ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

# Assessment of Adverse Drug Reactions and Drug Interactions Caused By Art with Other Co-Morbid Conditions

[1.]Sreshi Kumari,
Pharm.D Intern,
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bengaluru, 560035

[2.]Tana Donyi Tara,
Pharm.D Intern,
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bengaluru, 560035

[3.]Pooja Ajit Sonawane,
Pharm.D (PB) Intern,
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bengaluru, 560035

[4.] Dr. Beulah Milton,
Co-Author- Professor and HOD,
Department of Pharmacy Practice,
Krupanidhi College of Pharmacy,
Bengaluru, 560035

**Abstract:- Objective: The aim of the study focuses on the assessment Of Drug –Interactions and Adverse Drug Reactions caused by ART with other Co-Morbid Conditions. Method: This was a prospective observational study carried out in the ART Center, MVJ Medical College, and Research Hospital, Hoskote from April 2023 to September 2023. The study enrolled a total of 164 patients suffering from HIV infection associated with co-morbid diseases The patient's demographic details were obtained from WHITE cards in ART Center. Liverpool HIV DDI website was used to define each DDI and specific grade. CHI-SQUARE TEST was used to determine the association of Adverse Drug Reactions Result: Out of 162 patients, 16 were identified as drug-drug interactions, further of which 3 were categorized as red flagged and the remaining 13 were amber flagged interactions. Also, 3 ADRs were identified with a low incidence rate of 0.6%. The chi-square study shows a strong association between Drug-Drug Interactions, Age- CD4/Viral Count, and Age-Drug Interaction these factors can be taken into consideration to prevent DDI. Conclusion: As per our study we conclude that Therapeutic Drug Monitoring (TDM) and the involvement of clinical pharmacists can address these issues. TDM optimizes drug dosages to avoid interactions and adverse effects, ensuring safer and more effective treatment. Clinical pharmacists are crucial in identifying potential DDIs and ADRs, providing tailored interventions, and educating patients and healthcare providers. Their expertise is essential in improving health outcomes for PLWHA by ensuring the safe and effective use of medications, thereby overcoming the limitations we faced in our study.**

***Keywords:-*** *ART, ADR, DDI's, Liverpool HIV DDI, TDM.*

## I. INTRODUCTION

In India, the first HIV patient was detected in 1986 among female sex workers in Chennai [1]. In the year 2020, the National AIDS Control Organization Ministry of Health & Family Welfare Government of India estimated HIV prevalence at 0.22% with 0.23% among males and 0.20% among females [2]. HIV continues to be a serious health issue in many parts of the world. An estimated 27.4 million PLWH will access anti-retroviral therapy (ART) globally in 2020 [2].

As a result of effective antiretroviral therapy, life span and quality have increased in individuals with HIV [3][4]. Despite this achievement, it remains a challenge to continue the treatment regimen successfully. Strict adherence of at least 95% to the prescribed routine of ART is recommended for the success of treatment [4][5].

The people living with HIV experience non-AIDS conditions earlier in their life course, increasing use of concomitant medications and possible drug-drug interactions can be a concern [6][8]. Increased medications add potential concerns associated with increased pill burden, decreased medication adherence, and adverse drug reactions including organ system injury, hospitalization, and death [7].

Exposure to ART and non-ART medications could reduce the effectiveness and increase the chances of adverse effects due to alterations in pharmacokinetics and toxicities [8]. Also, aging leads to physiological, anatomical, and

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

biological modifications that alter the pharmacokinetics of the ART regimen [9]. Most prescribed medications in antiretroviral regimens such as pharmacologic boosters' ritonavir or cobicistat-boosted protease inhibitor (PIs)-based and non-nucleoside reverse transcriptase inhibitors which contribute to most well-recognized drug-drug interactions [10]. The additional benefits of Therapeutic Drug Monitoring in the optimal management of people living with HIV have been discussed [*].

