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Prevalence of Adverse Drug Reactions and Associated Factors to Antiretroviral Therapy among HIV Positive Patients at Ndola Teaching Hospital, Zambia

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Abstract

Introduction: Antiretroviral therapy has led to a rapid decrease in HIV related morbidity and mortality. However, most of the existing antiretroviral regimens have been established to cause adverse drug reactions, this problem is especially common in poor countries in which only cheap, and toxic drugs are available. Tenofovir Alafenamide+lamivudine+Dolutegravirs (TAFED) recently introduced in Zambia has little information concerning its associated adverse drug reactions. Hence, there is a need to assess the prevalence of adverse drug reactions due to this antiretroviral regimen. Generally, this study will assess the prevalence of adverse drug reactions and associated factors to antiretroviral therapy at Ndola teaching Hospital, Zambia. Inferences made from this study can be used to come up with better antiretroviral therapy with little or no adverse drug reactions in the future.

Methods: This was a hospital based retrospective cohort study and the target population was identified using a systematic random sampling technique in which the 13th record was obtained. The data was collected from the files of HIV-positive patients to determine the prevalence of adverse drug reactions and associated factors to ART from January 2019 to January 2022. The data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 26.

Results: A total of 356 files were reviewed and the prevalence of adverse drug reactions to antiretroviral therapy between January 2019 and January 2022 was approximately 62.1%. The common ADRS were general symptoms (43.4%), hypersensitivity reactions (27.6%), Peripheral neuropathy (11.8%), insomnia (8.1%), nephrotoxicity (5.9%), and anemia (3.2%). Among ART regimens only TLD (p-value <0.05) and TAFED (p-value<0.05) were associated with ADRS. Additionally, the time frame was also significantly associated with ADRS while age group and gender were not.

Conclusion: The prevalence of ADRS was calculated to be 62.1% and only ART regimens and time frames were significantly associated with ADRS. It was deduced that TAFED can cause adverse drug reactions; the common ones being general symptoms, hypersensitivity reactions, and respectively. Furthermore, those on TAFED had an approximately 2.6-fold increase in developing ADRS, while those on TLD had a 3.0-fold increase in developing ADRS.

Keywords: Antiretroviral Therapy (ART) • Hypersensitivity • Statistical Package for Social Sciences (SPSS) • Insomnia • Peripheral neuropathy

Abbreviations: ART: Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; ADRs: Adverse Drug Reactions; WHO: World Health Organization; TAF: Tenofovir Alafenamide; DTG: Dolutegravir; D4T: Starvudine 3TC: Lamivudine; EFV: Efavirenz; TDF: Tenofovir Disoproxil Fumarate; AZT: Zidovudine; NVP: Nevirapine; FTC: Emtricitabine; TLD: TDF 300 mg od+3TC 300 mg od+DTG 50 mg od; TLE: TDF 300 mg+3TC 300 mg+EFV 400 mg od; TAFED: TAF 25 mg+FTC 200 mg od+DTG 50 mg od

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Introduction

The introduction of Antiretroviral Therapy (ART) has been associated with a tremendous decrease in HIV AIDS related morbidity and mortality worldwide [1]. ART is a lifelong commitment of which the first months of therapy are important such that it leads to clinical and immunological improvements as well as viral suppression when individuals adhere to ART; nevertheless, these drugs may cause adverse drug reactions, especially in people starting ART and already have advanced HIV disease with severe immunodeficiency.

Adverse Drug Reactions (ADRs) have been reported to be the most important limiting factors to the efficacy of antiretroviral therapy [2]. An ADR is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medical product that predicts hazard from future administration and warrants prevention of specific treatment or alteration of the dosage regimen, or withdrawal of the product [3].

The risk of ADRs probably arises as a result of the impact of the disease on the immune system as well as the safety profile of the complex ART regimen [4]. ADRs in developing countries are different from those experienced in developed countries due to differences in the prevalence of conditions such as malnutrition, tuberculosis, and patients presenting with advanced HIV infection [5]. According to research in Nigeria, comorbid disease conditions may influence susceptibility to ADRs due to the use of many drugs [6]. Furthermore, several other risk factors for ADRs have been observed that include the patient's age, gender as well as disease biomarkers such as CD4 count, viral load, and body mass index [7].

Problem statement

When it comes to ADRs due to antiretroviral therapy, all ART drugs have been reported to cause ADRs and this is among the most common reasons why ART regimens are changed. This problem is especially common in underdeveloped countries in which mainly only cheaper and more toxic drugs are available for treatment [8].

Despite Zambia being ranked as a middle-income country in 2011 during a decade (2004-2014) of impressive economic growth, it ranks among the countries with the highest levels of poverty and inequality globally. Therefore, Zambia is not spared from these ADRs due to the availability of some ART drugs that are affordable but quite noxious.

