

# Relationship between Nevirapine Plasma Concentration and Abnormal Liver Function Tests in a Cohort of Heterogeneous HIV+ Patients

L Almond, M Boffito, P Hoggard, S Bonora, R Raiteri,  
H Reynolds, S Khoo, G Di Perri and D Back

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# Background

## NVP Hepatotoxicity

- NVP can cause hepatotoxicity due to hypersensitivity reactions (idiosyncratic)
- Hepatotoxicity may also be exposure related

**Gonzalez de Requena *et al.*** NVP- $C_{\text{trough}} > 6000$  ng/ml  
higher risk of liver toxicity.

**van Leth *et al.* 2NN Study** incidence of elevated ALT/AST  
in 400mg od  $>$  200mg bd.

Monitoring of NVP plasma concentrations may be useful?

# Therapeutic Drug Monitoring

- TDM can be useful to predict toxicity with some drugs e.g. IDV.
- TDM measures the **total** drug concentration in the plasma
  - composite of drug which is
    - 1) **bound** to plasma proteins (AAG, albumin)
    - 2) **unbound**
- Unbound drug concentration may also be useful to explain NVP related hepatotoxicity?

# Aims

1. Are TOTAL and UNBOUND trough concentrations related to NVP hepatotoxicity?
2. Do confounding patient factors (such as HCV/HBV, history of IVDU and ART experience) impact on NVP hepatotoxicity?

# Patients

## Cross-sectional Observational Study

- 82 patients on 2 NRTIs and NVP (200 mg *b.d.*)
- Median time on NVP = 65.6 weeks (3 – 201 weeks)
- 60 males and 22 females
- 59 patients VL < 50 copies/ml (50 - 150000)
- Median CD4 = 422 cells/mm<sup>3</sup> (115 - 993)
- 34 patients (42%) HBV/HCV +
- 38 patients (46%) IVDU
- 35 patients (44%) treatment experienced

