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RESEARCH ARTICLE

Antiretroviral Therapy-associated Adverse Drug Reactions and their Effects on Virologic Failure- A Retrospective Cohort Study in Nigeria

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Abstract: ***Background*:** Adverse drug reactions (ADRs) associated with antiretroviral therapy (ART) can rapidly reverse the gains of ART resulting in poor health outcomes. We need an improved understanding of specific ART-related ADRs that influence virologic outcomes.

***Objective*:** To investigate the frequency of clinical ADRs and assess their effect on virologic failure in patients on ART.

***Method*:** We described the prevalence of major clinical ADRs, and the association between specific ADRs and virologic failure in a clinic cohort of HIV-1 infected Nigerians aged ≥18 years, on first-line ART between June 2004 and February 2012. Multivariable logistic regression was run to identify predictors of virologic failure at 24 and 72 weeks of ART.

***Results*:** Data of 12,115 patients with a median age of 34 (interquartile range: 29-41) years, and predominantly females (67%) were evaluated. Overall, 957 (7.9%) patients experienced at least one ADR during a median follow-up period of 4 years (interquartile range: 1-7). The three most prevalent ADRs were lipodystrophy (2.6%), anemia (1.9%), and skin rash (0.7%). Virologic failure rate was 36% and 34% at 24 and 72 weeks of ART, respectively. Anemia independently predicted the odds of virologic failure at 72 weeks of ART (adjusted odds ratio, 1.74; 95% CI: 1.2-2.51); adjusted for sex, age, pre-treatment CD4+ cell count, antiretroviral regimen, and medication refill adherence.

***Conclusion*:** Antiretroviral therapy-associated anemia increases the likelihood of late virologic failure. We recommend routine monitoring of hemoglobin levels and prompt management of anemia in all patients on ART as a strategy to improve virologic success rates.

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1. INTRODUCTION

Among the strategies deployed to combat the HIV epidemic, the introduction of combination antiretroviral therapy (cART) is one of the most significant interventions that changed the landscape of HIV-related morbidity and mortality [1-5]. Antiretroviral therapy substantially modified the natural history of HIV infection and changed it from an end of life event to a manageable chronic condition [4, 5]. Despite the benefits of ART, it is not without challenges. Adverse drug reactions (ADRs) associated with the use of ARVs can rapidly reverse the gains of ART resulting in worse health outcomes [6-8] and increased mortality [9, 10]. Acute toxicities may lead to dose interruption and discontinuation of therapy. Some studies have reported treatment discontinuation rates ranging from 4% to 46% related to neuropsychiatric adverse effects of antiretroviral therapy [11, 12]. Treatment discontinuation and other forms of medication non-adherence associated with ADRs are significant risk factors for virologic failure [13, 14]. Failure of first-line ART regimens resulting from ADRs creates the need for more expensive and difficult-to-implement second-line regimens often unaffordable in most resource-constrained countries, which are largely donor dependent for their ART programs [15].

One of the aims for the UNAIDS international goal for 2020 termed the "90–90–90 target" is to achieve and maintain viral suppression in 90% of persons on ART [16]. An important strategy to achieve the viral suppression target, apart from the promotion of adherence, is the use of safer ART regimen to promote maximal viral suppression and immune reconstitution [17-19]. Estimates of viral suppression rates after 12 months of antiretroviral therapy in low-

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and middle-income countries, depending on the HIV RNA threshold, range from 50% to as high as 90% [20, 21]. In Nigeria, a study reported that only 50% of patients on standard care attained undetectable viral load of <400 copies per ml after one year of antiretroviral therapy [22]. The low rate of viral suppression among patients on ART in Nigeria is concerning and requires a critical evaluation to understand the factors that underlie the poor treatment response. Previous studies evaluated treatment outcomes among patients on first-line ART at Jos University Teaching Hospital (JUTH) HIV clinic and revealed a high level of treatment modification of 83% [23], treatment discontinuation of 28% [24], and early virologic failure of 49% [22] among patients receiving standard care. However, the studies did not evaluate the impact of ADRs on virologic outcomes. We need an improved understanding of the specific HIV treatment-related adverse events that influence virologic outcomes. This study described the frequency of major ADRs and its effect on virologic failure among adult patients on standard first-line ART at JUTH HIV Clinic.

