e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(5); 23-32

Original Research Article

# An Observational Study for Early Onset Adverse Drug Reactions of Antiretroviral Therapy in Tribal Population of Eastern Gujarat: Impact on Compliance and Course

**Shreyas Mukeshkumar Virvani[1], Sandeep Kumar Adwal[2]**

[1]MBBS House Surgeon, Zydus Medical College and Hospital, Dahod – 389151, Gujarat
[2]Professor, Department of Pharmacology, LNCT Medical College and Sewakunj Hospital, Indore - 452016, Madhya Pradesh

**Received: 18-03-2024 / Revised: 21-04-2024 / Accepted: 06-05-2024**
**Corresponding author: Dr. Sandeep Kumar Adwal**
**Conflict of interest: Nil**

**Abstract:**

**Background and Objectives:** Antiretrovirals, as most other chronically administered drugs, are reported to have adverse reactions, and particularly higher occurrences are seen at the beginning of ART. The main aim of this study is to gain knowledge on the profile of early onset ADRs associated with antiretroviral drugs, the burden of ADRs of ART in this setup with the ultimate goal of improving the patients' compliance and effectiveness of treatment.

**Methods:** An observational longitudinal study conducted at ART Centre of Tertiary care hospital of Eastern Gujarat. Data was collected through active pharmacovigilance and ADRs were recorded through ADR reporting forms. ADR causalities were assessed through WHO and Naranjo's causality scale, Severity was assessed through Modified Hartwig and Siegel Scale and Preventability was assessed through Modified Shumock and Thorton criteria.

**Results:** A total of 431 patients were interrogated in 6 months, of which 93 patients (21.58%) reported a total of 141 ADRs. ADRs were associated more with TDF+3TC+EFV Regimen. Most common system involved was gastrointestinal system (41.13%) followed by nervous system (34.04%) and the most frequently reported ADRs were of Nausea (17.73%) and Dizziness/Vertigo (17.02%). Majority of ADRs observed under Mild (83.69%) category. Causality assessment of suspected drug using WHO and Naranjo's scale revealed maximum ADRs were Possible (94.33% and 79.43%). Maximum ADRs were not preventable (59.57%).

**Interpretation & Conclusion:** We can improve the quality of care to patients living with HIV by providing an ADR profile, thus enabling a direct approach for the early detection and subsequent treatment of adverse drug reactions. To optimize adherence and hence effectiveness of treatment, clinicians must focus on preventing adverse effects whenever possible and distinguishing between self-limited and easily treatable ones from the potentially serious ones.

**Keywords:** Adverse Drug Reactions, AIDS, Antiretroviral therapy, Compliance, HIV.



## Introduction

Acquired Immunodeficiency Syndrome (AIDS), an advanced human immune virus disease is a fatal illness caused by a retrovirus known as Human Immuno-deficiency Virus (HIV). It is one of the most destructive epidemics the world has ever witnessed and remains one of the most significant public health challenges, particularly in low and middle-income countries. As per recent Indian HIV Statistical estimations 2019, 23.49 lakh PLHIV in the country, of which 69.22 thousand were newly infected in that respective year, 14.86 (63% of total PLHIV) lakh were on Anti-Retroviral Therapy (ART), and 59.0 thousand died due to HIV by 2019. Further Gujarat had around 1,03,057 PLHIV by 2019 of which 3.37 thousand were newly infected in that respective year, 75,842 [86%] were on ART and total AIDS-related deaths were estimated to be 1.57 thousand till the year 2019. [1] HIV disease is a chronic illness requiring life-long therapy on antiretroviral medications referred to as ART. There is a significant reduction in AIDS-related morbidity and mortality because of the use of Highly Active Antiretroviral Therapy (HAART). [2] Despite showing considerable efficacy in reducing mortality and morbidity in PLHIV, these drugs are associated with significant safety concerns including serious ADRs, with both short- and long-term effects. These untoward effects are

often mild, but sometimes they are more serious and can have a major impact on health or quality of life. Drug-related adverse events represent one of the most common reasons for treatment cessation or switch. [3] Recently, the introduction of newer antiretroviral drug formulations with improved efficacy and tolerability has resulted in a decline of treatment-limiting toxic effects; however, drug-related adverse events still remain an issue of concern. [4] Once started, antiretroviral treatment hinges patients on a lifelong commitment to adhere diligently to daily medication dosing schedules and timely periodic visits to the ART center. [5] Antiretrovirals, as most other chronically administered drugs, are reported to have adverse reactions, and particularly higher occurrences are seen at the beginning of ART. [6]

