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# Comparative Study on Liver Enzymes (ALT & AST) In the Intermittent and Daily Regimen Therapy in Patients of Tuberculosis

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***Abstract:*** *Tuberculosis (Tb) Which Is One Of The Oldest Diseases Known To Affect Humans And Is Likely A Major Cause Of Death Worldwide[1].Of The Standard Antitubercular Drug Used In Dots Strategy And Non-Dots Strategy, Isoniazid, Rifampicin And Pyrazinamide Metabolized By Liver By Different Enzymatic Reaction And Have Been Associated With Development Of Drug Induced Hepatotoxicity. The Population Residing In Jharkhand State Are Tribal People (27.6%) Who Are Not Only Economically, Socially And Educationally Backward But They Mostly Believe In The Orthodox Treatment Of Even Most Severe And Complicated Disease. The Incidence And Prevalence Of Pulmonary Tuberculosis In These Tribal Belts Are Alarming. The Good Compliance And The Ensured Institution Of Drugs For Tuberculosis Will Certainly Increase The Cure Rate Of Disease. The Intermittent Short-Course Therapy Would Certainly Have A Good Impact On The Facts. Most Of The Patients On Daily Regimen Therapy Discontinue Their Treatment And Turn To Be Treatment Failure Case.The Present Study Was Carried Out In 200 Cases Receiving Category 1 Therapy. Patients Were Selected From Outdoor Patients And Indoor Patients From The Department Of Medicine And Tb & Chest Unit, Rajendra Institute Of Medical Sciences, Ranchi From October 2016 To September 2017.On The Basis Of Above Observation Made In The Prospective Cohort Study, It Can Be Concluded That Liver Enzyme Alteration Is Most Common Finding In The Patient Receiving Anti-Tubercular Chemotherapy. Revised Who Regimen, Directly Observed Therapy Short (Dots) Course Is Most Cost-Effective Therapeutic Programme, Especially For Developing Countries Like India.*

***Keywords-*** *Intermittent And Daily Att Regimen, Liver Enzymes, Tribal, Jharkahnd*

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## I. Introduction

Tuberculosis Continues To Remain A Significant Infectious Disease Across Much Of The Developing World. It Causes A Significant Socioeconomic Burden On The Individual And Society. India Is The Highest Tb Burden Country In The World And Accounts For Nearly One Fourth (23%) Of Global Burden Of Tuberculosis, Every Year Approximately 2.2 Million Persons Develop Tuberculosis Of Which About 0.8 Million Are New Smear Positive Highly Infectious Cases. Tuberculosis Kills About 0.22 Million People Every Year. Annual Risk Of Becoming Infected With Tb Is 1.5% And Once Infected There Is 10% Lifetime Risk Of Developing Tb Disease.

Indian Dots Programme Against Tuberculosis Is Recognized As The Fastest Expanding Programme. Launched In March 1997 It Has Covered The Whole Country By March 2006[2].Of The Standard Antitubercular Drug Used In Dots Strategy And Non-Dots Strategy, Isoniazid, Rifampicin And Pyrazinamide Metabolized By Liver By Different Enzymatic Reaction And Have Been Associated With Development Of Drug Induced Hepatotoxicity.The Risk Of Hepatitis Depends On Age Occurs Rarely Under Age 20, 0.3% Of Those Age 21-35, 1 To 20% Those Age 36-50 And 2 To 3% Those Age 50 And Above[3].Work Done On The Incidence Of Hepatic Toxicity And The Clinical Efficacy In Patients On Dots Regimen, In Comparison To Daily Regimen In This Part Of Country Is Less. This Fact Attracted Our Mind To Work On The Present Study. So It Was Planned To Observe And Analyze The Hepatic Toxicity (Especially On Serum Alt And Ast Level) And Clinical Efficacy In Patients Of Tb (Category 1) In The 6 Months Of Therapy On Dots Regimen Versus Non-Dots (Daily Regimen).

## II. Material And Methods

The Present StudyWas Carried Out In 200 Cases Receiving Category 1 Therapy. Patients Were Selected From Outdoor Patients And Indoor Patients From The Department Of Medicine And Tb & Chest Unit, Rajendra Institute Of Medical Sciences, Ranchi From October 2016 To September 2017.

**Study Design**: Prospective Cohort Study

**Study Location**: This Was A Tertiary Care Teaching Hospital Based Study Done In Department Of General Medicine, At Rajendra Institute Of Medical Sciences, Ranchi

**Study Duration**: October 2016 To September 2017.

**Sample Size**: 200 Patients.

**Inclusion Criteria**:

Patients Diagnosed To Have Pulmonary Or Extra Pulmonary Tuberculosis For The First Time.

