A prospective study of adverse events to antiretroviral therapy in HIV- infected adults in Ekiti State, Nigeria

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Abstract

Objectives: Highly active antiretroviral therapy (HAART); the-current standard of antiretroviral therapy for Human Immunodeficiency Virus (HIV) infected persons, has been documented to drastically reduce the number of cases of Acquired Immune Deficiency Syndrome (AIDS). However, adverse events are a challenge to the use of HAART. This study intends to determine the nature and incidence of suspected adverse events to prescribed antiretroviral drugs in treatment centers in Ekiti State.

Method: One hundred and twenty participants were enrolled and followed up over a period of six months. At each clinic visit, there was an administration of a detailed interviewer questionnaire that was completed by the attending pharmacist together with the participant. The form is designed to obtain information on the demographics of the patients, WHO clinical stage of their HIV infection, HAART regimen for the patients, and suspected adverse events associated with the antiretroviral drugs used by the patients.

Results: Tenofovir/Lamivudine/Efavirenz (72.5%), Zidovudine/Lamivudine/Nevirapine (16.7%), Zidovudine/Lamivudine/Efavirenz (6.7%), Tenofovir/ Lamivudine/Nevirapine (3.3%), and Abacavir/ Lamivudine/Nevirapine (0.8%) were the HAART regimens prescribed to the patients. About half (57%) of the participants reported clinical adverse events; 92% of which were reported within two weeks of HAART initiation. Most of the reported adverse events were nausea (14.5%), abdominal discomfort (8.2%), and insomnia (7.5%). A few (6%) of those who reported adverse events required regimen switch or drug substitution.

Conclusions: Antiretroviral drugs exposure often presents with adverse events, an observation similar to other studies. Most of the clinical adverse events were not severe or life threatening.

Résumé

Objectifs: La thérapie antirétrovirale hautement active (HAART); type courant de thérapie antirétrovirale pour lespersonnes infectées duVirus d'Immunodéficience Humaine (VIH), a été documenté pour réduire considérablement le nombre de cas de Syndrome d'Immunodéficience Acquis (SIDA). Cependant, les événements indésirables sont un défi à l'utilisation de laHAART. Cette étude vise à déterminer la nature et l'incidence des effets indésirables présumés des médicaments antirétroviraux prescrits dans les centres de traitement dans l'État d'Ekiti.

Méthode: Cent vingt participants ont été recrutés et suivis sur une période de six mois. A chaque visite à la clinique, il y avait une administration d'un questionnaire d'entrevue détaillée qui a été complété par le pharmacien traitant ainsi qu'avec le participant. Le formulaire est conçu pour obtenir des informations sur les caractéristiques démographiques des patients, lestagecliniqueOMS de leur infection par le VIH, régime HAART pour les patients, et événements, indésirablessoupçonnés, associés aux médicaments antirétroviraux utilisés par les patients.

Résultats: Ténofovir / Lamivudine / Efavirenz (72,5%), Zidovudine / Lamivudine / Névirapine (16,7%), Zidovudine / Lamivudine / Efavirenz (6,7%), Ténofovir / Lamivudine / Névirapine (3,3%), et Abacavir / Lamivudine / Névirapine (0,8 %) ont été les régimes HAART prescrits aux patients. Environ la moitié (57%) des participants ont signalé des effets indésirables cliniques: dont 92% ont été signalés dans les deux semaines d'initiation à la HAART. La plupart des événements indésirables rapportés étaient les nausées (14,5%), les douleurs abdominales (8,2%) et l'insomnie (7,5%). Un peu (6%) de ceux qui ont signalé des effets indésirables nécessitait un changement de régime thérapeutique ou substitution du médicament.

Conclusions: L'exposition aux médicaments antirétroviraux présente souvent avec des événements indésirables, une observation similaire à d'autres études. La plupart des événements indésirables cliniques n'étaient pas graves ou mortelles.

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Introduction

Highly Active Antiretroviral Therapy (HAART) defined as a combination of three or more antiretroviral agents taken concurrently to suppress the replication of Human Immunodeficiency Virus (HIV) and to prevent the development of resistance which may compromise future therapeutic options [1]. HAART is the current standard of antiretroviral therapy for HIV-infected persons [2-4]. Despite the benefits of HAART, antiretroviral drugs are not completely free of adverse events [3]. In the Swiss HIV Cohort Study, 47% of the patients presented with clinical and 27% with laboratory adverse events probably or definitely attributed to ART [5].

