

ORIGINAL ARTICLE

Analysis of Adverse Drug Reaction Probability Based on The Clinical Stage of Patients with HIV Receiving Antiretroviral Therapy

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ABSTRACT

Patients with a more advanced stage of human immunodeficiency virus (HIV) infection are more prone to experience more complications. Meanwhile, long-term treatment of HIV with antiretrovirals (ARVs) may potentially cause adverse drug reactions (ADRs). This study aims to analyze the relationship between HIV clinical stages and the level of ADR probability based on the Naranjo scale. This study was designed as an observational, analytic cross-sectional study. Data were collected based on medical records of adult patients with HIV/AIDS under treatment with ARVs at a regional hospital in Denpasar during 2022-2024. The results showed that among the included HIV/AIDS patients (N = 69), the majority were male, aged 25-49 years (50-72%), with HIV clinical stage 3 (50.72%). The most common ADRs include itching, fever, nausea, and diarrhea (8-20%). ADR of diarrhea was found to be significantly different ($p = 0.007$) among HIV clinical stages. A statistically significant but weak correlation was observed between clinical stage and ADR probability ($\tau = 0.179$; $p = 0.039$). Future prospective longitudinal studies are needed to clarify this relationship over time and strengthen pharmacovigilance in HIV patient care.

Keywords: HIV/AIDS; ADRs; clinical stage; ARVs; Naranjo scale

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Introduction

Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) continue to represent a significant health threat to the global community, including Indonesia. According to data from the United Nations Program on HIV and AIDS (UNAIDS) in 2023, almost 40 million people were living with HIV in the world [1]. In Indonesia, from January to December 2023, 17,121 new AIDS cases were recorded nationwide. The highest number of cases was found in West Java, East Java, Central Java, Bali, and Jakarta [2-4]. Bali Province ranked fourth with 1,680 new cases, with Denpasar City reporting the highest number (898 cases) [5].

Antiretroviral (ARV) therapy is the mainstay of HIV treatment, but is frequently complicated by adverse drug reactions (ADRs). Studies from Africa and India report high rates of ARV-related ADRs, ranging from 28.6% to 78%, with concerns including hepatotoxicity, nephrotoxicity, and higher incidence in dolutegravir-based regimens [6,7]. Beyond regimen differences, the patient's HIV clinical stage plays a critical role in ADR susceptibility. Advanced clinical stages are characterized by severe immunosuppression, systemic inflammation, and multi-organ involvement, particularly liver and kidney function. Impairment in these systems can alter ARV pharmacokinetics, while immune dysregulation in later stages may heighten hypersensitivity responses [8-10]. Consequently, patients with more advanced HIV disease are more likely to experience ADRs.

Access This Article



Previous studies have examined ADRs in HIV/AIDS patients, generally using descriptive approaches. A survey by Wulandari et al, 2023 [11] employed a descriptive analysis of retrospective medical records of HIV patients undergoing ARV therapy at Undata Regional Hospital, Palu. The results showed that 255 ADRs occurred in 126 patients, with dizziness and insomnia being the most common symptoms. Furthermore, a cross-sectional study by Putra in 2021 [12] used the Naranjo scale as a tool to assess the causality of ADRs. The previous study showed that most ADRs were categorized as "probable" (86%), but the relationship between the Naranjo score and clinical conditions such as HIV clinical stage was not analyzed. Similarly, the latest observational study applying Naranjo assessment in Uganda [13] also reported that over 70% of patients on highly active antiretroviral therapy (HAART) experienced ADRs. However, the study noted that HAART was mostly initiated at clinical stage 1 of HIV, without associating this to the probability of ADRs.

Based on the explanation above, while previous studies have explored ADRs in HIV/AIDS patients undergoing ARV therapy, they have not analytically linked the causality of ADRs to HIV clinical stage according to the Naranjo scale. This relationship remains underexplored, particularly in Denpasar. Therefore, this study is crucial in bridging this gap, as it will provide evidence to support pharmacovigilance policies and strengthen the role of clinical pharmacists and physicians in objectively assessing ADR risk based on the patient's clinical condition. The results of this study are expected to contribute to improving therapeutic safety, enhancing patient adherence, and increasing the long-term effectiveness of ARV therapy. This study aimed to analyze the relationship between HIV clinical stage and the probability of ADR according to the Naranjo scale in HIV/AIDS patients undergoing ARV therapy.

