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Cardiovascular Risk Factors Among People being Treated for HIV in Nepal: a Cross-Sectional sSudy

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Abstract

Background: Human Immunodeficiency Virus (HIV) and antiretroviral therapy (ART) are found to be strongly associated with cardiovascular diseases. Data are sparse on the prevalence and distribution of cardiovascular risk factors among people being treated for HIV in South Asia region.

Methods: A cross-sectional study of 103 HIV patients (51 women and 52 men) attending routine follow-up consultations at the largest ART centre in Nepal was conducted. Data on several cardiovascular risk factors were collected through interview questionnaires, biophysical measurements and consulting medical records.

Results: The most common cardiovascular risk factors observed were central obesity [34.6%, 95% Confidence Interval (CI): 25.3% to 43.9%], chronic kidney disease [20.7% (95% CI: 11.6% to 29.7%)] and tachycardia [20.6% (95% CI: 12.7% to 28.5%)]. Females were significantly more likely to have central obesity (male 9.8% vs. female 60%, p=0.016) and chronic kidney disease (male 15.4% vs. female 26.3%, p=0.003) as compared to the males. Participants were fairly active but a large proportion, especially men, had smoked [65% (95% CI: 57%-72.3%)], used tobacco products [66% (95% CI: 56.4%-74.4%)] or drugs (53.8% of the men) and consumed alcohol [60.2% (95% CI: 50.5%-69.1%)].

Conclusion: A high prevalence of several cardiovascular risk factors was observed among patients being treated for HIV in Nepal. Further larger studies are warranted to better understand the relevance and public health impact of cardiovascular risk factors in this region.

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Introduction

Antiretroviral therapy (ART) has rendered dramatic improvements in the life span and quality of life in patients infected with the Human Immunodeficiency Virus (HIV). However, several health risks and side-effects are found to be strongly associated with HIV and/or the use of ART [1,2], including cardiovascular-related complications [3]. A number of observational studies have suggested that patients being treated for HIV are at elevated risk of cardiovascular diseases (CVD) [3,4,5]. Much of this elevated risk is thought to be mediated by dyslipidemia, clinical lipodystrophy, central obesity, insulin resistance, hypertension and kidney diseases [6,7]. Furthermore, lifestyle choices which increase cardiovascular risk, such as tobacco usage, unhealthy diets, physical inactivity and drug abuse, are frequently observed among people living with HIV [8-12].

The vast majority of previous studies of CVD among people with HIV were based in European, American and African settings, making it difficult to extrapolate findings to South Asia (which has distinct cultural, medical and lifestyle practices from other regions). Such lack of data from South Asia is in spite of rapid increases in the burden of CVD in the region [13], coupled with rapid increases in the usage of HIV treatments (reported to have increased 10 fold in the region in the past five years) [14].

Nepal is a developing South Asian country with a population of 30 million. Over 70,000 Nepalese people were living with HIV and AIDS in 2008 [15]. Since the inception of ART services in Nepal in 2004, the number of HIV patients on ART has increased 60 fold in five years with 3834 Nepalese reported to be on ART in 2010 [16]. Likewise, a high prevalence of cardiovascular-related risk factors (CVRF), mainly central obesity [17], hypertension [18], CKD [19], smokers and drinkers [20] were observed in the general Nepalese population. With the backdrop of the increasing rate of CVD in Nepal [21], a high prevalence of CVRF and improved access to ART, the aim of this study was to assess the prevalence and distribution of selected CVRF among patients being treated for HIV in Nepal.

Methods

Study Design: A cross-sectional study was conducted with non-randomly selected HIV infected patients receiving ARV medication and sequentially attending the routine follow up consultation at the Teku ART centre, Kathmandu, Nepal. This centre is the largest referral ART clinic in Nepal treating more than 800 HIV infected patients [22]. Ethical approval was obtained from the Nepal Health Research Council (NHRC) as per the guidelines of the University of Aberdeen college ethics review board.

A total of 103 HIV patients were enrolled during the study period (11 April, 2010-10 May, 2010). HIV patients aged 25 or above, currently receiving ART and those who could understand and speak Nepalese were included in the study. HIV patients on ART but hospitalized and/or critically ill, with hearing and

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speaking disabilities, pregnant and who failed to give written informed consent were excluded.

