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A study on Drug induced hepatotoxicity during Antiretroviral therapy for HIV/AIDS

KEYWORDS: Hepatotoxicity, ART therapy, HIV/AIDS

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ABSTRACT **Aim:** To find out the clinical profile and risk factors for the hepatotoxicity in patients receiving ART therapy for AIDS. **Materials and Methods:** A total of 1250 patients were screened and patients who developed liver injury during ART therapy were selected. About 50 adult patients of both the sexes were included in the study. Records of these patients were analysed. Further testing was done as needed. Various parameters were noted. Statistical analysis was done by Oneway ANOVA F test, in which correlation between various parameters and hepatotoxicity were analysed. Results were tabulated and compared with various published series worldwide. **Conclusion:** As per this study the major risk factors for hepatotoxicity were Hepatitis Binfection, Hepatitis C Infection, Low CD4 counts, alcohol abuse in HBV ,HCV positive patients. The risk of liver injury was independent of age, sex, BMI, various drug combinations, Duration of ART. These results were comparable with published series from various countries although subtle differences exist.

INTRODUCTION

Human immunodeficiency virus (HIV) infection/ Acquired Immunodeficiency Syndrome is a global pandemic, with cases reported from virtually every country. With more than 35 million fatalities, the AIDS epidemic now ranks alongside the influenza pandemic of the early 1900s and the Bubonic plague of the fourteenth century in terms of fatalities[1].

Statistics for the end of 2008 indicate that around 33 million people are living with HIV, the virus that causes AIDS. 2.7 million more people become infected with HIV and 2 million die of AIDS every year [2]. HIV and AIDS are found in all parts of the world, the worst affected region is sub-Saharan Africa, where in a few countries more than one in five adults is infected with HIV.

HEPATOBILIARY MANIFESTAIONS OF HIV/AIDS:

Hepatobiliary disease in HIV-infected patients can be divided into two groups: Those with severe immunosuppression, who commonly have opportunistic infections, and those with suppressed HIV viral loads and minimal immunosuppression. Clinical manifestations of hepatobiliary disease can vary from no symptoms to liver failure[3,4]

ART INDUCED LIVER DISEASE

Highly active antiretroviral therapy (ART) has dramatically changed the course of HIV infection, havingdecreased the morbidity and mortality derived from classical opportunistic infections.In the recentera of ART therapy (between 2000 and 2005), the estimated expectedsurvival for a 25-year-old HIV-infected person was 39 years, compared with only 7 years for the same individual in the pre-ART era[5].

Antiretroviral drug-related liver injury **(ARLI)** is a common cause of morbidity, mortality and treatment discontinuation in HIV-infected patients[6]. Prevention and management of ARLI have emerged as major issues among HIV-infected patients in the era of ART[7]. In addition, certain comorbidities, such as chronic hepatitis B (HBV) or hepatitis C (HCV) infection, may predispose patients to ARLI[8]. Several major mechanisms of ARLI have been described, including metabolic host-mediated injury, hypersensitivity reactions, mitochondrial toxicity, and immune reconstitution phenomena. The management of ARLI should be based on its clinical severity and underlying pathogenic mechanism. Therefore, it is imperative to rule out other potential aetiologies before discontinuing ART drugs.

DEFINITIONS OFART-ASSOCIATED HEPATOTOXICITY

The AIDS Clinical Trials Group currently uses the following toxicity grading scale:

Patients with normalpretreatment ALT/AST:

Grade 0 hepatotoxicity <1.25 times the ULN (upper limit of normal)Grade 1 hepatotoxicity 1.25 to 2.5 times the ULN, Grade 2 hepatotoxicity 2.5 to 5 times the ULN, Grade 3 hepatotoxicity 5.1 to 10 times the ULN, Grade 4 hepatotoxicity >10 times the ULN

INCIDENCE AND RISK FACTORS: After initiating ART, the reported incidence of severe liver toxicity ranges from **2 to 18%**.[8,9,10,11] Differences in study outcomes may reflectfrequency of liver enzymes determinations, heterogeneity in patient populations, other exogenous exposures, patterns ofmedication prescribing, chronic viral hepatitis prevalence, and criteria used for defining severe hepatotoxicity.