**82 patients recruited**

**Blood Sample**

**LFT, VL, CD4, albumin**

**Plasma Isolated and Inactivated**

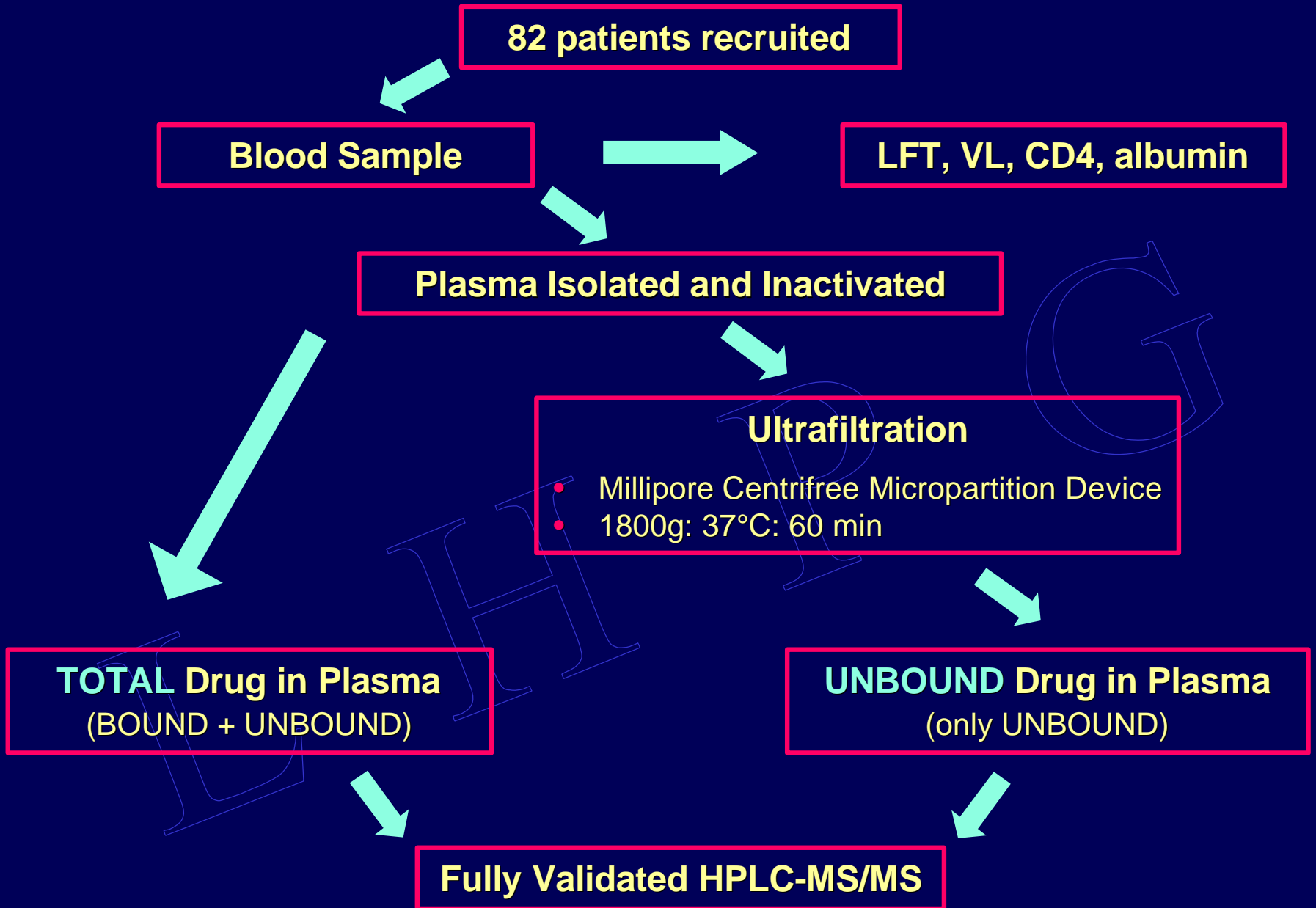
**Ultrafiltration**

- Millipore Centrifree Micropartition Device
- 1800g: 37°C: 60 min

**TOTAL Drug in Plasma**  
(BOUND + UNBOUND)

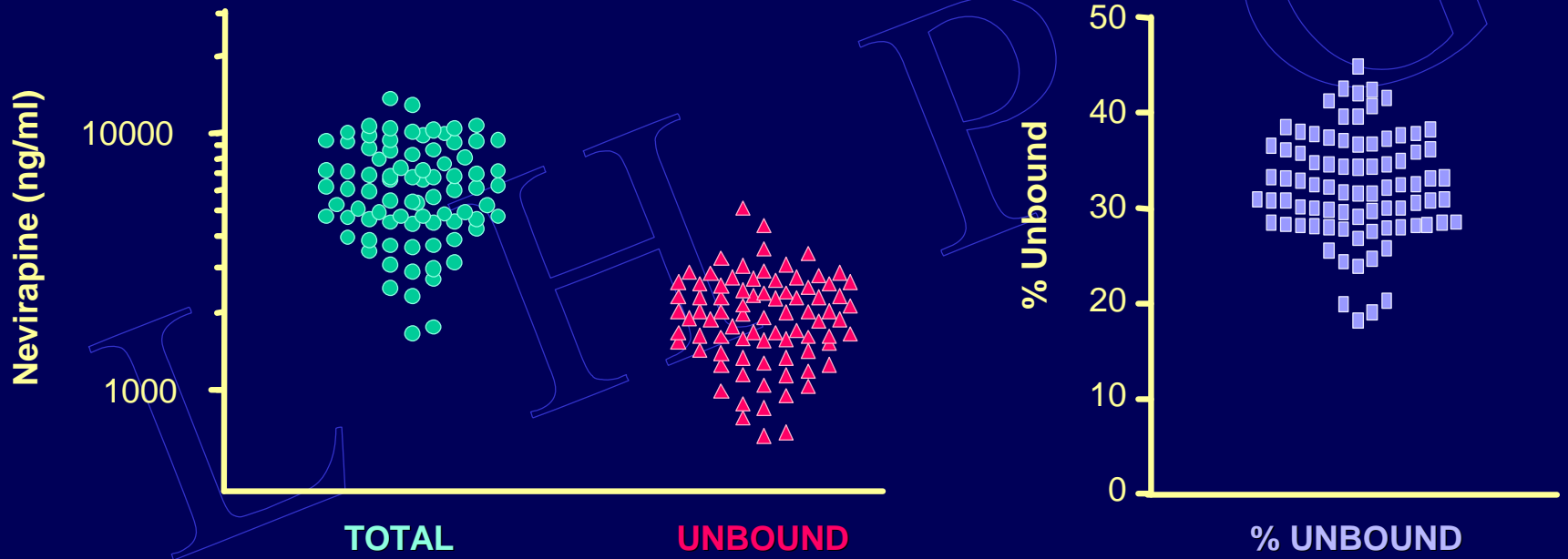
**UNBOUND Drug in Plasma**  
(only UNBOUND)

