



# HERBAL AND DIETARY SUPPLEMENT USAGE IN U.S. ACUTE LIVER FAILURE TRANSPLANT RECIPIENTS

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## ABSTRACT

**Objective:** Increased use of herbal/dietary supplements (HDS) in the US has led to more adverse reactions. Hepatotoxicity of some HDS has even necessitated urgent liver transplantation (LT). Our objective is to determine the frequency of US liver transplants secondary to HDS usage and to characterize this cohort.

**Study Design:** This was a retrospective chart review of Scientific Registry of Transplant Recipients (SRTR) data of patients who underwent urgent liver transplant (Status 1) from 2003-2015. Data collected included demographics, etiology of disease, blood type, waiting time, graft status and survival. Cases in which the etiology included HDS were identified and analyzed.

**Results:** Of 3,195 cases, 2,408 were adults and 787 were pediatrics (excluded from analysis). From the adult cohort, 25.96% of acute liver failure (ALF) was secondary to drugs; of this group, 21 cases were found to involve HDS and occurred from 2007-2014. The 4 most common drug groups causing ALF were acetaminophen (n=300), anti-tuberculosis drugs (n=30), antibiotics (n=30), and herbal/dietary supplements (n=20). The mean age of HDS-induced transplant patients was 36.76 ± 11.67 years (range 21-64 years). 14 (66.67%) were female. The racial distribution was as follows: 6 (28.57%) Asian, 2 (9.52%) Black, 2 (9.52%) Hispanic, 1 (4.76%) Multiracial, and 10 (47.62%) White, 18 (85.71%) are currently living. A total of 1,046 (43.44%) adult cases were classified as "Unknown/Difficult to Determine" or "FHF/ALF Unspecified"; 154 (24.64%) of DILI cases were "Unknown".

**Conclusion:** HDS use is the 3<sup>rd</sup> most common cause of drug-induced ALF leading to LT. Though 21 (0.87%) adult cases of HDS-induced Status 1 LT have been reported, the actual value may be higher since 1,200 (49.83%) total adult cases have an unspecified reason for LT. The literature names multiple hepatotoxic HDS not mentioned in the United Network for Organ Sharing (UNOS) database. Transplant professionals should specifically educate and inquire about HDS use in patients to identify inciting agents and properly notify the Food and Drug Administration (FDA) and SRTR of adverse effects. These measures will help discern etiologies as well as enhance liver utilization for non-preventable cases as the public more cautiously uses HDS.

## BACKGROUND

- The demand for liver transplant exceeds the supply with nearly 15,000 people on the waitlist and an estimated 7,000 performed annually.
- Drug-induced liver injury (DILI) is the most common cause of acute liver failure (ALF) in the US responsible for 15% of ALF transplants from 1990-2002.<sup>2</sup>
- Drug Induced Liver Injury Network (DILIN) found 15.5% of DILI cases to be from HDS in 8 US referral centers.<sup>7</sup>
- HDS found to be 2<sup>nd</sup> most common cause of *idiosyncratic* DILI.<sup>8</sup>
- HDS is a \$180 billion industry<sup>5</sup> and used by over 50% of US adults.<sup>3</sup>
- HDS bypass FDA safety measures and approval and therefore result in multiple adverse effects including hepatotoxicity<sup>4</sup> (see Table 1).
- 2013: Hawaii Department of Health (HDOH) notified of an ALF outbreak necessitating transplantation or resulting in death, all linked to OxyElite Pro (OEP), a dietary supplement.<sup>6</sup>

