Long-term implications of drug toxicity on the liver: What are the mechanisms of liver damage?

Dr Karine Lacombe,
INSERM UMR-S1136, IPLESP
SMIT St Antoine, AP-HP
Université Pierre et Marie Curie, Paris VI
Conflicts of interest

• Board member: Abbvie, BMS, Gilead Sciences, Janssen, Merck
• Travel grants: BMS, Gilead Sciences, Janssen, Merck
• Study grants: Gilead Sciences, Janssen, Merck
30 years of HIV drug development

Adapted from Palmisano L & Vella S. Ann Ist Super Sanita 2011;47:44–8.

## Current antiretroviral drugs

### CCR5 antagonists
- MRV (MVC) Maraviroc *Celsentri*

### Fusion inhibitors
- T20 enfuvirtide *Fuzeon*

### Nucl. RT inhib.
- **AZT** zidovudine *Retrovir*
- **ddl** didanosine *Videx*
- **d4T** stavudine *Zerit*
- **3TC** lamivudine *Epivir*
- **ABC** abacavir *Ziagen*
- **TDF** tenofovir *Viread*
- **FTC** emtricitabine *Emtriva*

### Non Nucl. RT inhib.
- **NVP** nevirapine *Viramune*
- **EFV** efavirenz *Sustiva*
- **ETR (ETV)** etravirine *Intelence*
- **RPV** rilpivirine *Edurant*

### Integrase inhib.
- **RAL** raltegravir *Isentress*
- **ELV** elvitegravir *Tivicay*

### Protease inhib.
- **SQV** saquinavir *Invirase*
- **IDV** indinavir *Crixivan*
- **NFV** nelfinavir *Viracept*
- **FPV** fosamprenavir *Telzir*
- **RTV** ritonavir *Norvir*
- **LPV** lopinavir *Kaletra*
- **ATV** atazanavir *Reyataz*
- **TPV** tipranavir *Aptivus*
- **DRV** darunavir *Prezista*

### Combined drugs
- **AZT + 3TC** *Combivir*
- **ABC + 3TC** *Kivexa*
- **TDF + FTC** *Truvada*
- **AZT + 3TC + ABC** *Trizivir*
- **TDF + FTC + EFV** *Atripla*
- **TDF + FTC + RPV** *Eviplera*
- **TDF+FTC+EVG+cobicistat** *Stribild*
Liver Disease in HIV-infected Patients?
Multifactorial!

Hepatitis viruses

Opportunistic diseases

Immune reconstitution

Pre-existing diseases

HIV

Co-morbidity treatment

HIV treatment
NNRTIs, PIs, NRTIs, INSTIs
Entry inhibitors

Fatty Liver Disease

Alcohol abuse/IVDU

Drug Induced Liver Toxicity (DILI)

- Based on the exclusion of other causes of liver damage
- Of idiosyncratic nature with occurrence at recommended doses, thereby excluding overdosing
- !! Liver damage sometimes wrongly attributed to drug toxicity
DILI and misdiagnosis

• Systematic review of papers reporting so-called drug induced liver damage: 2,906 cases reported in 15 publications between which discussed possible alternative causes
  – 14% due to alternative causes
  – 11% could not be classified because of missing data
  – 75% due to DILI

Teschke, Ann Hepatol 2014
Table 2. Analysis of alternative causes of initially suspected DILI cases.

<table>
<thead>
<tr>
<th>Alternative causes in initially suspected drug induced liver injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatitis B. Hepatitis B cirrhosis 1/138 cases.13</td>
</tr>
<tr>
<td>• Hepatitis C. Acute hepatitis C 4/254 cases;24 Chronic hepatitis C 2/40 cases.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specified alternative causes</th>
<th>Causes n</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>6</td>
<td>2.14</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>19</td>
<td>6.76</td>
</tr>
<tr>
<td>CMV hepatitis</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td>EBV hepatitis</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td>Virus hepatitis</td>
<td>18</td>
<td>6.41</td>
</tr>
<tr>
<td>Ischemic hepatitis</td>
<td>24</td>
<td>8.54</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>35</td>
<td>12.46</td>
</tr>
</tbody>
</table>

