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Thyroid Function Disorders in HIV/AIDS Patients in Nepal

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Abstract

Background: Thyroid disorder is one of the common endocrine dysfunctions in Human Immunodeficiency Virus (HIV)-infected individuals under antiretroviral therapy (ART). In Nepal, thyroid disorder is frequently reported in general population, however HIV infected patients under ART are rarely monitored for this problem.

Methods: A cross-sectional study was conducted at National Public Health Laboratory and Sukraraj Tropical and Infectious Disease Hospital, Kathmandu, Nepal to investigate the status of thyroid disorder in HIV sero-positive individuals with or without ART. Blood samples were collected and $CD4^+$ T-lymphocyte counts were determined by flow cytometry while thyroid function was assessed by quantitative ELISA.

Results: We investigated a total of 120 HIV/AIDS individuals (including 80 under ART) for thyroid function disorders. In the ART receiving group, 92.3% individuals had hypothyroidism while in ART naïve group only one (7.7%) individual had such disorder. Association between hypothyroidism and ART was statistically significant (p = 0.038). In addition, the rate of hypothyroidism was significantly higher in ART receiving females (p = 0.01). Hypothyroidism status in ART receiving or not receiving individuals and their gender was further fitted in a regression model. After adjusting for gender and ART status in this model, gender remained as an independent predictor of hypothyroidism (Odds Ratio-OR: 5.097, p = 0.031; CI: 1.15-22.47).

Conclusion: High rate of thyroid disorders was observed in ART receiving HIV/AIDS individuals in Nepal. Subclinical hypothyroidism was the most common disorder and females were more vulnerable.

Keywords: HIV/AIDS; Thyroid disorders; Hypothyroidism; Antiretroviral therapy; $CD4^+$ T lymphocyte count; Nepal

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; ART: Anti-Retroviral Therapy; CD: Cluster of Differentiation; ELISA: Enzyme Linked Immunosorbent Assay; fT3: Free Tri-iodothyronine; fT4: Free Thyroxine; HIV: Human Immunodeficiency Virus; MoHP: Ministry of Health and Population; NCASC: National Centre for AIDS and STD Control; NPHL: National Public Health Laboratory; STI: Sexually Transmitted Infection; TSH: Thyroid Stimulating Hormone; WHO: World Health Organization.

Introduction

Thyroid disorder is one of the common endocrine dysfunctions observed due to alteration in the production of thyroid hormones *viz.* Thyroxine (T4) and Tri-iodothyronine (T3). Altered production of these hormones often involves dysfunction of thyroid gland, pituitary gland, and hypothalamus [1-3]. Hyperthyroidism (overproduction of T3 and T4) and hypothyroidism (underproduction of T3 and T4) are regarded as the most common clinical forms of thyroid disorders [3].

Human Immunodeficiency Virus (HIV) infected individuals often present with abnormalities in several endocrine functions such as pituitary, thyroid, adrenal, gonads, and pancreas [4-6]. Such endocrine disturbances occur in the course of HIV infection, and underlying pathogenesis generally involves the direct infection of endocrine glands by HIV and opportunistic pathogens, or caused by neoplasm [7,8]. Besides this, adverse effects of prolonged antiretroviral therapy (ART) have also been reported to affect endocrine functions [9,10]. Subclinical hypothyroidism with elevated thyroid stimulating hormone (TSH) is common in individuals with HIV/AIDS [9,11-14]. Although most of the asymptomatic cases with early HIV infection and stable body weight maintain normal thyroid functions, thyroid dysfunctions can appear after the initiation of ART [15,16]. Among thyroid dysfunctions, subclinical hypothyroidism is related to the prolonged use of stavudine [9,14,17]. Although exact mechanism behind the relationship between stavudine use and subclinical hypothyroidism is unclear, stuvadine is believed to affect the production and/or metabolism of thyroid hormones [9]. Therefore, it is important to monitor HIV-infected individuals for thyroid disorders and explore the possible association of thyroid functions with HIV infection, immunodeficiency, and ART status.

