Hepatotoxicity of Antiretroviral Therapy

Liver friendly ART: fantasy or reality?

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Outline

- Methodological issues in defining hepatotoxicity
- Summary of pathogenic mechanisms
- Summary of “conventional” ART
- Newer ART agents and available data
- Approach to patient management
- Fantasy or reality?
Background

- Antiretroviral therapy has dramatically reduced HIV associated morbidity and mortality
  - Opportunity to reduce onward HIV transmission
  - Guidelines recommending earlier initiation

- Toxicity has emerged as one of the leading causes of HIV related morbidity, mortality and treatment discontinuation
  - Toxicity the major reason for hospital admission\(^1\)
  - Hepatotoxicity the most frequent (30\%)\(^1\)
  - Hepatotoxicity historically 3\(^{rd}\) most common reason for ART-toxicity related discontinuation\(^2\)

- High rates of HBV and HCV co-infection likely to increase risk of hepatotoxicity

\(^1\)Nunez et al, AIDS Res Hum Retroviruses 2006; \(^2\)Fisher et al, in press
Difficulties in defining hepatotoxicity

• Clinical endpoints rarely used
  – cf cardiovascular end-points
• Definition of laboratory abnormalities vary from study to study
  – Usually ACTG criteria, but
  – May be modified according to baseline values if elevated
  – Definitions of Upper Limit of Normal vary between labs
• Definitions of HBV and HCV co-infection vary from study to study
  – HBV: sAg positive or eAg positive
  – HCV: antibody positive or RNA detected
• Incidence versus prevalence
Defining Hepatotoxicity

Grade 3 toxicity

Grade 4 toxicity

Normal

ALT or AST

ULN

ULN → 1

0

1

5

10

‘Severe hepatotoxicity’
Defining Hepatotoxicity

ALT or AST

ULN

ULN → 1

0

10

5

‘Severe hepatotoxicity’
Defining Hepatotoxicity

ALT or AST

ULN

ULN → 1

1

5

10

‘Severe hepatotoxicity’
RCT evidence of hepatotoxicity

- Randomisation allows comparison between arms; differences due to chance
- Detailed data on adverse events
- Regular and pre-specified monitoring
- Short duration of follow-up
- Clinical trial patients not always representative
- Co-infected patients or patients with higher baseline LFTs or at higher risk often excluded

*Incidence rates likely to be underestimated*
Observational data of hepatotoxicity

- More representative of patient population
- Longer-term follow-up
- No exclusion of “higher risk” patients

- Reasons for treatment allocation unknown (possibility of confounding bias)
- Differential follow-up and monitoring patterns
- Complexity of previous treatments difficult to capture
- Possibility of recall bias in retrospective studies
- Wide variation in rates of co-infection between cohorts

- Incidence rates may be overestimated
• ULN of AST varies 35–57; ALT 31-40
  – Grade 4 AST therefore varies >350 to >570 and ALT 310-400

• Co-infection rates in cohorts vary from 4% to 13% (HBV) and 8% to 52% (HCV)

• Incidence/prevalence rates of hepatotoxicity vary from 1% to 29%

• If define hepatotoxicity by 2x abnormal ALT/AST decreases incidence by 50%

*After Smith and Sabin, Antiviral Therapy 2004; Sabin JID 2004 ; Bansi, JAIDS 2009*
Attributing cause for abnormal LFTs

Opportunistic diseases

Immune reconstitution

Hepatitis virus Co-infection

Other co-morbidities

Other treatment

HIV treatment
? Drug X
? Drug Y
? Drug Z

Fatty Liver Disease

Alcohol Recreational Drugs

[Image: Diagram of liver with arrows pointing to various causes]
# Mechanisms of drug-related liver injury in HIV-infected patients

