Original Article

Assessment of liver and renal functions in human immunodeficiency virus-infected persons on highly active antiretroviral therapy: A mixed cohort study

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Abstract

Background: Indian data on potential hepatorenal toxic effects of highly active antiretroviral therapy (HAART) in HIV/AIDS-affected persons is lacking.

Objectives: To assess hepatorenal abnormalities in HIV-infected persons on HAART in a hospital-based mixed cohort study using concurrent and nonconcurrent data analysis.

Methods: Hepatorenal function tests, urinalysis and ultrasonogaphy for liver/kidneys (when applicable) were assessed in 400 (men 185; women 215) persons aged 2–84 (mean 47.8) years on HAART. Acute liver toxicity, acute kidney injury and chronic kidney disease were defined depending upon abnormal serum alanine aminotransferase, urea and creatinine levels/clearance as per standard guidelines.

Results: The duration of HAART was 1 month to 9 years (mean 3.7 years) with 284 (71%) individuals being on treatment for ≤5years. The major HAART regimens included zidovudine + lamivudine + nevirapine in 175 (43.8%), tenofovir + lamivudine + efavirenz in 174 (43.5%) and zidovudine + lamivudine + efavirenz in 20 (5%) individuals and were associated with grade-1 hepatic dysfunction in 57 (14.3%) individuals, with men aged between 31 and 45 years on antiretroviral therapy for >5 years being mainly affected. Forty two (17.1%) of 246 individuals with anemia and 15 (9.7%) of 154 individuals without anemia showed hepatic dysfunction. None had acute kidney injury, chronic kidney disease or abnormal urinalysis or ultrasonography. In contrast, the pretreatment elevated serum alanine amiotranerase in 99 (22.3%) and blood urea and/or creatinine levels in 16 (4%) individuals decreased significantly post highly active antiretroviral therapy.

Conclusions: The study reflects the low frequency of regimen based highly active antiretroviral therapy-associated hepatic or nephrotoxicity despite prolonged use, especially in the absence of other risk factors. Preexisting anemia appears an important risk factor for highly active antiretroviral therapy-induced hepatotoxicity (OR 1.90, CI 95% CI 1.02–3.57, $P = 0.04$). Highly active antiretroviral therapy-associated nephrotoxicity was not a significant problem. Study of viral load or other risk factors and potential of each drug for hepatorenal toxicity/

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Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/ijdvl.IJDVL_169_18

How to cite this article: Mahajan VK, Wadhwa D, Sharma A, Chauhan S, Vashist S, Kumar P, *et al.* Assessment of liver and renal functions in human immunodeficiency virus-infected persons on highly active antiretroviral therapy: A mixed cohort study. Indian J Dermatol Venereol Leprol 2020;86:499-507.

Received: April, 2018. **Accepted:** October, 2019.

dysfunction in HIV affected were not part of the study. A small number of subjects and retrospective analysis of biochemical parameters were other important limitations.

Key words: Acquired immunodeficiency syndrome, anemia, CD4 counts, chronic kidney disease, hepatotoxicity, highly active antiretroviral therapy, Himachal Pradesh, human immunodeficiency virus, nephrotoxicity
MeSH terms: Acquired Immunodeficiency Syndrome; Antiretroviral Therapy; HIV infection