- Metastatic bladder cancer 1/95 cases;17 Liver metastasis from carcinoid tumor 1/114 cases.19
- Lymphoma. 2/138 cases.13
- Systemic sepsis. 2/110 cases;14 12/138 cases;15 1/215 cases;16 3/570 cases.18
- Chlamydial infection. 1/91 cases.13
- HIV infection. End-stage HIV disease 1/95 cases.17
- Past liver transplantation
  • Transplant related complications 17/110 cases;14
  • Liver or bone marrow transplant prior to DILI onset 2/474 cases.25
- Unknown liver disease
  • 2/254 cases;24 Abnormal liver biochemical tests 3/40 cases;22
  • Isolated γ-glutamyltransferase increase 1/95 cases.17
- Preexisting liver cirrhosis. Cryptogenic cirrhosis 1/138 cases;15 Unspecified cirrhosis 1/40 cases.22
Algorithm for DILI causality

Liver damage

- Biliary abnormalities
  - Abdominal US
  - Liver CT scan
  - MRI bd

- Auto-immune disease
  - anti-mitochondrial Ab
  - Anti-LKM1
  - Anti-smooth muscle

- Genetic and metabolic etiologies
  - ferritin
  - Ceruloplasmin
  - A1 anti-trypsin

- Viral hepatitis
  - HAV IgM
  - HBs Ag
  - HCV-RNA
  - HEV-RNA

- Alcohol
  - Recreatives drugs

- Heart disease
  - Vascular disease

Possible drug-related hepatotoxicity

Phenotypic profiles in DILI

‘International Serious Adverse Event Event Consortium’

- **Hepatocellular**
  - $>5 \times $ ULN ALT or $R >5$

- **Mainly cholestatic**
  - $2 \times $ ULN ALP or $R <2$

- **Mixt features**
  - $>2 \times $ ULN (ALT + ALP) or $2<R>5$

ULN = upper limit of normal value Or initial value if pre-existing hepatopathy

$R = $ ALT/ALP Ratio when both are elevated

Aithal, et al. Cin Pharm Ther 2011
## Severity criteria

### Grading of severity used in clinical trials

<table>
<thead>
<tr>
<th>Grade</th>
<th>ALT/AST</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>1.25 – 2.5 x ULN</td>
<td>1.1 – 1.5 x ULN</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2.6 – 5.0 x ULN</td>
<td>1.6 – 2.5 x ULN</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5.1 – 10.0 x ULN</td>
<td>2.6 – 5.0 x ULN</td>
</tr>
<tr>
<td>Grade 4</td>
<td>&gt; 10 X ULN</td>
<td>&gt; 5 x ULN</td>
</tr>
</tbody>
</table>
Natural history of DILI

1. Adaptative profile

2. Chronic liver disease

3. Fulminant Hepatitis

Hy’s law:
ALT > 3ULN + Bil > 2ULN = 10-50% mortality

Treatment continuation

Treatment

ALT
Treatment discontinuation

ALAT

Few weeks

1 ULN

10 ULN

Treatment
# Mechanisms of DILI associated to ARVs

<table>
<thead>
<tr>
<th></th>
<th>hypersensitivity</th>
<th>Mitochondrial Toxicity</th>
<th>Inbalance between Glucose / lipids metabolism</th>
<th>Direct oxydative stress</th>
<th>IRIS*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td>ABC</td>
<td>All (LAM-AZT-DDI-D4T++)</td>
<td>AZT-DDI-D4T+++</td>
<td>DDI</td>
<td>all</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>All (NVP++)</td>
<td>-</td>
<td>All</td>
<td>EFV-NVP</td>
<td>all</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td>F-APV, DRV</td>
<td>-</td>
<td>All Boost RTV+++</td>
<td>RTV, TPV</td>
<td>all</td>
</tr>
<tr>
<td><strong>Anti-CCR5</strong></td>
<td>MRV</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AIs</strong></td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mostly seen in hepatitis coinfected patients

Nunez M. Hepatology 2010
Nucleoside RTIs (NRTIs)

• Inhibition of mitochondrial DNA
  – “d” drugs: ddI > d4T = AZT > ABC = TDF = 3TC = FTC
  – Hepatic steatosis +/- fibrosis
  – Rarely lactic acidosis syndrome
  – Weeks to months

