Adverse Reactions Associated with Antiretroviral Regimens in Adult Patients of a University Teaching Hospital HIV Program in Zaria, Northern Nigeria: An Observational Cohort Study

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Abstract

Background: Highly active antiretroviral therapy (HAART) has reduced the morbidity associated with HIV infection, and prolonged the lifespan of HIV/AIDS patients, but reports of adverse reactions associated with the antiretroviral drugs exist in the literature. The aim of this research was to determine the frequency and pattern of adverse drug reactions (ADRs) in HAART-experienced patients in our facility from January 2000 to December 2009.

Method: Patients on HAART who had a defined temporal relationship between an adverse or noxious reaction and the administration of the drugs at doses normally used in man for the treatment of HIV disease were studied. Patients who developed adverse reactions to non-antiretroviral drugs were excluded.

Result: of 3641 patients, 380 (10.4%) comprising 289 females (76.1 %) and 91 males (23.9%) of respective mean ages, 35.1 ± 7.4 and 43.2 ± 5.9 years, and respective median CD4+ cell counts, 256/µL and 124/µL, had various forms of ADRs. Zidovudine/lamivudine/nevirapine (43.2%), stavudine/lamivudine/nevirapine (26.3%), zidovudine/lamivudine+efavirenz (12.4%), truvada+ nevirapine (9.5%), zidovudine + truvada + ritonavir-boosted lopinavir (8.2%) and truvada/efavirenz (0.5%) were responsible. Mean onset of ADR was 34 days, and there was a female predisposition. The common ADRs were: nausea/hypersalivation/vomiting (124, 34%), skin rash (100, 26.3%), Steven-Johnson syndrome (27, 7.1%) and anemia (27, 7.1%). Significant risk factors were: baseline CD4+ cell counts > 250/µL, on –therapy CD4+ cell counts > 250/µL, female gender, and type of regimen.

Conclusion: Current antiretroviral regimens are associated with various forms of ADRs, thus the need to strengthen pharmacovigilance and proper education of patients on the side effects and possible adverse reactions of ARV regimens.

Keywords: Adverse drug reactions; HAART; Antiretroviral regimens; Pharmacovigilance, Zaria, Nigeria

Background

Highly active antiretroviral therapy (HAART) has reduced the morbidity associated with HIV infection, and prolonged the lifespan of HIV/AIDS patients [1,2], but reports of morbidity and mortality from adverse reactions (ADRs) associated with the antiretroviral (ARV) drugs have tended to reduce these benefits [3-5]. In Africa and most resource-limited economics, the incidence of ADRs and toxicities have been shown to be responsible for frequent changes in first-line antiretroviral therapy (ART), and/or to the few available second-line regimens [4,5]. The first-line ART consist of the generic, fixed-dose combination (FDC) regimen of stavudine (d4T) or zidovudine (AZT) plus lamivudine (3TC) and nevirapine (NVP) or efavirenz (EFV) [6], although tenofovir disoproxilfumarate (TDF) plus 3TC or emtricitabine (FTC) and NVP or EFV combination regimens can be found in some settings [7]. The second-line ART comprises the protease inhibitors [ritonavir-boosted lopinavir (LPV/r)] plus TDF/FTC plus either AZT, d4T, or didanosine (ddI) [4,7].

Within the past decade, the World Health Organization (WHO) made ARV-associated ADRs the focus of many studies in patient safety and quality control, with the recognition that prevention of potential ADRs is a key element of efforts to improve patient care. This was sequel to increasing reports of ADRs and toxicities associated with the use of the first-line regimens from both developing and the developed countries [5,8-11]. These reports led to the revision of ART guidelines which recommended, among other things, the reduction of the dose of d4T from 40mg to 30mg for all patients, irrespective of body weight; the substitution of d4T with AZT or TDF in the presence of d4T toxicity, and of NVP with EFV in females and males with baseline CD4+ cell counts above 250/µL and 400/µL respectively [12-15].

Because ADRs may be influenced by many factors, it is necessary to monitor patients on ART by keeping accurate information on their morbidity. Such information can be helpful as a guide to the
were scheduled to return 2 weeks after initiation for review, and dose adherence counseling [17]. All patients started on NVP-based HAART given.

