ORIGINAL ARTICLE

Reasons for modifications of antiretroviral therapy among patients living with HIV at a tertiary care hospital

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ABSTRACT

Background: Antiretroviral therapy (ART) is frequently modified and alternative regimens are used to overcome the acute and chronic toxicities, drug resistance, cost, unavailability of the stock, comorbidities and treatment failure. In a resource-limited setting like Nepal, it is important to determine the magnitude and reasons for ART regimen modifications. The objective of the study was to find the reasons for modification in ART regimens among patients living with HIV (PLHIV).

Methods: It was a cross-sectional study conducted among PLHIV at ART Clinic, B.P. Koirala Institute of Health Sciences Dharan, Nepal from January to March 2019. The information on socio-demographics, duration of ART therapy, mode of HIV transmission, the latest ART regimen and reason for its modification were collected on a self-designed proforma through the review of patients' health cards and a face-to-face interview. Descriptive statistics were calculated.

Results: Out of 521 patients, modification of the ART regimen was made in 83 (15.9%) patients. The mean age (± standard deviation) was 36.57 ± 7.90 years. The majority of the patients (66.3%) were in the age group of 31-45 years and 50 (60.2%) were male. One-third of the patients (32.5%) were taking Tenofovir+Lamivudine+Efavirenz. Adverse drug reaction (82.2%) was the commonest cause of ART regimen modification. Anemia (24.1%) was the most common adverse drug reaction responsible for ART regimen modification.

Conclusion: ART modification had occurred at a lower rate in our setting and anemia was the most common reason for modification in the ART regime. The study findings might help the clinicians for the appropriate management of the PLHIV.

KEYWORDS: Antiretroviral therapy, Anemia, HIV, Nepal

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INTRODUCTION

The HIV/AIDS epidemic in Nepal continues to pose a threat to the lives of its people. As per July 2018, the estimated number of patients living with HIV (PLHIV) in Nepal was 29,944 and among them, only 17987 were on antiretroviral therapy (ART).[1] The World Health Organization (WHO) has recommended the initiation of ART in everyone living with HIV.[2] ART service was started in 2004 in Nepal and is available for free of cost for all PLHIV.[3] Being the cornerstone of care and treatment PLHIV, it has improved life expectancy and quality of life of PLHIV by reducing mortality and morbidity.[4,5]

The ART clinic delivers outpatient services to the PLHIV at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan since 2006. The first-line ART regimen includes a triple therapy of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). Commonly used NRTIs are Zidovudine (AZT), Lamivudine (3TC), Abacavir (ABC) and NNRTIs are Nevirapine (NVP) and Efavirenz (EFV). Based on the guideline, the preferred first-line ART regimens are Tenofovir (TDF)+3TC+EFV and the alternate first-line regimens are TDF+3TC+NVP, AZT+3TC+EFVor NVP, ABC+3TC+EFV or NVP. The second-line ART for adults should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).[6]

Once initiated the PLHIV must take the ART indefinitely. Despite the established efficacy of ART in PLHIV, it is frequently modified and alternative regimens are used to overcome acute and chronic toxicities, drug resistance, cost, unavailability of the stock, comorbidities and treatment failure.[7-10] In a resource-limited setting like Nepal where treatment options are limited for PLHIV, it is essential to design strategies to increase the durability of the first and second-line regimens. Therefore, it is important to determine the magnitude of ART regimen modification in PLHIV to achieve this goal. The data on the modification of ART is scarce in Nepal. The objective of the study was to know the reasons for ART modification PLHIV at a tertiary care hospital in Eastern Nepal.

MATERIALS AND METHODS

A cross-sectional study was conducted among PLHIV at ART Clinic, BPKIHS, Dharan, Nepal from January to March 2019. The PLHIV taking ART for at least six months and giving consent were enrolled in the study while patients below 18 years of age, pregnant and lactating women were excluded. Using the formula Z^2*p*q/L^2, the sample size of 176 was calculated taking the prevalence (p) of ART modification as 71.1% with the confidence interval of 95%, a margin of error (L) 5% and a non-response rate of 10%.[11] A self-designed data collection form was used to collect the information on socio-demographics, mode of transmission of HIV, duration of ART therapy, the latest ART regimen and reasons for ART regimen modification. The objective of the study was explained to the patients and written informed consent was taken. The patients' health cards were reviewed and a face-to-face interview was conducted to collect the relevant data. No personal information was collected to maintain the confidentiality of the patients. This study was a part of the project which has been published elsewhere and it was approved by the Institutional Review Committee (IRC/1197/017). The following operational definitions were made as per the national guidelines:

Modification of ART: the changing of at least one antiretroviral drug used in an initial ART regimen

Treatment failure: Immunological failure or virological failure

Immunological failure: CD4 count at or below 200 cells/mm^3 following persistent CD4 levels below initial reading despite ART

Virological failure: Viral load above 1000 copies/mL based on two consecutive viral load measurements in three months despite ART

The data were coded and entered into Microsoft Excel 2010. Descriptive statistics mean, frequency and percentage were used to summarize the study findings. All statistical analysis was conducted using Statistical Package for Social Science version 11.5 (SPSS Inc, Chicago, IL, USA).