**Table 1.** Tabular compilation of dietary supplements related to liver injury.<sup>4</sup>

DIETARY SUPPLEMENT*	# CASES	MARKETED PROPERTIES
<b>Camellia sinensis (green tea extract)</b> Euforia, Exolise, Onshido, SlimQuick, X-elles, Cha verde, Curr, Camilla-Arokapsulas, Lipolyz	92	Weight loss Stop hair loss
<b>Linoleic acid</b>	3	Reduction in body fat mass
<b>Ursolic acid</b> Lipokinetix, UCP-1 Lipolyz	18	Weight loss
<b>Vitamin A, Retinol</b> Plethoryl	60	Immunostimulant, prevention of night blindness, acne
Herbalife combinations	68	Weight loss nutritional support, well being
Hydroxycut	29	Weight loss
Oxy ELITE Pro	71	Weight loss, muscle building
<b>Illicit androgenic anabolic steroids:</b> Celtic dragon, Episidrol, Epistane, SUS500, Uprizing 2.0	153	Body-building, improving fitness and exercise performance
<b>Ma huang (ephedra)</b> Xenadrine, Excelerator, Metabolife 356, Thermolite, BetaLin, Thermo diet stack, Hydroxycut	10	Weight loss
<b>Garcinia cambogia</b>	2	Weight loss

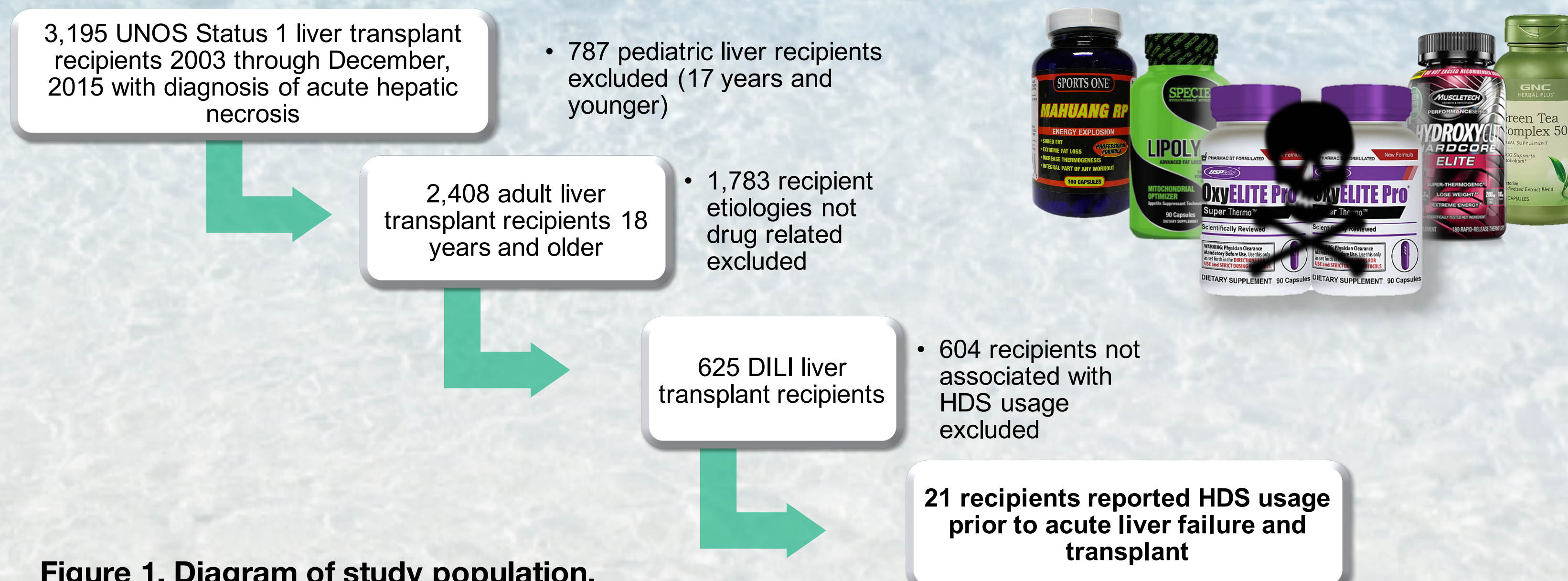
## Data Collection

- UNOS database of status 1 patients who underwent LT from January 1, 2003 to December 31, 2015
- Three initial categories
  - "Acute Hepatic Necrosis: Drug"
  - "Acute Hepatic Necrosis: Other"
  - "Acute Hepatic Necrosis: Etiology Unknown"
- Reorganized into etiologic categories (See Fig. 2)
- DILI etiologies were further categorized (see Fig. 2).
- Data included: recipient and donor age, ethnicity, gender, blood type; recipient waiting time, graft status, patient status, and diagnosis with etiology.