Introduction

Human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) is a major public health problem worldwide, particularly in developing nations of South-East Asia and Africa. As per World Health Organization (WHO) 2015 estimates, 36.7 million people are living with HIV worldwide despite impressive decline in new cases following HAART. India, with 21.17 lakh persons living with HIV/AIDS, accounts for the third-largest HIV affected in the world with estimated adult (15–49 years) prevalence of 0.26% (0.22%–0.32%) in 2015.[1] Manipur, Mizoram, Nagaland, Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Gujarat and Goa with a prevalence of 0.2% to 1.2% share the major burden.[2] Himachal Pradesh with approximately 70-lakh population had 5,723 HIV/AIDS-affected persons in 2015 with an estimated adult prevalence of 0.1%.[2] Approximately15.8 million people have access to HAART worldwide and the treatment coverage is likely to increase with the current strategy of initiating HAART in all HIV-positive individuals irrespective of CD4 counts.[3] However, potential toxic effects, occasionally life-threatening, of HAART over prolonged periods on hepatocytes and nephrons remain an important limitation for its long-term use.[4] The overall incidence of HAART-related hepatotoxicity varies across studies. It increases the risk of hepatitis C virus co-infection and resultant liver damage.[5,6] Acute, occasionally fatal, liver necrosis can occur from nevirapine and efavirenz-induced drug hypersensitivity syndrome.[7] Treatment with nucleoside reverse transcriptase inhibitors too has been associated with an overall rate of 12% severe hepatotoxicity.[8] Tenofovir disoproxil fumarate, in particular, gets accumulated actively in proximal renal tubules causing mitochondrial injury and functional disturbance.[9] Although Himachal Pradesh has a low disease prevalence, data on potential hepatorenal toxic effects of HAART in HIV/AIDS-affected persons is lacking. The study was performed with an objective to assess liver and renal functions in HIV-infected persons on HAART. This will help in the provisioning of comprehensive health care for affected persons envisaged in National AIDS Control Program.

Methods

The study design was a combined prospective and retrospective (mixed) cohort study with baseline data recorded at the time of first presentation in the institute affiliated antiretroviral therapy center, and new data (concurrent and nonconcurrent) obtained during the 9-month-study period between Feb and Oct 2017. It comprised 402 persons living with HIV/AIDS consecutively attending antiretroviral therapy center for consultation/drug supply on any day of the week during the study period. Sociodemographic details, HAART regimens with duration, last recorded CD4 counts and liver and kidney function test reports before initiating HAART were noted from antiretroviral therapy-booklets of enrolled subjects. They were examined for any clinical evidence of hepatorenal abnormality which could be attributable to HAART.Liver and kidney function tests and urinalysis, particularly for albuminuria and casts, were repeated in patients having no updated records or when available reports were >1 month old. Abdominal ultrasonography was performed for any hepatorenal abnormality in persons with altered serum alanine aminotransferase, blood urea and serum creatinine levels. Hepatotoxicity was graded based on serum alanine aminotransferase elevations >40.0 international units (IU; upper limit of normal range 6–40.0 IU) based on the AIDS Clinical Trial Group grading [Table 1].[10,11] Renal dysfunction was classified as acute kidney injury or chronic kidney disease [Table 2].[12-17] Acute kidney injury was defined as the development of any one of the following limits within 48 h: absolute increase in serum creatinine ≥0.3 mg/dl, percentage increase in serum creatinine ≥50% from baseline or decrease in urine output to <0.5 ml/kg/h for >6 h, and its clinical staging was according to diagnostic criteria by Acute Kidney Injury-Network based on serum creatinine.[12] Chronic kidney disease was defined and classified as kidney damage manifesting with albuminuria or decreased renal functions quantified by estimated glomerular filtration rate (eGFR) persisting for more than 3 months.[13-15] Staging of chronic kidney disease severity was as per National Kidney Foundation–Kidney Disease Outcomes Quality Initiative Classification.[14,16,17]

Data analysis

The recorded data for two patients was incomplete and they were excluded from final analysis. Mann–Whitney nonparametric test was used for variables that were not distributed normally. The χ^2 test/Student's *t*-test and one-way ANOVA test were used for statistical analysis of the categorical and parametric data. A P value <0.05 calculated at 5% level (95% confidence interval) was considered statistically significant.

Results

The baseline characteristics of study subjects are shown in Table 3. There were 185 (46.3%) males and 215 (53.8%)

Table 1: Biochemical parameters by duration of therapy and Grades of hepatic dysfunction based on serum levels of alanine aminotranferase before and after antiretroviral therapy by duration