• Abacavir hypersensitivity
  – B*5701 highly predictive
  – Days to 6 weeks

• Non-cirrhotic portal hypertension
  – ddI
  – Months to years
Non Cirrhotic Portal Hypertension

- Almost exclusively associated with didanosine (ddI) use
  - Related to duration of use
  - May present many years after discontinuation
- Histologically:
  - Nodular regenerative hyperplasia
  - Partial Nodular Transformation
  - Portal venopathy
  - May be normal
- Clinically: Portal hypertension
  - Variceal bleeding
  - Ascites
- Association with SNPs in 5-nucleotidase and xanthine oxidase (Vispo et al, CID 2013)
- ? Role of screening for ddI exposed patients

Fig. 1. (a) Nodular regenerative hyperplasia of the liver. Nodular architecture in the absence of significant fibrosis. Reticulin argentation (Gomeri’s method); original magnification ×5; patient number 1. CV, central vein. (b) Nodular regenerative hyperplasia of the liver. Thickened (arrow 1) and compressed liver cell plates (arrow 3) with dilatation of the sinusoidal space (arrow 2). Reticulin argentation (Gomeri’s method); original magnification ×10; patient number 1.

Mallet, AIDS 2007
Non-nucleoside RTIs (NNRTIs)

• Acute Hypersensitivity reaction
  – Nevirapine > others
  – Associated with higher CD4 (cut-off of 250 male, 400 female), female gender
  – Linked to HLA class II alleles
  – Days to weeks

• Chronic Hepatotoxicity
  – ? All NNRTIs
  – ? Association with HCV infection
  – ? Long-term risk or not
Protease Inhibitors (PIs)

- Hyperbilirubinaemia
  - Indinavir and Atazanavir
  - “Gilberts” like syndrome: benign?
- Direct hepatotoxic effect
  - ? Level related; higher levels with co-infection/advanced liver disease
- Indirect metabolic effect
  - Insulin resistance; Hyperlipidaemia

- Similar rates of raised ALT/AST with standard first/second PIs (SQV, LPV, ATV, DRV)$^1$

$^1$Cooper, Curr Opin HIV AIDS 2007; $^2$Mills et al, AIDS 2009
Entry inhibitors and INSTIs

• Entry Inhibitors
  – Maraviroc (CCR5 antagonist)

• INSTIs
  – Raltegravir, Elvitegravir, Dolutegravir

• New pharmacological booster
  – Cobicistat

• Generally lower LEEs

• Fewer hypersensitivity events

• Higher event rates in co-infected patients
Hepatic Safety Profile of ARVs

### Prevalence of DILI with NNRTI

<table>
<thead>
<tr>
<th>Study (sample size)</th>
<th>Drug (sample size)</th>
<th>Control (sample size)</th>
<th>Inclusion criteria</th>
<th>Follow-up (weeks)</th>
<th>HBV - HCV (% per arm)</th>
<th>Hepatic adverse effects Grade 3 or 4** (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUET I – II 1,5,6,7 (n=1203)</td>
<td>Etravirine (n=599)</td>
<td>OBT (n=604)</td>
<td>HIV-1 Tx-patients VL &gt; 5000 copies/ml</td>
<td>96</td>
<td>Mixed population 12%/67</td>
<td>Similar ALT 26 (4%)/14 (2%) AST 23 (4%)/15 (2%)</td>
</tr>
<tr>
<td>ECHO 12 (n=690)</td>
<td>Rilpivirine (n=346)</td>
<td>Efavirenz (n=344)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>48</td>
<td>HBV: 3% / 6% HCV: 2% / 3%</td>
<td>Lower ALT 4 (1%)/12 (4%) AST 8 (2%)/12 (4%)</td>
</tr>
<tr>
<td>THRIVE 13 (n=680)</td>
<td>Rilpivirine (n=340)</td>
<td>Efavirenz (n=340)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>48</td>
<td>HBV: 4% / 13 HCV: 5% / 6%</td>
<td>Lower for ALT ALT 6 (2%)/11 (3%) AST 6 (2%)/7 (2%)</td>
</tr>
</tbody>
</table>

- **Etravirine:**
  - sub-analysis HBV / HCV: θ diff. AEs 3-4 between arms, but higher rate in coinfection

- **Rilpivirine:**
  - Pooled analysis ECHO/THRIVE: AEs < AEs with EFV, but not at 96 and 192 weeks.