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Details</th>
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<tbody>
<tr>
<td>Direct liver cell stress</td>
<td>NNRTIs, Tipranavir&lt;br&gt;Usually within weeks</td>
</tr>
<tr>
<td>Metabolic (steatosis)</td>
<td>PIs (?associated with NAFLD)&lt;br&gt;Months to years</td>
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<tr>
<td>Hypersensitivity</td>
<td>NVP&gt;ABC&gt;fosAPV&lt;br&gt;Early, usually within 8 weeks&lt;br&gt;Often associated with rash&lt;br&gt;HLA-linked</td>
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<tr>
<td>Mitochondrial toxicity</td>
<td>NRTIs&lt;br&gt;ddl&gt;d4T&gt;AZT&gt;ABC=TDF=FTC/3TC</td>
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<tr>
<td>Immune reconstitution</td>
<td>Chronic Hepatitis B&lt;br&gt;Within first month&lt;br&gt;More common if low CD4 count/large rise</td>
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*After Soriano et al. AIDS 2008; Nunez Hepatology 2010; Surgers 2013*
Associated Risk factors for hepatotoxicity of ART

- Hepatitis B and C co-infection
  - Genotype 3?
- Higher baseline ALT/AST levels
- Alcohol
- Older age
- Female gender
- High or low CD4 count
- Lower BMI
- Use of ddI, d4T, NVP, RTV (>200mgs/d)

Nucleoside RTIs (NRTIs)

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

• Abacavir hypersensitivity
  – B*5701 highly predictive
  – Days to 3 weeks

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

• Almost exclusively associated withddl
  – Related to duration of use
  – May present many years after discontinuation

• Histologically:
  – Nodular regenerative hyperplasia
  – Portal venopathy
  – May be normal

• Clinically: Portal hypertension
  – Variceal bleeding \((Scourfield et al, IJSA 2011)\)
  – Ascites

• Association with SNPs in 5-nucleotidease and xanthine oxidase \((Vispo et al, CID 2013)\)
• Usually reversible with withdrawal of ddl
• ? Role of screening for ddl exposed patients
Non-nucleoside RTIs (NNRTIs)

• Acute Hypersensitivity reaction
  – Nevirapine > others
  – Associated with higher CD4, female gender
  – 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?
    - ? Association with Ca breast

- **Direct hepatotoxic effect**
  - ? Level related; higher levels with co-infection

- **Indirect metabolic effect**
  - Insulin resistance; Hyperlipidaemia

- **Similar rates of raised ALT/AST with conventional PIs (SQV, LPV, ATAZ)**¹
  - ?lower rates with DRV than r/LPV in Artemis²

¹Cooper, Curr Opin HIV AIDS 2007; ²Mills et al, AIDS 2009
Hepatic Safety Profile of ARVs

Caution

ddl d4T dddI d4T
AZT
EFV

Safe

NRTI

3TC FTC ABV TDF

NNRTI

NVP

RTV TPV

PI

APV DRV
ATV LPV
SQV NFV

Entry inhibitors

T20

Integrase inhibitors

Boosters

RTV

Rilpivirine

• Naïve patients (ECHO and THRIVE)
  – RPV vs Efavirenz
  – HBV 4% and HCV 5% co-infected
  – G3/4 ALT 2% v 3%: AST 2% v 2%
  – In HCV co-infected: similar rates of d/c 6% v 9%
    • But LEE rates 27% vs 4% in HCV- for rilpivirine

• Experienced patients (SPIRIT)
  – RPV vs r/PI
  – No significant difference in LFTs

Cohen et al Lancet 2011; Palella et al, IAS 2013
1 case of DILI reported; Ahmed 2012
Etravirine

• Naïve patients (SENSE)
  – ETV vs efavirenz
  – No reported differences in LFTs (CNS study)

• Experienced patients (DUET)
  – ETV vs OBR
  – AST G3/4 3.9% v 2.5%
  – ALT G3/4 4.4% v 2.3% (ns)
  – In HBV/HCV co-infected: no difference vs OBR
    • BUT higher than in HIV mono-infected

Rockstroh et al, IAS 2011; Mills et al, IAS 2009
Raltegravir

- Naïve patients (STARTMRK)
  - Vs efavirenz
  - G3/4 LFTs 2% vs 2%
    - BUT higher if co-infected

- Experienced patients (SWITCHMRK)
  - Vs stable regimen
  - G3/4 LFTs 4% vs 2%

- Experienced patients (BENCHMRK)
  - Vs OBR
  - G3/4 ALT 3 v 3.7%; AST 2.8 v 3.7%
    - More common if co-infected (15%); RTG = OBR

- Well tolerated if HBV/HCV co-infected (1.3% G3/4)

Vispa et al
Madrid Cohort analysis

Graph showing the percentage of patients with different grades of adverse events in HIV/HCV co-infected and HIV mono-infected groups for different antiretroviral drugs:

