

## Abstract

**Background:** A previous study (SALT) looked at all liver transplantations in 7 countries in Europe over 3 years (2005-2007). SALTII is a continuation of SALT, in France, over 2008-2013. **Methods:** All registrations for acute liver failure leading to registration for transplantation (ALFT) without identified clinical cause were retrieved from the 22 French liver transplant centers from 2008 to 2013. Clinical information and previous drug exposure were abstracted by trained assistants and validated by the Centre director. Previous exposure was considered within 30 days before onset of liver symptoms. Cases were classified in acute drug overdose (voluntary or not), drug-exposed, or non-exposed ALFT. Exposed cases were compared to national exposure data from EGB, the 1/97th permanent representative sample of SNDS, the National healthcare database system. Rates are given as cases per million patients (MPt) and per million patient-years (MPY). **Results:** Over 6 years in 66 million persons, 246 cases of ALFT were identified, of which 132 were acute drug overdoses, 82 had been exposed to non-overdose drugs, and in 32 no drug exposure was found. Cases were female for 73, 55 and 59% respectively, mean age was 37, 44, and 42 respectively, and 59%, 77% and 87% were transplanted. The drug most commonly found in overdose was paracetamol (96%), followed by anxiolytics (33%), antidepressants (22%), hypnotics 15%, as well as opioids and antipsychotics. 43% of paracetamol overdoses were non-intentional. For non-overdose ALFT, the most commonly found drugs were paracetamol (43%), antimycobacterials (AMB, 20%), direct acting antiretrovirals (ARV, 15%), antidepressants (16%), anxiolytics (13%), antiepileptics (13%), as well as NSAIDs (10%), lipid-lowering agents (10%), and antithrombotic agents (10%). Event rates were highest for AMB with 75/MPt and 63 per MPY, followed by ARV (2.5/MPt, 1.65/MPY). Non-overdose paracetamol was 0.74/MPt, 0.22/MPY, NSAIDs 0.2/MPt, 0.07/MPY; Antiepileptics were 2/MPt, 0.88 per MPY, antidepressants 1.15/MPt and 0.44/MPY. **Conclusion:** Most drug-associated ALFT were related to overdoses, especially of paracetamol. The highest ALFT risk for non-overdose drugs was by very far with antimycobacterials, followed by ARV, antiepileptics and antidepressants. Paracetamol was present in 43 of non-overdose ALFT. Similar results were found for hospital admissions for non-transplant acute liver injury (EPIHAM), presented elsewhere in this meeting.

1. Gulmez SE, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. *Drug Saf.* 2013;36(2):135-44.

## Declaration of Interest Statement

The study received funding from *Bordeaux University Foundation* and was conducted by Bordeaux Pharmacoepi Platform. All authors, none declared other relationships to disclose for this study.

## Background

- Acute liver injury has been reported with most drugs, and is one of the most common reasons for drug withdrawal from market or interruption of development. Most severe cases result in Acute Liver Failure leading to registration for Transplantation (ALFT).
- Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol have often been involved in liver injury.
- Because of a suspected greater risk of hepatotoxicity with an NSAIDs, the SALT-I study, required by the CHMP (Committee for Medicinal Products for Human Use), has been realised to assess the risk of ALFT in patients exposed to NSAIDs over the years 2005-2007. This retrospective study was conducted in 7 countries with the participation of 55 transplantation centres in Europe.
- The SALT-II study was conducted in France, covering the years 2008-2013. The methodology was similar to SALT-I but the objective was to assess all drug exposures, not only NSAIDs.

## Objectives

To estimate the risk of drug-exposed ALFT in adults in the 30 days prior to index date (ID, date of first symptoms) according to the drug dispensing in France over 2008-2013, estimated and extrapolated from data provided by the national healthcare insurance system (Echantillon Généraliste de Bénéficiaires: EGB).