Now The Study Was Made Of 2 Groups 'I' & 'Ii'.

**A.** Group – I (Intermittent Therapy) – It Comprised Of Patients (N=100) "Tb & Chest Unit", Rims, Receiving Dots, Category 1 Therapy.

**B.** Group – Ii (Daily Therapy) – It Comprised Of Patients (N=100) Attending Regularly The Opd Of Medicine And Indoor Of The Medicine Of Tuberculosis Receiving Daily Regimen Of Anti Tb Drugs.

In Group-I Category-1 Was Given Thrice Weekly, Whereas Group-Ii Taking Anti Tb Drugs With Daily Therapy. Patients Under Supervision Were Asked To Report Thrice Weekly For 2 Months And Then Monthly For 4 Months, Whereas Patients Of Daily Regimen Therapy Were Asked To Report Monthly And Were Reassured For Minor Problems With Drug Intake.

**Exclusion Criteria:**

1. History Or Any Indication Of Hepatitis Or Cirrhosis
2. Any History Of Regular Alcohol Intake
3. Pregnancy Of < 3 Months Postpartum
4. Abnormal Baseline Lft

**Statistical Analysis**

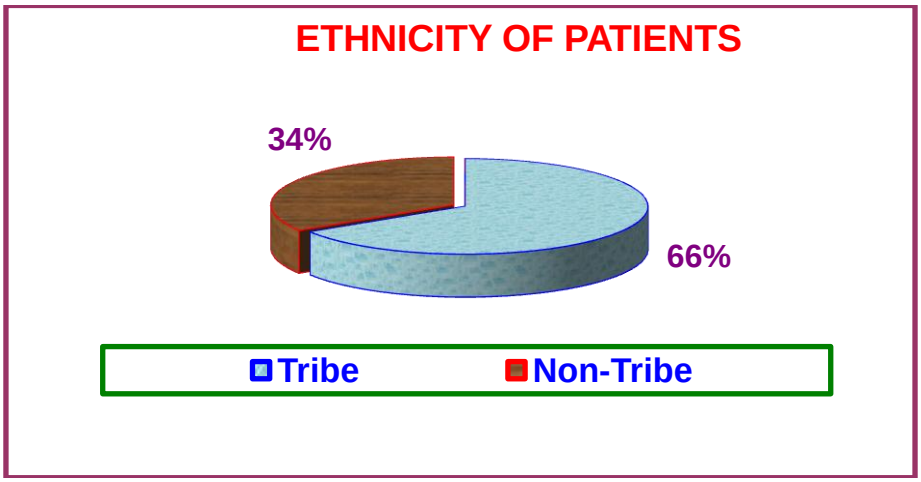
Pair Wise Comparison Between Various Variable Was Done For Different Parameters. The Range, Mean Value, Standard Deviation (S.D.), Standard Error Of Mean, 'T' Value And 'P' Values Were Calculated As Per The Applicability By Using Appropriate Formulas. Statistical Package Of Social Sciences (Spss) V. 22 Was Used For The Purpose Of Data Entry And Data Analysis. Chi-Square Test Was Used To Find Out Associations (Relations) Between 2 Categorical Variables,Anova Test Was Used To Find Out Associations Between Multiple Categorical Variables. Pearson's Correlation Coefficient Was Used For Numerical Variables. P-Value Less Than 0.05 Was Regarded As Statistically Significant.

