A STUDY ON LFT MONITORING IN ATT AND THE SPECTRUM OF ANTI-TUBERCULOUS DRUG INDUCED LIVER INJURY

DISSERTATION SUBMITTED FOR

DM MEDICAL GASTROENTEROLOGY

BRANCH- IV

AUGUST 2015

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY
CHENNAI-600032

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON LFT MONITORING IN ATT AND THE SPECTRUM OF ANTI-TUBERCULOUS DRUG INDUCED LIVER INJURY"** submitted by **Dr. Vaishnavi Priyaa.C** to the Faculty of Medical Gastroenterology, the Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out

by him under my direct supervision and guidance, during the academic year 2012 to 2015.

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DECLARATION

I **Dr. Vaishnavi Priyaa.C.,** declare that I carried out this work on **"A STUDY ON LFT MONITORING IN ATT AND THE SPECTRUM OF ANTI-TUBERCULOUS DRUG INDUCED LIVER INJURY"** at the Department of Medical Gastroenterology, Govt.Peripheral Hospital and Kilpauk Medical College. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the D.M. Degree examination in Medical Gastroenterology.

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8.4.2015

ACKNOWLEDGEMENTS

I am greatly indebted to my guide **Dr. P .Ganesh, M.D., D.M.,** Professor and Head of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai, for giving me the chance to undertake this dissertation work under his guidance. Also I express my deep sense of gratitude for his constant encouragement, directions, periodical discussions, rigorous reviews and precious suggestions that helped in the shaping of my dissertation.

I express my sincere gratitude to **Dr. T.Rajkumar Solomon, M.D., D.M.,** Professor of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai, for giving me permission to do this dissertation in Govt. Peripheral Hospital, Anna Nagar, Chennai-102 and also his kind encouragement and review of my work.

I also thank **Dr. S. Jeevan Kumar, M.D., D.M.,** Professor of Medical Gastroenterology, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai for his encouragement and suggestions for my study.

I am extremely grateful to **Dr. Narayana Babu**, **M.D.,DCH** Dean, Kilpauk Medical College, Chennai, for granting me permission to do this dissertation and for his constant encouragement.

I am very much thankful to **Dr.Ramkumar.G, M.D.D.M,** Assistant Professor, Department of Digestive Health and Diseases, Kilpauk Medical College, Chennai ,who have helped me a lot during my dissertation..

I am also extremely thankful to **Dr.R. Balamurali, M.D., D.M.,** and **Dr.K.Muthukumaran, M.D., D.M.,** who guided me a lot.

I am also extremely thankful to **Dr.V.Anand, M.D.,D.M** for his initiative support and periodic discussions that helped me to take up this study.

I am also very thankful to all my **Fellow Residents** who have helped me in this dissertation.

I am also thankful to **Dr.Ravanan,** Associate Professor, Department of Statistics, Presidency college., Chennai and **Dr.Balaji,** Department of Social and preventive medicine, SRM Medical college., Chennai for their help in the statistical analysis of my dissertation work.

I thank all the patients who voluntarily participated in this study, without whom this study would not have seen the light of the day.

I also thank all the paramedical staff attached to Govt. Peripheral Hospital, Anna Nagar, and Chennai who has helped me in doing this dissertation work.

Finally, I thank my husband **Dr.T.Gunasekaran**, who helped me in initiating and carrying out this study.

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INTRODUCTION

Drug reactions are often under reported and majority of drug reactions are minor. Some cases of adverse drug reactions may be major events like hepatotoxicity or nephrotoxicity. DILI is one of the leading causes of acute liver failure in the US, accounting for 13% of cases of acute liver failure; these events pose a major challenge for drug development and safety. Antimicrobials and agents for the central nervous system are the most common causes of DILI and health foods or dietary supplements account for 7% of cases of DILI in the US. In India and other developing countries, ATT is the most important drug implicated in DILI .AntiTuberculous drug induced liver injury is mostly due to inadequate evaluation of risk factors and "inappropriate dosing". Worldwide, incidence of Anti Tuberculous DILI, between 5 to 33% . This wide variation may be due to the predilection of TB towards developing count [1]ries than West. Even developed nations have a recent surge after the global HIV pandemic of HIV during 80s. In India, a nation contributing significant proportion of TB cases, the incidence of ATT DILI ranges between 33 to 35%. In India, Approximately 60% of all DILI cases are due to DILI and 70% cases are ATT induced Acute Liver Failure. (DIALF)

There are studies about risk factors and predisposing factors for DILI. But there are only few studies about the frequency of monitoring LFT in patients with these risk factors. WHO , which has put monumental effort in eradicating TB , says ,frequent LFT monitoring in all cases are far from reality due to financial drawbacks. The pathogenesis of DILI and contributory factors and mechanisms are not well established till now.

DILI may occur in all currently recommended regimes for treatment of TB. Pyrazinamide, INH, followed by Rifampicin in order, are the most common drugs causing DILI. DILI is most common among first line ATT drugs INH, PZ and Rifampicin, and the order of DILI with these drugs are also the same in decreasing order. Pyrazinamide with rifampicin appears more toxic than INH alone.

Alcoholics with baseline minor elevations of enzymes have to be closely monitored. Other patients who need close monitoring are underlying chronic liver disease like NASH, concomitant hepatotoxic drugs, other systemic diseases like autoimmune diseases, esp. SLE, or metabolic diseases. Patients with undiagnosed Chronic hepatitis B or chronic hepatitis C need complete evaluation, with viral load, Hepatitis B’e’ Antigen status, frequent LFTs, extent of fibrosis once diagnosed with HBsAg or Anti HCV positivity on screening.

Age, sex, comorbid illness, nutritional status, socioeconomic status, literacy, staff education, infrastructure, available lab resources and other possible confounding factors play a statistically significant role.

Careful patient selection, adequate basic screening for underlying liver diseases, careful selection of regime according to underlying risk factors and appropriate follow up may reduce serious DILI.

A patient with underlying liver disease, need safer regimes and frequent monitoring. This is based on the prognostic scores of the underlying liver disease.

When values of liver enzymes reach critical levels, withdrawal of all hepatotoxic drugs, is the most important step in preventing serious Drug Induced Acute Liver failure.

Screening for risk factors, based on the epidemiology, endemicity and prevalence of disease may help avoid unnecessary elaborate investigations.

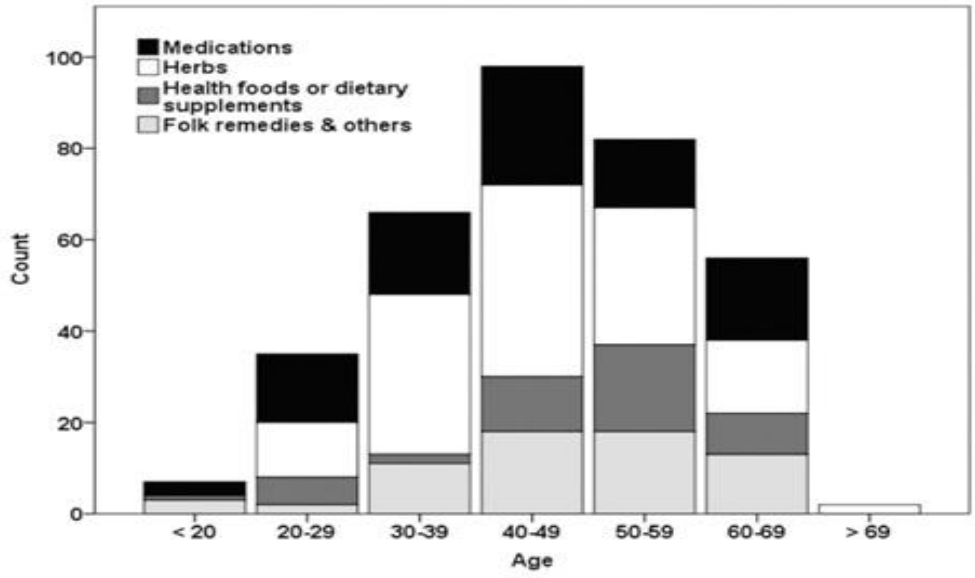
Screening for chronic viral hepatitis in risk groups, according to the endemic prevalence and region wise investigation panels may help overcome the financial constraints in applying all these tests. Anti-tuberculosis therapy is the commonest type of acute liver failure in South Asia followed by Hepatitis B related Acute Liver Failure and alcohol related Acute Liver Failure

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Drug induced Liver Injury has been described as ‘’PENALTY FOR PROGRESS”

. By Popper and Colleagues’ about 50 years ago. Drug induced liver injury is the one of the major cause for the drawl of drugs prescribed for major illness treatment and is also for withdrawal of drug from the market. A few drugs have been withdrawn and banned due to major adverse events. Hepatotoxicity constitutes one of major adverse effects due to drugs. There is a unique susceptibility of certain individuals to DILI called as idiosyncratic DILI.



DILI occurs mostly due to antimicrobials and ATT is one of the significant drugs, followed by Amoxicillin-clavulanic acid and flucloxacilin[1]

DEFINITION

The definition of DILI is as follows "Drug-induced liver injury (DILI) is defined as a liver injury caused by various medications, herbs, or other xenobiotic, leading to abnormalities in liver tests or liver dysfunction with the reasonable exclusion of other aetiologies".

Global burden of tuberculosis reduced by ATT:

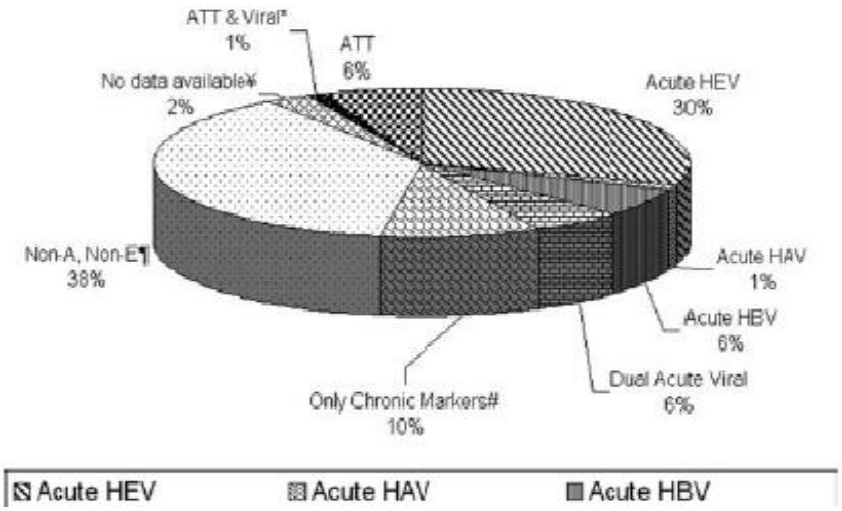
With the huge number patients being treated world-wide the safety of ATT drugs are placed on a large scale.

"Global TB reports 2013 by WHO '' has stated that 56 million patients have been cured of TB from 1995 to 2012[2]. The path to eradicate TB is still under way and treating any newly diagnosed TB by ATT is an economic emergency,[3]. Treating TB with the drugs available, over a period of 6 to 9 months has still been a double edged sword in patients with proven risk factors for DILI.

ATT and hepatotoxicity – "The double edged sword":

In a study done by S.K.Acharya, Shalimar and Vikram Bhatia, "Anti tuberculosis Therapy–Induced Acute Liver Failure: Magnitude, Profile, Prognosis, and Predictors of Outcome, Hepatology, May 2010.[4], a meta-analysis ''it is

concluded that the “frequency of overt clinical hepatitis caused by isoniazid, rifampicin, or both together was 0.6%, 1.1%, and 2.6%, respectively”.



Anti-tuberculous drugs are the most important cause of acute liver failure, especially in developing countries. Endemicity of locally prevalent diseases, decide the other causes of acute liver failure [5]. In west ,acetaminophen is the important cause for drug induced Acute liver failure. While in South Asia and South East Asia ,Acute viral Hepatitis are the other leading causes along with ATT DILI. Most studies in Acute Liver failure from Asia Pacific disclose Acute Hepatitis B as commonest cause. In India , especially in pregnany and underlying liver diseases, it is Acute Hepatitis E the cause for fulminant hepatitis with acute liver failure[6].The incidence of acute liver failure is higher when risk factors are present.

Hepatic Drug Metabolism Transporters, Enzymes, and Excretion:

The splanchnic circulation carries ingested drugs directly into the liver, a phenomenon known as the "first pass" through the liver.

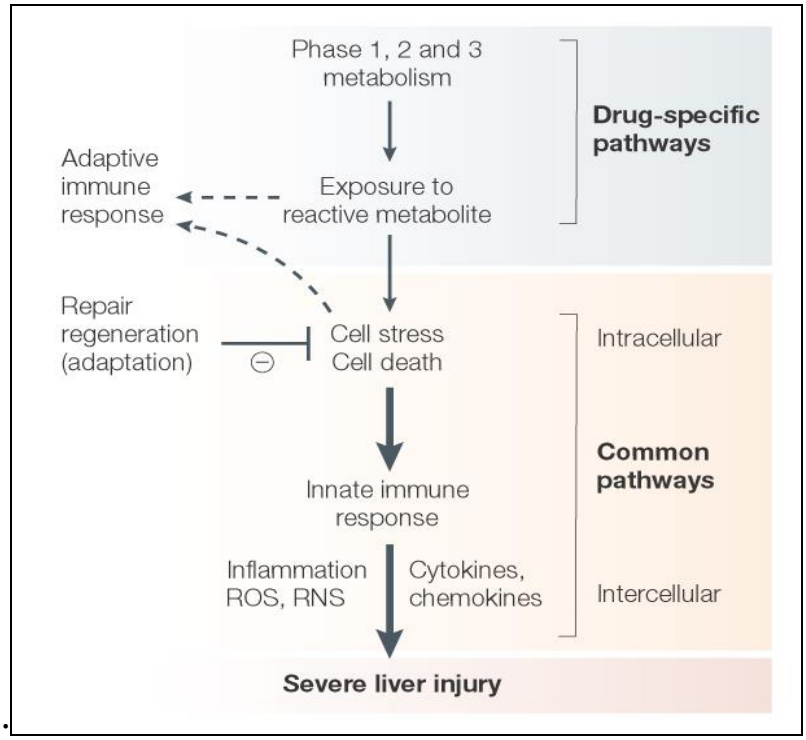
Drugs are converted to metabolites by three phases of metabolism in liver.

Phase 1 pathways of oxidation, reduction, or hydrolysis, which are carried out principally by the cytochrome p450 class of enzymes.

Phase 2 pathways include glucuronidation, sulfation, acetylation, and glutathione conjugation to form compounds that are readily excreted from the body. Other subsequent steps include Deacetylation and deamination. Many drugs may be metabolized through alternative pathways.

In phase 3 pathways, cellular transporter proteins facilitate excretion of these compounds into bile or the systemic circulation.

The production and functioning of these transporters and enzymes are influenced by endogenous factors like circadian rhythms, hormones cytokines, chronic illness, genetic factors, sex, age, ethnicity and nutritional status, as well as by exogenous drugs or chemicals[7].



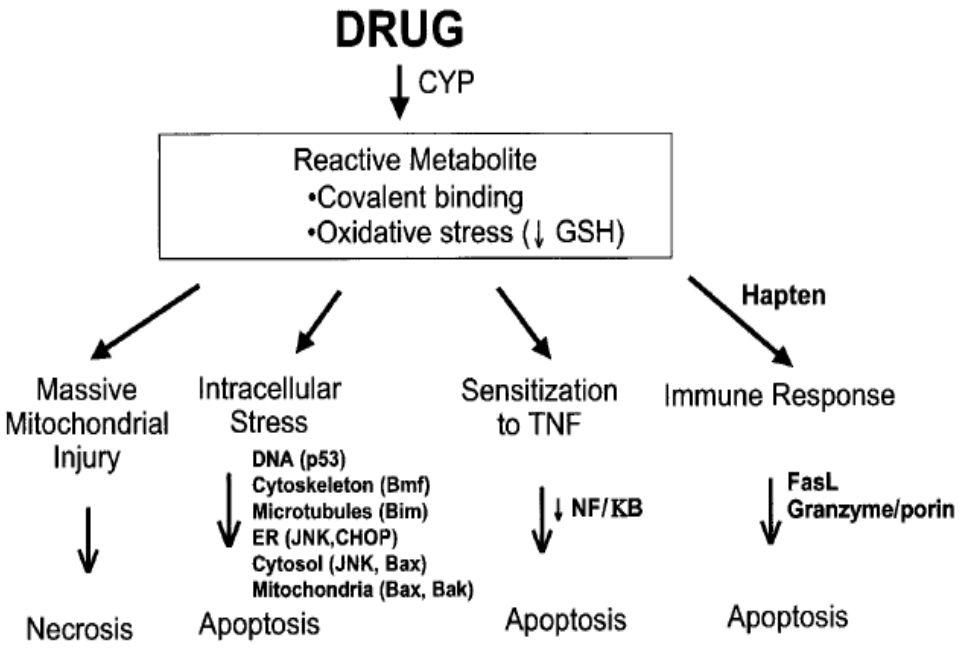
Pathogenesis of drug-induced hepatotoxicity:

This may be result from direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, or blood vessels.

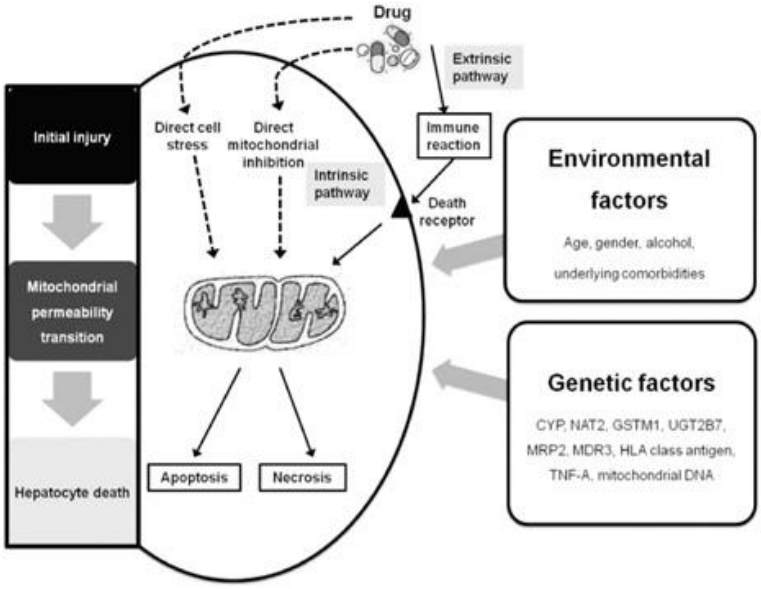
The exact mechanism contributing to the hepatotoxicity due to drugs is not clear yet.