Biochemical parameters (normal values)	Before ART (*n*=400)	After ART		*P*	Significance/remarks
		≤5 years (*n*=284)	>5 years (*n*=116)		
ALT (6-40 IU)					
Range	9-218	3-109	9-130	**<0.05**	**Significant**
Mean±SD	39.7±26.4	32.1±17.0	31.0±14.0		
Blood urea (13-45 mg/dl)					
Range	11-94	12-58	6-50	0.138	Not-significant
Mean±SD	28.4±10.4	27.0±7.9	27.5±7.6		
Serum creatinine (0.5-1.4 mg/dl)					
Range	0.3-4.7	0.1-2.7	0.1-6.9	NaN	Not-significant
Mean±SD	0.9±0.3	0.9±0.3	0.9±0.6		
Hepatic dysfunction improved after ART (*n*=99)					
Grades of hepatic dysfunction based on serum ALT levels[10,11] (normal 6-40 IU)	**Serum ALT levels (normal=6-40 IU)**			***P***	**Significance/remarks**
	Before ART (*n*=99)	**After ART**			
		<5 years (*n*=78)	**>5 years (*n*=21)**		
Grade-1 (ALT value lies between 1.25 and <2.5× ULN)					
Number of patients	83	65	18	**<0.05**	**Significant**/the elevated serum ALT levels before treatment decreased after ART
Range	41-96	8-61	17-41		
Mean±SD	60.83±17.6	28.83±9.9	29.88±9.34		
Grade-2 (ALT value lies between 2.5 and <5.0× ULN)					
Number of patients	15	12	3	**<0.05**	
Range	101-169	21-48	27-80		
Mean±SD	130.93±25.87	33.15±9.36	48.0±28.16		
Grade-3 (ALT value lies between 5.0 and <10× ULN)					
Number of patients	1	1	-	-	
Levels	218 IU	21 IU	-		
Mean±SD	-	-	-		
Grade-4 (ALT value lies ≥10×ULN)					
Number of patients	0	0	0	-	-
Hepatic dysfunction occurring following ART (*n*=57)					
Grades of hepatic dysfunction based on serum ALT levels (normal 6-40 IU)	**Before ART (*n*=57)**	**After ART**		***P***	**Significance/remarks**
		<5 years (*n*=33)	**>5 years (*n*=24)**		
Grade-1 (ALT value lies between 1.25 and <2.5 IU× ULN)					
Range	10-63	41-96	41-80	**<0.05**	**Significant**/the serum ALT levels before treatment increased after ART
Mean±SD	31.96±11.98	54.90±14.28	51.87±12.42		

One-way ANOVA test is used for comparison and a *P*<0.05 was considered statistically significant and depicted in bold. ALT: Alanine aminotransferase, IU: International units, ART: Antiretroviral therapy, ULN: Upper limit of normal, SD: Standard deviation

females aged between 2 and 84 (mean 47.8) years with majority, 302 (75.5%) individuals, being aged 16–45 years. None of them had other comorbidities like diabetes or hypertension. The majority, 223 (55.8%) individuals had CD4 counts of 200–500 cells/microliter and were in WHO stage-1 of the HIV disease while counts were <200 cells/microliter in 60 (15%) individuals. All were on regular highly active antiretroviral therapy for 1 month to 9 years (mean 3.7 years) and the majority, 284 (71%) individuals, were taking treatment for ≤5 years. The major antiretroviral therapy regimens comprised zidovudine + lamivudine + nevirapine in 175 (43.8%) and tenofovir + lamivudine + efavirenz in 174 (43.5%) individuals. The initial nevirapine-based antiretroviral therapy regimens in 6 (1.5%) persons were changed to tenofovir + lamivudine + efavirenz due to nevirapine hypersensitivity. Twenty nine (7.3%) individuals had been treated for pulmonary tuberculosis before HAART initiation. The only HBV co-infected subject had not received any additional drugs.

Tables 1 and 4 depict mean values of biochemical parameters with antiretroviral therapy duration. The mean values of serum alanine amiotransferase levels decreased significantly after antiretroviral therapy in 99 (22.3%) individuals;

Table 2: Staging of acute kidney injury and chronic kidney disease

Staging of acute kidney injury	Criteria
Stage 1	Increase in serum creatinine ≥0.3 mg/dl or ≥150%-200% from baseline
	Urine output <0.5 ml/kg/h for <6 h
Stage 2	Increase in serum creatinine ≥200-300% from baseline
	Urine output <0.5 ml/kg/h for >12 h
Stage 3	Increase in serum creatinine ≥300% from baseline
	Urine output <0.3 ml/kg/h for >24 h or no urine output for ≥12 h
Staging of chronic kidney disease	
Stage 1	Normal eGFR ≥90 mL/min per 1.73 m^2 and persistent albuminuria
Stage 2	eGFR between 60 and 89 mL/min per 1.73 m^2
Stage 3	eGFR between 30 and 59 mL/min per 1.73 m^2
Stage 4	eGFR between 15 and 29 mL/min per 1.73 m^2
Stage 5	eGFR <15 mL/min per 1.73 m^2 or end-stage renal disease

eGFR: Estimated glomerular filtration rate, AKI: Acute kidney injury.