Drug-drug interactions are the commonest causes of ADRs and these manifestations are commonly observed in the elderly due to concomitant medications [11]. ADR is a reaction to medicine that is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis, treatment, or modification of physiological functions. Reports from various countries suggest that adverse drug reactions are the 4th to 6th largest cause of mortality and 10 – 20% of hospitalization. [12]. The adverse drug reaction\event associated with antiretrovirals or non-ART medications is more likely to lead to poor adherence to the treatment, loss of patient's confidence in the safety of treatment, and negative impact on the public health system which may result in negative clinical outcomes [12][13].

The additional benefits of Therapeutic Drug Monitoring in the optimal management of people living with HIV have been discussed [14]. Potential drug-drug interactions due to polypharmacy among PLWH, the affect of adherence to treatment in people with HIV, and adverse drug reactions to antiretroviral therapy have been assessed in various studies. This study aimed to assess ADRs and DIs in PLWH with other co-morbid conditions.

## II. MATERIALS AND METHODS

This was a prospective observational study carried out in the ART Center, MVJ Medical College, and Research Hospital, Hoskote from April 2023 to September 2023. The study enrolled a total of 164 patients suffering from HIV infection associated with co-morbid diseases (Hypertension, Diabetes, Chronic kidney disease, Tuberculosis, Chronic infections). Patients receiving Anti-retro viral therapy along with concomitant medications were included in the study. Patients in the study were of the age group 16 – 65 years.

The patient's demographic details (Initials, age, sex, and weight), relevant laboratory tests (Viral load, CD4 count, Hemoglobin), ART regimen, concomitant medications, suspected medication (date of prescription, dose, frequency, route of administration, duration, and indication), suspected adverse reaction (date of start and end), outcome of the reaction were obtained from WHITE cards in ART Center.

The study was conducted after gaining approval from the Institutional Ethical Committee (IEC No. MVJMC&RH/IEC-82/2023). Before commencing the study, participating patients were provided with Informed consent. Confidentiality was maintained during the study.

Liverpool HIV DDI website was used to define each DDI and specific grade. DDIs were classified as yellow flag interaction (undefined grade), Amber flag interaction (precaution of use), and Red flag interaction (not recommended or contraindicated) [15]. For ADR assessment, the Naranjo Algorithm was used. It is a method to assess the causal relationship between an identified adverse reaction and a drug using a simple questionnaire to assign probability scores [16].

Statistical analysis of the data was done using Microsoft Excel and the result was expressed as numbers. CHI-SQUARE TEST was used to determine the association of Adverse Drug Reactions and Drug Interactions with clinical or demographic risk factors [17].

## III. RESULTS

A total of 172 patients which are groups of people affected by HIV with other co-morbid conditions were selected for the study based on the inclusion and exclusion criteria and their willingness to participate in the studies.

The majority were males,97 (56.39%), and in the age group of 31-45 years, and the remaining were females,75(43.60%)(Table1), Mean Age Of HIV patients included in the study.(Table 2), Graph: 1.

A p-value is a statistical measurement tool used for data to validate a hypothesis against observed data, used to measure the probability of obtaining the observed data. Therefore p-value less than 0.05 is typically considered to be statistically significant, in which case the null hypothesis should be rejected. Below are the factors whose p-value is less than 0.05. (Table2)The table presents the results of statistical analyses examining the interactions between various factors and their associated p-values. The interactions tested include demographic, clinical, and treatment-related factors. The factors assessed are:

- Gender and Age ($p = 0.001$): A significant interaction is observed between gender and age.
- Age and CD4 Count ($p < 0.001$): A highly significant interaction is detected between age and CD4 count.
- Age and Viral Count ($p = 0.042$): A statistically significant interaction between age and viral count.
- Age and WHO ($p = 0.009$): The interaction between age and WHO classification is significant.
- Age and Drug Interaction ($p < 0.001$): A strong interaction is noted between age and drug interactions.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

- Drugs and CD4 Count ($p < 0.001$): A significant relationship is found between drug use and CD4 count.
- Drugs and Viral Count ($p < 0.001$): The interaction between drugs and viral count is significant.
- Drugs and Adherence ($p < 0.001$): A significant association is detected between drug use and adherence.
- Drugs and WHO Stage ($p < 0.001$): A highly significant interaction between drug use and the WHO stage is observed.
- The p-values suggest that most interactions are statistically significant, with values below the conventional threshold of 0.05, indicating that the factors are likely associated with the outcome of interest.