Parent drugs or their reactive metabolites can cause cell stress to produce cytokines, chemokines, ROS, and reactive nitrogen species (RNS) which may cause apoptosis or necrosis .The inflammatory mediators released and innate immunity may decide the outcome of DILI.[8]

Mechanism of DILI:



Mitochondria plays the central role in DILI[9]:

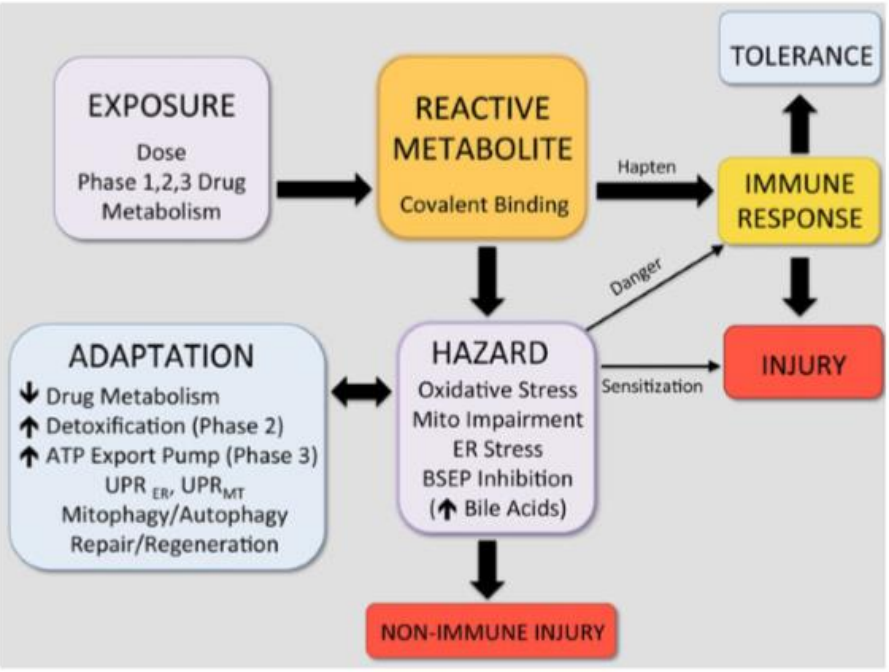


Types of DILI:

DILI may be either dose related or idiosyncratic. Idiosyncratic reactions are one of common types of drug injury. These hypersensitivity reactions are not related to dosage and duration of drugs[10]. In other words they are unpredictable. This idiosyncrasy may result in hepatocellular injury and or cholestasis. In idiosyncrasy, injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic arterioles, where metabolism is greatest and oxidant detoxifying capacity is the least.

In dose dependant DILI, the injury is intrinsic, and it is predictable .In dose dependent DILI hepatocyte necrosis is predominantly distributed throughout hepatic lobules rather than zonal.

Model of pathogenesis of idiosyncratic DILI:



This model shows the mechanism of liver injury when hepatocytes are exposed to a critical level of reactive metabolite leading to neoantigen or hapten formation and hazardous effects on hepatocytes. Both are needed for idiosyncratic DILI.

Adaptation and immune tolerance dissipates the toxic effect. So, always an impaired

Adaptation may lead to overt injury. Haptens or neoantigens formed by immunogenic drugs or its metabolites covalently binding to hepatic proteins, in hypersensitive reactions. Eosinophilic hypersensitivity reactions are provoked by Antibody dependent cytotoxic, T-cells. Tumour necrosis factor-alpha, interleukin (IL)-12, and IFN gamma are produced and promote hepatocellular apoptosis. This apoptosis is opposed by IL-4, IL-10, IL-13, and monocyte chemo tactic protein-1[11, 12].

MECHANISM OF HEPATOTOXICITY IN ATT:

1. Isoniazid:

Normally isoniazid is cleared mostly by the liver, primarily by acetylation by N-acetyl transferase2 (NAT-2). Acetyl-isoniazid is metabolized mainly to monoacetyl[14]

Hydrazine (MAH) and to the no toxic diacetyl hydrazine, as well as other minor metabolites. The reactive metabolites of monoacetyl hydrazine (MAH) are

probably toxic to tissues through free radical generation. The additional isoniazid metabolites acetyl hydrazine covalently binds to liver macromolecules, a process mediated by microsomal enzyme.[13, 16]

2. Rifampicin: Rifampicin may occasionally cause dose dependent interference with bilirubin uptake resulting in subclinical, unconjugated hyperbilirubinemia or jaundice without hepatocellular damage.[15] Conjugated hyperbilirubinemia probably is caused by rifampicin inhibiting the major bile salt exporter pump. Asymptomatic elevated bilirubin may also result from dose-depended competition with bilirubin for clearance at sinusoidal membrane or from impeded secretion at the canalicular level.

3. Pyrazinamide: It may exhibit both dose dependent and idiosyncratic hepatotoxicity. Pyrazinamide alters nicotinamide acetyl dehydrogenase levels in liver which might result in generation of free radical species[17]. There may be shared mechanisms of injury for isoniazid and pyrazinamide, because there is some similarity in molecular structure. Patients who previously had hepatotoxic reactions with isoniazid have more severe reaction with rifampicin and pyrazinamide[18].

4. Ethambutol: There has been one report of ethambutol related liver cholestatic jaundice with unclear circumstances[19].

EPIDEMIOLOGY OF ATT DILI:

Hepatitis develops in approximately 21 of 1000 persons exposed to isoniazid; 5% to 10% of cases are fatal .The risk and severity of isoniazid hepatitis increase with age; the risk is 0.3% in the third decade of life and increases to 2% or higher after age 50 INH toxicity is not dose dependant or with increased therapeutic levels.

Slow acetylators of isoniazid may be at increased risk of toxicity, but the data are conflicting. Risk factors: chronic alcohol use, concurrent use of Rifampin, pyrazinamide[20], acetaminophen, HBV, HCV, HIV.

Serum ALT levels increase in 10% to 36% of persons taking isoniazid during the first 10 weeks. Abnormalities typically are minor and resolve spontaneously. In persons in whom hepatitis develops, the latent period from exposure to disease ranges from 1 week to more than 6 months; the median is approximately 8 weeks, and 12 weeks for severe cases.

The prodromal symptoms occur in one third of patients and include malaise, fatigue, and early symptoms of hepatitis such as anorexia, nausea, and vomiting. Jaundice appears several days later and is the only feature in approximately 10% of cases. Most cases with a fatal outcome have been associated with a longer duration of therapy or continued ingestion of isoniazid after the onset of symptoms. Recovery is rapid if isoniazid is discontinued before severe liver injury is established.

Other Anti-Tuberculous drugs:

Most cases in which Rifampicin has been implicated with liver injury have occurred in patients taking isoniazid, but a few cases have been observed when Rifampicin was given alone to patients with underlying liver disease[21]. Pyrazinamide (as well as the related Ethionamide) was known as a dose-dependent hepatotoxin. Hepatotoxicity may be particularly severe in patients taking combinations that include isoniazid and pyrazinamide[22, 23]

Concomitant hepatotoxic drugs:

They add fuel to the fire. Drugs like methotrexate, chlorpromazine, long term acetaminophen, prolonged anti-microbial like fluocloxacillin are proven hepatotoxic. In these patients on prolonged hepatotoxic drugs, adding ATT, even though with normal baseline LFT results in acute fulminant steatohepatitis, or a massive parenchymal necrosis[24,25] and "HYPERACUTE LIVER FAILURE", in less than 7 days with a short latency and jaundice encephalopathy interval. Prognosis is guarded in these patients without an early transplant.

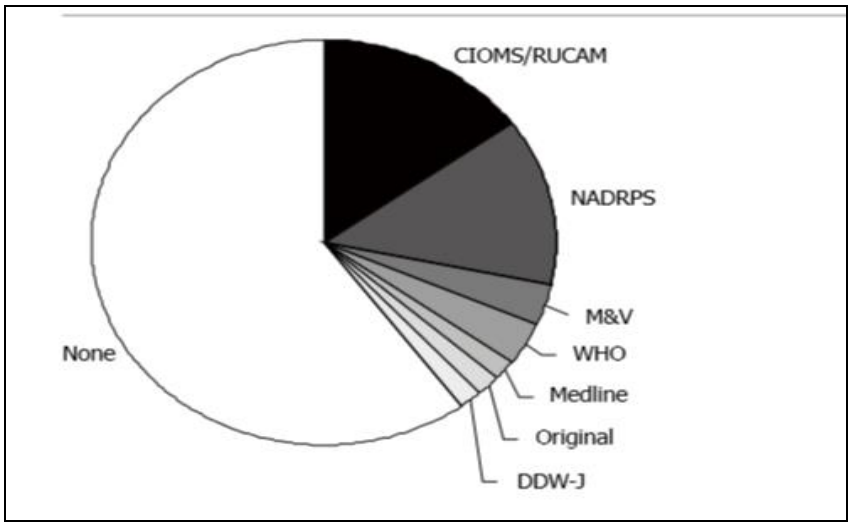
Pattern of DILI:

Drugs may cause hepatocellular, mixed or cholestatic injury. This calculated by the R-value, based on ALT and SAP levels.

Cholestatic	Mixed	Hepatocellular
Canalicular , ductular	Hepatitis and cholestasis	Cytotoxic, Parenchymal necrosis, Apoptosis.
R value <2	Rvalue 2 to 5	Rvalue >5

Causality Assessment of DILI:

"Percentages of methods for causality assessment in DILI, reported during the last decade" in a study done comparing causality assessment methods, shows that most cases are not assessed while, RUCAM and CIOMS are the most commonly employed methods[26].



Roussel Uclaf Causality Assessment Method (RUCAM):-

This is the most widely used. The RUCAM assesses non-organ specific drug reaction to well-defined hepatic reactions.

7 major criteria of RUCAM scale are

(1) Time to onset,

(2) Course of the reaction,

(3) Risk factors for the reaction,

(4) Assessing the role of concomitant therapies,

(5) Screening for non-drug-related causes,

(6) Weighing the information known about the DILI in question,

(7) Confirmation of the reaction by positive rechallenge or in vitro assays.

The grading of casual assessment is as follows:

Excluded, Unlikely, Possible, Probable, and highly probable. Many studies have quoted that "RUCAM assessment should not be taken as the only diagnostic tool. It has its suboptimal retest reliability and lack of robust validation, but it is useful in providing a diagnostic framework upon which to guide an evaluation in patients with suspected DILI". Causality assessment along with evaluation appears to be the most useful way of establishing DILI now, but presently cannot be practised[27].

There are various cut off levels used worldwide to stop ATT with onset of DILI like WHO Grading, American thoracic society, British thoracic society ,European Respiratory society and Hong KongTuberculosis society. 'Stopping the drug' is the most important step in preventing DILI.[28]

Authority	Monitoring in the presence of risk factors (especially liver diseases)	Cut-off levels for DILI and stopping drugs
ATS[10]	Yes	ALT >200 IU/l, or ALT >120 IU/l with symptoms
BTS[29]	Yes	ALT or AST >200 IU/l, rise in bilirubin
ERS, WHO, IUATLD[30]	-	ALT or AST >200 IU/l, icteric patient
HKTBS[31]	Yes	ALT >200 IU/l, bilirubin >40 μmol/l

DILI = drug-induced liver injury; ALT = alanine transaminase; AST = aspartate transaminase; ATS = American Thoracic Society; BTS = British Thoracic Society; ERS = European Respiratory Society; WHO = World Health Organization; IUATLD = International Union Against Tuberculosis and Lung Disease; HKTBS = Hong Kong Tuberculosis Service.

DIAGNOSIS OF DILI:

DILI as such is difficult to diagnose.With each drug being unique in its presentation, ruling out other causes might help diagnosing DILI.The most common competing etiologies must be in considered before DILI[29].

Table 1 Status of circulating biomarkers of hepatotoxicity

Type	In clinical use	Emerging
Proteins	ALT, AST, ALP, GGT, 5'-nucleotidase, TNFα, IL-1β, IL-6	PON1, PNP, MDH, GLDH, ARG1, αGST, HPD, K18, HMGB1
Nucleic acids		miR-122 and miR-192, mRNA Alb and mRNA Ambp
Excretory function markers	Bilirubin, total bile acids	Bile acid profiles (conjugated vs. unconjugated)
Genetic		*HLA-B*5701*, *HLA-A*0201* and *HLA-DQB1*0602*

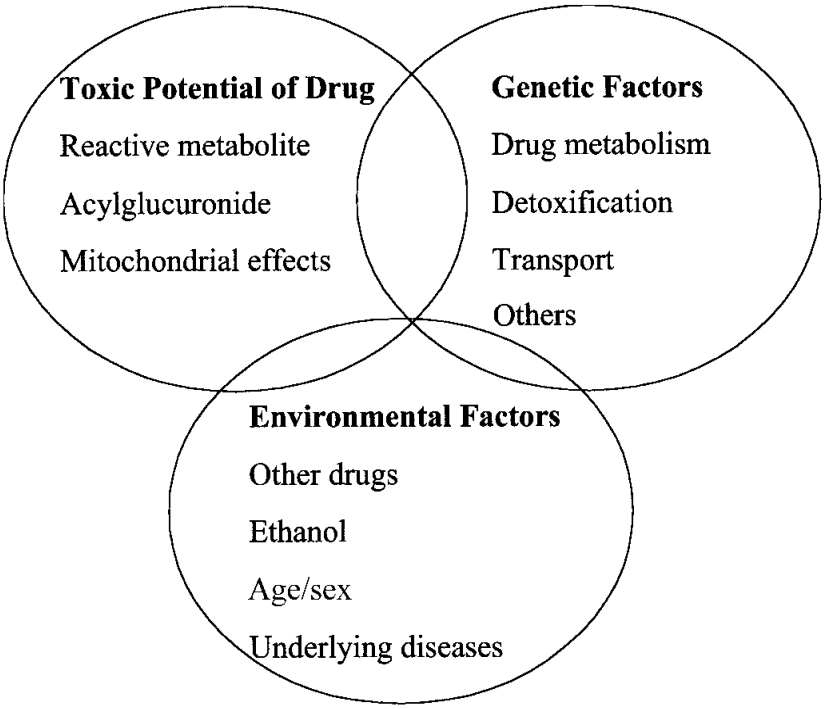
Recently Biomarkers play a role in diagnosing DILI, but are not put in for practice. They are still under research.

Biopsy: The role of biopsy in establishing DILI is still kept at bay, since diagnosing DILI, by an invasive method outweighs its fruitfulness.

Most biopsy, although unique to a drug overlies on the pattern of injury produced by the drug. e.g., cholestsatic or hepatocellular. Autoimmune hepatitis mimic, is frequent finding encountered in the biopsy specimen for

DILI. Biopsy will be gold standard in differentiating other causes from DILI ,rather than for unique pattern of a drug[32].

Risk factors for susceptibility to drug-induced hepatotoxicity:



Increasing age, underlying undiagnosed liver disease, female gender, low socio economic status, lower literacy levels, lack of knowledge, poor staff education[30].

Poor lab infrastructure, poor follow up is one of the most important causes for DILI in developing countries. While in western countries HAART (Highly Active Anti-Retroviral therapy) may attribute to the added risk of DILI. Diabetes and female gender, and other concomitant drugs[31] add to the risk of DILI

Severity of DILI:

Animal model studies, have established the risk of susceptibility to DILI is more in Diabetics, although human studies are not available and

Diabetes has not yet been established as the cause of DILI.

"A preliminary report from the United States Drug-Induced Liver Injury Network (DILIN) showed that underlying diabetes mellitus was independently associated with the severity of DILI (odds ratio = 2 .69; 95% CI = 1 .14– 6 .45)"

"Competing Aetiologies and Unmasking DILI":

"Acute hepatitis C and Acute hepatitis E infections are known masquerades' of DILI" as written according to the recent American college of Gastro Enterology Guidelines for DILI by Naga N Chalasani. The incidence of Acute Hepatitis C occurring as a masquerade of DILI is about 1.3%, in a prospective study by DILI Network.

Antibodies to Hep C may be initially negative and HEV RNA[33] also may be negative in the acute illness of hepatitis. DILI ACG guidelines 2014, have recommended HCV RNA in suspected DILI. Another published report from the DILIN showed that "3 % of individuals with suspected DILI tested positive for anti-hepatitis E Ig M". Hence Hep E IgM is needed while evaluating DILI[34].

The other most important disease to be considered in all causes of DILI especially DILI is autoimmune hepatitis[36]. Autoimmune Hepatitis is an important Differential Diagnosis in DILI to be had in mind. Patients may be ordered an

autoimmune profile including Antinuclear Antibody, Anti Mitochondrial Antibody,[37]

Smooth Muscle Antibody and Liver Kidney Microsomal Antibody according to their clinical presentation, when Autoimmune Hepatitis may be possible confounder of DILI. Liver biopsy might be rarely needed when diagnostic dilemmas still persist. High level titres often help diagnosing AIH while low titres may be found in otherwise asymptomatic females.

Other aetiologies causing moderate to fulminant hepatitis are Wilson's disease, Herbal and Dietary Supplements. There no confirmatory tests yet for Herbal and Dietary supplements induced toxic Hepatitis. A work up for Wilsons may be needed based on age, and other clinical features of neurologic or renal involvement. In many cases the other system involvement may be subtle. A slit lamp examination for KF ring, S.Ceruloplasmin, 24 hour Urinary copper is needed in fulminant hepatitis. Treating Wilson's may prevent deaths in Fulminant Hepatic Failure. ATP B7 gene testing may be needed in difficult to diagnose cases, but with strong suspicion of WD.

A tender hepatomegaly in acute hepatitis should raise a suspicion of Acute Budd Chiarri syndrome.

Other "Competing aetiologies" in DILI with a cholestatic picture are PancreatoBiliary causes; individuals with suspected cholestatic DILI are

Pancreato-biliary in nature and can be extrahepatic or intrahepatic. Extrahepatic etiologies such as choledocholithiasis or malignancies (e.g., pancreatobiliary or lymphoma) can be readily identified with abdominal imaging. Other competing aetiologies like Granulomatous hepatitis,

Primary biliary cirrhosis, and Primary sclerosing cholangitis must also be considered. Last, but not the least, are other aetiologies like sepsis, total parenteral nutrition and congestive cardiac failure.

Biopsy may not be the "one and all" investigation as in text book descriptions. Each drug may have a unique pattern but also may mimic a disease pattern, like cholestatic or hepatocellular injury. Few drugs overlap features of auto immune hepatitis.

More than diagnosing a particular drug pattern, liver biopsy helps rule out other causes "i.e., findings beyond DILI".

Typically, cholestatic DILI takes longer to resolve than the hepatocellular DILI.