Initial clinical trials may detect common and frequent adverse events. It is however known that some important adverse events occur infrequently or take longer to develop. Also, clinical trials are controlled medical situations and may not necessarily reflect product usage patterns in real life conditions [6-8]. Literature reports of controlled clinical trials of therapeutic drugs are generally poor at reporting adverse events [6]. As with other drugs, individual reports may be the only source of information concerning previously unknown or undetected adverse events or changes in product safety and effectiveness profiles of ARV agents currently in use [9].

Many studies have looked into the clinical and epidemiological pattern of HIV/ AIDS in Nigeria [10-12]; there is however scarce information on adverse events following exposure to antiretroviral drugs. We have previously reported some clinical and laboratory adverse events among HIV-infected children on HAART regimen in Nigeria [13]. Considering a larger population of HIV-infected adults than children in Nigeria, it is imperative to investigate the incidence of AEs among HIV-infected adults.

We sought to evaluate ARV drug combinations prescribed at selected HIV/AIDS clinics in Ekiti state, South-western Nigeria and to document the nature as well as the incidence of suspected adverse effects (AEs) associated with the HAART regimen.

Method
Study setting
This study was conducted at the Pharmacy Units of the HIV/AIDS Clinics of the Federal Medical Centre, Ido-Ekiti and Ekiti State University Teaching Hospital, Ado-Ekiti, Ekiti State, Nigeria. These are centres where comprehensive HIV/AIDS services such as Voluntary Counseling and Testing (VCT), Antiretroviral Therapy (ART) and Prevention of Mother to Child Transmission (PMTCT) are being provided.

Study population
As part of the strategies for monitoring adverse events, no fixed formula or specific number of reports is required and global recommendations are that all patients [6,14] including our focus subjects attending the HIV/AIDS clinics be screened for AEs routinely. This prospective and descriptive study thus enrolled all patients attending the clinics over a time frame of 6 months based on the following inclusion criteria: HIV-infected adults just being initiated on HAART at the start of this study; adults who have been switched to a new regimen at the start of this study, or those who have been previously lost to follow up and now restarted at the start of this study.

Participants were followed up over a period of six (6) months. At each visit to the clinic, either for routine drug refill or for other medical reasons such as presentation with concomitant illness or drug related problems, pertinent information was obtained with the aid of an interviewer (researcher) administered questionnaire completed by the attending pharmacist. The questionnaire was designed to capture the following information: the demographics (age, gender, educational status, and occupation), and HIV status of the patient (WHO clinical stage of the disease, comorbid diseases, and concomitant infections at presentation). Other important information extracted from the case file of the patients includes the results of routine laboratory investigations conducted during the study, ARV prescribed, the date commenced, and concomitant medications prescribed.

Adverse events defined as any untoward medical occurrence in the patient to prescribed ARV drugs (which does not necessarily have a causal relationship with treatment) were determined and based on an increase in the severity of presenting symptoms, presence of new symptoms after enrolment on HAART, known adverse events to each ARV drug documented in the WHO's HIV treatment guidelines [2], and rare adverse events to ARV drugs published as case reports. Laboratory adverse events are determined based on the abnormalities observed in the laboratory results before and after enrolment on HAART regimen with reference to the WHO's treatment guidelines [2].

Data analysis

Data are presented as frequency distribution and percentages. Statistical analysis (Bivariate analysis - logistic regression) on the results was done using the Statistical Package for the Social Sciences (SPSS) version 16. Results were considered significant at $p<0.05$.

Ethical issues

Ethical approvals were obtained from the Clinical and Ethics Committees of Federal Medical Centre, Ido-Ekiti and Ekiti State University Teaching Hospital, Ado-Ekiti prior to the conduct of this research. Each participant was duly informed both in official and native languages of the intent and reasons for the study; thereafter, verbal consent was obtained. All data extracted from the medical records of the patients remained anonymous.

Results

A total of 120 participants were enrolled in the study. Their demography is presented in table 1. They were predominantly female (72.5%) and mostly between 26-35years (44.2%). About half of the population had secondary education (52.5%).

