



## Pharmacoepidemiology of Antiretroviral Drugs in a Tertiary Care Teaching Hospital

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### Abstract

Background: India has a large population using antiretroviral drugs (ARV) which has potential therapeutic efficacy and high toxic properties resulting in diverse adverse drug reactions (ADRs). Adherence to the ART is a crucial challenge to be addressed as it plays a major role in the success of HIV management. Aim: To determine the prescribing pattern of antiretroviral drugs uses at an ART center and the levels of adherence to the drugs and the associated adverse effects. Materials and methods: It is a retrospective analysis of the clinical records related to HIV-infected adults who were receiving treatment at an ART Center in Andhra Pradesh state. The main outcomes of the study are demographic details of the patients, the pattern of ART combinations prescribed, adherence to the given ART, and analysis of reported ADRs. Simple descriptive statistics and chi-square tests are the statistics used to measure the outcomes. Results: A total of 430 HIV patients' records were selected and assessed. Tenofovir (TAF) + Lamivudine (3TC) +Efavirenz (EFV) (66.5%) were the most prescribed ARV combination. The majority of 348 patients (80.9%) was good adherence and showed a significant association with therapeutic outcomes. The most common clinical ADRs found in this study were gastrointestinal disturbances (30.9%) followed by dermatological problems (20.4 %). Conclusion: Despite drug toxicity, ART treatment bears potential therapeutic efficacy and is considered as the only means to increase life expectancy in HIV infected patients. Detailed patient counseling and monitoring improve therapeutic outcomes and patients adherence.

**Key words:** Antiretroviral drugs, Adherence, Adverse drug reactions.

### Introduction

HIV continues to be a major global public health issue, having claimed approximately 37.9 million people living in the world with HIV at the end of 2018. However, continuous international and national efforts turned HIV infection into a manageable chronic health condition [1]. In India by 2017 among the states and union territories, it was estimated over 21.40 lakhs people are living with HIV. Among them, the highest estimated number was reported from Maharashtra (3.30 Lakhs, 2.53-4.35) followed by Andhra Pradesh (2.70 Lakh, 2.00-3.58), Karnataka (2.47 Lakh, 1.91-3.23), Telangana (2.04 Lakh, 1.49-2.77).

The rate of prevalence of HIV in 2017 is at 0.25 % (0.18-0.34) among males and at 0.19% (0.14-0.25) in Females. Despite the heavy disease burden, India has remarkable achievements in HIV control and

management by the National AIDS Control Organization (NACO). NACO runs over 516 antiretroviral therapy (ART) centers nationwide that offer systematic HIV care by offering drugs and Psychological counseling free of cost [2]. HIV infection occurs by transmission of the virus from an infected individual by contact with blood or bodily fluids, by sexual contact or through breast milk. This eventually leads to a declined CD4 count (200-350) and the individual becomes likely to develop non-AIDS-defining infections such as herpes zoster and oropharyngeal candidiasis.

Hence, the expected therapeutic outcome of ART is to increase the CD4 count thereby eventually decreasing the chance of morbidity and mortality [3]. Until today, no treatment claim cure for HIV infection,

however, the prognosis of the diseases can be controlled and prevented by effective antiretrovirals (ARVs). By 2018, there are 62% of adults and 54 % of children receiving lifelong antiretroviral therapy (ART) in low- and middle-income countries. Adherence to the ART enables HIV patients to gain potential for normal or near-normal life expectancy [1].

Once initiated, the ART treatment should be continued throughout the lifetime. Over a period, there might be an instance of missing doses and experience of side effects and ADRs. There are 6 classes of drugs used in combinations in ART include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the fusion inhibitors (FIs), the CCR5 antagonists, and the integrase strand transfer inhibitors (INSTIs) [4].

Positive therapeutic outcomes are possible only on 100 % adherence to the given treatment. Non- adherence may not only lead to treatment failure but may also result in a fatal condition called antimicrobial resistance, which means the drugs can no longer act effectively on the viral loads. In a study, it is said “all or nothing”, which means it would be better to take no drugs at all than to have adherence of less than 90% [5, 6].

Adherence was expressed in a study by Arnsten et al. as the number of doses taken as a percentage of the total number of doses prescribed. For example, if the patient takes 28 doses out of 30 prescribed doses the adherence is 95%. Medication adherence can be said as all the prescribed drugs taken every day on prescribed time [7].