## Methods

- Study design:** multicentre **case-population** study focused on drug-exposure of patients with ALFT over 6 years (2008-2013) in France.
- Identification** of adult patients with ALFT from national transplant registry (CRISTAL).
- Data collection** through an electronic CRF completed by the Research Clinical Assistants using **hospital medical files** (all drug exposures collected, including herbal medicines).
- Classification of ALFT cases** by a Case Selection Committee:
  - ALFT with identified cause (viral hepatitis, auto-immune, etc.)
  - ALFT without identified clinical cause
    - acute drug overdose (with or without suicidal intent)
    - exposure to drugs without overdose
    - no drug exposure
- Index date:** Date of first symptoms of Acute Liver Injury, validated by Case Selection Committee.

- Drug exposure**
  - Cases:** all drug exposures (including herbal medicines), within the 30 days prior to ID, were collected for all ALFT cases **without identified clinical cause**.
  - Reference population:** number of adult patients with at least one drug of interest dispensed over the study period (2008-2013) identified in EGB, among adult patients affiliated to the national healthcare insurance system for salaried workers (CNAMTS), and extrapolated to the whole French population.
- Incidence rates (IR)**
  - Drug exposures within the 30 days before ID for ALFT without identified clinical cause were compared with the population exposure.
  - The IR for all ALFT without identified clinical cause exposed to drugs were computed for each drug of interest and expressed per million patients (MPt) and per million patient-years (MPY) with 95% confidence intervals.

## Results

### Study population

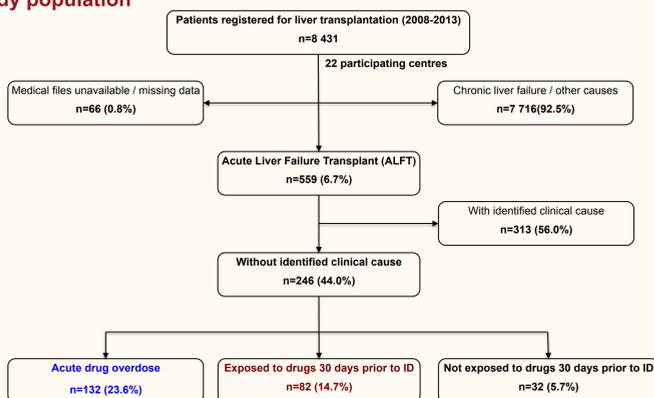


Figure 1 : Identification and selection of ALFT cases over the period 2008-2013

### Demographics

- 132 ALFTs with "acute drug overdose": mean age 36.9 ( $\pm$ 12.6) years, 72.7% female. Liver transplantation in 59.1%.
- 82 ALFTs "exposed to drugs without overdose": mean age 43.8 ( $\pm$ 12.9) years, 54.9% female Liver transplantation in 76.8%.
- 32 ALFTs "not exposed to drugs": mean age 42.2 ( $\pm$ 15.0), 59.4% female. Liver transplantation in 87.5% of cases.

### Drug exposure

Table 1. Drug exposures of ALFTs without identified clinical cause over the period 2008-2013

	Acute drug overdose n = 132	Exposed to drugs n = 82
Paracetamol (Plain and combinations)	130 (98.5)	35 (42.7)
Anxiolytics	43 (32.6)	11 (13.4)
Antidepressants	29 (22.0)	13 (15.9)
Hypnotics and sedatives	20 (15.2)	3 (3.7)
NSAIDs	16 (12.1)	8 (9.8)
Antiepileptics	14 (10.6)	11 (13.4)
Opioids	11 (8.3)	3 (3.7)
Antipsychotics	8 (6.1)	2 (2.4)
Lipid modifying agents, plain	3 (2.3)	8 (9.8)
Antithrombotic agents	2 (1.5)	8 (9.8)
Direct acting antivirals	1 (0.8)	12 (14.6)
Drugs for treatment of tuberculosis	0 (0.0)	16 (19.5)

Table 2. Paracetamol exposure of ALFTs without identified clinical cause over the period 2008-2013