**Fully Validated HPLC-MS/MS**



# NVP Trough Concentrations

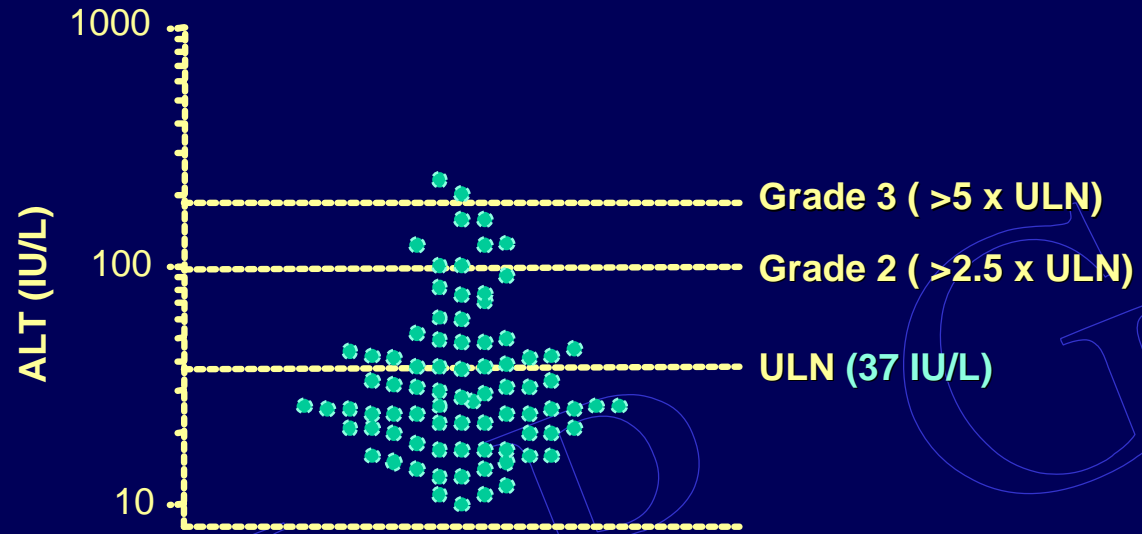
Median	6109 ng/ml	1981 ng/ml	32.2%
Range	1652 – 13649	655 – 5093	18.2 – 44.9
% c.v.	41.3%	39.6%	17.1%



