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Estimation of the Rationality of ARV Therapy in South India

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Abstract

The main objective of the present study was to perform and improve the rationality by looking for potential Drug-Drug Interactions and Adverse Drug Reactions associated with Anti-Retroviral Therapy and increase the adherence among Human Immunodeficiency Virus (HIV) patients attending to the Anti-Retroviral Therapy (ART) centre in south India. A prospective observational study was conducted in the city of Vijayawada, South India to assess the Adverse Drug Reactions (ADR's) and Drug-Drug interactions (DDI's) among the patients receiving Highly Active Anti RetroviralAnti-Retroviral Therapy (HAART) using approved scales and databases. A total of 530 patients were screened in a span of 1 year, resulting in 394 ADR's and 385 DDI's among the various drugs being used.The most commonly used drug combination was Tenofivir + Lamivudine + Efavirenz (63.3%). In looking at the reported ADR's the majority of them were mild in terms of severity, preventability and causality and none of the DDI's were severe enough to bring a change in the therapy. Statistical analysis was performed using SPSS 16 version by using Chi-square test. The risk caused by the associated ADR's and DDI's are observed and proven to be not deleterious in most of the cases. If adequate knowledge, prompt treatment and in-depth analysis of the associated risk factors and personal history were considered the HAART would be definitely more successful.

Keywords: Human Immunodeficiency Virus

1. Introduction

Human Immunodeficiency Virus (HIV-1) is a serious health problem[1] occurring worldwide with estimated number of around 38 million living with it by 2019, among which 1.7 million were new occurences[2]. This perception about the condition has changed drastically in developed countries from the time HAART introduction in the last part of the '90s. The therapy has proven a remarkable decrease in AIDS-related mortality and made this rapidly fatal syndrome into manageable infection[1]. Viral burden and the CD4 cell count are always maintained under control by regulating the virus replication and maintaining the CD4 cell count[3].

However, the clinical advantages seen from HAART don't appear to be totally unbiased, as they are related with undesirable impacts called Adverse Drug Reactions (ADRs). An ADR is any response which is harmful or undesirable, happened as the result of a drug's. The HAART is accompanied by multiple various unwanted ADR's, which limits their open usage them. This has forced the Health Care Professionals (HCP) either to

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alter the drug, dosage, combination or even withdrawal[4]. Pertaining to compromised immune system, HIV patients are at risk of co-morbidities; these adverse events/ reactions associated from the therapy had significantly impacted the adherence and directly or indirectly leading to treatment failure[5].

To identify and substitute the offending drug is quite cumbersome and at times impossible as most HAART regimens do exist in Fixed-Dose Combinations (FDC) of different classes, most of which are first-line drug. The pace of treatment failure due to the advancement of unwanted reactions is far more significant and almost incomparable in resource limited settings[2]. As such the availability of Resources and Ethical concerns are the two main hurdles for the success and invention of new drugs into the market. These issues are making the road narrow ahead for HIV patients. More so, the inexistence of adequate drug toxicity monitoring and reporting schemes[6], underestimates the burden of HAART associated ADRs by underreporting and no proper signal generation.

HAART is highly associated with potential drug–drug interactions (PDDIs) attributed to polypharmacy linked to age, gender and occurrence of multiple complications[7] among the known therapeutic classes of drugs antiretroviral (ARV) drugs are the most noteworthy class known for potential drug–drug interactions. Notably, the drug classes Protease inhibitors (PI's) and non-nucleotide reverse transcriptase inhibitors (NNRTI's) lead the race as they undergo extensive metabolism through cytochrome P450 enzyme[8]. The probability of DDI's is further escalated by the usage of OTC (over-the-counter) drugs, self-medication, and herbal medicines etc., which mostly go unnoticed[9]. Drug interactions might be associated with a substantial risk for toxicity, decreased efficacy and subsequent emergence of drug resistance and also lead to treatment failure directly. Therefore, proper identification, management and prevention of such unwanted drug interactions are crucial for patient care and treatment success[10]. Previous studies have indicated that PDDIs in HIV therapy are common, ranging from 23 to 41%[10-13]; however, most of them were performed retrospectively by medical chart or pharmacy record reviews, and thus might have underestimated the prevalence of PDDIs as the complete medication history is thoroughly documented[9-12]. In addition, some of these studies were done in limited sample population, which might prevent them from applying to the general population.