The prevalence of ADRs to antiretroviral therapy is common in Africa and has been studied in many African countries such as Eritrea, Cameroon, Nigeria, and South Africa. A study in Eritrea at Halibet national referral hospital established 62.8% of patients to have experienced at least one ADR [9]. Another study in South Africa found regimens such as zidovudine-lamivudine-nevirapine and stavudine-lamivudine-efavirenz to be associated with ADRs [10]. However, little or no such studies involving ADRs to ART have been conducted in Zambia. Furthermore, Tenofovir Alafenamide +Lamivudine+Dolutegravir (TAFED) which was introduced in Zambia in the year 2019 has little information concerning its associated ADRs, hence the need to assess the prevalence of ADRs due to this ART regimen.

Study justification

ADRs produce detrimental or undesirable effects on the body and it has been reported that the number of patients dying because of contrary effects of drugs per year increased up to 2.6-fold. Despite the ongoing drive to develop new antiretroviral agents, efforts to maximize the effectiveness of currently available regimens involve a better understanding and management of ADRs. TAFED recently made known to Zambia has little information concerning its associated ADRs hence the need to assess the prevalence of ADRs due to this regimen. Generally, the prevalence and associated factors of ADRs to antiretroviral therapy at Ndola teaching hospital have not been assessed. Therefore, this study will mainly access the prevalence of ADRs and the associated factors to antiretroviral therapy among HIV-positive patients at Ndola teaching hospital, Zambia. Inferences from this study will help medical practitioners as well as scientists to come up with or recommend ART regimens that are less likely to cause ADRs.

Various studies have established that HIV positive patients are a hundred times more likely to experience adverse drug reactions compared to the general population, and an advanced immunodeficiency indicates an even greater risk to ADRs.

Global perspective

According to research carried out in India concerning the ADRs profile of drugs used as first line ART, information was assessed by reviewing patients records and interviewing the individual patients in which some ADRs observed included anemia in response to zidovudine, nonspecific symptoms like headache and a general feeling of being unwell to tenofovir, stavudine, and efavirenz. Other effects recorded included dyslipidemia, pancreatitis, peripheral neuropathy as well as lactic acidosis in response to stavudine and generalized rash in response to nevirapine, and lastly nephrotoxicity to efavirenz. The number of patients in this study was 171 of which 79 of them experienced ADRs and 34 were male and 45 were female. Another study in Brazil horizonte involved the use of medical charts to analyze the availability of data on ADRs to antiretroviral drugs, the study used 233 medical charts of which 26.1% contained at least one long-term adverse reaction that included 45 cases of dyslipidemia (19.6%), 16 cases of lipodystrophy (6.9%) and 5 of type 2 diabetes (2.1%).

African perspective

Studies made in Cameroon at the general hospital in doula involving 399 files of HIV patients reported a total of 19.5% ADRs [10]. Despite women having reported more ADRs than men (21.6% *vs.* 16.3%) sex was not found to be associated with ADRs and age as well was not found to be related to ADRs. Common ADRs recorded included peripheral neuropathy (21%) whose median onset was 9 months, nervous system effects such as headaches, dizziness, tinnitus, and insomnia were present in 9.9% of patients. Gastrointestinal effects were present in 16.7% of patients and had a median onset of 6 months. Lipodystrophy accounted for 5.3% of ADRs and had a median onset of 23 months. Hematological effects accounted for 3.8% and the most common

being anemia with a median onset of 5 months. The regimen containing D4T-3TC-EFV alone was responsible for 29.6% of ADRs and D4T regimens were responsible for 56.1% of all ADRs. AZT-containing regimens were responsible for 39.4% of ADRs [11]. However, research carried out in Nigeria shows a slight controversy because stavudine based (D4T/3TC/NVP) and tenofovir based (TDF/FTC/EFV) regimens were found to be less likely to cause ADRs in patients compared to those who were on zidovudine-based (AZT/3TC/NVP) regimens [12].

In comparison with the study carried out in Cameroon doula, A study carried out in South Africa found age, the period of ART initiation, and ART regimen to be significantly associated with ADRs. This study involved 590 patients, 67% were female and 43% were male. An overall of 217 (37%) patients out of the 590 experienced at least one ADR, most of them being females (72%), older age groups had a higher rate of experiencing ADRs compared to the younger age group of 30 years and less. Patients who initiated ART from 2009 to 2011 had significantly lower rates of ADRs while the rate was higher in those who initiated ART from 2007-2008 [13].

According to another study that was conducted from 2005 to 2016 in Eritrea at Halibet national referral hospital, 309 patients were included in this study out of which only 62.8% experienced at least one ADR [14]. Still under the same study, 128 (64.6%) of these patients were female while 66 (59.5%) were males. 44.3% of them experienced at least three ADRs with a similar male-to-female ratio. Out of these ADRs experienced, 29.8% were found to be serious. Gastrointestinal upset (19.5%) was the most frequently reported ADR followed by non-specific symptoms (11.2%), hypersensitivity reactions (10%), and lipodystrophy (9.8%).