Comparison of Age and Drugs with other factors shown in (Table 3)

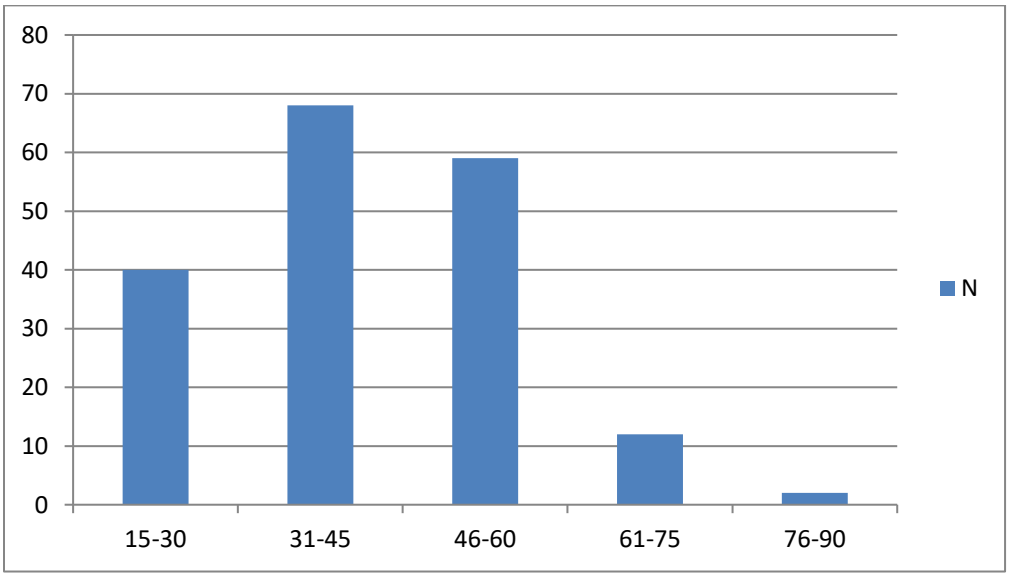
Graph 2 shows Age vs CD4 count after drug consumption, (Table 4) are the list of Drug-Drug Interactions observed in our study population

Table 1: Demographic Details

| Gender | No. of patients |
|---|---|
| Male | 97 |
| Female | 75 |
| Total | 172 |

Table 2: Age of HIV Patients

| Age (in years) | No. of patients | Mean |
|---|---|---|
| 15-30 | 40 | 23.25 % |
| 31-45 | 68 | 39.53 % |
| 46-60 | 50 | 29.06 % |
| 61-75 | 12 | 6.97 % |
| 76-90 | 2 | 1.16 % |
| Total | 172 | 100 % |




Graph 1: Distribution of Patients by Age group

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

Table 3: Comparison of Age and Drugs with other factors

| Factor | p-value |
|---|---|
| Age*Drugs | 0.001 |
| Age*CD4 Count | 0.000 |
| Age*Viral Count | 0.042 |
| Age*Drug Interaction | 0.000 |
| Drugs*CD4 Count | 0.000 |
| Drugs*Viral Count | 0.000 |
| Drugs*Drug Interaction | 0.000 |
| Drugs*Monitoring Parameters | 0.000 |

Graph 2: Age(years) vs CD4 Count(cells/mm3)