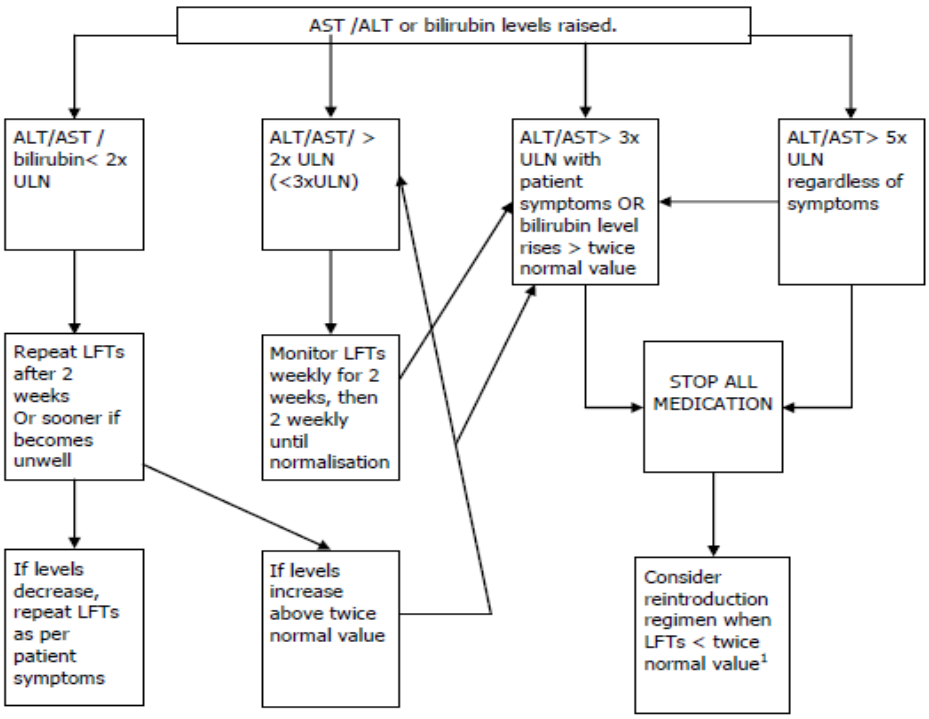
There are no prospective studies examining the yield of biopsy. However, considering a biopsy at 60 days for unresolved acute hepatocellular and 180 days for cholestatic DILI is reasonable.

MANAGEMENT OF DILI Identifying a drug, by its toxic potential is the most important step, in preventing DILI. "Compound selection and heightened vigilance in

developing specific agents to identify which chemical entities are entirely safe" with animal testing and other rigorous methods are the most important steps in drug development. The reasons include differences in metabolic pathways of drug handling and the current lack of suitable animal models that reproduce the human risk factors. But, except acetaminophen, most drugs are idiosyncratic and hence behave in an unpredictable way .One study has revealed the pre-determined genetic polymorphisms in major histocompatibility complex (MHC) Class I and II genes in the pathogenesis of IDILI.

In ATT induced severe DILI, discontinuation of PZ and INH, make improvement in 50% cases.

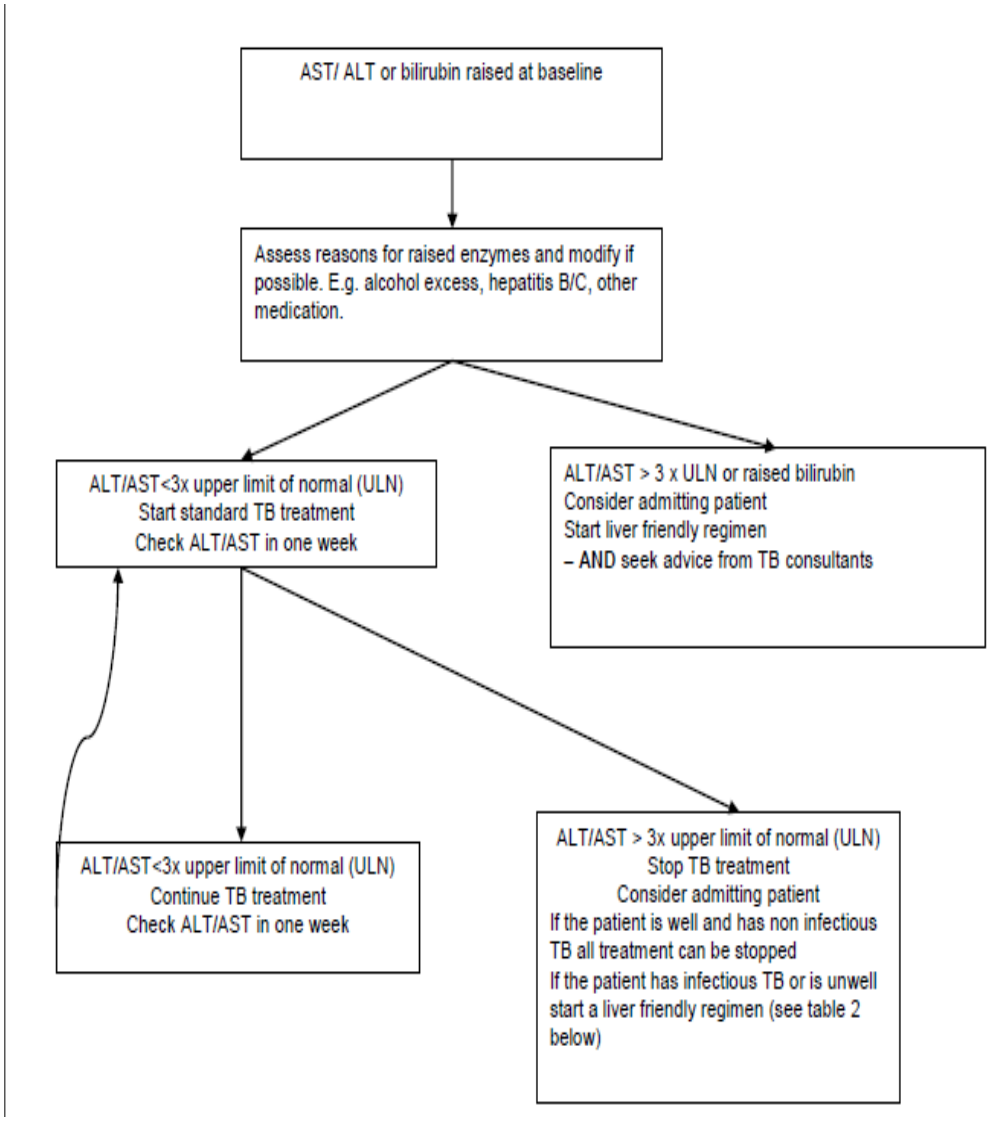
FLOW CHART 2. Liver enzymes become abnormal on treatment.



ATT and altered Baseline LFT values:

With the prevalence of alcoholism and diabetes more in developing countries, a significant proportion of patients have baseline altered LFT values. There are no clear cut evidence-based guidelines exist for the use prescribing ATT, in patients with cirrhosis. When no other alternatives are advisable, close monitoring is needed. Risk factors should also be evaluated. Patients. In alcoholics and cirrhosis, ATT is associated with hepatotoxicity in 10%. “Recommended ATT in Child class A cirrhosis is the same as a noncirrhotic population but strict follow up is required. In Child class B Pyrazinamide should be avoided”. Isoniazid and rifampicin may be avoided. Medications should be individualized depending upon various factors. Surveillance using liver enzymes though recommended routinely the use of INH can lead to acute liver failure despite the surveillance.

The cause for the underlying liver enzyme abnormality or the liver disease must be established before starting ATT.



Guidelines for management of ATT induced liver injury, Baljit Ahitan, Approved by ID & Resp Directorates ,July 2013. NHS foundation.

Day	Isoniazid dose	Rifampicin dose	Pyrazinamide dose	Check LFT
1M	100mg			
2T	200mg			X
3W	300mg			
4T	300mg	150mg		X
5F	300mg	150mg		
S	300mg	150mg		
S	300mg	150mg		
6M	300mg	300mg		X
7T	300mg	450mg / 600mg[1]		
8W	300mg	450mg / 600mg	250mg	X
9T	300mg	450mg / 600mg	500mg	
10F	300mg	450mg / 600mg	1g	X
S	300mg	450mg / 600mg	1g	
S	300mg	450mg / 600mg	1g	
11M	300mg	450mg / 600mg	1.5g/2g[2]	X
12T	300mg	450mg / 600mg	1.5g/2g	
13W	300mg	450mg / 600mg	1.5g/2g	X

1. <50Kg body weight = 450mg rifampicin, >50Kg body weight = 600mg rifamipcin
2. <50Kg body weight = 1.5g pyrazinamide, >50Kg body weight = 2g pyrazinamide
3. If the patient is well and non infectious start full dose ethambutol on day 13, if the patient is infectious or unwell start moxifloxacin 400mg daily, ethambutol 15mg/Kg daily (maximum 1.2g daily) and either amikacin or streptomycin 15mg/Kg daily (maximum 1g daily) immediately.
4. In patients who are well reintroduction can be managed as an outpatient in conjunction with the TB nursing team. In this case where it is not possible to check the LFT e.g. over a weekend doses should be left the same and not escalated or new medication introduced – see table – for inpatients omit days marked S (Saturday / Sunday)

Guidelines for management of ATT induced liver injury, Baljit Ahitan, Approved by ID & Resp Directorates ,July 2013. NHS foundation.

Hepatotoxicity requires withdrawal, modification and sequential reintroduction to achieve cure of tuberculosis In conclusion, acute liver failure is a serious complication of ATT. Monitoring of liver function parameters at regular intervals can help to prevent this condition .

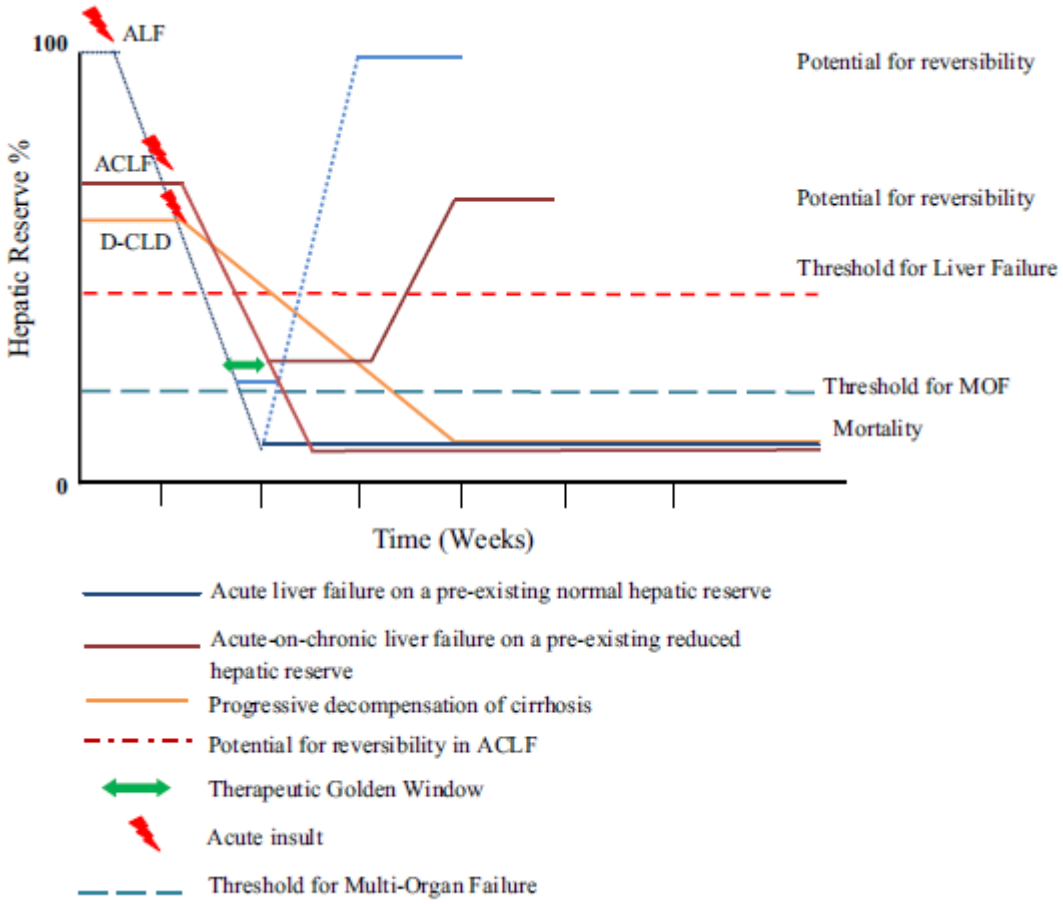
Medical management:

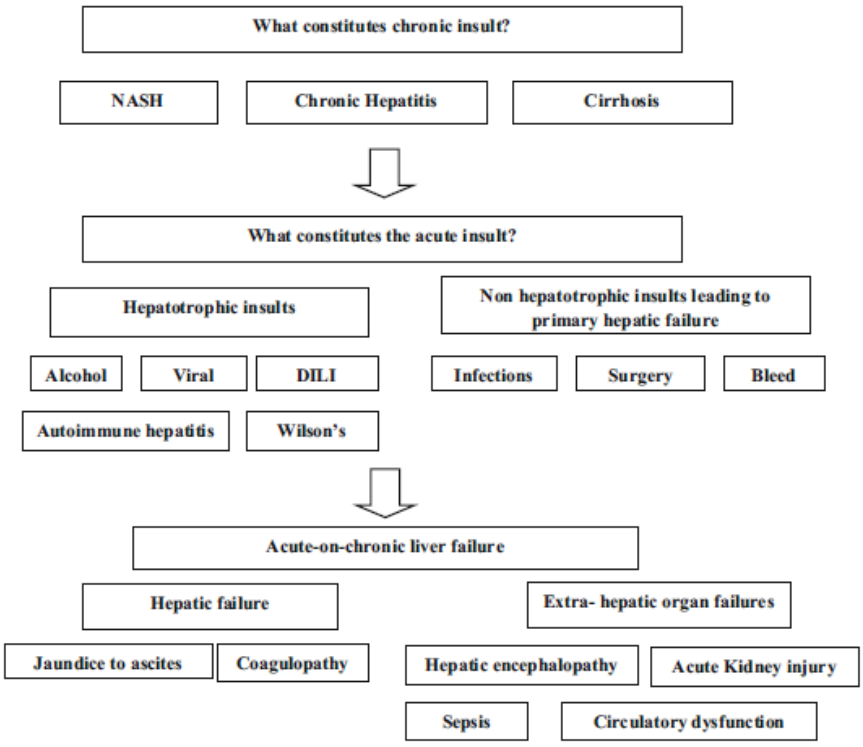
With varied ways of presentation, DILI is unpredictable, with a very short latency period and very short Jaundice Encephalopathy interval. A few carry a hyper acute course and high 7 day mortality. Some have fulminant course as, Fulminant liver failure. Cases with underlying chronic liver disease, have "golden therapeutic window" over worsening in few days and not weeks.(aclf-acute on chronic liver failure). Given below are the alternative drugs, given instead non Hepatotoxics

Drug omitted	Intensive phase	Continuation phase
RIF	INH, MOX, EMB, STR × 2 months*	INH, MOX, EMB × 16 months
INH	RIF, MOX, EMB × 2 months*	RIF, MOX, EMB × 10 months
PZA	RIF, INH, EMB × 9 months	

TB = tuberculosis; RIF = rifampicin; INH = isoniazid; MOX = moxifloxacin; EMB = ethambutol; STR = streptomycin; PZA = pyrazinamide.
*May consider PZA rechallenge and use during the intensive phase, particularly if DILI occurred early during the intensive phase.

Acute on chronic liver failure: Acute insult in a patient with low hepatic reserve by drugs, in underlying chronic liver disease , leading to acute on chronic failure, with a high short term mortality.





Intervening in the golden therapeutic window prevents

ALF mortality

Management of DILI WITH CONCOMITANT HAART:

1.Intensive phase of TB Treatment

Mild DILI: Clinically well with elevated ALT

<200 IU/l and total bilirubin <40 µmol/l

• Continue TB drugs in the event of confirmed or probable TB.

• Continue ART if the patient is receiving ART.

• Repeat ALT and bilirubin in one week.

• If ALT and bilirubin have improved or normalised, stop laboratory Monitoring.

• If ALT and bilirubin remain elevated but stable for 4 consecutive weeks, consider the other causes listed above, abdominal sonar and referral for further workup of liver dysfunction.

• If ALT and bilirubin increase further and meet the DILI definition, then move on to the relevant section below.

6.1.2 Moderate DILI: Clinically well and elevated ALT >200 IU/l irrespective of total bilirubin

• Discontinue the standard TB regimen.

• Start STR, moxifloxacin (MOX) and EMB

• Discontinue co-trimoxazole prophylaxis and other hepatotoxic drugs.

If the patient is on a PI-based regimen, stop all drugs at once. If the patient has been on a stable ART regimen for >6 months, consider continuing the therapy, as it is less likely that ART is the cause.

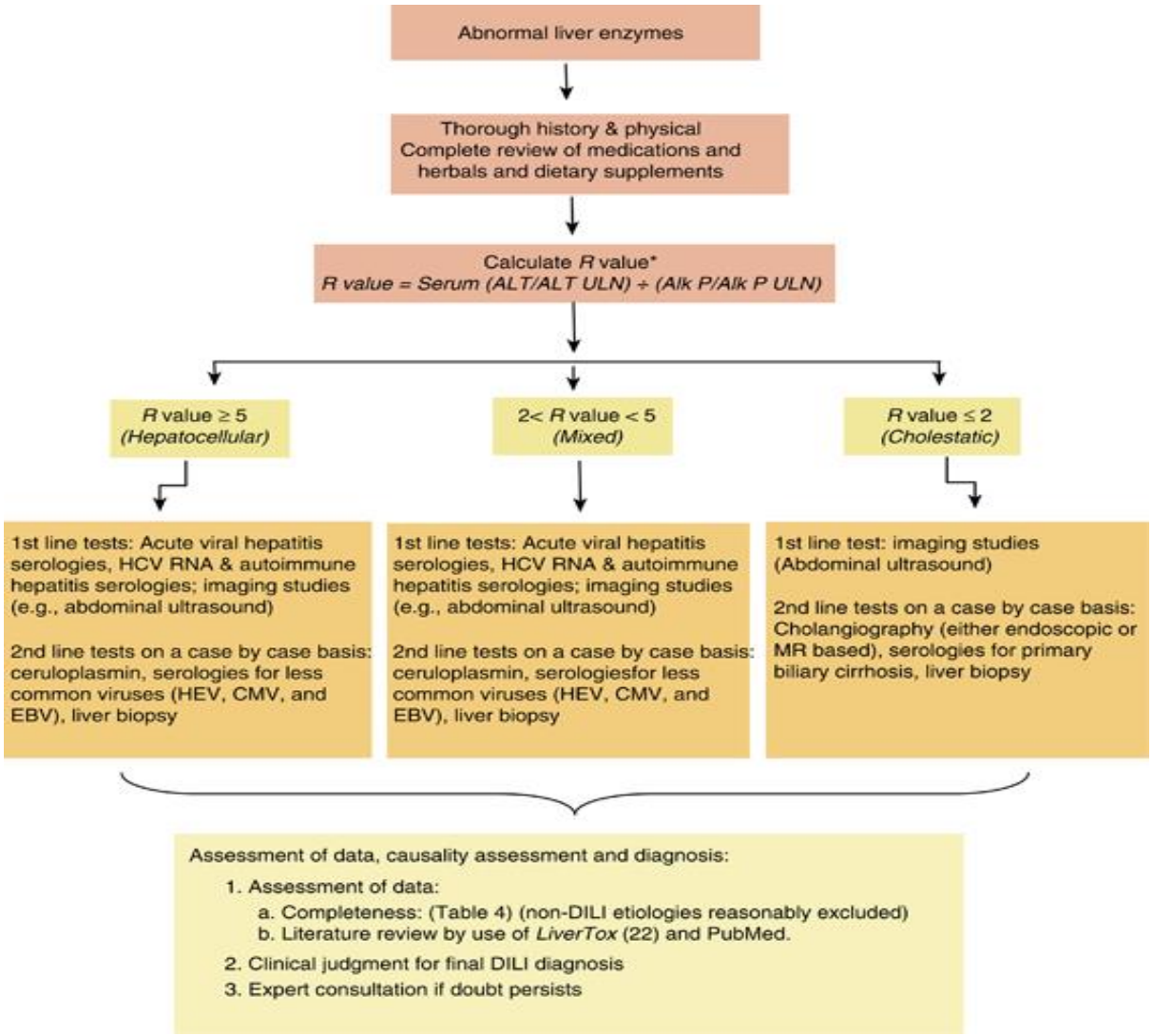
• Repeat ALT and bilirubin in 2 - 3 (inpatient) or 7 days (outpatient).

