Research Article

Prevalence of ADRs and Associated Factors of Antiretroviral Treatment on HIV Positive Adults at Jush

Ramanjireddy Tatiparthi*, Yitagesu Mamo

Department of Pharmacy, College of public health and medical sciences, Jimma University, Jimma, southwest, Ethiopia.

ABSTRACT

A cross sectional study is designed to assess the prevalence of adverse drug reactions and its associated factors on who are already under Highly Active Antiretroviral Therapy. Considerable progress has been made to access the therapy since the decades, even though; currently five million people do not have an access to HIV therapy, it just represents 35% only. The objective of present research is to assess the prevalence of ADRs and its associated factors on HAART at Jimma University Specialized Hospital. The data was pooled by reviewing the previous clinical records of HIV positive adults, who admitted from January 2010 to December 2013. The total sample size is found to be 233. The results showed from the total of 233 patients, 70.8% were developed ADRs and the most of them are nausea, vomiting and diarrhea at 18.9%, 15% and 7.7% respectively, and the least one is hepatotoxicity at 0.43% only. The prevalence of ADRs of HAART was high at JUSH. Low CD_4 cell count was identified at initial stages and concomitant use of cotrimoxazole with ARVs is the major risk factor for ADRs. Thus, health care providers working in the JUSH ART clinic need to monitor the CD_4 count of patients, particularly those treated with combination of antibiotics and ARVs.

Key words: Adverse drug reactions, associated factors, nausea, vomiting, HAART, CD_4 count, JUSH.

INTRODUCTION

Antiretroviral medicines are medications for the treatment of infection by retroviruses, primarily HIV. When several such medicines, typically three or four, are taken in combination, the approach is known as Highly Active Antiretroviral Therapy (HAART). Considerable progress has been made in providing global access to Antiretroviral Therapy (ART), with five million people currently on antiretroviral medicines around the world. This is a major public health achievement, however, still represents only 35% of the people who need HIV therapy now.[1]

In general, the use of HAART has had an important impact on the course and treatment of the disease and disease-related morbidity of HIV-infected patients, increasing their life span and quality of life.[2] However, it has been reported that these advantages have been accompanied by a marked increase in the number of adverse drug reactions (ADRs), including minor and serious cutaneous ADRs.[3]

The present trepidation of the WHO is, the people are living outside of antiviral treatment (ART) in low and middle income countries.[4] In 2001, United Nations General Assembly unanimously legitimates the Declaration of Commitment on HIV/AIDS and further, in 2003, WHO launched the "3 by 5" initiative program to fight against AIDS, Tuberculosis and Malaria.

Between 2001 and 2005, antiretroviral therapy is amplified more than fivefold from 240,000 to 1.3 million.[5] As of June 2005, 21

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Address for correspondence:
Dr. Ramanjireddy Tatiparthi,
Associate professor,
Department of Pharmacy,
Jimma University,
PO 378, Jimma, Ethiopia.
Phone no : +251-931977170
ramanjireddy.brahmareddy@ju.edu.et

www.ijopp.org

countries were provided the antiretroviral treatment to at least 50% of patients. The WHO estimated that by the end of 2005, out of 6.5 million people, only 1.3 million were received it.[6,7]

Antiretroviral therapy more than doubled in sub-Saharan Africa in 2005, with one in six received the treatment, with a coverage level of 50% or more have been achieved in some countries such as Botswana and Uganda, while in others levels remained at less than 10%. As at the same time, 250,000 to 350,000 deaths were averted even in the areas are in the treatment access.

By March of 2005, Global Fund funded free ART service has been started at least at one site in all regions. Currently, 132 sites are providing ART services.[8] Up to August 8, 2006, a total of 73,540 people living with HIV/AIDS were enrolled for HIV/care out of which 45,595 had been started on ART. Currently 35,460 are on ART. Some 10,135 (22.2%) constitute lost to follow up, died, and stopped treatment due to treatment failure or other problems.

