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Research Article

HIV and Endocrinological Disorders: A Cross Sectional Study in Nepal

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Abstract

Introduction: People living with HIV (PLHIV) are prone to non-communicable diseases. There is a growing concern for an increasing burden of endocrinopathy in PLHIV. The burden of endocrinopathies among PLHIV is lacking in the Nepal. We aim to measure the burden of endocrinopathies among adult PLHIV in Eastern Nepal.

Methods: We conducted a cross sectional study among patients receiving care in an Anti-Retroviral Treatment (ART) center in BP Koirala Institute of Health Sciences (BPKIHS). Hospital protocol was used to define endocrinopathies like Diabetes, Lipodystrophy. With 95% confidence interval and 95% power, we calculated sample size of 400 patients. Considering 25% as bias error the final sample size was 535. Case record form was used to record and tabulated in excel sheet. Descriptive and analytic statistics were used.

Results: The median age of PLHIV patients was 36 years. The prevalence of endocrinopathies was 38% among the cohort. Among 535 patients, 45% were men however among 93 cases of endocrinopathies 58% were males. The commonly observed endocrinopathies were dyslipidemia (5.2%) followed by type 2 Diabetes Mellitus (4.3%) and lipodystrophy (3%).

Conclusions: We found a substantial burden of endocrinopathies among PLHIV in low-income country despite 84% of cohort were less than 45 years. Our study recommends early screening and integration of care of endocrinopathies in among all PLHIV cases.

Keywords: *Endocrinopathies; PLHIV; Nepal*

Abbreviation

ART: Antiretroviral Therapy; BPKIHS: BP Koirala Institute of Health Sciences; COAD: Chronic Obstructive Airway Disease; DM: Diabetes Mellitus; Eps: Endocrinopathies; GLUT4: Glucose Transporter Type 4; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; NCD: Non Communicable Disease; PLHIV: People Living with HIV; RR: Relative Risk; SNPs: Single-nucleotide Polymorphisms

Introduction

According to WHO, among 36.9 million HIV/AIDS patients 3.5 million lives in South-East Asia [1]. Patients living with HIV (PLHIV) have an increased burden of non-communicable diseases (NCD) and it is estimated that more than a quarter of PLHIV will have three or more NCD by 2030 [2,3]. With Antiretroviral agents HIV-infected adults live longer placing these PLHIV adults increased cumulative risk

for NCD [4]. HIV infection is associated with a number of endocrine disorders together called as endocrinopathies (EPs). EPs may develop in early as well as late stages of HIV infection, ranging from subclinical to overt endocrine symptoms [5]. EPs associated with HIV result directly from the effects of HIV on endocrine function or arise secondary to interactions of endocrine organs with opportunistic infections, neoplasms, or antiretroviral therapy (ART) [6]. HIV affects almost all endocrine glands (adrenal, gonadal, hypothalamus-pituitary and thyroid) at varying rates [7,8]. PLHIV on ART from African countries and India experienced diabetes mellitus at higher rates compared to general public [9-12]. Antiretroviral drugs also increase the incidence of diabetes mellitus, cholesterol levels, abdominal fat and blood pressure according to Western studies [13]. More than 40,000 PLHIV are registered to ART centers in Nepal and EPs among them is likely to be profound [14]. A survey by National Public Health Laboratory Kathmandu, Nepal reported high rate (92.3%) of thyroid disorders in ART receiving PLHIV [15]. In Cameron 33.7% prevalence of hyperlipidemia was found among PLHIV [16]. Gaps of knowledge regarding high burden of EPs among PLHIV especially in developing countries might have underreported and undertreated the morbidities. The exact extent to which HIV patients are affected with EPs in Nepal is largely unknown. There is growing recognition of the contribution of EPs to the morbidity and mortality burden in the PLHIV. With regards to the HIV infected population, the burden of EPs remains unknown. We therefore set out to characterize the EPs burden among patients living with HIV infection in Eastern Nepal.