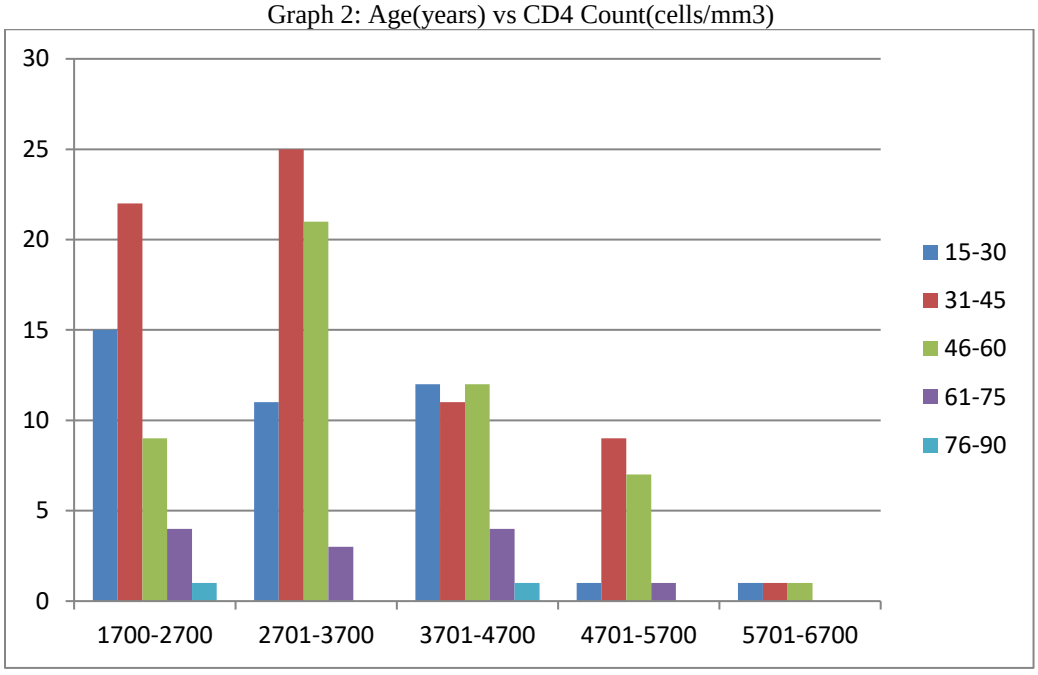



Table 5: Drug – Drug Interaction

| **Co Morbid Diseases** | **Co Morbid Medication** | **ART Drugs** | **Drug Interaction** |
|---|---|---|---|
| Diabetes (left foot necrosis) | Metformin | TLD | Monitor closely - Dolutegravir + Metformin |
| Tuberculosis | Rifampin, Pyrazinamide, Ethambutol | TLD | Serious - Rifampin + Dolutegravir |
| Diabetes and HTN | Teneligliptin, Metformin HCl, Amlodipine | DTG then ALD+DTG | Monitor closely - Dolutegravir + Metformin<br><br>Monitor closely - Abacavir + Lamivudine |

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

| | | | |
|---|---|---|---|
| Diabetes | Metformin | TLD | Monitor closely - Dolutegravir + Metformin |
| Diabetes and HTN | Glimepiride, Metformin, Telmisartan, Hydrochlorothiazide | TLD | Monitor closely - Dolutegravir + Metformin |
| HTN, Diabetes | Metformin | ZLN then TLD | Monitor closely - Dolutegravir + Metformin |
| HTN | Amlodipine | ALD | Monitor closely - abacavir + lamivudine |
| HTN and Diabetes | Telmisartan, Glimepiride, Metformin, | TLD | Monitor closely - Dolutegravir + Metformin |
| Diabetes and HTN | Metformin, Glimepiride, Telmisartan | TLD | Monitor closely - Dolutegravir + Metformin |
| Diabetes | Metformin, Glimepiride | ALD | Monitor closely - Dolutegravir + Metformin<br>Monitor closely - abacavir + lamivudine |
| Pulmonary TB(Category 1) | Rifampin, Pyrazinamide | TLD | Serious - Rifampin + Dolutegravir |
| Tuberculosis and MI | Rifampin, Pyrazinamide, Ethambutol, Atenolol | TLD | Serious - Rifampin + Dolutegravir |
| Diabetes, CAD | Metformin, Glimepiride, | ALE/EFV then TLD | Monitor closely - Dolutegravir + Metformin |
| Diabetes | Metformin | TLD | Monitor closely - Dolutegravir + Metformin |