Given these concerns and to know and understand the condition of HAART in South India, we prospectively conducted a hospital-based study in the Government General Hospital, Vijayawada. We are looking ahead to find any common ADR's and the PDDI's associated with the HAART.

2. Method

A community-based Prospective, observational study was carried out for a period of 1 year (September 2018–August 2019) in ART clinic, Old Government General Hospital (GGH), located in Vijayawada, South India. The clinic was held all during the week days; where many HIV positive patients around the state receive antiretroviral therapy (ART) throughout the year. This center maintains computer-based clinical data of all the patients receiving ART which includes, anthropometric details, medication history, patient response to the drugs, duration of therapy, co-morbidities and associated medication etc., The ARV (antiretroviral) drugs are dispensed free of charge, monthly, to about 4,000 registered HIV infected patients including men, pregnant and non-pregnant women, and children from different parts of the Andhra Pradesh state. Institutional ethics committee approval was taken before the initiation of the study and written informed consent (preferred local language) was obtained from all subjects before their inclusion. Confidentiality of information was duly maintained and basic principles of ethics in were strictly followed. The primary outcome of interest is looking after the ADR's and secondary being the DDI's reported. All consecutive treatment subjects of either gender aged 18 years or above, on ART, co-medications for opportunistic infections and concurrent diseases, as well as medications used for symptomatic relief, herbals and recreational drugs were included. Subjects having complications, treatment modifications, immunologic failure, pregnant women, lactating mothers were excluded from the study. Data regarding patient demographics and clinical information were collected in a pre-structured pro forma both from direct interview and the automated medical database.

ADR diagnosis was based on patient complaints and physician confirmed events (if any) during routine clinical examination. ADRs reported were subsequently followed up. We have followed the standards laid by Pharmacovigilance Program of India (PvPI) in obtaining the adverse events, their occurrence, history and other relevant information from the case sheets and the physician notes. To improve the accuracy of our investigations we have done the individual causality assessment using the Naranjo's scale of causality assessment[14], which classified the interactions to definite, probable, possible and doubtful. Seriousness of the ADR was surveyed utilizing ADR Severity Assessment Scale (Modified Hartwig and

Siegel)[15] – which classify the ADR into mild, moderate and severe. Preventability of the ADR was performed by Schumock and Thornton scale[16] which groups the ADRs into definitely preventable, presumably preventable and not preventable. The ADR's reported were organized based on the organ system in our previous work[17], and now we focus at scaling them.

For assessing Drug-Drug Interactions, the University of Liverpool drug interaction database[18] was followed with additional assessment by two other specialists in the department of Pharmacology. This database highlights the interactions of the HIV drugs to other HIV and non-HIV drugs and suggests appropriate alternatives and categorizes the seriousness of the interaction into three areas: Serious interaction for drugs that should not be co-administered, moderate interaction indicating requiring of dosage modification or close monitoring and mild/no interaction which represents no known or anticipated interaction and doesn't prompt any change. The results gave us a summary of the PDDIs as well as a recommendation for the management of them. The obtained information was taken to the clinicians for promptness and necessary action. Descriptive statistical analysis of the obtained data was performed, reviewed, authorized and analyzed using SPSS software 21 version.

3. Results

A total of 530 HIV patients, who satisfied the study criteria were enrolled, their data was collected both from personal interview and from the hospital records. The socio demographic data was recorded and the majority of the HIV patients were found to be females with 52.6%, in the age group between 18 and 28 years. The major portion of the individuals has less education and are married (Table 1). The therapy includes around 11 varied combination of ART drugs; however, we have included only the top three combinations and they contributed for around 95% of population receiving ART (Table 2). Highest prescribed regimen was found to be the combination of Tenofovir, Lamivudine and Efavirenz (TAF/3TC/EFV) reaching to around 60%.