Hepatitis B and C co-infections: Liver toxicity, especially severe toxicity (grades 3 and 4),is clearly more frequent in HCV and/or HBV co-infectedindividuals treated with ART [12-15]. In one study, ahigher risk of hepatotoxicity was found in patients carrying HCV genotype 3 compared to other genotypes [13]. In addition to drug injury, flares in serum transaminase concentrations in a patient with chronic HBV can be related to several different factors, including viral rebound after withdrawal of effective anti-HBV therapy, breakthrough of drug-resistant HBV strains or spontaneous flares of HBV viraemia[14,15] .The clinician must bear this in mind before misinterpreting hepatic flares as drug injury.

Alcohol: Alcohol is a known hepatotoxin and its use has been associated with an increased risk of ARLI in the studies that have examined this variable .Chronic use may also predispose to hepatocyte injury by increasing oxidative damage to mitochondrial DNA and depleting stores of glutathione, an important scavenger of free oxygen radicals [16].

Other Predisposing Factors: Multiple studies have demonstrated that the risk of liver injury is increased in those with amino-transferase elevations prior to initiating ART .Other risk factors associated with ARLI include older age female gender first exposure to antiretroviral treatment and significant CD4 cell gains followingARTinitiation[17]

Nucleoside Reverse Transcriptase Inhibitors: NRTIs are associated with low incidence of elevated liver enzyme values, **5% to 6%** ranging from 7% with zidovudine, 9-13% with stavudine and 16% with didanosine[18]. Newer NRTI such as emtricitabine, abacavir and tenofovir are associated with a low incidence of mild asymptomatic aminotransferase elevations. Mitochondrial toxicity is an infrequent

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but distinctive type of hepatotoxicity associated with the use of NRTI that may evolve to acute liver failure with severe hepatomegaly and lactic acidosis [19].

NonnucleosideReverseTranscriptaseInhibitors: The incidence of elevated liver enzyme values with either drug has been reported to range from less than **2% to 20%**[20]Women who have CD4counts higher than 250 cells/mL are especially at risk for nevirapine-relatedfulminant hepatic failure [21]. Several studies continue to find women atgreater risk than men for elevated liver enzyme values, especially with nevirapine.This finding remains unexplained [22,23].

Protease Inhibitors: The phenomenon of ARLI became more evident after the introduction of PI drugs. Rates of hepatotoxicity from registration trials of various PI have ranged from **1% to 9.5%,** but few patients had serious liver-related outcomes [24] In comparison with other drugs in its class, full-dose ritonavir has consistently been shown to be more hepatotoxic. However, the use of low-dose ritonavir for pharmacokinetic boosting of other PI drugs appears to be safe [25]. Inpatients taking PIs, the incidence of elevated liver enzyme values is higher inthose who have HIV/HCV coinfection than in those who have HIV alone**.**

AIM OF THE STUDY: The study was conducted with the objective of to estimate the incidence of drug induced hepatotoxicity in patient receiving ART therapy for HIV/AIDS to analyze the risk factors that are associated with drug inducedhepatotoxicity in these patients

MATERIALS & METHODS: About 1250 patients who receive ART were screened and patients with evidence of liver dysfunction were isolated. Sample population was selected as follows.50 adult patients of both sexes infected with HIV and fulfill the WHO criteria for clinical AIDS receiving ART for a period of more than one month were included in the study**.**

Inclusioncriteria : Patients with HIV infectionwho receive ART therapy for > 1 months.