In Ethiopia at Anbessa teaching hospital, a study involving 228 HIV patients was carried out. The patients were closely monitored for ADRs and a total of 392 ARV drug related ADRs occurred such as mild GI disturbances (36.8%) and headaches (35.9%), the two mentioned being the most frequently reported symptoms; Thirty (7.7%) of ADRs were severe requiring a change in therapy (19 hematological and 11 hepatotoxic). The severe hematological complications were anemia (4.8%), neutropenia (2.6%), and thrombocytopenia (0.9%). Anemia was found to occur early in the first 4 weeks of ART treatment. Hepatic toxicity was also observed early and other ADRs encountered by the patients were grade I/II toxicities like rash, peripheral neuropathy, and metabolic disturbances. Another study done in Ethiopia at the ART clinic of Gondar university hospital involving a total number of 384 participants by Tadesse TW, et al. Found a prevalence of ADRS to be 89.8%. The most frequently reported ADRs were nausea 56.5% and headache 54.9%, CNS symptoms 27.4%, as well as anemia 16.1%, were also reported [15].

A study in Zimbabwe focused on analyzing adverse drug reactions due to tenofovir, zidovudine, and stavudine in a cohort of 205 patients receiving antiretroviral treatment at Newlands clinic in Harare. The study aimed to assess the length of time it took for clinically significant adverse drug reactions to occur in patients taking the above-mentioned regimens and the findings were that the patients initiated on stavudine and zidovudine had a lower survival time before a clinically significant ADR compared to those who were on tenofovir. However, Patients on zidovudine fared better compared to those on stavudine (134 days; p-value<0.0005), and a mean survival time before ADRs for tenofovir was 618 days, followed by zidovudine with 388 days then stavudine with 254 days [16].

Research concerned with the adverse effects of first-line ART in Bangui the capital of the Central African Republic involved a cross-sectional analytical study that had 282 HIV positive patients; the prevalence of clinical ADRs was 82.98%. This prevalence was 83.52% among patients on TDF/FTC/EFV versus 82.00% among those under AZT/3TC/NVP. The main adverse effects observed were neuropsychiatric (65.65%), digestive (43.62%), musculoskeletal (35.82), dermatological (34.40%), general (anorexia and asthenia) in 23.76%, respiratory disorders (17.73%) and lipodystrophies (10.99%). The frequency of these disorders was variable according to the therapeutic combinations but without significant difference (p>0.05).

Materials and Methods

Objectives

General objective: To determine the prevalence of adverse drug reactions and associated factors to antiretroviral therapy among HIV-positive patients at Ndola teaching hospital, Zambia.

Specific objectives

- To evaluate the prevalence of ADRs to antiretroviral therapy among HIV positive patients at Ndola teaching hospital.
- To determine the common ADRs to antiretroviral therapy at Ndola teaching hospital.
- To determine the associated factors of ADRs to antiretroviral therapy among HIV positive patients at Ndola teaching hospital.

Research question

What is the prevalence of ADRs to antiretroviral therapy and its associated factors at Ndola teaching hospital?

Measurements

Operational definitions

Prevalence: It is the statistical concept referring to the number of cases of a particular condition that are present in a particular population at a given time.

Associated factors: Refer to one of the elements such as age, sex, the time frame, and ART regimens that can contribute to a particular situation, in this case, adverse drug reactions.

Time frame: This is the period from the initiation of ART to the occurrence of ADRs.

Adverse drug reactions: These are harmful unwanted effects that are related to a drug or combination of drugs.

General symptoms: Any or all of the following symptoms; headache, nausea, vomiting, diarrhea, abdominal pain, and asthenia (physical weakness or lack of energy).

Hypersensitivity: Any or all of the following symptoms; dry mouth, itchiness, body rash, swelling, and shortness of breath.

Peripheral neuropathy: Dysfunction of one or more peripheral nerves usually causing symptoms like pain, burning sensation, or numbness of arms or legs.

Nephrotoxicity: Deterioration in kidney function as evidenced by an increase in serum creatinine and Blood Urea Nitrogen (BUN).

Insomnia: It is a sleeping disorder in which an individual has difficulties falling asleep or maintaining sleep.

Anemia: It is the reduction in hemoglobin concentration or the number of red blood cells in the human body (Table 1).

The scale of measurement

Type of variable	Variable	Definitions	Indicator	Measuring scale
Dependent variables	ADRS	These are harmful unwanted effects that occur within 1 year of starting ART and are not attributed to any other cause, e.g general symptoms, hypersensitivity, nephrotoxicity, neuropathy, and anemia	0 as no ADRS 1 as having ADRS	Normal
Independent variables	ART regimen	These are a combination of hiv drugs used to treat HIV infection	TDF+FTC+DTG TAFED ABC+3TC+EFV TLE	Nominal
	Gender	The sex of an individual	Male female	Nominal
	Age group	The number of years a person is at the onset of ADRS	<25 25-50 >50-75	Interval
	Time frame	This is the period from the initiation of ART to the occurrence of ADRS	In 1 month, 2 months, etc.	Normal

Table 1. ADRs and associated factors.