Periodic monitoring of thyroid functions in HIV-infected individuals (especially those under ART) has been recommended by various studies across the globe [12,13,18]. Unfortunately, to date,

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Table 1: Demographic features of study participants.

No. of patients, n	120
Age (years), mean ± SD	34.28 ± 7.27
Male, n (%)	66 (55)
Female, n (%)	54 (45)
Weight (kg), mean ± SD	53.25 ±8.7
Hypothyroidism, n (%)	13 (10.8)
Hyperthyroidism, n (%)	1 (0.83)
ART Patients, n (%)	80 (66.7)
ART naïve patients, n (%)	40 (33.3)

Figures in parenthesis indicate percentage.
ART: Antiretroviral therapy; n: Number; SD: Standard Deviation; Kg: Kilogram.

Table 2: Hypothyroid status in ART receiving and ART naïve patients in Nepal.

ART	Hypothyroid, n (%)	total	*p*-value
Yes	12 (92.30)	80	0.038
No	1 (7.70)	40	
Total	13	120	

Figures in parenthesis indicate percentage.
ART: Antiretroviral therapy; n: Number.

there is no information available on the status of thyroid disorders among HIV-infected population of Nepal, despite the fact that the government has been providing ART services for more than a decade at no cost [19]. In this report, we describe the abnormalities in thyroid functions among Nepalese HIV sero-positive individuals with or without ART.

Methods

Study design, population, ethics and enrollment

A cross-sectional study was conducted at National Public Health Laboratory (NPHL), under the Ministry of Health and Population (MoHP)-Nepal between August 2011 and April 2012. HIV sero-positive individuals (n = 120) of all age, sex and social classes with different ART status (80 under ART and 40 ART naive) visiting NPHL for regular monitoring of $CD4^+$ T-lymphocyte level were enrolled in the study. HIV/AIDS patients under ART for less than six months and/or patients with proven thyroid disorder prior to HIV confirmation were excluded. Eight individuals who did not wish to participate in the study were also excluded. Approval for this study was obtained from the Research Committees of Tribhuvan University, Kantipur College of Medical Sciences and NPHL. Participants were randomly selected from the designated NPHL register for regular monitoring of $CD4^+$ T-lymphocyte counts and written informed consent was taken from each participant before enrollment in this study. Questionnaires regarding age, sex, duration of HIV, ART status, type and duration of ART were completed followed by blood sample collection. Additionally, relevant clinical information was also obtained from ART center located at Sukraraj Tropical and Infectious Disease Hospital, Kathmandu, Nepal.

Laboratory methods and interpretation criteria

All the participants of this study were HIV sero-positive individuals diagnosed by national HIV testing algorithm of National Center for AIDS and STD Control (NCASC). $CD4^+$ T-lymphocyte counts were determined in anticoagulated blood by flow cytometry (Trucount) on a FACS Calibur flow cytometer (BD Biosciences, San Jose, CA, USA). Thyroid function was assessed by measuring free T3, T4 and TSH levels in patient's serum by quantitative Enzyme-Linked Immunosorbent Assay (ELISA) (Human, Wiesbaden, Germany). As per the manufacturer's protocol, the normal ranges for TSH, fT3 and fT4 were 0.3-6.2 mIU/l, 1.4 - 4.2 pg/ml and 0.8-2.0 ng/dl, respectively. Thyroid disorders were categorized as hyperthyroidism (overproduction of T3 and T4) and hypothyroidism (underproduction of T3 and T4). Hypothyroidism or hypothyroid status was further categorized as ''overt'' (high TSH, low fT4), ''subclinical'' (high TSH, normal fT4) and "low fT4" (normal TSH, fT4 ≤ 1.4 pg/ml). Similarly, hyperthyroidism or hyperthyroid status was categorized as ''subclinical'' (TSH ≤ 0.3 mIU/l, normal fT4) and ''overt'' (TSH ≤ 0.3 mIU/l, fT4 > 4.2 pg/ml). This classification is in accordance to the published report [18].