Table 1: Demographics of study population

Demographic parameter	Frequency (n)	Percentage (%)
Sex		
Male	33	27.5
Female	87	72.5
Total	120	100.0
Age (years)		
15-25	25	20.8
26-35	53	44.2
36-45	27	22.5
46-55	12	10.0
>55	3	2.5
Total	120	100.0
Education		
Uneducated	5	4.2
Primary	15	12.5
Secondary	63	52.5
Tertiary	29	24.2
Vocational	8	6.7
Total	120	100.0

The clinical stage of the patient and the HAART regimen prescribed is presented in table 2. At enrollment, many of the patients (49.2%) had WHO stage 3 of the disease, 50.8% were in stage 1 and 2, while none had WHO stage 4 of the disease. Almost all the participants (94.2%) had never been on antiretroviral medications prior to enrolment. Majority of the participants (72.5%) were initiated on Tenofovir/Lamivudine/Nevirapine (TDF/3TC/NVP) while only one person was initiated on Abacavir/Lamivudine/Nevirapine (ABC/3TC/NVP).

Table 2: Clinical characteristics of study population

	Frequency (n)	Percentage (%)
WHO Clinical Stage		
Stage 1	19	15.8
Stage 2	42	35.0
Stage 3	59	49.2
Stage 4	0	0.0
Total	120	100.0
ARV Experience		
Naïve	113	94.2
Re-Started	7	5.8
Total	120	100.0
Regimen		
TDF/3TC/EFV	87	72.5
AZT/3TC/NVP	20	16.7
AZT/3TC/EFV	8	6.7
TDF/3TC/NVP	4	3.3
ABC/3TC/NVP	1	0.8
Total	120	100.0

ARV=Antiretroviral; TDF= Tenofovir; 3TC=Lamivudine; EFV=Efavirenz; AZT=Zidovudine; ABC=Abacavir; NVP=Nevirapine

Figure 1 shows the distribution of antiretroviral drugs among our study population. All the participants took Lamivudine, while 79.2% and 75.8% were on Efavirenz and Tenofovir containing regimens, respectively.

Figure 2 shows the prevalence of co-infections or symptoms of disease among our study population. While 33.3% had no existing symptoms of co-infection or disease; 20% had co-existing tuberculosis infection.

Additional medications prescribed to the participants are presented in Figure 3. Most of the patients (80%) routinely used Cotrimoxazole as prophylaxis against *Pneumocystis jiroveci*.