Conceptual framework

Many factors can affect the prevalence of ADRs due to ART. However, ART regimens are the major factors hence making them the independent variables that bring about ADRs. Below is a summary of the major factors (ART regimen), as well as other factors (extraneous variables) that may accelerate the process of adverse drug reactions (Figure 1).

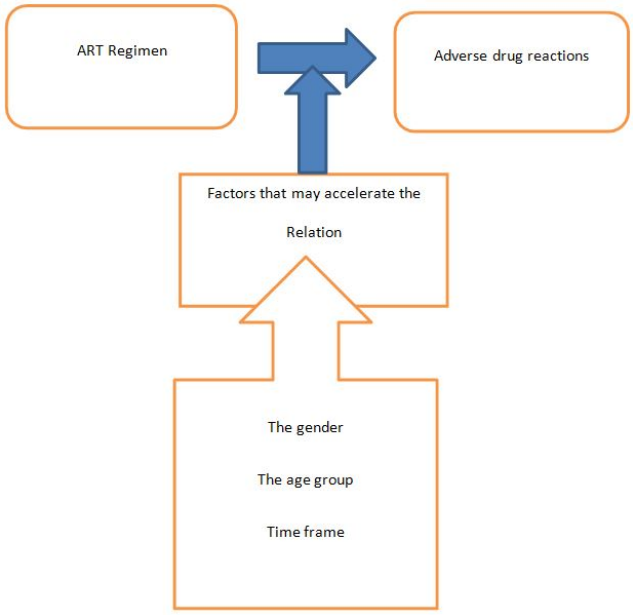

Figure 1. Conceptual framework

Study site

The study was conducted at Ndola teaching hospital on the copper belt province of Zambia. Ndola teaching hospital is the second-largest health institution in Zambia, which has a capacity of 851 beds and 97 baby cots. It serves a population of 503,649 in the Ndola district.

Target population

The study involved HIV positive patients at Ndola teaching hospital who experienced adverse drug reactions to ART in the period from January 2019 to January 2022.

Study design

This was a hospital based retrospective cohort study because it measured the prevalence of ADRs and associated factors to antiretroviral therapy among HIV positive patients at Ndola teaching hospital using recorded data obtained from the ART clinic in the years 2019 to 2022.

Sample size

The sample size for the study was calculated using the formula:

Sample size=n/((population+n)/population)

Where, $n=Z^2(p(1-p))/e^2$

n=1.96^2 0.5(1-0.5)/0.05^2

The information needed for a sample size determination includes the following;

Level of confidence (Z)=1.96 (at 95% confidence level); The margin of error (e^2)=5%; expected Prevalence (P)=50%.

Using the above formulas and information, the determined sample size using the population of HIV positive patients at NTH of 4,840 is approximately 356.

Sampling procedure

A systemic sampling technique was used to come up with the stipulated sample size, in that the 13th of each hospital record will be considered. HIV patients were eligible for inclusion in the study so long as they met the following criteria.

Inclusion criteria: Patients who experienced ADRs were considered if they experienced them between January 2019 to January 2022.

Exclusion criteria: Those who experienced ADRs before January 2019 and after January 2022 were excluded.

Data collection

Data was collected from the hospital files of HIV positive patients at NTH to determine the prevalence of ADRs and associated factors using a data collection tool.

Data analysis

Data collected was entered in a computerized database and spreadsheet, and it was then analysed using IBM Statistical Package for Social Sciences (SPSS) Version 26. Associations were done using binary logistic regression, univariate analysis, and *chi-square* tests. The results were categorized into frequency counts, bar charts, percentages, and/or tables.

Study limitations

The study was limited to data recorded by clinicians as there was inadequate data in the ADRs record books at the ART pharmacy. Information about the study conducted was difficult to find locally as well as globally.

Results

Demographic characteristics

A total number of 356 files of HIV positive patients were reviewed. With reference to Table 2, 160 (44.9%) patients were male and 196 (55.1%) were female. With regards to age, 108 (30.3%) were below 25, 144 (40.4%) between 25 and 50, and 104 (29.2%) were those greater than 50. 161 (45.2%) patients were found to be on TLD, 109 (30.6%) were on TAFED, 31 (8.7%) were on ABC+3TC+EFV, 31 (8.7%) were on AZT+3TC+DTG, and 24 (6.7%) were on TLE.

Variable	Indicators	Frequency (n=358) (%)
Gender	Males	160 (44.9%)
	Females	196 (55.1%)
Age	<25	108 (30.3%)
	25-50	144 (40.4%)
	>50	104 (29.2%)
Art regimen	TLD	161 (45.2%)
	TAFED	109 (30.6%)
	ABC+3TC+EFV	31 (8.7%)
	AZT+3TC+DTG	31 (8.7%)
	TLE	24 (6.7%)

Table 2. Demographic results.