Data was collected by the researcher and trained research assistants using standardised operating protocols in conducting interview questionnaires, bio-physical measurements and retrieving medical records.

Interview Questionnaire: The questionnaire was adapted from previously validated questionnaires [23,24]. Questions were modified to the Nepalese context and culture, and face validity was tested by piloting among six volunteers. The accuracy of the English-Nepalese translation was checked by back-translation by a local Nepalese journalist and reviewed by bilingual research team members. The questionnaire included six sections comprising questions on demographics and socio-economic information, physical activity, alcohol consumption, tobacco use/addiction, medical/medication history and dietary habits.

For demographics and socio-economic information, data was collected on age, gender, ethnicity, education, occupation and income. The physical activity section included questions on physical activities at work and during leisure time, and total walking duration per day. For alcohol consumption information, data was collected on drinking status (current, past, never) as well as frequency, amount and type of alcohol use. Data on tobacco use and addiction was focussed on status of tobacco and smoking usage (current, past, never), types and duration of tobacco products use, number of cigarettes and other tobacco products consumed each day, second hand smoking, addiction status (current, past, never) and types of addiction. Dietary information was collected on the amount and frequency of fruit and vegetable; salt; fats and oils; dairy, meat, poultry, meat and fish products intake per day. The salt use was stratified into three groups of 'low', 'moderate', and 'high' according to what the respondents reported using while cooking food.

For the data on medical/medication history, questions included participants' own and family history of major CVDs and its risk factors as diagnosed by the doctor. Also, history of any medications for particular CVDs and its risk factors was recorded.

Physiological Measurements: Body weight, height, hip and waist circumferences were measured using the World Health Organisation (WHO) standard protocols [25]. Blood pressure (BP) and heart rate (HR) were measured by the oscillometric method using digital automatic BP measuring devices (OMRON M2 HEM-7117 -E, OMRON Health Care Co. Ltd., Kyoto, Japan). BP and HR were taken at the seated position in a chair with feet on the floor and back straight. At the start and midpoint of the study, the reliability of these devices was verified with each other and with the blood pressure measuring machine used by clinical staff at the Teku ART centre. All bio-physical measurements were recorded twice and the average was considered for analysis. In the case of BP and HR, it was ensured that the second measurement was at least 10 minutes after the first one.

Medical Records Retrieval: Selected biochemical values (White Blood Cell (WBC), lymphocytes, platelets, CD4+, serum creatinine), HIV medical history (mode of HIV transmission, date of HIV diagnosis and ART initiation) and HIV medication history (type and doses of

medication) were accessed from the Teku ART centre medical records (such data was retrievable for all participants).

Definitions and Preferred Cut-off Values: Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). Waist to Hip (W-H) ratio was determined as waist circumference (cm) divided by hip circumference (cm). Obesity and overweight were classified using the redefined cut points for Asia-Pacific (obesity: BMI≥25kg/m^2 and overweight: ≥23kg/m^2), as per the guidelines of the International Diabetes Institute [27]. Central obesity was classified according to the WHO report on obesity 1997 (W-H ratio of 0.85 for women and 1.0 for men) [28]. Hypertension was defined according to the 1999 World Health Organisation -International Society for Hypertension (WHO-ISH) guidelines, that is, systolic BP≥140mmHg and/or diastolic BP≥90mmHg [26]. Tachycardia was defined according to the established cut point - HR >100 b/m. Chronic kidney disease (CKD) was defined according to the guidelines of the American National Kidney Foundation [29], which is eGFR<60 ml/min/1.73 m^2. eGFR was calculated using the Cockcroft-Gault formula [30].

Statistical Analysis: The statistical analysis was carried out using the IBM SPSS 20 package. Prevalence rates were presented in percentages, separately for males and females. Independent T test, Mann Whitney test and Chi -squared test methods were employed to assess bivariate relationships at 0.05 significance level.

Results

A total of 103 participants was included in this study, of whom 52 (50.5%) were men and 51 (49.5%) women from a variety of ethnic groups (Table 1). The median age of men and women was 38 years (interquartile range [IQR] 33,42), and 34 years (IQR 32, 39.5) respectively. Most of the participants were living in an urban area (64.0%), 16.5% were unemployed and 56.9% of the women and 15.4% of men had never attended school.