2. MATERIALS AND METHODS

2.1. Study Design and Setting

This was a retrospective cohort study conducted at the Jos University Teaching Hospital, a Federal Tertiary Healthcare Facility located in the cosmopolitan city of Jos in North-central Nigeria. The Federal Government of Nigeria established the HIV treatment facility in January 2002 as part of an expanded response to care and support for people living with HIV [25]. Rapid scale-up of ART services at JUTH started in 2004 through collaboration between JUTH, the University of Jos and the Harvard School of Public Health (HSPH)/ AIDS Prevention Initiative in Nigeria (APIN) program, supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) grant.

2.2. Study Population

2.2.1. Inclusion Criteria

Those included in the study were HIV+ patients, ≥18 years of age, enrolled in the HSPH/APIN program, and treatment naïve at enrolment. Included patients had received first-line ART at JUTH for a minimum period of 12 months between June 2004 and February 2012. Eligibility for ART for treatment naïve patients in the HIV treatment program followed the Nigerian National HIV treatment guidelines [26, 27], which closely mirrored the World Health Organization (WHO) guidelines at the time of patient enrolment [28-31]. In brief, from the year 2004 to 2009, patients were eligible for ART if their CD4+ cell counts dropped below 200 cells/mm^3 or if symptomatic with CD4+ cell counts below 350 cells/mm^3. However, from 2010 to the study end, CD4+ cell counts eligibility was below 350 cells/mm3 regardless of symptoms. The first line therapy based on the Nigerian National Adult ART guidelines [27, 32] involved combination antiretroviral therapy consisting of two nucleoside backbone of either AZT (AZT)/lamivudine (3TC), stavudine (d4T)/3TC, ABC (ABC)/3TC, (DDI)/3TC or Tenofovir (TDF)/3TC in combination with either nevirapine (NVP) or efavirenz (EFV).

The study start point corresponded to the introduction of an electronic medical record system in the HIV treatment program at the study site, while the study end date marked a period of transition in program management. We included only patients with available viral load results at 24 and 72 weeks in the virologic outcome analysis.

2.2.2. Exclusion Criteria

We excluded those who picked up ARVs only once at the pharmacy and those with insufficient baseline data such as missing the first ARV dispensing date.

2.3. Data Collection and Processing

Data utilized included patients' demographic, clinical, laboratory and prescription records maintained in an electronic database (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA) of the Harvard/APIN program.

2.3.1. Independent Variables (Exposure)

This included baseline (pre-treatment) demographics (age, sex, education, employment status, marital status, and enrollment year) and clinical (ART regimen, WHO clinical stage, TB co-infection, hepatitis B virus, and hepatitis C virus co-infection, CD4+ cell count) characteristics. Other exposure variables were adverse drug reactions, defined as clinical ADRs documented on the ADR report form or toxicity form using International Classification of Diseases 10 (ICD-10) codes for ADRs [33]. The criteria for assessment of anemia was hemoglobin levels below the normal level of 12.9 and 12.7 g/dL for men aged 20-59 years and 60+ years respectively and 11.5 g/dL for women aged 20 years and above [34]. Patients were reviewed for ADRs monthly in the first year of ART initiation and subsequently every other month. Time-updated characteristics such as adherence to ART refill schedules measured at 24 and 72 weeks of ART were also treated as an exposure variable. We determined adherence to ART using drug refill adherence. A computerized pharmacy appointment system utilized the total number of days that the patient was behind for drug-refill visits to calculate drug refill adherence. The following formula estimated percentage of cumulative adherence: the total number of days the patient was assumed to be exposed to ART given the dispensed number of pills minus the total number of days behind schedule, divided by the total number of days the patient was assumed to be exposed to ART given the dispensed number of pills multiplied by 100 [35, 36]. Age, CD4+ cell count, and adherence to drug refill schedules were measured on a continuous scale. Baseline clinical assessments or laboratory evaluations for naïve patients were the measurements closest to, and up to six months before or 0.5 months after, their first ART pick-up date. CD4+ lymphocyte count was measured by flow cytometry (Partec GmbH, Munster Germany) and hepatitis B serum antigen (HBsAg) was determined using Enzyme Immunoassay (EIA) (Monolisa HBsAg Ultra3; Bio-Rad, Hercules, USA).