Antiretroviral regimens

A. The following first-line ARV regimens were provided by the Program [7]

i. AZT 300mg/3TC 150mg (as FDC “combivir”) BD + NVP 200mg BD (200mg once daily for first 14 days) or EFV 600mg nocte.

ii. AZT 300mg/3TC 150mg/NVP 200mg (FDC, code 107) BD

iii. D4T 30mg/ 3TC 150mg/NVP 200mg (as FDC) BD or EFV 600mg nocte (d4T was withdrawn from the Program in 2008, in compliance with the revised WHO recommendations of 2006).

iv. TDF 300mg/FTC 200mg (as FDC “truvada”) once daily + NVP 200mg BD

v. TDF 300mg/FTC 200mg/EFV 600mg (as FDC “atripla”) nocte. Tenofovir – based regimens were introduced in June 2007

B. Patients who failed first-line ART were switched to second-line regimen, comprising AZT 300mg BD + LPV/r 400mg/100mg BD +TDF 300mg/FTC 200mg once daily. This regimen was introduced in June 2007.

Patient’s evaluations and clinic visits

According to our protocol, all HIV-infected patients (including pregnant women) referred to the center underwent a uniform enrollment procedure [16]. At the first (pre-ART assessment) visit, ART-naïve HIV-infected patients underwent post-test counseling, complete clinical evaluation; screening for OIs/malignancies; phlebotomy for Western blot confirmation, hepatitis B and C serology, complete clinical evaluation; screening for OIs/malignancies; monitoring of CD4+ cell count, plasma viral load (pVL), blood chemistry and hematology, at no cost to patients.

Study site

The ABUTH HIV PROGRAM started in January 2000, under the Nigerian National ARV Program, to provide antiretroviral therapy (ART) at subsidized rates, using d4T or AZT plus 3TC plus NVP as the two first-line regimens, to a population of more than 15 million people spread across 10 states in northern Nigeria, including the Federal Capital, Abuja. In 2006, ABUTH/HAIVARDPEPFAR expanded the HIV Program through provision of more ARV regimens and drugs for opportunistic infections (OIs) prophylaxis; monitoring of CD4+ cell count, plasma viral load (pVL), blood chemistry and hematology, at no cost to patients.

Materials and Methods

Study design

For the purpose of the study, we modified the WHO definition of ADR as “an appreciably harmful or unpleasant reaction that is potentially life-threatening, or can cause permanent bodily damage, congenital abnormality (in pregnancy) or even death, resulting from the use of an antiretroviral regimen at doses normally used in man for the treatment of HIV, which may warrant reduction of dosage regimen or withdrawal of regimen, and also excludes medication error as a source of adverse reaction” [18].

The clinical team

The pharmacovigilance team (which is headed by OOR) was responsible for the detection, confirmation and reporting of ADRs, as well as management of affected patients. It consists of nurses, clinicians, physicians, pharmacologists and pathologists with vast knowledge of HIV and ARVs. The authors are members of this team, and collaborated with one another throughout the study. ADRs were either reported by affected patients, or were detected by nurses and clinicians, who in turn referred the patients to OOR for confirmation and documentation, in consultation with other members of the team. The prescription pads of affected patients were then scrutinized to ensure that the ADRs were not due to medication errors.

Surveillance tools for the evaluation of ADRs

The surveillance tools used were:

1. The National Agency for Food and Drug Administration and Control (NAFDAC) Pharmacovigilance Form [19].

2. AIDS Prevention Initiative in Nigeria (APIN)/HarvardPEPFAR adult prescription pad [20].

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The onset of ADR was maximal in majority (280, 74%) of the patients between 31 and 90 days after ARV initiation, being significantly earlier in females (median 32 days) than males (median 66 days) (Figure 1). However, the time of onset of ADRs varied from 10 to 1090 days. These were distributed as follows: skin rash (10 to 96 days, median 32); insomnia (14 to 42 days, median 36); somnolence (12 to 130 days, median 48); bad dreams (12 to 30 days, median 16); nausea, hyper-salivation and vomiting (10 to 38 days, median 32); severe headache (14 days); SJS (28 to 40 days, median 36); jaundice (14 to 90 days, median 36); diarrhea (11 to 29 days, median 15); anemia (34 to 482 days, median 38); peripheral neuritis (86 to 294 days, median 92); discolored nails (184 to 1080 days, median 220); palm hyperpigmentation (230 to 365 days, mean 298); proximal muscle pain and weakness (78 to 378 days, median 90) and facial lipodystrophy (270 to 1090 days, median 254).