The median duration of HIV positive status and ART use was nearly two-fold in women as compared to men (Table 1). The median duration of HIV positive status was 24 months (IQR 3.5, 42.5) in women, but among men it was 12 months (IQR 3.7, 41.2). Women participants were receiving ART for 11 median months (IQR 1, 31.2), as compared to the six months (IQR 1, 32) for men. The median CD4+ count was 177 cells/ mm^3 (IQR 84.25, 260.25) in men, however it was slightly higher among women at 213.5 cells/mm^3 (IQR 133.5, 348.5).

Regarding lifestyle factors, 66% (95% CI: 56.8% to 75.1%) of the participants had ever used tobacco products, 65% (95% CI: 55.7% to 74.3%) had ever smoked and 60.2% (95% CI: 50.7% to 69.6%) had ever consumed alcohol (Table 1). All of these three factors were extremely prevalent in males, and the differences in the proportion between males and females were statistically highly significant at <0.001 significance level. As regards relevant dietary intake in terms of

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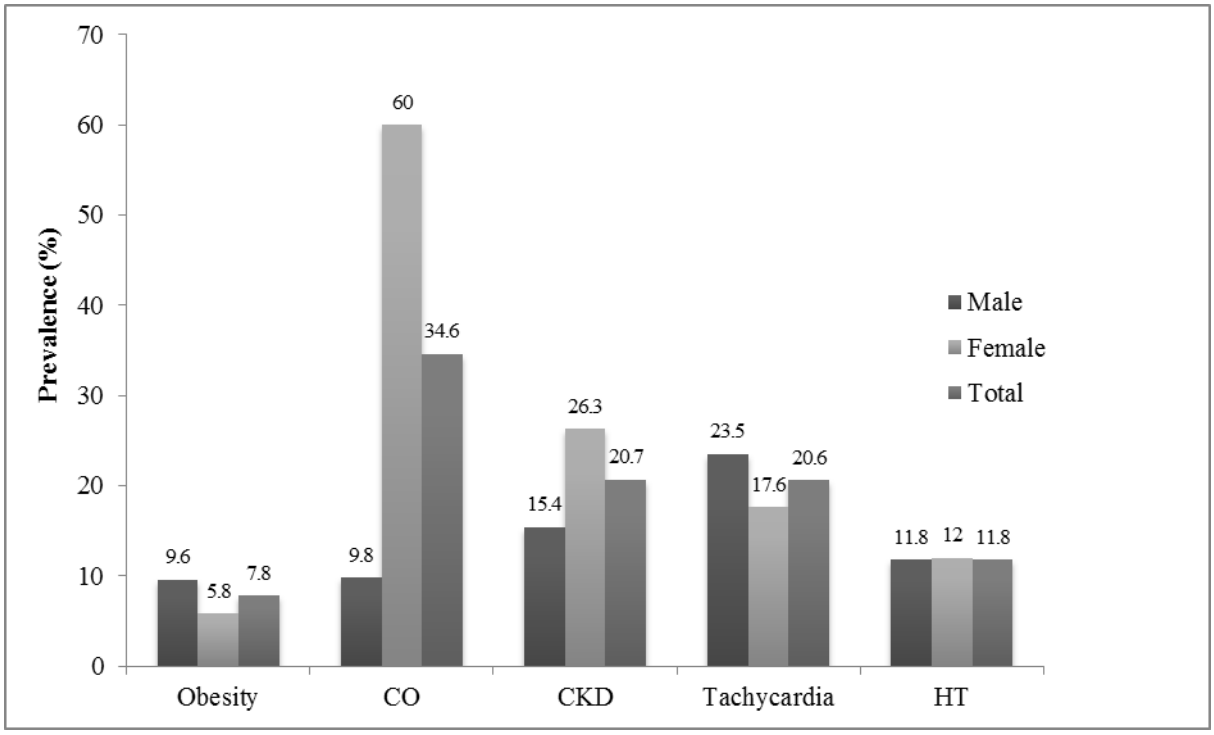
Table 1: Socio-demographic and lifestyle characteristics and medical history of Nepalese HIV+ patients (N=103)