## IV. DISCUSSION

In this study, out of 16 identified drug-drug interactions (DDIs), three were categorized as red flag interactions. Specifically, the combination of rifampicin and dolutegravir (an HIV integrase inhibitor) was observed three times (1.7%), indicating a potential threat to patient outcomes. In contrast, Schlaeppi C et al. [10] identified red flag interactions between rifampicin and protease inhibitors (lopinavir/ritonavir, atazanavir/ritonavir, or nevirapine). The difference in DDIs involving rifampicin and other HIV drug classes is likely due to the predominant use of the TLD regimen (Tenofovir/Lamivudine/Dolutegravir) at the ART center in MVJ Medical College and Research Hospital, which accounted for 161 cases (93.6%). However, a study by Barcelo C et al. [9] also found a similar potential interaction between rifampicin and dolutegravir, where rifampicin increased the clearance (CL/F) of dolutegravir, thereby reducing its levels and effectiveness.

In our study, 13 interactions were flagged as amber, whereas Schlaeppi C et al. [10] reported 33% of interactions at the patient level and 7% at the prescription level as amber. The difference in the frequency of amber-flagged interactions between the studies may be due to variations in study populations and the shorter duration of our study. Chi-Square study shows strong association between Drug-Drug Interactions, Age- CD4/Viral Count, and Age-Drug Interaction these factors can be taken into consideration to prevent DDI.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

In our study, we identified three adverse drug reactions (ADRs) with a low incidence rate of 0.6%. These ADRs included taste disruption, anemia, and blurred vision, all caused by antidiabetic drugs, which had an incidence rate of 5.2%. In contrast, a study by Jha et al. [11] reported a higher incidence rate of 16.21% for ADRs, with antitubercular drugs accounting for 28.3% of the cases. The higher incidence rate in their study compared to ours may be due to differences in sample sizes and the severity of HIV infection in the study populations. These variations highlight the importance of considering sample size and patient characteristics when comparing ADR incidence rates across different studies.

Our study includes various ART regimens, such as TLD (Tenofovir, Lamivudine, Dolutegravir), ALD (Abacavir, Lamivudine, Dolutegravir), ZLN (Zidovudine, Lamivudine, Nevirapine), ALE/EFV (Abacavir, Lamivudine, Efavirenz), and others. These combinations are the backbone of HIV treatment, but they can have significant interactions with medications used to manage comorbid conditions. The study also covers a range of comorbid conditions commonly seen in HIV patients, such as diabetes, hypertension (HTN), tuberculosis (TB), dyslipidemia, and coronary artery disease (CAD). These conditions often require long-term pharmacotherapy, which can complicate HIV treatment.

Our study highlights the importance of Therapeutic Drug Monitoring (TDM), as TDM can be a valuable tool to ensure that drug levels remain within therapeutic ranges, particularly when managing complex drug regimens involving ART and medications for comorbid conditions. Similarly, a study conducted by Cattaneo et al [12 ] showed the importance of TDM for instance TDM helps clinicians monitor drug levels in individual patients, ensuring that therapeutic concentrations are maintained. TDM also allows personalized adjustments to drug doses based on individual patient characteristics (e.g., age, weight, renal function). TDM-guided ART leads to shorter hospital stays and reduced healthcare costs and lastly TDM helps prevent both subtherapeutic and supratherapeutic drug levels.