Exclusioncriteria: Patients with base line LFT abnormal, Evidence of extrahepatic cause of jaundice ,Past history of jaundice, clinical evidence of liver disease at the institution of ART, Antenatal mothers, Children< 13yearsAll patients who receive ART therapy who met the above criteria were included in the study The following were noted in each patient age, sex, BMI, alcohol usage. smoking , H/o jaundice in the past, drug allergy ,diabetes, tuberculosis (pulmonary/extra pulmonary),mode of acquisition of HIV, nadir CD4 countlatest CD4 count ,socio economic status, dose of each drug ,duration of therapy of each drug ,Drug withdrawal. other adverse reaction with the drug ,Anti tubercular therapy (ATT) ,Anti fungals, AntibioticsBase line LFTs were measured Those who have abnormal LFT following were noted: USG, HBsAg, anti HCVantibodies, Prothrombintime, Chest X ray ,complete blood count ,bleeding time

Study design: Retrospective Analytical Study Venue: TVMCH, Tirunelveli. Period:2009 to 2010.Collaborating departments **:**ART Clinic; Department Of Medical Gastro enterology and Liver Clinic, TVMCH, Tirunelveli. Statistical analysis were made by Oneway ANOVA F test. Difference between variables calculatedby Student independent t- test using SSPS software. P value less than 0.05 considered significant

RESULTS:

Totalscreened:1250;Samplesize:50: Hepatotoxicity:4%

Table: 1 Descriptive Statistics

Table:1	N	Min.	Max	Mean	S.D
AGE	50	23	58	38.92	8.926
BMI	50	14.2	25.7	18.982	2.5976
CD4COUNT	50	41	211	110.14	37.861
TB	50	3	7	4.40	0.910
SGOT	50	250	397	332.10	45.651
SGPT	50	235	499	395.44	64.074
ALP	50	184	285	235.18	29.230
DURATION OF ART	50	2.92	7.54	4.4030	1.0977

AGE GROUP

Table:2 Considering Age as an independent factor for elevated liver enzymes, 2 age groups were analysed (A < 40 yrs, B >40). Though age >40 yrs showed elevated liver enzymes,There was no stastistical significance between age and hepatotoxicity

Table2	< 40 yrs		>40 yrs		
	Mean	SD	Mean	SD	Oneway ANOVA F Test
TB	4.02	0.551	4.92	1.056	F =4.179 P =0.000
SGOT	314.10	44.481	356.95	34.896	F =2.050 P =0.040
SGPT	376.03	51.211	422.24	71.321	F =1.302 P =0.258
ALP	219.52	19.057	256.81	27.164	F =1.817 P =0.072

SEX

Table :3 Comparing the means of liver function tests with Sex (table 3) showed no statistically significant correlation

Table 3	Male		Female		Oneway ANOVAF test
	Mean	SD	Mean	SD	
TB	4.52	1.100	4.20	0.414	F=1.495 P=0.227
SGOT	319.81	53.296	352.16	15.942	F=6.591 P=0.013
SGPT	393.94	78.328	397.89	30.663	F=0.044 P=0.835
ALP	244.32	31.899	220.26	15.846	F=9.339 P=0.004

BODY MASS INDEX (BMI)-

Table:4 - Analysis of data with BMI as an independent variable showed no correlation with elevation of Total Bilirubin, AST, ALT, ALP ($p<0.05$)

Table 4	BMI				
	<18.5		> 18.5		Oneway ANOVA F Test
	Mean	SD	Mean	SD	
TB	4.23	0.937	4.55	0.875	F=1.566, P=0.217
SGOT	325.71	54.357	338.00	35.930	F=0.903 P=0.347
SGPT	390.33	68.908	400.15	60.250	F=0.289 P=0.593
ALP	230.92	33.060	239.12	25.210	F=0.981 P=0.327

ALCOHOL :

Table:5 -Correlation with alcohol and hepatotoxicity did not show any statistical significance. (p =0.53).The risk of hepatotoxicity did not have correlation with alcohol consumption.

Table 5	ALCOHOL				
	YES		NO		Oneway ANOVA F Test
	Mean	SD	Mean	SD	
TB	4.61	1.216	4.27	0.650	F=1.577 P=0.215
SGOT	335.53	51.418	330.00	42.492	F=0.170 P=0.682

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SGPT	426.68	69.585	376.29	52.945	F=8.385 P=0.006
ALP	247.00	30.944	227.94	26.043	F=0.006 P=0.024

Cd4 COUNT:

Table:6-The association of hepatotoxicity with different CD4 counts categories was analysed. Patients belonging to CD4 count < 110 have significant correlation with TB, AST, ALT, and ALP. (p <0.04). hepatotoxicity correlates well with low CD4 count .