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Surgers, Clin Res Hepatol Gastroenterol 2012
Prevalence of DILI with PI

- **Darunavir:**
  - sub-analysis HBV-HCV: slight diff. AEs 3-4 between arms (favoring DRV), more frequent if coinfection
  - « warning » because of reports of acute hepatitis when associated to other drugs (anti-TB +++)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Control</th>
<th>Inclusion criteria</th>
<th>Follow-up (weeks)</th>
<th>HBV - HCV (% per arm)</th>
<th>Hepatic adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITAN (n=595)</td>
<td>Darunavir (n=298)</td>
<td>Lopinavir (n=297)</td>
<td>HIV 1 Tx patients VL &gt; 1000 copies/ml</td>
<td>96</td>
<td>Mixed population 18% / 13%</td>
<td>Similar (grade 2-4 48 w) ALT 28 (9%)/26 (9%) AST 20 (7%)/26 (9%)</td>
</tr>
<tr>
<td>ARTEMIS (n=689)</td>
<td>Darunavir (n=343)</td>
<td>Lopinavir (n=346)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>96</td>
<td>Mixed population 13% / 14%</td>
<td>Similar (grade 2-4) ALT 38 (11%)/40 (12%) AST 39 (11%)/35 (10%)</td>
</tr>
</tbody>
</table>
Prevalence of DILI with antiCCR5

Maraviroc:
- sub-analysis HBV-HCV:θ diff. AEs 3-4 between arms and coinfection status,
- in a cohort of patients with impaired liver function: no grade 3-4 AEs but increased Cmax
- « warning » because of 1 case of fulminant hepatitis leading to transplantation, but concomitant use of INH
## Prevalence of DILI with AI

<table>
<thead>
<tr>
<th>Study (sample size)</th>
<th>Drug (sample size)</th>
<th>Control (sample size)</th>
<th>Inclusion criteria</th>
<th>Follow-up (weeks)</th>
<th>HBV - HCV (% per arm)</th>
<th>Hepatic adverse effects Grade 3 or 4** (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENCHMRK</strong>&lt;sup&gt;26,32&lt;/sup&gt; (n=699)</td>
<td>Raltegravir (n=462)</td>
<td>OBT (n=237)</td>
<td>HIV-1 Tx patients VL&gt; 5000 copies/ml</td>
<td>96</td>
<td>HBV: 8% / 7% HCV: 8% / 11.4%</td>
<td>Similar ALT 6 (2.2%)/7 (2.5%) AST 12 (4.3%)/8 (2.9%)</td>
</tr>
<tr>
<td><strong>STARTMRK</strong>&lt;sup&gt;28,29,30&lt;/sup&gt; (n=566)</td>
<td>Raltegravir (n=281)</td>
<td>Efavirenz (n=282)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>156</td>
<td>Mixed population 6% / 6%</td>
<td>Similar ALT 6 (2.2%)/7 (2.5%) AST 12 (4.3%)/8 (2.9%)</td>
</tr>
<tr>
<td>102 STUDY&lt;sup&gt;43&lt;/sup&gt; (n=700)</td>
<td>Elvitegravir (n=348)</td>
<td>Efavirenz (n=352)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>48</td>
<td>HBV: 1% / 3% HCV: 5% / 4%</td>
<td>Lower (grade 2-4) ALT 15% / 34% AST 18% / 31%</td>
</tr>
<tr>
<td>103 STUDY&lt;sup&gt;44&lt;/sup&gt; (n=708)</td>
<td>Elvitegravir (n=353)</td>
<td>Atazanavir (n=355)</td>
<td>HIV-1 Nv patients VL &gt; 5000 copies/ml</td>
<td>48</td>
<td>HBV : 1% / 2% HCV : 5% / 3%</td>
<td>Lower (grade 2-4) ALT 15,3% / 21,8% AST 17,6% / 21,9%</td>
</tr>
<tr>
<td>145 STUDY&lt;sup&gt;42&lt;/sup&gt; (n=702)</td>
<td>Elvitegravir (n=351)</td>
<td>OBT + raltegravir (n=351)</td>
<td>HIV-1 x patients VL &gt; 1000 copies/ml</td>
<td>48</td>
<td>HBV : 5% / 3% HCV : 16% / 13%</td>
<td>Lower (grade 2-4) &lt;sup&gt;M&lt;/sup&gt; ALT 6 (2%) / 18 (5%) AST 5 (1%) / 10 (5%)</td>
</tr>
<tr>
<td><strong>SPRING II</strong>&lt;sup&gt;26&lt;/sup&gt; (n=822)</td>
<td>Dolutegravir (n=411)</td>
<td>Raltegravir (n=411)</td>
<td>HIV-1 x patients VL &gt; 1000 copies/ml</td>
<td>48</td>
<td>HBV: 2% / 2% HCV: 10% / 9%</td>
<td>Similar ALT : 2% / 2% AST : 3% / 2%</td>
</tr>
</tbody>
</table>