# LFTs in the whole cohort following NVP

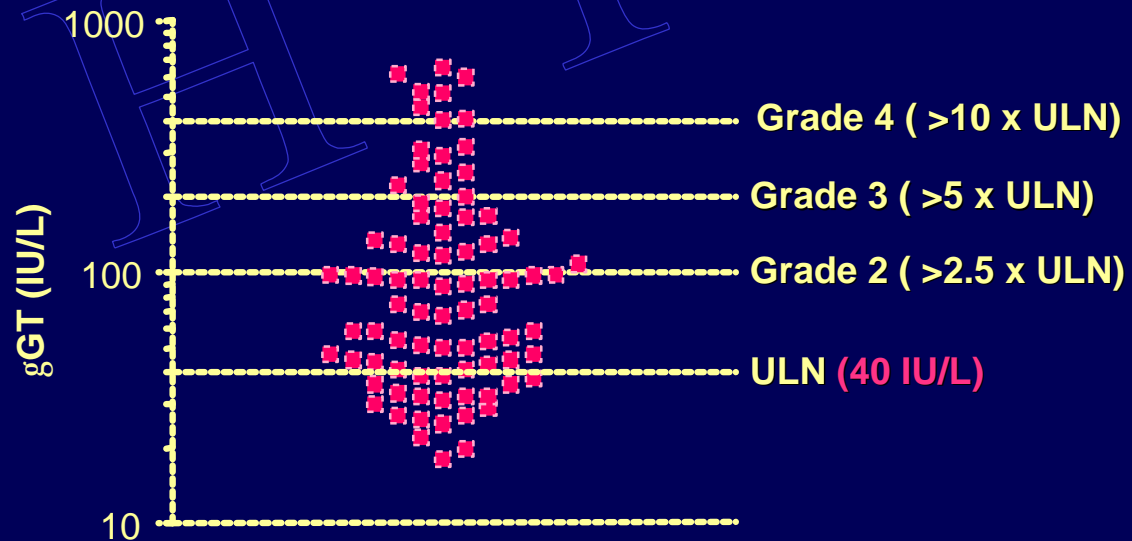
**ALT**

**Median = 27.5 IU/L**

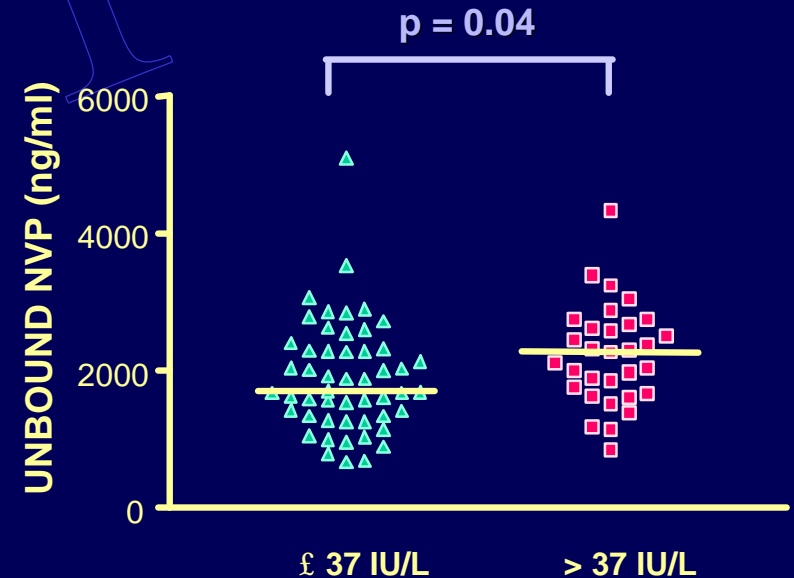
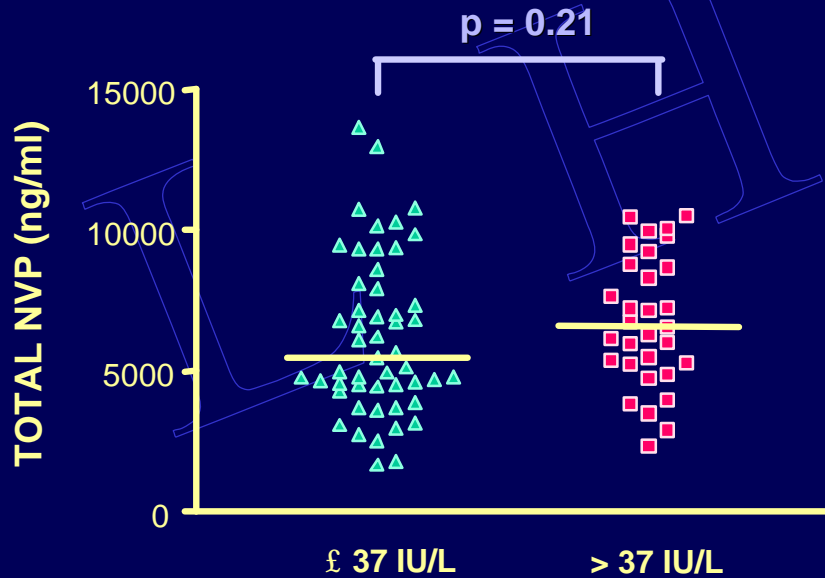
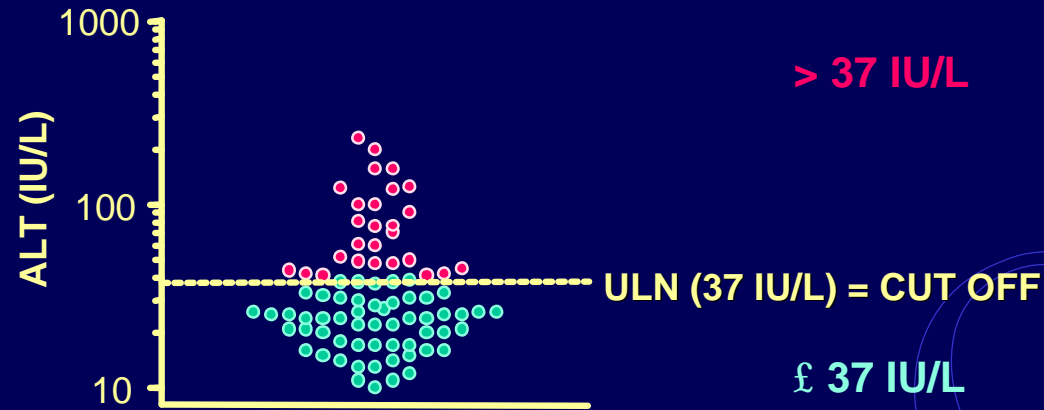