These three drug combinations were closely monitored for the primary and secondary outcomes. A total of 394 ADR's and 385 DDI's were found in these combinations of drugs. The ADR's were assessed for the severity, preventability and causality and found that 88% were mild 94% can be definitely preventable and 89% to be in possible range respectively (Table 3). In looking at the Potential Drug-Drug Interactions (PDDI's), older age population had more than one DDI's compared to other age groups. The interactions between the HIV drugs and other recreational or herbal drugs were not looked. Among the various drug interactions; the interaction between Efavirenz + Midazolam and Zidovudine + Ribavirin were found to be the serious interaction. Moderate interactions contribute for around 85% of the total DDI's which can be definitely controlled by proper care (Table 4).

Table 1. Socio demographic characters of HIV patients

Variable	Frequency (N=530)	Percentage %
Gender		
Male	250	47.1
Female	278	52.6
Others	2	0.3
Age (Years)		
18-28	141	26.6
29-38	125	23.5
39-48	120	22.7
49-58	122	23.1
≥59	22	4.1
Educational status		
None	157	29.7
Primary	194	36.5
Secondary	114	21.6
Post-secondary	65	12.2
Marital status		
Married	311	76.1
Unmarried	51	11.7
Widow	13	5
Divorced	11	2.2
Separated	31	3.9
Unreported	13	6.1

Table 2. Prescribed ARV drug combinations and associated ADR's

Antiretroviral drug combination	Number and percentage of Patients 530(%)	Number and percentage of ADR's occurred 394(%)	P value
TAF /3TC / EFV	335(63.3)	235(59.6)	<0.05
ZVD/ 3TC / NVP	137(25.8)	97(24.6)	<0.05
ZVD/ 3TC / EFV	20(3.7)	21(5.32)	<0.05

*Tenofivir (TAF), Lamivudine (3TC), Efavirenz (EFV), Nevirapine (NVP), Zidovudine (ZVD)

Table 3. Assessing ADR's for causality, severity and preventability

Naranjo's Causality assessment scale			P value
Possible Number (%)	**Probable Number (%)**	**Definitive Number (%)**	
351 (89.3)	28 (7.7)	None	<0.05
Modified Hartwig's& Siegel severity scale			
Mild Number (%)	**Moderate Number (%)**	**Severe Number (%)**	
348 (88.2)	44 (11.1)	3 (0.7)	<0.05
Schumonk& Thornton Preventability scale			
Definitely preventable Number (%)	**Probably preventable Number (%)**	**Not preventable Number (%)**	
365 (92.7)	29 (7.3)	None	<0.05

Table 4. DDI's associated with the HIV and non-HIV drugs

SEVERE INTERACTIONS					
DRUG A	**DRUG B**	**Description of the interaction**	**Number**	**Percentage**	**Intervention**
Efavirenz	Midazolam	Risk of prolonged sedation, respiratory depression	3	< 1	Discontinued midazolam
Zidovudine	**Ribavirin**	**Exacerbation of anemia and hepatic enzymes decompensation,**	1	< 1	Close monitoring, high alert
MODERATE INTERACTIONS					
DRUG A	**DRUG B**	**Description of the interaction**	**Number**	**Percentage**	**Intervention**
NNRTI's & NRTI's	Lipid lowering drugs	Predominantly decreases the effect of statins; mixed effect.	76	20	Dosage adjustment for statins, monitor serum drug concentrations

	Anxiolytics/ sedatives	Predominantly decreases the effect of anxiolytics and sedatives; mixed effect.	17	5	Dosage adjustment for precipitant drug, monitor serum drug concentrations
	Calcium channel blockers	Predominantly decreases the effect of calcium channel blockers; mixed effect.	52	14	Dosage adjustment for precipitant drug, monitor serum drug concentrations
	Narcotic Analgesics	Slightly decreases the concentrations of narcotic analgesics; mixed effect.	56	15	Monitor drug concentrations
	Anti-depressants	Further studies are required; few evidences of NNRTI's decreasing the levels of antidepressant exist; mixed effect.	96	25	Monitor the depressive action, rule out other confounding parameters
	Anti-convulsants	Predominantly decreases the effect of NNRTI's leading to treatment failure. Often contraindicated.	11	3	Discontinue the drug, if required switch for alternatives.
MILD/NO INTERACTIONS					
DRUG A	**DRUG B**	**Description of the interaction**	**Number**	**Percentage**	**Intervention**
NNRTI's	Calcium channel blockers, aspirin,	No interaction	79	NA	NONE
Nevirapine	Diclofena, celecoxib, morphine, naproxen, levitiractam	No interaction	135	NA	NONE
NRTI's	Calcium channel blockers, statin	No interaction	56	NA	NONE

