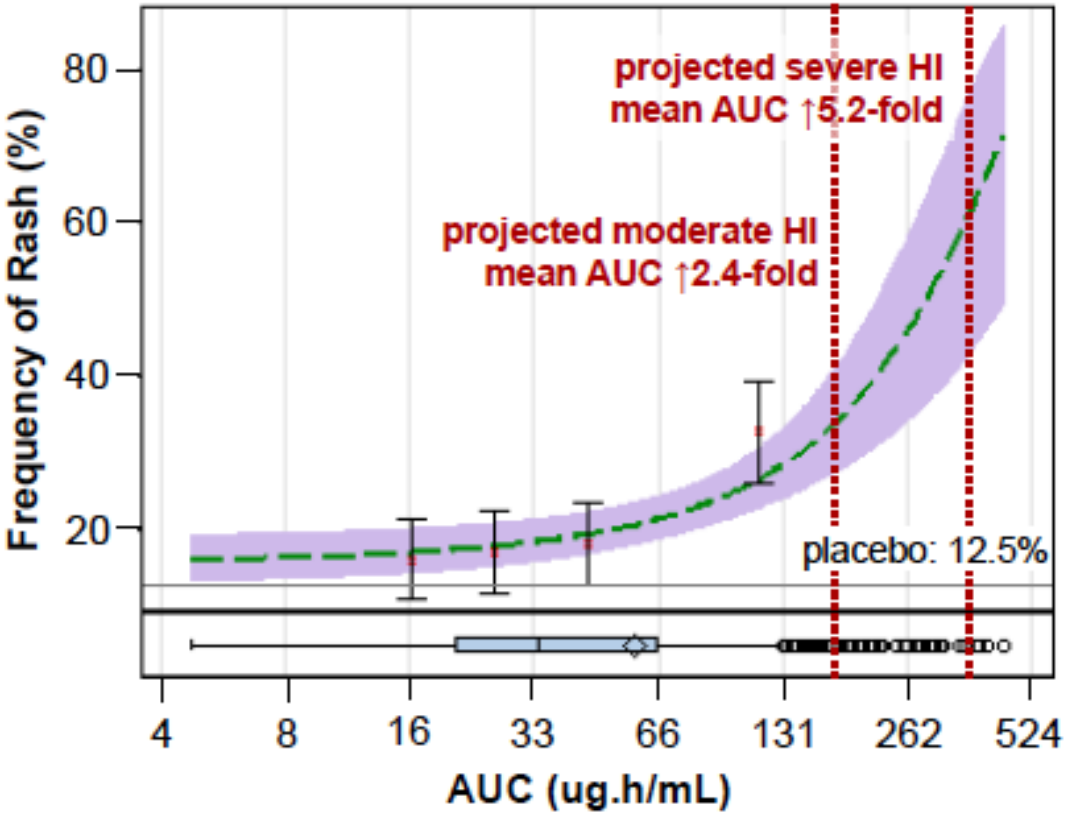
## Simeprevir PK Fact Sheet

UNIVERSITY OF LIVERPOOL

*Hepatic Impairment*

Plasma exposure of simeprevir in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects. Compared to healthy subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in non-HCV infected subjects with moderate hepatic impairment (Child-Pugh class B) and 5.2-fold higher in non-HCV infected subjects with severe hepatic impairment (Child-Pugh class C). No dose adjustment of simeprevir is necessary in patients with mild or moderate hepatic impairment; no dose recommendation can be given for patients with severe hepatic impairment (Child-Pugh class C). The safety and efficacy of simeprevir have not been studied in HCV infected patients with moderate or severe hepatic impairment (Child-Pugh class B or C), therefore particular caution is recommended in these patients.