Given the rapid prevalence of HIV in India, there is a paucity of medical literature on adherence to ART among HIV patients in Asia. Despite showing potential therapeutic effects, ART is associated with a wide range of mild to fatal ADRs leading to patient's non-adherence and treatment failure. Hence ADRs play a significant role in the success of the ART program. In developing countries like India, ADRs are not being properly reported are being overlooked until the emergence of active pharmacovigilance activities in recent years. This made the availability of ample literature on ADR reported among HIV patients treated

with ART in India; however there is paucity in data from Andhra Pradesh state in India. In this instance we aimed to determine the prescribing pattern of antiretroviral drugs uses at an ART center. Also, we determined the levels of adherence to the drugs and the associated adverse effects.

## Materials and Methodology

### Study Design

We retrospectively analyzed the clinical records of HIV-infected adults who were receiving treatment at the ART Center, Old Government general hospital, located in Vijayawada city, Andhra Pradesh state in South India between January 2019 and January 2020. The clinic is held every Monday through Friday, where many AIDS patients around the state receive antiretroviral therapy throughout the year.

This center maintains computer-based clinical data of all the patients receiving ART which includes, demographic details, medication history, patient response to the drugs, 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.

### Inclusion Criteria

Only adult patients (male and female) were included in this study. Other inclusion criteria were patients older than 12 years, non-pregnant women confirmed HIV infection with western blot test, patients with or without AIDS presentation according to the criteria set out by the World Health Organization (WHO) [8].

The patient must have been enrolled on ART only at the ART Center, Old Government general hospital, Vijayawada and they must have used ARV drugs, at least once, after enrolment. Patient's complete demographic information and prescribed medications should be documented in the case files. Patients who died during treatment nor stopped or changed treatment were also included in the study.

### Exclusion Criteria

Children and pregnant women are a special population group that was excluded.

## Ethical Clearance

The process was assessed and endorsed through the ethical review committee of the GGH teaching hospital Vijayawada, India.

## Sample Size Determination

A sample size of 351 was calculated from the 4000 population of registered patients on ARV drugs using a 5% error margin at 95% confidence interval, assuming 50% of the patients have all the measured outcomes documented in their case files. However, a sample size of 430 patients was used for ease of data analysis [9].

## Data abstraction: Data abstraction

Initial permission for access to patient's surveillance data was obtained from the department of ART, GGH. From the database, the eligible cases were identified and were retrieved for the study. The case files were selected by using a web-based random sampling method. Each selected study subject was reviewed and assigned an identification number by the researchers. The complete data of each case was extracted using a purposely pre-designed data collection form for the study which includes; the demographic details, co-infections, co-prescribed drugs, and the baseline ART

regimen prescribed, and follow-up CD4 count, laboratory investigations. We also extracted the rate of adherence and reported adverse drug reactions (ADRs).

## Data Analysis

Data analysis performed using simple descriptive statistics to measure types and frequencies of the prescribed ART regimens, adherence to the treatment and various categories of ADR's reported. A Chi-square test with Yates correction was used to determine an association between adherence and therapeutic outcome at a 5% level of significance. The data analysis was performed by using SPSS software version 21.

## Results

The records of 430 patients were analyzed in the present study. The median age was 35 years, most of the patients are between age 32-41(31.3%). Female are 220 (51.2%) and male 204 (47.4 %). The majority of people are uneducated (27.9 %) to primary educated (35.3%) and most of the people are married (72.3%) and 5.3 % of patients have tuberculosis as co-infection and receiving anti-tubercular treatment along with ART (Table-1).

**Table1: Socio demographic characters of patients**

Variable	Frequency (N=430)	Percentage
<b>Gender</b>		%
Male	204	47.4
Female	220	51.2
Others	6	1.4
Total	430	
<b>Age</b>		
12-21 years	20	4.65116279
22-31	130	30.2325581
32-41	169	39.3023256
42-51	86	20
>51	25	5.81395349
Sum	430	100
<b>Educational status</b>		
None	120	27.9
Primary	152	35.3
Secondary	85	19.8
Post-secondary	73	17
Total	430	
<b>Marital status</b>		
Married	311	72.3
unmarried	51	11.9
Widow	13	3
Divorced	11	2.6
Separated	31	7.2
Unreported	13	3
People infected with Tuberculosis	23	5.3%

From Table 2, total 11 different Antiretroviral combinations were prescribed

for the treatment of HIV in 430 patients, of which Tenofovir (TAF)+ Lamivudine (3TC)

+Efavirenz (EFV) (66.5%) was prescribed most frequently followed by Zidovudine (ZVD) + Lamivudine (3TC) + Nevirapine (NVP) (22.8%).