Table 6	< 110		>110		Oneway ANOVA F test
	Mean	SD	Mean	SD	
TB	4.61	1.042	4.15	0.663	F=3.433 P=0.070
SGOT	353.48	34.440	307.00	44.946	F=17.109 P=0.000
SGPT	413.78	60.292	373.91	64.074	F=5.222 P=0.027
ALP	238.44	30.808	231.35	29.230	F=0.728 P=0.398

HBV -

Table:7-: The risk of Coinfection with HBV increases the risk of hepatotoxicity.The data analysed show positive correlation with HBV positivity with TB, AST, ALT, ALP(p<0.01)..On combining HBV coinfection and alcohol abuse there was a positive correlation with TB, AST, ALT, ALP. (p< 0.03).

Table 7	HBV				
	YES		NO		Oneway ANOVA F test
	Mean	SD	Mean	SD	
TB	4.98	1.133	4.25	0.910	F=5.549 P=0.023
SGOT	372.40	22.192	322.02	45.651	F=11.910 P=0.001
SGPT	463.70	36.185	378.38	64.074	F=19.561 P=0.000
ALP	259.10	28.041	229.20	29.230	F=9.890 P=0.003

HCV -

Table:8-: Coinfection with HCV increases the risk of hepatotoxicity. The data analyzed show positive correlation with HCV positivity with TB, AST, ALT, ALP (p<0.05). Patients with HCV infection had higher levels of T.B, AST, ALT

Table 8	HCV				
	YES		NO		Oneway ANOVAF test
	Mean	SD	Mean	SD	
TB	6.13	0.252	4.29	0.819	F=14.851 P=0.001
SGOT	386.00	12.767	328.66	44.847	F=4.794 P=0.033
SGPT	487.67	8.386	389.55	61.482	F=5.422 P=0.024
ALP	271.67	5.508	232.85	28.573	F=5.422 P=0.024

ALCOHOL ,HBV and HCV -

Table:9 -significant risk associated with presence of combined factors of alcohol and HBV, HCV.(P<0.05)

Table 9	ALCOHOL-HBV-HCV				
	YES		NO		Oneway ANOVA F Test
	Mean	SD	Mean	SD	
TB	5.31	1.075	4.20	0.745	F=13.897 P=0.001
SGOT	376.56	24.414	322.34	43.491	F=12.946 P=0.001
SGPT	480.78	16.791	376.71	54.539	F=31.646 P=0.000
ALP	271.56	9.235	227.20	25.817	F=25.495 P=0.001

REGIMEN, DURATION-

Table:10,11,12 Considering associations between various treatment regimens

Table 10	REGIMEN			
	ALN		ALE	
	Mean	SD	Mean	SD
TB	4.41	1.035	3.98	0.340
SGOT	322.69	48.981	291.00	61.281
SGPT	386.13	65.207	389.00	115.761
ALP	231.13	26.066	229.75	32.725

Table11	REGIMEN				
	SLN		SLE		Oneway Anova F Test
	Mean	SD	Mean	SD	
TB	4.34	0.894	4.64	.916	F=0.549 P=0.651
SGOT	337.53	40.315	351.36	35.767	F=2.201 P=0.101
SGPT	404.11	51.097	396.36	68.701	F=0.231 P=0.874
ALP	233.63	31.261	245.73	30.365	F=0.629 P=0.600

Table12	DURATION OF ART				
	Mean	SD	Mean	SD	OnewayAnovaFTest
T.B	4.82	0.944	4.18	0.826	F=5.976 P=0.018
SGOT	357.41	31.853	319.06	46.563	F=9.252 P=0.004
SGPT	409.18	64.189	388.36	63.831	F=1.188 P=0.281
ALP	242.82	31.235	231.24	27.811	F=1.790 P=0.187