Virologic and immunologic status of patients at time of ADRs

The females had significantly higher median CD4+ counts than males (256 cells/µL; 124 cells/µL, P=0.00) at time of ADR. They also demonstrated a rapid rise of CD4+ counts from a median baseline of 110 to 256 cells/µL, in contrast to the static CD4 levels in males. The females also showed appreciable reduction in the number of person with detectable plasma viral load at the time than the males (Table 2).

Frequency distribution of antiretroviral regimens and their ADRs

Table 3 showed that 2025 (55.6%) and 78 (2.1) of the patients on the program were on AZT/3TC/NVP and AZT/3TC+EFV from 2000 to 2009 respectively; 1145 (31.4%) and 5 (0.1%) were on d4T/3TC/NVP and d4T/3TC+EFV from 2000 to 2008 respectively; 170 (4.7%) and 58 (1.6%) were on TDF/FTC+NVP and TDF/FTC/EFV respectively from 2007 to 2009, and 160 (4.4%) patients who failed first-line ART were switched to the only second-line regimen, AZT+ LPV/r +TDF/FTC from 2007 to 2009.
Of the 380 (10.4%) patients with ADRs, 164 (4.5%) and 100 (2.7%) were on AZT/3TC/NVP and d4T/3TC/NVP, respectively, while the remaining 116 (3.2%) were on AZT/3TC+EFV (47.1%), TDF/FTC+nVP (36.1%), AZT+LPV/r+TDF/FTC (31.0%) and TDF/FTC/EFV (2.0%) respectively. Patients on d4T/3TC+EFV had no ADR. However, patients on AZT/3TC+EFV had the highest incidence of 60.3 ADRs per 100-person years, followed by those on TDF/FTC+NVP (21.2), AZT + TDF/FTC+LPV/r (19.4), d4T/3TC/NVP (8.7), AZT/3TC/NVP (8.1) and TDF/FTC/EFV (3.4) respectively.

The commonest ADRs were nausea, vomiting and hypersalivation which occurred in 129 (34%) of the patients on 5 regimens with the exception of d4T/3TC+EFV and TDF/FTC/EFV. These were followed by skin rash in 62 (16.3%) and 38 (10.0%) patients on AZT/3TC+NVP and d4T/3TC+NVP respectively; anemia in 24 (6.3%) and 3 (0.8%) patients on AZT/3TC+NVP and AZT + TDF/FTC+LPV/r respectively; Steven-Johnson syndrome (SJS) in 20 (5.3%) and 7 (1.8%) patients on d4T/3TC+NVP and AZT/3TC+NVP respectively; and diarrhea in 10 (2.6%) and 8 (2.1%) patients on TDF/FTC+NVP and AZT+TDF/FTC+LPV/r respectively. Only patients on AZT/3TC+NVP had jaundice (16, 4%) and discoloration of fingernails (10, 3%) respectively; while only those on d4T/3TC+NVP reported peripheral neuritis (12, 3%), facial lipodystrophy (6, 2%), and palm hyperpigmentation (2, 0.5%)
respectively. Insomnia, somnolence and severe headache were reported by 10 (2.6%), 7 (1.8%) and 1 (0.3%) patients on AZT/3TC+EFV. Also, 4 (1.1%) patients on this regimen complained of bad dreams, although 2 (0.5%) others on TDF/FTC/EFV also had similar ADR. Finally, proximal muscle pain and weakness were reported by 5 (1.3%), and 2 (0.5%) each respective patients on AZT/3TC/NVP, AZT/3TC+EFV and TDF/FTC+NVP.

Causality assessment, severity and outcome of adverse drug reactions

The Naranjo score of 235 (61.8%) of ADRs diagnosed were >9, while 135 (35.5%) and 10 (2.6%) others received the score of 5-8 and 1-4 respectively. The severity grading showed that 64 (16.8%), 193 (50.8%), and 2 (0.5%) each of the ADRs were severe, moderate and mild, respectively. The outcomes of the ADRs were generally good, as 338 (88.9%) of the patients recovered fully with treatment, 39 (10.2%) recovered with some physical residual disability and only 3 (0.9%) patients died (Table 4).