GFR is measured time and is the standard for determining kidney function. Normal GFR is approximately 125 milliliters per minute in an adult averagely weighing 70 kg. Practically, calculated creatinine clearance is used as a correlate of GFR and is commonly estimated by using the following Cockcroft-Gault equation

$$*eCcr = \frac{(140 - age) \times (weight\ in\ kilograms) \times (0.85\ if\ female)}{72 \times serum\ creatinine\ in\ mg/dl}$$

*(eCcr = estimated Creatinine Clearance)

83 with grade-1, 15 with grade-2 and one with grade-3 hepatic dysfunction, particularly among individuals on tenofovir + lamivudine + efavirenz and abacavir + nevirapine regimens. The mean values of serum alanine aminotransferase before highly active antiretroviral therapy were 39.7 ± 26.4 IU which decreased to 32.1 ± 17.0 and 31.0 ± 14.0 IU in patients with ≤5 years and more than 5 years of HAART respectively. The difference was statistically significant suggesting improvement after therapy. Further analysis of hepatic dysfunction revealed that 57 (14.3%) individuals with normal serum alanine aminotransferase levels before HAART developed grade-1 hepatic dysfunction after therapy [Tables 1 and 5]. Among them, 36 (63.2%) individuals were aged between 31 and 45 years, 26 (45.6%) were on antiretroviral therapy for >5 years, and men outnumbered women by one and half times [Table 3]. However, the same antiretroviral therapy regimen was continued in all these patients by the treating physician.

Anemia (hemoglobin ≤11 g/dl) was present in 246 (61.5%) persons. Amongst this population, 42 (17.1%) versus 15 (9.7%) of the 154 individuals without anemia showed hepatic dysfunction suggesting HIV-affected persons with preexisting anemia are at increased risk for HAART-induced hepatotoxicity (OR 1.90, Cl 95% CI 1.02–3.57, $P = 0.04$).

None of the HIV-affected individuals fulfilled acute kidney injury or chronic kidney disease criteria before or after HAART or showed any investigative abnormality. Before HAART, the baseline values (mean±SD) for blood urea and creatinine were 28.4 ± 10.4mg/dl and 0.9 ± 0.3 mg/dl, respectively. These baseline values did not show significant alteration in patients who had received HAART either for ≤5 years or >5 years [Table 1]. The increased blood urea levels (>40 mg/dl) in ten patients and elevated serum creatinine (>1.4 mg/dl) levels in eight individuals, decreased after antiretroviral therapy most significantly in individuals on tenofovir + lamivudine + efavirenz, tenofovir + lamivudine + nevirapine or abacavir + nevirapine regimens [Tables 4 and 6].

There was history of nevirapine hypersensitivity in six, and treatment for pulmonary tuberculosis prior to initiating HAART in 29 individuals but no abnormality in hepatorenal function tests was noted. There was no information on alcohol abuse or concurrent infections, their treatment or prophylaxis, especially for *Pneumocystis jiroveci* pneumonia or viral hepatitis, recorded in the antiretroviral therapy booklet.

Discussion

The overall demographic profile of our study subjects was similar to that described in our previous report.[18] The majority, 75.5% persons, were between 16–45 years of age and women outnumbered men by 1.7 times. All individuals were on regular antiretroviral therapy for 1 month to 9 years (mean 3.7 years) having mean CD4 counts of 408.9 (range 33–1254) cells/µl. The majority, 223 (55.8%) individuals, had CD4 counts of 200–500 cells/µl and were in WHO stage-1 of the HIV disease.