## III. Result

Followings Were The Findings Of The Present Study-

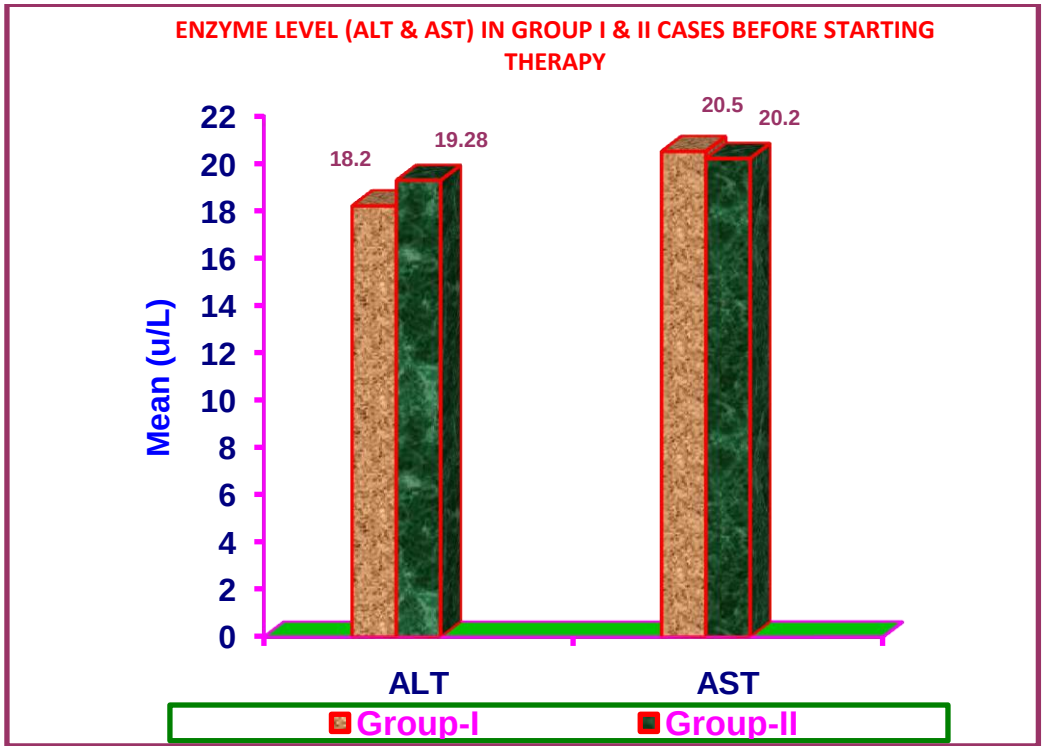
**Observation 1**- Ethnicity Of Patients

| | **No. Of Patients** | **%** |
|---|---|---|
| Tribe | 132 | 66 |
| Non-Tribe | 68 | 34 |



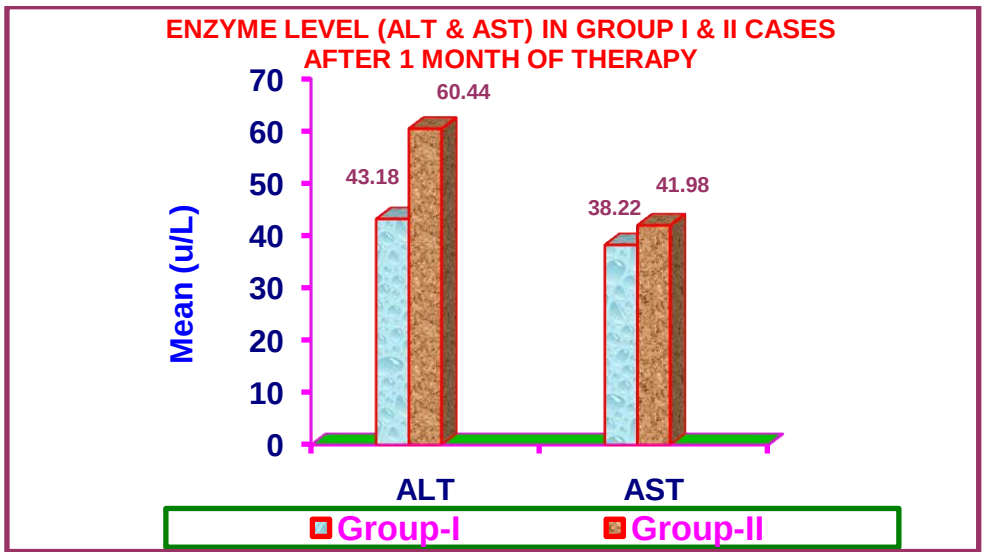
**Observation 2**- Enzyme Level (Alt &Ast) In Group I & Ii Cases Before Starting Therapy

| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group-I | 100 | 12-26 | 18.2 | 5.3 | T = 1.07 P = 0.28 | 15-28 | 20.5 | 3.94 | T = 0.31 P = 0.75 |
| Group-Ii | 100 | 12-25 | 19.28 | 4.7 | | 12-30 | 20.2 | 5.59 | |