Therefore it becomes indispensable to monitor and report these Early onset ADRs as early as possible during the course of initiation of treatment to improve patient compliance, adherence, and most importantly public health resources. Every missed dose increases the risk that the drugs will stop working due to increased chances of resistance. It is therefore vital that people receiving ART get all the help they need to minimize the impact of side effects. In India, often ADRs are not emphasized upon and go unnoticed or are not reported. [7] Therefore monitoring and reporting of ADRs to HAART among the Indian population becomes very important. ADRs severely affect treatment adherence and reduction in patients' quality of life which may consequently lead to loss of follow-up of patients and thus treatment failure. [8] As per the latest NACO data of 2019, an estimated 9,347 PLHIV on ART in Gujarat lost to follow-up for treatment by 2019. [1] Mehta KG et al. in their study carried out in Gujarat found literacy as a significant parameter contributing to adherence to ART. [5] Amongst literacy in the rural populations, it is lowest in the districts of Eastern Gujarat, of which tribal people constitute a major population. [9] Therefore it becomes evident to conduct here study.

The aim of this study is to gain knowledge on the profile of Early onset ADRs associated with antiretroviral drugs, the burden of ART associated ADRs in this setup with the ultimate goal of improving patients' compliance and effectiveness of treatment.

## Materials and Methods

This study is an observational longitudinal study conducted in ART Centre of tertiary care hospital of Eastern Gujarat for a period of 6 months. The source population consisted of HIV-positive patients on anti-retroviral therapy. HIV-positive cases who were already on ART and who got newly registered for ART were included. Any patient with deliberate or unintended overdose, missing clinical record, inadequate data was excluded from the study.

Active pharmacovigilance (intensive monitoring by active follow-up after treatment and the event is detected by asking patients directly or screening patient records) was adopted. Information regarding ADRs was collected with the help of treating physician and other health care professionals. All relevant information was recorded in the ADR reporting form obtained from Central Drug Standard Control Organization (CDSCO) website.[10]. Cases were further analyzed for drug regimens associated with ADRs and their causality and severity assessment were performed.

Assessment of causality of ADR was done by WHO causality assessment scale [11] and The Naranjo adverse drug reaction probability scale [12]. ADR severity assessment scale: Modified Hartwig and Seigel Scale [13] was used for assessment of Severity of ADRs. For the assessment of Preventability of ADR we used Modified Shumock and Thorton criteria [14]

The data collected was recorded on monthly basis in Microsoft Excel sheet and was analyzed using software. Institutional Ethics Committee's approval was taken prior to the start of the study.

## Observation and Results

A total of 431 patients on ART were interrogated during the study period. Out of the total patients, 93 patients reported a total of 141 ADRs. As some patients had reported more than one ADR, the total number of ADRs was greater than the total number of patients. A brief description of the demographic data is presented followed by a detailed analysis of the ADRs observed in the patients below. There were more Male patients 55.68% (n=240) compared to the female patients 44.32% (n=191) observed. More patients were from the age group 31-40 years (i.e. 85 males and 60 females) and the least from the age group above 60 years (i.e. 11 male and 2 female patients).

The occurrence of ADRs to ART was compared between both male and female patient's categories. Out of 431 patients, 93 patients developed ADRs with an overall incidence of 21.58 %. More numbers of male patients with ADRs (58.06%) were detected as compared to female patients (41.94%). Maximum numbers of patients with ADRs were observed in age group 31-40 years (35.48%) followed by 21-30 years (23.66%), 41-50 years (22.58%), 51-60 years (6.45%), below 20 years (6.45%) and least with age group above 60 years (5.38%). [Table 1]

**Table 1: Age and sex wise distribution of patients with ADRs observed**

| Age Group | Male | Female | Total | Percentage |
|---|---|---|---|---|
| <20 years | 3 | 3 | 6 | 6.45% |
| 21-30 years | 10 | 12 | 22 | 23.66% |
| 31-40 years | 21 | 12 | 33 | 35.48% |
| 41-50 years | 13 | 8 | 21 | 22.58% |
| 51-60 years | 4 | 2 | 6 | 6.45% |
| >60 years | 3 | 2 | 5 | 5.38% |
| Total (Percentage) | 54 (58.06%) | 39 (41.94%) | 93 | 100% |

Drug Regimens allocation to the patients was based on baseline clinical assessment results.

Table 1 shows prescribed antiretroviral drug regimens in total patients observed and patients with ADRs.

