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Research Article

FACTORS INFLUENCING THE SUBSTITUTION OF ANTIRETROVIRAL THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME PATIENTS ON FIRST LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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ABSTRACT

Objectives: The aim was to determine the reasons for initial highly active antiretroviral therapy (HAART) regimen changes among human immunodeficiency virus/acquired immunodeficiency syndrome patients on HAART.

Methods: The present study is conducted retrospectively by reviewing the patient treatment records at antiretroviral therapy (ART) center RIMS Teaching Hospital, Raichur. Assessment and analysis were performed inpatient treatment records showing initial regimen changes and to identify the common reasons that resulted in these changes. The data were analyzed using SPSS version 16.0.

Results: A total of 3510 patient records were assessed, 520 cases (14.8%) among these had to change initial HAART regimens. The majority of the patients (53.7%) were males. The most common primary regimen, before the first substitution, was zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) (33%), stavudine/3TC/NVP (25%), tenofovir/3TC/NVP (23%) and AZT/3TC/efavirenz (14%). Main reasons for the substitution to HAART regimens were comorbidity (58.26%), followed by adverse drug reactions (ADR) (38.46%).

Conclusion: Comorbidity was the main reason for the modification of initial HAART among the study population, followed by ADR in ART patients. Reports of comorbidity warrant further investigation, particularly because identifying these conditions are challenging in resource-limited settings.

Keywords: Highly active antiretroviral therapy, Initial regimen, Substitution, Comorbidity, Adverse drug reactions, Raichur.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) is a major global health problem. In India HIV/AIDS epidemic is concentrated in nature, based on sentinel surveillance 2008-09 adult prevalence is about 0.31%, with 23.9 lakh people living with HIV/AIDS [1]. The high prevalence among high-risk groups is about 20 times more than in the general population [1]. In order to provide access to antiretroviral therapy (ART) drugs, government of India announced free national ART program on December 1st, 2003 and first patient was started on free ART on April 1st, 2004, significantly scaled up to 324 ART center and nearly 4.5 lakh are on ART by September 2011 [2].

Presently more than 16 approved therapeutic agents are available for treatment of HIV infection. Approved antiretroviral (ARV) drugs include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors and protease inhibitors. Entry inhibitors and integrase inhibitors are also used currently [3-5]. However, these improvements are associated with drawbacks like drug-resistance and side-effects [3].

Currently, the national program provides the following drugs/combinations for first-line regimens, zidovudine (AZT) (300 mg)+lamivudine (3TC) (150 mg), tenofovir (TDF) (300 mg)+3TC (150 mg), AZT (300 mg)+3TC (150 mg)+nevirapine (NVP) (200 mg), efavirenz (EFV) (600 mg) and NVP (200 mg). Principles for selecting the first-line regimen, to choose 3TC in all regimens, one NRTI to combine with 3TC (AZT or TDF) and lastly one NNRTI (NVP or EFV) [6].

Risk of long-term toxicity, poor adherence, a desire for pregnancy, a sub-optimal regimen, comorbidity with other chronic diseases or virological failure [7-9], are common reasons for treatment substitution.

With the scaling up access to ART in Raichur, there is an opportunity to better understand the benefits and drawbacks of these regimens. Data on the modification of the initial highly active antiretroviral therapy (HAART) are scarce among Raichur patients. The aim of this study is, therefore, to assess the causes of the initial HAART regimen changes among patients on ART in Raichur.

METHODS

Ethics

The study was approved by the Institutional Ethics Committee, RIMS Teaching Hospital, Raichur. The confidentiality of the data obtained was assured, and no disclosure was made of any name of the patients, the healthcare provider or drug product in relation to the finding.

Study setting

The study was conducted from January 2010 to December 2012 at ART center RIMS Teaching Hospital Raichur, staffed with health professionals trained in ART treatment and adherence counseling services.

Study design

The cross-sectional study conducted retrospectively by reviewing the patient treatment card and physician diagnosis cards was conducted, to assess the initial HAART regimen changes. A data collection format was used to collect data on the demographic conditions, the starting and changing regimens, duration of the initial therapy, CD4 count, World Health Organization (WHO) stage of the disease, and reasons for substitution of the regimen.

Data collection

Prior to the start of actual data collection, the data collection format and the whole method was screened on randomly selected patient clinical records, at the ART center, RIMS teaching hospital to ensure their completeness. The data collection was done using a pretested questionnaire containing socio-demographic variables and patient

information, and clinical information and ART information, such as, the CD4 count at the start (CD4 cell count/µl), WHO stage at the start of treatment, initial (starting) regimen, date on which treatment was started, date of the initial ARV drug regimen substitution, duration of the initial ARV therapy before first substitution, regimen substituted to, and reason for changing the regimen.