All antiretroviral therapy drugs have been reported to cause hepatotoxicity varying from transaminitis to frank liver failure and nephrotoxicity varying from acute kidney injury to chronic kidney disease.[19-22] Further, highly active antiretroviral therapy-induced hepatotoxicity with a prevalence of 12% to 23% remains one of the major concerns for treatment compliance and adherence, and possibly drug resistance.[8,23] Nucleoside reverse transcriptase inhibitors (nevirapine, efavirenz, etravirine), in particular, have been associated with severe hepatotoxicity with overall prevalence of 12 per cent.[8] Nevirapine and tipranavir (a protease inhibitor) are particularly notorious in causing severe liver failure. Tipranavir is reported to cause grade-3 alanine aminotransferase elevations in 6.3% of patients.[24,25] Although hepatotoxicity occurs more frequently with nevirapine than efavirenz (1·4–17% versus 1.1–8% patients), drug hypersensitivity syndrome from both can cause acute/severe liver necrosis that may end fatally.[7,26-28] However, abacavir-associated hepatic or renal failure is less common.[29] We also made similar observations in 57 (14.3%) individuals on nevirapine or efavirenz based highly active

Table 3: Baseline characteristics of study subjects

Baseline characteristics	Number of HIV-affected individuals (%) (*n*=400)	Individuals with increased serum ALT levels after ART (Grade-1 hepatic dysfunction) Number of individuals (%) (*n*=57)	Individuals with increased blood urea and creatinine levels that improved after ART Number of individuals (%) (*n*=16)
Gender			
Men	185 (46.25)	34 (59.65)	8 (50)
Women	215 (53.75)	23 (40.35)	8 (50)
Men: Women	1:1.7	1.47:1	1:1
Age (years), range (mean)	2-84 (47.84)		
<15	30 (7.5)	3 (5.26)	2 (12.5)
16-30	66 (16.5)	8 (14.03)	3 (18.75)
31-45	236 (59.0)	36 (63.15)	8 (50)
46-60	59 (14.75)	9 (15.78)	2 (12.5)
>60	9 (2.25)	1 (1.75)	1 (6.25)
CD4 cell count (cells/µl), range (mean)	33-1254 (408.9)		
>500	117 (29.25)	16 (28.07)	4 (25)
>350-500	117 (29.25)	19 (33.33)	6 (37.5)
>200-350	106 (26.5)	12 (21.05)	4 (25)
>100-200	44 (11.0)	7 (12.28)	2 (12.5)
<100	16 (4.0)	3 (5.26)	0
Duration of ART (years), range (mean)	1 month-9 years 4 months (3.7 years)		
<1	27 (6.75)	4 (7.01)	1 (6.25)
>1-2	66 (16.5)	3 (5.36)	3 (18.75)
>2-3	59 (14.75)	7 (12.28)	1 (6.25)
>3-4	63 (15.75)	10 (17.54)	4 (25)
>4-5	69 (17.25)	7 (12.28)	2 (12.5)
>5-6	52 (13.0)	8 (14.03)	3 (8.75)
>6-7	38 (9.85	10 (17.54)	1 (6.25)
>7	26 (6.5)	8 (14.03)	1 (6.25)
ART drug regimens			
ZDV + 3TC + NVP (ZLN)	175 (43.75)	27 (47.36)	7 (43.75)
TDF + 3TC + EFV (TLE)	174 (43.5)	23 (40.35)	7 (43.75)
ZDV + 3TC + EFV (ZLE)	20 (5.0)	4 (7.01)	0
TDF + 3TC + NVP (TLN)	11 (2.75)	2 (3.5)	0
d4T + 3TC + NVP (SLN)	2 (0.5)	0	0
d4T + 3TC + EFV (SLE)	1 (0.25)	0	0
Abc + NVP	13 (3.25)	1 (1.75)	1 (6.25)
Abc + EFV	4 (1.0)	0	1 (6.25)
Other medical history			
Treatment for Pulmonary tuberculosis before ART	29 (7.25)	0	1 (6.25)
Nevirapine hypersensitivity	6 (1.5)	0	0
Hepatitis B (HbsAg)	1 (0.25)	0	0