Prevalence of ADRS

The prevalence of adverse drug reactions to antiretroviral therapy between January 2019 and January 2022 was approximately 62.1%. Based on specific ART regimens in Tables 3-5, approximately 68.3% of those on TLD experienced ADRS. Nearly 65.1% of those on TAFED had ADRs (Figures 2 and 3). About 48.4% of those on ABC +3TC+EFV had ADRS. Approximately 48.4% of those on AZT+3TC +DTG experienced ADRS and roughly 41.7% of those on TLE experienced ADRs.

	Frequency	Percent (%)
NO ADR	135	37.90%
ADRs	221	62.10%
Total	356	100%

Table 3. The prevalence of adverse drug reactions.

Unadjusted crosstab					
			ADRs		Total
			NO ADR	ADRs	
ART Regimen	TLD	Count	51	110	161
		% within ART regimen	31.70%	68.30%	100%
		% within ADRS	37.80%	49.80%	45.20%
		% of Total	14.30%	30.90%	45.20%
	TAFED	Count	38	71	109
		% within ART regimen	34.90%	65.10%	100%
		% within ADRS	28.10%	32.10%	30.60%
		% of Total	10.70%	19.90%	30.60%
	ABC+3TC+ EFV	Count	16	15	31
		% within ART regimen	51.60%	48.40%	100%
		% within ADRS	11.90%	6.80%	8.70%
		% of Total	4.50%	4.20%	8.70%
	AZT+3TC+ DTG	Count	16	15	31
		% within ART regimen	51.60%	48.40%	100%
		% within ADRS	11.90%	6.80%	8.70%
		% of Total	4.50%	4.20%	8.70%
	TLE	Count	14	10	24
		% within ART regimen	58.30%	41.70%	100%
		% within ADRS	10.40%	4.50%	6.70%
		% of Total	3.90%	2.80%	6.70%
Total		Count	135	221	356
		% within ART regimen	37.90%	62.10%	100%
		% within ADRS	100%	100%	100%
		% of Total	37.90%	62.10%	100%

Table 4. The prevalence based on specific ART regimen.

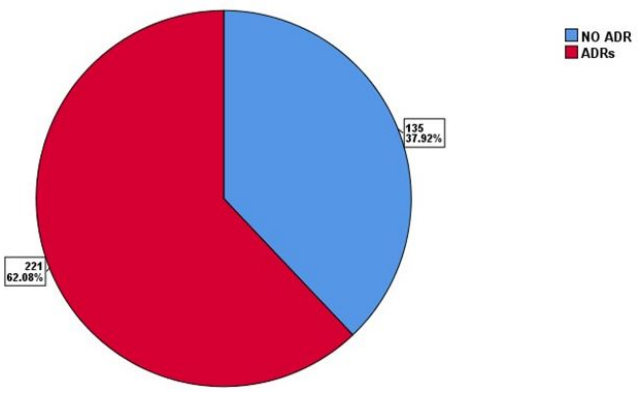

Figure 2. Representation of the prevalence of adverse drug reactions.

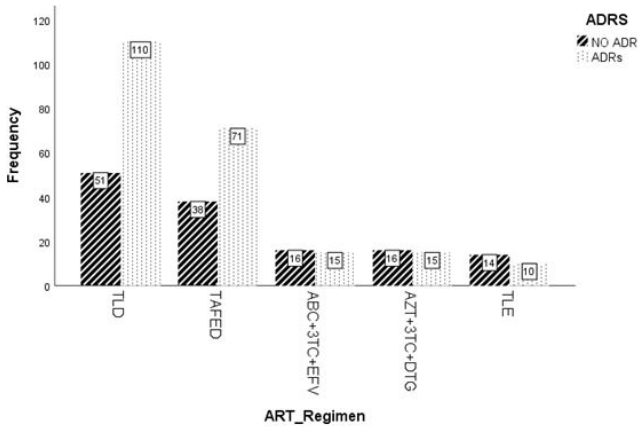

Figure 3. Frequency of ADRs based on ART regimens.

The common ADRS

The common ADRs were general symptoms (43.4%), hypersensitivity reactions (27.6%), Peripheral neuropathy (11.8%), insomnia (8.1%), nephrotoxicity (5.9%), and anemia (3.2%) (Figure 4).

		ART regimen					Total N (%)
		TL D	TAF ED	ABC+3TC+EFV	AZT+3TC+ DTG	TL E	
ADR	General symptoms	42	28	13	4	9	96 (43.4%)
	Hypersensitivity reactions	36	22	1	1	1	61 (27.6%)
	Peripheral neuropathy	12	13	1	0	0	26 (11.8%)
	Insomnia	8	7	0	3	0	18 (8.1%)
	Nephrotoxicity	12	1	0	0	0	13 (5.9%)
	Anemia	0	0	0	7	0	7 (3.2%)
Total		110	71	15	15	10	221 (100%)

Table 5. Distribution of the total number of adverse drug reactions to ART.