**gGT**

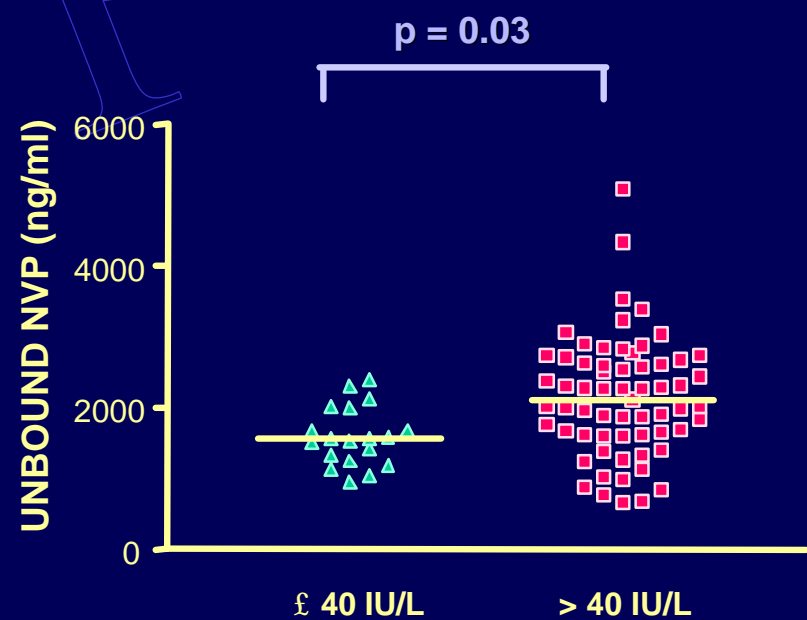
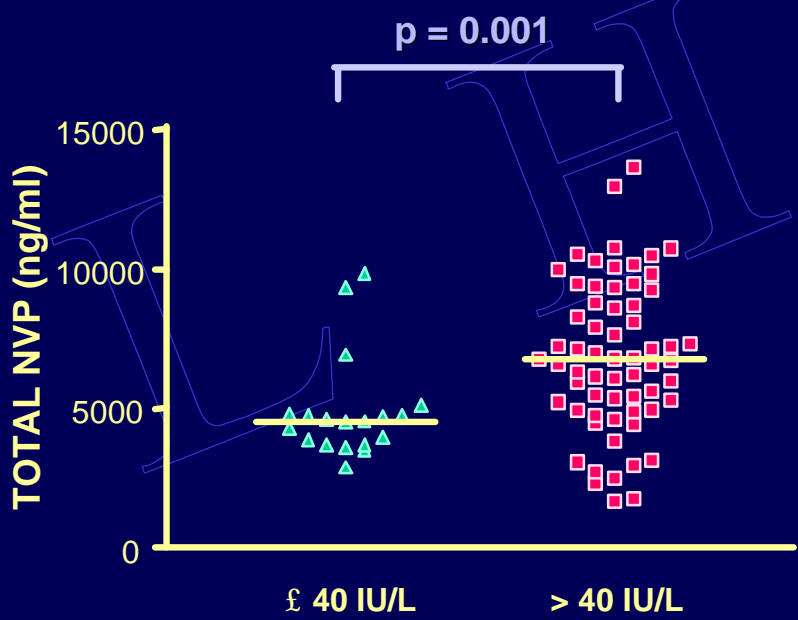
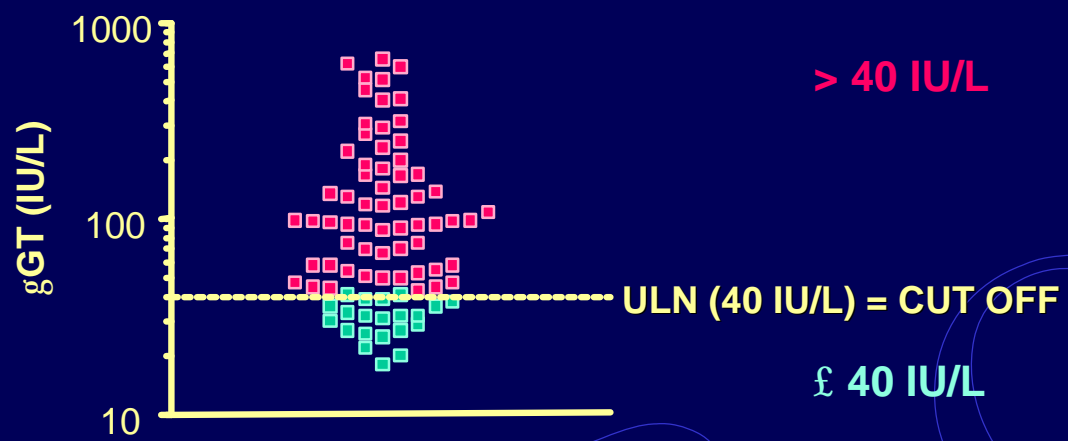
**Median = 81.5 IU/L**