Methodology

A hospital based cross sectional study was done at B.P. Koirala Institute of Health Sciences which is a referral center and a university teaching hospital in Eastern Nepal. PLHIV aged 15 year and above were enrolled in the study after written consent. Pregnant and lactating patients were excluded. With 95% confidence interval and 95% power, we calculated sample size of 400 patients. Considering 25% as bias error the final sample size was 535. A validated and structured proforma that included socio-demographic details, HIV staging, underlying comorbidities, physical examinations, prescribed ART and other drugs, routine laboratory results and EPs was used as a tool to collect the data. Suspected EPs were confirmed by the expert from the endocrinology division and treated as per the division protocol. Diabetes mellitus, hypothyroidism, hyperthyroidism, lipodystrophy, hypovitaminosis were EPs of study interest. Diabetes mellitus and thyroid disorders were diagnosed using American Diabetes Association (ADA) and American Thyroid Association (ATA) Guidelines. Lipodystrophy was diagnosed clinically. Hypovitaminosis was defined as level of vitamin less than lower normal limit. The data were entered into MS Excel 2007 and descriptive statistics using mean, SD, percentages and frequencies were measured. The individual endocrinopathy was statistically correlated with the gender, stages of HIV/AIDS disease, ART regimen, and body mass index (BMI). An independent Student's t-test was used for continuous variables. Chi square test or Fisher's exact test was used for categorical variables to explore associations with patient characteristics at p-value of 0.05. SPSS version 11.5 was used for statistical analysis. The study's main outcome variables were the prevalence of EPs among PLHIV.

Results

More than half (53.1%) of the patients were from tropical regions, Sunsari district followed by Jhapa and Morang (Figure 1).

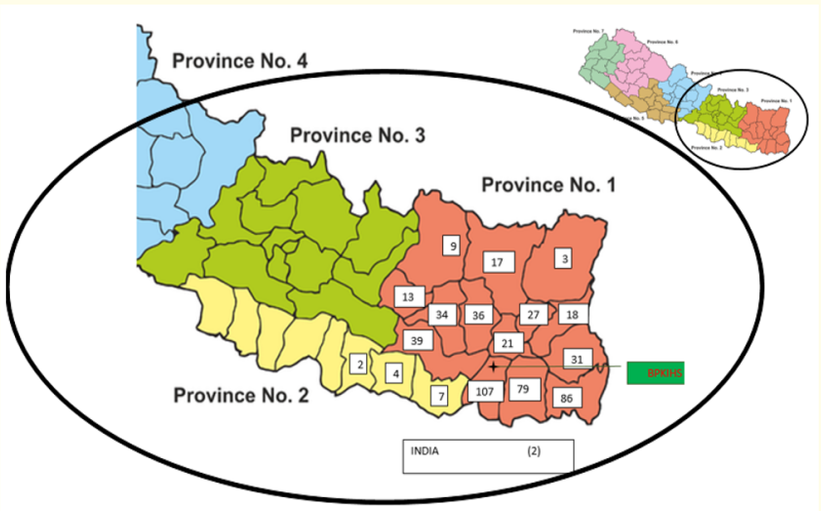

Figure 1: *Geographic distribution of the patients (n = 535).*

The mean and median age of the patients were 36.6 and 36 years respectively. Female outnumbered male among PLHIV with ratio of 1.2 and more than 70% of PLHIV were married. Around 70% of PLHIV were alcoholic beverage consumer and tobacco smoker. Unemployment was observed among 7.3% of the cases. More than 50% of them had received at least secondary level education (Table 1).

S.N.	Demographic characters	Measurement
1.	Age	
	1. Mean	36.6 ± 10.57 year
	2. Median	36 years
2.	Gender	
	1. Male	241 (45.0%)
	2. Female	290 (54.4%)
	3. Third Gender	4 (0.6%)
3.	Marital Status	
	1. Married	390 (72.9%)
	2. Widow/Widower/Divorcee	94 (17.6%)
	3. Unmarried	51 (9.5%)
4.	Alcoholic beverage consumption	
	1. Alcoholic	370 (69.2%)
	2. Nonalcoholic	60 (11.2%)
	3. Past-alcoholic	105 (19.6%)
5.	Tobacco consumption	
	1. Smoker	375 (70.1%)
	2. Non-smoker	82 (15.3%)
	3. Former-smoker	78 (14.6%)
6.	Occupation	
	1. Farmer	155 (29.0%)
	2. Housemaker	107 (20.0%)
	3. Businessman	83 (15.5%)
	4. Skilled Job	67 (12.5%)
	5. Government Job	54 (10.1%)
	6. Unemployed	39 (7.3%)
	7. Student	22 (4.1%)
	8. Unskilled job	8 (1.5%)
7.	Educational status	
	1. Illiterate	73 (13.6%)
	2. Primary	185 (34.6%)
	3. Secondary	211 (39.4%)
	4. Higher secondary	54 (10.1%)
	5. Bachelor and above	12 (2.2%)