METHODS

Research Type and Design

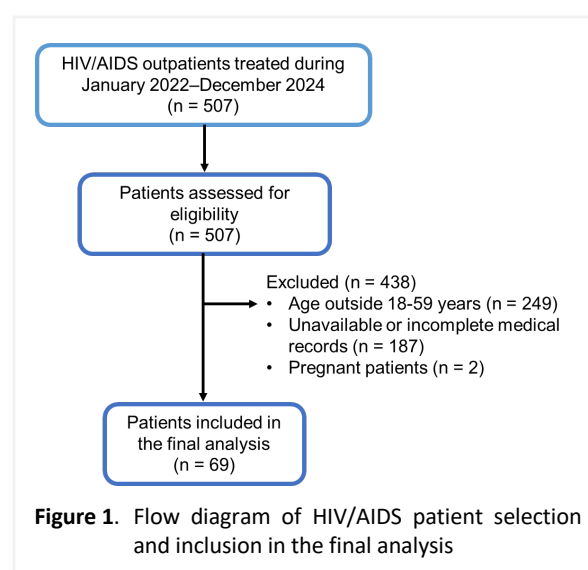
The research permit has been granted by Wangaya Regional General Hospital, Denpasar (Number.

000.9.2/1228/RSUDW). Furthermore, this study has also received ethical approval from the Health Research Ethics Committee of Wangaya Regional General Hospital, Denpasar (Number. 000.9.2/4423/RSUDW). All the mentioned administrative requirements had ensured the responsible and ethical conduct of this study.

This study employed an analytical observational design to investigate the relationship between the independent variable (clinical stage of HIV) and the dependent variable (ADRs probability rate). A retrospective analytical cross-sectional study approach was used for ADRs causality assessment. Data was collected from patient medical records. Causality assessment referred to the Naranjo algorithm [14,15].

Population and Research Sample

The study population comprised all HIV/AIDS outpatients treated at the hospital from 2022-2024. A total sampling method was applied, in which all patients who met the predefined eligibility criteria were included. The inclusion criteria were patients diagnosed with HIV/AIDS, aged 18–59 years according to the hospital's adult age classification recorded in the medical records, receiving ARV therapy, and having medical records containing sufficient clinical information to support ADR causality assessment using the Naranjo Algorithm. Patients who were pregnant, breastfeeding, or deceased were excluded. During the study period, 507 HIV/AIDS outpatients were screened for eligibility. After applying the inclusion and exclusion



criteria, 69 patients were included in the final analysis. The participant selection process, including the number of screened patients, excluded patients with reasons for exclusion, and the final sample included in the analysis, is presented in **Figure 1**.

Data Collection

Data were collected at Wangaya Regional Hospital, Denpasar, from June through August 2025. This hospital recorded a higher number of new HIV/AIDS cases compared with the average count of new cases in Denpasar, the city with the highest number of new HIV cases in Bali in 2024 [16]. The data collection instrument for this study consisted of a data collection sheet containing the censored medical record number, age, gender, education, occupation, medical diagnosis, medication use, potential ADRs, and a Naranjo analysis form. To minimize information bias, missing data were addressed using complete-case analysis for each ADR recorded during the study period (2022-2024). In addition to medical records, multiple sources, including laboratory data and medication charts, were also collected to triangulate the information, following a standardized ADR identification form for data extraction.

The initial causality assessment and scoring were performed by a trained research assistant using clinical information extracted from patients' medical records. All assessments were subsequently reviewed and verified by the principal investigator, a licensed clinical pharmacist with training and experience in clinical pharmacy and medication safety. Any discrepancies identified during the review process were resolved through discussion between the research assistant and the principal investigator, with the principal investigator making the final causality classification. The final causality category was assigned according to the total Naranjo scores (≥ 9 classified as definite, 5–8 as probable, 1–4 as possible, and ≤ 0 as doubtful).

Data Analysis

Patients' baseline characteristics data and clinical profile were presented in proportion (%) or average $\pm$ SD (unit). Clinical stage of HIV in this study was classified as stage 1, 2, 3, and 4 [8]. ADRs causality was assessed using the Naranjo Scale, relying on patients' medical

records, supplemented by relevant literature. While the Naranjo Scale is valid for systematically evaluating ADRs in documented clinical histories, some questions (e.g., drug rechallenging and placebo comparison) were not feasible in this retrospective study [17,18]. Despite using triangulation to address incomplete documentation, these limitations, along with the availability of hospital services should be acknowledged.