**Table 2: Prescribed antiretroviral drug regimens**

| Drug Regimens | Total Patients Observed (n=431) | Patients With ADRs (% with same regimen) |
|---|---|---|
| TDF + 3TC + EFV | 182 | 55 (30.22%) |
| TDF + 3TC + DTG | 180 | 10 (5.56%) |
| AZT + 3TC + NVP | 24 | 17 (70.83%) |
| AZT + 3TC + EFV | 17 | 10 (58.82%) |
| ABC + 3TC + EFV | 16 | 0 |
| AZT + 3TC + DTG | 6 | 0 |
| ABC + 3TC +LPV/r | 6 | 1(16.67%) |
| **Total** | **431** | **93** |

*Abbreviations {TDF – Tenofovir, 3TC – Lamivudine, EFV – Efavirenz, DTG – Dolutegravir, AZT – Zidovudine, NVP – Nevirapine, ABC – Abacavir, LPV/r – Lopinavir/ritonavir}

**Adverse Drug Reactions (ADRs) Reported With ART**

A number of ADRs associated with the use of ART were reported from patients. In this study we collected only early onset Adverse Drug reactions, preferably within 20-24 weeks of initiation of antiretroviral therapy.

Table 3 represents frequency of ADRs with different HAART regimen.

**Table 3: Adverse Drug Reactions – Frequency**

| Frequency-Adverse Events (AE) | Regimen | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | TDF + 3TC + EFV (n=55) | TDF + 3TC + DTG (n=10) | AZT + 3TC + NVP (n=17) | AZT + 3TC + EFV (n=10) | AZT + 3TC + DTG (n=0) | AZT + 3TC + DTG (n=0) | ABC + 3TC+ LPV/r (n=1) | **Total Patients with ADRs (n=93)** |
| 1AE | 33 | 6 | 14 | 7 | 0 | 0 | 0 | 60 (64.52%) |
| 2-3AE | 20 | 3 | 2 | 3 | 0 | 0 | 1 | 29 (31.18%) |
| >3AE | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 04 (4.30%) |

In this study one AE was observed in 64.52% patients, 2-3 AEs were observed in 31.18% patients, and >3 AEs were observed in 4.30% patients from total patients observed with ADRs. [Table 3] A total of 141 ADRs were collected from 93 patients. The frequency of ADRs in male was 61.07% and in female was 38.03%. ADRs were more in male patients. ADRs were more in age group 31-40 years and least in age group 51-60 years. [Figure 1]

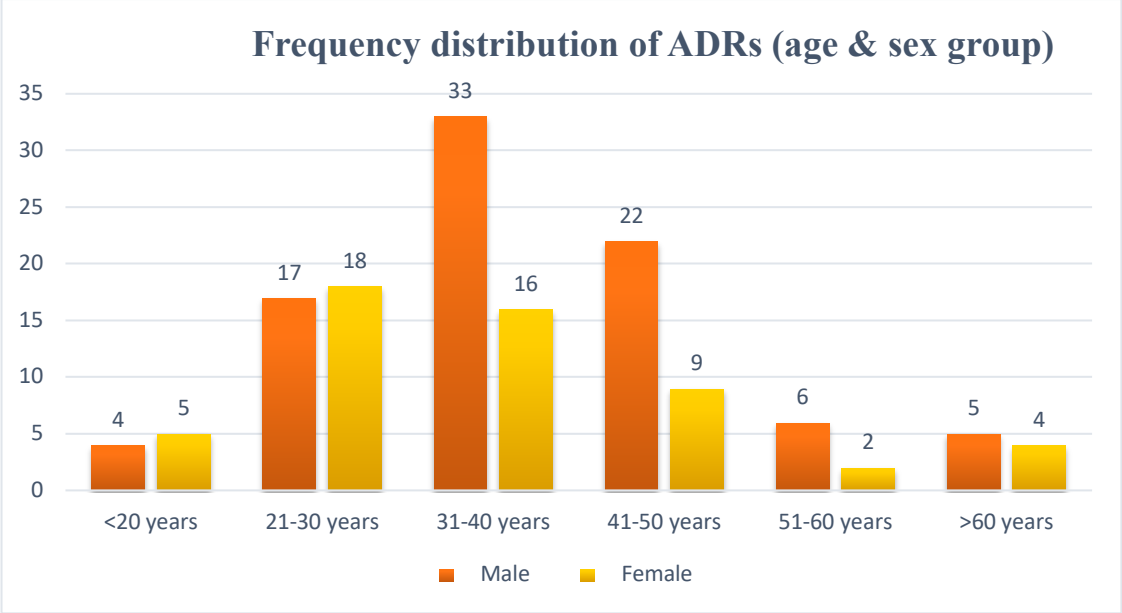


**Figure1: Frequency distribution of ADRs according to age & sex group**

Table 4 represents organ system involved in ADRs, types of ADRs and the number of times they were reported by different patients during ART**.**

