Hepatotoxicity of Antiretroviral Therapy

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Outline

• Background
• Methodological issues in defining hepatotoxicity
• Summary of pathogenic mechanisms
• Summary of conventional ART
• Newer ART agents and available data
• Approach to patient management
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

Nunez et al, AIDS Res Hum Retroviruses 2006; Fisher unpublished
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

ALT or AST

ULN

Grade 4 toxicity

Grade 3 toxicity

Grade 1 or 2 toxicity

Normal

ULN → 1

ULN →

‘Severe hepatotoxicity’
Defining Hepatotoxicity

ALT or AST

ULN

ULN → 1

0

10

5

‘Severe hepatotoxicity’
Defining Hepatotoxicity

ALT or AST

ULN

‘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 AST 4 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

Hepatitis virus Co-infection

Immune reconstitution

Other co-morbidities

Other treatment

HIV treatment
? Drug X
? Drug Y
? Drug Z

Fatty Liver Disease

Alcohol Recreational Drugs
# 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>Metabolic host-mediated (intrinsic and idiosyncratic)</td>
<td>NNRTIs and PIs &lt;br&gt;Usually 2-12 months after initiation &lt;br&gt;Occurrence can vary by agent &lt;br&gt;Dose-dependence for intrinsic damage</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;ddI&gt;d4T&gt;AZT&gt;ABC=TDF=FTC/3TC</td>
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<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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*Soriano et al. AIDS 2008; 22: 1-13*
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 (>200)

Nucleoside RTIs (NRTIs)

• Inhibition of mitochondrial DNA
  – “d” drugs: ddl > d4T = ddC > ABC = TDF = 3TC = FTC
  – Rarely lactic acidosis syndrome
  – Weeks to months

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

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

- Almost exclusively associated with ddl
  - Related to duration of use
  - May present many years after discontinuation
- Histologically:
  - Nodular regenerative hyperplasia
  - Portal veinopathy
  - May be normal
- Clinically: Portal hypertension
  - Variceal bleeding (Scourfield et al, IJSA 2011)
  - Ascites

- ? Reversibility with withdrawal of ddl
- May need shunting or transplant
- ? Role of screening for ddl exposed patients ?fibroscan
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 Artemis\(^2\)

\(^1\) Cooper, Curr Opin HIV AIDS 2007; \(^2\) Mills et al, AIDS 2009
Hepatic safety profile of ARVs

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% (10x)

- Experienced patients (SPIRIT)
  - RPV vs r/PI
  - no significant difference in LFTs

Cohen et al Lancet 2011; Palella et al, IAS 2013
Etravirine

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

• Experienced patients (DUET)
  – ETV vs OBR
  – Co-infection rate unpublished
  – AST G3/4 3.9% v 2.5%
  – ALT G3/4 4.4% v 2.3% (ns)

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

• Naïve patients (STARTMRK)
  – Vs efavirenz
  – G3/4 LFTs 2% vs 2%

• 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%

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

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 hepatotoxicity)

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 hyperbilirubinaemia 63%v45% (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 hyperbilirubinaemia 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
Elvitegravir and Cobicistat in hepatic impairment

- 20 subject volunteer study
  - 10 healthy volunteers
  - 10 hepatic impairment (CPT scores 709)
- 10 day dosing; 21 day follow-up
- No Grade 3 or 4 Adverse Events
- No Grade 3 or 4 transaminase elevations
  - 1 G2 hyperbilirubinaemia

Ramanathan et al; IWCPH, Barcelona 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%

*Van Lunzen, Lancet 2011; Raffie et al, Lancet 2013; Walmsley et al, IAS 2012*
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

Hepatic safety profile of ARVs

Starting ART

• Benefits >> Risk

• Be aware of patient status
  – HBV/HCV status
  – Baseline LFTs
  – Other co-morbidities
  – Other concomitant 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\(^3\)

Median AST in patients with LEE

Median AST (IQR)

- continued HAART
- modified HAART
- upper limit normal

Weeks since start LEE

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

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

SMART study: stopping NNRTIs

Fox et al. AIDS 2008; 22(17): 2279-89
DART Study: Adverse events

Proportion event-free

Years from randomisation (ART initiation)

SAE $p=0.20$
ART-modifying AE $p=0.85$
Grade 4 AE $p=0.18$
Grade 3/4 AE $p=0.52$

LCM
CDM
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
Toxicity in ALT from randomisation

Global P=0.53 estimating individual comparisons at each timepoint

Weeks (where >150 at risk)
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 recommended by DHHS, EACS, BHIVA
Summary

- 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 isse
- 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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