2.3.2. Dependent Variables (Outcome)

The main study outcome measure was virologic failure defined as plasma viral load above 1000 copies/mL after 6 to

12 months of ART initiation [37]. We obtained viral load data at baseline, 24 weeks, and 72 weeks of ART. HIV RNA was determined using the Roche Ampliprep TaqMan (Roche Diagnostics, GmbH, Germany). For the purpose of this study, early virologic failure was defined as having an HIV viral load of >1000 copies/mL after ≥6 months (24 weeks) of ART [26, 37], while late virologic failure was defined as having an HIV viral load of >1000 copies/mL after ≥ 18 months (72 weeks) of ART.

2.4. Ethical Considerations

The University of Western Cape (UWC) Research Ethics Committee approved the study protocol. Jos University Teaching Hospital ethical committee and Harvard T.H. Chan School of Public Health approved the use of data obtained from the patients. As the study involved the use of retrospective data, patient consent was waivered. To ensure the confidentially of patients' information, data extracted from the electronic medical record system was de-identified and stored in an encrypted format in a secure computer system accessible only to the researcher.

2.5. Data Analysis

Descriptive analyses, including frequencies and proportions for categorical variables, and median and interquartile ranges (IQRs) for numerical variables; were performed. Factors associated with virologic failure at 24 and 72 weeks of ART were assessed by chi-square analysis. To identify the associations between major ADRs such as lipodystrophy, anemia, peripheral neuropathy, skin disorders [27-29] and virologic failure we used chi-square analysis. A multivariate logistic regression model was fitted to identify Independent predictors of early (24 weeks) and late (72 weeks) virologic failure. Variables that were associated with virologic failure to a p value of 0.05 in the bivariate analysis were included as covariates in the multivariable model. Sex and age were included in the model to account for any residual confounders based on a priori knowledge of their association with virologic failure [38, 39]. All statistical tests were two-tailed and a p-value < 0.05 considered statistically significant. Stata version 13 (College Station, TX) was used for the statistical analyses.

3. RESULTS

3.1. Cohort Characteristics

The pretreatment demographic and clinical characteristics of study participants (Table **1**) showed that participants were predominantly females (67%), and mostly young adults with a median age of 34 years. Married individuals constituted over half of the study participants, while secondary and tertiary education was the highest educational attainment by one-third of the participants.

The clinical characteristics of participants before the commencement of ART indicated that the median baseline CD4+ cell count was low and 35% of the participants had severe immunosuppression (CD4+ cell count ≤100 cells/mm3) at baseline. Hepatitis B and HIV co-infection was less than 20%, while a high proportion of the participants (84%) did not have a documented tuberculosis (TB) result. Of those with available TB data (17%), about 5% were positive for TB

3.2. Prevalence of Adverse Drug Reactions

The prevalence of major ADRs summarized in Table **2** shows that 957 out of the 12,115 (7.9%) patients experienced at least one ADR, with Severe ADRs being the most prevalent (4.5%) followed by moderate (2.6%), and mild ADRs (0.8%) as shown in Table **2**. Life-threatening ADRs were rare and recorded in only 12 patients (0.1%) during the study period. The three most prevalent types of ADR were lipodystrophy (2.8%), anemia (2%), and skin disorders (1.3%).

3.3. Prevalence and Factors Associated with Virologic Failure

The proportion of patients with virologic failure was 36% (2882 out of 7975) at 24 weeks of ART, and 34% (2670 out of 7975) at 72 weeks of ART. Table **3** shows the association of virologic failure rates with participants' baseline demographic, clinical, and regimen characteristics, as well as with time-updated characteristics such as adherence to ART refill schedules. Compared to females, the proportion of males with virologic failure was significantly higher at 24 weeks of ART, but not at 72 weeks. There was no age-related difference in the proportion of subjects with virologic failure at 24 weeks of therapy. However, at 72 weeks, the virologic failure rate was significantly higher among younger subjects; 40%, 33%, 32% for the age group 15-24, 25-45, and >45 years, respectively.