RESULTS

Out of 521 patients, ART was modified in 83 (15.9%) patients**.** The age of the patients ranged from 22-62 years. Median and mean age were 36 and 36.57±7.99 years respectively (**Table 1**). Most of the patients

(32.5%) were on TDF+3TC+EFV (**Figure 1**).

Table 1: Sociodemographic characteristics of the patients (n=83)

Variables	Category	Frequency	Percentage
Gender	Male	50	60.2
	Female	33	39.8
Age groups in year	18 – 30	18	21.7
	31 – 45	55	66.3
	46 – 60	9	10.8
	More than 60	1	1.2
Marital status	Married	66	79.5
	Single	5	6.0
	Others	12	14.5
Educational Level	Illiterate	8	9.6
	Literate	75	90.4
Occupation	Employed	44	53.0
	Unemployed	39	47.0
Mode of transmission	Unprotected sex	56	67.5
	Intravenous drug use	25	30.1
	Others	2	2.4
Duration of antiretroviral therapy in years	Upto 5	35	42.2
	More than 5	48	57.8

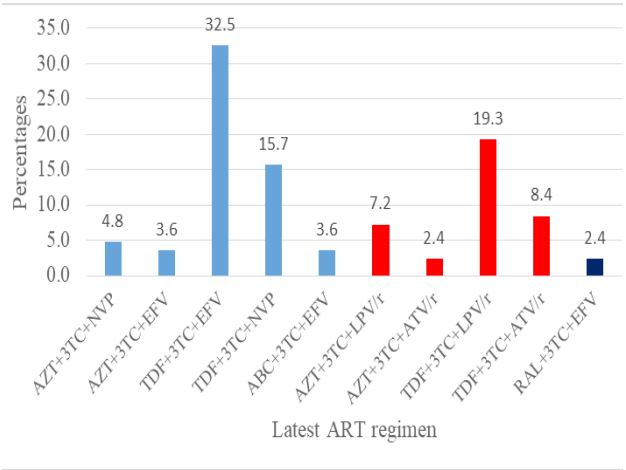

Figure 1: The latest ART regimen prescribed* (n=83)

*AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; TDF: Tenofovir; ABC: Abacavir; LPV/r: Liponavir/Ritonavir; ATV: Atazanavir/Ritonavir: RAL: Raltegravir

A total of 101 modification in the ART regimen was made in 83 patients. The ART regimen was modified once in 67 (80.7%) patients, twice in 14 (16.9%) and thrice in two (2.4%) patients. TDF+3TC+EFV (31.7%) was the most common regimen involved in the modification followed by AZT+3TC+EFV (21.8%) (**Table 2**).

Table 2: Reason of the modification in the ART regimen (n=101)

ART regimen	Reasons of ART regime modification							
	Adverse drug reaction		Immunological failure		Virological failure		Treatment inter-ruption	
	N	%	N	%	N	%	N	%
TDF+3TC+EFV (n=32)	27	84.4	2	6.2	3	9.4	-	-
TDF+3TC+NVP (n=10)	8	80	2	20	-	-	-	-
AZT+3TC+EFV (n=22)	17	77.3	3	13.6	1	4.5	1	4.5
AZT+3TC+NVP (n=20)	14	70	5	25	1	5	-	-
d4T+3TC+EFV (n=5)	5	100	-	-	-	-	-	
ABC+3TC+EFV (n=1)	1	100	-	-	-	-	-	-
AZT+3TC+ATV/r (n=8)	8	100	-	-	-	-	-	-
TDF+3TC+LPV/r (n=2)	2	100	-	-	-	-	-	
RAL+3TC+EFV (n=1)	1	100		-	-	-	-	-
Total	83	82.2	12	11.9	5	5.0	1	1.0

*AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; TDF: Tenofovir; ABC: Abacavir; LPV/r: Liponavir/Ritonavir; ATV: Atazanavir/Ritonavir: RAL: Raltegravir: d4T: Stavudine

Adverse drug reaction (82.2%) was the most common cause of regimen modification in PLHIV followed by immunological failure (11.9%). Anemia was the most common reason for modification in the ART regimen (**Table 3**).