Characteristics	Men	Women	Total (%)
Demographic Variables			
Gender (%)	52 (50.5)	51 (49.5)	103 (100)
Ethnicity (%)			
Brahmin/Chhetri	23 (44.2)	22 (43.1)	45 (43.7)
Tamang/Rai/Gurung/Magar	11 (21.1)	19 (37.2)	30 (29.1)
Newar	8 (15.4)	3 (5.9)	11 (10.7)
Others	10 (19.2)	7 (13.7)	17 (16.5)
Age (Years)			
Median (IQR)	38 (33,42)	34 (32, 40)	35 (32,41)
Currently living region (%)			
Kathmandu valley	33 (63.5)	33 (64.7)	66 (64.0)
Highway districts	13 (25.0)	9 (17.6)	22 (21.4)
Hilly districts	6 (11.5)	9 (17.6)	15 (14.6)
Socio-economic Variables			
Monthly Household Income* (%)			
<NRs. 5000	11 (21.1)	16 (31.4)	27 (26.2)
NRs. 5000-10000	22 (42.3)	15 (29.4)	37 (36.0)
> NRs. 10000	8 (15.4)	3 (5.9)	11 (10.7)
Not known	4 (7.7)	5 (9.8)	9 (8.7)
Prefer not to answer	7 (13.5)	12 (23.5)	19 (18.4)
Occupation (%)			
Unemployed	10 (19.2)	7 (13.7)	17 (16.5)
Agriculture	8 (15.4)	8 (15.7)	16 (15.5)
Business	7 (13.5)	6 (11.8)	13 (12.6)
Service	11 (21.1)	1 (1.9)	12 (11.6)
Labour	7 (13.5)	4 (7.8)	11 (10.7)
Others	9 (17.3)	25 (49.0)	34 (33.0)
Education (%)			
Never attended school	8 (15.4)	29 (56.9)	37 (36.0)
School level	40 (76.9)	22 (43.1)	62 (60.2)
Certificate level	2 (3.8)	0 (0)	2 (1.9)
Undergraduate level	2 (3.8)	0 (0)	2 (1.9)

Lifestyle variables			
Total walking period/day (%)			
<30 minutes	11 (21.1)	11 (21.6)	22 (21.4)
30-60 minutes	9 (17.3)	6 (11.8)	15 (14.6)
1-2 hours	18 (34.6)	21 (41.2)	39 (37.9)
> 2 hours	14 (26.9)	13 (25.5)	27 (26.2)
Alcohol intake status (%)			
Never	3 (5.8)	38 (74.5)	41 (39.8)
Past	43 (82.7)	12 (23.5)	55 (53.4)
Current	6 (11.5)	1 (2.0)	7 (6.8)
Tobacco intake status (%)			
Never	4 (7.7)	31 (60.8)	35 (34.0)
Past	13 (25)	7 (13.7)	20 (19.4)
Current	35 (67.3)	13 (25.5)	48 (46.6)
Smoking status (%)			
Never	4 (7.7)	32 (62.7)	36 (35)
Past	13 (25)	6 (11.8)	19 (18.4)
Current	35 (67.3)	13 (25.5)	48 (46.6)
Drug use (%)	28 (53.8)	0 (0)	28 (27.2)
Dietary intake (%)			
Fruit & veg consumption (n=101)			
<5 portions/day	43 (86.0)	48 (94.1)	91 (90.0)
≥ 5 portions/day	7 (14.0)	3 (5.9)	10 (9.9)
Salt intake			
High	15 (53.6)	13 (46.4)	28 (27.2)
Moderate	27 (45.0)	33 (55.0)	60 (58.2)
Low	10 (66.7)	5 (33.3)	15 (14.6)
HIV history (%)			
Mode of HIV transmission (n=69)			
Heterosexual route	19 (50.0)	29 (93.5)	48 (69.6)
Injecting drug use	18 (47.4)	1 (3.2)	19 (27.5)
Unknown	1 (2.6)	1 (3.2)	2 (2.9)
HIV diagnosis period (months) (n=83)			
Median (IQR)	12 (3.7, 41.2)	24 (3.5, 42.5)	16 (4, 41)
ART uptake period (months) (n=89)			
Median (IQR)	6 (1, 32)	11 (1, 31.2)	8 (1, 31.5)
Biochemical measurements			
WBC (cells/μL) (n=89)			
Median (IQR)	5300 (4250, 7400)	4675 (4025, 5975)	4900 (4100, 6700)
CD4+ (cells/mm^3) (n=92)			
Median (IQR)	177 (84.25, 260.25)	213.5 (133.5, 348.5)	193 (129, 292.75)
eGFR (mL/min/1.73m^2) (n=77)			
Mean (SD)	86.28 (24.04)	78.59 (49.79)	82.49 (38.87)