Table 1: *Socio-demographic characteristics of the patients (n = 535).*

More than 80% of the PLHIV were less than 45 years age (Figure 2).

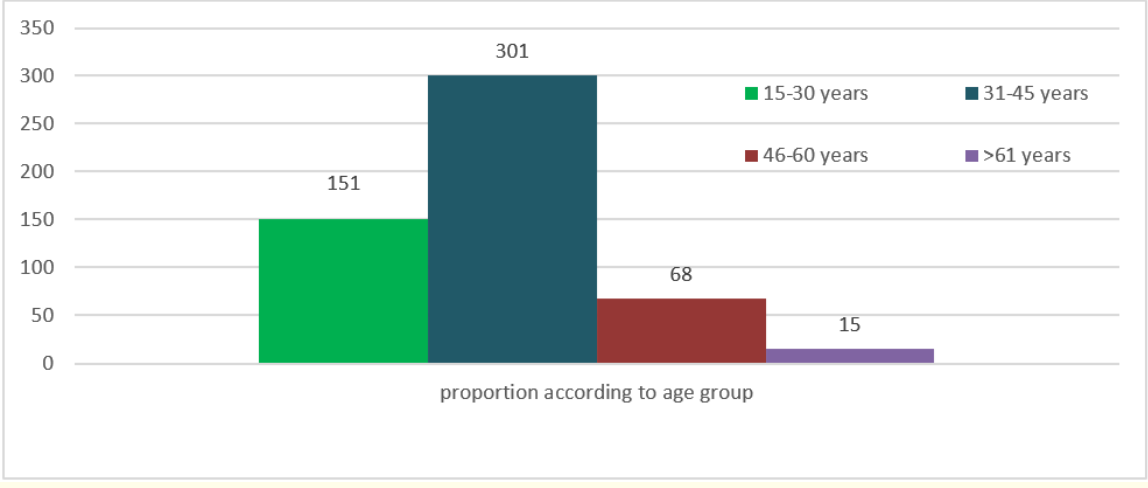

Figure 2: *Age distribution of PLHIV (n = 535).*

All PLHIV were on ART. 76.65% were on first line ART. All of them were in Lamivudine (3TC) followed by 70% on Tenofovir (TDF) and 53.5% on Efavirenz (EFV). The other ART prescribed were Zidovudine (ZDV), Nevirapine (NVP). Protease inhibitor (PI) and Raltegravir. Cotrimoxazole was well tolerated by 72.15% of the cases (Table 2).

S.N.	Drug regimen	Number
1.	Mean duration of HAART	6.1 years
2.	1st line ART	508 (76.6%)
	1. TDF/3TC/EFV	278 (54.7%)
	2. TDF/3TC/NVP	32 (6.3%)
	3. ZDV/3TC/EFV	94 (18.5%)
	4. ZDV/3TC/NVP	100 (19.7%)
	5. ABC/3TC/EFV	4 (0.8%)
3.	2nd and 3rd line ART Protease Inhibitor (PI)	27 (5%)
	1. Combination with Lopinavir (LVP)	18 (72%)
	2. Combination with Atazanavir (AZV)	7 (28%)
	3. Combination with Raltegravir	2 (0.4%)
5.	Prophylaxis against Opportunistic Infections	393 (73.5%)
	1. Cotrimoxazole	386 (72.1%)
	2. Azithromycin (1.2 gm/week)	5 (0.9%)
	3. Cotrimoxazole + Azithromycin	4 (0.8%)
	4. Isoniazid Prevention Therapy	12 (2.2%)

Table 2: *ART and other drugs consumed (n = 535).*

Non-communicable Disease (NCD) was present among 30.1% (161) cases the most common being steatohepatitis (5.8%) followed by dyslipidemia (5.2%). EPs contributed 57% of NCDs. EPs was diagnosed among 17.4% (93) of the PLHIV cohort. The common EPs besides dyslipidemia were type 2 diabetes mellitus (4.3%) and lipoatrophy (3%) (Figure 3).

