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Pharmacovigilance of Antiretroviral Drugs at B.P. Koirala Institute of Health sciences

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ABSTRACT

Background: Antiretroviral drugs are lifeline for patients living with HIV. Adverse drug reactions can compromise the compliance to antiretroviral therapy. The objectives of the study were to estimate the prevalence of adverse drug reactions and to assess its risk factors in patients living with HIV and receiving antiretroviral therapy.

Methods: A prospective cohort study was conducted among 496 patients living with HIV at B.P. Koirala Institute of Health Sciences for a period of one year. Adverse drug reactions were evaluated based upon clinical history, clinical examination and investigations.

Results: Majority of patients were of 31-45 year age group (58.1%) and on first-line antiretroviral therapy regimen (94.3%). Total of 240 adverse drug reactions were documented. Prevalence of adverse drug reaction was 34.7%. Skin rash, anemia and nausea and vomiting were the three most common adverse drug reactions. The adverse drug reactions were more common in patients having non-communicable diseases, chronic co-infections, taking more than 3 non-HIV drugs, second and third-line antiretroviral regimen and it was statistically significant (P-value < 0.05).

Conclusions: Prevalence of adverse drug reaction was high in the patients living with HIV. Age, gender, co-infections, non-communicable diseases, taking more than three non-HIV drugs and second and third-line antiretroviral regimen were identified as possible risk factor for occurrence of adverse drug reactions and their prior identification is important to optimize the best suited antiretroviral regimen.

Keywords: Adverse drug reactions; antiretroviral therapy; pharmacovigilance

INTRODUCTION

Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.[1] It helps to establish and/or identify risk factors.[2] Nepal has around 28865 patients living with HIV (PLHIV) and 12446 are receiving antiretroviral therapy (ART) as per of July 2016.[3] B.P. Koirala Institute of Health Sciences (BPKIHS) initiated its ART Clinic in 2006 and it has served around 1500 PLHIV till date.

The incidence, patterns and severity of adverse drug reactions (ADR) due to ART may differ markedly owing to local environmental and patient characteristics. ADR may also be a cause of loss to follow-up.[4,5] There are limited data on ADRs associated with ART among Nepalese PLHIV. The objectives of the study were to estimate the prevalence of ADR and to assess the risk factors for occurrences of ADR in the PLHIV and receiving ART.

METHODS

A prospective cohort study was conducted among 496 PLHIV at ART Clinic, Tropical and Infectious Disease Center at BPKIHS, Dharan, Nepal from April 2018 to March 2019. HIV-infected patients taking ART and aged 18 years and above who consented for the study were enrolled. Pregnant and lactating women were excluded. Presuming maximum prevalence of ADRs as 50%, the required sample size was calculated as 481.

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A semi-structured proforma was prepared using the relevant literatures to collect the data.[6-8] It consisted of sociodemographic data, mode of transmission, laboratory investigations, date of HIV diagnosis and initiation of ART, physical and systemic examinations, drugs prescribed and ADRs. The patient were followed up on monthly basis when they visited the ART clinic for refilling of the prescription. Face-to-face interview was carried out using the questionnaire and general physical and systemic examinations were performed to identify ADRs. Hospital records and laboratory reports, clinician's notes and prescriptions were also reviewed for relevant data related to sociodemographic characteristics, CD4 count and viral load, drugs prescribed and reported ADRs. Baseline investigations done were Complete Blood Count, Liver Function Test, Lipid profile, Urine RE/ME and were repeated at interval of three months.

Epidemiological data and mode of transmission of HIV, World Health Organization (WHO) staging of AIDS, initiation of ART, ART regimen, non-HIV drugs, co-morbidities and laboratory investigations were the independent variables and ADR was the dependent variable. All patient data were anonymized and de-identified prior to the descriptive analysis.

The WHO guideline was used to categorize the patients into clinical stages of HIV.[9] ADR was defined as any response to a medicine which is noxious and unintended, and which occurs at doses normally used in patients.[10,11] ADRs were evaluated using standard clinical signs and symptoms. Lipodystrophy was assessed through patient history according to the following criteria: fat wasting of the face, arms, legs, buttocks, and/or fat accumulation in the abdomen. The operational definitions used in the study are given in the Table 1.

Table 1. Operational definitions.