* £1 = Nepalese Rupees (NRs.) 130, as of 20th October 2011



CO: Central Obesity, CKD: Chronic Kidney Diseases, HT: Hypertension

Figure 1: Prevalence of CVD risk factors in the sample population.

cardiovascular risk, 88.3% (95% CI: 82.0% to 94.6%) of participants reported not attaining the recommended five portions of fruits and vegetables per day. Also, 27.2% (95% CI: 18.6% to 35.8%) of participants reported a high salt intake.

Prevalence of cardiovascular risk factors

The most common CVRF observed were central obesity [34.6%, 95% Confidence Interval (CI) : 25.3% to 43.9%], CKD [20.7% (95% CI : 11.6% to 29.7%)] and tachycardia [20.6% (95% CI :12.7% to 28.5%)] (Figure 1). Females were significantly more likely to have central obesity (male 9.8% vs. female 60%, p=0.016) and CKD (male 15.4% vs. female 26.3%, p=0.003) as compared to the males. Family history of CVD was reported by 42.7% (95% CI: 33.1% to 52.2%) of the participants, and was significantly higher in males (male 57.7% vs. female 27.4%, p=0.004). Likewise, 8.7% (95% CI: 3.3% to 14.2%) of the participants had a history of CVD, 3.9% (95% CI: 0.2% to 7.6%) reported being diagnosed with diabetes and 4.8% (95% CI : 0.7% to 8.9%) were currently on medication for either CVD or hypertension or diabetes or in combination.

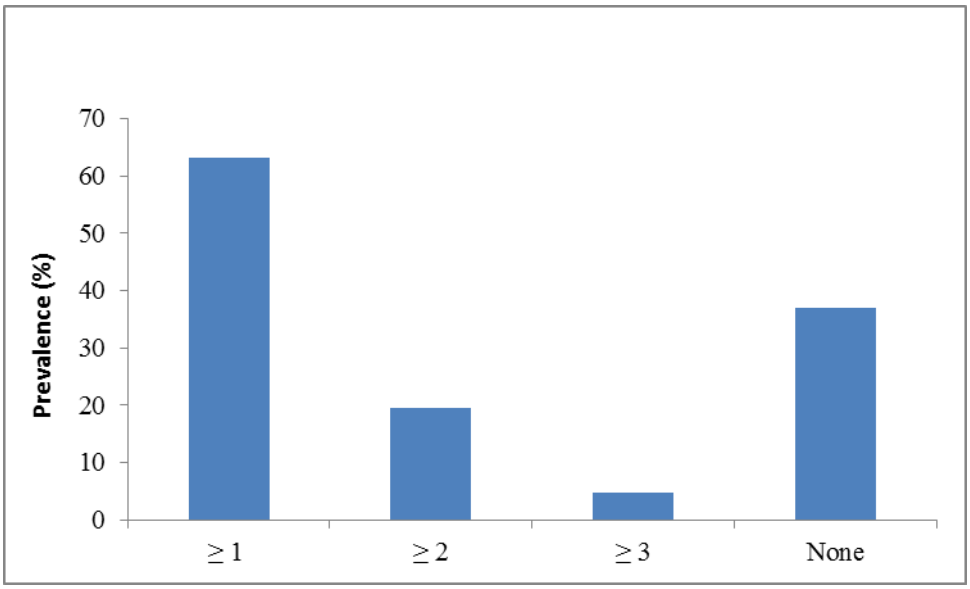
We also examined the number of cardiovascular risk factors prevalent among the individual participants. For this analysis, we considered BMI, W-H ratio, heart rate, eGFR and hypertension (systolic or diastolic or both) as the risk factors. At least two CVRF were concurrently prevalent among the 19.4% (95% CI: 12.9% to 28.2%) of the participants (Figure 2). Females were more likely to have ≥2 CVRF as compared to males (males 13.5% vs. females 25.5%), but this difference was statistically non-significant (p=0.196).