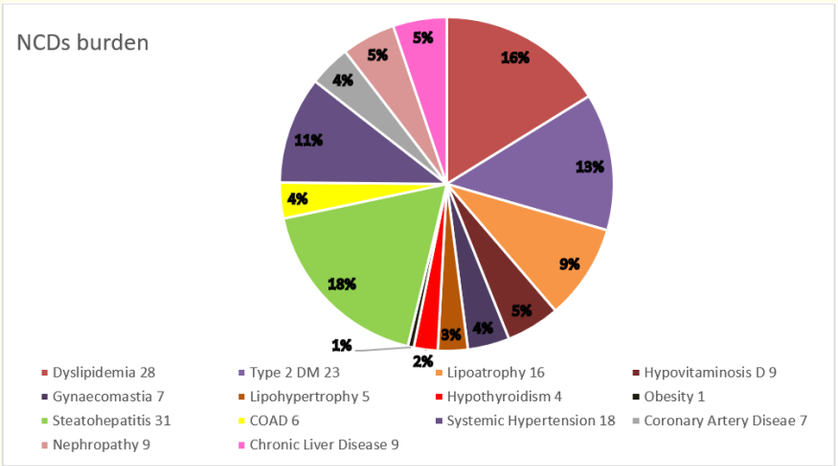

Figure 3: *Proportion of NCDs and EPs.*

Among EPs male gender was predominant (58%). Six patients had more than one endocrinopathy. Gynaecomastia was statistically significant with male PLHIV (p value 0.05) (Table 3).

Endocrinopathy	Male	Female	Total	Percentage	P Value
Dyslipidemia	17	11	28	5.2	0.75
Type 2 diabetes	14	9	23	4.3	0.78
Lipoatrophy	13	3	16	3.0	0.93
Hypovitaminosis D	0	9	9	1.7	0.13
Gynecomastia	7	0	7	1.3	0.05
Lipohypertrophy	3	2	5	0.9	0.96
Hypothyroidism	0	4	4	0.7	0.08
Obesity	0	1	1	0.2	0.54
Total	54	39	93	16.2	0.91

Table 3: *Association of EPs with gender.*

EPs in form of dyslipidemia and type 2 diabetes mellitus was statistically associated age categories less than 30 years whereas hypothyroidism was statistically significant with age categories less than 45 years (Table 4).

Endocrinopathy	Age < 30	Age > 30	P value	Age < 45	Age > 45	P Value
Dyslipidemia	2	26	0.01	22	6	0.37
Type 2 diabetes	0	23	0.002	18	5	0.39
Lipoatrophy	3	13	0.39	13	3	0.71
Hypovitaminosis D	1	8	0.25	9	0	0.19
Gynecomastia	1	6	0.41	6	1	0.91
Lipohypertrophy	2	3	0.55	2	3	0.06
Hypothyroidism	1	3	0.88	2	2	0.05
Obesity	1	0	0.11	1	0	0.66
Total	11	82	0.78	73	20	0.78

Table 4: *Association of EPs with age distribution.*

Base line CD4 cell count less than 250 was among 44% of EPs as compared to 11.4% of 535 PLHIV (p value < 0.0001). Hypovitaminosis D was significantly associated with CD4 counts less than 250/ml whereas subclinical hypothyroidism was significantly associated with CD4 counts more than 500/ml (Table 5).