In Ethiopia, 1.32 Million people have been infected with HIV/AIDS in 2005 and 134,450 have died of AIDS including 20,929 children. Currently, some 277,757PLWHA including 213,306 adults are in need of ART. In January 2005, the Ethiopian government launched a program on "Accelerating Access to HIV/AIDS Treatment" to providing the universal access to ART by the year 2008. The program enrolled 100,000 patients by the end of 2006 and a total of 132 facilities were started across the country. The 22.2% of the patients missed follow up the treatment due to failure or other problems.[9]

In 2009, WHO estimated 33.4 million people are suffering with HIV/AIDS, there were 2.7 million new HIV infections per year and 2.0 million annual deaths occurring due to AIDS.[10] According to UNAIDS reports in 2010, the Sub-Saharan Africa region is more seriousness exaggerated by the HIV, more than 67% of the people infected with HIV and 72% of patients have died in 2008 due to AIDS.[11]

The success of the anti-retroviral treatment is highly dependent on motivation of HIV positive individuals to adhere to complex ARV regimens.[12] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or treatment failure within the first 8 months of therapy.[13] The occurrence of side effects can vary dramatically among different people.[14] Continuous evaluation will be the benefit of ART help to achieve the ultimate goal of making safer and more effective treatment to the patients[15,16] by constituting the ADRs monitoring centers, responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluations are made and safety measures are taken.

In Ethiopia, there has been an ADR Monitoring Division organized at the Drug Administration and Control Authority (DACA) since 2003. The Division has so far received 110 ADR reports out of which, 60 were ADRs on Anti-Retroviral Drugs.[17]

Therefore, the aim of this study was to gain knowledge on the profile of ADR associated with ARV drugs, the burden of adverse drug reactions of ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

Statement of the problem

Different types of antiretroviral adverse drug reactions occur commonly among patients. Some of ADRs occur early in the course of the therapy, others at the end of treatment. These ADRs vary in their severity; a common cause is poor adherence. Short-term threats are probable to the successful maintenance of HAART. For the last five years of ARV treatment, some of ADRs are observed in the course of therapy. The present study targets the adult patients having HIV/AIDS who already started HAART therapy at JUSH.

Significance of the study

Once antiretroviral therapy is initiated, patients generally remain on medications indefinitely. A switch in the antiretroviral (ARV) regimen is often necessary because of both acute and chronic toxicities, concomitant clinical conditions and virological failures need to switch other medications.[18] This study conducted to assess the fundamental causes for switching the treatment. It is also provides a valuable assistance to the concerned organizations, especially for the health facilities in handling the causes for switching. Moreover, this research is to create a baseline for study of causes.

More than 95% treatment adherence levels are required to maintain virologic suppression in people on a combination of ARV drugs, but most studies showed only 40% to 60% of adherence. The most common reasons for non-adherence are complexity of medication regimens, the difficulty of integrating treatment schedules into their daily activities, side effects, uncertainties about HIV disclosure, and poor memory in medication. Higher percentage of patients in Africa, are falling into the category of poor adherers.[19] The recent findings from African countries showed that patients in Africa are also able to achieve wonderful adherence.[20-22]

In an assessment of adherence among the patients at the national defense force hospitals, the average adherence rate to antiretroviral medication was found to be

82.8%.[23] In another similar study, 81.2% of patients were >95% adherent by self-report in the week before the assessment and 78.9% claimed never to have missed a single dose over the past week.[24] The highest rate of adverse reaction (16.8%) was also found in the non-adherent patients than in the adherent patients 5.8%.

ADR and Magnitude of ADRs of ARV drugs

USFDA defined serious adverse event as one when the patient outcome has one of the following events: death, life-threatening, hospitalization, resulted in switching/discontinued and disability (i.e., significant impairment, damage or disruption) in the patient's body function/structure.[25] ADRs may occur following a single dose or prolonged administration of medicine or result from the combination of two or more medicines.

HIV-infected patients at the beginning of the antiretroviral treatment can frequently show a wide variety of adverse drug effects such as rashes, hyper pigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiform, toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS).[26] Further, it has been reported that up to 80% of HIV-infected patients experience ADRs at some point during their therapy, presumably as a result of immune dysregulation, altered medicine metabolism and/or polypharmacy.[27] However, HIV-infected patients are more prone to developing cutaneous reactions than the non-infected population.[28] It has been reported that the severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage. Cutaneous adverse drug reactions have been reported with all antiretroviral medications. So far, clinical trials have not given conclusive safety results. It is critical to be very cautious when including these agents into HIV treatment regimens.