Table 3 shows the proportion of participants who reported adverse events, the onset of these events and the actions taken during their follow-up. About half (57.5%) of the participants reported adverse events, most (94.2%) of which were reported within two (2) weeks of initiating ART. Treatment was continued in
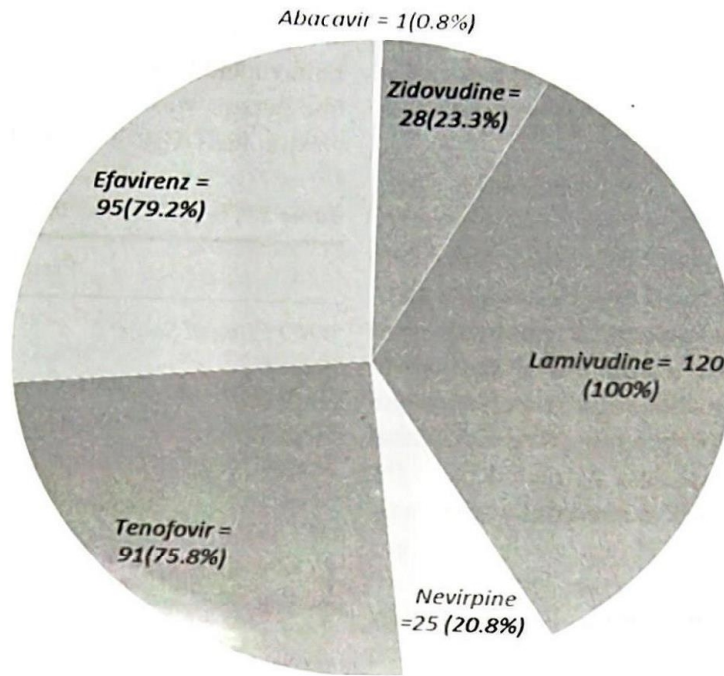
Fig. 1: Distribution of antiretroviral drugs in prescribed regimens among the HIV-infected adult populations that were studied
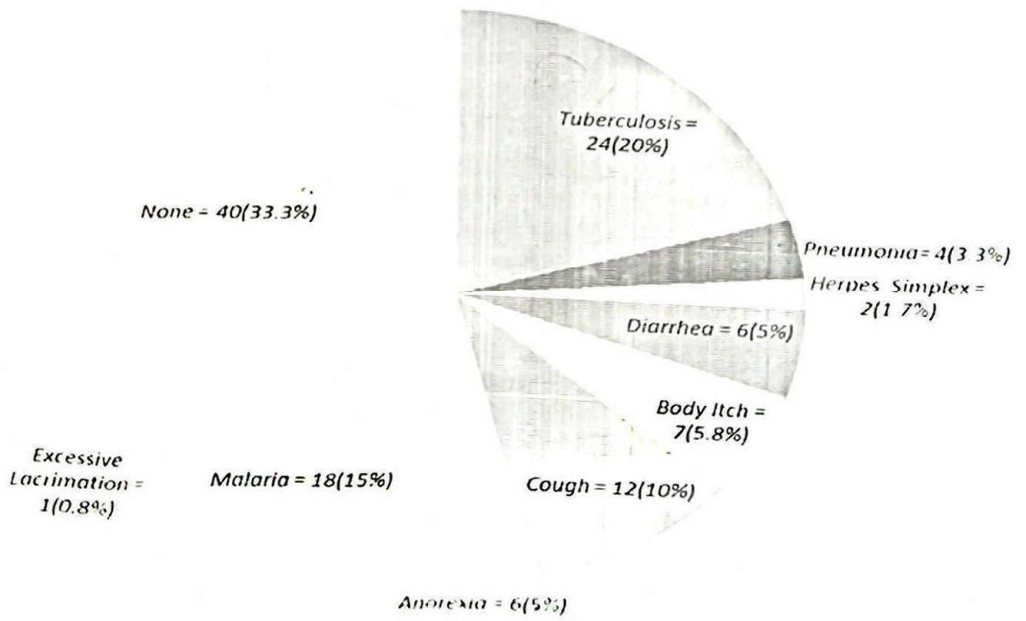

Fig. 2: Pattern of co-infections or symptomatology among the HIV-infected participants
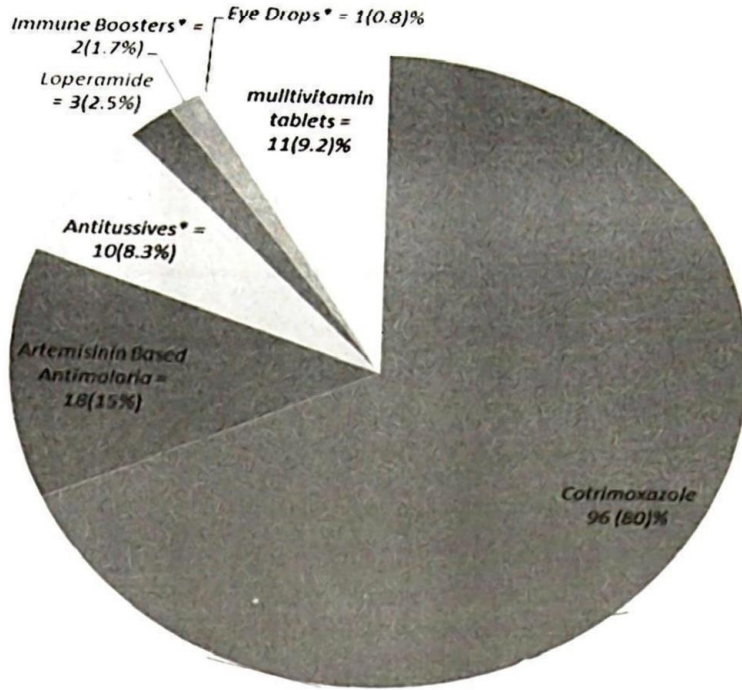
Fig. 3: Pattern of co-medications used by the HIV-infected patients in our study population
Immune boosters: Immunace, Immiflex
Antitussives such as Coflin, Emzolyn, Benylin
Eye drops: Gentamicin eye drops