• When ALT is <100 IU/l and total bilirubin is normal, start the rechallenge.

• Day 1: RIF 450 or 600 mg daily, depending on weight.

• Day 3: Check ALT.

• Day 4 - 6: Add 300 mg INH daily.



American college of Gastro enterology Guidelines ,2014 for evaluating DILI.

AIM AND OBJECTIVES

AIM OF THE STUDY

Primary Aim:

1. To identify DILI even before onset of symptoms, which may prevent serious drug induced Acute Liver failure.

2. To identify the risk factors for DILI due to Anti Tubercular Treatment.

3. To formulate the way of monitoring for DILI in patients who are started ATT

Secondary:

1. To study the Prevalence of ATT DILI in patients with deranged baseline LFT values.

2. To study the Incidence of Hepatic adaptation and its significance in monitoring patients on ATT.

MATERIALS AND METHODS

MATERIALS AND METHODS

This is a prospective study from our Institute, Department of Digestive Health and Diseases. Government peripheral Hospital Anna Nagar., a tertiary care Centre, fed by a chest clinic and many DOTS (Directly Observed Short Term Chemotherapy) centers.

The study period is from January 2014 to January 2015.

THE STUDY GROUP:

The Study population is patients who are registered under dots and started on ATT, at chest clinic, Govt. Kilpauk medical college. They were patients diagnosed with TB, pulmonary or extra pulmonary. Also, they were not on previous anti-TB chemotherapy higher than two weeks .

All patients were followed till the end of their ATT COURSE and LFT was monitored.

EXCLUSION CRITERIA:

1. HIV POSITIVE AND ON HAART,
2. PREGNANT FEMALES,
3. POSTPARTUM 3 MONTHS,
4. PATIENTS ON CANCER CHEMOTHERAPY,
5. AGE LESS THAN 18 YEARS
6. MORIBOUND STATE

LFT and clinical monitoring in patients who are selected under the inclusion criteria in the study were followed up till the end of their therapy by serial LFTs. Patients were divided into two groups according to their baseline LFT as follows.,

1. GROUP 1 –PATIENTS WITH NORMAL BASELINE LFT VALUES

2. GROUP 2- PATIENTS WITH BASELINE ALTERED LFT VALUES

LFT was done baseline and every week for the first month, then fortnightly for the next 2 months and then monthly until the end of therapy. Patients with clinical and lab evidence of DILI were evaluated for risk factors.

All results were analysed for both groups. Patients with referred with ATT DILI to this tertiary care were analyzed for Risk factors and the Demographic profile of DILI.

Finally the incidence of DILI in both groups was analysed.

The incidence of hepatic adaptation was analysed

Also, the mortality rate in patients taking ATT and significance of risk factors in, mortality of DILI was analysed.

An ATT DILI criterion is taken according to American Thoracic Society Guidelines-2006, when any one of these three criteria was met ATT was stopped.

1. S.Transaminases >3 ULN with Symptoms

2. S.Transaminases >5ULN without Symptoms

3. Any increase in Bilirubin

DILI Grading is according to WHO criteria.

Grading (WHO)**Grade**	**ALT**
1	≤ 2.5x ULN
2	2.6 –5x ULN
3	5 –10x ULN
4	> 10x ULN

Written informed consent was obtained from all participating subjects in regional language. Privacy was insured. Statistical analysis was done by statistical software SPSS version 22.

The outcome measures analysed were as follows:

Outcome measures:

1. Latency

2. Identification of risk factors for DILI

3. Role of comorbid illness in DILI

4. Masquerades' of DILI

5. Requirement of hospitalization;

6. Severity of liver dysfunction;

7. Outcome of DILI was taken as,

1. MILD

2. SEVERE

3. ACUTE LIVER FAILURE

4. ACUTE ON CHRONIC LIVER FAILURE

5. PERSISTANT ENZYME ELEVATION

6. RECOVERY

7. DEATH

8. IMPACT OF ANTI-TB TREATMENT ON OUTCOME OF DISEASE.

Patients who developed Liver Injury are assessed according to Roussel Uclaf Causality Assessment Method (RUCAM).

The **7 major criteria** of RUCAM scale are

(1) Time to onset,

(2) Course of the reaction,

(3) Risk factors for the reaction,

(4) Assessing the role of concomitant therapies,

(5) Screening for non-drug-related causes,

(6) Weighing the information known about the DILI in question,

(7) Confirmation of the reaction by positive rechallenge or in vitro assays

Modification/Re-challenge of ATT is according to guidelines of American **Thoracic Society, 2006**

STATISTICAL ANALYSIS

Data were analysed with SPSS version 1.5.

Descriptive statistics including mean, median, p value, and frequencies were analysed.

Fisher value was analysed.

Odds ratio and risk benefit ratio was also analysed.

Values were considered significant if $p<0.05$ (95%CI)

Incidence of DILI in two groups and recovery or mortality were analysed.

Frequency distribution of hepatic adaptation was analysed in both groups.

RESULTS

RESULTS

A total number of 145 patients who were on ATT were enrolled for study. Patient with normal baseline LFT values were taken as Group 1. Patients with Altered baseline LFT were taken as Group 2.

1 patient Defaulted in group 2.

n=145	GROUP 1 Normal Baseline LFT	GROUP 2 Altered baseline LFT
No.of cases	116	29
Males	62	28
Females	54	1
Diabetics	14	5
Age >50 years	33	12

1. Study population:

Table 1

n=145	GROUP 1 Normal Baseline LFT	GROUP 2 Altered baseline LFT
No. of cases	116	29

Group 1 patients were started on conventional DOTS ATT drugs, according to Category of TB.

Patients in Group 2 were started on ATT according to their AST, ALT and Bilirubin levels. In cases of Decompensated Chronic Liver Disease, one or two hepatotoxic drugs were prescribed according to prognostic scoring Child Turcotte Pugh classification as single, or two hepatotoxic drugs DOTS ATT. Other parameters like Albumin, MELD, Prothrombin time, INR were also taken into account.

2. Gender distribution of study population:

Group 1 had 116 patients, of whom 54 were females and 62 were males.

Among Group 2, with 29 patients there were 28 males and only one female.

3. Age distribution of cases among group 1 & 2:

Majority of patients were <50 years of age in Group 1, whereas almost equal in Group 2.

78% were <50years in Group 1 and 58.6% were <50 years in Group2.

TABLE 2: AGE DISTRIBUTION AMONG STUDY GROUPS:

Age group	Group 1	Group 2
<50 years	83 (71%)	17 (58.6%)
≥50 years	33 (29%)	12 (41.3%)

4. Concomitant drugs: In Group 1 , all diabetics were on Oral Hypoglycaemic Agents and one patient , a known case of crippling Rheumatoid arthritis was on 4 years of Methotrexate, with LFT monitoring. The partient on Methotrexate had normal baseline LFT.

In Group 2, all patients with Decompensated Chronic Liver disease were on diuretics and propranolol, Diabetics were on insulin. One Group 2 one patient was on long term chlorpromazine >20 years , and he stopped , the drug for 7 months when he was referred for Ascites.

	OHAs	INSULIN	DIURETICS	PROPANOLOL	OTHERS
Group 1	14	0	0	0	Methotrexate
Group 2	0	5	15	15	1- Chlorpromazine

5. Causes of altered baseline LFT values- Group 2

Alcohol	CHB	? Drug related	NASH
24	2	1	2
82%	6.8%	3.4%	6.%

6. Serum albumin levels in group 2 : Since all our patients were in CTP B, the Serum Albumin was >2.5 gm/dl in 82% cases.

S.Albumin <2.5	5cases	18%
S.Albumin >2.5	24cases	82%

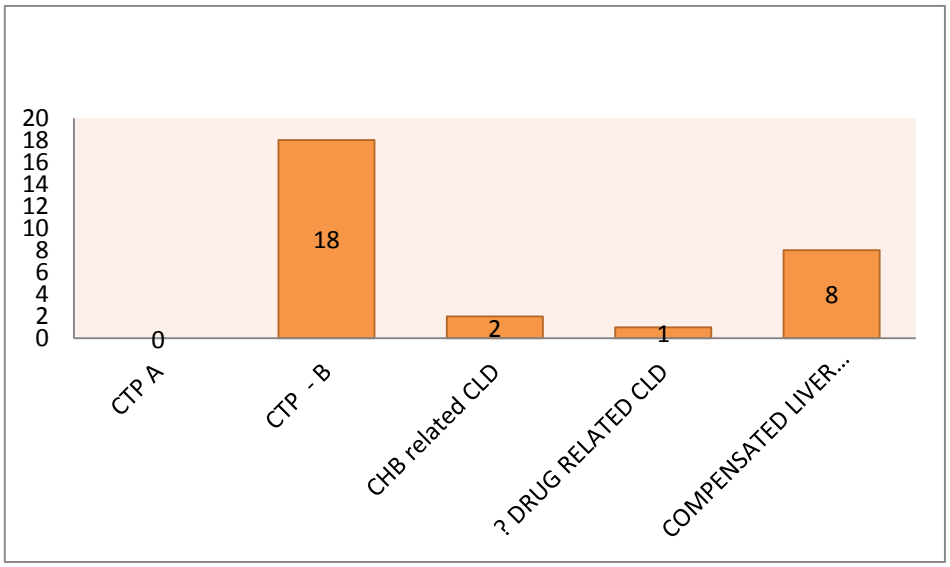
7.PROFILE OF CASES -ALTERED BASELINE LFT VALUES, GROUP 2

Patients had various causes and stages of liver disease. They were also analysed.

N= cases

CTP A DCLD	0 cases	0%
CTP - B DCLD	18	62.3%
CHB related CLD	2	6.8
? DRUG RELATED CLD	1	3.4
COMPENSATED LIVER DISEASE	8	27.5

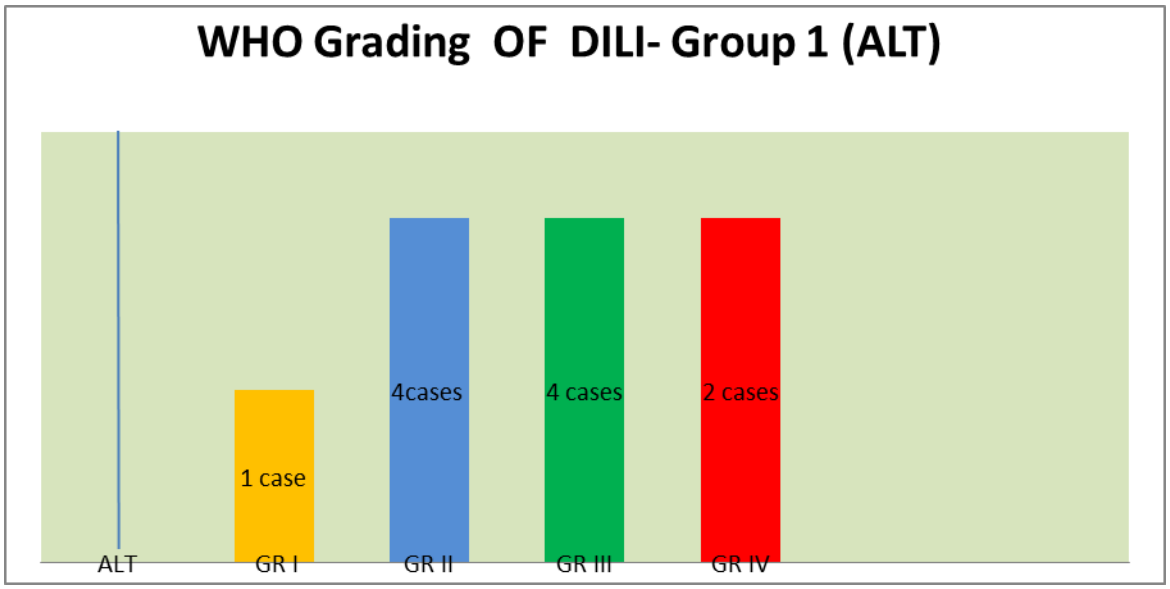
In group 2, a total of 18 patients were in CTP Class B Decompensated Chronic Liver Disease irrespective of etiology. 2 patients had compensated chronic liver disease due to Chronic Hepatitis B infection. 1 patient had chlorpromazine related altered LFT values ? Chronic cholestatic liver injury.



WHO GRADING OF DILI :

DILI patients were classified according to WHO criteria for grading of DILI according to ALT levels.

Grading (WHO)**Grade**	**ALT**
1	≤ 2.5x ULN
2	2.6 –5x ULN
3	5 –10x ULN
4	> 10x ULN



Grade 1	Grade 2	Grade 3	Grade 4
ALT<3ULN	ALT3-5ULN	5-10 ULN	>10ULN
1 case	4cases	4 cases	2cases

Who grading DILI

1. Incidence of DILI:

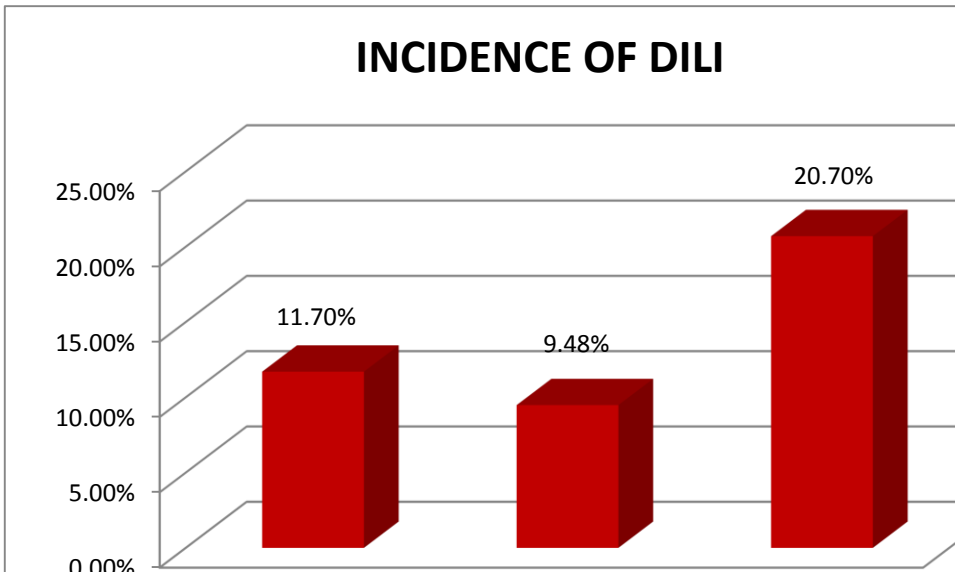
N=cases	GROUP 1	GROUP 2
Total	116	29
DILI	11	6

The incidence of Drug induced liver injury in Group 1 & 2 Both is 11.7%

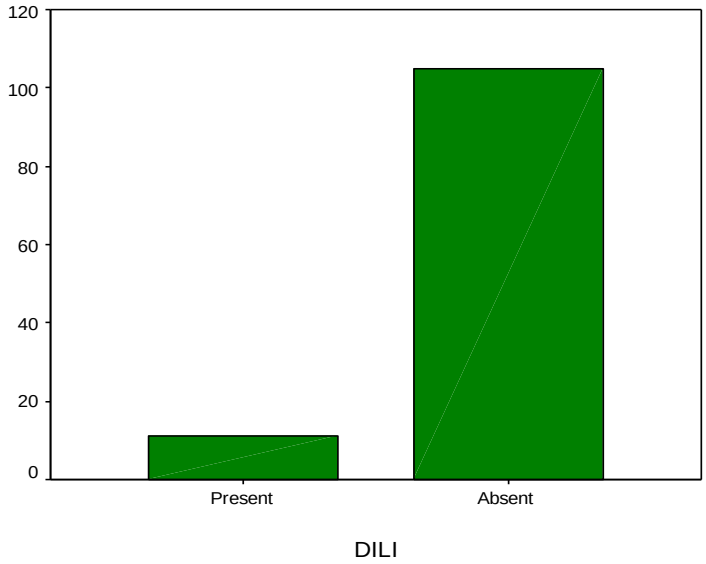
Incidence of DILI in Group 1 is 9.48%

Incidence of DILI in Group 2 is 20.7%

Figure-1:



2. Incidence of DILI Group1



Incidence of DILI among Group 1, has a statistical significance with p <0.001

Group 1(n=116)

Non DILI	DILI	P value
105	11	0.001
90.5%	9.4%	

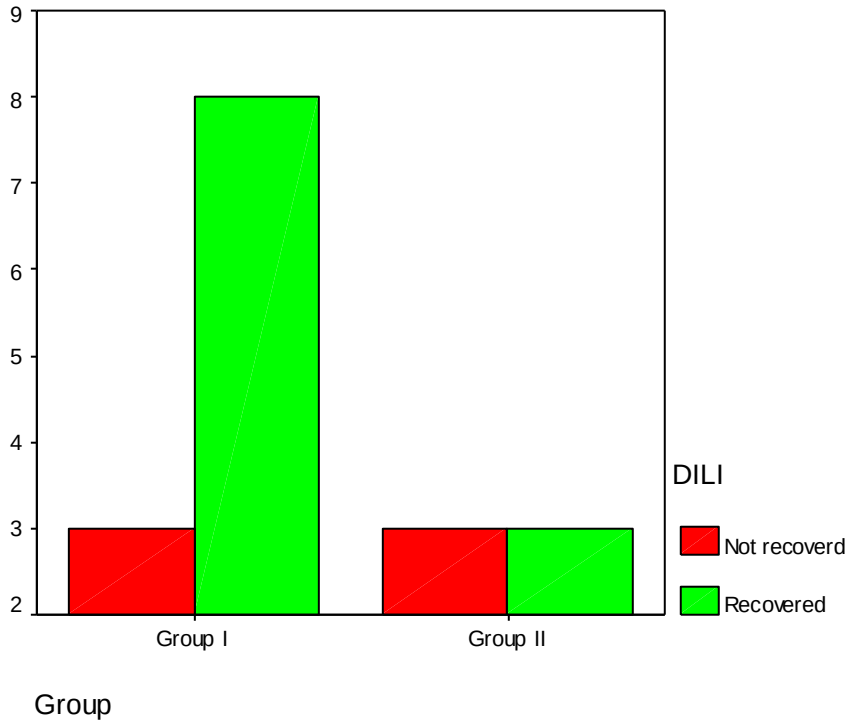
Patients with normal baseline LFT had stastically significant incidence of DILI of 9.4%(p<0.001)

3. Mortality Rate:

a.Mortality due to ATT, among the total study population is 4.1%.(n=145)

Mortality due to ATT among Group 1 is 2.5%.