Anemia	Hemoglobin concentration <11 g/dL in male and <10 g/dL in female
Neutropenia	Absolute neutrophil count equal to or less than 1500 cells/mm^3 following ART initiation
Thrombocytopenia	Absolute platelet count equal to or less than 150000 cells/mm^3 following ART initiation
Hepatotoxicity	Increase in serum alanine transaminase or aspartate transaminase or alkaline phosphatase to greater than three times the upper limit of normal with or without clinical symptoms of hepatitis
Dyslipidemia	Triacylglycerol >200mg/dL or total cholesterol >200 mg/dL or low density lipoproteins >160 mg/dL
Hyperbilirubinemia	Total bilirubin level more than 1.2 mg/dL
Non-HIV drugs	Drugs other than antiretroviral drugs

The data were entered in Microsoft Excel 2007. Categorical data were reported numerically as numbers and percentages of the total. Continuous data were reported using mean and standard deviations (SD). Chi-square test was used for analyzing categorical data at P-value <0.05. All statistical calculations were performed using SPSS version 11.5 (Chicago, USA). The study was approved by both Institutional Review Committee (IRC/1197/017), BPKIHS, Dharan, Nepal and Nepal Health Research Council (Reg. no. 487/2017), Kathmandu, Nepal.

RESULTS

The age of the PLHIV ranged from 18-70 years with mean age 37.23±9.67 years. Most of the PLHIV were male (54.2%), aged 31-45year (58.1%), literate (87.1%), married (75%) and unskilled worker (57.7%). Alcohol and tobacco consumption was found among 10.7% and 15.5% patients respectively (Table 2).

Table 2. Socio-demographic characteristics of the patients living with HIV (n=496).

Variables		Frequency	Percent
Gender	Male	269	54.2
	Female	227	45.8
Age group (years)	18-30	131	26.4
	31-45	288	58.1
	46-60	63	12.7
	More than 60	14	2.8
Level of education	Illiterate	64	12.9
	Literate	432	87.1
Occupation	Self-employed	83	16.7
	Office Job	59	11.9
	Skilled worker	61	12.3
	Unskilled worker	286	57.7
	Students	7	1.4
Alcoholic status	Non-alcoholic	443	89.3
	Alcoholic	53	10.7
Smoking status	Non-smoker	419	84.5
	Smoker	77	15.5
Marital status	Unmarried	33	6.7
	Married	372	75.0
	Divorcee/Widow/ Widower	91	18.3

Unsafe sexual practice (80.2%) was the most common mode of transmission of HIV infection followed by intravenous drug use (16.3%), blood and blood products (1.8%), unknown (1.2%) and vertical (0.4%). Mean duration of HIV diagnosis and initiation of ART were 7.24 and 5.51 years respectively. At the time of diagnosis of HIV/AIDS, majority of the PLHIV (39.3%) were in WHO stage 1 followed by 21% in stage 2, 27.4% in stage three and 12.3% in stage 4.

Majority of the patients (94.3%) were prescribed first-line antiretroviral drugs [Nevirapine (NVP), Lamivudine (3TC), Efavirenz (EFV), Zidovudine (AZT), Tenofovir (TDF) and Abacavir (ABC)] followed by second-line antiretroviral drugs [Lopinavir boosted with Ritonavir (LPV/r) and Atazanavir boosted with Ritonavir (ATV/r) in 5.2% patients. Most commonly prescribed first-line ART regimen was TDF+3TC+EFV (52%) followed by AZT+3TC+EFV (17.9%) and AZT+3TC+NVP (17.3%). TDF+3TC+LPV/r (2.2%) was the most common second-line ART followed by TDF+3TC+ATV/r (1.6%) and AZT+3TC+LPV/r (0.8%). Raltegravir (RAL)+3TC+EFV was used in 2 (0.4%) patients. Non-communicable diseases (NCD) and chronic co-infections were present among 63 (12.7%) and 61 (12.1%) of the cohort respectively. Non-HIV drugs were prescribed in 63 (12.7%) patients.

Out of 496, 172 patients experienced at least one ADR resulting in prevalence of 34.7%. A total of 240 ADRs were documented in the study cohort. Skin rash, anemia and nausea and vomiting were three most common ADR (Figure 1). Most of the ADRs were observed with TDF+3TC+EFV (51.25%) (Table 3).

Table 3. Antiretroviral therapy regimen and frequency of adverse drug reactions (n=240).