- **Protease inhibitors (n=330):**
  - 33% HIV/HCV co-infected
  - 19% HIV mono-infected
  - Grade 3–4: 3, Any grade: 48

- **Non-nucleoside analogues (n=316):**
  - 29% HIV/HCV co-infected
  - 18% HIV mono-infected
  - Grade 3–4: 2, Any grade: 41

- **Raltegravir (n=218):**
  - 20% HIV/HCV co-infected
  - 7% HIV mono-infected
  - Grade 3–4: 1, Any grade: 17
  - Grade 3–4: 9, Any grade: 126
Maraviroc

- Naïve Patients (MERIT)
  - MVC vs efavirenz
  - HBV and HCV co-infection rates not stated
  - G3/4 AEs 3.1% vs 3.7%

- Experienced Patients (MOTIVATE)
  - MVC (bd vs od) vs “OBR”
  - G3/4 AEs (3-4%) similar for MVC od, bd, PBO
  - 6/34 (18%) v 1/19 (5%) with HCV had G3/4 transaminase elevations

- Maraviroc studies in patients with HCV co-infection to slow disease progression

- (Aplaviroc discontinued due to hepatototoxicity; CCR5 deficiency associated with hepatitis)

Recent case of DILI

Cooper et al, JID 2010; van Lelyveld, ExRevAntilInfecTher 2012; Wasmurth, Ex Opin Drug Saf 2012
Cobicistat

• Naïve patients (Study 105)
  – TVD + Atazanavir with COBI or RTV (Blinded)
  – HBV and HCV co-infection excluded
  – Grade 3/4 hyperbilirubinemia 63% vs 45% (ns)
  – Transaminase results not reported, but no overall difference in d/c due to AEs

• Naïve patients (Study 114)
  – TVD + Atazanavir with COBI or RTV (Blinded)
  – HBV 5% and HCV 6% co-infected
  – Higher rates of hyperbilirubinemia with COBI
  – G3/4 ALT or AST 3% vs 2%

Elion et al; AIDS 2011; Gallant et al; IAS 2012
Elvitegravir ("Stribild")

- Naïve patients (Study 102 and 103)
  - Versus efavirenz or r/Atazanavir
  - 1% HBV and 5% HCV co-infected
  - 2.3% G3/4 AST v 5% v 6%
  - 1.4% G3/4 ALT vs 4% v 3%

- Experienced patients (Study 145)
  - Versus raltegravir
  - 5% HBV and 13% HCV co-infected
  - More G3 ALT (5%v2%) and AST (5%v1%) with raltegravir
  - Liver AEs leading to d/c: 1.7%v0.8%

Zolopa et al, CROI 2013; Molina et al; LancetID, 2012
Dolutegravir

• Naïve patients (SPRING 1)
  – Dolutegravir vs efavirenz
  – 9% HCV coinfected
  – Liver AEs: G3/4 0.6% (DTG) and 2% (EFV)

• Naïve patients (SPRING 2)
  – Dolutegravir vs raltegravir
  – 2% HBV and 10% HCV co-infected
  – Liver AEs: G3 2% each arm; G4 1%
    • D/C with DTG: 2 acute HCV, 2HBV IRIS, 1 con-med, 1 drug-induced

• Naïve patients (SINGLE)
  – Dolutegravir vs efavirenz
  – 7% HCV at baseline; HBV and “impairment” excluded
  – No G3/4 LFT abnormalities; G2 1 vs 4%

Dolutegravir

• Experienced patients (VIKING)
  – No comparator (od vs bd)
  – 4% HBV and 16% HCV co-infected
  – No G3/4 transaminase abnormalities

• Experienced patients (SAILING)
  – Dolutegravir vs raltegravir
  – HBV/HCV coinfected: 14% vs 18%
  – G3/4 ALT: 3% vs 2%
  – “high rate of IRIS with HBV/HCV; more with DTG”

Eron et al; JID 2012; Pozniak et al, CROI 2013
Hepatic Safety Profile of ARVs

Starting ART

• Benefits >> Risk

• Be aware of patient status
  – HBV/HCV status
  – Baseline LFTs
  – Other co-morbidities
  – Other concomitantly medications