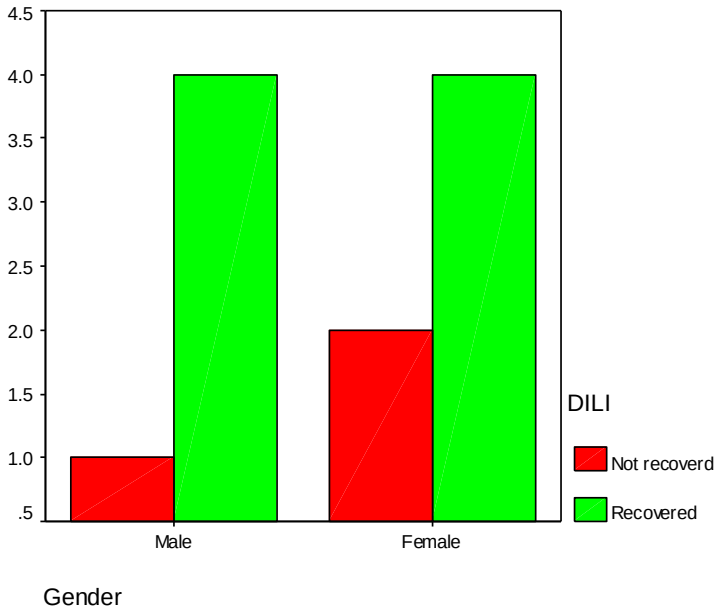
Mortality due to ATT in Group 2 is 10.3%



The cause specific mortality rate for Group 1 patients with DILI-27.2%

The cause specific mortality rate fort Group 2 patients with DILI- 50%

4. Mortality in Group 1

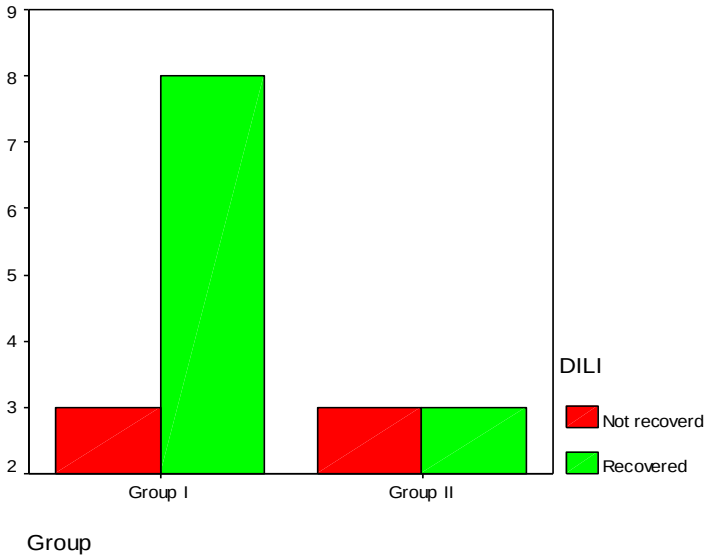


a. Mortality rate between male and female in Group 1 and 2 was not stastically significant,

b. But females had a slightly higher incidence of DILI deaths.

Total DILI	n=11	Died	P value
Male	5	1	0.621
Female	6	2	

5. Mortality rate in Group 2:



Mortality among Group 2 (n=25)

The mortality rate in Patients on ATT in Group 2 is 10.3%

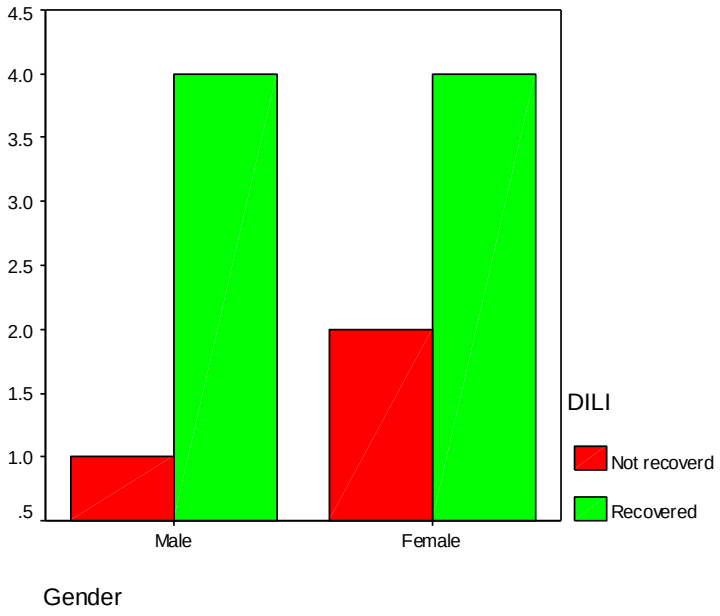
There is stastical significance between patients recovered and not recovered in Group 2. (p<0.001)

DILI	Recovered	Died	p
Present	3	3	0.001
Absent	23	0	

6. Mortality in females - Group 1

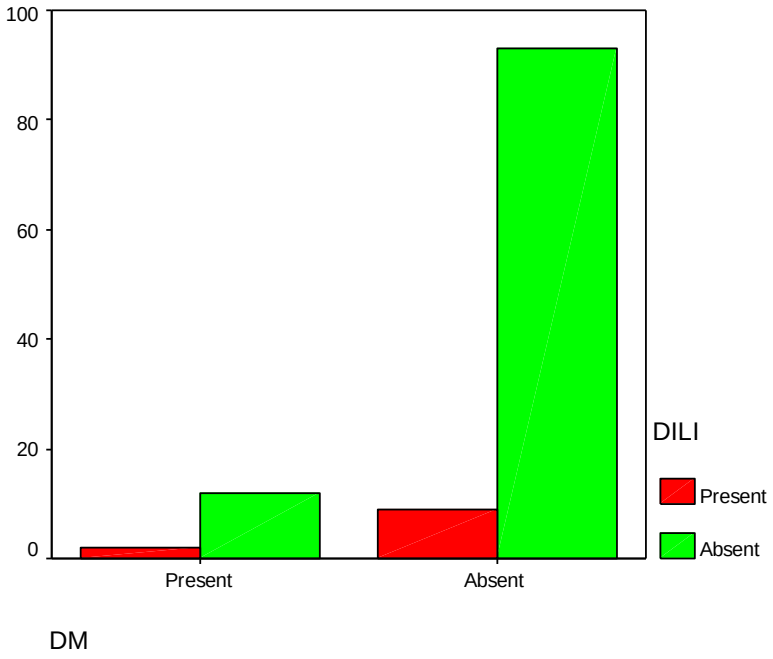
Females have higher Odds for DILI deaths compared to males.

n=11	Total DILI	Recovered	Died	Odds Ratio
Male	5	4	1	M/F 0.5
Female	6	4	2	95%CI (0.31-7.94)

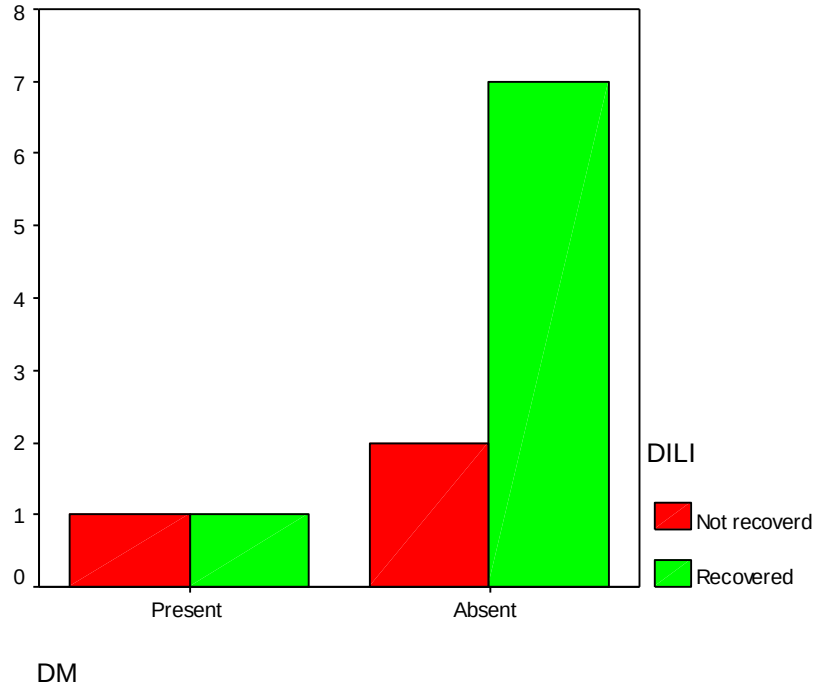


2.Since there were no females died of DILI in Group 2 , p value and odds ratio was not applicable.

7. Mortality in Diabetics:



DILI	DIABETIC	NON DIABETIC	P VALUE
Present	2	12	0.425
Absent	9	93	



Mortality in Diabetics- Group 1

	Diabetics	Non diabetics	Odds Ratio
DILI Recovered	1	2	3.5
DILI died	1	7	95% CI (0.145 -84.4)

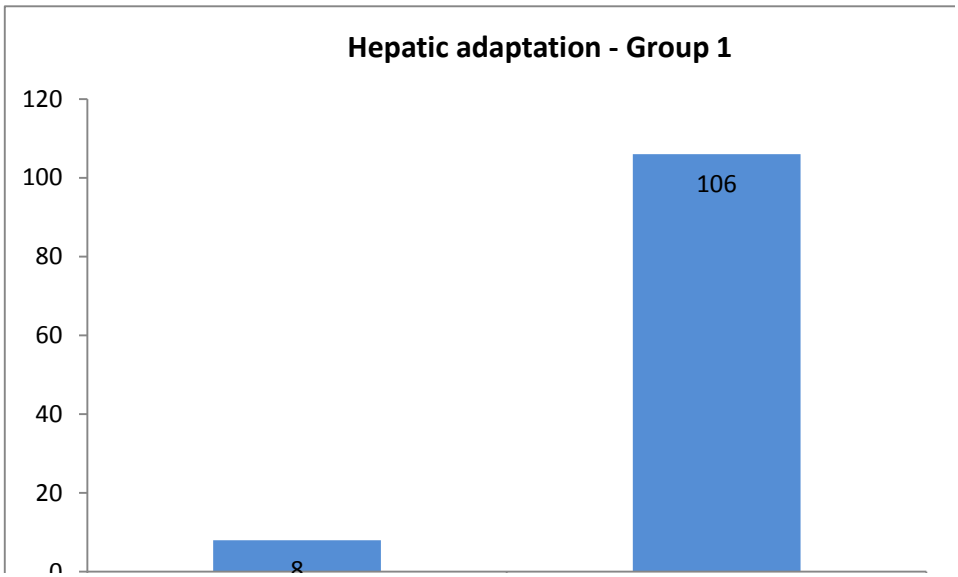
Diabetics have higher Odds in DILI related mortality than Non Diabetics in Group 1.

2. Since there were no diabetics, who died in Group 2, p value and Odds ratio was not applicable.

8. Hepatic adaptation in Group 1 patients:

Hepatic adaptation in Group 1 was 6.9%.

8/116 patients had hepatic adaptation.



Hepatic Adaptation in Group 2:

Hepatic adaptation in Group 2 was seen among 14 out of 29 patients. The incidence of hepatic adaptation was 48.3% in Group2

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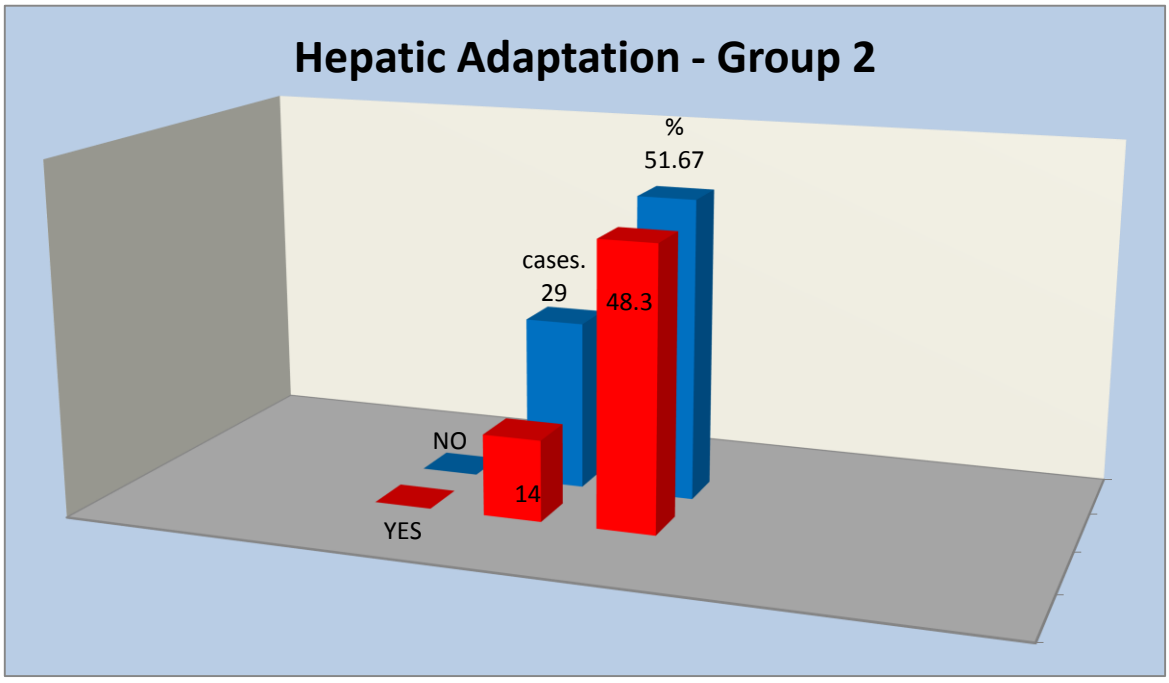
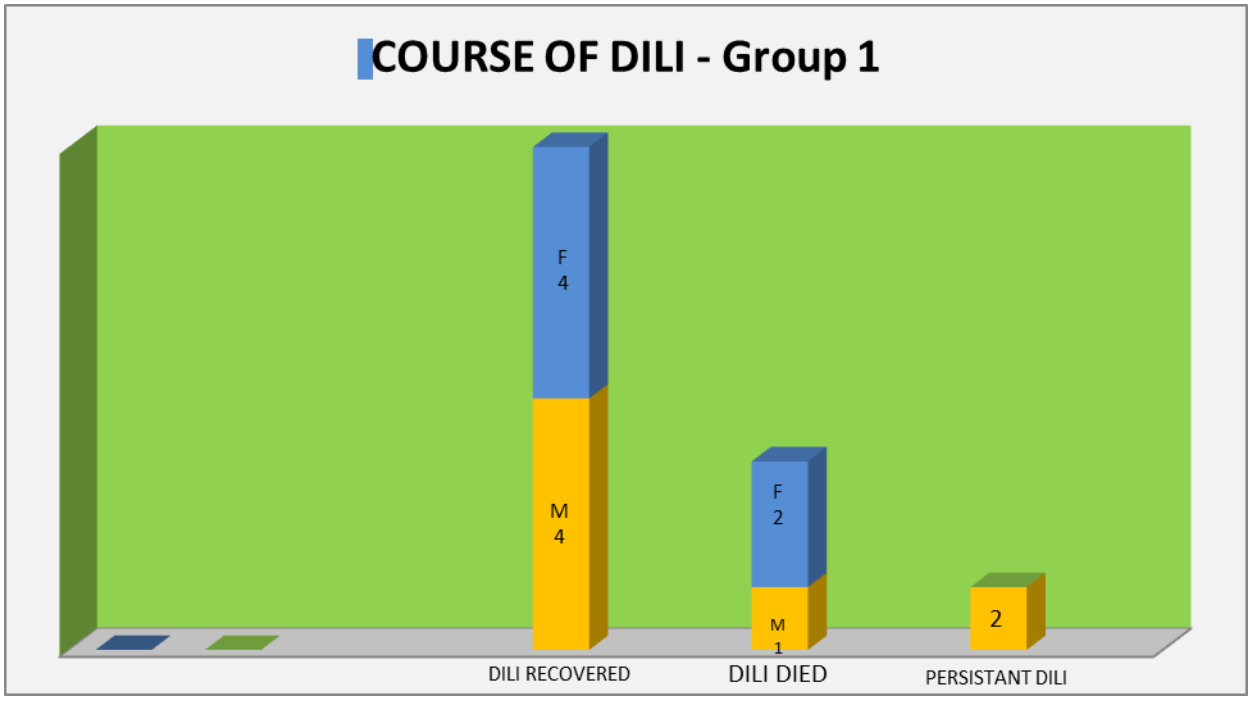


9. Outcome of DILI -Group 1

MILD DILI	SEVERE DILI	DIALF	DIACLF	PERSISTANT DILI
1	4	1	3	2
All recovered	All recovered	1 died	2died. 1 recovered	Recovered