Table 3: Adverse event reporting among study population

	Frequency (n)	Percentage (%)
Adverse events reporting status		
None	51	42.5
Reported	69	57.5
Total	120	100
Onset of AEs		
<2 weeks	65	94.2
2-4 weeks	3	4.3
4-6 weeks	1	1.4
>6 weeks	0	0.0
Total	69	100
Follow up Actions		
Encouragement	64	92.8
Drug Substitution	4	5.8
Regimen Change	1	1.4
Total	69	100

AE= Adverse Event.

most of the patients (92.8%) with an assurance that the events would stop with time. Table 4 shows the pattern of adverse events reported to the various antiretroviral regimens by the study participants. Nausea (14.5%), abdominal discomfort (8.2%), and insomnia (7.5%) are most common adverse events reported by the patients Bivariate analysis showed that there was a significant association ($p<0.007$) between regimen and the reporting of adverse events (table 5). However, no statistically significant relationship was found between adverse events and age, gender, level of education or use of other medications.

Discussion

Towards the achievement of zero new HIV infections, United States Agency for International Development (USAID) and their partners have been working towards reduction of transmission. It is reported that the rate of new HIV infections has been reduced by more than 50% among adults (15-49 years) in 25 countries between

Table 4: Adverse events reported by the study participants

Adverse Events	Regimen AZT/3TC NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV	ABC/3TC/NVP	Frequency	Percentage
Insomnia	5	-	-	7	-	12	7.5
Dizziness	-	1	-	9	-	10	6.3
Decreased appetite	3	-	—	7	-	10	6.3
Headache	-	2	3	3	1	9	5.7
Double vision	-	2	-	7	-	9	5.7
Blurred vision	-	1	-	3	-	4	2.5
Agitation	-	-	-	2	1	3	1.9
Sleepiness	-	-	-	3	-	3	1.9
Delusion	-	-	-	3	-	3	1.9
Confusion	-	-	-	2	-	2	1.3
Depression	-	-	-	1	-	1	0.6
Feeling of drunkenness	-	-	-	1	-	1	0.6
Stupor	-	-	-	1	-	1	0.6
Nausea	9	-	-	13	1	23	14.5
Abdominal discomfort	5	3	1	4	-	13	8.2
Body itching	7	1	1	-	1	10	6.3
Skin rashes	6	-	3	-	-	9	5.7
Weakness of the body	-	-	-	6	-	6	3.8
Palpitations	-	-	-	5	-	5	3.1
Cough	4	-	-	-	-	4	2.5
Diarrhea	4	-	-	-	-	4	2.5
Prickling sensations	-	-	-	3	—	3	1.9
Fever and chills	-	-	-	3	-	3	1.9
Skin darkening	2	-	-	-	---	2	1.3
Vomiting	1	-	-	1	-	2	1.3
Amenorrhea	-	-	-	2	-	2	1.3
General feeling of discomfort	-	-	-	2	-	2	1.3
Dysmenorrhea	1	-	-	-	-	1	0.6
Joints swelling	1	-	-	-	-	1	0.6
Dystonic reactions	1	-	-	-	-	1	0.6
Total	49	10	8	88	4	159	100

Table 5: Association between regimen and presence or absence of adverse event to ARV

Regimen	Adverse events to ARV		X²(df)	P-value
	None	Yes		
ABC/3TC/NVP	-	1.4%(1)	13.958(4)	0.007*
AZT/3TC/EFV	4.0%(2)	8.6%(6)		
AZT/3TC/NVP	4.0%(2)	25.7%(18)		
TDF/3TC/EFV	90.0%(45)	60.0%(42)		
TDF/3TC/NVP	2.0%(1)	4.3%(3)		

2001 and 2011 [15]. The report was quick to point that recent national trends for the most part compellingly indicate that with expanded and sustained HIV prevention and treatment programmes rapid declines are possible. The total percentage of people in this study initiated (and to a much lesser extent re-started) on therapy within the age bracket (15-45years) was 87.5% suggesting that Nigeria is surely keying into this vision. This also agrees with a report [16] where about 80% of the patients were between the ages of 15-46 years. It is important to note that this population constitutes the reproductive and productive age group who are likely to spread the disease as well as contribute to the economic growth of the country. Adequate educational campaigns may be necessary to drastically curtail the incidence of HIV in this age group.