**Table 4: Types of ADRs**

| **Types of ADRs (n= 141)** | | | |
|---|---|---|---|
| **Organ System** | **Types of ADRs** | **Number (n)** | **Percentage** |
| **Gastrointestinal (GIT) 41.13% (58)** | Nausea | 25 | 17.73% |
| | Vomiting | 22 | 15.60% |
| | Diarrhoea | 08 | 05.67% |
| | Anorexia | 03 | 02.13% |
| **Nervous system 34.04% (48)** | Dizziness/Vertigo | 24 | 17.02% |
| | Drowsiness | 09 | 06.38% |
| | Headache | 07 | 04.96% |
| | Sedation | 04 | 02.84% |
| | Peripheral Neuropathy | 02 | 01.42% |
| | Insomnia | 01 | 00.71% |
| | Anxiety | 01 | 00.71% |
| **Red blood cell disorders 12.06% (17)** | Anaemia | 17 | 12.06% |
| **Skin 08.51% (12)** | Skin Rashes | 08 | 05.67% |
| | Pruritus | 04 | 02.84% |
| **Renal 04.26% (06)** | Increase Serum Creatinine | 06 | 04.26% |
| **Total** | | **141** | |

Most common organ system involved was gastrointestinal tract (41.13%) followed by nervous system (34.04%). Most commonly observed ADRs were nausea (17.73%) and Dizziness/Vertigo (17.02%). [Table IV/ Figure 2]

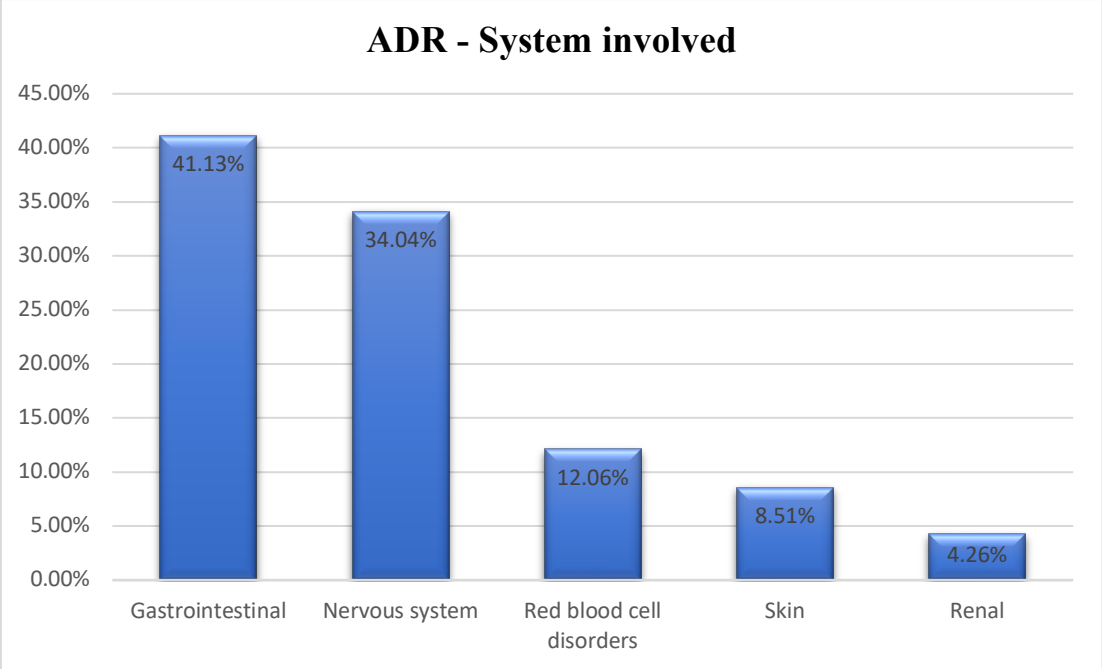


**Figure 2: Types of ADRs**

**Severity assessment of ADRs:** According to Modified Hartwig and Siegel Scale majority of ADRs observed were Mild (83.69%). In moderate category total 16.32% ADRs presented in which 12.77% were in level 3 and 03.55% were in level 4b. No severe ADRs were reported according to Modified Hartwig and Siegel Scale. [Table 5]

**Table 5: Severity assessment of ADRs - Modified Hartwig and Siegel Scale**

| Category | | No. Of ADRs (n=141) | Percentage |
|---|---|---|---|
| **Mild** | **Level -1** | 118 | 83.69% |
| | **Level -2** | 00 | 00 |
| **Moderate** | **Level -3** | 18 | 12.77% |
| | **Level -4a** | 00 | 00 |
| | **Level -4b** | 05 | 03.55% |
| **Severe** | **Level -5** | 00 | 00 |
| | **Level -6** | 00 | 00 |

**Management of ADRs**

**Table 6: Management of ADRs**

| Management | No of ADRs | % |
|---|---|---|
| Withdrawal | 17 | 12.06% |
| Symptomatic | 47 | 33.33% |
| No Treatment | 77 | 54.61% |

In 87.94% patients suspected drugs were continued. Symptomatic treatment was given in 33.33% of ADRs and withdrawal of suspected drugs was required in 12.06% ADRs. [Table 6]

