A Study to Evaluate the Safety of Second Line Antiretroviral Therapy Given To HIV Patients At Tertiary Care Hospital In Western India

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Abstract: Introduction: Prescription of multiple drugs are common in HIV positive individuals particularly after initiation of ART. Therefore, they are at a higher risk of drug interactions and adverse drug reactions. So monitoring of safety in drugs can be helpful to change or design future treatment protocols. Methods: In our ART plus centre patient had to come after 30 days of last visit to refill antiretroviral therapy for next month. After consultation with physician, patient was interviewed and details of any adverse drug reactions due to second line ART or with other drugs were recorded. Results: Most commonly documented ADRs were vomiting [17.02%] and itching [12.76%], followed by hyperbilirubinemia [10.64%] and GI upset [10.64%]. Nausea and vomiting were mainly recorded with tenofovir+lamivudine+atazanavir/ritonavir. There were more number of cases of hyperbilirubinemia with tenofovir+lamivudine+atazanavir/ritonavir than any other regimen. 87.24% of recorded ADRs were of mild severity, 12.76% were of moderate severity according to modified hartwieg and siegel scale. As per causality assessment 76.60 % ADRs were possible and 23.40% were probable ADRs. Conclusion: All the NACO prescribed regimens were well tolerated in majority of the patients, with mild and tolerable adverse effects. [J Modi Natl J Integr Res Med, 2018; 2018; 9(1):68-72]

Key Words: Adverse Drug Reaction, HIV, Secondline ART, Safety.

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Introduction: According to the World Health Organization [WHO] there were approximately 35 million people worldwide living with HIV/AIDS in 2013.Of these, 3.2 million were children. An estimated 2.1 million individuals worldwide became newly infected with HIV in 2013.[1]India has the third largest HIV epidemic in the world. In India, first HIV positive case was detected in Tamil Nadu in 1986.[2]In 2013, HIV prevalence in India was an estimated 0.3 percent. It is estimated that around 2.1 million people are currently living with HIV in India.[3] The Government of India launched the ART programme in 2004 under National AIDS Control Programme [NACP] – II. Due to increase emergence of resistance in first line ART, Second Line ART was rolled out on 1st January 2008 in India.[4]According to National Aids Control Organization [NACO] as on September 2014, a total of 453 ART centers are functional in country and approximately 8.10 lakh patients are receiving first line antiretroviral treatment [ART] at these centers. In order to expand the access to second line treatment, 37 "ART Plus" centers started and capacitated to provide second line/alternative first line treatment to eligible Patients. Till Sept. 2014, 10223 patients were received second line ART drugs from ART plus Centers.[5]

Prescription of multiple drugs are common in HIV positive individuals particularly after initiation of ART. Therefore, they are at a higher risk of drug interactions and adverse drug reactions. Adverse drug reaction monitoring and assessment helps in identifying and managing these adverse events.[6] The principal aim of this drug research is to facilitate rational use of drugs in populations. For the individual patient, rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price.[7]So monitoring of safety in drugs can be helpful to change or design future treatment protocols.

Methods: This was a record based, observational, prospective, longitudinal follow up study conducted at the Anti-Retroviral Therapy plus centre under Department of Medicine of tertiary care teaching hospital. Line of management and prescription of drugs was decided by the physician in ART plus centre. Prior permission of Departmental Screening Committee of Department of Pharmacology of the same institute, Institutional Ethics Committee of same institute, Gujarat State AIDS Control Society and National AIDS Control Society was taken before the conduct of the study.

Selection criteria of patients:

Inclusion criteria: Registered HIV positive patients of either sex with any age who are going to receive second line ART at the ART plus centre, tertiary care teaching hospital were included in the study.

Patients transferred from other Government ART centers or patients with history of ART from Private ART clinics who registered and initiate second line antiretroviral therapy in ART plus centre, tertiary care teaching hospital were include in the study.

Exclusion criteria: Patients are on first line ART.

Method of collection of data: Patients selected on the basis of inclusion and exclusion criteria were explained in detail about this study. Written informed consent of all the patients was obtained before enrollment into the study as participant. Patients were explained about the nature of HIV infection, importance of ART and adherence to ART during treatment. Patients were also explained in brief about the possible adverse effects related to ART.

In our ART plus centre antiretroviral therapy is usually provided for 30 days. The patient had to come after 30 days of last visit to refill antiretroviral therapy for next month. At each encounter patient has to consult physician in charge of the ART plus centre. Line of management, ART and other drug prescription was carried out by physician.

Patient coming for follow up before monthly interval either because of adverse events or any other health related condition; follow up data was recorded for that.