REGIMEN 1: Zidovudine + Lamivudine + Nevirapine (ALN) REGIMEN 2: Zidovudine + Lamivudine + Efavirenz (ALE)REGIMEN 3: Stavudine + Lamivudine + Nevirapine (SLN)REGIMEN 4: Stavudine + Lamivudine + Efavirenz (SLE) andLiver Function Test (TB, AST, ALT, ALP,). The data were analysed by One way ANOVA F test. There was no statistical difference between different regimens in causing hepatotoxicity (p> 0.05).Correlation with duration of ART and hepatotoxicity did not show any statistical significance. (p =0.53).The risk of hepatotoxicity did not have correlation with duration of ART

DISCUSSION: There is an increase in the reporting of drug induced liver injuryfollowing ART therapysince 1995 following wide spread usage of antiretrovirals[26] .

The incidence of drug hepatotoxicity has been variously reported. It ranged from 5% to 30% in different series (17 cohorts and 2 metaanalysis). Less often they cause steatosis, Lactic acidosis and encephalopathy with mortality rates between 0.1 to 7%.Our incidence is likely to be around 4%when grade 3 or 4 injury is taken as cut off limit.

We compared our results with that of the literature available on this issue. Much of the data came from large trials like Amsterdam, CHORUS, ICONA and TARGET which involved more than 5100patients [27,28]

AGE, SEX AND BMI: Age was not considered to be an individual risk factor in most of the published series.Age has not been found

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consistently to be an independent risk for elevatedliver enzyme values[29,30]. As large trials like Saves failed to demonstrate any correlation with age. Our series alsofound no correlation to the incidence of hepatotoxicity with age.Female sex was associated with increased incidence of hepatotoxicity in two of the major trials. Martin-Carboneroet al and Wit et al have shown independently that female sex is an independent risk factor and the risk increases with females who are obese and who drink alcohol. Our data found no correlation of hepatotoxicity with gender. Both sexes had equal incidence of liver injury. Obese patients had a higher risk of hepatic steatosis and liver injury (Carr A et al).

Other studies have shown that malnutrition and low BMI are also contributory factors in hepatic injury in Asian and African populations (Sampras K et al). In our series there is a no correlation with liver injury (Bilirubin level, AST, ALT) with BMI .

DRUGS AND REGIMENS: Previously number of reports of increased liver injury were attributed to certain drugs like Zidovudine, Nevirapine , full dose Ritonavir. Review of 17 clinical trials between 1991 to 2001 in FDA database attributes risk of liver injury for Nevirapine (NVP) and Efavirenz (EFZ).

In 2NN study, post exposure prophylaxis of NVP was associated withsevere liver injury and it was recommended to exclude NVP from PEP programs. Our series included 4 standard regimen (AZT + Lamivudine + Nevirapine , AZT + Lamivudine + Efavirenz, ,Stavudine + Lamivudine + Nevirapine, Stavudine + Lamivudine + Efavirenz,). When these were compared with the incidence of liver injury there was no correlation. All regimens had equal incidence of hepatotoxicity following therapy [31,32].

ALCOHOL: Alcohol usage did not predispose to severe liver injury in studies by Saves et al [33], Suikowski et al[34] and Rodriguez-Rosado. However Nunez et al14 foundalcohol hascorrelation particularly following PI based regimens and in obese females (Martin –Carbonero). Our study did not find any correlation of hepatotoxicity with alcohol usage.However we found that there were significant risk associated with presence of combinedfactors of alcohol and HBV, HCV.

HEPATITIS B AND HEPATITIS C: There are atleast 10 studies which show consistent association of liver toxicity with HBV infection. Studies by Saves, Sulkowski, Den Brinker, D'Armino, Aceti[35] Wit , DeMaat have shown that HBV is an individual risk factor. The risk increased with high viral load, HBeAg positivity and raised baseline AST and ALT. Co infection with HCV is also identified as a contributing factor in these studiesWithdrawal of Lamivudine in HBV positive patients also found to have higher incidenceof hepatotoxicity.