**Causality Assessment of Adverse Drug Reactions**

The causality of suspected drug was assessed by using WHO scale of ADR causality assessment and also by Naranjo's scale of ADR causality assessment. Suspected drug selected from regimen was according to their most common ADRs profile described in various literature for the causality assessment. The causality of suspected drug was assessed using WHO scale of ADR causality assessment. The assessment revealed 94.33 % ADRs were Possible and 05.67 % ADRs were Probable. [Figure 3]

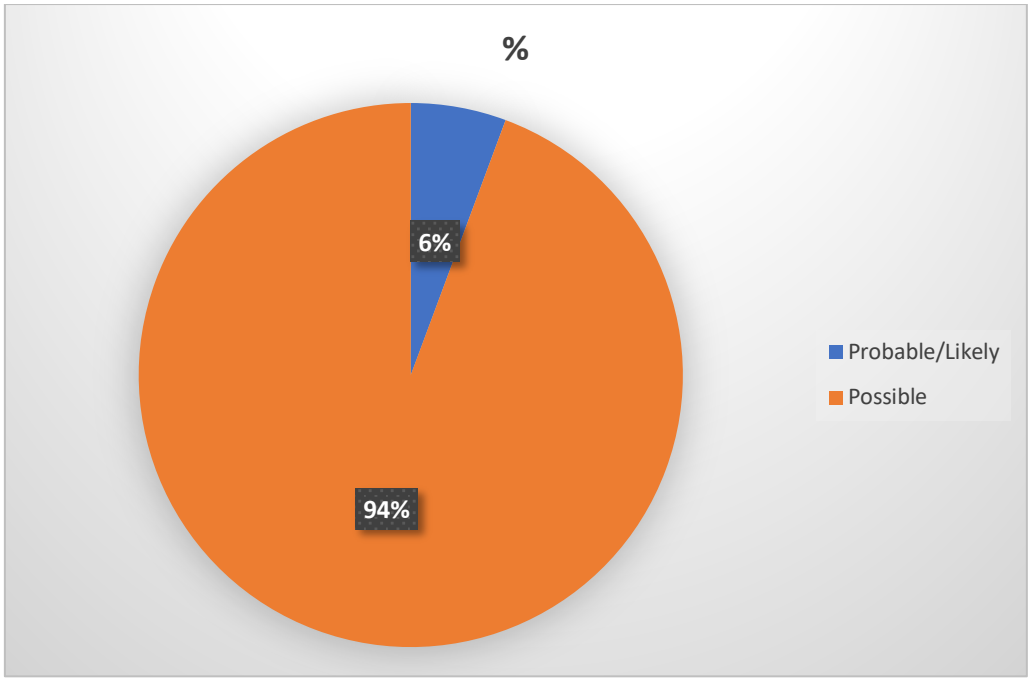


**Figure 3: Causality Assessment of the ADRs by WHO Probability Scale**

According to Naranjo's scale of ADR causality assessment 20.57% ADRs were Probable and 79.43 % ADRs were Possible. [Figure 4]