**Table 2: Prescribed Antiretroviral drug combinations and their frequencies**

Antiretroviral drug combination	Number of Patients	Percentage of each combination (%)
ABC/ 3TC + ATV / RPV	1	2
ZVD/ 3TC / NVP	98	22.8
ABC / 3TC / NVP	1	2
ABC / 3TC / EFV	1	2
D4T / 3TC / EFV	1	2
D4T / 3TC / NVP	8	1.9
TAF / 3TC / ATV / RPV	14	3.3
TAF / 3TC / EFV	286	66.5
TAF / 3TC / NVP	11	2.6
ATZ / 3TC / ATV / RPV	2	5
ATZ / 3TC / EFV	7	1.6

Abbreviations: Abacavir (ABC), Tenofovir (TAF), Lamivudine(3TC), Atazanavir (ATV), Ritonavir (RPV), Efavirenz (EFV), Nevirapine (NVP), Stavudine (D4T), Zidovudine (AZT)

### Adherence and Therapeutic Outcome

In the surveillance data, adherence was given as good and poor, and this was compared with baseline and follow-up CD4 count. Usually, the patient's CD4 count is less during the initiation of the therapy and is expected to rise on ART initiation. The majority of 348 patients (80.9%) were good adherence while 19% reported poor

adherence. Among good adherence patients (348), 285 (81.8%) patients showed positive therapeutic outcomes (raise of CD4 count, no complaint of infection) while, 63 (18.2%) patients showed no response to the ART, and few patients were reported with death. Subjecting adherence and therapeutic outcomes to chi-square analysis showed a significant association between (*p value* <0.0001) them in Table-3.

**Table 3: Relationship between adherence and therapeutic outcomes**

Adherence	Frequency	Failure of the treatment	Good therapeutic response	P value P-value
Good	348(80.9%)	63 (18.2%)	285 (81.8%)	
Poor	82(19%)	36 (43.9%)	46 (56%)	
Total	430	99(23%)	331(76.9%)	<0.0001

### Adverse Drug Reactions

The complaints that are said by the patients and observed by the physicians are reported in the clinical data files that were used for ADRs analysis. A total of 210 ADRs ranging

from mild to severe clinical symptoms are observed. The most common clinical ADRs found in this study were gastrointestinal disturbances (30.9%) followed by dermatological problems (20.4 %) (Table-4).

**Table 4: Organ wise distribution of ADR's**

Adverse drug reaction	Frequency (n=210)	Percentage (9%)
<b>Gastro-intestinal system disorders</b>	<b>65</b>	<b>30.95238</b>
Nausea & Vomiting	21	10
Diarrhea	19	9.047619
Abdominal Pain/cramps	6	2.857143
Flatulence	1	0.47619
Gastritis	18	8.571429
<b>Skin</b>	<b>43</b>	<b>20.47619</b>
Rashes	15	7.142857
Eruptions / Acne	21	10
Itching	5	2.380952
Steven-johnson syndrome	1	0.47619
Nail pigmentation	1	0.47619
<b>Central nervous system disorders</b>	<b>36</b>	<b>17.14286</b>
Headache	8	3.809524
Insomnia	5	2.380952
Giddiness	6	2.857143
Anorexia	3	1.428571
Malaise	5	2.380952
Tremors in the limbs	9	4.285714
<b>Musculoskeletal disorders</b>	<b>29</b>	<b>13.80952</b>
Parasthesia of legs	1	0.47619
Joint pains	5	2.380952
Muscle aches	2	0.952381

Generalized weakness	21	10
<b>Others</b>		0
Fever	37	17.61905
Hepatitis	1	0.47619
Pancreatitis	1	0.47619
Weight loss	5	2.380952
Anemia	15	7.142857
Total	210	100
Death	71	

The most commonly reported ADRs were Nausea & vomiting (10 %), generalized weakness (10%), rash (7.1 %), anemia (7.1 %), and central nervous system disturbances such as headache, dizziness, and insomnia (17. 9%). From Table-5, the higher numbers of ADRs were reported among patients

receiving Tenofovir + Lamivudine + Efavirenz (TLE) (56%) followed by 31.2% ADRs reported in patients treated with Zidovudine + Lamivudine + Nevirapine (ZLN) regimen. A total of 71 (16.5%) deaths were reported either due to treatment failure or as a result of adverse drug events.