# NVP-C<sub>trough</sub> above and below the ULN for ALT

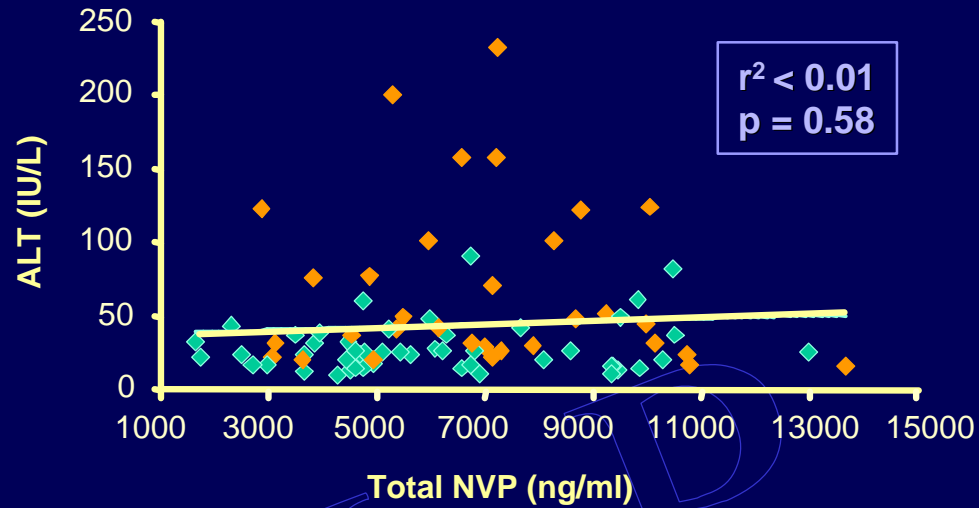


# NVP-C<sub>trough</sub> above and below the ULN for $\gamma$ GT



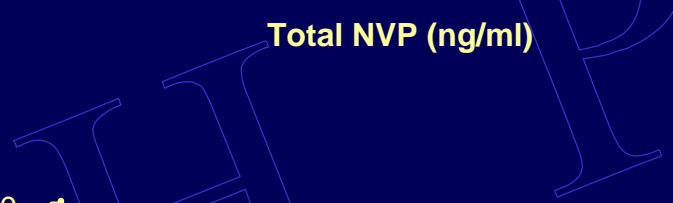
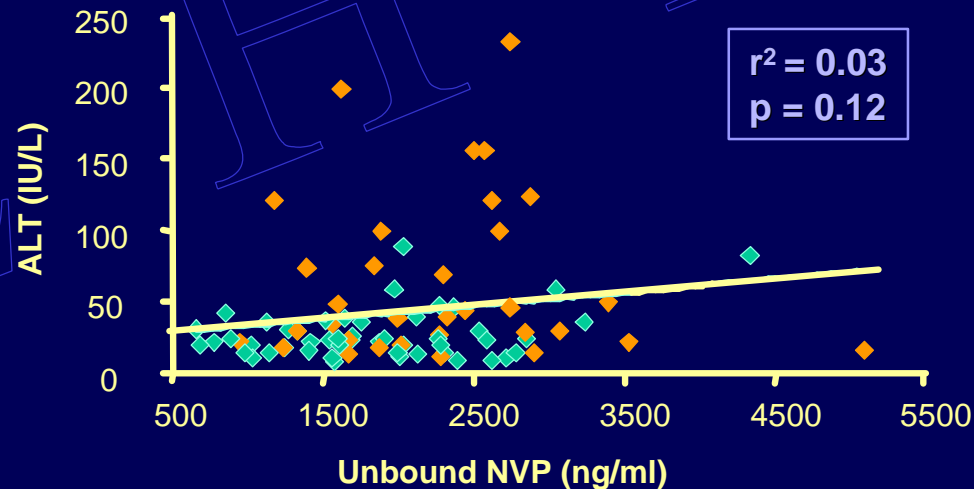
# Relationship between ALT and NVP-C<sub>trough</sub>