ADRs were initially identified and analyzed at the event level. Multiple ADRs may occur in a single patient, and each suspected ADR was assessed independently for causality. When multiple drugs were suspected, causality assessment was performed separately for each agent where applicable. For fixed-dose combination (FDC) regimens, all components were considered potential contributors, as individual drug effects could not be reliably distinguished. Points acquired from the Naranjo assessment were categorized into doubtful, possible, probable, and definite [14].

For inferential analysis, the unit of analysis was the identified ADR event. Each ADR event was assessed using the Naranjo Algorithm and assigned an original numerical Naranjo score. The Kruskal–Wallis test was used to compare the distribution of Naranjo scores across independent groups, including ARV regimen (categorical variable) and HIV clinical stage (ordinal variable). The relationship between HIV clinical stage and ADR causality level was analyzed using Kendall's tau-c test in SPSS, as both variables were considered ordinal. The categorized ADR probability classifications (doubtful, possible, probable, and definite) were presented in the tables for descriptive purposes only, to facilitate interpretation of the distribution of ADR causality categories across treatment regimens and clinical stages. All statistical tests were conducted with a 95% level of confidence.

RESULT AND DISCUSSION

Patient Demographic Characteristics

There were 69 patients identified who met the inclusion criteria. The patients' profile in **Table 1** shows that individuals of productive age (25–49 years) are more likely to be infected with HIV/AIDS due to several

Table 1. Demographic characteristics of HIV/AIDS patients

Information	Amount (N=69)	Percentage (%)
Age (years)		
18-24	5	7.25%
25-49	50	72.46%
50-59	14	20.29%
Gender		
Male	37	53.62%
Female	32	46.38%
Education		
Junior high school	2	2.90%
Senior high school	64	92.75%
Diploma	1	1.45%
Bachelor	2	2.90%
Employment status		
Employed	54	78.26%
Unemployed	15	21.74%

factors. This group tends to have higher levels of sexual activity, including risky behaviors such as multiple partners or not using protection. Furthermore, a lack of awareness of routine health checks and social stigma, which discourages them from seeking information or early treatment, might also play a role. Other factors, such as injecting drug use and high mobility, also increase exposure to the virus [19].

The results of the gender characteristics in this study indicate that the majority of patients were male, at 53.62%. Based on the HIV/AIDS information system (SIHA) data, the percentage of HIV cases found in men was 71% [4]. The high number of cases in men is associated with high male involvement in risky sexual behaviors, such as multiple partners and injecting drug use. In addition, men are also more frequently found in risk groups, such as men who have sex with men (MSM). A survey conducted in Bali in 2024 of 165 MSM showed that 23% of them had had unprotected sex, and also identified violence in partner relationships that contributed to risky sexual behavior [20].

Patient Clinical Characteristics

HIV clinical staging was determined based on documentation in medical records, following the World Health Organization (WHO) clinical staging criteria as recorded by treating physicians. The highest proportion

Table 2. Clinical characteristics of HIV/AIDS patients

Aspects (N=69)	n (%) or average±SD (units)
Clinical Stage	
Stage 1	13 (18.84%)
Stage 2	11 (15.94%)
Stage 3	35 (50.72%)
Stage 4	10 (14.49%)
Vital Signs Examination	
Body Weight	55.39±12.18 kg
Systolic Blood Pressure	115.85±20.33 mmHg
Diastolic Blood Pressure	74.13±14.18 mmHg
Heart Rate	96.66±20.69 bpm
Respiratory Rate	17.76±3.77 x/minute
Opportunistic Infections	
Pulmonary Tuberculosis	9 (13.04%)
Oral Candidiasis	5 (7.25%)
Pneumonia	2 (2.90%)
Cerebral Toxoplasmosis	2 (2.90%)
Severe/Chronic Scabies	1 (1.45%)
Anemia	3 (4.35%)
Upper Respiratory Tract Infection	6 (8.70%)
Other Comorbidities	
Asthma	1 (1.45%)
Hypertension	2 (2.90%)
Dyspepsia	5 (7.25%)
Latent Syphilis	2 (2.90%)
Dermatitis	5 (7.25 %)
Hypokalemia	1 (1.45%)
Edema	2 (2.90%)
Tinea cruris	1 (1.45%)
Prurigo	9 (13.04%)
Headache	4 (5.80%)
Hematozemia	1 (1.45%)
Typical HIV Symptoms	
Fever	7 (10.14%)
Muscle Pain	2 (2.90%)