ART Algorithm

According to Nepal ART guidelines 2014 [19], first-line ART consists of two Nucleoside Reverse-Transcriptase Inhibitors (NRTIs) and a Non-Nucleoside Reverse-Transcriptase Inhibitor (NNRTI). The recommended fixed dose combination to initiate ART in Nepal is Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV). But when TDF + 3TC + EFV regimen is contraindicated or not available, the recommended alternatives are - Zidovudine (AZT) + 3TC + EFV, or AZT + 3TC + Nevirapine (NVP), or TDF + 3TC + NVP.

Second line therapy is available at the higher centers with up-to-date follow up mechanisms. When Abacavir (ABC) or TDF + 3TC based first-line regimen fails, AZT + 3TC are used as the NRTI backbone in second-line regimens. Similarly, on failure of AZT or Stavudine (d4T) + 3TC based first-line regimen, ABC or TDF + 3TC are used as the NRTI backbone in second-line regimens. Lopinavir (LPV/r) is the preferred boosted Protease Inhibitor (PI).

Data analysis

Data were analyzed by SPSS (Statistical Package for Social Sciences) version 16.0. Normally distributed continuous variables such as age and weight were presented as mean± SD. A significance level > 0.05, and skewness/kurtosis ≈ 0 were regarded as normally distributed population. Chi-square (χ^2) test was applied for categorical variables. Bivariate regression model was used to measure the risk predictors of thyroid disorder. A p-value < 0.05 was considered significant for all statistical inferences.

Results

Of the total individuals recruited in this study (n = 120), 66 (55%) were male (male: female = 1.2:1). Mean age of the participants was 34.28 ± 7.3 years, while the mean weight was 53.25 ± 8.7 kg. Two third (66.7%) of the enrolled cases were under ART (Table 1).

Among ART-receiving HIV/AIDS individuals, 15% (12/80) had hypothyroidism. Of the hypothyroid patients, 11.25% (9/80), 2.50% (2/80) and 1.25% (1/80) had subclinical hypothyroidism, isolated low fT4 and overt hypothyroidism, respectively. One patient, (1.25%, 1/80) had subclinical hyperthyroidism. About 93% cases of hypothyroidism belonged to ART-receiving individuals and one (i. e. overt hypothyroidism) case belonged to ART naïve group (Table 2). Proportion of hypothyroid status in ART receiving and ART naïve

Table 3: Risk factors associated with hypothyroidism among HIV/AIDS individuals under ART in Nepal.

Factor	Normal thyroid function (n = 67)	Hypothyroid (n = 12)	*p*-value
Age group (years)			0.94
upto 20	2	0 (0.0)	
21 to 45	61	11 (13.9)	
>45	4	1(1.3)	
Sex			0.01
Male	43	3(3.8)	
Female	24	9(11.4)	
CD4 count (cells/cumm)			0.36
<350	33	5(6.3)	
351-700	27	7(8.9)	
>700	7	0(0)	
Weight (kg)			0.16
<40	3	1(1.3)	
40-60	49	11(13.9)	
>60	15	0(0)	
HIV duration			0.18
<1 year	9	0(0)	
>1year	58	12(15.2)	
ART duration			0.11
<1 year	18	0(0)	
>1year	49	12(15.2)	
ART regimen types			0.98
3TC/AZT/EFV	9	2(2.5)	
3TC/AZT/NVP	46	9(11.4)	
3TC/NVP/TDF	1	0	
3TC/d4T/EFV	2	0	
3TC/d4T/NVP	8	1(1.3)	
DDI/TDF/EFV	1	0	

Figures in parenthesis indicate percentage.
n: Number; CD: Cluster of Differentiation; Kg: Kilogram; ART: Antiretroviral therapy; HIV: Human Immunodeficiency Virus; 3TC: Lamivudine; AZT: Zidovudine; EFV: Efavirenz; NVP: Nevirapine; TDF: Tenofovir; d4T: Stavudine; DDI: Didanosine.

individuals was significantly different ($p = 0.038$). Hypothyroid status was significantly associated with gender ($p = 0.01$) and was more common in females (Table 3). All ART receiving hypothyroid cases (n= 12) had HIV duration > 1 year although the association between duration of HIV and hypothyroidism was not significant ($p = 0.18$).