ALT: Alanine aminotransferase, ART: Antiretroviral therapy, Abc: Abacavir, d4T: stavudine, EFV: efavirenz, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir disoproxil fumarate, ZDV: zidovudine, TLE: tenofovir + lamivudine + efavirenz, ZLN: zidovudine + lamivudine + nevirapine, SLE: stavudine + lamivudine + efavirenz, ZLE: zidovudine + lamivudine + efavirenz, SLN: stavudine + lamivudine + nevirapine, TLN: tenofovir + lamivudine + nevirapine

antiretroviral therapy having grade-1 hepatic toxicity as elevated serum alanine amiotranerase levels not requiring treatment discontinuation. Among them, almost 63% were aged between 31 and 45 years, 45.6% were on highly active antiretroviral therapy for ≥5 years, and men were affected one and half times more than women. In contrast, 99 (22.3%) individuals with grade-1 to grade-3 liver dysfunction initially showed improvement after highly active antiretroviral therapy suggesting that HIV infection *per se* may be an important cause of liver function abnormalities at least in some individuals. Similar observations have been made previously, especially during early stage of uncontrolled HIV replication or later from systemic opportunistic/concurrent infections with hepatitis B or C virus, Cytomegalovirus and

Table 4: Biochemical parameters by antiretroviral therapy regimens and its duration

Parameters	ZDV + 3TC + NVP (ZLN) *n*=175	TDF + 3TC + EFV (TLE) *n*=174	ZDV + 3TC + EFV (ZLE) *n*=20	TDF + 3TC + NVP (TLE) *n*=11	d4T + 3TC + NVP (SLN) *n*=2	d4T + 3TC + EFV (SLE) *n*=1	Abc + NVP *n*=13	Abc + EFV *n*=4
Duration of ART Range (mean)	1 year, 8 months-9 years (4 years 7 months)	1 month-7 years 5 months (2 years 7months)	7 months-7 years 6 months (3 years 2 months)	1 year 7 months-7 years (3 years 9 months)	6 years 9months-9 years 3 months (8 years)	7 years 5 months	4 years 3 months-7 years 5 months (5 years 3months)	3 months-5 years 2 months (1 year 9 months)
ALT (normal=6-40 IU)								
Before ART	31.21±21.96	42.42±30.35	36.45±20.89	42.90±31.57	19.0±4.24	30	38.76±16.12	39.25±33.77
After ART	31.0±14.35	30.94±12.98	32.3±17.91	38.09±25.04	21.0±0.01	16	26.69±9.63	37.0±7.70
P	0.9157	**<0.0001**	0.5041	0.6964	0.5716	-	**0.0293**	0.9009
Blood urea (normal=13-45 mg/dl)								
Before ART	28.35±10.99	28.97±10.93	26.65±7.99	27.18±12.48	22.0±8.48	30	30.61±16.88	20.75±5.05
C	28.06±7.40	28.13±7.58	27.25±8.05	25.45±6.80	15.0±1.41	37	19.69±5.45	19.25±2.87
P	0.7723	0.4054	0.8143	0.6907	0.3686	-	**0.0361**	0.6240
Serum Creatinine (normal=0.5-1.4 mg/dl)								
Before ART	0.94±0.41	0.95±0.30	0.86±0.28	1.0±0.29	0.8±0.1	0.9	1.17±1.66	0.77±0.17
After ART	0.93±0.53	0.88±0.25	0.83±0.33	0.8±0.13	0.65±0.21	0.5	0.69±0.18	0.62±0.12
P	0.8436	**0.0186**	0.7583	**0.0499**	0.4192	-	0.3103	0.1995

Student's *t*-test is used for comparison and a *P*<0.05 was considered statistically significant and depicted in bold. All data are presented as mean±standard deviation. ALT: Alanine aminotransferase, ART: Antiretroviral therapy, Abc: abacavir, d4T: stavudine, EFV: efavirenz, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir disoproxil fumarate, ZDV: zidovudine, TLE: tenofovir + lamivudine + efavirenz, ZLN: zidovudine + lamivudine + nevirapine, SLE: stavudine + lamivudine + efavirenz, ZLE: zidovudine + lamivudine + efavirenz, SLN: stavudine + lamivudine + nevirapine, TLN: tenofovir + lamivudine + nevirapine

Table 5: Grade-1 hepatic dysfunction by increased serum alanine aminotransferase levels after Antiretroviral therapy and its regimens and duration