in stage 3 (**table 2**) indicates that most patients presented to health facilities with clear clinical symptoms, such as weight loss of ≥10% body weight or opportunistic infections [10]. Based on vital signs, the average patient weight was 55.39±12.18 kg, which was close to the lower limit of the normal range. Weight loss in HIV/AIDS patients is often a manifestation of wasting syndrome, namely, unintentional weight loss of ≥10%, which is

associated with a weakened immune system ($CD_4 < 200$ cells/ μ L) [21].

HIV/AIDS Patient Treatment Profile

Based on the data in Table 3, the fixed-dose combination (FDC) of TLD (tenofovir 300 mg, lamivudine 300 mg, dolutegravir 50 mg) regimen is the most dominant, administered by approximately 55.07%, meaning more than half of the patient population received this combination. This is because TLD is considered first-line therapy for HIV due to its high efficacy, good tolerability, and low risk of resistance [22]. In addition to TLD, 31.88% of patients used the TLE (tenofovir 300 mg, lamivudine 300 mg, efavirenz 600 mg) regimen, making it the second most common choice. Previously, efavirenz was widely used as first-line therapy before being replaced by dolutegravir due to neuropsychiatric adverse events such as dizziness and sleep disturbances. The continued use of TLE in some patients may be due to patients being stable on this regimen before the recommendation change. Meanwhile, approximately 7.25% received the TLD + dolutegravir (DTG) combination, indicating therapy adjustments in certain cases, such as failure of the previous regimen. The addition of DTG can increase the potential for viral suppression, especially in patients at risk of resistance [9].

Based on the findings, a pattern of ARV therapy regimen switching from TLE to TLD was observed in all recorded cases. This shift from TLE to TLD aligns with the latest WHO recommendation that DTG-based regimens are accounted as the first-line therapy for HIV treatment [9]. This shift is clinically justified by the superior efficacy of DTG, characterized by faster and

more potent viral suppression compared to efavirenz (EFV), along with a higher genetic barrier to resistance [23].

Other Drug Treatments

The use of additional medications besides ARVs varies considerably, reflecting the complex clinical conditions of HIV/AIDS patients due to opportunistic infections, comorbidities, and HIV symptoms. The most frequently used non-ARV medications are systemic corticosteroids, as seen in Table 4. These medications are often prescribed to treat severe inflammation, excessive immune reactions, or conditions such as dermatitis and cerebral toxoplasmosis. Furthermore, proton pump inhibitors (12.39%) are also among the most frequently prescribed medicines. These medications are used to treat gastrointestinal complaints, particularly those caused by gastric mucosal stress, drug effects, or comorbidities such as dyspepsia. Second-generation H1 antihistamines (11.97%) are also widely used, given that typical HIV symptoms such as prurigo and allergic skin reactions are quite common in patients with low immune status. The use of these antihistamines is also appropriate for the management of chronic pruritus, which often occurs due to immune system activation or skin infections in HIV/AIDS patients [9,24]. The observed polypharmacy in this study should be considered as a known risk factor for ADRs due to increased potential for drug–drug interactions and overlapping toxicities [25]. As such, it may confound the observed association between HIV clinical stage and ADR occurrence, potentially influencing the interpretation of causality.

Table 3. ARV Treatment Profile

Drug name and dose (N=69) (N=69)	Frequency	n (%)
FDC duviral (AZT 300mg + 3TC 150 mg) + NVP 200 mg	s.b.d.d	4 (5.80%)
FDC TLD (TDF 300 mg, 3TC 300 mg, DTG 50 mg)	s.d.d	38 (55.07%)
FDC TLD (TDF 300 mg, 3TC 300 mg, DTG 50 mg) + DTG 50 mg	s.d.d	5 (7.25%)
FDC TLE (TDF 300 mg, 3TC 300 mg, EFV 600 mg)	s.d.d	22 (31.88%)
ARV Treatment Profile Replacement		
FDC TLE (TDF 300 mg, 3TC 300 mg, EFV 600 mg) becomes FDC TLD (TDF 300 mg, 3TC 300 mg, DTG 50 mg)		3 (4.35%)