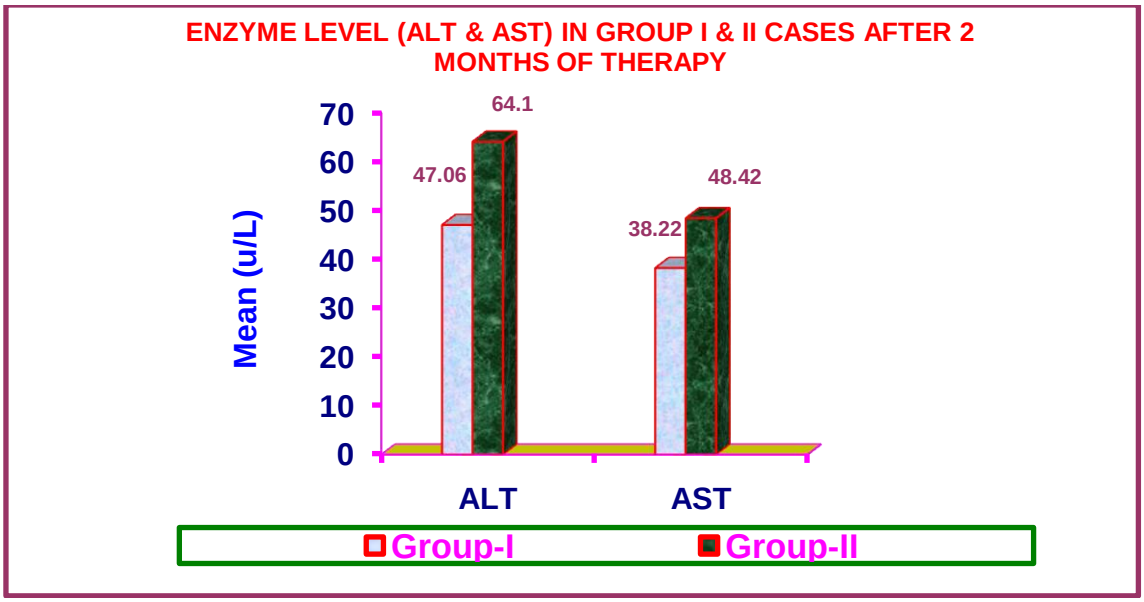

**Observation 3**- Enzyme Level (Alt &Ast) In Group I & Ii Cases After 1 Month Of Therapy

| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 20-82 | 43.18 | 19.6 | T = 3.09 P = 0.0026 | 30-60 | 38.22 | 8.85 | T = 2.006 P = 0.04 |
| Group Ii | 100 | 30-240 | 60.44 | 34.21 | | 24-60 | 41.98 | 9.87 | |



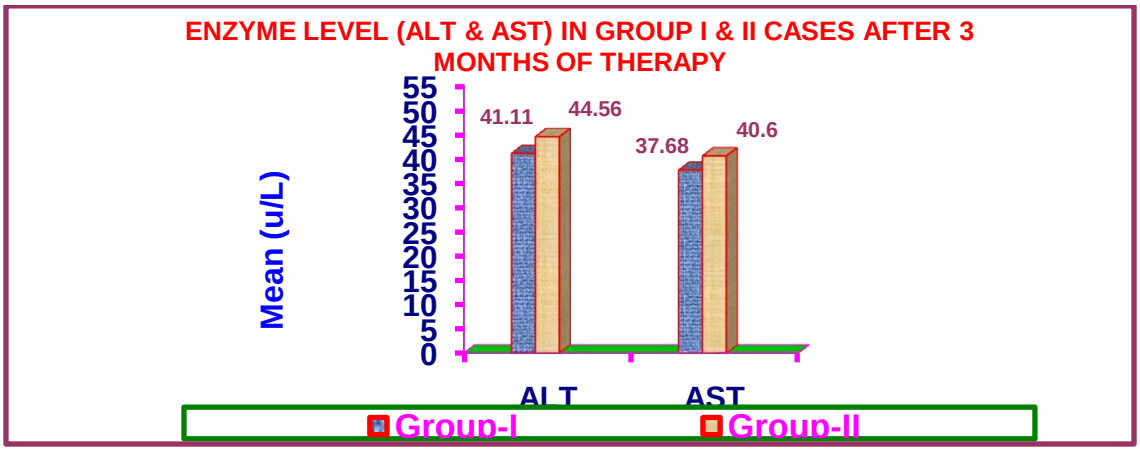
**Observation 4**- Enzyme Level (Alt &Ast) In Group I & Ii Cases After2 Month Of Therapy

| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 25-160 | 47.06 | 25.62 | T = 2.95 P = 0.004 | 30-60 | 38.22 | 8.85 | T = 4.82 P = <0.001 |
| Group Ii | 100 | 35-175 | 64.1 | 31.81 | | 24-72 | 48.42 | 12.05 | |