Most of the ADRs are relatively mild can be disappear, if the drug is stopped, or some gradually subside as the body adjusts to the drug. Other side some of ADRs are lasting longer. In every 3-7% of hospital admissions, at least one ADR estimated in the United States.[29]

The safety profile of ARV drugs and magnitude of ADRs among patients on ART in Ethiopia is virtually unknown. None the less, patients on HAART suffer from ADRs. Several factors such as the sex of the patient, clinical condition, drug classes or agent used, pre- existing illness like liver dysfunction, are known to be associated with the occurrence, type and severity of ADRs among patients taking ART.[30]

The use of HAART has had an important impact on the course and treatment of the disease and disease-related morbidity of HIV-infected patients, increasing their life span and quality of life. However, it has been reported that these advantages have been accompanied by a marked increase in the number of adverse drug reactions (ADRs), including minor and serious adverse drug reactions.[31]

Thus, it is expected that these and other several unknown factors could also affect the prevalence of ADRs among patients taking ART in our setup. Therefore, this study tried to assess the prevalence of ADRs and identify factors associated with patients taking ARV drugs at JUSH.

MATERIAL AND METHODS

Study design

This study is conducted in the period of January 2014 to Feb 2014 at JUSH; it is 350 km away from Add is Ababa to the south west of Ethiopia. It was an institution based cross sectional study by reviewing clinical records of HIV positive adult patients on HAART from January 2010 to December 2013. Data abstract form was used to collect information on adult demographics, WHO clinical stage, CD_4 count, initiation and change of regimen, and duration of therapy.

Sampling size and study variables

The total of 2525 adult HIV positive patients registered from January 2010 to December 2013 for HAART treatment in ARV clinic at JUSH. From 2525 patients, 233 were selected for the study based on inclusion criteria, which aged greater than or equal to 15 years on HAART and those who are greater than or equal to 6 months in duration of therapy. Any patient with identified with unintended overdose, missing clinical record, incomplete data were excluded from the study. The sample size for the study was determined based on patients taking ART develop ADRs from research done in Ambo zonal hospital.[32] Taking critical value at 95% confidence level, degree of precision 0.05, missing or incomplete record by adding 10% of the contingency (21 patients) minimum actual sample size is 233. Every 10th patient's clinical record is included in the sample. Those patient's clinical records which did not fulfill the inclusion criteria or missing were substituted with the next patient on the list. The Independent variables are socio-demographic characteristics, Clinical stage at the beginning of treatment, type of regimen, and usage of concomitant regimens. The dependent variables are typed and frequency of ADRs.

Data collection

The data were analyzed by entering into SPSS version 16.0. Descriptive statistics were generated to meet the objective of the study. The estimated prevalence of ADRs was presented as in the form of tables, charts

and graphs. The quality of the study is maintained by the proper training to the data collectors on patient information sheets and clinical records. Supervision has made by the principal investigator to check up by accurate filling of data abstract forms. A pilot study also conducted to maintain the quality of the information. Before the data abstraction, the study is ethically approved by the JUSH in writing consent. The total information was kept confidential.

RESULTS

Socio demographic characteristics

From a total of 233 HIV positive adult patients on HAART treatment, 141 (60.5) were females, 211 (90.6%) aged between 15-49 years and 22 (9.4%) aged greater than 50 years. of 233 patients 117 (50.2%) have a BMI in the range of 17-24 and 55 (23.6%) have more than 24, out of 233 patients 114 (48.9%) have primary or secondary education, 75 (32.2%) patients were illiterates and 44 (18.9%) was above grade 12th. 139 (59.66%) were married and 9 (3.7%) were divorced. Out of 233 patients 136 (58.4%) living in urban areas and 97 (41.6%) were in rural. the socio demographic characteristics of HIV positive adult patients can see in Table 1.