Clinically, the commencement of treatment at the more advanced stage of HIV disease (WHO clinical stage 3 or 4) was significantly associated with virologic failure at 24 and 72 weeks of ART. Similarly, the virologic failure rate at 24, and 72 weeks of ART was significantly higher among those who initiated treatment at a lower CD4+ cell count (<200 cell/mm3) compared to those who initiated treatment at CD4 cell count >200 cells/mm3. Additionally, study subjects who initiated treatment at higher viral load thresholds of >100,000 copies/mL had higher virologic failure rates at 24 and 72 weeks of treatment. The difference was more pronounced at 24 weeks of treatment; 25% compared to 38%, for those with a baseline viral load of ≤10,000 compared to viral load >100,000 copies/ml, respectively. A comparison of the proportion of patients with virologic failure according to the baseline ARV regimen revealed that a significantly higher proportion of study subjects who initiated treatment with an ARV regimen of triple nucleoside reverse transcriptase inhibitor (NRTI) had virologic failure at 24, and 72 weeks of therapy compared to those who commenced treatment with EFV- or NVP-based regimens. Virologic failure rate at 24 weeks according to the NRTI backbone was 40% for abacavir and didanosine, 35% for tenofovir, 30% for zidovudine, and 28% for stavudine. At 72 weeks of therapy, patients who initiated ART with tenofovir-containing regimens had the highest virologic failure rate of 38%, followed by didanosine (36%), zidovudine (32%), abacavir (31%), and stavudine (30%).

The proportion of patients with early virologic failure (24 weeks of ART) was significantly higher among those who initiated treatment from 2004 to 2009 compared to 2010 to

Table 1. Pre-treatment demographic and clinical characteristics of study participants (N=12,115).

Characteristics	Sub-group	Frequency	Percent
Sex	Females	8150	67.3
	Males	3965	32.7
Age, years	Median (IQR)	34 (29-41)	
Age range, years	15-24	711	5.9
	25-45	9445	78.0
	>45	1911	15.8
	Missing data	48	0.4
Marital Status	Divorced/Separated	995	8.2
	Married	6443	53.2
	Single	2375	19.6
	Widowed	1958	16.2
	Missing data	344	2.8
Highest Education	No formal education	1993	16.5
	Primary	2473	20.4
	Secondary	3651	30.1
	Tertiary	3654	30.2
	Missing data	344	2.8
WHO disease stage	1	3964	32.7
	2	3567	29.4
	3	3085	25.5
	4	711	5.9
	Missing data	788	6.5
CD4 cell count, cell/mm3	≤100	4240	35.0
	101 – 199	3921	32.4
	200 – 349	2888	23.8
	≥350	959	7.9
	Missing data	107	0.9
	Median (IQR)	142 (72 – 230)	
Viral load, copies/ml	≤10,000	3226	26.6
	10,001-100,000	4664	38.5
	>100,000	4164	34.4
	Missing data	61	0.5
	Median (IQR)	43,680 (8,475–160,213)	
Hepatitis B status	Negative	8406	69.4
	Positive	2208	18.2
	Missing	1501	12.4
Tuberculosis infection	No	1388	11.5
	Yes	573	4.7
	Missing	10154	83.8

Table 2. Prevalence of major adverse drug events in 12,115 patients on first-line ART at Jos University Teaching Hospital HIV clinic June 2004 to February 2012.

Major ADRs	Number (%) Patients	Severity of Events Number (%) Patients that had an Event			
		Mild	Moderate	Severe	Life-threatening
All events, n (%)	957 (7.90)	98 (0.81)	312 (2.58)	532 (4.47)	12 (0.10)
Lipodystrophy[a]	326 (2.69)	33 (0.27)	148 (1.22)	144 (1.18)	1 (0.008)
Anemia[b]	238 (1.97)	3 (0.025)	41 (0.34)	189 (1.56)	5 (0.041)
Skin disorders[c]	162 (1.34)	25 (0.21)	48 (0.39)	88 (0.72)	1 (0.008)
CNS disorders[d]	77 (0.64)	3 (0.03)	23 (0.19)	46 (0.38)	5 (0.041)
Peripheral neuropathy	59 (0.49)	17 (0.14)	23 (0.19)	19 (0.16)	-
Gastro-intestinal symptoms[e]	50 (0.41)	11 (0.09)	14 (0.12)	25 (0.21)	-

[a]lipodystrophy: lipoatrophy, lipohypertrophy, gynecomastia
[b]Haemoglobin levels below the normal level of 12.9 and 12.7 g/dL for men aged 20-59 years and 60+ years respectively and 11.5 g/dL for women aged 20 years and above.
[c]Skin disorders: skin rash and itching, erythema multiforme, exfoliative skin eruptions, Steven Johnson Syndrome, and hyperpigmentation
[d]CNS disorders, central nervous system disorders: Nightmares, Insomnia, Anxiety/restlessness, aggression/irrational talk, somnolence, dizziness, seizures, forgetfulness/confusion, and hallucination
[e]Gastro-intestinal symptoms: nausea and vomiting, diarrhoea, abdominal pain, Others

2012. This trend was however reversed at 72 weeks; with the highest virologic failure rate observed among those initiated on treatment from 2010 to 2012 compared to those commenced on ART earlier than 2010.