After consultation with physician of ART plus centre, patient was interviewed and details of patient's case record was obtained. At each encounter patient's adverse drug reactions, associated medical conditions, second line ART and other drug prescription was recorded in preformed case record form for the study.

Aim and Objectives:

- To evaluate safety of drugs during second line ART.
- To evaluate reasons for substitutions, shift and hold during second line ART.
- To monitor and analyze causality and severity of encountered adverse drug reactions.

Observations and Results

Utilization Pattern of Second Line ART Regimens

Table I: Utilization pattern of 2nd line ART regimens at start of second line ART

ART regimen	No of patients [n=70]	Percentage of total patients	No. of encounters with ART prescription	Percentage of total encounters
TDF+3TC+ATV/r	45	64.29	264	66.49
D4T+3TC+ATV/r	15	21.42	75	18.89
AZT+3TC+ATV/r	6	8.57	34	8.56
AZT+3TC+LPV/r	2	2.86	12	3.022
ABC+3TC+ATV/r	2	2.86	12	3.022
Total	70	100	397	100

Treatment Substitution, Shift, Hold and Restart during Study Period: In this study, 4 substitutions were made within second line ART regimens. Among specified causes, most common causes for substitutions recorded were hyperbilirubinemia, Anemia and lactic acidosis. Which regimen was substituted by other regimen and the reason for substitution is mention in table II [A]. In one patient treatment was put on hold and again restarted, which is mention in table II [B].

Table II [A]: Treatment substitutions [within second line ART regimens]

2nd line ART regimen before substitution	Specified reason for substitution	Number of substitutions [n=4]	2nd line ART regimen after substitution
AZT+3TC+ATV/r	Anemia	1	D4T+3TC+ATV/r
TDF+3TC+ATV/r	Hyperbilirubinaemia	2	TDF+3TC+LPV/r
D4T+3TC+ATV/R	Lactic acidosis	1	ABC+3TC+ATV/R

Table II [B]: Treatment hold and restart

2nd line ART regimen hold	Reason for treatment hold	Number of treatment hold [n=1]	Regimen at restart of treatment
AZT+3TC+ATV/R	hyperbilirubinaemia	1	AZT+3TC+ATV/R

TDF-Tenofovir D4T- Stavudine AZT- Zedovudine 3TC- Lamivudine ABC-Abacavir ATV/r-Atazanavir/Ritonavir LPV/r-Lopinavir/Ritonavir

Analysis of Adverse Drug Reactions Documented By ART Centre Physician

Table III: Analysis of adverse drug reactions [ADRs]

ART Regimen	ADR	No. of Incidence [n=47]	%	Causality assessment [Naranjo scale]			Severity assessment [Hartwig-siegel scale]		
				Possible	Probable	Definite	Mild	Moderate	Severe
D4T + 3TC +ATV/R	Hyperbilirubinemia	1	2.13	0	1	0	0	1	0
	Fever	2	4.25	2	0	0	2	0	0
	Skin rash	1	2.13	1	0	0	1	0	0
	Vomiting	1	2.13	1	0	0	1	0	0
	Oral ulcer	2	4.25	2	0	0	2	0	0
	Altered sensorium	1	2.13	1	0	0	1	0	0
	GI upset	1	2.13	1	0	0	1	0	0
	Constipation	1	2.13	1	0	0	1	0	0
	Neuropathy	2	4.25	2	0	0	2	0	0
	Lactic acidosis	1	2.13	0	1	0	0	1	0
	Nausea	1	2.13	1	0	0	1	0	0
ABC + 3TC + ATV/R	Neuropathy	1	2.13	1	0	0	1	0	0
	Vomiting	1	2.13	1	0	0	1	0	0
AZT + 3TC +ATV/R	Anaemia	1	2.13	0	1	0	0	1	0
	Hyperbilirubinemia	1	2.13	0	1	0	0	1	0
	GI upset	3	6.38	3	0	0	3	0	0
	Oral ulcer	1	2.13	1	0	0	1	0	0
AZT + 3TC +LPV/R	Itching	1	2.13	1	0	0	1	0	0
	Nausea	2	4.25	2	0	0	2	0	0
	Vomiting	6	12.76	4	2	0	6	0	0
	Vertigo	1	2.13	1	0	0	1	0	0
TDF+ 3TC +ATV/R	Itching	5	10.63	4	1	0	5	0	0
	Hyperbilirubinaemia	3	6.38	0	3	0	2	1	0
	Headache	1	2.13	1	0	0	1	0	0
	Neuropathy	1	2.13	1	0	0	1	0	0
	GI upset	1	2.13	1	0	0	1	0	0
	Constipation	1	2.13	1	0	0	1	0	0
	Skin rash	1	2.13	1	0	0	1	0	0
	Nephrotoxicity	1	2.13	0	1	0	0	1	0
	Fever	1	2.13	1	0	0	1	0	0