Since hypothyroidism was found more common among ART-receiving individuals, we also compared hypothyroidic and non-hypothyroidic ART-receiving patients in relation to other factors such as ART duration, $CD4^+$ T-lymphocyte counts and gender. Among ART receiving group (n = 80), 77.5% had ART duration >1 year. Interestingly, all hypothyroidism cases had ART duration >1 year. The association between duration of ART and hypothyroidism was not statistically significant ($p = 0.11$). ART receiving individuals in our study had higher mean HIV duration (37.5 months) than the ART naive counterparts (32 months).

Among ART-receiving group, 48% had $CD4^+$ T-lymphocyte count < 350 cells/cumm and 44% had $CD4^+$ T-lymphocyte count in the range of 351-700 cells/cumm. Absolute $CD4^+$ T-lymphocyte count of hypothyroid patients receiving ART (364 cells/cumm) was lower than absolute $CD4^+$ T-lymphocyte count of all ART treated individuals (401 cells/cumm). However, the relationship between $CD4^+$ T-lymphocyte count and hypothyroidism was not statistically significant ($p = 0.36$).

Among the ART receiving individuals, highest rate of hypothyroidism (11%) was found in those receiving 3TC + AZT+NVP regimen, followed by 3TC + AZT+EFV. However, the association between ART regimen type and hypothyroidism was not statistically significant ($p = 0.98$). ART receiving and ART naïve patients and sex were further fitted into a regression model. After adjusting for sex and ART receiving subjects in this model (Table 4), sex remained as an independent predictors of hypothyroidism (odds ratio-OR: 5.097, p=0.031; CI: 1.15-22.47).

Table 4: Multivariate logistic regression analysis of risk factors for hypothyroidism among HIV/AIDS individuals receiving ART in Nepal.

Variables	B	SE	OR	*p*-value	95% CI	
					Lower	Upper
Sex (female)	1.629	0.757	5.097	0.031	1.156	22.473
ART (+)	-2.002	1.085	0.135	0.069	0.016	1.13

ART: Antiretroviral therapy; B: Regression equation; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

Discussion

Over five million people in South Asia are living with HIV/AIDS [20]. In Nepal, the prevalence of HIV is low in general population but higher among sub-populations engaging in high risk behaviors [20]. Thus, HIV is currently considered as the 'concentrated epidemic' in Nepal with about 0.23% HIV prevalence in adult population [21]. An estimated 40,723 people are living with HIV/AIDS in Nepal. Since the inception of ART services in Nepal in 2004, about 10,000 HIV/AIDS patients have already received this service (data as of July 2014) [21]. As per the NCASC Nepal guidelines, $CD4^+$ T-lymphocyte count has been used as the basis for both ART initiation and monitoring its progress [22]. However, monitoring of HIV-infected individuals for possible side effects of ART (e.g. thyroid disorders) has not yet been institutionalized in Nepal.

Although most asymptomatic HIV-infected patients with stable body weight maintain normal thyroid function, chances of thyroid dysfunctions increase among a proportion of HIV-infected individuals under ART [15,16]. We found a high rate of hypothyroidism among HIV patients receiving ART, and this observation is in agreement with previous reports from different parts of the globe [9,11,23-26].