ART regimens*		Adverse drug reactions	
		Frequency	Percent
First-line	TDF+3TC+EFV	123	51.3
	TDF+3TC+NVP	16	6.7
	AZT+3TC+EFV	55	22.9
	AZT+3TC+NVP	34	14.2
	ABC+3TC+EFV	1	0.4
Second-line	Combined with LPV/r	4	1.7
	Combined with ATV/r	6	2.5
Third-line	Combined with Raltegravir	1	0.4

**TDF: tenofovir, EFV: efavirenz, AZT: zidovudine, NVP: nevirapine; ABC: Abacavir; 3TC: lamivudine, LPV/r: Lopinavir boosted with ritonavir, ATV/r: Atazanavir boosted with Ritonavir*

None of the ADRs were life threatening or had permanent loss of function of any organs in the patients; however, modification of ART was demanded among 68 (13.7%) PLHIV due to drug intolerance (Table 4). ADRs were more common in male, literate, unskilled worker, non-alcoholic, non-smokers and married PLHIV; however, it was statistically not significant (P value>0.05). ADRs were also more common in patients having NCD, chronic co-infections, taking more than 3 non-HIV drugs and 2nd and 3rd line ART regimen and it was statistically significant (P value <0.05) (Table 5).

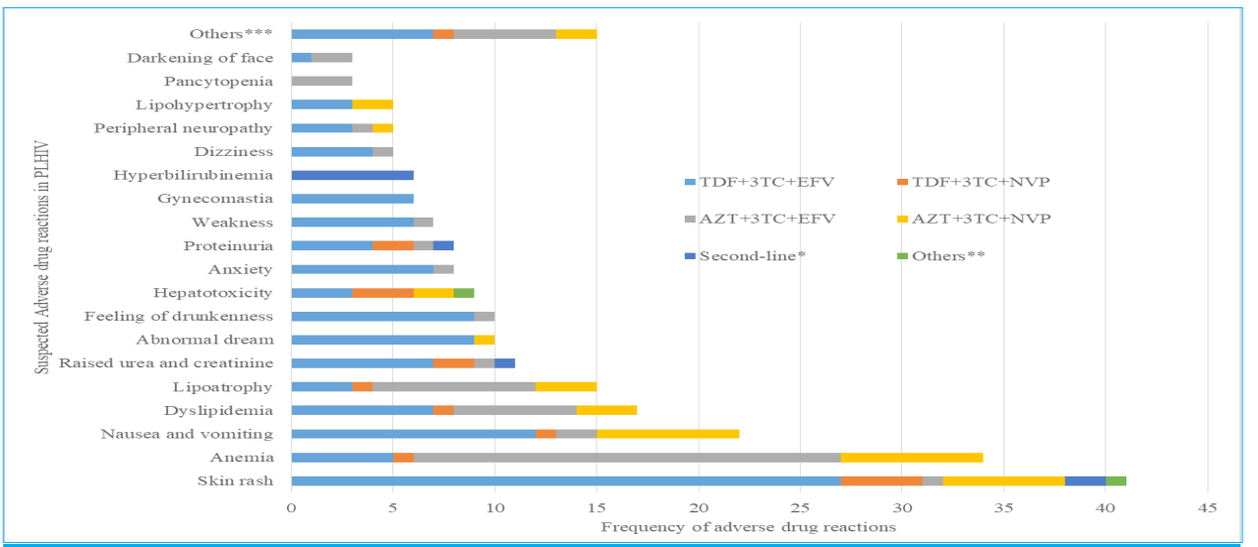

Figure 1. List of adverse drug reactions among the patients living with HIV (n=240).

*Includes ART regimens combined with protease inhibitors AZT/r and LPV/r, **Includes ABC+3TC+EFV and combined with Raltegravir, ***Includes neutropenia, thrombocytopenia, hypothyroidism, photo allergic reaction, parotitis, hematuria, myositis, dementia, weight gain, hearing impairment, alopecia, epistaxis, and anorexia.

Table 4. List of intolerant drugs and modification in the antiretroviral regime (n=68).

Intolerant drugs	Number of patients	Management
Zidovudine	32 out of 234	Changed to Tenofovir
Efavirenz	27 out of 397	Changed to Nevirapine
Tenofovir	4 out of 345	Changed to Zidovudine
Nevirapine	3 out of 147	Changed to Efavirenz
Abacavir	1 out of 3	Changed to Tenofovir
Atazanavir	1 out of 20	Changed to Raltegravir
Cotrimoxazole	9 out of 327	Stopped

Table 5. Risk factors for adverse drug reactions in the patients living with HIV (n=496).