- **raltegravir**: sub-analysis HBV-HCV: θ diff. AEs 3-4 between arms, more frequent in coinfection
- **elvitegravir**: less grade 2-4 AEs compared to RAL, ATZ, EFV
- **dolutegravir**: no AEs even in patients with impaired liver function (cohort study)
Specific risk factors for DILI in HIV+ patients

• Use of a « d » drug (DDI, D4T, DDC)
• Use of ATZ/r: maybe in patients with hepatitis coinfection
• Use of anti TB drugs
• HCV or HBV coinfection
• NASH ? Through mitochondrial toxicity

Liver toxicity of ARVs: ART-associated HCC?

Specific antiretroviral agents & HCC/ESLD risk

Analysis of 45,544 HIV-infected patients from D:A:D

<table>
<thead>
<tr>
<th>ARV</th>
<th>aIRR/5 years (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4T</td>
<td>1.46 (1.20-1.77)</td>
</tr>
<tr>
<td>DDI</td>
<td>1.32 (1.07-1.63)</td>
</tr>
<tr>
<td>TDF</td>
<td>1.46 (1.11-1.93)</td>
</tr>
<tr>
<td>APV</td>
<td>1.47 (1.01-2.15)</td>
</tr>
<tr>
<td>FTC</td>
<td>0.51 (0.32-0.83)</td>
</tr>
<tr>
<td>NVP</td>
<td>0.76 (0.58-0.98)</td>
</tr>
</tbody>
</table>

Adjustment for calendar year, age, gender, ethnicity, mode of HIV-acquisition, previous AIDS-event, HCV and HBV status, cumulative exposure to ARVs listed above.

Beware of bias!

Things to consider:

<table>
<thead>
<tr>
<th>DR4/D DI</th>
<th>Hepatotoxicity well-established in previous studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APV</strong></td>
<td>Only PI with dose-adjustments for liver disease Only PI for Child-Pugh B or C Indication bias?</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>Needs validation, but <em>separately</em> in HIV mono and HIV-HBV co-infected patients</td>
</tr>
<tr>
<td><strong>FTC</strong></td>
<td>Combination with 3TC and/or TDF? Need models to identify individual effects.</td>
</tr>
<tr>
<td><strong>NVP</strong></td>
<td>Associated with elevated liver enzymes. If well-tolerated, not as hepatotoxic as thought?</td>
</tr>
</tbody>
</table>

Management of DILI

HAART

Severe Liver Toxicity

Symptoms Present

Hypersensitivity Reaction

NRTI-related Lactic Acidosis

Jaundice/Symptoms of Acute Hepatitis

STOP HAART and ALL POTENTIAL HEPATOTOXIC DRUGS

Asymptomatic

Rule out causes of increased ALT: Acute hepatitis, alcohol, non-HIV hepatotoxic drugs

Transitory elevation in the setting of chronic viral hepatitis

Grade 3

Consider Options

Change HAART if other effective combinations available

Grade 4

STOP and start new HAART avoiding suspected culprit, preferably after ALT improved

Continue current HAART and monitor closely if no effective alternative regimen available and benefits outweigh the risks

Manage accordingly

Continue HAART and monitor closely
Acknowledgements

• Sanjay Bhagani
• Anders Boyd