## Statistical Analyses

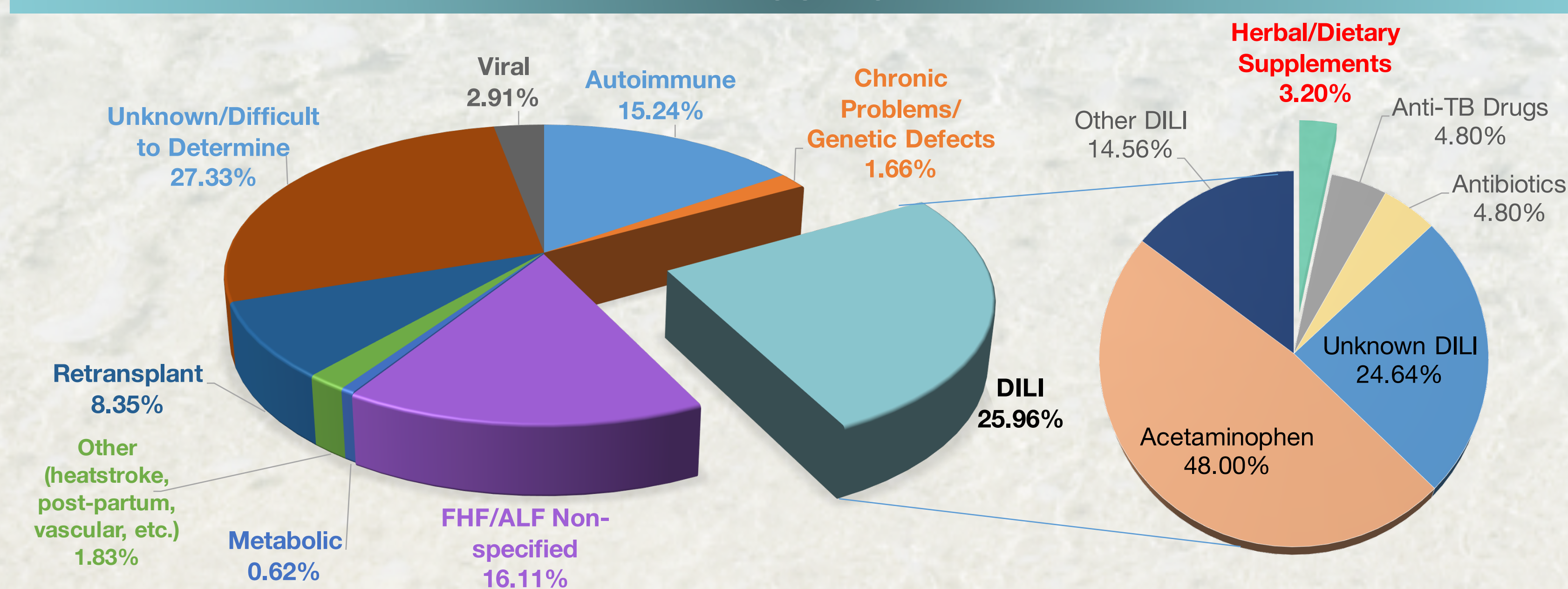
- Descriptive statistics
- Fisher's exact test for categorical variables
- Student's t test for continuous data (comparing means)

## MATERIALS AND METHODS



**Figure 1.** Diagram of study population.

## RESULTS



**Figure 2.** Distribution of Status 1 adult liver recipients based on etiology with secondary chart displaying etiological distribution of acute hepatic necrosis secondary to drugs (DILI). Three largest categories include Unknown/Difficult to Determine (27.33%), DILI (29.96%), and FHF/ALF Non-specified (16.11%). Drugs included in the "Other DILI" designation are: anti-inflammatory (NSAIDs), anti-seizure, amiodarone, anesthetics, methotrexate, narcotics (Tylenol/other), anti-hypertensives, disulfiram, HIV antiviral drugs, PTU, statins/anti-cholesterol, and "multiple drug" combinations.

**Table 2.** Cases for liver transplant where herbal/dietary supplements were involved.

Tx: Transplant. OTC: Over the counter. \*Recipient listed under "Other: Multiple Drugs" and not "included within the 20 "Herbal/ Dietary Supplements"-only cases.