Compared to patients with average percentage adherence to on-time ARV refill schedules of ≥ 95%, those with <95% adherence had a significantly higher virologic failure rate at 24 and 72 weeks of therapy.

3.4. Association between Adverse Drug Reactions and Virologic Failure

Table **4** reflects the proportion of participants with virologic failure at 24 and 72 weeks of ART according to adverse drug reactions experienced. The proportion of participants with virologic failure at 24 and 72 weeks was significantly higher among those who had ART-related anemia compared to those without anemia; 38% versus 32%, and 47% versus 33% for those with or without anemia at 24 and 72 weeks of ART, respectively. Antiretroviral therapy related central nervous system (CNS) disturbance was not significantly associated with virologic failure at 24 weeks of therapy. However, at 72 weeks of ART, the proportion of patients with virologic failure was significantly higher among participants who experienced a CNS adverse event; 39% compared to 24%, for CNS disorder versus no CNS disorder. On the other hand, ART-associated lipodystrophy was significantly associated with a lower prevalence of virologic failure at 24, and 72 weeks of therapy. Likewise, peripheral neuropathy was associated with a lower prevalence of virologic failure at 72 weeks of ART, but not at 24 weeks.

In the adjusted analysis (Table **5**), the likelihood of late virologic failure was 19% higher in males compared to females. The use of NVP-based ART was associated with a 29% greater likelihood of late virologic failure compared to EFV-based ART. For the NRTI regimens, the use of AZT-compared to TDF-based NRTI was associated with 21% and 24% lower likelihood of early and late virologic failure respectively. Similarly, d4T-based NRTI compared with TDF-based regimen was associated with a 34% lower likelihood of early virologic failure.

The likelihood of early virologic failure increased by 27%, 15%, and 39% among participants who commenced ART at WHO disease stages 2, 3, and 4 respectively compared to those who initiated treatment at WHO disease stage 1. Similarly, subjects who initiated treatment at WHO disease stage 2 and 3 were 15% and 25% respectively more likely to have late virologic failure compared to those who had WHO stage 1 disease at treatment initiation. Pretreatment CD4+ cell count of ≤100 compared to >200 cells/mm3 was associated with 41% and 27% greater odds of early and late virologic failure respectively. Also, pretreatment CD4+ cell count in the range of 101 to 200 compared to >200 cells/mm3 was associated with 29% greater odds of early virologic failure and 14% lower odds of late virologic failure.

Compared to those initiated on treatment in the period 2010 to 2012, the odds of early virologic failure was higher by 72% among those who initiated ART in the period 2004 to 2006 and by 7% among those commenced on treatment from 2007 to 2009. For late virologic failure, the odds were lower by 53% among those initiated on ART in the period 2004 to 2006 and by 40% among those commence on treatment from 2007 to 2009 compared to those commence on ART in the period 2010 to 2012.

Poor adherence to drug refill schedules (<95%) increased the odds of early and late virologic failure by 83% and 81%, respectively. Antiretroviral therapy related anemia was independently associated with a 74% greater likelihood of late virologic failure.

Table 3. Association of participants demographic, clinical, and regimen characteristics with virologic failure.