Table 2: Association of HIV medication and CVD risk factors

		Duovir* + Nevirapine (N= 54)	Other** (N=41)	P value
BMI (Kg/m²)	Median IQR	20.32 (n=53) (18.88, 23.03)	19.95 (n=41) (18.75, 21.86)	0.288
W-H Ratio	Median IQR	0.89 (n=53) (0.83, 0.94)	0.88 (n=40) (0.82, 0.93)	0.778
Heart Rate (b/m)	Mean SD	87.99 (n=53) 14.83	89.17 (n=40) 14.70	0.703
eGFR (ml/min/1.73m²)	Mean SD	77.17 (n=45) 20.19	81.38 (n=31) 27.34	0.442
Sys BP (mmHg)	Mean SD	116.39 (n=53) 14.31	111.47 (n=40) 14.57	0.107
Dias BP (mmHg)	Mean SD	77.37 (n=53) 10.72	75.20 (n=40) 10.64	0.335

*Duovir = Lamivudine + Zidovudine, **Drug combinations mainly included Duovir + Efavirenz (n=16), Lamivudine+Stavudine+Nevirapine (n=15)

Figure 2: Prevalence of number of CVD risk factors in the sample population.



The association between CVRF and HIV drug groups was also assessed (Table 2), but no significant associations were observed. Most of the participants were on a combination of duovir and nevirapine drugs (52.4%), followed by duovir and efavirenz (15.5%), and lamivudine, stavudine and nevirapine (14.6%).

Discussion

This is the first study in Nepal to document CVRF among the HIV population on ART. The key findings of this study are a high prevalence of central obesity, CKD and tachycardia. Risky lifestyle habits such as a high prevalence of smoking and alcohol consumption, especially in males and poor dietary habits (low fruit and vegetable and high salt intake) were also found. Overall, a third (34.6%) of the participants had central obesity and females had a disproportionately higher prevalence (60.0%) than the males (9.8%). This corroborates findings in larger studies, where the prevalence of central adiposity among HIV patients on HAART was 30% to 62% [31]. Falutz suggested that factors such as female gender and treatment with antiretroviral drugs zidovudine (AZT) and efavirenz (EFV) may contribute to raise the risk of central adiposity [32]. In our study, the vast majority of the participants (84.2%) were on AZT, EFV was also used by 24.2% and 17.9% were concurrently treated with both AZT and EFV along with other drug combinations. However, we could not demonstrate significant associations between HIV drug combinations and any of the CVRF. Due to the small sample size, we had to categorize nine drug combinations of the participants into two groups (duovir + nevirapine and remaining combinations) for analysis.

Very little research has been conducted in Nepal on central obesity based on W-H ratio and findings are hugely conflicting. In a study on healthy Nepalese males, central obesity was observed in 51.2% of the 1000 participants [17]. By contrast, a recent study among 241 Nepalese men and women, found a prevalence of 2.5% in males and 10% in females [33]. The difference in cut-off values used to classify central obesity might have partly contributed to the difference in findings as Vaidya and colleagues [17] used a cut-off value of ≥0.95 for males and Adhikari and colleagues [35] did not mention the cut-off point. Geographical and cultural differences of the study sites may also have played role in the variation. Nonetheless, the finding of a higher prevalence of central obesity in females may underpin the notion that abdominal lipohypertrophy is predominant in HIV treated females [34], taking into consideration findings that South Asian populations, especially females, are more vulnerable to abdominal obesity [35]. This finding suggests the possible added risk of central obesity among HIV infected Nepalese females on ART.