Total



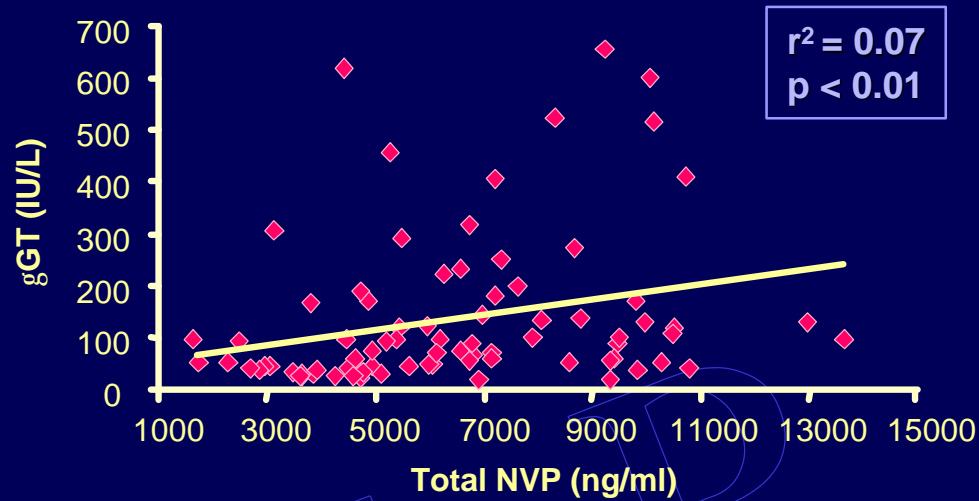
- ◆ HCV/HBV +
- ◆ HCV/HBV -

Unbound

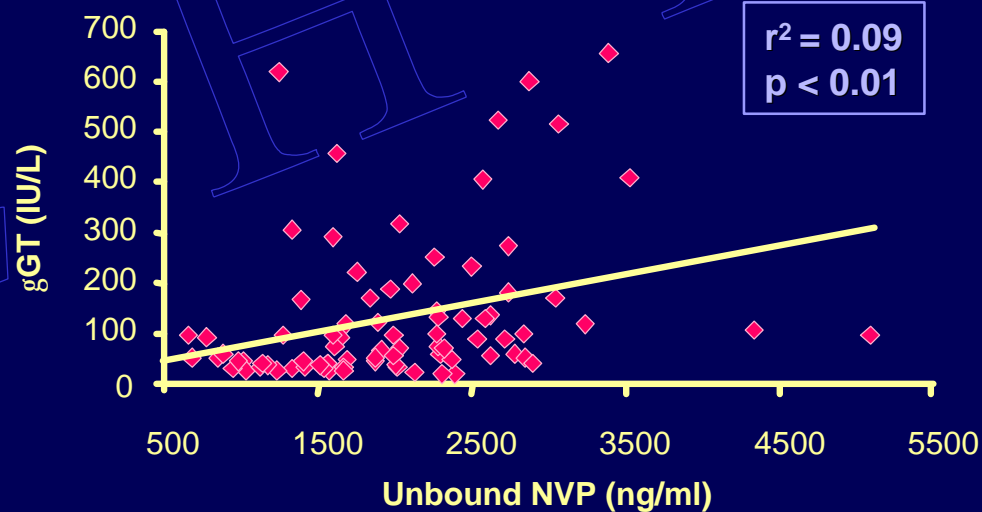


# Relationship between $\gamma$ GT and NVP-C<sub>trough</sub>

Total



Unbound



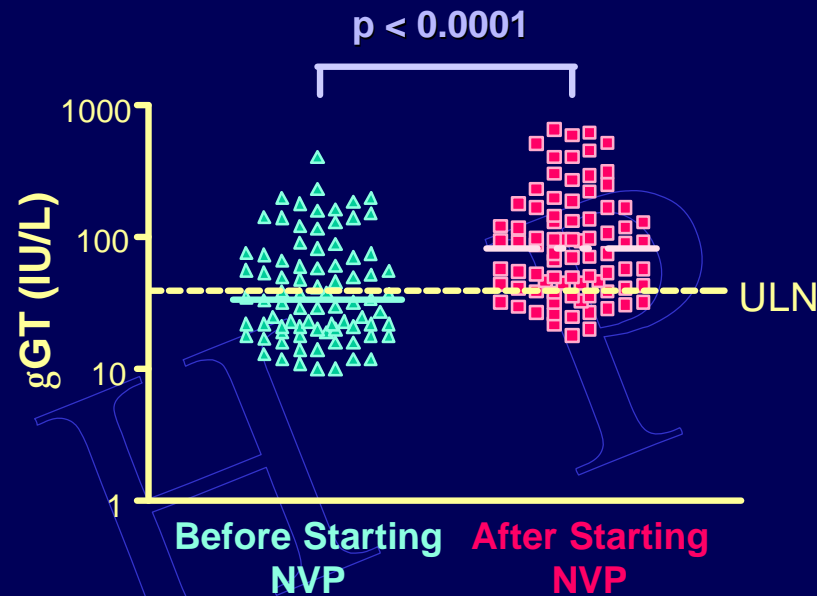
1. Are TOTAL and UNBOUND trough concentrations related to NVP hepatotoxicity?

- Low incidence of elevated ALT
- ALT was elevated ( $>ULN$ ) with higher NVP- $C_{trough}$  UNBOUND
- $\gamma$ GT was elevated ( $>ULN$ ) with higher NVP- $C_{trough}$  TOTAL + UNBOUND
- Weak association between  $\gamma$ GT elevations and NVP- $C_{trough}$

2. Do confounding patient factors (such as HCV/HBV, history of IVDU and ART experience) impact on NVP hepatotoxicity?

# LFTs Prior to NVP Treatment

- $\gamma$ GT was significantly increased following NVP therapy (median 65.6 weeks; range 3 – 201 weeks)



- ALT was not altered after NVP therapy
- No relationship between ALT or  $\gamma$ GT and duration of NVP therapy

# Results

Significant increase in  $\gamma$ GT after NVP

- Were there any confounding factors?

Bivariate analysis with  $\gamma$ GT (50% increase from baseline)