Characteristics	Sub-group	Number (%) of Patients with Early Virologic Failure (24 Weeks)	*P* value	Number (%) of Patients with Late Virologic Failure (72 Weeks)	*P* value
Sex	Female	2516 (31.02)	*0.001*	1768 (32.86)	0.093
	Male	1336 (33.89)		902 (34.76)	
Age, years	15-24	224 (31.64)	0.734	181 (39.61)	*0.008*
	25-45	3021 (32.14)		2071 (33.35)	
	>45	593 (31.24)		405 (31.71)	
WHO disease stage	1	975 (24.71)	*<0.001*	791 (29.88)	*<0.001*
	2	1119 (31.5)		826 (33.05)	
	3	1318 (42.89)		792 (38.06)	
	4	254 (35.93)		145 (34.04)	
CD4 cell count cells/mm3	≤100	1610 (37.97)	*<0.001*	1103 (38.91)	*<0.001*
	101-200	1300 (33.15)		824 (28.97)	
	201-350	767 (26.56)		587 (31.39)	
	>350	159 (16.58)		151 (38.42)	
HIV viral load copies/ml	≤10,000	814 (25.23)	*<0.001*	634 (31.31)	*0.001*
	10,001-10^5	1461 (31.33)		1015 (32.64)	
	>10^5	1577 (37.87)		1021 (35.95)	
Hepatitis B status	Negative	2780 (33.23)	0.10	1877 (32.94)	0.605
	Positive	691 (31.38)		469 (33.67)	
Tuberculosis	Yes	243 (42.41)	<0.001	138 (31.65)	0.56
	No	401 (28.95)		319 (30.12)	
Baseline regimen backbone	efavirenz	902 (34.1)	*0.001*	543 (33.5)	*<0.001*
	nevirapine	2875 (31.2)		2062 (33.1)	
	Triple NRTI	75 (39.9)		65 (52)	
Baseline NRTI	abacavir	124 (39.87)	*<0.001*	72 (30.9)	*<0.001*
	zidovudine	1879 (29.7)		1379 (31.7)	
	stavudine	317 (28.3)		244 (30.1)	
	didanosine	108 (40.2)		69 (36.3)	
	tenofovir	1424 (35.4)		906 (37.9)	
ART start year	2004-2006	1692 (33.6)	*<0.001*	1162 (30.3)	*<0.001*
	2007-2009	1811 (33.6)		1285 (34.9)	
	2010-2012	346 (21.5)		221 (47.9)	
Adherence†	<95%	715 (43.2)	*<0.001*	473 (45.7)	*<0.001*
	≥95%	3137 (30.2)		2197 (31.7)	

†average adherence at 24, and 72 weeks were included in the analysis of virologic outcome at 24, and 72 weeks respectively; the comparison was by chi-square analysis; Values in italics show a significant association.

Table 4. Comparison of virologic failure among study participants who experienced an adverse drug reaction and those who did not experience an adverse drug reaction.

Type of ADR	Had ADR	Number (%) of Patients with Early Virologic Failure (24 Weeks)	*P* value	Number (%) of Patients with Late Virologic Failure (72 Weeks)	*P* value
Any ADR	No	2647 (36.31)	0.297	2436 (33.42)	0.686
	Yes	235 (34.31)		234 (34.16)	
Grade 3 or 4 ADR	No	114 (29.08)	0.223	101 (32.69)	0.462
	Yes	171 (32.88)		134 (35.36)	
Anemia	No	3765 (31.83)	*0.03*	2599 (33.22)	*<0.001*
	Yes	87 (38.84)		71 (46.71)	
CNS disorder	No	3739 (31.8)	0.326	2574 (33.10)	*0.048*
	Yes	38 (36.2)		31 (44.3)	
Lipodystrophy syndrome	No	3779 (32.18)	*<0.001*	2601 (33.76)	*<0.001*
	Yes	73 (23.47)		69 (25.46)	
Peripheral neuropathy	No	3835 (31.97)	0.725	2664 (33.61)	*<0.001*
	Yes	17 (29.82)		6 (12.5)	
Skin disorders	No	3814 (31.96)	0.851	2641 (33.44)	0.431
	Yes	38 (31.15)		29 (37.66)	

Table 5. Multivariate risk factor analysis for virologic failure at 24 and 72 weeks of antiretroviral therapy.