10. Types of DILI: Group 1

TYPE OF DILI	NUMBERS	REMARKS
CONVENTIONAL ATT DILI	4 (3M+1F)	2 DIABETICS (ALCOHOLIC)
UNMASKING DILI	2F	1 - LUPOID HEPATITIS + WILSONS 1- ?AIH
FULMINANT HEP E MASQUERADING	1F	1 DIABETIC, DIED
FULMINANT HEP A MASQUERADING	1M	ALCOHOL AND NSAIDS -CONFOUNDING FACTORS
MTX CUMULATION INDUCED ATT HEPATITIS	1F	4YRS OF MTX , BUT NORMAL BASAL LFT.
PERSISITING DILI	2M	?ALCOHOL

11. Outcome of DILI -Group 2:

MILD DILI	ATT INDUCED DECOMPENSATION	ALCOHOL AND HBV ACLF	REGIME CHANGE FOR TB	CHRONIC CPMZ INDUCED ATT ACLF
0	1	3	1	1
		2 DIED		1-DIED

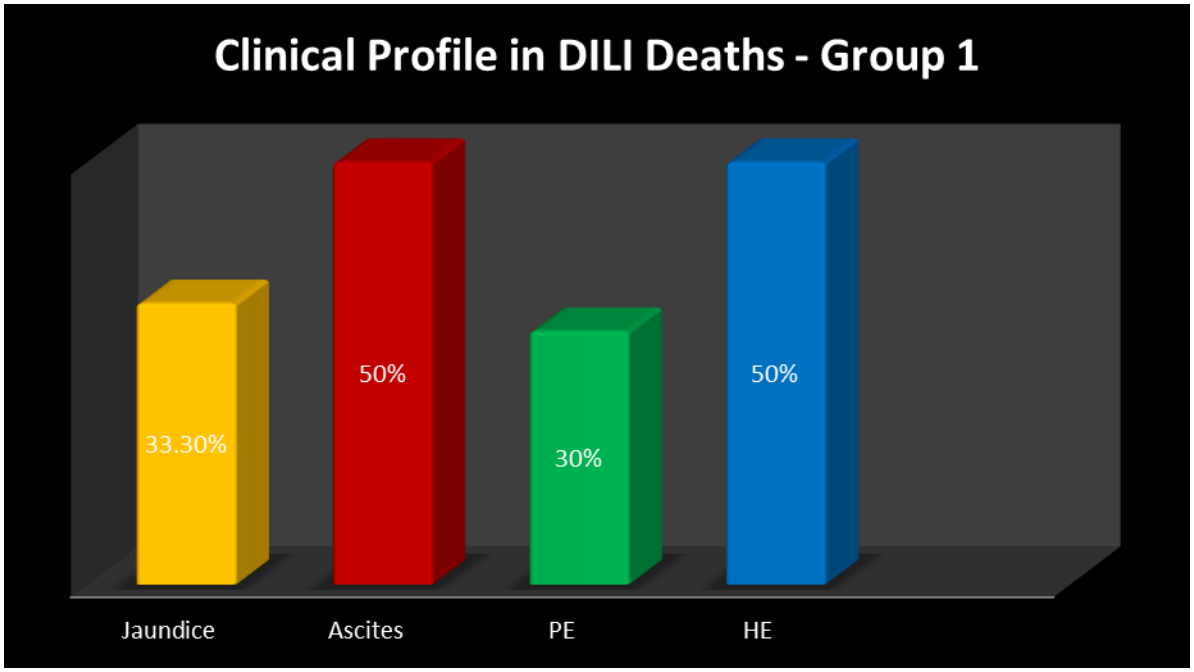
12.Persistent DILI

% of Persistent DILI was 18.1%. According to this study 2 patients had persistent high LFT values after ATT, in spite of their baseline LFT being normal. 2 out 11 patients had persistent DILI.

13.CLINICAL PROFILE IN DEATHS DUE TO DILI IN GROUP 1:

33% presenting with jaundice died

50% presenting with ascites died



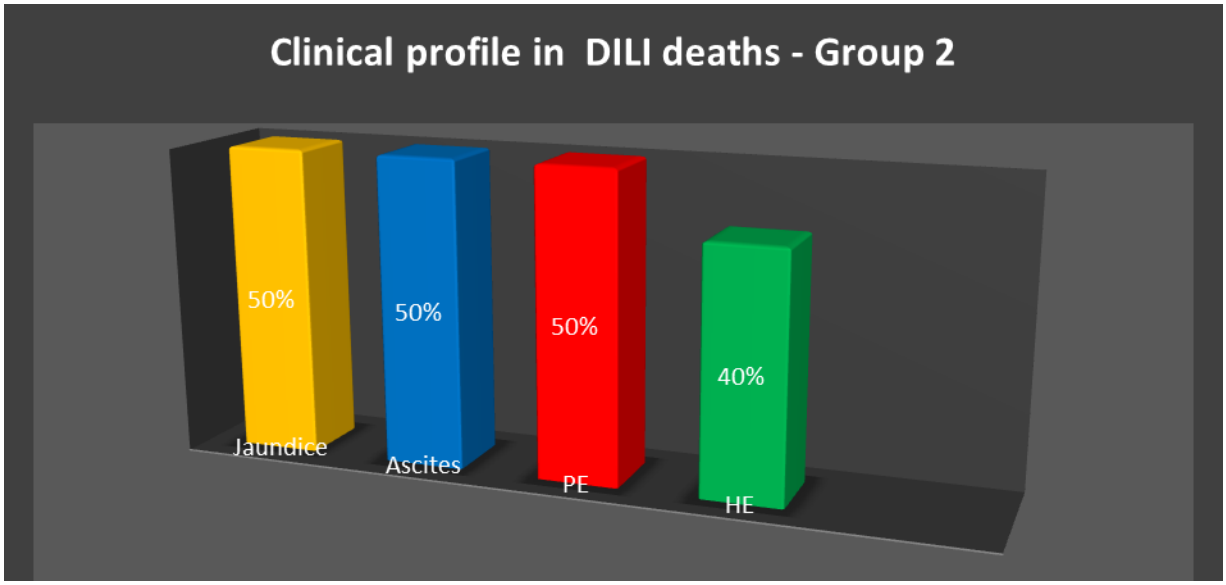
14.Group 2:

50% patients presenting with jaundice died due to DILI

50% patients presenting with ascites died.

50% patients with pedal edema died

40% patients presenting with encephalopathy died.



15.AGE WISE DISTRIBUTION OF DILI in Group 2:

Age Group distribution of DILI:

Age group	DILI recovered	DILI not recovered	Odds ratio	95% CI
<50 years	4	3	Not possible	
≥50 years	3	0		

There was no stastical significance between the two age groups <50 years and >50 years among patients with DILI .

ESTABLISHING DIAGNOSIS OF TB IN STUDY GROUPS:

Except for 2 cases who were started on Empirical ATT all cases were adequately proven of tuberculosis and started on ATT from our Chest clinic and DOTS centre. The other Cases DILI referred to us were also adequately proven to diagnose tuberculosis.

In the demographic profile, among Group 1 patients , 3 patients had TB ascites proven by lab analysis. All of them had normal baseline LFT and were ruled out of underlying CLD with the protocol investigations.

In group 2, patients ie, with altered baseline LFT , 4 patients had mixed ascites and 4 patients had TB ascites all of which were adequately proven .

TO CONCLUDE , among group 1, 17 had hepatic adaptation, while patients still continued same regime. Five had Enzymes > 5ULN, at third week. They were changed over to Non DOTS Non hepatotoxic SEOregime (Streptomycin, Etambutol, Ofloxacin) . Diabetes , Female gender was a significant comorbid factor . One Chronic HBV infected individual with low virology and normal baseline LFT had ,ALT>3, continued same with enzymes <3ULN till completion.3 had ACLF (One diabetic) & of them 1 died.

DISCUSSION

DISCUSSION

The incidence of overall DILI in total cases is 11.2%. The incidence of DILI in group 1 is 9.4%. The incidence of DILI in Group 2 is 20.6%.This shows the higher incidence of DILI in patients with underlying liver diseases.

This incidence at our institute is in par with other studies like, Andrade AJ et al[38],

According to Harshad Devar Bhavi[39], many of the ATT DILI is under reported and the overall incidence in the population is unknown.

Kapanoff, D.E, et al[40] have studied on the Incidence of INH related Hepatitis and and found incidence of ATT DILI ranging from 5 -33%,

According to American Thoracic Society Guidelines the overall incidence of ATT DILI is 5 to 33%.

The higher incidence of ATT induced hepatotoxicity is in par with Rakesh Tandon's article where he says there is an increased incidence of DILI and lower completion rates of ATT in Patients with liver disease. He refers "Westphal, et al –and and "Keiding et al[41].

This is also in par with Deepak Amrapurkar's "Prescribing medications in patients with CLD".

According to DILI by Naga Chalasani[42], –women have a slightly higher risk of liver injury due to "certain medications" and not "all cause DILI". This study has also come out with similar results in Group 1 , where the incidence is 55.4% in females, while it is 44.6% in males. This is in par with Kaplowitz.n, where it is stated that females with high CD4 count have Nevirapine toxicity.

A preliminary report from DILI Network (DILIN), states that diabetics have increased risk of all cause DILI and it was independently associated with severity of DILI. Diabetics have more severe disease outcome in DILI with an ODDS RATIO of2.69; CI=1.14-6.45.

The ODDS RATIO in this present study is 3.5; (95%CI 0145-84.4).

Naga Chalasani, has brought out this poor outcome in diabetics, in The recent American college of Gastro Enterology Guidelines ,Idiosyncratic DILI, 2014.

The ODDS ratio in Group 2 was not applicable since there were no Diabetic deaths.

The Mortality rates in various studies have shown higher rates in TB DILI, from

More serious liver disease like ALF ranges from 1-3% is as quoted by F Smink[43] Risk factors of acute hepatic failure during ATT, Netherlands Journal of Medicine, in the study done by "Girling DJ. The rate of mortality in this study is 27.2% in Group 1 and 50% in Group 2. This shows almost twice the mortality in patients with altered baseline LFT or underlying liver disease s normal individuals.

As established in various studies Females had a higher mortality rate and severity with the onset of DILI. The mortality rate in females in group 1 is twice high as in males.

The ODDS ratio of mortality in DILI between Male and Female deaths is 0.5; (95%CI 0.81-7.94).

The studies by Ormerod et al [49] and Shakaya R, et al[50], are in par with these results.

"Kumar & Shalimar et al[51], reported ATT as the leading cause of Drug induced Acute Liver failure with a mortality rate of 67% in ATT ALF. This holds true in our study where the one patient with DIALF died (50% mortality in DIALF).

Harshad Devar Bhavi[52] had found that ATT ALF is also the common cause of DIALF in South India, with concordance of 97% mortality.

S.K.Sarin, has stated that “Hepatotoxic Drugs and complementary and alternative medicines are an important cause of ACLF in Asia Pacific Region.,as proved by studies like Duseja[56], Y K Chawla, R K Dhiman,[56] - Non hepatic insults are common in ACLF.

ACLF has high 28 day mortality, of 50- 90%, as in various studies, one by Jalan[57] et al, and the other by S K Sarin, et al.

The mortality rate in 28 day mortality in ACLF in this study was 66.4% in Group 1, and 33.4%in Group 2.The close monitoring and effective ways of follow up of their underlying liver disease, watch for adverse reactions on prescribing special drugs and better compliance of drugs prevented DIACLF mortality in Group 2.

Hepatic Adaptation was 6.9% in Group 1 and 48.3% in Group 2.This shows the adequate hepatic reserve in patients with underlying liver disease, and the capacity to detoxify drugs.

Hepatic adaptation had no predictive value in DILI in this study and most DILI were unpredictable, idiosyncratic reactions.

The incidence of persistent DILI was 28%, who had persistent mild enzyme raise <3ULN, after the 6 months course, on follow up of 6 months.

Alcohol was found to be the most important confounding factor in persistant DILI.

Concomitant Hepatotoxic drugs play an important role in prescribing ATT .The long term effects ,cumulative or dose dependant ,may be silent , causing hyperacute or acute course of decompensation and short latency period for HE and death on addition of an acute insult. One patient was on 4 years Methotrexate for Rheumatoid arthritis and another was on chlorpromazine, both had a FHF and succumbed in

<1 week of ATT. “Progression to chronicity is seen 5-10% of DILI and more in cholestsatic /mixed pattern injury , in a study done by Andrae RJ et al. The cumulative hepatoxicity of methotrexate , may silent with periportal fibrosis and Macrovesicular steatosis and may be exacerbated by alcohol or ATT, to severe hepatocellular necrosis.This is described by Langman G, NASH in MTX liver injury .

Prolonged Cholestastic hepatitis may persist in Chlorpromazine ,with severe ductopenia, the vanishing bile duct syndrome which may lead to biliary

cirrhosis ,like Primary biliary cirrhosis.

CONCLUSION

CONCLUSION

1. There is increased incidence of DILI in patients with

   Altered Baseline LFT values.

2. Females with Normal baseline LFT have higher Odds for DILI deaths than

   Males.

3. Diabetics with Normal baseline LFT, have higher Odds for DILI deaths than

   Non Diabetics

4. The patients with altered baseline LFT values have higher mortality with ATT

5. Periodic monitoring of LFT prevents mortality in DILI.

BIBLIOGRAPHY

BIBLIOGRAPHY

1.R Kazuto Tajiri, Yukihiro Shimizu World J Gastroenterol November 28, 2008 Volume 14 Number 44 *World J Gastroenterol* 2008 November 28; 14(44): 6774-6785

2.Global TB reports 2013, by WHO

3.Indian J Med Res 132, July 2010, pp 81-86Evaluation of risk factors for anti-tuberculosis treatment induced hepatotoxicity

4. Kumar R, Shalimar Bhatia V, Sreenivas V, Gupto SD, Panda SK, et al. Antitubercular therapy-induced acute liver failure: magnitude, profile, prognosis and predictors of outcome. HEPATOLOGY 2010;51: 1665-1674.

5. Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A, et al. Fulminant hepatitis in a tropical population: clinical course, cause and early predictors of outcome.HEPATOLOGY 1996;23:1448-1455.

6. Khuroo MS. Acute liver failure in India. HEPATOLOGY 1997;26:244-246.

7.Kaplowitz N.Drug-Induced Liver Injury: Introduction and Overview in Drug-Induced Liver Disease.Kaplowitz N,DeLeve L, eds. New York:Elsevier; 2013, Chapter 1, p 3-14.

8. Hughes JD, Blagg J, Price DA, Bailey S, Decrescenzo GA, Devraj RV, et al. Physiochemical drug properties associated with in vivo toxicological outcomes. Bioorg Med Chem Lett 2008;18:4872-4875.

9.Porceddu M, Buron N, Roussel C, Labbe G, Fromenty B, Borgne_Sanchez A. Prediction of liver injury induced by chemicals in human with a multiparametric assay on isolated mouse liver mitochondria. Toxicol Sci 2012;129:332-345.

10. Avoiding Idiosyncratic DILI: Two Is Better Than One HEPATOLOGY, Vol. 58, No. 1, 2013 KAPLOWITZ

11 Han D, Hanawa N, Saberi B, Kaplowitz N. Hydrogen peroxide and redox modulation sensitize primary mouse hepatocytes to TNF-induced apoptosis. Free Radic Biol Med 2006;41:627-639.

12. Lou H, Kaplowitz N. Glutathione depletion down-regulates TNF*a*induced

NF-kB activity via IKK-dependent and independent mechanisms.
J Biol Chem 2007;282:29470-2948

13.(Wen *etal.,* 2002; Desta *et al.,* 2001

14.Wen X., Wang J.S., Neuvonen P.J., Backman J.T. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes. Eur J Clin Pharmacol. 2002; 57: 799–804.

15.Padma *et al.,* 1998; Tostmann *et al.,*2008)

16. Dickinson DS, Bailey WC, Hirschowitz BI, Soong SJ, Eidus L, Hodgkin MM. Risk factors for isoniazid (INH)-induced liver dysfunction. *J Clin Gastroenterol* 1981;3:271–279.

17.Yamamoto T, Moriwaki Y, Suda M, Nasako Y, Takahashi S, Hiroishi K, Nakano T, Hada T, Higashino K. Effect of BOF-4272 on the oxidation of allopurinol and pyrazinamide in vivo: is xanthine dehydrogenase or aldehyde oxidase more important in oxidizing both allopurinol and pyrazinamide? *Biochem Pharmacol* 1993;46:2277–

2284.

18. Centers for Disease Control and Prevention, American Thoracic Society. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations: United States, 2001. *MMWR Morb Mortal Wkly Rep* 2001;50:733–735.

19.Harshad Devar Bhavi, AntiTuberculous DILI., Current Perspective., Tropical Gastro Enterology., 2011.

20.Knobel B, Buyanowsky G, Dan M, Zaidel L. Pyrazinamide-induced granulomatous hepatitis. *J Clin Gastroenterol* 1997;24:264–266., Gronhagen-Riska C., Hellstrom P.E., Froseth B.

21.Predisposing factors in hepatitis induced by isoniazid-rifampicin treatment of tuberculosis. Am Rev Respir Dis 1978; 118:461-66

22.Grosset J, Leventis S. Adverse effects of rifampin. Rev Infect Dis 1983; 5:S440-S50.

23.Shakya R, Rao B.S., Shrestha B. Incidence of hepatotoxicity due to anti-tubercular medicines and assessment of risk factors. Ann Pharmacother. 2004; 38:1074-1079.

24.Whiting-O'Keefe QE, Fye KH, et al. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991;90:711–6.

25.. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 2001;16:1395–401.

26 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245

27 **García-Cortés M**, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008; **27**:

28. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB Jong,1 MD, PhD;0-789 SAJHIVMED SEPTEMBER 2013, Vol. 14, No. 3

29.ACG , Guidelines ., Naga Chalasani.,Sep.,2014

30.Christe C, Stoller R, Vogt N. Omeprazole-induced hepatotoxicity? A case report. *Pharmacoepidemiol Drug Saf* 1998; **7** Suppl 1: S41-S44

31.Moradpour D, Altorfer J, Flury R, et al. Chlorpromazine-inducing vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology **1994**; 20:1437–41. Kleiner DE ,

32. Chalasani N , Lee W *et al.* Hepatic histological fi ndings in suspected drug-induced liver injury: systematic evaluation and clinical associations . Hepatology 2014 ; 59 : 661 ‑ 70

.

33. Chalasani N , Fontana RJ , Bonkovsky HL *et al.* Causes, clinical features, and outcomes from a prospective study of drug induced liver injury in the United States . Gastroenterology 2008 ; 135 : 1924 ‑ 34 .

34. Davern TJ , Chalasani N , Fontana RJ *et al.* Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury . Gastroenterology 2011 ; 141 : 1665 ‑ 72 e1-9

35.Rakesh Tandon, Epidemiology of Hepatitis E, CLD, 2012,

36..Agarwal VK , McHutchison JG , Hoofnagle JH . Important elements for the diagnosis of drug-induced liver injury . Clin Gastroenterol Hepatol 2010 ; 8 : 463 ‑ 70 .