The CKD prevalence in this study (20.7%) was the highest compared to other Asian studies conducted on HIV infected patients on ART - A Japanese study found 15.4% [36] and a Chinese study found 16.8% prevalence of CKD [37]. Notably, the prevalence found was also higher than in the general Nepalese population, where Sharma and colleagues reported CKD in 14.4% of 8398 Nepalese adults [19]. The methodological differences in defining CKD though should be noted (this study estimated eGFR using a Cockcroft-Gault formula,

whereas Sharma and colleagues and the Chinese study followed the Modification of Diet in Renal Disease Equation (MDRD), and the Japanese study followed the equation suggested by Japanese Society of Nephrology).

Among the antiretroviral agents, Tenofovir disoproxil fumerate (TDF) has been found to be associated with increased renal dysfunction [37], and the WHO has recognized it's renal toxicity. However, in this study only two participants were being treated with TDF. This is an important factor for future studies as the use of TDF among the Nepalese HIV population is likely to increase rapidly in the future due to the recent guidelines of the WHO [38] which recommends the reduction of stavudine (d4T) and use of TDF in a first line regimen. Stavudine is currently the dominant HIV drug in the Nepalese HIV population. Thus, clinicians and researchers should be more aware of renal health of HIV treated patients in Nepal.

Hypertension (systolic or diastolic) was found in 11.8% of the participants, which is significantly lower than the findings from other studies conducted in developed countries [39,40], but is similar to a study conducted in Africa (11.2%) [41]. It is interesting to note that the prevalence found is also lower than that of the general Nepalese population of 19.7% to 33.9% [18,42]. Several studies have demonstrated an association between hypertension and the duration of HAART. A large multi-centered study suggested a significant association after two years on HAART [43], and an American study showed no association till six months [44]. In this study, the median duration of HAART use was eight months and could partly explain the lower rates. Larger studies are required to confirm the prevalence and aetiology of hypertension in the HIV treated Nepalese population.

Findings suggest that health education should target certain lifestyle habits i.e. smoking, alcohol consumption, diet and physical activity within the HIV treated Nepalese population to decrease their CVRF. The prevalence of smoking in this study was higher than in the general Nepalese population (current smokers: 46.6% vs. 23.8%) [20], but is consistent with findings among other HIV+ populations [3,45]. A propensity for smoking among people living with HIV could be due to its perceived role in emotional support and stress reduction [46]. Men especially should be targeted to educate them regarding the increased cardiovascular risk of smoking and other stress reduction therapies introduced.

In contrast, a considerably lower prevalence of current alcohol consumption was reported in the HIV infected participants than in the general Nepalese community (6.9% vs. 28.5%) [20]. This is also in contradiction to common trends found in studies conducted in developed countries [10,47]. It is noteworthy that the prevalence of ever having consumed alcohol is higher though which could indicate that participants may have under-reported their alcohol consumption owing to social desirability bias or alternatively, due to the fact that two-thirds of the participants were poor, were not able to afford the high cost of alcohol. Alternatively, health education may have targeted this and resulted in a change in alcohol consumption habits.

As this was a cross-sectional study, a cause-effect relationship between CVRF and ART cannot be inferred.

As participants were non-randomly selected and all based at one ART centre, the results shouldn't be extrapolated to Nepal as a whole. Further limitations of self-reported responses could have introduced bias and restricted recorded biochemical measurements resulted in not being able to investigate the prevalence of other CVRF such as dyslipidaemia, clinical lipodystrophy and diabetes mellitus.

Although this was a cross-sectional study on a small sample, it provides important insights on the apparent risk of CVRF among HIV infected Nepalese patients on ART and warrants the need for further prospective and longitudinal studies.

Conclusion and Recommendations

This study provides important insights on the prevalence of CVRF among HIV infected Nepalese patients on ART, finding a high prevalence of central obesity, CKD and tachycardia as well as risky lifestyle habits. Not only does this warrant the need for further prospective and longitudinal studies, but it has implications for treatment and intervention within this population group. It also seems that health education messages should be gender -specific, with women being targeted with messages to avoid the risk of abdominal obesity and men regarding smoking and alcohol consumption as well as stress reduction therapy provided. Both groups should be educated about following a healthy diet and encouraged to continue doing physical activity. Finally, renal function should be monitored more closely if WHO guidelines are followed and TDF used more widely.

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Conflict of Interest

The authors have no financial and non-financial conflict of interest to disclose.

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