Clinical stage, CD_4, BMI at the beginning of ARV treatment

Out of 233 patients, most of the patients, 126 (54.1%) were at WHO clinical stage III and 66 (28.3%) were at stage II. Among 233 patients, 136 (58.4%) had CD_4 count of 200-400 cells/mm^3 and 59 (25.3%) patients had more than 200 cells/mm^3 at the initiation of HAART. From a total of 233 patients, 132 (56.6%) were ambulatory and the 14 (6%) were bed ridden in condition, depicted in the Table 2.

From a total of 233 patients, 118 (50.6%) of the patients had BMI of between or equal to 17 and 24, 61 (26.2%) patients had BMI below 17 and the rest 54 (23.2%) patients had BMI above 24 showed Table 2.

From a total of 233 patients 131 (56.2%) patients started with TDF/3TC/EFV, 63 (27%) with ZDV/3TC/NVP and 17 (7.3%) with TDF/3TC/EF. D4T/3TC/EFV was the list prescribed regimen, 5 (2.1%) showed in Figure 1.

Table 1: Socio-demographic characteristics of the patients on HAART

Demographic characteristics		Frequency (%)
Variables	**Categories**	
Age of the patient in years	15-49	219 (94.0)
	> or =50	14(6)
Sex of the patient	Male	92(39.5)
	Female	141(60.5)
Initial BMI of the patient	<17	61(26.2)
	17-24	117(50.2)
	>24	55(23.6)
Marital status of the patient	Single	71(30.9)
	Married	139(59.66)
	Divorced	9(3.86)
	Widowed	13(5.58)
Educational status	No formal education	75(32.2)
	Primary	82(35.2)
	Secondary	32(13.7)
	Tertiary	44(18.9)
Residence of the patient	rural	97(41.6)
	urban	136(58.4)

Table 2: Clinical stage of patients at the beginning of ARV

Clinical stage		Frequency (%)
WHO clinical stage	**Stage I**	22(9.4)
	Stage II	66(28.3)
	Stage III	126(54.1)
	Stage IV	19(8.2)
Functional state	**Work**	87(37.3)
	Ambulatory	132(56.7)
	Bed ridden	14(6.0)
CD_4 count	**<200**	59(25.3)
	200-400	136(58.4)
	>400	38(16.3)
BMI	**<17**	61(26.18)
	17-24	118 (50.64)
	>24	54(23.18)

ADRs and associated factors

Most patient with CD_4< 200 cells/mm^3 developed ADR (86.4%), followed with CD_4 200-400 cells/mm^3 (68.4%) and CD >400 cells/mm^3 (64.7%) patients. (With a p value=0.009). Among the patients that developed ADRs, 161 (69.09%) patients were on cotrimoxazole prophylaxis shown in Table 3.

Among 165 patients that developed adverse drug reactions, (41.6%) developed GI tract ADR followed by CNS ADR (insomnia and night mare), (12%) and anemia (4.3%). ZDV/3TC/EFV and TDF/3TC/EFV were the main regimen caused gastro intestinal ADR (60%) and (48%) of the regimen respectively. TDF/3TC/EFV and ZDV/3TC/EFV was mainly caused CNS adverse drug reaction (20.7%) and (10%) of the regimen respectively, can be seen in Table 4. The duration of the patients to develop ADRs has been identified and graphed in Figure 2.