It is crucial to educate patients about potential drug interactions, the importance of adherence, and the need to report any new symptoms or side effects promptly. This is especially important in managing chronic comorbid conditions alongside HIV.

Our study also highlights the importance of A collaborative approach involving infectious disease specialists, pharmacists, and primary care providers to optimize the treatment of HIV patients with comorbidities. This collaboration can help in developing personalized treatment plans that minimize the risk of drug interactions. Similarly, a systematic review done by Ahmed et al[8] showed that Clinical pharmacists with specialized training in antiretroviral (ARV) stewardship play a pivotal role in managing these issues.

## V. CONCLUSION

As per our study we came to conclude that Therapeutic Drug Monitoring (TDM) and the involvement of clinical pharmacists can address these issues. TDM optimizes drug dosages to avoid interactions and adverse effects, ensuring safer and more effective treatment. Clinical pharmacists play a crucial role in identifying potential DDIs and ADRs, providing tailored interventions, and educating patients and healthcare providers. Their expertise is essential in improving health outcomes for PLWHA by ensuring the safe and effective use of medications, thereby overcoming the limitations we faced in our study.

## LIMITATION

Our study at MVJ Hospital and Research Centre encountered several limitations while researching drug-drug interactions (DDIs) and adverse drug reactions (ADRs) in people living with HIV/AIDS (PLWHA) with other comorbidities. We faced challenges due to limited access to comprehensive medication records and advanced laboratory facilities, which hindered the accurate tracking and monitoring of DDIs and ADRs. Additionally, the presence of multiple comorbidities and a diverse patient population introduced variability and the lack of standardized protocols led to inconsistent practices. Resource constraints and restricted access to alternative medications further complicate effective management.

## ACKNOWLEDGMENT

The authors would like to acknowledge the physicians and the staff of ART center MVJ. The authors would like to thank Dr. P.G Kumar Sir, Department Of ART Centre, and also Dr. Beulah Milton, Department Of Pharmacy Practice for their valuable support throughout the study.

Conflict Of Interest – The authors have no Conflict Of Interest.

Funding – NIL

## REFERENCES

[1]. Solomon S, Solomon SS, Ganesh AK. AIDS in India. Postgrad Med J. 2006.
[2]. NACO. National Guidelines for HIV Care and Treatment 2021.
[3]. So-Armah K, Benjamin LA, Bloomfield GS, Feinstein MJ, Hsue P, Njuguna B, Freiberg MS. HIV and cardiovascular disease. Lancet. 2020.
[4]. Rukmangathen R,Brahmanapalli VD, Thammisetty DP, Pemmasani D, Gali SD, Atmakuru RB. Study of adverse drug reactions to antiretroviral therapy in a tertiary care hospital, Tirupati. PerspectClin Res. 2020.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV966