Endocrinopathy	CD4 < 250	CD4 > 250	p value	CD4 < 500	CD4 > 500	p value
Dyslipidemia (n = 28)	12	16	0.567	19	9	0.237
Type 2 diabetes (n = 23)	13	10	0.058	21	2	0.096
Lipoatrophy (n = 16)	5	11	0.586	10	6	0.161
Hypovitaminosis D (n = 9)	7	2	0.012	7	1	0.393
Gynecomastia (n = 7)	2	5	0.614	7	0	0.146
Lipohypertrophy (n = 5)	2	3	0.917	5	0	0.220
Hypothyroidism (n = 4)	0	4	0.118	1	3	0.013
Obesity (n = 1)	0	1	0.436	1	0	0.584
Total (n = 93)	41	52	NA	72	21	NA

Table 5: *Association of EPs with baseline CD4 count.*

The relative risk of EPs was 4.86 among patient with protease therapy (p value < 0.0001). The relative risk of EPs on ZDV/3TC/EFV, TDF/3TC/NVP and ZDV/3TC/NVP were 1.28, 1.28 and 1.04 respectively. TDF/3TC/EFV was statistically associated as protective factor against EPs (p value 0.0001) (Table 6).

Endocrinopathy	TDF/3TC/EFV (n = 278)		ZDV/3TC/EFV (n = 94)		TDF/3TC/NVP (n = 32)		ZDV/ 3TC/NVP (n = 100)		Protease Inhibitor (n = 25)		Total
	N	RR	N	RR	N	RR	N	RR	N	RR	
Dyslipidemia	8	0.3	4	0.78	3	1.89	7	1.45	6	5.56	28
Type 2 diabetes	9	0.59	4	0.99	1	0.71	4	0.92	5	5.67	23
Lipoatrophy	3	0.21	3	1.08	2	2.25	4	1.45	4	6.8	16
Hypovitaminosis D	4	0.74	3	2.35	0	0	1	0.54	1	2.55	9
Gynecomastia	3	0.69	3	3.51	0	0	0	0	1	3.4	7
Lipohypertrophy	1	0.23	1	1.17	1	3.92	1	1.09	1	5.1	5
Hypothyroidism	2	0.92	1	1.56	0	0	1	1.45	0	0	4
Obesity	0	NA	1	NA	0	0	0	0	0	0	1
Total	30	0.44	20	1.28	7	1.28	18	1.04	18	4.9	93

Table 6: *Distribution of EPs with ART.*

Discussions

HIV has been associated with increase morbidities of endocrine disorders. In our study female PLHIV outnumbered with female to male ratio of 1.2 however EPs was common among male with female to male ratio of 0.72. Similar findings were also reported by Magodoro., *et al.* with 69% PLHIV were female [10]. In contrast to our findings, male outnumbered female in a study conducted in India by Tripathi., *et al* [17]. In another cohort study gender distribution of EPs were more common among male with female to male ratio of 0.67 [10]. Median age and mean age of the patients in our study was 36 years and 36.6 years (SD ± 10.57 years) respectively. A lower mean age of 34.1 years had been reported by Jain., *et al* [18]. A higher mean age (37.88 years) had been reported by Tripathy., *et al.* in India [17]. 84.5% of the patients were less than 45 years age. Similar findings were also reported by Fonsah., *et al.* in which more than half of the patients belonged to age group less than 40 years [19]. Mean duration of HAART in our study was 6.1 years. PLHIV in developing world is very common among productive age groups. Around two third of the participants were alcoholic beverage consumer and tobacco smoker.

In a study conducted in Ethiopia, a low percentage of patients were smoker and alcoholic beverage consumer [20]. More than 48% patients had not completed secondary level education. PLHIV is common among young productive age groups with poor literacy level. This demographic character could be strong barrier for community interventional program among PLHIV.

Above 94% PLHIV in our study were on first line ART. Similar finds were reported by Fonsah., *et al.* with 98.34% patients on the first line ART [19]. Participants on ZDV based regimen accounted for 42.5% in our study. More than 70% the patients were on EFV based ART regimen and similar findings were also reported by Tesfaye., *et al.* in which 58% of the cases were receiving regimen containing EFV and 66% on TDF [20]. Cotrimoxazole has been associated with higher rate of adverse drug reactions in PLHIV than non PLHIV however it was well tolerated in more than 70% of the patients in our study. Cotrimoxazole has been proven to prevent gastrointestinal infections and malaria among PLHIV besides prophylaxis of several opportunistic infections like pneumocystis carnie pneumonia and toxoplasmosis.