Description: N: total number of patients, n: number of patients, %: percentage of number of patients, AZT: zidovudine, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir, DTG: dolutegravir, EFV: efavirenz, ARV: antiretroviral, s.b.d.d: twice daily, s.d.d: once daily

Table 4. Other Drug Uses

Drug class	Route	Amount	Percentage
Systemic Corticosteroids	Po	38	16.24%
Proton Pump Inhibitors	Po	29	12.39%
Second-Generation H1 Antihistamines	Po	28	11.97%
Non-NSAID Analgesics & Antipyretics	Po	22	9.40%
Vitamins and Supplements	Po	21	8.97%
Third-Generation Cephalosporins	Po	13	5.56%
Topical Corticosteroids	u.e	13	5.56%
Antifungals	Po	11	4.70%
Mucolytics	Po	11	4.70%
Anti-Tuberculosis Drugs	Po	10	4.27%
NSAIDs	Po	9	3.85%
Antacids	Po	6	2.56%
Lincosamides	Po	5	2.14%
Sulfonamides (combination)	Po	4	1.71%
Antihypertensives	Po	4	1.71%
Antiemetics	Po	3	1.28%
Tetracyclines	Po	1	0.43%
Nitroimidazoles	Po	1	0.43%
Penicillins	Po	1	0.43%
Fluoroquinolones	Po	1	0.43%
Macrolides	Po	1	0.43%
Antiscabies	Po	1	0.43%
H2 Blockers	Po	1	0.43%

Description: Po: per oral, u.e: usus externus, NSAID: nonsteroidal anti-inflammatory drugs

ADR Analysis Based on Clinical Stages

Based on the data presented in **Table 5**, various types of ADRs experienced by HIV/AIDS patients can be observed. Of the total recorded ADRs, itching was the most frequently reported ADR at 20.28%, indicating that dermatological symptoms are a major problem associated with ARV treatment. Itching as an ADR of ARV treatment generally occurs due to a hypersensitivity reaction or immune response to the drug. Some ARV drugs, such as nevirapine and EFV, might develop skin reaction within 6-8 weeks after initiation [26,27]. Gastrointestinal symptoms such as diarrhea (7.69%) and vomiting (5.59%) were also quite common, reflecting the impact of ARVs on the digestive system. Some ARVs, particularly protease inhibitors and

NRTIs, can irritate the intestinal mucosa or inhibit digestive enzymes, thus triggering diarrhea. Meanwhile, vomiting is often caused by stimulation of serotonin receptors in the area postrema of the brain or gastric irritation due to the drug's cytotoxic effects. In addition, rapid ARV metabolism or liver toxicity can also worsen these symptoms by increasing the accumulation of compounds that stimulate nausea and impaired intestinal motility [28].

In terms of the number of ADR events identified using the Naranjo scale, the most common type of drug reaction was itching, with a total of 29 probable cases, primarily in patients using the FDC TLD regimen (17 cases) and FDC TLE (7 cases). This was followed by fever with 24 probable cases, and nausea with 12 probable and possible cases. Furthermore, symptoms of vomiting,