- Co-infection HCV/HBV  $\chi^2 = 9.86, p = 0.002$
- IVDU  $\chi^2 = 10.6, p = 0.001$
- Antiretroviral Drug Experience  $\chi^2 = 5.25, p = 0.022$
- Association between HCV/HBV and higher total NVP- $C_{\text{trough}}$   
 $\chi^2 = 5.25, p = 0.022$

# Results

## Logistic Regression Analysis

No independent association between elevated  $\gamma$ GT and ...

- NVP-C<sub>trough</sub> (TOTAL or UNBOUND)
- HCV/HBV Co-infection
- History of IVDU
- Antiretroviral Drug Experience

# Summary

- Low incidence of hepatotoxicity – 2/82 Grade 3 ALT elevation
- Weak association between  $\gamma$ GT and NVP-C<sub>trough</sub> (TOTAL and UNBOUND)

HOWEVER

- $\gamma$ GT was also associated with other factors (IVDU, HCV/HBV and drug experience)
- Higher NVP-C<sub>trough</sub> was associated with HCV/HBV co-infection

# Discussion

Does liver damage cause decreased clearance and higher NVP-  
 $C_{\text{trough}}$ ?

OR

Are higher NVP concentrations responsible for liver damage?

Further studies are required to isolate the contribution of NVP to hepatotoxicity in patients with other hepatic risk factors.

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