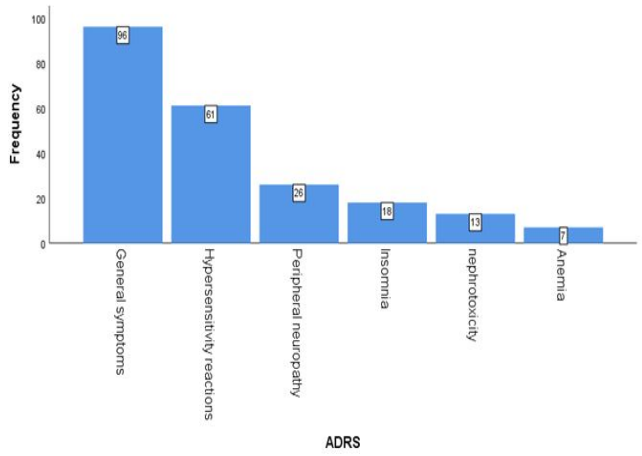

Figure 4. Frequency of the common adverse drug reactions.

Associated factors

Association with art regimens: Having used binary logistic regression (Table 6) and Pearson *chi-square* (Table 7) in SPSS, a p-value of <0.05 was calculated which signified a general association between ART regimens and ADRs. The odds ratios (Exp) indicated that those on TLD had an approximately 3.0-fold increase in developing ADRs, while those on TAFED had a 2.6-fold increase in developing ADRs. However, it was noted that ABC+3TC+DTG, AZT+3TC+DTG, and TLE were not significantly associated with ADRs.

Association with gender: According to Table 8, it was noted that out of 160 males, only 97 (60.6%) experienced ADRs and out of 196 females only 124 (63.6) experienced ADRs. Despite females having recorded a higher frequency of ADRs than males, a univariate analysis as depicted by Table 9 calculated the p-value to be >0.05 hence, implying that gender had no significant association with ADRs.

Association with age: According to Table 10, it was noted that out of 108 of those below 25 yrs of age, only 60 (55.6%) had ADRs; out of 144 of those in the range of 25 to 50 yrs old only 87 (60.4%) experienced ADRs, and out of 104 of those above 50 yrs old only 74 (71.2%) experienced ADRs. Despite having noticed an increase in the frequency of ADRs with age, a univariate analysis conducted using SPSS depicts a p-value of >0.05 in Table 11, hence age had no significant association with ADRs.

Association with time frame: According to Table 12, it was noted that general symptoms, as well as hypersensitivity reactions, occurred within the first month of therapy; peripheral neuropathy had a median onset of 5.5 months but the majority occurred in 3 months, nephrotoxicity had a median onset of 4 months but majority occurred in the first month; insomnia had a median onset of 1 month and lastly anemia had a median onset of 3 months. Furthermore, the pearson *chi-square* in Table 13 showed a positive relationship between time frame and ADRs.

ART regimen	Gender	Age	Mean	Std. deviation	N
TLD	Male	<25	0.52	0.512	21
		25-50	0.83	0.384	29
		>50	0.73	0.452	33
		Total	0.71	0.456	83
	Female	<25	0.69	0.471	26
		25-50	0.65	0.486	31

		>50	0.62	0.498	21
		Total	0.65	0.479	78
	Total	<25	0.62	0.491	47
		25-50	0.73	0.446	60
		>50	0.69	0.469	54
		Total	0.68	0.467	161
TAFED	Male	<25	0.38	0.518	8
		25-50	0.45	0.522	11
		>50	0.83	0.383	18
		Total	0.62	0.492	37
	Female	<25	0.69	0.471	29
		25-50	0.62	0.496	26
		>50	0.71	0.47	17
		Total	0.67	0.475	72
	Total	<25	0.62	0.492	37
		25-50	0.57	0.502	37
		>50	0.77	0.426	35
		Total	0.65	0.479	109
ABC+3TC+EFV	Male	<25	0.5	0.577	4
		25-50	0.33	0.5	9
		>50	1	.	1
		Total	0.43	0.514	14
	Female	<25	0.2	0.447	5
		25-50	0.63	0.518	8
		>50	0.75	0.5	4
		Total	0.53	0.514	17
	Total	<25	0.33	0.5	9
		25-50	0.47	0.514	17
		>50	0.8	0.447	5
		Total	0.48	0.508	31
AZT+3TC+DTG	Male	<25	0.75	0.5	4
		25-50	0.4	0.516	10
		>50	0	.	1
		Total	0.47	0.516	15
	Female	<25	0	0	5
		25-50	0.57	0.535	7
		>50	1	0	4
		Total	0.5	0.516	16
	Total	<25	0.33	0.5	9

		25-50	0.47	0.514	17
		>50	0.8	0.447	5
		Total	0.48	0.508	31
TLE	Male	<25	0.33	0.577	3
		25-50	0	0	5
		>50	0.33	0.577	3
		Total	0.18	0.405	11
	Female	<25	0.33	0.577	3
		25-50	0.75	0.463	8
		>50	0.5	0.707	2
		Total	0.62	0.506	13
	Total	<25	0.33	0.516	6
		25-50	0.46	0.519	13
		>50	0.4	0.548	5
		Total	0.42	0.504	24
Total	Male	<25	0.5	0.506	40
		25-50	0.56	0.5	64
		>50	0.73	0.447	56
		Total	0.61	0.49	160
	Female	<25	0.59	0.496	68
		25-50	0.64	0.484	80
		>50	0.69	0.468	48
		Total	0.63	0.483	196
	Total	<25	0.56	0.499	108
		25-50	0.6	0.491	144
		>50	0.71	0.455	104
		Total	0.62	0.486	356

Table 6. Unadjusted descriptive statistics.