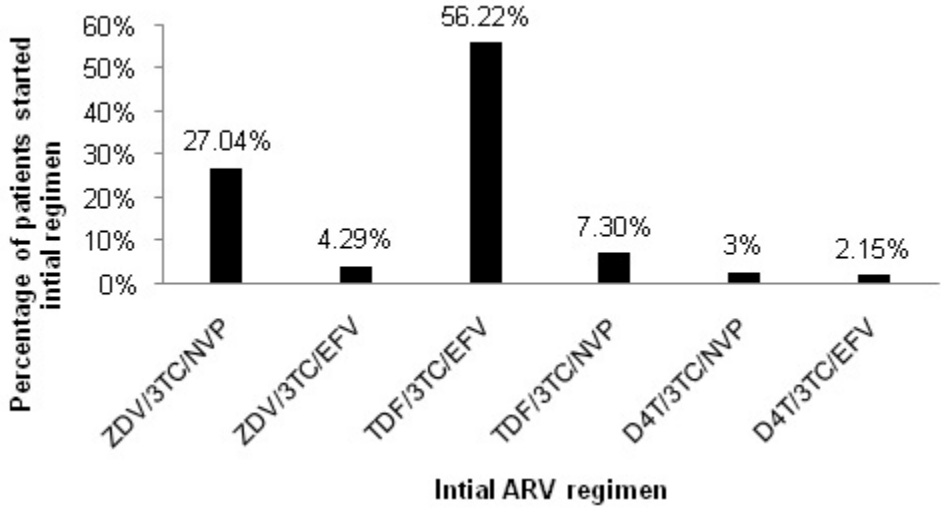

Figure 1: ARV regimen the patient has taken at initiation of treatment

Table 3: Adverse drug reactions and CD_4 count of the patient

		Initial CD_4 count			P value
		<200	200-400	>400	
ADRs	YES	86.4%	68.4%	64.7%	0.009
	NO	13.6%	31.6%	35.3%	
			INH prophylaxis		
		NO	YES		0.092
	YES	69.2%	86.4%		
	NO	30.8%	13.6%		
			Cotrimoxazole prophylaxis		
		NO	YES		----
	YES	--	69.09%		
	NO	--	30.91%		

Table 4: ARD regimen and prevalence of ADR developed at JUSH

ADRs	INITIAL ARV						Total
	ZDV/3TC/NVP	ZDV/3TC/EFV	TDF/3TC/EFV	TDF/3TC/NVP	D4T/3TC/NVP	D4T/3TC/EFV	
Peripheral neuropathy	4.8%	-	-	-	-	60.0%	2.6%
Hepatotoxicity	1.6%	-	-	-	-		0.4%
Lipid dystrophy	-	-	-	-	14.3%	20.0%	0.9%
Diarrhea	9.5%	20.0%	5.3%	11.8%	14.3%	-	7.7%
Nightmare	-		11.5%	-	-	-	6.4%
Nausea	15.9%	30.0%	22.1%	11.8%	-	-	18.9%
Vomiting	7.9%	10.0%	20.6%	11.8%	-	-	15.0%
Headache	-	-	5.3%	17.6%	-	-	4.3%
Fatigue	1.6%	-	0.8%	-	14.3%	-	1.3%
Skin rash	4.8%	-	3.8%	-	-	-	3.4%
Insomnia	-	10.0%	9.2%	-	-	-	5.6%
Anemia	7.9%	10.0%	3.1%	-	-	-	4.3%
Total	54.0%	80.0%	81.7%	52.9%	42.9%	80.0%	70.8%

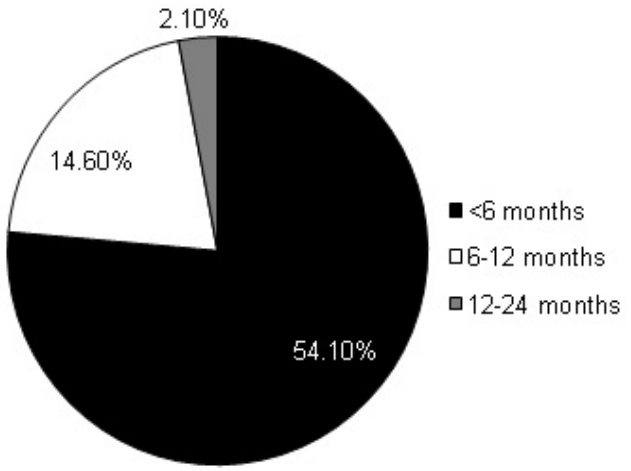

Figure 2: Duration patient on ARV regimen before developed ADRs

DISCUSSION

The use of HAART has had an important impact on the course and treatment of the disease and disease-related morbidity of HIV-infected patients, increasing their life span and quality of life. However, it has been reported that these advantages have been accompanied with marked increase in the number of ADRs, including minor and serious ADRs.