**Observation 5**- Enzyme Level (Alt &Ast) In Group I & Ii Cases After3 Month Of Therapy

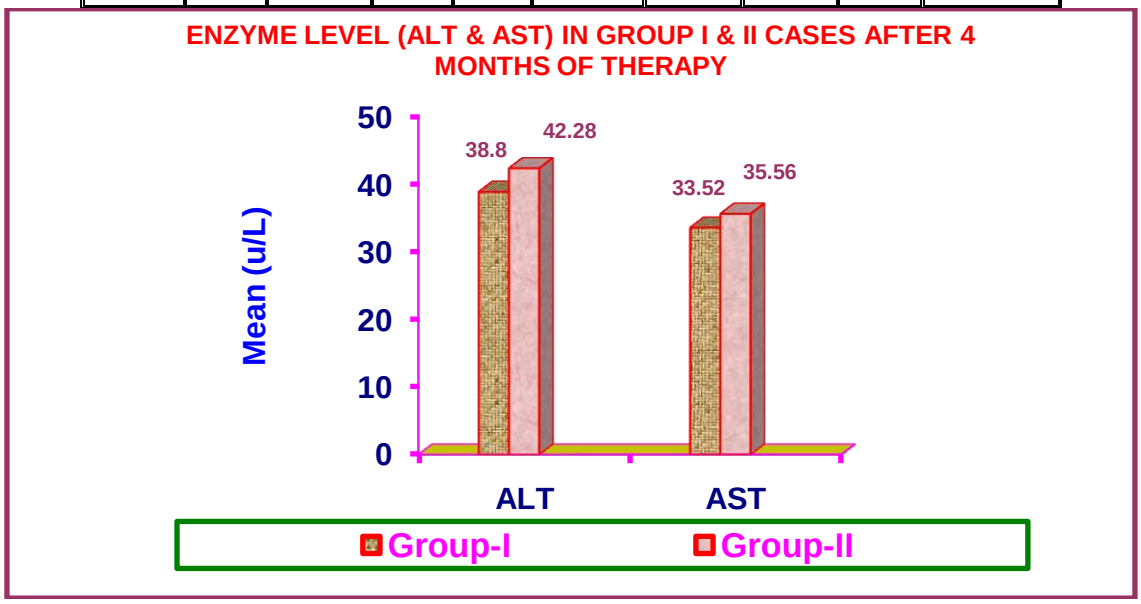
| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 27-56 | 41.11 | 14.96 | T = 4.60 P = 0.073 | 27-74 | 37.68 | 7.56 | T = 1.77 P = 0.07 |
| Group Ii | 100 | 30-78 | 44.56 | 11.97 | | 24-65 | 40.6 | 8.83 | |




**Observation 6**-Enzyme Level (Alt &Ast) In Group I & Ii Cases After4 Month Of Therapy

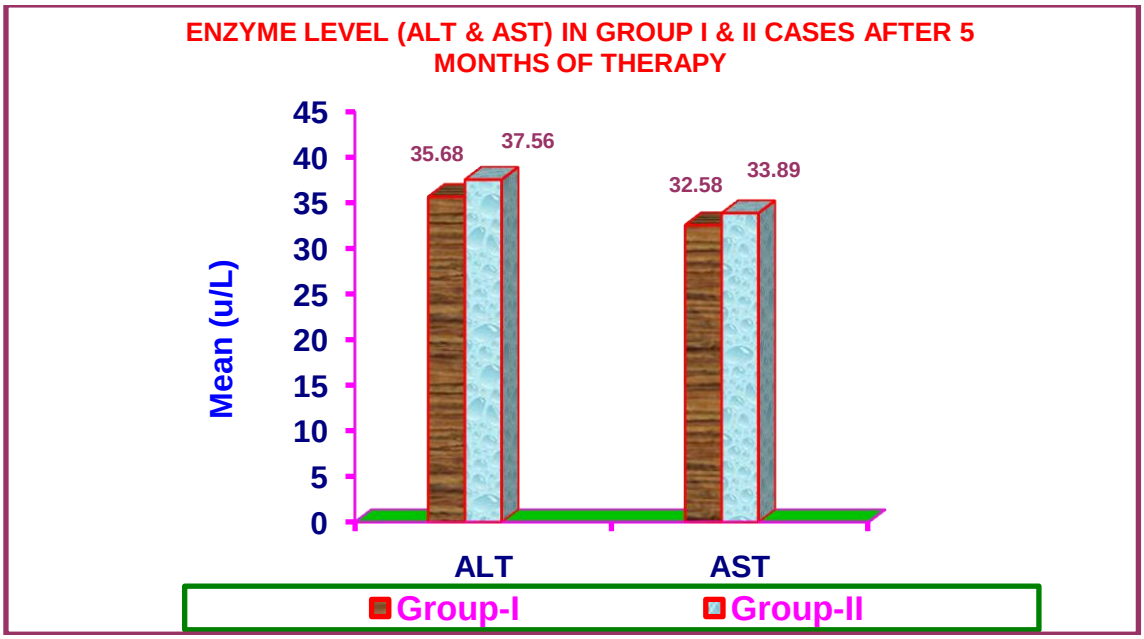
| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 20-55 | 38.80 | 12.21 | T = 4.51 P = 0.063 | 23-42 | 33.52 | 5.71 | T = 6.07 P = 0.051 |
| Group | 100 | 30-72 | 42.28 | 14.09 | | 20-48 | 35.56 | 8.7 | |