Unadjusted binary logistic regression									
		B	S.E.	Wald	Df	Sig.	Exp (B)	95% C.I. for EXP (B)	
								Lower	Upper
Step 1a	ART regimen			11.902	4	0.018			
	TLD	1.105	0.447	6.103	1	0.013	3.02	1.256	7.257
	TAFED	0.962	0.46	4.365	1	0.037	2.616	1.061	6.447
	ABC+3TC+EFV	0.272	0.548	0.246	1	0.62	1.312	0.448	3.844
	AZT+3TC+DTG	0.272	0.548	0.246	1	0.62	1.312	0.448	3.844
	Constant	-0.336	0.414	0.66	1	0.416	0.714		

Table 7. Association with ART regimens; binary logistic regression.

Unadjusted *chi-square* tests			
	Value	**Df**	**Asymptotic significance (2-sided)**
Pearson *chi-square*	12.285[a]	4	0.015
Likelihood ratio	12.035	4	0.017
Linear-by-linear association	11.188	1	0.001
N of valid cases	356		
a. 0 cells (0.0%) have an expected count of less than 5. The minimum expected count is 9.10.			

Table 8. Association with ART regimens; *chi-square*.

		ADRS		**Total**
		NO ADR	**ADRs**	
Gender	Male	63 (39.4%)	97 (60.6%)	160 (100%)
	Female	72 (36.7)	124 (63.3	196 (100%)
Total		135	221	356

Table 9. Frequency of ADRs according to gender.

		ADRS		**Total**
		NO ADR	**ADRs**	
Age	<25	48 (44.4%)	60 (55.6%)	108 (100%)
	25-50	57 (39.6%)	87 (60.4%)	144 (100%)
	>50	30 (28.8%)	74 (71.2%)	104 (100%)
Total		135	221	356

Table 10. Frequency of ADRs according to age group.

Source	**Type III sum of squares**	**Df**	**Mean square**	**F**	**Sig.**
Corrected model	12.015[a]	29	0.414	1.881	0.005
Intercept	40.841	1	40.841	185.458	0
ART regimen	2.177	4	0.544	2.471	0.045
Gender	0.269	1	0.269	1.221	0.27
Age	0.811	2	0.405	1.84	0.16
ART regimen gender	0.851	4	0.213	0.966	0.426
ART regimen * age	1.309	8	0.164	0.743	0.654
Gender * age	1.103	2	0.551	2.503	0.083
ART regimen gender * age	4.726	8	0.591	2.683	0.007
Error	71.791	326	0.22		
Corrected total	83.806	355			
a. R squared=.143 (Adjusted R squared=.067)					

Table 11. Shows the association of ADRs with gender and age.

Count										
ADR		Months								Total
		1	2	3	4	5	6	7	8	9	
	General symptoms	96	0	0	0	0	0	0	0	0	96
	Hypersensitivity reactions	61	0	0	0	0	0	0	0	0	61
	Peripheral neuropathy	1	3	7	1	1	5	5	1	2	26
	Nephrotoxicity	3	0	2	2	0	2	2	2	0	13
	Insomnia	14	3	0	0	0	1	0	0	0	18
	Anemia	1	0	3	2	0	1	0	0	0	7
Total		176	6	12	5	1	9	7	3	2	221

Table 12. Shows the frequency of ADRs with the time frame.

Unadjusted *chi-square* tests			
	Value	Df	Asymptotic significance (2-sided)
Pearson *chi-square*	253.800[a]	40	0
Likelihood ratio	204.281	40	0
Linear-by-linear association	44.731	1	0
N of valid cases	221		
a. 47 cells (87.0%) have an expected count of less than 5. The minimum expected count is .03.			
b. This model took into account the common ADRS as the dependent variables and time frame as the independent variables.			

Table 13. *Chi-square* association of ADRs with time frame.

Discussion

The prevalence of ADRs

The prevalence of adverse drug reactions to antiretroviral therapy between January 2019 and January 2022 was approximately 62.1% at Ndola teaching hospital, Zambia. This was similar to a study carried out in Eritrea at Halibet national referral hospital, in which 309 patients were included, and only 62.8% experienced at least one ADR. However, research in Bangui the capital of the Central Republic of Africa involving 282 patients found a higher prevalence which was estimated at 82.98%. Furthermore, a study in Ethiopia at the ART clinic of Gondar university hospital involving a total number of 384 participants establish an even higher prevalence of ADRS that was approximately 89.8%.