Baseline variables		Adverse drug reactions		P-value
		Present	Absent	
Gender	Male	96	173	0.637
	Female	76	151	
Age group (years)	18 - 30	41	90	0.747
	31 - 45	10.	185	
	46 - 60	22	41	
	More than 60	6	8	
Level of education	Illiterate	17	47	0.056
	Literate	155	277	
Occupation	Self-employed	28	55	0.145
	Office Job	29	30	
	Skilled worker	18	43	
	Unskilled worker	94	192	
	Students	3	4	
Alcoholic status	Non-alcoholic	159	284	0.126
	Alcoholic	13	40	
Smoking status	Non-smoker	148	271	0.517
	Smoker	24	53	
Marital status	Unmarried	12	21	0.668
	Married	125	247	
	Divorcee/ Widow/ Widower	35	56	
Non-communicable diseases	Present	38	25	0.0001*
	Absent	134	299	
Chronic co-infections	Present	39	31	0.021*
	Absent	143	293	
Numbers of non-HIV drugs	0 - 3	163	320	0.014*
	4 and above	9	4	
ART regimen	First-line	152	316	0.0001*
	Second-line	18	8	
	Third-line	2	0	

**Statistically significant at P-value <0.05 (Pearson Chi-square test)*

DISCUSSION

This is the first comprehensive report on ADR of ART among PLHIV from an ART Clinic in Eastern Nepal. Our study highlights the fact that one fourth of our cohort were young (18-30 year) signifying high prevalence of HIV/AIDS in sexually more active patients. Similar finding was also reported in other study.[12] HIV/AIDS is a disease of working and young adult in the developing world as compared to older age group in the developed world.[13] Policy regarding reproductive health education, safe sex, and volunteer screening of HIV infections with risk of exposure is likely to be effective tools for prevention and early diagnosis of HIV among these cohort. This is an alarming situation. PLHIV who are in the age group of 18-45 years needs intensive counselling regarding ADRs of available ART regimen for better patient compliance.

Majority of PLHIV were literate in our study and therefore, it is easy to educate such patients regarding nature of HIV/AIDS, the available treatment and ADRs than can result in higher patient compliance.[14] As more than half of the PLHIV were unskilled worker, vocational training among them could be instrumental against psychosocial stress. Heterosexuality was the most common mode of HIV transmission in our study and similar finding was also reported in other study.[15] Safe sexual practice among PLHIV should be re-emphasized. As TDF+3TC+EFV was the most frequently prescribed regimen in the cohort, our study findings recommends to use this regimen to initiate treatment of naïve PLHIV.

In spite of predominant heterosexual practice in our society, we had predominantly male patients in the study cohort. Similar finding was also reported elsewhere.[6] This may be due the fact the most of the females living with HIV positive husband may be unknown of their HIV status and their husband may not disclose his HIV status due to fear of marital conflict.[16] This is an indicator of gendered health seeking behavior in our part of the world. Besides active screening of the wife

and kids of the PLHIV positive husbands, we should trace the burden at early stages. In contrast to our findings, female patients were predominant in a South African study.[12] Most probably in African continent HIV was more common to men and later on the burden shifted to women population.[17] The transition might had happened due to lack of adequate ART among male population, inadequate safety measures during sexual intercourse, poor screening among females to diagnose HIV in early stages and death of male who had been affected.[18] If measures to prevent the transmission of epidemiological shift in gender are not taken in time, there will serious threat to women health and kids delivered by them. However, in developed world like USA and European countries more males are diagnosed with HIV due to higher prevalence of homosexuality.[19]

We found a high prevalence of ADRs (34.7%) in our study cohort. One in every three patients reported at least one ADR and this finding was in consistent with that of Reddy et al.[20] A higher prevalence of ADRs was reported in other study.[12] A lower prevalence (5%) of ADR was found in a study conducted in Central India.[15] These variations in the prevalence of ADRs may be due to difference in its monitoring and reporting, concurrent medications used for treating opportunistic infections and other co-morbid conditions. Regional or ethnic susceptibilities to ADRs and lack of uniformity in the reporting style of ADRs across different study settings and methodology might also explain these differences. A higher prevalence of ADR demands discovery of safer antiretroviral drugs for better patient compliance. Skin rash, itching and anemia were the three commonest ADR in our study. Similar finding was also reported in other study.[15] In contrast to these findings, polyneuropathy was the commonest ADR in a South African study.[12] This may be due to the use of Stavudine in South African countries which is known to cause neuropathy. As per latest National STD guidelines, Stavudine is not used for treatment of HIV/AIDS in Nepal.[21]

Our study identified age (31-45 years), male gender, co-infections, NCD, taking more than 3 non-HIV drugs and 2nd and 3rd line ART regime as possible risk factor for occurrence of ADRs. Counselling regarding possible ADR among PLHIV with these characteristics is possible options to detect ADR early and to optimize the best suitable ART regimen. Most of the ADRs were not life threatening or had permanent loss of function of any organs. The patient who are beginning ART could be counselled by those who had ART for long duration regarding its benefit and safety. This approach will possibly minimize fear and increases the patient compliance.