• Caution with patients at higher risk for hepatotoxicity
  – ?shouldn’t alter decision on when to start

See Cooper, Curr Opin HIV AIDS 2007
Monitoring ART

BHIVA Monitoring Guidelines:
• Full baseline LFTs
• Repeat transaminases after 1 and 3 months
• Then 3-6 monthly once established on ART

• If commencing nevirapine:
• Weekly for first 2 months

• Consider closer monitoring if HBV or HCV co-infected
• ?role for therapeutic drug monitoring if hepatic damage

Asboe et al, HIV Medicine 2011
Managing abnormal LFTs

- Repeat specimen to confirm

- Include alkaline phosphatase, gamma GT, albumin and INR to help determine aetiology

- Check for other co-infections: acute HCV, syphilis

- Check for other medications (including unprescribed)

Asboe et al, HIV Medicine 2011; Walker Curr Opin HIV AIDS 2007
‘Hy’s Law’

- 10–50% patients with **hepatocellular** jaundice will have fatal liver failure\(^1\)

- ↑ ALT or total bilirubin are relatively common
  - BUT **combination** is rare in drug development

- FDA: Combination of ‘ALT >3x ULN and total bilirubin >1.5x ULN’ as an indicator of clinical concern\(^2\)

- Clinical relevance validated: 12.7% prevalence of mortality/liver transplantation in subjects with hepatocellular jaundice\(^3\)

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Median AST in patients with LEE

Median AST (IQR)

Weeks since start LEE

AST (U/L)

- continued HAART
- modified HAART
- upper limit normal

den Brinker, AIDS 2000
When to stop ARVs for hepatotoxicity?

- Symptomatic hepatitis
- Jaundice
- Lactic acidosis
- Hypersensitivity
- ALT or AST >10xULN
- Newly-marketed drugs

HAART

Severe Liver Toxicity

- Symptoms Present
  - Hypersensitivity Reaction
  - NRTI-related Lactic Acidosis
  - Jaundice/Symptoms of Acute Hepatitis
    \[\text{STOP HAART and ALL POTENTIAL HEPATOTOXIC DRUGS}\]

- Asymptomatic
  Rule out causes of increased ALT: Acute hepatitis, alcohol, non HIV hepatotoxic drugs
  - Yes
    Manage accordingly
  - No
    Transitory elevation in the setting of chronic viral hepatitis
      - Yes
        Continue HAART and monitor closely
      - No
        \[\text{Grade 3}\]
        Consider Options
        - Change HAART if other effective combinations available
  \[\text{Grade 4}\]
  STOP and start new HAART avoiding suspected culprit, preferably after ALT improved

\[\text{Nunez, Hepatology, 2010}\]
SMART study: stopping NNRTIs

Percentage re-suppressing

- Simultaneous
- Staggered
- Switched

Fox et al. AIDS 2008; 22(17): 2279-89
Mean absolute ALT (U/l) from LCM/CDM randomisation

Global P=0.83 overall
(65028 measurements)
Global P=0.14 estimating individual comparisons at each timepoint
Impact of ART on Overall Liver Mortality in HIV/HCV Co-infected Patients

- Bonn cohort (1990–2002)
  - 285 HIV/HCV co-infected patients
- Liver-related mortality rates per 100 person-years
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70
- Predictors for liver-related mortality
  - No HAART
  - Low CD4 cell count
  - Increasing age

Hepatic Safety Profile of ARVs: Current Guideline Recommended agents

Some caution with new “friendly” drugs

- RCTs may exclude patients with HCV/HBV
- RCTs may exclude patients with abnormal baseline LFTs
- RCTs may exclude key patient groups
- Cirrhosis usually an exclusion
- Duration of follow-up is limited
- Cohort studies will not report for some time
Liver Friendly ART?

• The “new” ART agents have no hepatotoxicity
  • *Fantasy*

• The newer ART options appear (so far) to be less hepatotoxic than the older drugs
  • *Reality*
  • *Maintain pharmacovigilance*
Difficulties in analysing studies to determine frequency of hepatotoxicity

Hepatotoxicity described with all antiretroviral agents

Less hepatotoxicity with newer recommended ART options
  - ? Hepatotoxicity may become less of an issue

Caution with those “at risk”

Evaluate for non-ART causes of abnormal liver function

Benefits of ART significantly outweigh the risks
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