Despite the high results stated above, some other studies in Africa recorded a lower prevalence like a study done in Cameroon at the general hospital in doula involving 399 files of HIV positive patients reported a prevalence of 19.5%. Furthermore, another study in South Africa reported an overall of 217 (37%) out of the 590 patients to have experienced ADRS (Supplementary file).

In other similar studies outside Africa, a study in India involving 171 patients found only 79 patients to have experienced ADRs giving a prevalence of 46.2%. Another study in Brazil Horizonte involving the use of medical charts to analyze the availability of data on ADRs to antiretroviral drugs, found about 26.1% to contain at least one long-term adverse drug reaction.

Based on specific ART regimens, the prevalence of ADRS at NTH, Zambia was approximately 68.3% for those on TLD, Nearly 65.1% for those on TAFED; About 48.4% for those on ABC+3TC+EFV; Approximately 48.4% for those on AZT+3TC+DTG; and roughly 41.7% for those on TLE.

Common ADRS

The common ADRs were general symptoms (43.4%), hypersensitivity reactions (27.6%), Peripheral neuropathy (11.8%), insomnia (8.1%), nephrotoxicity (5.9%), and anemia (3.2%).

The common ADRs for those on TAFED were mostly general symptoms with a count of 28, followed by hypersensitivity reactions with a count of 22, peripheral neuropathy with a count of 13, insomnia with a count of 7, and lastly nephrotoxicity with a count of 1.

Associated factors

Association with ART: Generally antiretroviral therapy (p-value<0.05) was significantly associated with adverse drug reactions. Those on TLD had an approximately 3.0-fold increase in developing ADRS, while those on TAFED had a 2.6-fold increase in developing ADRs. However, among ART regimens AZT+3TC+DTG, ABC+3TC +EFV, and TLE did not show significant association with ADRs. This is most likely due to the inadequate number of patients who were on these regimens as there was a change in ART regimens in Zambia

during the period 2019 to 2020 in order to provide better antiretroviral therapy Ministry of health, 2020.

Association with ART age and gender: From the results above, only 97 (60.6%) out of 160 males experienced ADRS and only 124 (63.6) out of 196 females experienced ADRs. Despite females having recorded a higher frequency of ADRs than males, the p-value was >0.05 hence, implying that gender had no significant association with ADRSs.

It was noted that out of 108 of those below 25 yrs of age, only 60 (55.6%) had ADRs; out of 144 of those in the range of 25 to 50 yrs old only 87 (60.4%) experienced ADRs, and out of 104 of those above 50 yrs old only 74 (71.2%) experienced ADRs. Even though there was an increase in the percentage of ADRs with age group, the age group (p-value>0.05) had no significant association with ADRs.

The results of this study were similar to a study done by Luma, et al. in Cameroon at the general hospital in Doula in which sex and age were not related to ADRs. However, a study carried out in South Africa found age to be significantly associated with ADRs.

Association with time frame: From the results stated above, the pearson *chi-square* showed a positive relationship between the time frame and ADRs. It was further noted that general symptoms, as well as hypersensitivity reactions, occurred within the first month of therapy; peripheral neuropathy had a median onset of 5.5 months but the majority occurred in 3 months, nephrotoxicity had a median onset of 4 months but the majority occurred in the first month of therapy; insomnia had a median onset of 1 month and anemia had a median onset of 3 months. However, a study done in Cameroon doula reported peripheral neuropathy to have had a median onset of 9 months and anemia a median onset of 5 months.

Conclusion

The prevalence of ADRs was calculated to be 62.1% and only ART regimens and time frames were significantly associated with ADRs. It was deduced that TAFED can cause adverse drug reactions; the common ones being general symptoms, hypersensitivity reactions, and peripheral neuropathy respectively. Furthermore, those on TAFED had an approximately 2.6-fold increase in developing ADRs, while those on TLD had a 3.0-fold increase in developing ADRs. Additionally, the dissimilarities in the results above might be due to different ART regimens, geographical areas, study designs/ pharmacovigilance tools, and operational definitions of ADRs.

Recommendation

Proper pharmacovigilance is required at NTH to come up with more accurate documentation of ADRs as it was noted that only basic side effects have a provision for recording data in the patient's files. It was also noted that only limited records of ADRs at the ART clinic pharmacy were found, hence the need to encourage pharmacovigilance.

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Ethical Consideration

Ethical approval for the study was obtained from Tropical Disease Research Center (TDRC). Further approval was also obtained from the copperbelt provincial health offices. Then later permission was gotten from the senior medical superintendent of NTH before collecting data. Completed forms were kept in a secured setting where no other persons had access to the information obtained from the records. All the information which was collected was only used for this research. Furthermore, the data was collected under strict adherence to COVID-19 preventive measures which included; masking up, sanitizing, and/or washing hands and ensuring that the minimum one (1) meter social distance was equally observed.

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