In our study prevalence of NCD was 30.1% among PLHIV out of which more than 58% were EPs. A lower prevalence of NCD (15.3%) had been reported by Magodoro., *et al* [17]. Dyslipidemia was the second most common endocrinopathy followed after steatohepatitis in our study. Similar findings was also reported by Chhoun., *et al.* in which 33.7% patients had dyslipidemia [16]. Lipodystrophy was most common endocrinopathy among PLHIV as reported by Jacobson., *et al* [21]. Gonadal dysfunction (88.3%) was the most common endocrine dysfunction in a study conducted in India [17]. Many patients with HIV infection have a dyslipidemic profile of decreased HDL-C and increased triglyceride and LDL-C levels [22]. Both increased visceral fat and decreased subcutaneous adipose tissue are associated with increased circulating free fatty acid and elevated triglyceride levels [23]. Many protease inhibitors impair adipocyte differentiation and decrease triglyceride accumulation in adipocytes, leading to increased circulating triglyceride levels [24]. Ritonavir-boosted lopinavir and atazanavir decrease fatty acid oxidation in skeletal muscle cells *in vitro* [25]. Lipoatrophy was 17% among endocrinopathy PLHIV in our study patients. The mechanisms of lipoatrophy include the inhibition of adipocyte differentiation by protease inhibitors and the impairment of mitochondrial function by nucleoside reverse transcriptase inhibitors [24-26]. The etiology of lipohypertrophy and ectopic fat accumulation is less clear. Lipohypertrophy may be related to elevated levels of inflammatory cytokines [27].

Type 2 Diabetes Mellitus (DM) was observed in 4.3% patients. Similar results could be found in a study conducted by Calza., *et al* [28]. This was much higher than what has been found in a study conducted by Rhee., *et al.* in Cameroon in which prevalence was 3.9% [29]. A higher prevalence of type 2 DM (14%) had been reported by Brown., *et al* [11]. Prevalence of DM among PLHIV observed in our study was less than prevalence (9.1%) in general population of Nepal. The low burden of diabetes among endocrinopathy in our study could be because of lower median age population in our study group in contrast to high burden studies. Abnormal fat distribution, particularly visceral adiposity, lower extremity fat atrophy, intramyocellular lipid levels are primary contributors to impaired glucose homeostasis in the HIV-infected population [30]. Protease inhibitors induce suppressor of cytokine signaling 1, which upregulates tumor necrosis factor alpha and other inflammatory cytokines which are associated with increased risk of developing diabetes in HIV infection [31]. Many protease inhibitors also block the glucose transporter GLUT4, impairing insulin-stimulated glucose use and directly affect glucose sensing by beta cells of pancreas resulting in impaired insulin release [32,33]. Genetics also contribute to the development of diabetes in PLHIV. Several common single-nucleotide polymorphisms (SNPs) are associated with diabetes in the general population. Rotger and colleagues evaluated 22 SNPs associated with the development of DM in 94 patients with diabetes in the Swiss HIV Cohort and in 550 HIV-infected nondiabetic controls [34].

Protease inhibitors therapy has been found to be a risk factor for EPs in our study as well as others with statistical significance. Protease inhibitor are usually second line drugs hence these are prescribed usually after half decades after first line antiretroviral agents failure or intolerance. Higher burden of EPs among PLHIV with protease inhibitors are outcome of other factors like prolong duration of living with HIV, higher cumulative risk of infections and early aging besides the drug. TDF/3TC/EFV was found to have protective effects against EPs.

Conclusion

Among PLHIV with EPs 44% had baseline CD4 less than 250/ml. PLHIV not more than 45 years were dyslipidemia, type 2 DM, low vitamin D and hypothyroidism. CD4 count was inversely associated with thyroid disease in our study. EPs had been associated with ART

but the benefit of ART in terms of preventing baseline CD4 count to drop, delaying progression of early aging and decreasing burden of NCDs overcomes the risk.

Limitation of the Study

The study was conducted at a single center in Nepal.

Acknowledgement

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Conflict of Interest

The authors claim no conflict of interest.

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