Risk factors for ADRs

Baseline CD4+ cell counts >250/µL, on-therapy CD4+ cell counts >250/µL, age between 16-59 years, female gender, and type of regimen, were the significant risk factors for ADRs identified in this study. Age 16-59 years, had Pearson’s correlation coefficient (r) of 0.954 and odds ratio (OR) of 2.5 [95% 1.0-3.7], followed by on-therapy CD4+ cell counts >250/µL with r of 0.637 and OR of 2.3 [95% 0.84-4.7], female gender with r of 0.425 and OR of 1.8 [95% CI, 0.31-2.20], type of regimen with r of 0.37 and OR of 1.6 [95% CI 0.22-1.5], and baseline

### Table 2: The frequency and proportional distribution of antiretroviral regimen and adverse reactions.

| Variable | Antiretroviral regimens prescribed from 2000 to 2009 | Total number of patients (%) |
|----------|-----------------------------------------------------|-----------------------------|
| AZT/3TC / NVP | 2025 (55.6)   | 3641 (100.0) |
| 3T3C / VP | 1145 (31.4)   |   |
| AZT/3TC + EFV | 78 (2.1) | 27 (7.1) |
| TDF/FTC + NVP | 170 (4.7) | 18 (4.7) |
| AZT + TDF/FTC + LPV/r | 160 (4.4) | 16 (4.2) |
| TDF/FTC/EFV | 58 (1.6) | 0 |
| 4T3TC + EFV | 5 (0.1) | 0 |
| Patients per regimen (%) | 838 (100.0) |   |
| Incidence of ADR per 100 | 380 (10.4) |   |
| – person years | 0 |
| Patients with ADR (%) | 129 (34.0) |   |
| Type of ADRs | 380 (10.4) |   |
| Nausea, vomiting, hypersalivation | 40 (1.0) |   |
| Skin rash | 36 (1.0) |   |
| Anemia | 31 (0.9) |   |
| Jaundice | 2 (0.05) |   |
| Peripheral neuritis | 129 (34.0) |   |
| Discoloration of fingernails | 10 (2.6) |   |
| Insomnia | 16 (4.2) |   |
| Proximal muscle pain and weakness | 3 (0.8) |   |
| Somnolence | 27 (7.1) |   |
| Facial lipo-dystrophy | 6 (1.6) |   |
| Bad dreams | 12 (3.2) |   |
| Palm hyperpigmentation | 6 (1.6) |   |
| Severe headache | 16 (4.2) |   |
Both regimens were the only ARV regimens in our center from 2000 to 2007, until 'truvada' and LPV/r were introduced in June 2007. The popularity of these regimens might be due to their availability and accessibility as cheap, generic, once daily FDC tablets [6], which may have contributed to the reluctance of most HIV programs in resource-limited countries to comply with WHO recommendations of 2006 concerning the use of stavudine-based regimens [6,14]. The peculiar socio-demographic characteristics of HIV-infected patients in resource-limited countries which revealed that many of them were unemployed, poor and indigent, and therefore could not afford the expensive branded ARVs used in developed countries, may have contributed to the popularity of the cheap, generic ARVs [4,6,24]. The result of this study, as shown in table 4, which indicated that the respective toxicity profiles of AZT/3TC/NVP and d4T/3TC/NVP, defined in terms of incidence of ADR per 100-person years, were lower than those of AZT/3TC+EFV, TDF/FTC+NVP and AZT+TDF/FTC+LPV/r respectively, could be a reason for their tolerability and safety. In spite of this, our program complied with the WHO recommendation by withdrawing stavudine-based regimens from our facility in December 2008, and substituting it with zidovudine- or 'truvada'-based regimens (if zidovudine was contra-indicated). From June 2007, when both 'truvada' and ritonavir-boosted lopinavir became available, patients who had failed first-line boosted lopinavir became available, patients who had failed first-line contra-indicated). From June 2007, when both 'truvada' and ritonavir-boosted lopinavir became available, patients who had failed first-line ARV were switched over to AZT+truvada+LPV/r, and by December 2009, 60% of patients were on this regimen.