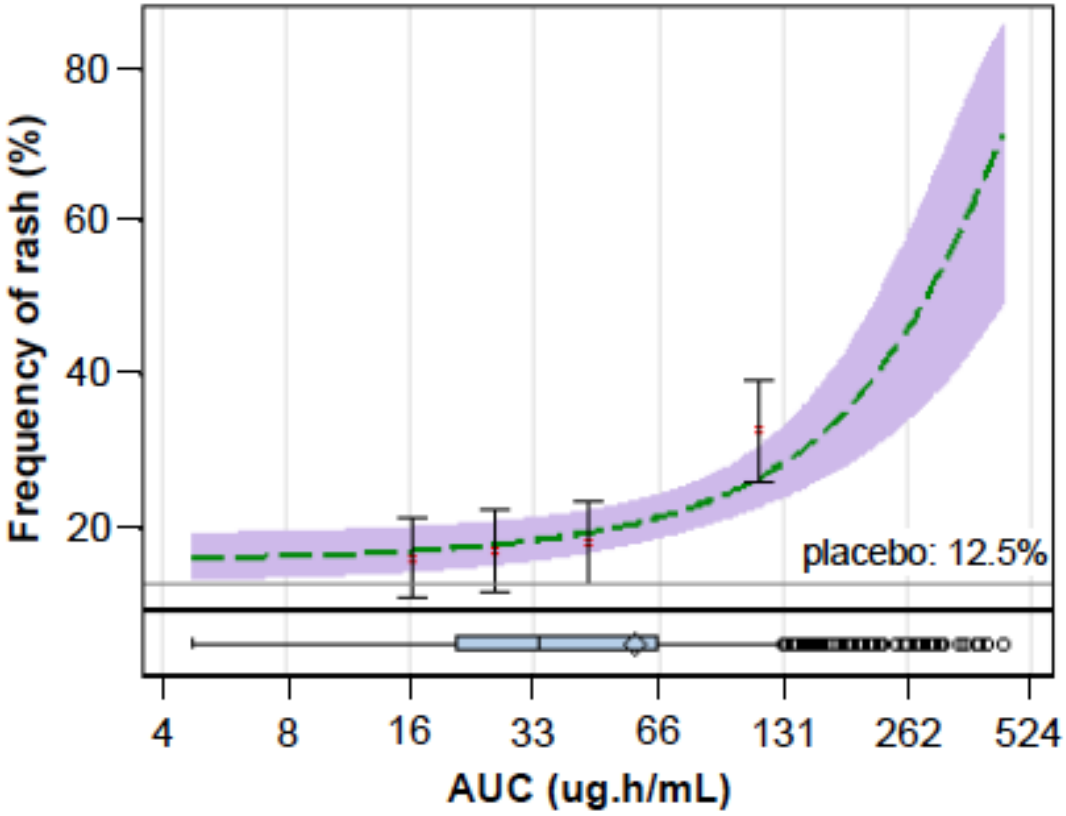
# HCV-Uninfected Subjects with Moderate or Severe Hepatic Impairment had Higher Exposures Compared to Healthy Controls




- PegIFN is contraindicated in Child-Pugh class B or C
- Simeprevir PK will be evaluated in patients with moderate or severe hepatic impairment during ongoing IFN-free development

Phase 3 trials (C208, C216, HPC3007)

# An Increased Incidence of Rash was Associated with Higher Exposures in Phase 3




Similar relationships between exposures and:

- photosensitivity
- pruritus
- dyspnea
- increased bilirubin

Phase 3 trials (C208, C216, HPC3007)

*Hepatic Impairment*

Hepatic function does not affect the pharmacokinetics of ribavirin, therefore, no dose adjustment is required in hepatic impairment. However, use is contraindicated in severe hepatic dysfunction or decompensated cirrhosis of the liver.

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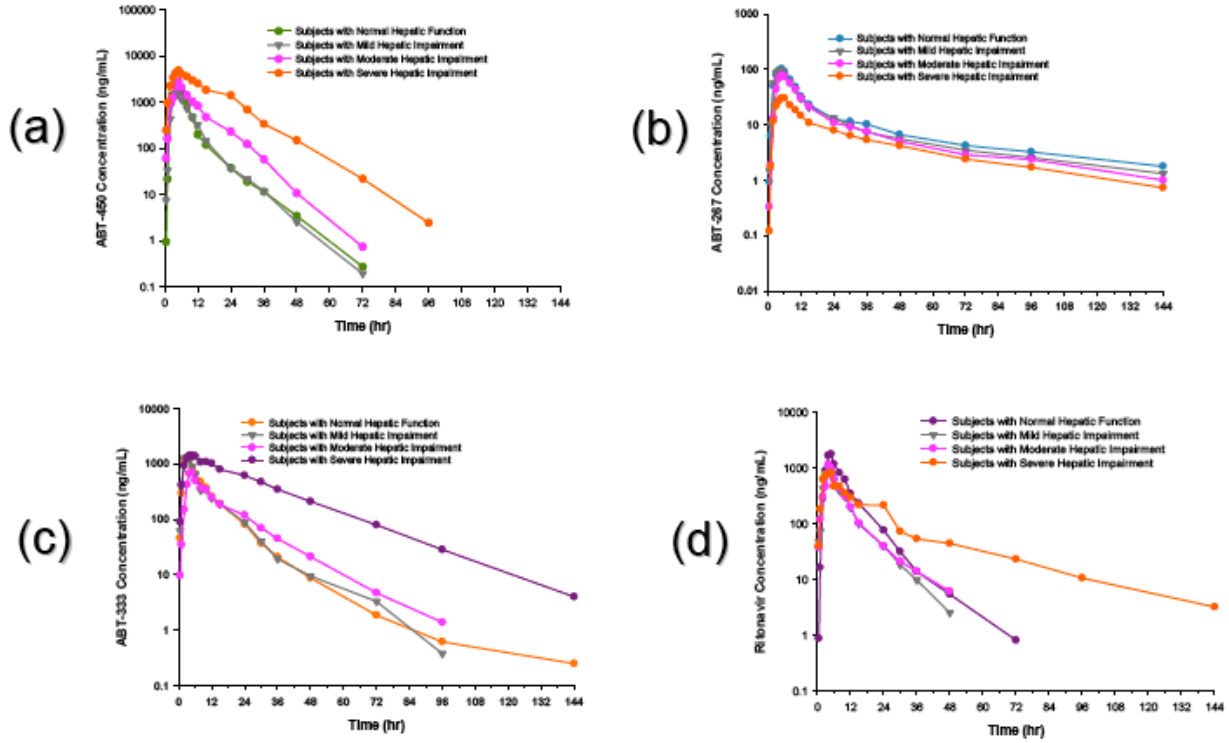
## HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use
## Initial U.S. Approval: 2014