Table 5. Overview of the number of ADR incidents with ARV drug users

Types of ADR n (%)	ARV regimens	Naranjo Category				p-value (Kruskal- Wallis) ^a
		Definite ≥9	Probable 5-8	Possible 1-4	Doubtful 0	
Diarrhea 11 (7.69%)	FDC TLE	0	0	4	0	0.450
	FDC TLD	0	1	6	0	
	FDC TLD+DTG	0	0	0	0	
	FDC duviral	0	0	0	0	
Tingling 7 (4.90%)	FDC TLE	0	0	1	0	0.475
	FDC TLD	0	1	2	0	
	FDC TLD+DTG	0	0	1	0	
	FDC duviral	0	0	2	0	
Nausea 23 (16.08%)	FDC TLE	0	1	5	0	0.170
	FDC TLD	0	3	7	0	
	FDC TLD+DTG	0	1	3	0	
	FDC duviral	0	1	0	0	
Vomiting 8 (5.59%)	FDC TLE	0	0	2	0	0.155
	FDC TLD	0	2	3	0	
	FDC TLD+DTG	0	0	0	0	
	FDC duviral	0	1	0	0	
Insomnia 5 (3.50%)	FDC TLE	0	0	1	0	0.717
	FDC TLD	0	1	2	0	
	FDC TLD+DTG	0	0	1	0	
	FDC duviral	0	0	0	0	
Weakness 11 (7.69%)	FDC TLE	0	0	4	0	0.659
	FDC TLD	0	1	5	0	
	FDC TLD+DTG	0	0	1	0	
	FDC duviral	0	0	0	0	
Fever 24 (16.78%)	FDC TLE	0	7	0	0	0.701
	FDC TLD	0	14	0	0	
	FDC TLD+DTG	0	1	0	0	
	FDC duviral	0	2	0	0	
Itching 29 (20.28%)	FDC TLE	0	7	0	0	0.545
	FDC TLD	0	17	0	0	
	FDC TLD+DTG	0	3	0	0	
	FDC duviral	0	2	0	0	
Dizziness 7 (4.90%)	FDC TLE	0	0	3	0	1.000
	FDC TLD	0	0	3	0	
	FDC TLD+DTG	0	0	0	0	
	FDC duviral	0	0	1	0	
Rash 9 (6.29%)	FDC TLE	0	2	0	0	0.779
	FDC TLD	0	6	0	0	
	FDC TLD+DTG	0	1	0	0	
	FDC duviral	0	0	0	0	
Headache 9 (6.29%)	FDC TLE	0	0	5	0	1.000
	FDC TLD	0	0	3	0	
	FDC TLD+DTG	0	0	0	0	
	FDC duviral	0	0	1	0	

Description: FDC TLE (TDF 300 mg, 3TC 300 mg, EFV 600 mg), FDC TLD (TDF 300 mg, 3TC 300 mg, DTG 50 mg), FDC duviral: (AZT 300mg + 3TC 150 mg) + NVP 200 mg, AZT: zidovudine, 3TC: lamivudine, NVP: nevirapine, TDF: tenofovir, DTG: dolutegravir, EFV: efavirenz, NA = not applicable due to insufficient observations in one or more groups.

^aP-values were calculated using the original numerical Naranjo scores. The Naranjo probability categories are presented for descriptive purposes only.

dizziness, headache, tingling, and weakness also occurred, but with lower frequency. Symptoms such as itching and skin rashes are allergic manifestations often

associated with the use of efavirenz or nevirapine, early-generation ARVs. However, in this study, itching was also frequently found in patients using DTG,

particularly in the TLD combination. This is consistent with the literature stating that although DTG is generally safe, it can still cause ADRs such as mild skin and gastrointestinal disorders [29].

The FDC TLD regimen is the combination most frequently associated with ADRs, especially in the probable category. This is likely because FDC TLD is currently the first-line regimen recommended by the WHO and is widely used in healthcare [30]. Therefore, its high prevalence also increases the likelihood of ADRs. The Kruskal–Wallis test results showed that all *p*-values were > 0.05 , for example, diarrhea ($p = 0.450$), nausea ($p = 0.170$), vomiting ($p = 0.155$), tingling ($p = 0.475$), insomnia ($p = 0.717$), and weakness ($p = 0.659$). This means that there is no significant difference between the type of ARV regimen and the level of ADR causality. In other words, ADRs can occur in all regimens without statistically significant differences.

The analysis results in **Table 6** show that ADRs were found in all clinical stages of HIV, with a more dominant distribution in stages 3 and 4. Itching was the ADR most frequently associated with ARV therapy, probabilistically, with 29 cases spread across all clinical stages, especially stage 3 (15 cases). The mechanism of itching in patients on ARVs may also be influenced by drug interactions and the patient's immunological status, which is more complex in advanced clinical stages, such as stage 3. This suggests that dermatological reactions are a consistent ADR regardless of HIV severity, but are more frequent in patients with advanced infection [31]. Fever also showed a similar pattern with 24 probable cases, mostly in stage 3 (15 cases), indicating that this systemic reaction may be related to the immune response to ARVs or opportunistic infections that are more common in advanced stages [8,31].