Definitions

Comorbidity is defined as the occurrence of one or more additional disorders (or diseases) simultaneously with a primary disease (tuberculosis [TB], diabetes, hypertension), immunological failure (a fall in CD4 cell count below baseline pretreatment level) or virology failure (increase in viral load after complete suppression). Adverse drug reactions (ADR) is defined as the occurrence of adverse events such as diarrhea, nausea, vomiting, anemia, rash, fatigue, peripheral neuropathy, lipodystrophy, metabolic disturbances or any other related to HAART.

Data analysis

All data collected were analyzed using the Statistical Package for the Social Sciences, version 16.0 software.

RESULTS

Records of 520 patients who had changed their initial HAART regimen at ART center, RIMS Teaching Hospital were assessed. 173 (33.3%) were aged between 30 and 39 years, 279 (53.7%) of them were males. 348 (67%) were married, 374 (71.9%) were from the rural area. With regard to the educational background, the majority of the patients 154 (29.6%) were illiterate (Table 1).

300 (57.4%) of them had CD4 count in the range of 101-200 cells/mm^3, 33.3% had a CD4 count ≤100 cells/mm^3, 9.3% were in the range of 201-350 cells/mm^3. A majority of the patients (66.7%) had their initiation of treatment at clinical WHO Stage III, while (29.6%) at Stage II, (2.2%) at Stage I, and (1.5%) at Stage IV. A majority of the patients (33%) were on AZT+3TC+NVP at the beginning of the ARV treatment and the rest were on stavudine (D4T)/3TC/NVP (25%), TDF/3TC/NVP (23%) and AZT/3TC/EFV (14%), D4T+3TC+EFV (3%), TDF+3TC+EFV (2%) (Table 2 and Fig. 1).

The main reason reported for modification of treatment regimen was comorbidity among 303 (58.26%) of the patients, ADR in 200 (38.46%), pregnancy in 17 (3.28%).

Table 1: Socio-demographic distribution of the study population

S. no.	Variables	N (%)
1	Age group	
	20-29	87 (16.7)
	30-39	173 (33.3)
	40-49	164 (31.5)
	50-59	71 (13.7)
	60-69	17 (3.3)
	>70	8 (1.5)
2	Sex	
	Male	279 (53.7)
	Female	241 (46.3)
3	Marital status	
	Unmarried	17 (3.3)
	Married	348 (67)
	Widowed	106 (20.4)
	Divorced	49 (9.3)
4	Place	
	Rural	374 (71.9)
	Urban	146 (28.1)
5	Education	
	Illiterate	154 (29.6)
	Primary	125 (24.1)
	Secondary	96 (18.5)
	High school	77 (14.8)
	Pre university	38 (7.4)
	Degree	30 (5.6)

TB 303 (58.26%) was the only comorbidity reported in this study. Among this 189 (36.34%) were cured of TB and rest 114 (21.92%) were newly diagnosed with TB (Fig. 2).

A majority of the patients (33%) were on AZT+3TC+NVP at the beginning of the ARV treatment and the rest were on D4T/3TC/NVP (25%), TDF/3TC/NVP (23%) and AZT/3TC/EFV (14%), D4T/3TC/EFV (3%), TDF/3TC/EFV (2%).

TB 303 (58.26%) was the only major comorbidity reported in this study. Among this 189 (36.34%) were cured of TB and rest 114 (21.92%) were newly diagnosed with TB. ADR was reported in 200 (38.46%), and pregnancy in 17 (3.28%) (Table 3).

DISCUSSION

The main reasons for treatment change can be due to comorbidity, adverse events, poor adherence, a desire for pregnancy, treatment failure [10]. Comorbid conditions in patients with advanced disease and concurrent therapy for opportunistic infections could affect ARV tolerance and thereby increase the risk of toxicities [11]. Comorbidity was the main cause for HAART substitution. TB 303 (58.26%) was the only comorbid condition observed in this study. This was similar to the study in UK [7] and Coite d'lvoire [12].

Due to TB, 114 (21.92%) were newly diagnosed with TB and substitution was made from NVP-based regimen to EFV based regimen and

Table 2: Overall pattern of HIV/AIDS patients on HAART

S. no.	Variables	N (%)
1	Initial CD4 cell count/µl	
	≤100	172 (33.3)
	101-200	300 (57.4)
	201-350	48 (9.3)
	>350	0 (0)
2	Initial WHO clinical staging	
	Stage I	11 (2.2)
	Stage II	154 (29.6)
	Stage III	347 (66.7)
	Stage IV	8 (1.5)
3	Initial HAART regimen	
	AZT+3TC+NVP	171 (33)
	D4T+3TC+NVP	133 (25)
	TDF+3TC+NVP	118 (23)
	AZT+3TC+EFV	73 (14)
	D4T+3TC+EFV	16 (3)
	TDF+3TC+EFV	9 (2)

HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome, HAART: Highly active antiretroviral therapy, WHO: World Health Organization, AZT: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, D4T: Stavudine, TDF: Tenofovir, EFV: Efavirenz