Distribution

The Naranjo algorithm, a well-recognized and fully validated tool widely used for assessing the likelihood that a specific drug is the cause of an ADR, was applied as one of our surveillance tools, in order to enhance the accuracy and reproducibility of this study. Since clinical judgment alone may not be sufficient for us to decide whether a drug was the likely cause of an adverse reaction, the algorithm was able to assist us to establish a definite temporal relationship between the ARVs used in developed countries, may have contributed to the popularity of the cheap, generic ARVs [4,6,24]. The result of this study, as shown in table 4, which indicated that the respective toxicity profiles of AZT/3TC/NVP and d4T/3TC/NVP, defined in terms of incidence of ADR per 100-person years, were lower than those of AZT/3TC+EFV, TDF/FTC+NVP and AZT+TDF/FTC+LPV/r respectively, could be a reason for their tolerability and safety. In spite of this, our program complied with the WHO recommendation by withdrawing stavudine-based regimens from our facility in December 2008, and substituting it with zidovudine- or 'truvada'-based regimens (if zidovudine was contra-indicated). From June 2007, when both 'truvada' and ritonavir-boosted lopinavir became available, patients who had failed first-line ART were switched over to AZT+truvada+LPV/r, and by December 2009, 60% of the patients were on this regimen.

The distribution of ADRs revealed that gastrointestinal symptoms of nausea, vomiting and hypersalivation were the commonest ADRs,

| Variable | Pearson’s correlation coefficient (r) | Odd ratio (OR) 95% Confidence Interval (CI) | P-value |
|----------|--------------------------------------|-------------------------------------------|---------|
| Age 16-59 years | 0.954 | 2.5 (1.03-7) | 0.00 |
| On -ART CD4+ > 250 cells/µl | 0.637 | 2.3 (0.84-4.7) | 0.00 |
| Female gender | 0.425 | 1.8 (0.31-2.20) | 0.011 |
| ARV Regimen | 0.371 | 1.6 (0.22-2.5) | 0.024 |
| Baseline CD4+ > 250 cells/µl | 0.248 | 1.5 (0.1-2.9) | 0.032 |
| Male gender | -2.431 | 1.00 (0.69-1.54) | 0.728 |
| Baseline pVL | -0.382 | 1.00 (0.42-1.24) | 0.972 |

Table 5: Risk factors for adverse reactions.
and were produced by five out of the seven regimens, the exceptions being d4T/3TC+EFV and TDF/FTC/EFV. This is not unusual as most drugs are apt to produce these either as side effects, or as ADRs [24]. Skin rash, SJS and jaundice which were prominent in patients on AZT/3TC/NVP and d4T/3TC/NVP can be attributed to the nevirapine in both regimens [25]. Anemia was found in 24 (6.3%) patients on the first-line regimen, AZT/3TC/NVP and 3 (0.8%) patients on the second-line regimen, AZT+TDF/FTC+LPV/r. The anemia in these patients was attributed to AZT in both regimens, because anemia has been described severally in patients on AZT-based regimens [26,27], and has been a major cause of substitution of AZT with TDF [28]. Also, fingernail discoloration and proximal muscle weakness/pain have been reported as significant late ADRs of AZT, which occurs in patients who have received the drug for more than 6 months [28,29].

Diarrhea is a common side effect of many antiretroviral drugs [30], but it has also been reported as an ADR in patients on protease inhibitors (particularly ritonavir and lopinavir) [31], and nucleotide reverse transcriptase inhibitor (tenofovir) [32]. In this study, diarrhea was an ADR in 10 (2.6%) and 10 (2.1%) patients on TDF/FTC+NVP and AZT+TDF/FTC+LPV/r respectively. This result was lower than those of Boeseck and Cooper [31] who reported diarrhea as a major ADR in 78% of patients on ritonavir-boostered lopinavir and Tosini et al. [32] who reported that diarrhea was a major cause of discontinuation of therapy in many patients on postexposure prophylaxis with tenofovir/emtricitabine. However, while the pathophysiological basis of protease inhibitor-induced diarrhea has been described by Braga Neto et al. [33], that of tenofovir is yet to be elucidated.