Following the WHO recommendations, Nepal government has recently adopted a policy of providing ART to all HIV-infected individuals regardless of their HIV duration. Due to this new policy, number of people with endocrine disorders, such as thyroid or metabolic disorders may increase as a consequence of ART. Earlier, the ART initiation was exclusively based on the criteria of decreased $CD4^+$ T-lymphocyte counts compared to the established normal national reference ranges [27]. Therefore, periodic screening of HIV/AIDS patients under ART is necessary to understand the side effects of ART (i.e. thyroid function and other metabolic disorders) in Nepal. Higher mean HIV duration among ART receiving individuals observed in our study is in concordance with previous report [13]. It is common to see longer HIV duration of ART-receiving individuals compared to ART naïve ones [13,18]. Moreover, all of our hypothyroidic individuals had ART duration >1 year suggesting that longer ART duration may further increase the risk of thyroid disorders. In a report from France, longer duration of disease in HIV-infected patients treated with ART was found to have autoimmune thyroiditis [18].

Among different ART regimen types, the highest prevalence of hypothyroidism was found among those receiving 3TC + AZT+NVP regimen, followed by 3TC+AZT+ EFV. This is probably because most of our patients were under 3TC + AZT+NVP therapy. NVP has been considered an alternative drug for use in resource-limited settings due to its low cost availability as Fixed Dose Combination (FDC) and the long-term experience with the drug's proven efficacy and safety profile. Also, NVP is the safest drug for use in people with low CD4 cell counts [28].

Stavudine therapy has been found to be associated with subclinical hypothyroidism in some studies [17]. However, lower prevalence of hypothyroidism in individuals under stavudine treatment in this study may be associated with its exclusion (phase-out) from the first line regimens in Nepal [19]. Although ART treatment improves immunological status of HIV patients, this may also increase the possibility of side effects due to longer ART duration. Therefore, a careful balance between these two factors along with regular monitoring of ART mediated metabolic and hormonal disorders in HIV patients receiving ART is essential.

In this study, HIV-infected females who received ART were found more prone to develop hypothyroidism (OR: 5.097; CI; 1.15-22.47) and female's susceptibility towards hormonal jump might be an explanation for this. Our result is in agreement with the observation made by Beltran *et al.* (2003) and Quirino *et al.* (2004) [18,29]. A number of other reports show higher rate of hypothyroidism even in general female population [30,31] and data on males having higher rate of hypothyroidism in HIV-infected population is scarce [13].

It can be inferred from our observation that the hypothyroidic individuals under ART might have more severe HIV/AIDS disease progression than non-hypothyroidic individuals because we found lower value of absolute $CD4^+$ T-lymphocyte counts among hypothyroid HIV patients under ART compared to all other ART treated individuals. Correlation of low levels of free T4 and subclinical hypothyroidism with low $CD4^+$ T-lymphocyte counts were also reported in Spanish [14] and French population [18]. It has also been reported that $CD4^+$ T-lymphocyte count correlates well with free T3 and free T4 values, while an inverse correlation exists between $CD4^+$ T-lymphocyte count and serum TSH levels [32,33]. Besides ART, several other factors including opportunistic infection, local neoplasm [34], severe systemic illness, or caloric deprivation [35] can also contribute to thyroid disorders among HIV/AIDS patients.

We found only one case of overt hypothyroid, which may be due to small sample size. So, future study with bigger sample size may provide better clinical significance in similar settings. A multicenter study may provide more information for making comparison between the results from different geographical and socio-economic settings.These limitations should be considered for interpretation and generalization.

Conclusion

We observed a higher rate of hypothyroidism in Nepalese HIV/AIDS individuals under ART. Among the categories of hypothyroidism, subclinical hypothyroidism was the most common thyroid disorder. Similarly, females were found to be more vulnerable towards thyroid disorders, suggesting the need for regular monitoring of HIV/AIDS individuals under ART for thyroid disorders.

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Authors' Contributions

BJ designed study, performed laboratory test, collected data, analyzed data and wrote manuscript; DA contributed in designing of the study, data analysis, and review; UTS and NRB helped in study design and reviewed manuscript; RKB contributed in laboratory testing; SKS helped for data analysis and drafting of manuscript; RB helped during manuscript writing, SPD contributed in designing of the study, supervision, data analysis, manuscript writing and review. All authors read and approved the final version of the manuscript.

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