| Ii | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|



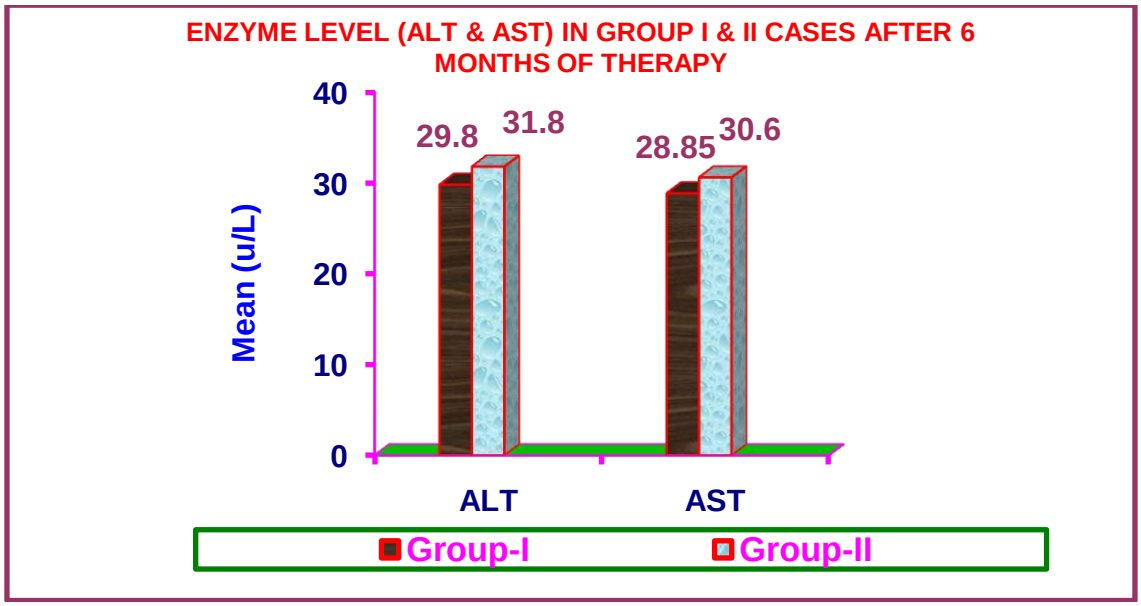

**Observation 7**-Enzyme Level (Alt &Ast) In Group I & Ii Cases After5 Month Of Therapy

| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 28-46 | 35.68 | 6.8 | T = 3.79 P = 0.073 | 24-42 | 32.58 | 4.65 | T = 4.66 P = 0.051 |
| Group Ii | 100 | 30-52 | 37.56 | 7.9 | | 26-45 | 33.89 | 4.80 | |