Table 3: Common reasons for substitution by initial treatment regimens

S. no.	Initial regimens	Reasons for ART regimen change (%)			
		Comorbidity		ADR	Pregnancy
		New TB	TB cured		
1	AZT/3TC/NVP	75 (66)	-	96 (48)	-
2	D4T/3TC/NVP	30 (26)	-	102 (51)	-
3	AZT/3TC/EFV	-	114 (60)	2 (1)	14 (82)
4	D4T/3TC/EFV	-	59 (31)	-	2 (11)
5	TDF/3TC/EFV	-	16 (9)	-	1 (7)
6	TDF/3TC/NVP	9 (8)	-	-	-
Total		114 (100)	189 (100)	200 (100)	17 (100)

AZT: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, D4T: Stavudine, TDF: Tenofovir, EFV: Efavirenz, TB: Tuberculosis, ADR: Adverse drug reactions, ART: Antiretroviral therapy

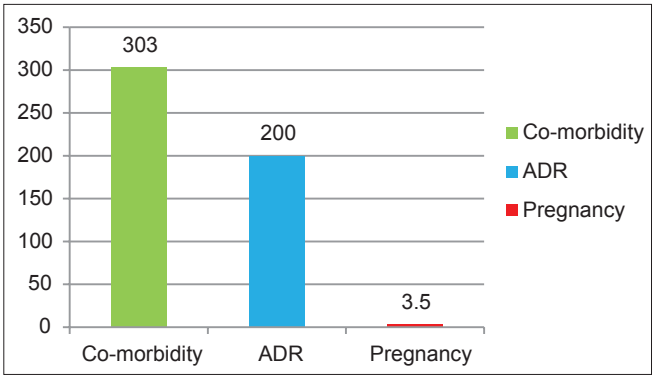

Fig. 1: Common reasons for initial regimen substitution among human immunodeficiency virus patients on highly active antiretroviral therapy

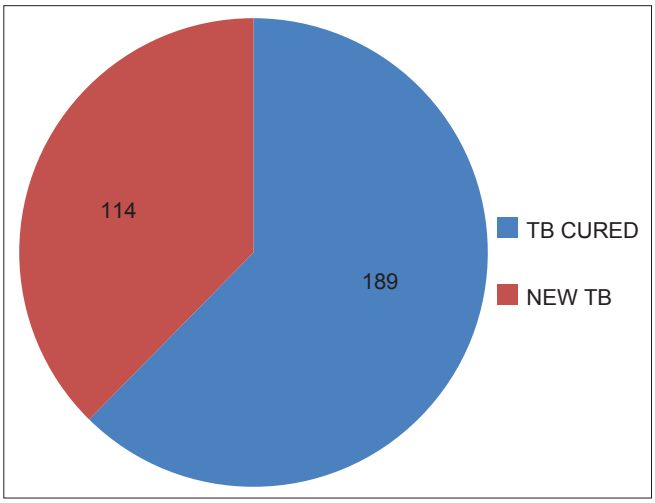

Fig. 2: Comorbidity associated for initial regimen substitution among human immunodeficiency virus patients on highly active antiretroviral therapy highly active antiretroviral therapy

189 (36.34%) substituted back to NVP-based regimen from EFV-based regimen once ART patients were cured of TB. As NVP was a CYP 3A4 enzyme inducer, hence the probable suggestion for this NVP change to EFV was the overlapping drug toxicity of NVP with anti-TB drugs, which was hepatotoxicity, and the potential for drug interaction. ADR-200 (38.46%), was the next most common reason for initial HAART regimen substitution in this study. It was not similar with other studies [7,11,13-18] were the most probable cause for the ARV substitution, was toxicity.

The third major reason for modifying ARV drugs in this study was planning pregnancy or being pregnant. This was similar to the other finding [2,11,12,19]. This change was mainly due to the teratogenicity of EFV, which should mainly be avoided during the first trimester of pregnancy.

Earlier studies [7,12-14], reported higher treatment failure as a reason for a regimen substitution. In the study in Coite d'Ivoire, treatment failure was seen in 12.4% of the patients [12] and according to the study in India, treatment failure accounted for 14% of the reasons for modifying therapy [13]. But treatment failure as a reason for initial HAART regimen substitution could not be reported in this study.

Study conducted in Uganda [14], predicated immunological failure alone as a reason for virological failure in 56% of the patients. This may be due to lack of the viral load measuring device, lack of continuous monitoring of patients with a CD4 count, and on the occurrence of opportunistic infection in this study setting.

Cost was one of the major causes for discontinuation and modification of ARV drugs according to a study conducted in India (64%) [13] and Uganda (23%) [14]. However, it was not a reason for modification of ARV drugs in this study, due to the free supply of ARV drugs for the patients in Raichur.

CONCLUSION

The result of this study indicated TB as the major comorbid condition for modification of the initial HAART regimens and pregnancy as the minor reason for ARV regimen change. Identifying these comorbid conditions is very important, particularly because these are challenging in resource-limited settings.

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