Peripheral neuropathy, facial lipodystrophy and palm hyperpigmentation were found only in patients on d4T/3TC/NVP regimen. While peripheral neuropathy and facial lipodystrophy are known toxic effects of stavudine [5,9], palm hyperpigmentation may be an uncommon effect of 3TC, which is related to FTC, known to produce skin discoloration or hyperpigmentation on palms and/or soles in nonwhite patients, particularly children [34]. Insomnia, somnolence, bad dreams and severe headache reported by 22 (5.8%) patients on AZT/3TC+EFV can be attributed to EFV, because those symptoms are the known neuropsychiatric side effects of the drug [35]. The differences in the toxicity profile of the regimens must be a reflection of differences in their formulations and constituent drugs because these two factors are strong predictors of adverse events related to each regimen [4,11,17,18]. Thus a regimen may produce 2 or more unrelated toxicities while 2 regimens containing a specific drug can produce similar adverse reactions [36].

Although more than 20% of these ADRs were severe, the outcome of treatment was generally good, as about 89% of the patients recovered fully, 10% recovered with some residual disability, and 1% (3 patients) died from complications of anemia and SJS. These results are similar to those described by Castelnuovo et al. [4,5] in Uganda. The patients whose jaundice and SJS were thought to be due to NVP had this drug substituted with EFV; those with discoloration of fingernails, proximal muscle pain and weakness, and anemia were switched from AZT- to ‘truvada’-based regimen; while those with peripheral neuropathy, facial lipodystrophy and palm hyperpigmentation were ‘switched’ from d4T-to AZT-based regimens. There was no alternative ARV for the two patients who developed anemia on second-line regimen. Therefore AZT was removed from the regimen, and they were given blood transfusion, just before their demise. These patients, in addition to those who had neither drug switch nor drug substitution, were managed either conservatively or through hospitalization.

The time of onset of ADRs varied from 10 to 1090 days. This wide gap may be due to differences in the complexity, nature and pathophysiology of the various reactions, which ranged from bad dreams with a median interval as short as 16 days to facial lipodystrophy with an interval as long as median of 254 days. However, the majority of the ADRs occurred between 31 to 91 days with median interval being significantly earlier in females (32 days) than males (36 days) (t = -1.936, P = 0.042). It is also important to note that the proportion of females (213, 56%) at maximal onset of ADR were significantly more than males (67, 18%) (X² = 12.154, P = 0.00). These results support the fact that the majority of the patients on ART and with ADRs in this study were females. This is also supported by the result of bivariate correlate and multinomial logistic regression analyses which identified pre-ART and on-ART CD4+ cell counts above 250/µL, female gender, ages 16 to 59 years, and type of regimen as significant risk factors for ADRs in this study. Baseline CD4+ cell counts above 250/µL and > 400/µL are known to predispose females and males respectively to NVP-induced hepatotoxicity [3,11,36], while a rapid rise of CD4+ lymphocytes soon after ART initiation can be an important stimulus of ADR, either as part of an immune reconstitution inflammatory syndrome, or as an isolated disease entity, particularly in patients with very low baseline CD4+ cell counts [37]. Females have been reported to be at greater risk for toxicities due to stavudine and nevirapine [3,5], apart from the fact that the number of females accessing ART in most HIV programs was usually more than the males [5,38-40]. Also, the age groups 16-39 and 40-59 years were the major patient groups accessing ART, and they also had the highest number of persons with ADRs. Many reports attribute their vulnerability to HIV to their agility and propensity to engage in risky life styles [38,40].

Some of the limitations of this study are that some ADRs may have been unreported, or under-reported by many of our patients who were mostly illiterate. Also, we were unable to identify or report any case of lactic acidosis due to lack of tools for measuring serum lactate. However, the results of other hematologic and metabolic toxicities have been described in a previous publication [41].

In conclusion, we hope we have been able to show that some of the current ARV regimens have serious clinical toxicities associated with their use, and that the enormous nature of this problem will continue to be of serious concern to all HIV workers, particularly in sub-Saharan African settings. Clearly, less toxic drugs are needed for our HIV patients, at least, to serve as substitutes when toxicities occur. The present situation of very limited choice of alternative drugs is very precarious. In the meantime health care givers working with HIV programs in resource-poor countries should strengthen pharmacovigilance services, adverse drug reporting systems and patient education on adverse drug reactions.

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