Parameters	ZDV + 3TC + NVP (ZLN) *n*=27		TDF + 3TC + EFV (TLE) *n*=23		ZDV + 3TC + EFV (ZLE) *n*=4		TDF + 3TC + NVP (TLN) *n*=2		Abc + NVP *n*=1	
Duration of ART	≤5 years *n*=16	>5 years *n*=11	≤5 years *n*=16	>5 years *n*=7	≤5 years *n*=2	>5 years *n*=2	≤5 years *n*=2	>5 years *n*=0	≤5 years *n*=0	>5 years *n*=1
ALT (normal 6-40 IU)										
Before ART (range)	31.92±12.24 (14-63)		33.34±11.97 (11-49)		20.5±7.32 (10-26)		38.5±13.43 (29-48)		34	
After ART (range)	54.03±13.51 (41-94)		53.43±12.07 (41-80)		58.5±25.09 (43-96)		47.0±4.24 (44-50)		41	
P	**<0.0001**		**<0.0001**		**0.0272**		0.4833		-	
Significance	**Significant**		**Significant**		**Significant**		Not-significant		-	

Student's *t*-test is used for comparison and a *P*<0.05 was considered statistically significant and depicted in bold. All data are presented as mean±standard deviation when not specified. ALT: Alanine aminotransferase, ART: Antiretroviral therapy, Abc: abacavir, d4T: stavudine, EFV: efavirenz, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir disoproxil fumarate, ZDV: zidovudine, TLE: tenofovir + lamivudine + efavirenz, ZLN: zidovudine + lamivudine + nevirapine, SLE: stavudine + lamivudine + efavirenz, ZLE: zidovudine + lamivudine + efavirenz, SLN: stavudine + lamivudine + nevirapine, TLN: tenofovir + lamivudine + nevirapine

Epstein Barr virus, or their therapies, autoimmune hepatitis, or alcohol abuse.[30-32] However, details of these foregoing risk factors for abnormal liver functions were not available in our study. On the other hand, preexisting anemia appears to be a significant risk factor for antiretroviral therapy-induced hepatotoxicity in this study, in contrast to a report by Ugiagbe and Eze.[30]

Long-term HIV infection itself is associated with a wide spectrum of kidney damage (focal segmental glomerulosclerosisis, cryoglobulinemia, IgA nephropathy, amyloidosis, lupus-like immune complex glomerulopathy) in 6% to 48% HIV-infected persons.[33,34] Although no comparative Indian data could be found, young males of black races or individuals aged >40 years from other ethnic backgrounds, and preexisting diabetes or hypertension are important risk factors for HIV-associated nephropathy/chronic kidney disease before and after antiretroviral therapy.[10,20,21,35,36] Nephropathy typically presents with nephritic-range proteinuria (>3.5 g/d), azotemia, hypoalbuminemia and hyperlipidemia. Tenofovir and indinavir are well known for renal toxicity but isolated cases of nephrotoxicity with almost all HAART agents exist.[22] Highly active antiretroviral therapy for long periods is also strongly associated with increased risk for chronic kidney disease.[35,37,38] Antiretroviral therapy-induced renal toxicity with or without hepatotoxicity occurs in nearly 1.2% to 48% HIV-affected individuals leading to increased risk for acute renal failure, chronic kidney disease and mortality related to hemodynamic stress, volume depletion, radiocontrast or nephrotoxic drugs administration.[35,37,39-41] No clinical or laboratory evidence of acute kidney injury or chronic kidney disease, or intake of