	AGE/SEX	RACE	YEAR	DAYS WAITING TO TX	CURRENT STATUS	ETIOLOGY LISTED
1	43F	White	2007	1	Living	Herbal medicine
2	33F	Black	2007	15	Dead	Natural herbal diet medication
3	64F	White	2008	2	Living	OTC Herbs
4	39F	Asian	2008	2	Living	Herbal hepatotoxicity induced
5	30F	White	2009	2	Living	Lipolyze
6	31F	Hispanic	2009	3	Living	Hydroxycut toxicity
7	24M	White	2010	6	Living	Nutritional supplements
8	56F	Asian	2011	6	Dead	Herbal drugs
9	26F	White	2011	3	Living	Herbal supplements
10	37F	White	2012	1	Living	Unknown herbs
11	25F	Hispanic	2013	8	Living	Herbal medication
12	21M	Asian	2013	0	Living	Non-FDA approved testosterone
13	48F	Black	2013	2	Living	Unknown herbal supplements
14	35F	White	2013	2	Living	Diet supplement induced
15	22M	Multiracial	2013	19	Living	Oxy ELITE Pro
16	45F	Asian	2013	2	Living	Oxy ELITE Pro
17	28M	White	2013	8	Living	OTC muscle builder
18	43M	Asian	2013	6	Living	Oxy ELITE Pro
19	36M	White	2014	6	Dead	Oxy ELITE Pro
20	33M	Asian	2014	3	Living	Oxy ELITE Pro
21*	53F	White	2014	1	Living	Herbal supplement and Tylenol

## SUMMARY OF RESULTS

- HDS use was found to be the 3<sup>rd</sup> most common cause of drug-induced ALF leading to urgent liver transplantation, after acetaminophen (1<sup>st</sup>) and anti-tuberculosis drugs tied with antibiotics for 2<sup>nd</sup>.
- Of 2,408 adults, 25.96% had ALF by DILI; of this group, 21 cases involved HDS. The mean age of HDS-induced transplant patients was 36.76 ± 11.67 years (range 21-64 years). 66.67% were female. Racial distribution: 28.57% Asian, 9.52% Black, 9.52% Hispanic, 4.76% Multiracial, and 47.62% White. Transplants were received from deceased donors with a mean wait time of 4.7 days (range 0-19).
- Looking at the treatment years, there is an increased frequency of cases being reported (Tab. 1). In the first half of the 13-year period, only 6 cases associated with HDS were reported, compared to 15 cases in the last 6.5 years. The OEP outbreak in Hawaii most likely explains the large number of cases in 2013.
- For the 21 cases, 1-year survival was 95.24% and 3-year survival was 92.31%. 85.71% of patients transplanted for HDS use are still alive leading to a relatively positive prognosis after transplantation.

## CONCLUSION/DISCUSSION

- The actual frequency of cases secondary to HDS may be higher. HDS involvement was reported in only 21 out of 2,408 adult cases as the etiology behind urgent liver transplantation while 154 (24.64%) of DILI cases remained unknown. In addition, 1,046 (43.44%) cases of the entire cohort were classified as "Unknown/Difficult to Determine" or "FHF/ALF Unspecified" (Fig. 1). Also, many HDS known to be hepatotoxic from literature reviews (Table 1) were not mentioned in the UNOS reports (Table 2) as a cause for ALF. Underreporting and/or lack of detailed descriptions are possible causes for the scarce data and uncertain etiologies found in our review. It is difficult to isolate HDS as the cause for ALF when other medications are involved and/or the patient neglects to mention any HDS use.
- The increase in reported HDS use in 2013 near the OEP outbreak displays the impact of public awareness. Transplant professionals should specifically question patients/family members about HDS use when diagnosing. Since the FDA doesn't perform safety measures, negative outcomes with HDS have to be reported for the public to know about adverse effects. Detailed reporting to the SRTR about HDS associated etiology should be increased so the problem is more quantifiable. Through increased awareness and caution with HDS usage, livers can be utilized more for those with serious, non-preventable diseases.

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