On the other hand, diarrhea and nausea were more frequently categorized as possible, with diarrhea occurring most frequently in stage 3 (7 cases) and nausea occurring in stage 1 (5 cases) and stage 3 (8 cases). This finding suggests that gastrointestinal symptoms may be more influenced by factors other than ARVs, such as opportunistic infections or the patient's gastric condition. Tingling and weakness were mostly possible in stage 3 (5 and 6 cases, respectively). Skin rashes were

categorized as probable across all stages, especially stage 4 (4 cases), which may reflect a hypersensitivity reaction to ARVs and warrants caution due to the potential for progression to severe reactions such as Stevens-Johnson Syndrome [32]. Meanwhile, headaches and insomnia were mostly categorized as possible, indicating a weaker association with ARVs and may be influenced by other factors such as stress or underlying neurological conditions [33,34].

The Kruskal–Wallis test signified that the ADR for diarrhea had a *p*-value of 0.007, indicating a meaningful difference in the distribution of ADR causality levels across HIV clinical stages (Table 6). Most cases of diarrhea were found in stage 3, indicating that patients with advanced stages are more susceptible to diarrhea-related ADRs. Meanwhile, other ADRs, including nausea, vomiting, insomnia, and weakness ($p > 0.05$), showed no statistically significant differences across HIV clinical stages. Nevertheless, the descriptive findings provide additional insight into the distribution and patterns of ADR events across clinical stage groups.

Of the 143 cases observed in **Table 7**, there is a trend of increasing ADR incidence across advancing HIV stages. Stage 1 included 23 ADR cases (16 possible, 7 probable), followed by stage 2 with 13 cases (5 possible, 8 probable), stage 3 with 74 cases (35 possible, 39 probable), and stage 4 with 33 cases (12 possible, 21 probable). The Kendall's tau-c test demonstrated a weak but statistically significant positive association between HIV stage and ADR causality ($\tau = 0.179$; $p = 0.039$). While this suggests a tendency for higher HIV stages to be associated with increased ADR causality, the small effect size indicates that the strength of this relationship is limited. Therefore, the clinical relevance of this association should be interpreted with caution, as other factors may play a more substantial role in the occurrence of ADRs.

These findings are supported by a meta-analysis by Zewdu et al. (2025), which reported that individuals in advanced stages of HIV were more likely to experience ART-related adverse drug reactions, with an adjusted hazard ratio (AHR) of 3.571 (95% CI: 2.351–4.791; $I^2 = 74.37\%$) [31]. In addition, another earlier meta-analyses have demonstrated a similar trend, with patients in clinical stages II and IV showing

Table 6. Overview of the number of ADR events by clinical stage

Types of ADR n (%)	Clinical stage	Naranjo Category				p-value (Kruskal- Wallis) ^a
		Definite ≥9	Probable 5-8	Possible 1-4	Doubtful 0	
Diarrhea 11 (7.69%)	Stage 1	0	0	3	0	0.007
	Stage 2	0	0	0	0	
	Stage 3	0	0	7	0	
	Stage 4	0	1	0	0	
Tingling 7 (4.90%)	Stage 1	0	1	0	0	0.050
	Stage 2	0	0	1	0	
	Stage 3	0	0	5	0	
	Stage 4	0	0	0	0	
Nausea 23 (16.08%)	Stage 1	0	0	5	0	0.251
	Stage 2	0	0	0	0	
	Stage 3	0	5	8	0	
	Stage 4	0	1	4	0	
Vomiting 8 (5.59%)	Stage 1	0	0	2	0	0.497
	Stage 2	0	0	0	0	
	Stage 3	0	2	2	0	
	Stage 4	0	1	1	0	
Insomnia 5 (3.50%)	Stage 1	0	0	1	0	0.472
	Stage 2	0	0	0	0	
	Stage 3	0	0	2	0	
	Stage 4	0	1	1	0	
Weakness 11 (7.69%)	Stage 1	0	0	0	0	0.417
	Stage 2	0	0	1	0	
	Stage 3	0	0	6	0	
	Stage 4	0	1	3	0	
Fever 24 (16.78%)	Stage 1	0	2	0	0	1.000
	Stage 2	0	1	0	0	
	Stage 3	0	15	0	0	
	Stage 4	0	6	0	0	
Itching 29 (20.28%)	Stage 1	0	3	0	0	1.000
	Stage 2	0	5	0	0	
	Stage 3	0	15	0	0	
	Stage 4	0	6	0	0	
Dizziness 7 (4.90%)	Stage 1	0	0	2	0	1.000
	Stage 2	0	0	2	0	
	Stage 3	0	0	3	0	
	Stage 4	0	0	0	0	
Rash 9 (6.29%)	Stage 1	0	1	0	0	1.000
	Stage 2	0	2	0	0	
	Stage 3	0	2	0	0	
	Stage 4	0	4	0	0	
Headache 9 (6.29%)	Stage 1	0	0	3	0	1.000
	Stage 2	0	0	1	0	
	Stage 3	0	0	2	0	
	Stage 4	0	0	3	0	