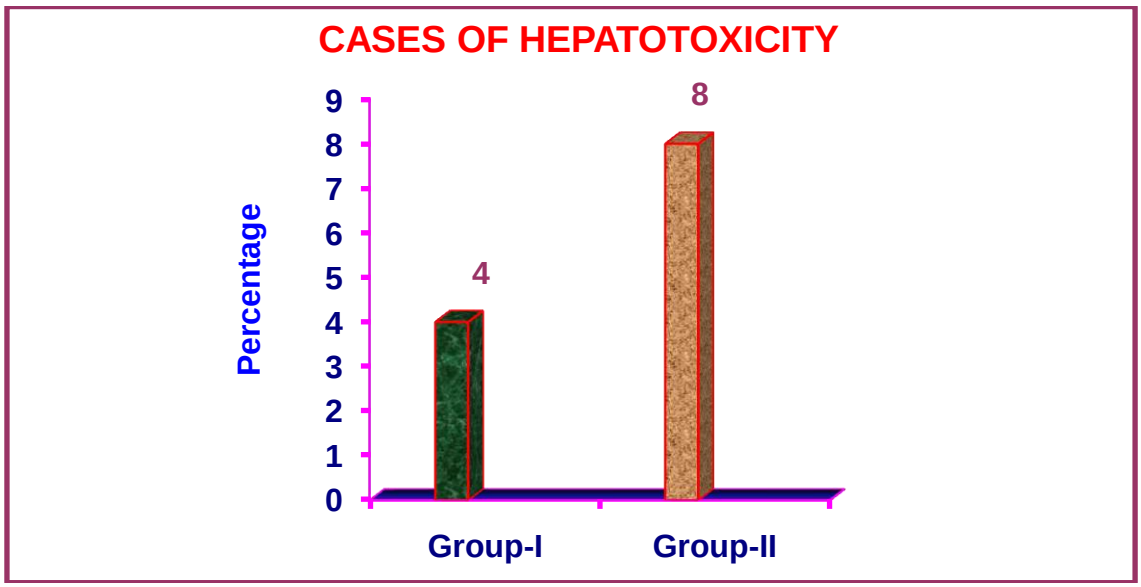

**Observation 8**-Enzyme Level (Alt &Ast) In Group I & Ii Cases After6 Month Of Therapy

| Group | No. Of Cases | Alt | | | | Ast | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Range | Mean | S.D. | Result | Range | Mean | S.D. | Result |
| Group I | 100 | 22-38 | 29.80 | 7.70 | T = 5.27 P = 0.070 | 20-38 | 28.85 | 6.70 | T = 6.85 P = 0.069 |
| Group Ii | 100 | 24-48 | 31.9 | 7.85 | | 20-40 | 30.6 | 6.85 | |




**Observation 9**- Cases Of Hepatotoxicity

| Group | No. Of Tb Patients | No. Of Patients With Hepatotoxicity | % | Result |
|---|---|---|---|---|
| Group I (Intermittent Regimen) | 100 | 4 | 4 | Odds Ratio = 2.08 P =0.40 |
| Group Ii (Daily Regimen) | 100 | 8 | 8 | |




## IV. Discussion

General Demographic Characteristics Of The Patients Were Having Mean Age 39.79±11.64 Years, 136 Males, 64Females And Mean Weight 43.5±7.5kg. There Were 132 Tribal Patients, 68 Non-Tribal Patients Signifying Prevalence Of Tuberculosis In Low Socioeconomic Group In The State.

In Both Group I And Group Ii, Enzyme Level Before Therapy Was Within Normal Limit. In Group I, Mean Alt Level Was 18.2±5.3 Iu/Lit. With S.E.M. 0.75 And In Group Ii Mean Alt Level Was 19.28±4.7 Iu/Lit. S.E.M. 0.67 With 'T' Value 1.07 And 'P' Value 0.28 Which Is Not Significant(Because P>0.05). Whereas Mean Ast Value In Group I Was 20.5±3.94 Iu/Lit. With S.E.M 0.55. In Group Ii Mean Ast Level Was 20.2±5.59iu/Lit., S.E.M 0.79 'T' Value 0.31 And 'P' Value 0.75 Which Is Not Significant (Because P>0.05). Thus Difference Of Values Was Not Significant.

After 1 Month Of Therapy It Was Analyzed That Most Of The Patients In Both Groups Showed Increase In Liver Enzymes Alt &Ast But Mostly Were Asymptomatic With < 3 Fold Elevation Of Serum

Transaminases. Mean Value Of Alt In Group I Was 43.18±19.6 Iu/Lit. And In Group Ii It Was 60.44±34.21 Iu/Lit. With S.E.M 2.77 And 4.83 Respectively ('T' Value 3.09, P Value 0.0026) I.E. Highly Significant. The Difference Of Mean Is Highly Significant Statistically But Not Significant Clinically Because 2-3 Times Of Upper Limit Of Normal (Uln) Were Of Not Much Significant After Anti Tuberculosis Drugs. The Incidence Of Hepatotoxicity In Both Groups (Group I And Group Ii) Is Much Higher Than Previous Studies From Usa And Uk (Timbrell Ja, 1985).[4] The Incidence Of Hepatotoxicity Has Been Reported To Be Higher In Developing Countries And Factors Such As Acute And Chronic Liver Disease, Poor Nutrition, Wide Spread Parasitism, Chronic Infections, Indiscriminate Use Of Various Drugs, Ethnic Factors, Severity Of Disease Or Genetic Predisposition May Play A Role Individually Or Collectively (Kumar A, 1991; Ungo J R, 1998).[5,6]

At The 2 Months Of Therapy, There Was Again Variation In The Liver Enzymes. In Group I, Mean Alt Level Was 47.06 ± 25.62 Iu/Lit. With S.E.M 3.62 And In Group Ii It Was 64.1 ± 31.81 Iu/Lit.With S.E.M 4.49. The T Value Was 2.95 And P Value Was 0.004, Which Was Statistically Significant. There Was Increase Level Of Enzymes In Both Group I And Ii But More In Group Ii.However, When Drug Induced Liver Injury Occurs Following The Use Of 4 Drug Combination Regimen, It Is Impossible To Quantify The Contribution Of Each Drug In The Development Of Drug Induced Liver Injury (HarshadDevarbhavi, 2012).[7]