*Patients with Hepatic Impairment:* The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe hepatic impairment (Child-Pugh Class C). Ledipasvir plasma exposure ($AUC_{0\text{-}inf}$) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure of ledipasvir

**Figure 1. Mean Plasma Concentration vs Time Profile for ABT-450 (a), ABT-267 (b), ABT-333 (c) and Ritonavir (d) in Subjects with Mild, Moderate and Severe Hepatic Impairment Compared with Subjects with Normal Hepatic Function.**




63rd Annual
Meeting of the
American Association for the
Study of Liver Diseases
Boston, MA Nov 9-12 2012

**by Jennifer Kiser**

## Pharmacokinetics of DAAs and Ritonavir

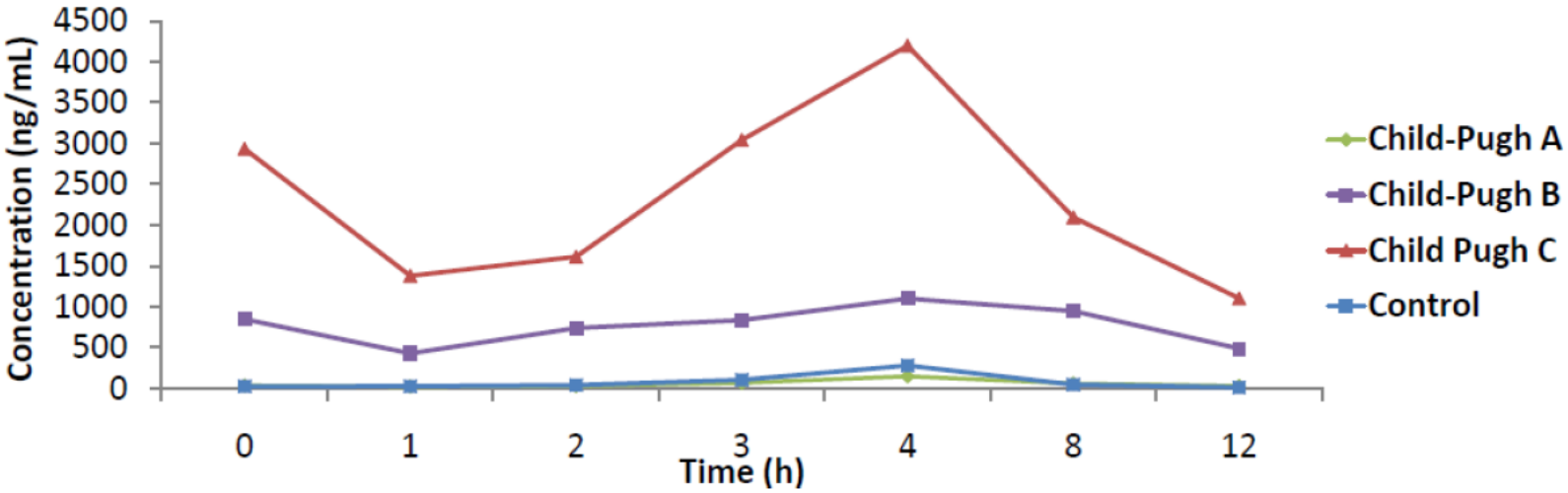
- In subjects with **mild hepatic impairment**, ABT-450, ABT-267, and ABT-333 exposures were comparable (AUC was ± 30% different), while those of ritonavir were about 34% lower than matched healthy control subjects.
- In subjects with **moderate hepatic impairment**, ABT-267, ABT-333 and ritonavir exposures were comparable (AUC was ≤ 30% lower) to subjects with normal hepatic function; while the exposures of ABT-450 were moderately higher (AUC was 62% higher) than subjects with normal hepatic function.
- In subjects with **severe hepatic impairment**, ABT-267 exposures were moderately lower (AUC was 55% lower), ritonavir exposures were comparable (AUC was only 13% higher), and ABT-450 and ABT-333 exposures were significantly higher (ABT-450 AUC was 920% higher and ABT-333 AUC was 320% higher) compared to subjects with normal hepatic function.
- In subjects with **mild and moderate hepatic impairment**, ABT-450, ABT-267, ABT-333 and ritonavir half-lives were comparable to subjects with normal hepatic function.
- In subjects with **severe hepatic impairment**, ABT-450 and ABT-267 half-lives were comparable to subjects with normal hepatic function; however, the half-lives of ABT-333 (75% higher) and ritonavir (250% higher) were significantly higher.

‡

# Asunaprevir Increased with Moderate and Severe Hepatic Impairment

- Metabolized by CYP3A, substrate for OATP1B1 and OATP2B1

**Figure 3. Mean ASV Plasma Concentrations in Hepatic Impairment Groups and Controls at Day 7 (0-12 hr)**




- AUC ↑ 9.8-fold and 32-fold in moderate and severe impairment

Eley T et al. AASLD 2012, #1873

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