This study showed the prevalence ADRs and its factors related in ART clinic at JUSH. The overall prevalence of ADRs in this study was 70.8%. In line of specific prevalence's observed high to low, for TDF/3TC/EFV (81.7%), ZDV/3TC/EFV (80%), and D4T/3TC/NVP (80%), these results are not comparable with a study conducted at Nekemte hospital in Ethiopia33 is 46.5% were due to D4T/3TC/NVP, and the remaining 29.8%, 12.8%, 5.3%, 3.5%, 1.8%, and 0.9% were D4T/3TC/EFV, AZT/3TC/EFV, TDF/3TC/EFV, AZT/3TC/NVP, TDF/3TC/NVP and AZT/3TC/LPV respectively.

D4T containing regimens accounted peripheral neuropathy and lipid dystrophy are 60% and 20% respectively, while 3TC containing regimens accounted for diarrhea and ZDV containing regimens accounted for hepatotoxicity observed.

This prevalence was very high compared to (26.75%) reported in India[34] and 6.7% in U.S.A at 95 % CI.[35] This may because of exclusion of mild ADRs may be contributory to the low ADR in the study done in India, but lower when compare to study done in Ambo zonal hospital[36] is 81.5%. There is another assessment of adherence to ARV therapy at the Ministry of National Defense Force hospitals showed that 54.0% developed mild ADRs,[37] it is also less than our study results.

Major of the ADRs, GI tract related accounted for 41.6% followed by CNS ADRs and anemia were 12% and 4.3% respectively, when compared to a study conducted in India, the most common ADRs were rash (66%), hepatotoxicity (27%) and anemia (23%).[38]

In this study, majority of the patient in age group of 15-49 has been affected with more ADRs to ARV treatment. A study conducted in India showed age group 21-40 years (66.5%) has been more affected.[39] This is because majority of the patients are in age between 15-49 years or reproductive age.

Most patients of that developed ADRs had CD_4<200 cells/mm^3, when ARV was initially experienced more ADRs, when compared to patients with CD_4 count >200 cells/mm^3 this is in line with the research done in India.[39] Yet, most patients had CD_4 between 200 and 400 cells/mm^3 in this study. This is in line with a research done in Ambo hospital.[36] A significant association was observed between ADRs and ARV treatment regimen (p value=0.00) and also between CD_4 count and ADRs (p value=0.009).

The prevalence of ADRs was high in females (43.6%) as compared to male (27.2%) patients. This was in line with a research done in Nigeria[40] and Italy,[41] (64% vs 59) and (67% vs. 61%) respectively. In another investigation found that women were at high risk of ADRs like neutropenia, hepatitis B and hepatitis C were significantly associated.[42] The data Italian registry showed that the rates of side effects were higher among females (67% vs. 61%).[43]

In this study TDF/3TC/EFV was the most common regimen that causes ADRs. In contrast to this finding, the research done in Nigeria has found ZDV/3TC/NVP had high prevalence. This difference could be due to differences between prevalence of the drug prescribed, in this study the most prescribed drug was TDF/3TC/EFV(56.2%), but in research conducted in Nigeria it was ZDV/3TC/NVP(66.45%).

Most of the patients on HAART treatment commonly suffer from ADRs.[44,45] In our present research nausea and vomiting is the commonest ADRs, The toxicity rate at 80% while D4T/3TC/EFV is prescribed, this is greater than a study conducted in Uganda[46] (50%), but it is in line with a study 79% in Kenya.

All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from class to class, and from patient to patient.[47] A review on HIV and drug allergy showed that drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population, but in our research the rashes are only 3.4%

CONCLUSION AND RECOMMENDATION

The prevalence of ADRs of ARV is high. Advanced stages of AIDS has highly related to the development of ADRs. Low CD_4 cell count at treatment initiation is a risk factor for the occurrence of ADRs also, some of the recommendations has done following

- Health care providers working in the JUSH, ARV clinic, should monitor patients with laboratory findings for cause of ADRs, especially with concomitant medication
- Patients should be routinely request to check the CD_4 count and renal function tests and glucose levels.
- As much as possible, clinicians should stick to the national guidelines to manage and follow up of patients, who receiving HAART.
- Patients should be educated on the possible ADRs of ARV drugs.
- Finally, further prospective study is recommended to overcome the limitations of retrospective cross sectional study and use of secondary data from clinical records with the existing clinical record keeping condition

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