The findings of this study show that 20% of the patients were co-infected with Tuberculosis (TB). This is consistent with an earlier report that states that the majority of TB cases in people living with HIV/AIDS occur in sub-Saharan Africa, where up to 80% of TB patients may be co-infected with HIV [17]. HIV/AIDS and TB are commonly called the "deadly duo" and nearly 40 million people are living with HIV infection worldwide and as many as one-third are co-infected with TB [17]. Previous studies in Nigeria have reported prevalence of co-infection of TB in HIV/AIDS patients that ranged from 12.0% in Ile-Ife [18], 10.0% in Kano [19], 10.5% and 14.9% among children and adults respectively in Sagamu [20,21], 10.8% in Irrua [22], 6.1% among those aged 20-40 years in Jos [23], 37.5% in Benin City [24], 4.2% in Oyo state, 35.1% in Benue State [25], and 41.2% in Nasarawa state [26].

In the Swiss HIV Cohort Study [5], 47% of patients presented with clinical adverse events; the results from this study show a similarity with 57% of the participants reporting clinical adverse events. From this study, the most reported adverse events were nausea (14.5%), abdominal discomfort (8.2%), insomnia (7.5%), with body itching, dizziness and decreased

appetite (6.3% each), and skin rashes (5.7%). This also agrees with the report from the Swiss cohort study [5] where gastrointestinal complaints were the AEs most frequently reported. In a prospective study conducted from 2001 to 2003 to assess the factors that were associated with adverse reactions among individuals initiated on antiretroviral therapy at HIV/AIDS centres in Belo Horizonte, MG, Brazil [27], at least one adverse event was recorded on 34.5% of the 130 medical charts, while nausea (14.5%) and vomiting (13.1%) were the most common ones. Also, these adverse events were substantial among participants being initiated on antiretroviral therapy.

This study was also designed to obtain information on laboratory adverse events. However, incomplete documentation makes it impossible to present such data. This underscores the importance of appropriate and adequate documentation of the results of routine laboratory investigations in the management of HIV infection. This is however one of the limitations of this study.

Adverse events were majorly reported among patients taking Zidovudine/Lamivudine/ Nevirapine (AZT/3TC/NVP) (49/159) and Tenofovir/Lamivudine/ Efavirenz (TDF/3TC/EFV) (88/159) regimens. This however may be termed 'expected' as the two regimens are the most prescribed ARV combinations. In a study designed to evaluate the incidence, type and risk factors associated with adverse drug events among patients on antiretroviral drugs [16], in contrast to observations from the current study, 54% of events were reported by patients on AZT with 47% of these occurring in patients on AZT/NVP. The commonest adverse events reported were pain (30%) and skin rash (18%). However, similar to our findings, they reported that adverse events were less likely to occur in patients on d4T (Stavudine) and AZT compared to those on TDF.

The onset of adverse events reported in this study was majorly less than two weeks. This was at variant to the onset period of 3-6 months reported in

previous studies [16]. In the previous studies, regimen switch and dose adjustments were identified and used to manage adverse events to antiretrovirals. Similar method was adopted in our patients; however, only a few patients had a treatment switch or drug substitution in our study compared to the previous studies [19].

Bivariate analysis of data obtained from this study showed no associations between age, gender, education, use of additional medication and the reporting of adverse events. Although a statistically significant ($p<0.05$) association between regimen and reporting of adverse effect was noted in this study, the small population of the patients enrolled on ABC/3TC/NVP, AZT/3TC/NVP and TDF/3TC/NVP will require that we interpret this result with caution.

There are mixed reports from studies on associations between age and incidence of adverse events. Some studies reported a higher tendency to develop adverse events among participants over 35years old [28-31]; other studies [27] however showed no such associations. In agreement with the findings of this study, certain studies have found no differences in total adverse event count or severity by gender [32].

Conclusion

Despite the limitations of this study, we found that exposure to ARV drugs was generally often associated with adverse events. Most of the clinical adverse events observed were neither severe nor life threatening and tapers off (mostly after two weeks of therapy), thus suggesting a good safety profile of the ARV drugs. However, events such as dizziness or double vision following ARV exposure may be potentially life threatening in certain context such as driving a vehicle or operating machinery.

Staff training on pharmacovigilance of ARV drugs, institution of a detailed questionnaire to elicit pertinent adverse events of ARV drugs, and adequate documentation of laboratory results could improve monitoring of adverse events associated with the use of ARV drugs in a resource limited country like Nigeria.

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