37.Lee WM , Senior JR . Recognizing drug-induced liver injury: current problems, possible solutions . Toxicol Pathol 2005 ; 33 : 155 ‑ 64 .

38.Andrade AJ et al, an analysis of DILI in Spanish registry over a period of 10 years,Gastro enterology 2005.

39. Harshad Devar Bhavi , Anti Tuberculous Drug induced Liver Injury- Current perspective, Tropical Gastro Enterology, 2011

40. Kapanoff, D.E, et al .,Am Rev Resp Dis1979

41.“Westphal ,et al – Drug administration in chronic liver disease , Drug Safe 1997’’ and and “Keiding et al , Aspects of Liver pathophysiology- Seminars Liver Dis -1995”

42. According to American College of Gastroenterology guidelines- idiosyncratic DILI by Naga Chalasani, 2014

43. F Smink, Risk factors of acute hepatic failure during ATT, Netherlands Journal of Medicine, in the study done by “Girling DJ,Adverse effects of ATT ., DRUGS 1982.”

49. Ormerod et al, “Frequency and types ofreactions ofATT observations in routine treatment,Tubercul Lung Dis ,1996”

50. Shakaya R,et al “Incidence of Hepatotoxicity due to ATT and assessment of risk factors, ANN of Pharmacotherapy 2004”

51. “Kumar & Shalimar et al ,ATT induced ALF, magnitude profile and predictors of outcome”.,Hepatology,2010

52.“Harshad Devar Bhavi et al, Single centre experience with DILI from India, Am J of Gastro Enterol , 2010”.

55.ACLF Asia Pacific , consensus statement., 2014., S.K.Sarin

56. Duseja, Y K Chawla, R K Dhiman, - Non hepatic insults are common in ACLF.Dig.Dis.Sci 2010.

57.”Jalan et al ,J of Hepatolgy 2010” and “APASL consensus statement S K Sarin, et al Hepatol.Int 2009

LIMITATIONS OF THIS STUDY:

1. Smaller sample size

2. DILI needs a larger population size to extrapolate the risk according to HY'S law

3. Management aspects of acute liver failure or acute on chronic liver failure are not analysed.

4. Severe complications of DILI need more analysis pertaining to risk factors and inciting events.

5. The tropism for hepatotropic viruses (ACUTE A, E, C) in DILI are not established

ANNEXURE

ABREVIATION

1. DILI – DRUG INDUCED LIVER INJURY
2. ALF-ACUTE LIVER FAILURE
3. ACLF-ACUTE ON CHRONIC LIVER FAILURE
4. ATT- ANTI TUBERCULOUS TREATMENT
5. DCLD-DECOMPENSATED CHRONIC LIVER DISEASE
6. HBV- HEPATITIS B VIRUS
7. P- PULMONARY
8. EP-EXTRA. PULMONARY

.

6. Genetic causes of susceptibility not established

PROFORMA

NAME : AGE/SEX: DDHD NO:

DOA: RNTCP NO:

HISTORY:

YELLOWISH DISCOLORATION : PRURITIS: PALE STOOLS:

FEVER: ANOREXIA: NAUSEA/VOMITING:

LOA: LOSS OF WT: HYPERPIGMENTATION:

ABD DISTENSION: ABD PAIN: COUGH/ EXPECTORATION:

PAST HISTORY:

JAUNDICE: BLOOD TRANSFUSION: TATOOING:

DM: SHT: TB:

PERSONAL HISTORY:

Iv DRUG ABUSE: DRUG INTAKE: ALCOHOL:

FAMILY HISTORY:

GENERAL EXAMINATION:

CONSCIOUS/ORIENTED: PALLOR: ICTERUS:

CYANOSIS: CLUBBING: EDEMA:

LYMPHADENOPATHY: SCRATCH MARKS:

OTHER SIGNS:

VITALS: HT: WT: BMI:

PULSE: BP: TEMP: URINE OUTPUT:

SYSTEMIC EXAMINATION:

P/A:

RS :

OTHER SYSTEMS:

CVS: CNS:

INVESTIGATIONS:

Hb : BT: CT: Pl COUNT: PT: T C INR:
ESR: TC : DC:P L E M

RBS : UREA : Sr. CREATININE :

BT: CT: Pl COUNT: PT: T C INR:

DATE								
TOTAL BR								
DIRECT								
I.D								
SGOT								
SGPO								
ALP								
GGT								
T. PRO								
ALB								
GLO								

VIRAL MARKERS:

HbsAg: AntiHCV: HIV:

CHEST X RAY:

USG ABDOMEN:

SPUTUM AFB:

OTHRES :

TREATMENT:

DURATION :

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Protocol ID. No.7/02/2015 Dt.27/03/2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on LFT monitoring in ATT and the spectrum of Anti-Tuberculosis drug induced liver injury"- For Project Work submitted by Dr.C.Vaishnavi Priyaa, Post Graduate in DM (Medl. Gastro), Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

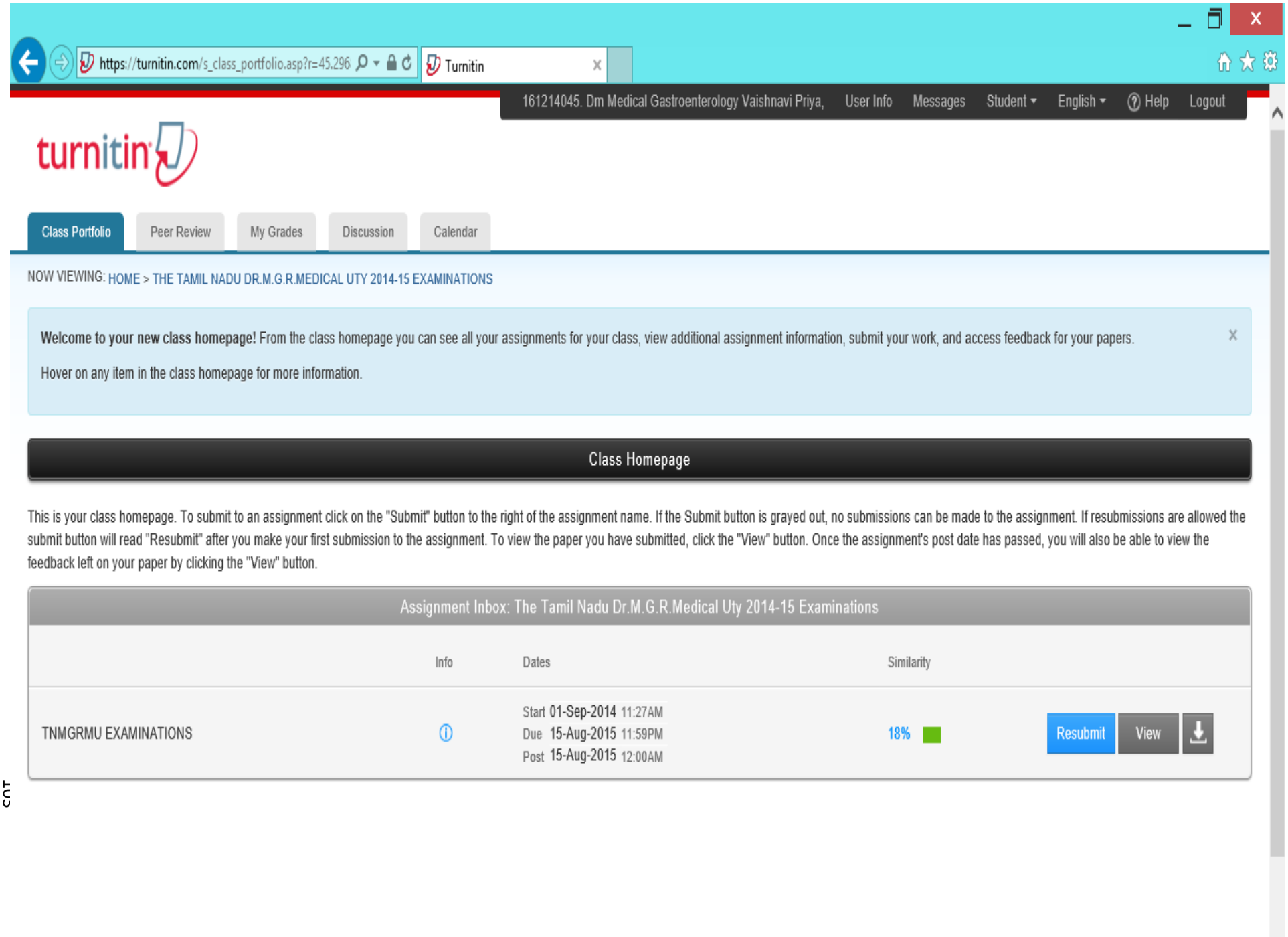
The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE 27 MAR 2015

27/3/15

CHAIRMAN,
Ethical Committee
Govt. Kilpauk Medical College, Chennai

27/3/2015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NAME	AGE/SEX	SEX	TB -PULM/EP	CO-MOR	CBC	HB	USG ABD	REGIME	S.BIL	DIR	SGOT	SGPT	SAP	STP	ALB	INR	BASELINE LIVER DIS	JAUNDICE	ASITES	HE	PE	FEVER	ALCOHOL	HEP B,C	CONCOMITANT DRUGS	H.ADAPTATION	LATENCY	J/E INTERVAL	DILI Y/N
SARAVANA MUTHU	42	M	DISSEMINATED	DM	9100	11	ASCITES	HRE	1.4	0.7	58	27	50	6	2.3	1.1	CTP B	N	Y	Y	Y	N	N	POS	INSULIN	N	2 WKS	2 WEEKS	Y- DIACLF-RECOVERED
AMUDHAVANAN	60	M	DISSEMINATED	DM	1200	10.4	ASCITES	HEC	1.7	0.9	160	40	97	6.2	2.5	1.2	CTP B	Y	Y	N	Y	N	Y	NEG	DIURETICS,PPNL	Y	NA	NA	N
ARUMUGAM	44	M	PT	DM	10200	10	ASCITES	HEO	1.5	0.8	76	78	142	6.4	3.1	1.1	CTP B	Y	Y	Y	N	N	Y	NEG	DIURETICS,PPNL	N	NA	NA	Y - REGIME CHANGED
VENKATESAN	28	M	DISSEMINATED	N	6500	11.3	ASCITES	HRE	2	0.3	45	54	322	6.2	2.5	1.5	CTP B	Y	Y	Y	Y	N	Y	NEG	DIURETICS,PPNL	N	1 WK	1 WK	Y- DIACLF-RECOVERD
RAVI	54	M	MIXED ASCITES	N	8900	10.1	ASCITES	SHE	1.4	0.7	79	20	52	6.1	3.1	1.2	CTP B	N	Y	N	N	N	Y	NEG	NO	Y	NA	NA	N
DHAYALAN	45	M	PT	N	9900	11.2	FATTYLIVER	SHE	0.4	0.3	33	44	112	6.9	3.6	1.2	UNDIAGNOSED CHB	Y	Y	N	N	N	Y	CHB	TENOFOVIR	N	10 DAYS	NA	Y- ATT INDUCED DECOMP
SURESH BABU	45	M	MIXED ASCITES	DM	10200	8.7	ASITES/CIRRHOSIS	HRE	1.3	0.5	54	35	187	6.8	2.5	1.1	CLD /PANC. ASCITES	N	Y	N	Y	Y	Y	NEG	NO	DEFAULTED		DEFAULTED	DEFAULTED
SETTU	40	M	TB ASCITES	N	9000	9.6	ASCITES	HRE	2.5	1	89	36	462	7.9	4.1	1.1	CTP B / TB ASCITES	N	Y	N	N	N	Y	NEG	NO	Y	NA	NA	N
VENKATESAN	38	M	BIL PT	N	9300	10.6	ASCITES	HRE	1.8	1	59	27	127	5.8	2.8	1.2	CTP B	N	Y	N	N	N	N	NEG	DIURETICS,PPNL	N	NA	NA	N
SURESH	35	M	PT	N	7800	11.8	ASCITES	HEO	1.5	0.9	67	54	112	6.3	3.1	1.1	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS	N	NA	NA	N
MOHAN	55	M	PT/TB ASCITES	N	8900	10	ASCITES	HEO	1.3	0.5	65	45	105	5.4	3	1.2	CTP B	N	Y	N	Y	N	Y	CHB	DIURETICS,PPNL	Y	NA	NA	N
CHOCKALINGAM	57	M	PT	N	7900	9.1	ASCITES	HEO	1.2	0.6	47	42	180	6.2	3	1.1	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS,PPNL	Y	NA	NA	N
BALAKRISHNAN	55	M	PT	N	9600	8.4	ASCITES	HRE	1.3	0.5	142	54	112	6.1	2.5	1.2	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS	N	NA	NA	N
THIAGARAJAN	51	M	PT	N	7600	7.5	ASCITES	HRE	2.4	1.5	93	89	143	6.3	3.2	1.2	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS,PPNL	Y	NA	NA	N
SUBRAMANI	68	M	PT	N	9600	10	ASCITES/CIRRHOSIS	HRE	1.4	0.6	57	26	102	7.2	3.5	1.2	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS	Y	NA	NA	N
DHEENADHAYALAN	53	M	PT	N	10200	8.5	ASCITES/PT	SHE	1.5	1.2	66	94	289	6.4	3.2	1.3	CTP B	N	Y	N	Y	N	Y	NEG	DIURETICS	Y	NA	NA	N
SUBRAMANIAN	32	M	TB ASCITES	N	9800	9	ACITES	HRE	1.2	0.8	34	25	227	6.9	3.7	1.1	CTP B/TB ASCITES	N	Y	N	Y	Y	Y	NEG	NO	N	NA	NA	N
RAVI	54	M	MIXED ASCITES	N	6800	12	ASC/CIRR	HRE	1.4	0.7	79	20	52	6.1	3.2	1.1	CTP B	N	Y	N	N	N	Y	NEG	DIURETICS,PPNL	Y	NA	NA	N
SUBRAMANI	45	M	PT	N	14100	9.9	N-STUDY	HRE	0.7	0.3	53	41	6.3	3.5	3.1	1.1	CTP B	N	N	N	N	N	Y	NEG	DIURETICS,PPNL	N	NA	NA	N
SIVA	22	M	PT	N	7800	11.2	N-STUDY	HRZE	1.9	0.8	42	21	165	6.8	3.8	1.1	CHB	N	N	N	N	N	Y	POS	NO	N	NA	NA	N
SURESH	25	M	PT	N	9800	11.5	N-STUDY	HRZE	0.8	0.5	55	84	160	7.4	4.6	1.2	CLD	N	N	N	N	N	Y	NEG	NO	Y	NA	NA	N
BALAMURUGAN	35	M	PT	N	8900	9.6	N-STUDY	HRZE		0.6	59	38	62	7.2	3.4	1.1	CLD	N	N	N	N	N	Y	NEG	NO	Y	NA	NA	N
PARTHIBAN	39	M	PT	N	6300	9.7	FATTYLIVER	HRZE	1.2	1.4	0.9	131	68	6.2	3.8	1.2	CLD	N	N	N	N	N	Y	NEG	NO	Y	NA	NA	N
VIJAYAKUMAR	35	M	PT	N	9200	10.1	HEPATOMEG	HRE	1.2	0.6	65	42	209	7.3	3.6	1.1	CLD	N	N	N	N	N	Y	NEG	NO	N	NA	NA	N
MUTHURAMALINGAM	51	M	PT	N	7600	11.3	HEPATOMEG	HRZE	0.8	0.5	90	204	132	7.2	3.4	1.2	CLD	N	N	N	N	N	Y	NEG	NO	Y	NA	NA	N
VENKATESAN	44	M	PT	ICTHYOSIS)	8900	9	ASCITES	HRE	1.7	0.5	41	23	179	7.4	3.3	1.3	CLD	Y	Y	Y	Y	N	Y	NEG	DIU, PPNL	N	1 WEEK	2DAYS	Y-DICLF -DIED
GOWRI	61	F	MIXED ASCITES	N	8800	9	ASCITES	HRE	1.9	1	80	42	402	6.8	3.5	1.2	DCLD?NASH	N	N	N	N	N	N	NEG	PPNL,DIUTETICS	Y	NA	NA	N
SHAJAHAN	40	M	PT	DM	6200	12	FATTYLIVER	HRE	0.7	0.4	51	20	350	6.4	3.5	1	CLD	N	N	N	N	N	Y	NEG	OHAS,INSULIN	N	NA	NA	N
ARULRAJ	54	M	TB ASCITES	N	9400	10.3	FATTY LIVER	HRZE	1.2	0.8	34	41	214	6.8	3.6	1.4	?CHRONIC DILI	N	Y	Y	Y	Y	N	NEG	CHLORPROMAZINE	N	1WK	1WK	Y - ?CHR.DILI -DIACLF-DIED