^aP-values were calculated using the original numerical Naranjo scores. The Naranjo probability categories are presented for descriptive purposes only

Table 7. Relationship between HIV clinical stage and ADR causality level

Clinical stage	Naranjo Category				p-value (Kendall's tau-c)	τ
	Definite ≥ 9	Probable 5-8	Possible 1-4	Doubtful 0		
1	0	7	16	0	0.039	0.179
2	0	8	5	0		
3	0	39	35	0		
4	0	21	12	0		

approximately 3.7-fold and 6.3-fold higher risks of ADRs, respectively [10]. These studies suggest that patients in advanced stages of HIV may benefit from closer monitoring due to their increased vulnerability to clinical complications, including ADRs. This increased susceptibility to ADRs may be explained by factors such as immunosuppression and greater treatment complexity in advanced disease. Despite this, the overall relationship is likely multifactorial. Other factors, such as initial antiretroviral regimen, body composition, sex, comorbidities, CD₄ count, and treatment adherence, may also contribute to the occurrence of ADRs among HIV patients [10,31].

Advanced HIV patients experience more severe immune dysfunction, which increases their susceptibility to opportunistic infections and other clinical conditions requiring additional treatment. This may increase the risk of drug interactions and metabolic burden, which in turn could contribute to a higher likelihood of ADRs. In addition, the observed association between advanced HIV stage and ADR causality may reflect the increased clinical complexity of therapy in these patients. Furthermore, the data showed widespread use of additional medications outside primary ARV therapy, such as corticosteroids, proton pump inhibitors, and antihistamines. This polypharmacy may increase the risk of drug-drug interactions, thereby contributing to ADR occurrence. A study by Poojar et al. (2024) [35] also reported that more complex drug regimens are associated with a higher risk of ADRs in terms of both frequency and severity. Nonetheless, the limitation of the cross-sectional design of this study does not allow for causal inferences between immunosuppression, polypharmacy, and ADR risk.

Among the previous relevant studies about ADRs of ARVs and their attributing factors, this study has augmented a further analytical approach. The relationship between HIV clinical stage and the level of ADR causality based on the Naranjo scale was rarely used simultaneously in similar studies. This provides a clinical picture regarding the potential for ADRs of ARV drugs in the context of varying immunosuppression. Therefore, clinical practitioners taking care of patients with HIV/AIDS taking ARVs in the long term should be more prepared to tackle the challenges of potential ADRs. However, some limitations of this study were unavoidable during ADR causality assessment using the Naranjo scale as this study was conducted retrospectively. Some questions' fulfillment may need a more specialized approach, such as the absence of a placebo evaluation (question 6), the absence of blood drug concentration measurements (question 7), and the absence of an evaluation by increasing or decreasing the drug dose (question 8). Regardless, the above questions were basically more suitable for either an interventional or a prospective study to establish an ethical responsibility. Another possible limitation is that some patients experienced more than one ADR, resulting in pseudoreplication when these were analyzed as separate events. This may affect the independence of the data and could influence the statistical results. Therefore, future studies are recommended to use prospective designs with larger, multicenter populations and patient-level analyses to better establish causal relationships. Key confounders such as CD₄ count, ARV regimen, concomitant drugs and comorbidities, and drug-specific ADR patterns should also be adjusted to improve pharmacovigilance in HIV patients.

CONCLUSION

The findings among 69 HIV/AIDS patients in this study showed that most patients were aged 25-49 years (72.46%), male (53.62%), with HIV clinical stage 3 (50.72%). The dominant types of ADRs included itching, fever, nausea, and diarrhea (8-20%), which were documented across most ARV regimens without significant differences in causality levels. However, differences in HIV clinical stages were observed, where diarrhea varied significantly between stages ($p = 0.007$), with the highest number of cases in stage 3. This study identified a statistically significant association between clinical stage and ADR causality level based on the Naranjo scale ($\tau = 0.179$; $p = 0.039$), indicating that higher

clinical stages were associated with higher ADR probability levels, despite the weak strength of the association.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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