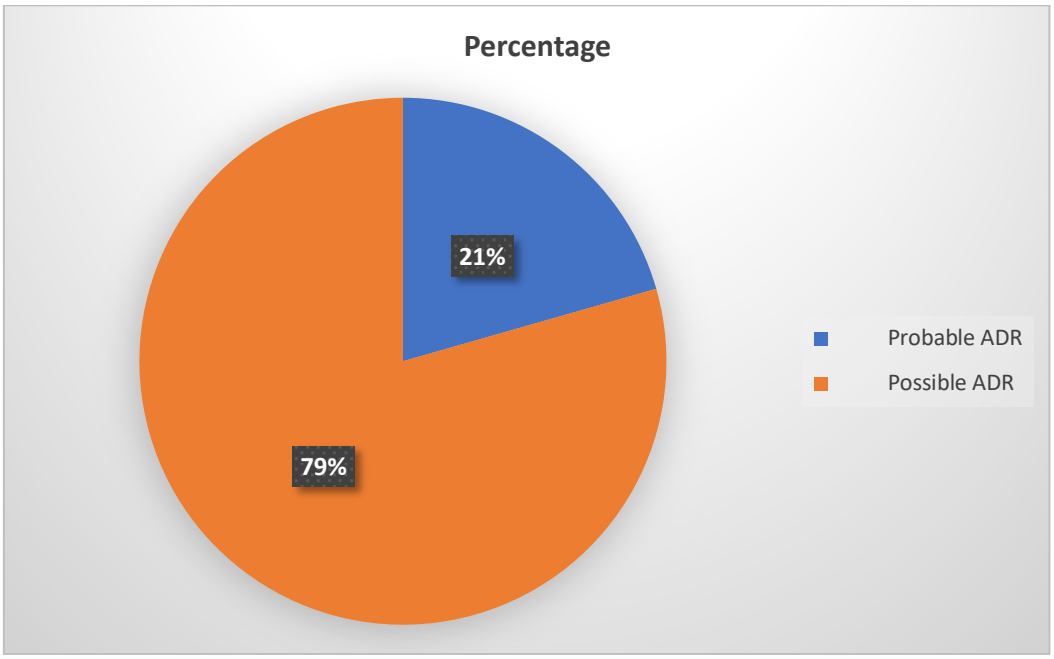


**Figure 4: Causality Assessment of The ADRs by Naranjo's Scale**

**Preventability of ADRs:** Preventability of reported ADRs was studied using Modified Shumock and Thorton criteria.

**Table 7: Preventability of ADRs: Modified Shumock and Thorton criteria**

| Preventability Criteria | Number of ADRS (N-141) | Percentage % |
|---|---|---|
| **Definitely preventable** | 00 | 00 |
| **Probably preventable** | 57 | 40.43% |
| **Not preventable** | 84 | 59.57% |
| **Total** | 141 | 100.00% |

59.57% ADRs were not preventable and 40.43% ADRs were probably preventable. There were no ADR which was definitely preventable using Modified Shumock and Thorton criteria. [Table VII]

**Discussion**

Total of 431 patients were observed during the study period. Our findings show that about 1 in every 5 patients (21.58%) on ART, reported at least one ADR within a minimum period of 20-24 weeks. This incidence rate was less than the study of Mukherjee S et al. [8] in which 32.45% patients experienced ADRs. Also Reddy AK et al.[15] reported 31% of patients experienced ADRs and Menezes de Pádua CA et al.[16] reported 33.7 % of patients experienced ADRs to ART, which was high as compared to our study. Incidence rate of ADRs observed in our study was higher than the study of Modayil RR et al.[17] in which the prevalence of ADRs was 17.5%. Incidence rate of ADRs observed in our study was almost equal with Tamirat T et al. [18] study in which the prevalence was 22.9%.

These differences in the incidence rate of ADRs maybe because of concurrent medications used for the treatment of opportunistic infections and other co-morbid conditions which may result in an increase of ADRs incidence. This difference may also be explained by the lack of uniformity in the reporting style of ADRs across settings even though all of the patients in these settings are on similar FDC generic drugs. However, other factors like regional or ethnic susceptibilities to ADRs might also explain this difference.

In our study, the prevalence of ADRs was high in males as compared to female patients. In contrast to this finding, Mukherjee S et al. [8] have found a high prevalence of ADRs in females.

These sex differences in adverse drug reactions might be due to differences between men and women in fat composition and body mass index, hormonal effects on drug metabolism, or genetic constitutional differences on the levels of various enzymes. In our study most of the patients belonged to the age group of 21-40 years; therefore, we might have detected the majority of ADRs from this group which can be also a possible reason.

**Adverse Drug Reactions (ADRs) Reported With ART**

We observed that the maximum number of ADRs was related to the gastrointestinal system which is in agreement with the findings of Modayil et al. [17]. In our study, 41.13% of the total ADRs were related to the gastrointestinal (GI) system mainly presented in the first 4 weeks of therapy. Among various GI disorders, the majority presented with complaints of nausea and vomiting. Many other studies showed similar findings. [8,19,20,21] We also took many precautions to prevent GI adverse events because these are one of the most common causes of non-adherence to drugs and leading to early treatment failure.

The neurological disorders that were commonly reported (34.04%) by patients mainly included dizziness/vertigo (17.02%), drowsiness (06.38%), and headache (04.96%) of total ADRs observed. Many other studies showed similar findings. [20,22] We also observed sedation, peripheral neuropathy, insomnia, and anxiety as early onset adverse reactions of ART. Early onset CNS side effects such as dizziness, drowsiness, insomnia, headache, numbness, etc., were mainly associated with EFV. [23] These CNS side effects generally become tolerable and resolve within the first 4 -8 weeks of therapy. These CNS adverse events may affect adherence to treatment and lead to poor compliance.

Out of 93 patients who experienced ADRs, 17 patients developed anaemia within 20-24 months of therapy who were receiving Zidovudine based regimen. Pádua CA et al.[21] study reported anaemia in 8.9% of patients and in Max B et al. [24] study reported that incidence of anaemia ranges from 1-7%. Anaemia can be associated with zidovudine therapy. [25,26] The mechanism of zidovudine-induced myelosuppression is unclear. It has been suggested that zidovudine inhibits both erythroid burst-forming units and human granulocyte-macrophage colony-forming units. [26]

Rash and pruritus are most frequently reported adverse effects of the NNRTIs. Some studies have reported high incidence of mild to moderate maculopapular rash within first 6 week of therapy with Nevirapine [27]. In our study, 8 patients experienced rash and 4 patients experienced pruritus within 4 weeks of therapy.