	Acute drug overdose n = 132	Exposed to drugs n = 82
Paracetamol, plain and combinations	130 (98.5)	35 (42.7)
Paracetamol	109 (82.6)	32 (39.0)
Paracetamol, combinations excl. psycholeptics	22 (16.7)	4 (4.9)
Paracetamol, combinations with psycholeptics	2 (1.5)	2 (2.4)
Codeine, combinations excl. psycholeptics	0 (0.0)	0 (0.0)
Tramadol, combinations	6 (4.5)	0 (0.0)
<b>Overdose, n (%)</b>	<b>126 (95.5)</b>	<b>0 (0.0)</b>
Intentional overdose, n (%)	69 (52.3)	0 (0.0)
Non-intentional overdose, n (%)	57 (43.2)	0 (0.0)

### Incidence rates

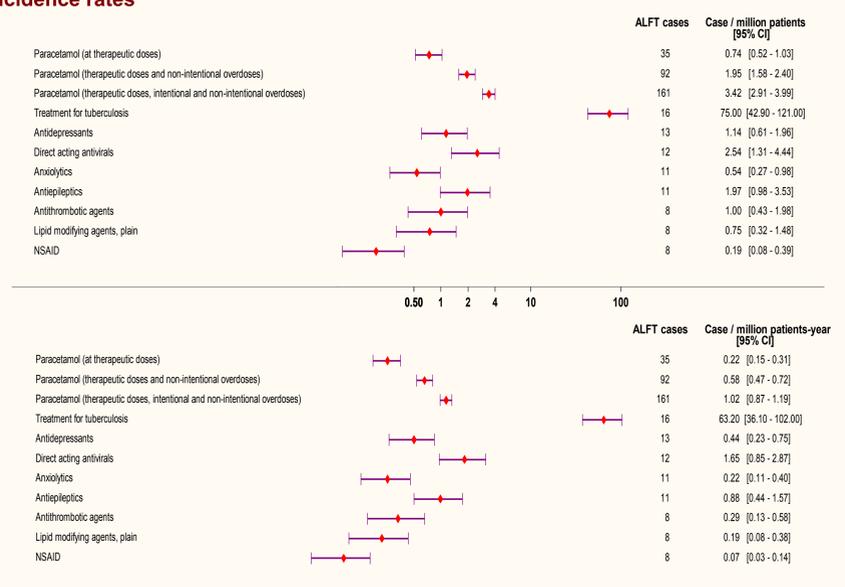


Figure 2. Drug-exposed ALFT incidence rates (30-days exposure window) for the 6-year period (2008-2013) per million patients (upper panel) and per million patient-years exposed (lower panel)

### Pooled SALT-I/SALT-II data (9-years, 2005-2013)

- 347 ALFT cases "without identified clinical cause": 22.3% with "acute drug overdose", 20.0% "exposed to drugs without overdose" and 4.9% "not exposed to drugs".
- More than 2-fold increase of acute drug overdose per year in SALT-II compared to SALT-I.
- Demographic characteristics similar in SALT-I and SALT-II.
- Drug exposure frequency within 30-days prior to ID remained constant except for ALFT "exposed to drugs without overdose" for which paracetamol exposure increased for the pooled period compared to SALT-II (55.8% vs 42.7%).
- IR per MPY was 0.36 for non-overdose paracetamol, 0.64 with non-intentional paracetamol overdoses and 1.06 when all paracetamol exposures were considered. Per MPt, IR ranged from 1.59 to 4.64.
- IR for NSAID was: 0.11/MPY, 0.39/MPt. The other drug exposures were not computed in SALT-I.

## Conclusion

- Most drug-associated ALFT were related to overdoses, especially of paracetamol.
- Paracetamol was present in 43% of non-overdose ALFT.
- The highest ALFT risk for non-overdose drugs was by very far with treatment for tuberculosis, followed by ARV, antiepileptics and antidepressants.
- Similar results were found for hospital admissions for non-transplant acute liver injury (EPIHAM), presented elsewhere in this meeting.
- Paracetamol exposure at therapeutic dose or at overdose is still main cause for liver transplantation and this has increased since SALT-I.