[5]. Bandyopadhyay A, Chaurasia RC, Palepu S, Yadav RK. A study of adherence to antiretroviral therapy in a tertiary care hospital at Allahabad, India. Indian J Sex Transm Dis AIDS. 2019.
[6]. Palleria C, Di Paolo A, Giofrè C, Caglioti C, Leuzzi G, Siniscalchi A, De Sarro G, Gallelli L. Pharmacokinetic drug-drug interaction and their implication in clinical management. J Res Med Sci. 2013.
[7]. Sherfa A, Haile D, Yihune M, Sako S. Incidence and predictors of Adverse Drug Reaction (ADR) among adult HIV positive patients on anti-retroviral treatment in Arba Minch town public health facilities, southern Ethiopia: A retrospective cohort study, 2020. PLoS One. 2021.
[8]. Anbessa O,Hawulte B, Dingeta T, Birhanu A. Incidence and predictors of severe adverse drug reactions among patients on antiretroviral drugs in Harari Regional State, Eastern Ethiopia. Can J Infect Dis. 2024.
[9]. Ruellan AL,Bourneau-Martin D, Joyau C, Secher S, Fialaire P, Hitoto H, Leautez S, Michau C, Vatan R, Billaud E, Briet M. Assessment of drug–drug interaction in an elderly human immunodeficiency virus population: Comparison of 3 expert databases. Br J Pharmacol. 2020.
[10]. Ahmed A,Tanveer M, Dujaili JA, Chuah LH, Hashmi FK, Awaisu A. Pharmacist-Involved Antiretroviral Stewardship Programs in People Living with HIV/AIDS: A Systematic Review. AIDS Patient Care STDs. 2023; PMID: 36626156.
[11]. Barcelo C,Aouri M, Courlet P, Guidi M, Braun DL, Günthard HF, Piso RJ, Cavassini M, Buclin T, Decosterd LA, Csajka C. Population pharmacokinetics of dolutegravir: influence of drug-drug interactions in a real-life setting. J AntimicrobChemother. 2019 Sep.
[12]. Schlaeppi C,Vanobberghen F, Sikalengo G, Glass TR, Ndege RC, Foe G, Kuemmerle A, Paris DH, Battegay M, Marzolini C, Weisser M. Prevalence and management of drug–drug interactions with antiretroviral treatment in 2069 people living with HIV in rural Tanzania: a prospective cohort study. HIV Med. 2020 Jan;21(1):53-63
[13]. Jha AK,Gadgade A, Shenoy AK, Chowta MN, Ramapuram JT. Evaluation of adverse drug reactions in HIV positive patients in a tertiary care hospital. PerspectClin Res. 2015 Jan-Mar;6.
[14]. Cattaneo D, Baldelli S, Cozzi V, Clementi E, Marriott DJE, Gervasoni C. Impact of Therapeutic Drug Monitoring of Antiretroviral Drugs in Routine Clinical Management of People Living With HIV: A Narrative Review. Ther Drug Monit. 2020 Feb;42(1):64-74.
[15]. López-Centeno B,Badenes-Olmedo C, Mataix-Sanjuan Á, McAllister K, Bellón JM, Gibbons S, Balsalobre P, Pérez-Latorre L, Benedí J, Marzolini C, Aranguren-Oyarzábal A, Khoo S, Calvo-Alcántara MJ, Berenguer J. Polypharmacy and Drug–Drug Interactions in People Living With Human Immunodeficiency Virus in the Region of Madrid, Spain: A Population-Based Study. Clin Infect Dis. 2020;71(2):15 July.
[16]. Xia H, Gao L, Gong X, Zaongo SD, Zhang T, Wu H, Ma P, Huang X. The Challenge of Potential Drug–Drug Interactions Among People Living With HIV on Antiretroviral Therapy: A Cross-Sectional Study in Selected Provinces in China. Front Pharmacol. 2020.
[17]. de Oliveira Costa J, Lau S, Medland N, Gibbons S, Schaffer AL, Pearson SA. Potential drug–drug interactions due to concomitant medicine use among people living with HIV on antiretroviral therapy in Australia. Br J ClinPharmacol. 2023 May;89(5):1541-53.
[18]. Peng A-T, Huang S-H, Lee H-Y, Wu P-Y, Kuo H-Y, Hung C-C. Polypharmacy and potential drug–drug interactions among people living with HIV in the era of integrase strand transfer inhibitor-based antiretroviral therapy. Int J Antimicrob Agents. 2024;63(2).
[19]. Back D, Marzolini C. HIV treatment in an era of polypharmacy. J Int AIDS Soc. 2020.
[20]. More SA, Atal S, Mishra PS. Inter-rater agreement between WHO-Uppsala Monitoring Centre system and Naranjo algorithm for causality assessment of adverse drug reactions. J PharmacolToxicol Methods. 2024.
[21]. McHugh ML. The Chi-square test of independence. Biochem Med (Zagreb). 2013.