Out of 93 patients who experienced ADRs, 6 patient's findings showed increased serum creatinine levels within 20-24 months of therapy who were receiving Tenofovir based regimen. Increased serum creatinine is most likely associated adverse effect of Tenofovir. Tenofovir is found to be nephrotoxic altering Renal Function Tests and causing renal damage. [28]

**Severity Assessment of Adverse Drug Reactions**

Severity of ADRs was also assessed. Assessment of severity is subjective assessment made by the patient and/or the clinician. Although subjective, it may be useful in identifying adverse drug reactions that may affect adherence.

We evaluated the severity of ADRs by Modified Hartwig and Siegel Scale. Majority of ADRs

observed were Mild (83.69%). This is similar with study by Kumar V et al. [22] which had maximum ADRs severity 73.81% under mild category.

**Causality Assessment of Adverse Drug Reactions:** Suspected drug for causality assessment was selected from regimen according to their most common ADRs profile described in various literature.

According to WHO probability scale 94.33 % ADRs were "Possible" and 05.67 % ADRs were "Probable". Most of the ADRs were in possible category because withdrawal of drug was done in only few cases. In a study by Kumar V et al. [22] most of the ADRs were possible (80.95%).

Causality assessment of ADRs by Naranjo scale showed that most of the (79.43 %) ADRs were "possible" while remaining (20.57%) ADRs were "probable". None of the ADRs were "definite and unlikely". In a study by Reddy AK et al. [15] most of the (63.75%) ADRs were possible.

**Preventability of ADRs:** We used Modified Shumock and Thorton criteria to assess Preventability of reported ADRs. 40.43% ADRs were probably preventable. A similar finding was observed in a study by Mehta U et al. [29] Findings of preventability (46.39%) were substantially lower than (56.76%) observed in a study conducted by Rajesh R et al. [30] In most of preventable cases of ADRs, preventive measures for ADRs were administered or prescribed to patients: for example, common instructions were given to patients to avoid dairy products and fatty foods for prevention of nausea and vomiting in patients.

## Conclusion

ART is becoming increasingly effective for patients' survival, but also increasingly complex because of its long-term use and associated adverse effects. Significant problems related to compliance and both short-term & long-term toxicity can be expected with life-long therapies. Although current antiretroviral regimens used by NACO are potent from an antiviral perspective, they often fail because of patient nonadherence related to the complexity of treatment. To optimize adherence and hence effectiveness, clinicians must focus on preventing adverse effects whenever possible and distinguishing those that are self-limited and easily treatable from those that are potentially serious.

Overall, monitoring of early-onset toxicities associated with HIV represents an area of research. Active Pharmacovigilance of ADRs of ART has increased the documentation of the profile of these reactions and should be scaled up to all facilities providing extensive care to HIV patients. We can improve the quality of care to patients living with HIV by providing ADRs profile, so provides an approach for early detection and subsequent treatment of adverse drug reactions.

For the effectiveness of ART, we need to understand more precisely the occurrence of adverse drug reactions and the overall effect of these reactions on patients' clinical outcomes. Without the understanding of this, the successful outcome of our current therapies can, for a considerable number of individuals, be assumed to be short-lived.

Continuous monitoring and evaluation of the benefit and harm of ART helped us to achieve the ultimate goal of making safer and more effective treatment available to patients.

Relatively high prevalence of HIV in tribal population of Eastern Gujarat necessitates close monitoring and implementation of AIDS Control Programme. Our study had ultimate goal of improving the tolerability and effectiveness of HIV treatment in this region.

**Acknowledgements:** We would like to extend our heartfelt thanks to Indian Council of Medical Research (ICMR), New Delhi, for supporting and funding this Project.

**Funding:** This project was funded by ICMR under Short Term Studentship Programme 2020 (ICMR-STS 2020, Reference ID: 2020-04770)

## References

1. National AIDS Control Organization – "Sankalak; Status of National AIDS Response". Available at: http://naco.gov. in/ sites/default/files/Sankalak_Report.pdf . Accessed on: 8th November, 2021
2. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, Nachega JB, Dybul M, Hogg RS. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. Annals of internal medicine. 2011 Aug 16; 155(4):209-16.
3. Sobrino-Jiménez C, Jiménez-Nácher I, Moreno-Ramos F, González-Fernández MÁ, Freire-González M, González-García J, Herrero-Ambrosio A. Analysis of antiretroviral therapy modification in routine clinical practice in the management of HIV infection. European Journal of Hospital Pharmacy. 2017 Mar 1; 24(2):96-100.
4. Prosperi MC, Fabbiani M, Fanti I, Zaccarelli M, Colafigli M, Mondi A, D'Avino A, Borghetti A, Cauda R, Di Giambenedetto S. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC infectious diseases. 2012 Dec; 12(1):1-1.