Table 3: List of the toxicities associated with the modification in the ART regimen (n=83)

Adverse drug reactions	ART regimen*								
	Z3N	Z3E	T3E	T3N	T3L	Z3A	Abc3E	R3E	d3E
Anemia (n=20)	8	11	-	-	-	-	-	-	1
Skin rash (n=17)	2	-	10	3	1	-	1	-	
Hyperbilirubinemia (n=8)	-	-	-	-	-	8	-	-	-
Hepatitis (n=8)	2		2	3	-	-	-	1	
Lipoatrophy (n=7)	1	2	-	1	-	-	-	-	3
Raised urea/creatinine (n=7)	-	-	6	-	1	-	-	-	-
Gynecomastia (n=5)	-	-	5	-	-	-	-	-	-
Neuropsychiatric reactions (n=5)	-	-	5	-	-	-	-	-	-
Pancytopenia (n=2)	-	2	-	-	-	-	-	-	-
Hematuria (n=1)	-	-	-	1	-	-	-	-	-
Lipohypertrophy (n=1)	1	-	-	-	-	-	-	-	-
Peripheral Neuropathy (n=1)	-	-	-	-	-	-	-	-	1
Vomiting (n=1)	-	-	1	-	-		-	-	-

*Z: Zidovudine, 3: Lamivudine, T: Tenofovir, Abc: Abacavir, L: Liponavir/r, N: Nevirapine, d: stavudine, R: Raltegravir, E: Efavirenz

DISCUSSION

In the present study, the mean age was 36 years. Higher mean age was reported by Bokore et al (43.68years).[12] Male patients (60.2%) were predominant in this study and this was not consistent with a Brazilian study in which female patients (52.3%) predominated.[12] Most of the patients were married in this study and similar findings were reported in other studies.[12,13] Majority (57.8%) of the patients had been on ART for 1-5 years. This finding indicated a shorter duration of ART therapy as compared to another study in the which majority (59.67%) of the patients had been on ART for more than 10 years.[12]

Nearly one-third of the patients (32.5%) were on TDF+3TC+EFV and this finding was not consistent with the other studies.[14-17] Stavudine is not used in Nepal as better drugs are available and its use is phased out at most of the ART centers worldwide.[18]

A total of 101 modification in the ART regimen was modified in 83 (15.9%) patients. A higher prevalence of ART modification had been reported in other studies.[13,19,20] This may be due to the difference in comorbidities, other drugs prescribed and genetic makeup among the study populations. The ART regimen was modified once in most of the patients in this study and similar finding had been reported in another study.[13]

TDF+3TC+EFV (31.7%) was the most common regimen involved in the ART modification. Adverse drug reaction (82.2%) was the most common cause of regimen modification in PLHIV in this study and this was higher than other studies.[13,20,21] Adverse drug reaction is a potential threat to patient compliance during antiretroviral therapy in PLHIV. Less toxic and better-tolerated treatment choices for HIV should be used more frequently.

Anemia was the most common reason for modification in the ART regimen which was in contrast to the other studies.[13,20] The rash was mainly observed in the patients taking the TDF+3TC+EFV regimen which did not coincide with another study in which the NVP based ART regimen caused skin rash.[22] Despite the free service of ART for all PLHIV in Nepal, treatment interruption also accounted for the ART regimen modification which signifies poor patient counseling and fear toward antiretroviral drugs.

ART failure is associated with virologic failure, immunologic failure, and/or clinical failure.[23] Due to the scarcity of drug resistance, the prevalence of undetected virological failure remains unknown in many PLHIV in resource-limited settings.[24] In this study, treatment failure was another factor for modification of ART regimen and immunological failure was the most common. The number of patients of treatment failure and need second-line ART has risen in other countries as well.[25] Second-line ART is generally the last treatment option in these settings and is more expensive than first-line ART and also not available in most of low-income countries.[24] Viral load testing is the gold standard technique for diagnosing ART failure and recommended method to monitor ART switching; however, it is not universally available.[25] Because of poor laboratory support and follow-up, viral loads were not routinely measured in our setup. In these settings, the priority should be to confirm failure in patients in whom treatment failure is suspected based on clinical or immunological criteria.[26] Change of the entire regimen from first-line to second-line ART is required in case of treatment failure. The preferred strategy for second-line ART for adults was a boosted PI and two NRTI combinations in this study and it was as per the recent National guideline.[6]

All PLHIV should be evaluated regularly after a change in ART regimen to assess for potential concerns with the new regimen and to assess the tolerance and effectiveness. Information is also needed on the patterns of resistance of antiretroviral drugs across the population to recommend future therapy options. Therefore national and health institution-based surveillance of antiretroviral drug resistance should be promoted which will help to know the resistance pattern and select the locally effective ART regimen.

Limitations: The study collected the reasons for ART modifications as reported by the patients themselves and recall bias may have influenced the results. However, the patient's health card reviews were used to validate the self-report as far as possible. Time intervals between switching of the ART regimens could not be traced. Baseline CD4 and Viral load data were not available. Although the study was conducted at one ART clinic in Eastern Nepal, it is likely to represent many other ART clinics in the district as most of the clinics face similar challenges.

CONCLUSIONS

It is concluded that ART modification has occurred at lower than expected rates in our setting and adverse drug reaction was the commonest reason for the modification. Anemia was the common reason for modification in the ART regimen. More suitable ART regimens with lower toxicity profiles should be used first. The findings of the study should be investigated further in longitudinal studies at multiple ART centers.

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