In our patients HBV is strongly associated with increased incidence of hepatotoxicity. Ithas good correlation with Bilirubin, AST, ALT, The incidence ofHBVcoinfection in the sample is 20% and HCV 6%.

Cd4 COUNT: The correlation with CD4 count and hepatotoxicity was found in our study. Patients with CD4 < 100 cells ran a higher risk of hepatotoxicity and death. This is attributed to profound state of immune suppression and loss of liver regeneration functions. Studies by Saves had similar results.A study by Sulkowski showed that a rise in CD4 count following ART predisposes to severe hepatic injury. He attributes this phenomenon to immune reconstitution syndrome where restoration of cell mediated immunity caused aggressive hypersensitivity reaction to drugs. This phenomenon was also confirmed by other recentstudies[34,35,36]

Most of our patients had CD4 counts moderately elevated after induction of ART and this phenomenon was not observed in our series

CONCLUSIONS: The following were concluded at the end of the study

1. Drug induced liver injury occurs in 4% of patients following ART therapy

2. The risk factors for hepatotoxicity identified were low CD4 count, HBV co-infection, HCV infection and combined HBV, HCV co-infection & alcohol usage.

3. Age, Sex, BMI, alcohol usage alone, various regimens, duration of ART did not have any correlation with the incidence and severity of hepatotoxicity.

REFERENCES

1. Sulkowski MS, Moore RD, et al. Hepatitis C and progression ofHIVdisease. JAMA2002
2. UNAIDS (2009, November), 'AIDS epidemic update.
3. MelWicox C. Gastrointestinal Consequences of Infectionwith HIV.Sleisinger & Fordtran'sGASTROINTESTINAL AND LIVER DISEASE 8th Edition.Saunders 2006.
4. CemCengiz, James S. Park. HIVandLiverDiseases:Recent ClinicalAdvances: Clin Liver Dis 9 (2005).[3]1989;96:949–951.[181]
5. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005.Ann Intern Med 2007;146(2):87–95[new 3]
6. Nuñez MJ, Martin-Carbonero L, Moreno V, Valencia E, Garcia-Samaniego J, Gonzalez-Castillo J, et al. Impact of antiretroviral treatment-related toxicities on hospital admissions in HIV-infected patients. AIDS Res Hum Retroviruses 2006; 22:825-829.[med 1]
7. Palella F, Baker R, Moorman A, Chmiel J, Wood K, Brooks J, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune DeficSyndr 2006; 43:27-34.[med 2]
8. Núñez M, Lana R, Mendoza J, Martín-Carbonero L, Soriano V. Risk factors for severe hepatic injury following the introduction of ART. J Acquir Immune DefSyndr 2001; 27:426-431.[med 3]
9. Den Brinker M, Wit F, Wertheim-van Dillen P, Jurriaans S, Weel J, van Leeuwen R, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS 2000; 14:2895-2902.[med 5]
10. Rodríguez-Rosado R, García-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. AIDS 1998; 12:1256.[med 15]
11. Bonfanti P, Landonio S, Ricci E, Martinelli C, Fortuna P, Faggion I, et al. Risk factors for hepatotoxicity in patients treated with highly active antiretroviral therapy. J Acquir Immune DefSyndr 2001; 27:316-318.[med 18]
12. D'Arminio Monforte A, Bugarini R, Pezzotti P, De Luca A, Antinori A, Mussini C, et al. Low frequency of severe hepatotoxicity and association with HCV coinfection in HIV-positive patients treated with ART. J Acquir Immune DeficSyndr 2001; 28:114-123.[med 19]
13. Aceti A, Pasquazzi C, Zechini B, De Bac C, and the LIVERART Group. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV - the role of hepatitis B and C virus infection. J Acquir Immune DeficSyndr 2002; 29:41-48.[med 20].
14. Wit F, Weverling G, Weel J, Jurrians S, Lange J. Incidence and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis 2002; 186:23-31.[med 21]
15. Bessesen M, Ives D, Lawrence S, Condreay, , Sherman K. Chronic active hepatitis B exacerbations in HIV-infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis 1999; 28:1032-1035.[med 27]
16. Fromenty B, Pessayre D. Impaired mitochondrial function in microvesicularsteatosis. Effects of drugs, ethanol, hormones and cytokines. J Hepatol 1997; 26(suppl 2):43-53.[med 30]
17. Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated with antiretroviral combinations. Aquitain Cohort, France, 1996-1998. Grouped Epidemiologie Clinique de Sida en Aquitaine (GECSA). AIDS 1999;13(17):F115–21.[new 41]
18. Birkus G, Hitchcock M, Cihlar T. Assessment of mitochondrial toxicity in human cells treated bytenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother 2002; 46:716-723.[med 80]
19. Brinkman K, terHofstede H, Burger D, Smeitink J, Koopmans P. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. AIDS 1998; 12:1735-1744.[med 51]
20. Palmon R, Koo BC, Shoultz DA, et al. Lack of the hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. J Acquir Immune DeficSyndr 2002;29(4):340–5.[new 7]
21. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. HIV Med 2006;7 (4):255–60.[new 85]
22. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine in HIV-infected subjects. J Infect Dis 2005;191(6):825–9.[new 15]
23. Martin-CarboneroL,NunezM,Gonzalez-Lahoz J, et al. Incidence of liver injury after antiretroviral therapy with efavirenz or nevirapine. HIV Clin Trials 2003;4(2): 115–20.[new 60]
24. Sulkowski M. Drug-induced liver injury associated with antiretroviral therapy includes HIV-1 protease inhibitors. Clin Infect Dis 2004; 38(suppl 2):90-97.[med 102]
25. Cooper C, Parbhakar M, Angel J. Hepatitis associated with antiretroviral therapy dual versus single protease inhibitors in individuals coinfected with hepatitis C virus and HIV. Clin Infect Dis 2002; 334:1259-1263.[med 103]of antiretroviral therapy. J Acquir Immune DeficSyndr 2002; 30:65-68.[med 23]
26. Rodriguez-Rosado R, Garcia-Samaniego J, .Hepatotoxicity after introduction of highly active antiretroviral therapy. AIDS 1998 [12]
27. Nunez M, Lana R, Mendoza JL, et al. Risk factors for severe hepatic injury after highly active antiretroviral therapy. J Acquir Immune DeficSyndr 2001.[14]
28. Reisler R, Servoss JC, Sherman KE, et al. Incidence of hepatotoxicity and mortality 21