5. Mehta KG, Baxi R, Patel S, Parmar M. Drug adherence rate and loss to follow-up among people living with HIV/AIDS attending an ART Centre in a Tertiary Government Hospital in Western India. Journal of family medicine and primary care. 2016 Apr; 5(2):266.
6. Eluwa GI, Badru T, Akpoigbe KJ. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. BMC clinical pharmacology. 2012 Dec; 12(1):1-9.
7. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India. Indian journal of pharmacology. 2015 Jan; 47(1):65.
8. Mukherjee S, Era N, Saha B, Tripathi SK. Adverse drug reaction monitoring in patients on antiretroviral therapy in a tertiary care hospital in Eastern India. Indian journal of pharmacology. 2017 May; 49(3):223.
9. Tribal Development Department – Government of Gujarat. Available at: https:// tribal.gujarat.gov.in/tribal-demography-of-gujarat . Accessed on: 11th November, 2021.
10. Suspected Adverse Drug Reaction reporting form – CDSCO. Available at: https://cdsco. gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/Consumer_Section_PDFs/ ADR RF_2.pdf .
11. The use of the WHO-UMC system for standardised case causality assessment https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics. 1981 Aug; 30(2):239-45.
13. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. American journal of hospital pharmacy. 1992 Sep 1; 49(9):2229-32.
14. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hospital pharmacy. 1992 Jun 1; 27(6):538.
15. Reddy AK, Lihite RJ, Lahkar M, Choudhury U, Baruah SK. A study on adverse drug reactions in HIV infected patients at a art centre of tertiary care hospital in Guwahati, India. Asian J Pharm Clin Res. 2013; 6(2):102-4.
16. Menezes de Pádua CA, César CC, Bonolo PF, Acurcio FA, Guimarães MD. High incidence of adverse reactions to initial antiretroviral therapy in Brazil. Brazilian journal of medical and biological research. 2006; 39:495-505.
17. Modayil RR, Harugeri A, Parthasarathi G, Ramesh M, Prasad R, Naik V, Giriyapura V. Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India. Pharmacoepidemiology and drug safety. 2010 Mar; 19(3):247-55.
18. Tamirat T, Woldemichael K, Tewelde T, Laelago T. Anti-retro viral therapy adverse drug reaction and associated factors among human immuno deficiency virus infected adult patients at Nigist Eleni Mohammed Memorial hospital, South Ethiopia. African Health Sciences. 2020 Jul 22; 20(2):560-7.
19. Chowta MN, Kamath P, Ramapuram JT, Shenoy KA, Hadigal S. Evaluation of adverse drug reaction profile of drugs used as first-line antiretroviral therapy. Interdisciplinary perspectives on infectious diseases. 2018 Aug 2; 2018.
20. Tadesse WT, Mekonnen AB, Tesfaye WH, Tadesse YT. Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. BMC pharmacology and Toxicology. 2014 Dec; 15(1):1-9.
21. Pádua CA, César CC, Bonolo PF, Acurcio FA, Guimarães MD. Self-reported adverse reactions among patients initiating antiretroviral therapy in Brazil. Brazilian Journal of Infectious Diseases. 2007; 11:20-6.
22. Kumar V, Singh J. A prospective study on impact of early initiation of antiretroviral therapy in human immunodeficiency virus-positive adults on immunological status and adverse events. Journal of global infectious diseases. 2019 Apr; 11(2):73.
23. Bartlett JA, Chen SS, Quinn JB. Comparative efficacy of nucleoside/nucleotide reverse transcriptase inhibitors in combination with efavirenz: results of a systematic overview. HIV clinical trials. 2007 Aug 1; 8(4):221-6.
24. Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. Clinical infectious diseases. 2000 Jun 1; 30(Supplement_2):S96-116.
25. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals. Drug safety. 1998 Dec; 19(6):481-94.
26. McLeod GX, Hammer SM. Zidovudine: five years later. Annals of Internal Medicine. 1992 Sep 15; 117(6):487-501.
27. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. The Lancet. 2000 Oct 21; 356(9239):1423-30.
28. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Nino MD, Izquierdo MC, Poveda J, Sainz-Prestel V, Ortiz-Martin N, Parra-Rodriguez A, Selgas R, Ruiz-Ortega M.

Tenofovir nephrotoxicity: 2011 update. AIDS research and treatment. 2011 Jun 7; 2011.
29. Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. British journal of clinical pharmacology. 2008 Mar; 65(3):396-406.
30. Rajesh R, Vidyasagar S, Nandakumar K. Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients. Pharmacy Practice. 2011; 9(1):48-55.