Table 6: HIV-affected individuals with abnormal blood urea and creatinine levels

Age/ gender	Blood urea (normal=13-45 mg/dl)		Serum creatinine (normal=0.5-1.4 mg/dl)		ART regimens	Duration of ART
	Before ART	After ART	Before ART	After ART		
27 male	52	29	1.6	1.3	TLE	<5 year
37 female	56	28	1.2	1.0	TLE	<5 year
45 male	22	35	1.8	0.7	TLE	<5 year
30 female	53	26	1.6	0.8	TLE	<5 year
45 female	81	26	3.1	1.3	TLE	>5 year
48 female	62	29	0.9	1.0	TLE	<5 year
38 female	94	27	0.9	1.0	TLE	<5 year
42 male	79	40	2.0	1.0	ZLN	<5 year
32 male	27	20	4.7	0.9	ZLN	<5 year
42 male	36	27	1.9	1.0	ZLN	<5 year
45 male	59	32	1.1	1.0	ZLN	>5 year
65 female	72	39	0.6	1.0	ZLN	>5 year
28 female	24	30	0.8	6.9	ZLN	>5 year
60 male	21	20	2.8	2.7	ZLN	<5 year
10 female	82	25	0.6	1.0	Abc + NVP	>5 year
9 male	20	30	6.7	0.7	Abc + NVP	<5 year

ART: Antiretroviral therapy, Abc: abacavir, NVP: nevirapine, TLE: tenofovir + lamivudine + efavirenz; ZLN: zidovudine + lamivudine + nevirapine

nephrotoxic drug (s) (itraconzole, foscarnet, amphotericin, acyclovir, aminoglycosides, etc) for HIV-related opportunistic infections, the potential risk factors for renal dysfunction, was observed in our study. However, we did not perform renal biopsy for microscopic tissue damage. On the other hand, elevated urea in 10 (2.5%) and creatinine levels in 9 (2.3%) individuals on tenofovir + lamivudine + efavirenz, tenofovir + lamivudine + nevirapine or abacavir + nevirapine regimen decreased following therapy reflecting their possible low nephrotoxic potential despite prolonged use, particularly in the absence of other risk factors.

Although 29 individuals had treatment for pulmonary tuberculosis prior to initiating highly active antiretroviral therapy and other 6 individuals developed nevirapine hypersensitivity, details of any abnormal hepatorenal functions were not available.

Limitations

The Cockcroft–Gault equation used for defining/staging chronic kidney disease is not specifically validated in the HIV affected. Viral load studies or evaluation of other risk factors precipitating hepatorenal disease/toxicity/dysfunction in HIV affected were not part of the study. An analysis of recorded biochemical parameters on yearly basis was not possible from the antiretroviral therapy records. Since antiretroviral therapy in all HIV affected was regimen based, individual drugs responsible for hepatorenal abnormalities remained unidentified. Information on concomitant infections and their treatment/prophylaxis particularly for *Pneumocystis jiroveci* pneumonia, viral hepatitis, as well as history of alcohol abuse in study subjects was unrecorded. Thus, hepatic or renal function abnormalities from these potential risk factors in some of the HIV-affected study subjects cannot be ruled out. A small number of subjects and retrospective data analysis were other important limitations.

Conclusions

Nevirapine or efavirenz-based regimens of variable duration caused grade-1 hepatic toxicity in some individuals while HAART improved preexisting HIV-associated hepatic or renal dysfunction in the majority of cases. Preexisting anemia remains a significant risk factor for HAART-induced hepatotoxicity in this study. However, HAART nephrotoxicity was not a significant problem. The study reflects low potential of HAART-associated hepatic or nephrotoxicity despite prolonged use, especially in the absence of other risk factors. Nevertheless, better designed prospective studies are recommended for drug wise analysis and to delineate highly active antiretroviral therapy-associated hepatorenal dysfunction or other risk factors contributing toward it.

Statement of ethics

The study was approved by Institutional Scientific Review and Ethics Committee (Regn no.- ECR/490/Inst/HP/2013/RR-16). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. All patients were provided treatment and care as per standard guidelines.

Acknowledgements

The authors gratefully acknowledge the erudite help and support extended by Dr. B. S. Rana, Associate Professor of Gastroenterology and Hepatology and Dr. Pankaj Kumar, Assistant Professor of Internal Medicine, all from Dr. R. P. Govt. Medical College, Kangra (Tanda), H.P., India, in interpretation of liver and renal functions tests. We also thank

Mr. Sushant Sharma of Community Medicine (Biostatistics) and the staff members at antiretroviral therapy center, Dr. R. P. Govt Medical College, Kangra (Tanda), H.P. for providing useful inputs for the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients or their parents/guardians have given their consent for the patient's images and other clinical information to be reported in the journal. The patient/parents/guardians understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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