With The Continuation Of Therapy With Rifampicin And Isoniazid At Third, Fourth And Fifth Month, It Was Observed That Liver Enzymes Were Declining.At The Completion Of Therapy (6 Months) The Mean Of Alt In Group I & Ii (In Unit/L) Were 29.80±7.70 And 31.8±7.85 With Paired 'T' Test 5.27 And P=0.070. Ast Level 28.85±6.70 And 30.6±6.85 In Group I And Ii Respectively, 'T' Value Is 6.85 And P=0.069 (Not Significant). Thus Even On Completion Of Therapy, There Is Difference In Alt And Ast In Group I And Ii, Although Both Were Within Normal Limit (Table-10). These Values Are In Accordance With K.C. Chang C.C. Et Al, 2007; De Souza Af, 1996; Singh J 1996, Altman 1993.[8,9,10,11]

In The Patients Of Hepatotoxicity, After Recovery, Low Dose Of Inh And Ethambutol Were Reintroduced And After One Week Rifampicin Was Added. None Of The 12 Patients Had Reoccurrence Of Hepatotoxicity Later On. So This Cohort Study Revealed That It Is Possible To Reinstitution Of Potentially Hepatotoxic Agents After Recovery. Mechanism For This Adaptation Is Not Known. It Was Observed That Gradually Introducing The Drugs By Giving Them In Increasing Number And Dosage Is The Reason For The Successful Retreatment Procedure (L.P. Omerod, C. Skinner; Hepatotoxicity Of Att 1996).[12]Normally Pyrazinamide Is Avoided For Reintroduction Because Some Studies Have Reported Fatal Hepatic Necrosis Caused By Pza (Durand F Et Al, 2005).[13]

There Were Total 136/64 Male/Female Patients With 64/36 In Group I And 72/28 In Group Ii In This Study. Overall Percentage Hepatotoxicity Rate Were 4.4%/9.37% In The Male/Female Population. Previous Studies By Snider De, 1992; DesouzaAf, 1996; Singh J 1996 Showed The Independent Predictor For Drug Induced Hepatotoxicity For Female Gender.[8,9,10] Although Women Have Traditionally Been Considered More Susceptible To Develop Tb Drug Induced Liver Injury, Recent Reports Suggest That Men Outnumber Women In The Incidence Of Tb Drug Induced Liver Injury. This Likely Reflects The Demographic Disparity Where More Men Than Women Are Under Treatment For Tuberculosis. However Female Gender Is A Positive Predictor Of More Severe Liver Disease Including Death (Devarbhavi H Et Al, 2010).[14]

The Incidence Of Hepatotoxicity In Both Group I And Ii Which Was 4% In Intermittent Therapy And 8% In Daily Regimen Therapy With Odds Ratio 2.08 And P Value 0.40 Which Was Not Significant. This Value Was Higher Than The Previous Studies Done In Uk And Usa (LpOmerod Et Al, 2996).[12] But The Value Was Lower Than The Studies Done In Nepalese Population (8% In Supervised Therapy) (Shakya R, Rao Bs, 2004).[15]

Att Can Cause Varied Degree Of Hepatotoxicity From A Transitory Asymptomatic Rise In Transaminases To A Acute Liver Failure In Both Daily And Thrice Weekly Therapy. The Frequency Of Hepatotoxicity In Different Countries Varies Widely From 2-39% Shown In Previous Studies (Anand Ac Et Al, 2000).[16]Previous Randomized Controlled Trials Involving Combination Therapy With Isoniazid, Pyrazinamide And Rifampicin In The Initial Phase Showed That Daily Treatment May Be More Hepatotoxic Than Thrice Weekly Treatment But This Is Not Applicable For The Standard 6 Months. Moreover There Is Paralleled Rise In Transaminases With Drugs.

## V. Conclusion

On The Basis Of Above Observation Made In The Prospective Cohort Study, It Can Be Concluded That Liver Enzyme Alteration Is Most Common Finding In The Patient Receiving Anti-Tubercular Chemotherapy. Revised Who Regimen, Directly Observed Therapy Short (Dots) Course Is Most Cost-Effective Therapeutic Programme, Especially For Developing Countries Like India. Hence, Every Patient Of Tuberculosis Should Be Given Antitubercular Drugs Under Direct Supervision, As It Increases The Patient Adherence To Treatment Regimens, Less Increase Of Alt And Ast, Thus Less Prone To Develop Hepatotoxicity, More Compliant To Patient, Increased Effectiveness With Easy Availability In All Government Hospitals And Awareness Of Patient About The Disease.

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