Characteristics	Virologic Failure at 24 Weeks of ART		Virologic Failure at 72 Weeks of ART	
	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Males	1.07 (0.96 - 1.19)	0.25	1.18 (1.03 - 1.36)	*0.02*
Age, one-year increment	1 (0.99 - 1)	0.50	0.99 (0.99 - 1)	0.08
WHO disease stage (3 or 4 versus 1 or 2)	1.74 (1.59 - 1.9)	*<0.001*	1.11 (0.98 - 1.24)	0.09
CD4 cell count, cells/mm^3 (≤100 versus >100)	1.27 (1.16 -1.38)	*<0.001*	1.37 (1.23 - 1.53)	*<0.001*
Viral load (>10,000 versus ≤10,000)	1.42 (1.28 -1.56)	*<0.001*	1.09 (0.97 - 1.24)	0.16
NVP versus EFV	1.12 (0.99 -1.28)	0.07	1.39 (1.17 - 1.65)	*<0.001*
ABC versus TDF	1.2 (0.93 - 1.54)	0.16	0.79 (0.57 - 1.11)	0.17
AZT versus TDF	0.78 (0.71- 0.85)	*<0.001*	0.77 (0.68 - 0.87)	*<0.001*
D4t versus TDF	0.66 (0.55- 0.79)	*<0.001*	0.88 (0.7 - 1.11)	0.28
ddi versus TDF	1.08 (0.83- 1.41)	0.56	1.22 (0.87 - 1.71)	0.26
Year of ART initiation				
2007-2009 versus 2004-2006	0.91 (0.8 - 1.01)	0.07	1.25 (1.1 - 1.42)	*<0.001*
2010-2012 versus 2004-2006	0.52 (0.45- 0.61)	*<0.001*	1.93 (1.51 - 2.46)	*<0.001*
Adherence (<95% versus ≥95%)*	1.82 (1.63- 2.04)	*<0.001*	1.74 (1.47 - 2.06)	*<0.001*
Anaemia	1.34 (1 - 1.8)	*0.048*	1.76 (1.22 - 2.55)	*<0.001*
lipodystrophy	0.81 (0.6 - 1.1)	0.18	0.85 (0.61 - 1.18)	0.33
CNS disturbance	-		1.19 (0.68 - 2.05)	0.54
peripheral neuropathy	-		0.42 (0.18 - 1.02)	0.06

*average adherence at 24, and 72 weeks were included in the analysis of virologic outcome at 24, and 72 weeks respectively. Values in italics show a significant association.

4. DISCUSSION

In this retrospective cohort analysis, we described the prevalence and pattern of ART-related clinical ADRs among adult patients on ART and examined the association between specific ADRs and virologic failure. Overall, less than 10% of the studied population experienced at least one ADR, while over one-third had virologic failure at 24 and 72 weeks of ART respectively. Virologic failure at 24 weeks of ART was independently predicted by pre-treatment WHO HIV disease stage 3 or 4, severe immunosuppression (CD4+ cell count < 100 cell/mm3), HIV RNA levels >100,000 copies/mL, and use of TDF NRTI compared to AZT or d4T as well as adherence to ART refill schedules <95%. Independent predictors of virologic failure at 72 weeks of ART included male gender, severe immunosuppression (CD4+ cell count < 100 cell/mm3), use of NVP NNRTI compared to EFV, use of TDF NRTI compared to AZT, adherence to ART refill schedules of <95%, and ART-related anemia,.

The prevalence (7.9%) of ART-related ADRs reported in this study was lower than that reported in previous Nigerian studies; 10.4% in Zaria North-West Nigeria [40], 53.4% in Maiduguri North-East Nigeria [41], and 73% in South-South Nigeria [42]. Also, higher ART-related ADR prevalence of 9.4% to 63% has been documented in other African studies [43-45]. Several factors may have contributed to the observed differences in the ADR rate between the cited studies and the finding of the current study: the different pharmacovigilance practices in the different settings, the number of patients involved in the studies, and the duration of follow-up. Severe ADRs had the highest prevalence in the current study suggesting a tendency to under-report or overlook mild events, which potentially might have underestimated the reported ADR rates.

4.1. Prevalence of Virologic Failure and Associated Factors

The virologic failure rates in the current study (36% at 6 months and 34% at 18 months) were higher than rates reported in Uganda (20% at 12 months) [46], and South Africa (10% at 16 months) [47, 48]. However, the virologic failure rate observed in this study was close to estimates of virologic failure rates reported in a systematic review and meta-analysis of African studies which put the proportion of patients with an undetectable viral load above 64% (35% failure rate) for all time points [49]. The results of low viral suppression rates in limited resource settings highlights the need to adopt more practical and effective strategies to achieve a higher virologic success rate of 90% in line with the United Nations 90-90-90 target [16].

The multivariate risk factor analyses revealed that males were more likely to have late virologic failure compared to females. This finding contrasts with two studies in developed settings; China and Canada, in which the risk of virologic failure was higher in females compared to males [38, 39, 50]. The variability in gender-related HIV treatment outcomes may be setting specific, and underlying factors in each setting need further investigation.