Discussion: In this study, 5 second line ART regimens were used. Most common ART regimen prescribed at the initiation of ART was TDF+3TC+ATV/r in 64.29% patients followed by D4T+3TC+ATV/r in 21.42% patients, AZT+3TC+ATV/r in 8.57% patients, AZT+3TC+LPV/r in 2.86% patients and ABC+3TC+ATV/r in 2.86% patients[Table I]. This is in accordance with the National guideline which recommends TDF+3TC+ATV/r should be preferred as first choice ART regimen.[8]According to NACO, second-line regimens should include at least three active drugs; one of them from a new class, in order to increase the likelihood of the success of the treatment and to minimize the risk of cross-resistance. The PI class should be reserved for second-line treatments. If AZT is used in first-line; NRTI choices in second-line could be TDF. If TDF is used in first-line, NRTI choices could be AZT. If both TDF and AZT can't be used, the last option is d4T. Thai national guidelines for antiretroviral therapy also suggest that zidovudine [AZT] or Tenofovir [TDF] in combination with lamivudine [3TC] is recommended as the preferred NRTI backbone.[9] A multi country survey by the WHO found highly variable rates of switching to second-line regimens.[10]It seems unlikely that this variability is explained by differences in primary resistance to NRTIs or NNRTIs.[Abbreviations of the drugs are under Table II (B)]

In this study, most common cause for substituting/hold 2nd line ART regimen was adverse events, recorded in five patients [Table II(A)(B)]. Out of five patients 2 were substituted from their regimen due to hyperbilirubinemia while in two patients the cause were anemia and lactic acidosis respectively for substitution. One study done in India, which shows 203 patients [16.2%] developed anemia out of 1256 in which zidovudine was initiated.[11] The high incidence of Anaemia mandates close monitoring of patients receiving second line ART. Another study of 250 patients shows, 41% [n=102] developed hyperbilirubinemia due to Atazanavir[12], which was comparable to 67% in Rotger M et al study[13]and 44% in Castle study[14]

Most commonly documented ADRs were vomiting [17.02%] and itching [12.76%] followed by hyperbilirubinemia [10.64%] and GI upset [10.64%].(Table 3) Nausea and vomiting were mainly recorded with TDF+3TC+ATV/r. There were more number of cases of hyperbilirubinemia with TDF+3TC+ATV/r than any other regimen. Hyperbilirubinemia mainly caused by Atzanavir which was shown in various studies. A study of 250 patients shows, 41% [n=102] developed hyperbilirubinemia due to Atazanavir, which was comparable to 44% in Castle study[14]and 67% in Rotger M et al study.[13]

Anemia was reported only with Zidovudine containing regimen AZT+3TC+ATV/r. Zidovudineinduced down-regulation of erythropoietin [Epo] receptor expression followed by loss of Eporeceptor mediated signal transduction is a significant contributory factor to Zidovudineinduced erythroid toxicity.[15] In another Indian study, anemia was most commonly reported ADR with zidovudine based ART regimen [42.8% of reported ADRs with zidovudine based regimens].[16]

Neuropathy was reported as ADRs with incidence of 6.38% of all ADRs. [2.13% with TDF+3TC+ATV/r and 4.25% with D4T+3TC+ATV/r]. Reason behind this observation may be related to higher number of prescription with Stavudine. This is supported by an Indian study in which neuropathy was reported with Stavudine based regimen [39.6% of all ADRs reported with Stavudine based regimens] but not with Zidovudine based regimen.[16] In another Indian study, neuropathy was the most commonly [20.83%] reported ADR.[17]Causation of neuropathy may be linked to mitochondrial toxicity of Stavudine.

Majority of ADRs reported by ART plus centre physician, 87.24% of recorded ADRs were of mild severity, 12.76% were of moderate severity according to modified hartwieg and siegel scale. Of moderate ADRs nephrotoxicity, lactic acidosis, anemia and hyperbilirubinemia were recorded. As per causality assessment 76.60 % ADRs were possible and 23.40% were probable ADRs.

Conclusions: All the NACO prescribed regimens were well tolerated in majority of the patients, with mild and tolerable adverse effects. Findings of our study may prove useful for the successful management of treatment-failure HIV positive patients. Further, research is needed with large sample size to determine if these early outcome can be sustained over the following years of treatment.

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