**Table 5: Frequency of ADR reports with ART combinations**

TART combinations	No of patients (n=430)	No of ADR's (n=189)	
ABC/ 3TC + ATV / RPV	1	1	0.52 %
ZVD/ 3TC / NVP	98	59	31.2 %
ABC / 3TC / NVP	1	1	0.52%
ABC / 3TC / EFV	1	0	--
D4T / 3TC / EFV	1	0	--
D4T / 3TC / NVP	8	4	2.1 %
TAF / 3TC / ATV / RPV	14	9	4.76 %
TAF/3TC / EFV	286	106	56 %
TAF/3TC / NVP	11	3	1.6 %
ATZ/ 3TC / ATV / RPV	2	1	0.52%
ATZ/ 3TC / EFV	7	5	2.64%

Abbreviations: Abacavir (ABC), Tenofovir (TAF), Lamivudine(3TC), Atazanavir (ATV), Ritonavir (RPV), Efavirenz (EFV), Nevirapine (NVP), Stavudine (D4T), Zidovudine (AZT)

## Discussion

The present study aimed to highlight the most used ART combinations at an ART center in Andhra Pradesh and the ADRs reported during their use. A total of 11 different ARV combinations are used, among them, Tenofovir + Lamivudine + Efavirenz (56%) was most frequently prescribed and these are consistent with the guidelines of WHO and the national guidelines for the use of ARV drugs in India [1, 10]. When compared to prescribing practices in other countries like Nigeria where 23 different ARV drug combinations have been used in a single clinic, our study site was evident for adhering to rational prescribing guidelines [11].

In our study female (51.2 %) patients were slightly higher than men. The most concerning issue is the majority of females are in their reproductive ages and married with low educational status. This is evident that most of them are infected by unprotected sex from the sexual partner due to a lack of sex education. Even though many national HIV awareness programs are being executed, they may not have enlightened these people.

The most frequently prescribed combinations were Tenofovir (TAF) + Lamivudine (3TC) + Efavirenz (EFV). These combinations and others prescribed are consistent with the guidelines of the WHO (2019). The same combination TLE was majorly prescribed (66.4%) in Allahabad [12]. While in a similar study at an African country Nigeria, reported 23 different ARV drug combinations were prescribed, of which AZT-3TC-NVP followed by D4T-3TC-NVP where majorly prescribed [11].

Medication Adherence is the key to the success of ART and in our present study 19 % had poor adherence. A systematic review and meta-analysis study done by Mhaskar et al on adherence to ART in India showed the pooled adherence rate was only 70% [13]. When compared with the adherence rate reported in different studies across India, this study shows analogous results [12]. Rate of adherence is appreciable in the present ART center when compared with the result in other parts of Andhra Pradesh where 49.9% had poor adherence [14]. In our study, Tenofovir + Lamivudine + Efavirenz (TLE)

(56%) accounted for the majority of ADRs followed by Zidovudine + Lamivudine + Nevirapine (ZLN) (31.2%) regimen. This might be because TLE was a highly prescribed combination with a potential therapeutic efficacy and fewer toxicities being reported than Zidovudine combinations. While in other studies, ZLN combination accounts for the majority of ADRs, Zidovudine was responsible for the majority of adverse events said in a study by Anita shet et al., [15-17].

In our present study, a total of 210 ADRs were reported among them, gastrointestinal disturbances (30.9%) followed by dermatological problems (20.4 %) accounts for the highest numbers. A similar result was observed in the study by Anita Shet et al., were gastrointestinal disturbances (15.8 %), generalized fatigue (10.7 %), rash (6.3 %), and anemia (10.3 %) [17]. While in another study, reported, Anemia (76.52%) was the commonest ADR reported followed by skin rash (11.36 %) [15]. Indian retrospective studies where similar regimens were used have noted ADR incidence rates of 34–53% [18, 19]. In our study, ADRs were observed in patients who had baseline CD4 count < 250 cells/ $\mu$ l.

Similar results were observed in a study from Kadapa, India that patients with a CD4 count of <250cells/ $\mu$ l was affected with more ADRs [19, 20]. Hence we suggest estimation of ADRs based on the CD4 T- cell count at initiation of therapy. This would aid in accurate follow-up and decrease the chance of ADR events, hence improve adherence and

thereby results in good therapeutic responses. In-country like India, ADR reporting by the patients is not an active process, hence many considerable ADRs are left unreported which have been indirectly associated with patient's non-adherence and thereby treatment failure. Detailed counseling before initiation of ART along with clinical and laboratory monitoring can improve the condition.

There are certain limitations in the study like, surveillance data used in the study did not grade the severity of ADRs and there was no information on the medical history of the patient before initiation of ART. As it is a retrospective study, re-challenges and de-challenge are not possible. Hence causality assessment is not being performed in this study. A further limitation of analysis includes, there was no data on co-administered medication and treatments as well.

## Conclusion

Despite drug toxicity, ART treatment bears potential therapeutic efficacy and is considered as the only means to increase life expectancy in HIV infected patients. Our present study is a retrospective study with certain limitations. Our present study does not suggest discontinuation of treatment on presentation of toxic effects or use safer alternative treatments. We would suggest detailed counseling and monitoring improve the therapeutic outcomes and patients adherence. Updating of national guidelines with WHO guidelines can also result in good therapeutic outcome.

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