Consistent with results of previous studies [20, 51-54], we found an increased likelihood of early virologic failure with the commencement of ART at more advanced HIV disease stages such as WHO disease stage 3 or severe immunosuppression (pre-treatment CD4+ cell count of ≤100 cells/cm^3). Late presentation for treatment, which was a prominent finding in this study, as well as in an earlier report in the studied setting [55] could be a contributing factor to the poor virologic success rate observed in our study. The adoption of the WHO "test and treat" strategy by the Nigerian National guidelines for HIV prevention, treatment and care in 2016 [30, 56] is expected to support early detection of HIV infection and engagement into care in the studied setting. This will ultimately result in improvement in treatment outcomes in patients on ART [57-60].

Similar to the report of an Ethiopian study [61], a higher likelihood of late virologic failure was identified among patients commenced on ART with a nevirapine-based ART regimen compared to efavirenz. Additionally, our study finding is supported by a 2017 systematic review of 17 studies in sub-Saharan Africa, involving 121,092 individual patients, in which the risk of treatment failure was lower in patients who initiated treatment with efavirenz than nevirapine-containing regimen [62]. Furthermore, we reported a lower likelihood of early and late virologic failure among patients on zidovudine containing ART compared to tenofovir, similar to a previous multicenter Nigerian study [51]. Some other studies, however, did not establish a difference between zidovudine and tenofovir in viral suppression rates [63, 64].

Adherence to on-time ARV refill schedules (<95%) significantly increased the odds of early and late virologic failure in this study. The relationship between sub-optimal adherence to drug refill schedules and increased risk of virologic failure had been documented in several published reports [35, 65, 66]. The clinical utility of adherence to ARV refill schedules as an early warning indicator to identify patients at risk of virologic failure and to provide targeted interventions had been advocated by several studies [35, 65, 66].

When specific ADRs were considered in the current study, we found that ART-related anemia increased the odds of late virologic failure. Studies comparing the impact of ART-related anemia are scarce, but a recent study found that ADRs were significantly associated with poor immunologic and virologic outcomes in HIV/AIDS patients [67-69]. Additionally, in support of the current study findings, some earlier studies reported better survival among HIV patients on ART with the absence of ADRs [8, 69, 70]. The relationship between ADRs and virologic suppression may be explained by the fact that ADR is a risk factor for poor adherence [69, 71], which is on the causal pathway to virologic failure [72-74]. This fact was supported by some studies which reported that patients who experienced severe ADR were less likely to be ≥90 % adherent to ART [69, 75, 76].

4.2. Strengths and Limitations

The findings presented in this study reflect real-life HIV management practices and patients' experiences concerning ADRs and virologic success rates in a resource-limited setting, which is a major strength. The large cohort of patients examined, the period of follow-up, and the availability of ADR and viral load data added strength to the finding of a

causal association between ADRs and virologic failure. Despite the strengths of the study, the generalization of the study results to other settings should be done cautiously, considering the fact that it was a single institutional study. Other limitations of the study included the focus of the study on clinical ADRs; apart from anemia, we did not examine other laboratory markers of drug toxicity with potentials to affect virologic outcomes. Additionally, we may have missed some adverse drug events, which overlapped with symptoms of HIV/AIDS, with a resultant underreporting of the prevalence of such ADRs in the study. Furthermore, we recommend additional studies to examine the association between the severity of ADRs and virologic failure, as that was not done in this study. Finally, missing data on certain variables was a challenge in this study. For instance, only patients with viral load data were included in the virologic outcomes analysis. The Missing individual-level potential outcomes or counterfactual outcomes could introduce some level of bias into our estimates. However, we evaluated virologic outcomes in close to 8000 patients, which added strength to the aggregated causal effect observed in the study.

CONCLUSION

Our findings indicate a low rate of adverse drug reaction and a high rate of virologic failure at 24 and 72 weeks of ART in the studied population. Antiretroviral therapy related anemia increased the likelihood of late virologic failure; hence, routine monitoring of hemoglobin levels and prompt management of anemia in all patients on ART is recommended as a strategy to improve virologic success rates. Also, we recommend close follow-up of patients throughout the duration of ART, to track and manage both early and late onset ADRs with the potential to impact on treatment success.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The University of Western Cape (UWC), South Africa, Research Ethics Committee approved the study protocol.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20 activities/10 ethics/10helsinki/).

CONSENT FOR PUBLICATION

Jos University Teaching Hospital ethical committee and Harvard T.H. Chan School of Public Health approved the use of data, obtained from the patients. As the study involved the use of retrospective data, patient consent was waived. To ensure the confidentially of patients' information, data extracted from the electronic medical record system was de-identified and stored in an encrypted format in a secure computer system accessible only to the researcher.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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