*NNRTI'S: Non-nucleotide reverse transcriptase inhibitors, NRTI'S: Nucleotide reverse transcriptase inhibitors, NA: Not Applicable

4. Discussion

The present study was aimed at evaluating the incidence of ADR's and the DDI's among the patients receiving ARV drugs at the ART center, Vijayawada. Our findings show that about 2 in every 5 patients (40.2%) on HAART, reported at least ADR. This is in contradiction with findings in an Indian study of 400 patients on HAART, where the prevalence of ADRs was 17.5%[19] and was in accordance with a study in Kenya where HAART-related ADRs were present in 40.6% of patients[20]. This can be viewed as the difference in reporting structure of ADR's, treatment and the patient's socio-demographics[6]. Among

the reported ADR's majority were ought to be possible and if possible are mild and are usually in definitely preventable range. No ADR reported in our study are significant, requiring a treatment change. We haven't preferred looking for Dechallenge and Rechallenge.

Tenofivir + Lamivudine + Efavirenz (63.3%) was highly prescribed ARV combination and was in consistent with the guidelines of WHO and the national guidelines for the use of ARV drugs in India[2,21] this was in accordance with a study conducted in Allahabad[22] to around (66.4%). While in another study conducted at Nigeria, the same combination is highly prescribed while replacing Efavirenz with Zidovudine[23]. As expected, the risk for DDIs increased with increase in the number of co-medications – polypharmacy[7], the majority of identified DDIs occurred between the two most commonly prescribed HIV drug categories including NNRTI- or NRTI- and CNS- (32%) or CVS (34%) drugs which are the two most commonly prescribed non-HIV drug categories. The high proportion of these non-HIV drugs is explained by the fact that the patients were suffering with anxiety, depression, fear and insecurity pertaining to majorly social beliefs representing a considerable part among the HIV-infected population[24]. Cardiovascular drugs result from the various risk factors associated with occurrence of the associated cardiovascular diseases[25]. Most of the documented DDIs was moderate in nature and required a potential dose adjustment or close monitoring to minimize unwanted clinical consequences.

Polypharmacy was more frequent in older or obese patients as a consequence of increased risk for various conditions, mainly cardiovascular diseases and in patients with HCV infection[26-27]. The goal of ADR observation, monitoring their severity and assessing the potential DDI's was to early recognize, minimize or antagonize the impact to increase compliance and quality of care. The knowledge of various factors pertaining to DDIs will help clinicians to either minimize or prevent them. The establishment of a comprehensive interaction alert system will promote particular attention in terms of drug prescription and drug interaction screening.Efficient and solid surveillance methods including organized Pharmacovigilance system is definitely the need of the hour. However, such databases come with certain disadvantages including discrepancies between databases[28], the reliability is exceptionally subjected to regularity in updates and the significance of the interaction. In addition, most of the databases provide data only between two drugs, whereas ART is often the combination of multiple drugs that commonly interact. Of course, the interaction observed might not always turn into a real interaction, pertaining to inter-subject variability and genetic makeup; often the major issue of under-reporting. Linked to poor resource settings, affordability and unavailability of alternate drug combinations the management of DDI's is quite problematic[29].

In summary, the associated occurrence of DDI's and ADR's has made the HAART therapy not fully successful, which is also linked to ageing population and occurrence of co-morbidities. However, the major portion of these can be resolved if prompt care is provided with proper monitoring and attention towards the dosage adjustments and interacting drug's, which was observed in our study. For which, availability of a standard database, clinician's self-education about interacting drugs, the knowledge of a patient's complete drug regimen and the risk factors associated with DDIs are crucial.

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