NAME	AGE/SEX		TB - P/EP	CO-MORB	CBC	Hb	USG ABD	S.BIL	DIRECT	SGOT	SGPT	SAP	STP	S.ALB	INR	JAUNDICE	ASCITES	HE	PE	FEVER	HEP B,C	CONCOMITANT DRU	ADAPTATION	LATENCY	HEP A,E	J/HE INTERVAL	DILI Y/N
MAHALINGAM	44	M	PT	N	7700	13.2	N- STUDY	0.5	0.2	36	21	105	8.2	4.2	1	N	N	N	N	N	NEG	NO	YES	NA		NA	N
SAROJA	65	M	PT	N	10250	9.2	N- STUDY	0.7	0.3	19	12	112	8.2	4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
RAJESH	21	M	PT	N	10200	9.8	N- STUDY	0.8	0.3	23	28	157	7.2	4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SASIKALA	50	F	L.PL EFF	N	9800	11.2	L- PL EFF	0.6	0.4	24	23	776	8.2	3.9	0.9	N	N	N	N	N	NEG	NO	YES	NA		NA	N
KAVIMALA	23	F	PT	N	8800	10.8	N- STUDY	1.1	0.8	44	59	109	8.6	3.9	1.1	N	N	N	N	N	NEG	NO	YES	NA		NA	N
BALARAMAN	54	M	PT	N	8900	12.8	FATTY LIVER	3.9	2.1	29	647	136	7.1	3.6	0.9	Y	N	N	N	N	NEG	OHAs	NO	10DAYS	NEG	NA	Y- RECOVERED
HARIBABU	43	M	PT	N	8900	11.2	N-STUDY	1	0.7	36	28	102	7.7	3.9	1.2	N	N	N	N	N	NEG	NO	YES	NA		NA	N
MANIGANDAN	23	M	TB ASCITES	N	9300	12	ASCITES	0.9	0.4	29	15	103	7.3	3.5	1.1	N	N	N	N	N	NEG	NO	YES	NA		NA	N
CHANDRASEKAR	47	M	PT	N	10,700	12.4	N-STUDY	0.7	0.4	17	19	109	7.3	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KRISHNAMOORTHY	68	F	PT	N	10,100	10.8	N- STUDY	0.9	0.3	19	17	104	7.2	3.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
DURGA DEVI	27	F	TB LN	N	7800	12.1	N-STUDY	0.8	0.3	18	19	102	7.3	3.5		N	N	N	N	N	NEG	NO	NO	NA		NA	N
CHANDRASEKAR	47	M	PT	N	7900	11.2	N-STUDY	0.9	0.5	19	21	105	7.5	3.9		N	N	N	N	N	NEG	NO	NO	NA		NA	N
DHANALAKSHMI	35	F	PTT	N	8700	10.2	N-STUDY	0.6	0.4	18	23	105	7.4	3.5		N	N	N	N	N	NEG	NO	NO	NA		NA	N
ELUMALAI	66	M	PT	N	7900	12.1	N-STUDY	0.6	0.4	23	22	104	7.4	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
ANUSHYA	45	F	PT	N	7600	11.1	L PL EFF	0.7	0.5	24	25	101	7.2	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
CHINNAIYAH	60	M	PT	N	9800	10.9	N-STUDY	0.8	0.5	22	30	143	6.5	3.3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
DEEPA RANI	34	F	PT	N	9900	11.1	N-STUDY	0.8	0.3	31	37	104	6.9	3.6	1.1	N	N	N	N	N	NEG	NO	YES	NA		NA	N
AMUDHA	28	F	PT	N	11000	10.1	N-STUDY	0.9	0.7	26	27	106	6.7	3.5	1	N	N	N	N	N	NEG	NO	YES	NA		NA	N
SANGAMITHRAN	45	M	PT	N	8700	10.6	N-STUDY	0.8	0.3	22	25	55	6.9	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
ANUSHYA	65	F	PT	DM	8900	11.3	FATTY LIVER	4.3	3.2	89	93	420	6.5	3.2		Y	N	N	N	N	NEG	OHAS	NO	1 MONTH	NEG	NA	Y/R
KANDASAMY	34	M	L .PL EFF	N	8700	11.5	N-STUDY	0.9	0.5	24	28	64	6.1	3.6		N	N	N	N	N	NEG	NO	NO	NA		NA	N
NIRMALA	45	F	TB LN	N	9800	10.5	N-STUDY	1.1	0.5	10	16	73	6.3	3.7		N	N	N	N	N	NEG	NO	NO	NA		NA	N
NIRMALA	32	F	PT	N	9700	10.5	N-STUDY	0.7	0.4	42	19	124	6.2	3.1		N	N	N	N	N	NEG	NO	NO	NA		NA	N
BOOPALAN	28	M	PT	N	8900	11.4	N-STUDY	0.6	0.3	22	25	102	6.4	3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
GEETHA	25	M	PT	N	9300	12.1	N-STUDY	0.7	0.3	19	21	57	6.4	3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
DEEPA	41	F	PT	N	7600	11.2	N-STUDY	0.8	0.4	18	23	58	6.3	4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
ZAIRA BEGUM	40	F	PT	N	7800	12	N-STUDY	1	0.5	27	17	72	6.9	3.6		N	N	N	N	N	NEG	NO	NO	NA		NA	N
LAKSHMI	33	F	TB LN	N	4100	13	N-STUDY	0.7	0.4	23	16	108	6.4	4.3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
VELAN	35	F	PT	N	6300	11.2	N-STUDY	0.9	0.5	22	17	109	6.2	4.1		N	N	N	N	N	NEG	NO	NO	NA		NA	N
POORNIMA	24	F	PL. EFF	N	7800	12.1	N-STUDY	0.8	0.7	24	18	102	6.5	4.1		N	N	N	N	N	NEG	NO	NO	NA		NA	N
MUMTAJ BEGUM	25	F	PT	N	9800	11.4	N-STUDY	0.9	0.6	22	21	101	6.5	3.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
JAYPAUL	56	M	PT	N	10100	11.5	N-STUDY	0.4	0.2	24	15	74	6.4	3.6		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SOWMYA	15	F	PT	N	7900	10.4	N-STUDY	0.7	0.5	25	33	78	6.2	3.3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KUSCHITRE	31	F	PT	N	9500	11.2	N-STUDY	0.8	0.6	26	22	76	6.1	3.1		N	N	N	N	N	NEG	NO	NO	NA		NA	N
RENUKHA	23	F	PT	N	9600	9.9	N-STUDY	0.9	0.4	37	32	8	6.3	3.1		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KALAISELVI	45	F	PT	DM	11800	11	FATTY LIVER	8.9	5.6	560	408	182	7.2	3.6	1.5	N	Y	Y	N	N	NEG	OHA,ANTI HT	NO	4 MTHS	HEV	1 WK	Y- NR
VARUNKUMAR	33	M	PT	N	10,700	11.2	N-STUDY	3.4	2	293	245	144	7.6	4.1	1.3	N	Y	N	N	N	NEG	OHAS	NO	8MTHS	NEG	NA	Y- R
WAHEEDHA	46	F	PT	N	7800	12	N-STUDY	O.5	0.3	16	16	100	6.5	4.3		N	N	N	N	N	NEG	OHAS	NO	NA		NA	N
BHUVANESWARI	19	F	TB ASCITES	N	11000	10.1	ASCITES	0.6	0.4	15	13	71	7.1	3.8		N	Y	N	N	N	NEG	NO	NO	NA		NA	N
HAJIRA BEE	54	M	PT	N	11700	10.6	N-STUDY	0.7	0.4	39	30	166	6.5	3.3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
PUNITHAMARY	44	F	PT	N	10100	9.5	N-STUDY	1.5	1.1	172	60	178	6.2	3.4		Y	N	N	N	N	NEG	NO	NO	NA		NA	N
MANIKANDAN	18	M	PT	N	9400	11.2	N-STUDY	0.9	0.6	59	127	158	7.2	3.9		N	N	N	N	N	NEG	NO	YES	NA		NA	N
BABU	52	M	PT	DM	6290	12.4	N-STUDY	0.4	0.3	17	15	99	7.4	3.3		N	N	N	N	N	NEG	OHAS	NO	NA		NA	N
ANBANANDHAN	47	M	PT	N	7120	10.2	N-STUDY	0.3	0.2	13	16	103	7.2	4.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
JEYAKUMAR	58	M	PT	N	12640	8.2	N-STUDY	0.3	0.2	20	25	102	7.3	3.6		N	N	N	N	N	NEG	NO	NO	NA		NA	N
RAYAPPAN	49	M	PT	N	7700	9.2	N-STUDY	0.6	0.3	25	23	99	6.9	3.8		N	N	N	N	N	NEG	NO	NO	NA		NA	N
RESHMA	18	F	PT	N	5460	9.5	N-STUDY	0.4	0.2	21	24	93	6.4	3.3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SAROJA	50	F	TB LN	N	10100	11.8	N-STUDY	0.7	0.4	24	29	56	6.9	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
THIRUVENKATAM	48	M	PT	N	9960	11.6	N-STUDY	1.1	0.7	28	24	78	6.3	3.7		N	N	N	N	N	NEG	NO	NO	NA		NA	N
MOHAMMED YUSUF	45	M	PT	DM	6840	11.2	N-STUDY	0.6	0.4	18	25	98	6.8	3.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SUBRAMANI	45	M	PT	N	14100	9.9	N-STUDY	0.8	0.3	24	27	76	7.1	3		N	N	N	N	N	NEG	NO	NO	NA		NA	N
ANJARIAH	32	M	PT	DM	14050	8.9	N-STUDY	0.7	0.5	21	29	67	3.5	3.5		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KUMAR	60	M	PT	DM	11400	10.6	N-STUDY	0.8	0.5	22	13	78	7.5	3.5		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SIVAKUMAR	32	M	PT	N	9380	14.4	N-STUDY	0.6	0.4	12	25	98	6.8	3.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
RAJESHWARI	29	F	PT	N	7290	11.7	N-STUDY	0.4	0.3	28	38	77	7.2	3.9		N	N	N	N	N	NEG	NO	NO	NA		NA	N
PARAMESHWARI	12	F	PT	N	14,320	10.7	N-STUDY	0.5	0.3	36	38	89	7.9	3.5		N	N	N	N	N	NEG	NO	NO	NA		NA	N
LIDYA	55	F	PT	N	6700	12.8	N-STUDY	0.7	0.4	28	35	120	6.4	3.7		N	N	N	N	N	NEG	NO	NO	NA		NA	N
SARAWATHY	43	F	PT	N	5364	8.1	N-STUDY	0.6	0.4	27	32	107	6.6	3.4		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KARTHICK	25	M	PT	N	4700	8.1	N-STUDY	0.3	0.2	13	12	67	6.4	3.2		N	N	N	N	N	NEG	NO	NO	NA		NA	N
KARUNANITHI	40	M	TB ASCITES	N	9800	10.1	ASCITES	0.7	0.3	98	110	666	6.7	3.7		Y	N	N	N	N	NEG	NO	NO	NA	NEG	NA	Y/R

NAME	AGE	SEX	TB- PULM/EP	CO-MOR	TC	Hb	USG ABD	S.BIL	D.BIL	SGOT	SGPT	SAP	STP	ALB	JAUND	ASCITES	PE	HE	FEVER	HEP B,C	CONCOMITANT DRUGS	H.ADAPATATION	HEP A,E	JE INT	DILI Y/N
ANGEL MARY	34	F	TB LN	N										3.2	Y	N	N	N	N	NEG	NO	NO	NEG	2WEEKS	Y- R
KRISHNAMURTHY	68	M	PT	N	9700	11.2	N-STUDY	0.7	0.5	23	33	110	7.4	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
SELVAKUMAR	22	M	PT	N	9560	11.2	N-STUDY	0.8	0.3	28	41	101	7.4	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
SAFIQ	46	M	TB LN	N	6500	13.1	N-STUDY	0.9	0.6	27	29	121	7.1	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
MURUGAN	49	M	PT	N	9100	12	N-STUDY	0.5	0.3	21	27	105	7.5	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
SEKAR	53	M	PT	N	9500	9.4	N-STUDY	0.5	0.4	26	10	98	7.3	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
SATHYANARAYANAN	51	M	PT	N	11200	9.3	N-STUDY	0.6	0.3	35	20	89	7.8	4.1	N	N	N	N	N	NEG	NO	NO		NA	N
BASKARAN	43	M	PT	N	9170	11.4	N-STUDY	0.8	0.3	14	24	112	8	4.1	N	N	N	N	N	NEG	NO	NO		NA	N
ANBARASU	34	M	PT	N	8840	12.3	N-STUDY	0.4	0.2	21	19	97	7.4	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
VENKAMMAL	40	F	PT	N	4650	9.1	N-STUDY	0.3	0.1	31	37	96	7.5	3.6	N	N	N	N	N	NEG	NO	NO		NA	N
SRINIVASAN	45	M	PT	N	9600	13.6	N-STUDY	1	0.4	41	24	95	7.8	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
BALAMURUGAN	27	M	PT	N	8310	12.2	N-STUDY	1.1	0.5	31	34	88	7.5	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
HARI	18	M	PT	N	4900	11.3	N-STUDY	0.9	0.4	32	34	89	7.8	3.6	N	N	N	N	N	NEG	NO	NO		NA	N
GOVINDASAMY	60	M	PT	N	5600	12.1	N-STUDY	0.7	0.4	33	41	93	7.4	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
NANDHINI	16	F	PT	N	7700	11.2	FATTY LIV	0.6	0.3	25	19	87	7.3	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
NEELAKANDAN	45	M	PT	N	12780	10.8	N-STUDY	0.6	0.3	39	27	97	7.3	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
NAGAMMAL	52	F	PT	N	7600	11.6	N-STUDY	0.4	0.2	17	18	103	7.5	4.1	N	N	N	N	N	NEG	NO	NO		NA	N
ARUUGAM	63	M													Y	Y	Y	Y	Y	NEG	NO	NO	HEP A +	1WK	Y/NR
VALARMATHI	51	F	PT	N	7180	11.2	N-STUDY	0.6	0.3	17	19	102	7.2	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
SUBRAMANI	70	M	PT	DM	11400	12.9	FATTY LIV	1.1	0.8	25	23	80	7.3	3.6	N	N	N	N	N	NEG	OHAS	NO		NA	N
HERCULES	48	M	PT	N	10420	11.7	N-STUDY	0.6	0.3	20	10	89	7.9	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
MOORTHY	45	M	PT	N	7100	10.7	FATTY LIV	0.9	0.5	33	34	98	7.4	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
BALARAMAN	60	M	PT	N	9140	10.3	N-STUDY	0.7	0.3	19	23	99	7.3	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
LAKSHMI	53	F	PT	N	8120	10.8	FATTY LIV	1	0.5	31	27	98	7.9	3.4	N	N	N	N	N	NEG	NO	NO		NA	N
VIJAYACHANDRAN	34	M	PT	N	6080	12.2	FATTY LIV	0.9	0.7	44	40	79	7.2	3.2	N	N	N	N	N	NEG	NO	NO		NA	N
RAVANAMMAL	46	F	PT	DM	7780	10.7	FATTY LIV	0.9	0.4	16	30	59	7.4	3.2	N	N	N	N	N	NEG	OHAS	NO		NA	N
NARMADA	32	F	PT	N	5660	8.8	N-STUDY	1	0.4	16	30	78	7.2	3.1	N	N	N	N	N	NEG	NO	NO		NA	N
SAROJA	65	F	PT	N	10250	9.2	FATTY LIV	1	0.6	19	12	89	7.3	3.1	N	N	N	N	N	NEG	NO	NO		NA	N
POOJA	16	F	TB LN	N	8200	6.9	N-STUDY	3.6	2.9	152	167	1156	6.8	3.8	Y	N	N	N	N	NEG	NO	NO	NEG	NA	Y/R
ARUL	40	M	PT	N	8920	13.3	FATTY LIV	0.8	0.5	15	12	89	7.3	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
SIGAMANI	54	M	PT	N	9600	9.2	N-STUDY	0.7	0.3	34	26	132	6.5	3.4	N	N	N	N	N	NEG	NO	NO		NA	N
RAJAKUMARI	19	F	TB LN	N	6100	11.8	N-STUDY	0.8	0.4	18	12	43	6.9	3.9	N	N	N	N	N	NEG	NO	NO		NA	N
THILAGAM	58	F	PT	DM	6200	11	FATTY LIV	0.5	0.3	18	23	98	7.4	3.8	N	N	N	N	N	NEG	OHAS	NO		NA	N
UMA MAHESHWARI	23	F	EMP ATT	WILSONS & SLE	7600		N-STUDY	4.5	3.1	356	235	486	6.7	3.9	Y	N	N	N	Y	NEG	NO	NO		NA	Y /R
CHARLES	59	M	PT	DM	7100	10.4	N-STUDY	0.7	0.5	21	29	160	7.5	3.6	Y	N	N	N	N	NEG	OHAS	NO		NA	N
MOHANA	39	F	PT	N	7460	13.2	N-STUDY	1.2	1	26	33	151	7.3	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
KAVITHA	32	F	TB LN	N	8330	10.5	FATTY LIV	0.7	0.6	21	14	65	6.3	3.9	N	N	N	N	N	NEG	NO	NO		NA	N
JAMUNA RANI	45	F	TB SPINE	RA	9140	12.9	FATTY LIVER	12..5	10	348	235	765	6.5	3.1	Y	Y	Y	Y	Y	NEG	MTX	NO	NAG	1 WK	Y/NR
INDRANI	60	F	PT	DM	9800	9	FATTY LIV	0.4	0.9	12	18	94	8.2	4.1	N	N	N	N	N	NEG	OHAS	NO		NA	N
SIVAKUMAR	25	M	TB LN	N	6460	11.6	N-STUDY	0.6	1	22	37	102	7	3.8	N	N	N	N	N	NEG	NO	NO		NA	N
MAHALAKSHMI	26	F	PL EFF	N	4200	10.6	FATTY LIV	0.9	0.8	43	24	124	8.1	3.9	N	N	N	N	N	NEG	NO	NO		NA	N
RANI	70	F	PT	DM	8150	11.4	FATTY LIV	0.5	0.3	16	18	130	7.5	4.2	N	N	N	N	N	NEG	NO	NO		NA	N
KRISHNAN	18	M	TB LN	N	8440	12.1	N-STUDY	0.6	0.3	24	19	79	6.4	3.4	N	N	N	N	N	NEG	NO	NO		NA	N
LILLY	33	F	TB LN	N	8200	11	FATTY LIV	0.4	1	15	18	52	7.1	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
TAMILSELVI	42	F	TB LN	N	9800	12	N-STUDY	0.9	0.8	87	54	102	7.3	3.1	N	N	N	N	N	NEG	NO	NO		NA	N
MOHAN	50	M	PT	DM	11200	11.2	FATTY LIV	0.8	0	30	27	65	6.3	3.3	N	N	N	N	N	NEG	OHAS	NO		NA	N
KALIMUTHU	67	M	PL EFF	N	8200	12	FATTY LIV	0.7	0.6	48	28	69	6.5	3.6	N	N	N	N	N	NEG	NO	NO		NA	N
VASANTHAKUMAR	17	M	PL EFF	N	9800	10.4	N-STUDY	0.7	0.6	22	18	54	5.6	3.4	N	N	N	N	N	NEG	NO	NO		NA	N
VENKATTAIAH	64	M	PT	DM	4790	7.5	FATTY LIV	0.9	0.7	20	16	72	7.3	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
BALAMURUGAN	35	M	PT	N	12100	10.6	N-STUDY	0.6	0.4	29	22	45	7.5	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
GAYATHRI	23	F	TB SPINE	N	7800	9.6	N-STUDY	1.2	0.7	19	17	39	7.6	3.6	N	N	N	N	N	NEG	NO	NO		NA	N
PRAVEENA	18	F	IC TB- EMP	N	8900	9.4	N-STUDY	0.9	0.6	18	22	76	7.8	3.7	N	N	N	N	N	NEG	NO	NO		NA	N
THIRUMOORTHY	45	M	PT	N	9500	10.4	FATTY LIV	1.2	0.4	26	34	78	7.3	3.5	N	N	N	N	N	NEG	NO	NO		NA	N
MOSES	49	M	PT	N	880	10.5	FATTY LIV	2.4	0.9	50	132	795	7.5	2.9	Y	N	N	N	N	NEG	NO	NO		NA	Y/R
USHA	15		IC TB	N	6700	10.6	N-STUDY	0.9	0.5	28	22	6	6.3	3.3	N	N	N	N	N	NEG	NO	NO		NA	N
KALAISELVI	35	F	IC TB	N	9800	11.1	N-STUDY	0.8	0.6	48	62	156	7.1	3.1	N	N	N	N	N	NEG	NO	NO		NA	N