Anemia consisted of 14.17% of total ADRs in our study and it was higher than the findings in Cameroon.[22] PLHIV often presents with coexisting nutritional deficiencies, concomitant opportunistic infections and other chronic diseases that may precipitate anemia.[23] This high level of background anemia is in turn exacerbated by the use of AZT; however, TDF-based regimens were found to be milder in this regard in our study. Regimen containing AZT was substituted with TDF containing regimen in patients who developed anemia.

More than two third of dyslipidemia was observed with EFV-based first line ART regimen and the remainder with NVP-based first line regimen. In contrast to these findings the regimen having ATV/r had caused more dyslipidemia in other study.[6] NRTI, NNRTI and PI adversely affect the lipid profile in PLHIV by increasing serum triglycerides, total cholesterol, HDL and LDL. With ART, PLHIV lives decades changing the demography to older age.[24] Aging occurs earlier among PLHIV as compared to normal population and they are also more prone to NCD.[25,26] Policy on primary and secondary prevention of NCD like dyslipidemia, atherosclerotic disease needs to be practiced as the HIV population grows older.

Serum urea and creatinine level were mostly raised in those patients who were on TDF based ART regimen. The pathogenesis of impaired renal function and its progression to chronic kidney disease among PLHIV is multifactorial and includes nephrotoxic antiretroviral drugs, HIV viremia, chronic systemic inflammation, hypertension, diabetes mellitus and smoking.[27] TAF (Tenofovir alafenamide) is safer in terms of nephrotoxicity compared to TDF.[28] Rolling out of TAF could be another policy to avoid the nephrotoxicity in PLHIV.

Most of neuropsychiatric ADRs (anxiety, dizziness, abnormal dream, feeling of drunkenness) were observed with EFV-based 1st line ART regimen. These ADRs generally became more tolerable and resolved within the first four weeks of the ART therapy in most of the patients and in some patients the regimen was changed to non-EFV combination. EFV-associated ADRs may compromise patient compliance and lead to treatment discontinuation.[29] Clinicians should counsel the patients having possible neuropsychiatric effects of EFV and look for behavioral and cognitive changes. In case of persistent or intolerable side effects, a switch to other ART regimen may be found appropriate. Safer NNRTI as substitute of EFV is another potential demand for the first line ART.

Almost half cases of hepatotoxicity was observed with the first-line ART regimen containing NVP. Liver

enzymes elevations is one of the several clinical reasons for discontinuation of ART in clinical practice. As tuberculosis is highly prevalent among PLHIV and anti-tubercular drug are notorious to cause hepatotoxicity, it is a cumbersome condition when PLHIV has to go under treatment of reactive or latent tuberculosis.[30]

Gynecomastia was observed in 1.2% patients and all cases were with TDF+3TC+EFV. There are various hypothesis regarding ART related gynecomastia. It mimics the effects of estrogen on breast tissue, increases breast tissue estrogen availability due to immune restoration and EFV induced elevation in the estrogen-androgen ratio.[31] EFV based ART might decrease the patient compliance among male PLHIV due to fear of gynecomastia.

Modification of ART was demanded in 68 (13.7%) PLHIV due to intolerance. Similar findings were also reported in other study in which 67% of the regimens were changed due to intolerable ADRs.[15] As the spectrum of ADR is wide and depends upon immune status of PLHIV, it is very difficult to differentiate those ADRs with that of due to HIV/AIDS themselves and its exact cause may be difficult to identify.[32] Therefore, monitoring for ADR should be an ongoing process among PLHIV. Adding a laboratory component to the ADR screening would be instrumental to detect ADR in preclinical setting.

Our study takes strength in its large sample size. This is one of the largest cohort of PLHIV who have been surveyed in Eastern Nepal for ADRs using active surveillance of clinical and laboratory parameters. Moreover, there was minimal loss of data due to the prospective nature of the study. However, the study also included patients who had initiated ART before active surveillance of ADR commenced and hence the early ADRs from those patients might have been missed. The study was conducted at only one ART center of Nepal and hence the findings cannot be generalized. The causality, severity and preventability assessment of ADR could not be conducted.

CONCLUSIONS

Prevalence rate of ADRs was 34.7% in PLHIV and taking ART. None of the ADRs were life threatening. Skin rash, nausea and vomiting and anemia were the commonest ADRs. Age, gender, co-infections, NCD, taking more than 3 non-HIV drugs and 2nd and 3rd line ART regime were identified as possible risk factor for occurrence of ADRs and their prior identification is important to optimize the best suited ART regimen to enhance patient compliance. Active pharmacovigilance programme would guide us on future prospective of ART.

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CONFLICT OF INTEREST

None

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