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adult antiretroviral treatment trials: ACTG Liver Diseases Focus Group Program International AIDS Society Conference , Buenos Aires(Argentina): 2001.[15]
29. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis 2002. [16]
30. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. J Acquir Immune DeficSyndr 2003;32(3):259–67 [new14]
31. MeravigliaP,SchiaviniM,Castagna A, etalLopinavir/ritonavir treatment in HIV antiretroviral- experienced patients: evaluation of risk factors for liver enzyme elevation. HIV Med 2004;5(5):334–43 [new 159]
32. Cahn P, Johnson M, Nusrat R, et al. Hepatic safety with nevirapine (NVP) and two nucleosides in patients with advanced HIV infection, from a placebo controlled clinical endpoint trial (1090). AIDS 2000 [20]
33. 154.Saves M, Vandentorren S, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort,France, 1996-1998. Grouped'Epidemiologie Clinique de Sida en Aquitaine(GECSA). AIDS [17]
34. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral treatment in adults infected with HIV and the role of hepatitis B or C virus infection. JAMA 2000 [13]
35. Aceti A, Pasquazzi C, Zechini B, et al. Hepatotoxicity development duringantiretroviral therapy containing protease inhibitors in patients with HIV: therole of hepatitis Band C vims infection. JAcquir Immune DeficSyndr 2002[26]
36. Reisler R, Servoss JC, Sherman KE, et al. Incidence of hepatotoxicity and mortality of 21 adult antiretroviral treatment trials: ACTG Liver Diseases FocusGroup Program International AIDS Society Conference , Buenos Aires(Argentina): 2001[15]