Nature and prevalence of adverse drug reaction of antiretroviral medications in Halibet National Referral Hospital: a retrospective study

Lidya Hagos*, Siyoma Fessehay and Indermeet Singh Anand

Abstract

Background: Monitoring the safety of antiretroviral therapy (ART) remains a challenge in resource-constrained countries such as Eritrea due to their serious adverse drug reactions (ADRs). This study was aimed at assessing the prevalence, nature, seriousness and possible risk factors of ART associated ADRs in Halibet National Referral Hospital in Eritrea.

Method: A three month retrospective, longitudinal, descriptive study of patients treated with ART between September 2005 and December 2016 was conducted in Halibet National Referral Hospital. Demographic characteristics, treatment details, reaction and outcome details, laboratory investigations and other information was abstracted manually from patients’ clinical cards. Statistical analysis was conducted using both univariate and multivariate analysis and statistical significance was tested using 95% confidence intervals and/or \( p \)-value. A \( p \)-value < 0.05 was regarded as being statistically significant.

Results: Of the 309 patients screened, 62.8% encountered at least one ADR and 29.8% of the reactions were serious with similar male to female ratio. Gastrointestinal symptoms were the most common ADR and were associated mostly with Atripla followed by AZT + 3TC + NVP drug combinations, but lipodystrophy followed by peripheral neuropathy which were both commonly associated with Stavudine and anemia associated with Zidovudine were the most serious. Patients with CD4 count below 200 were more likely to develop ADRs \( (p = 0.000) \).

Conclusion: ADRs associated with ART drugs in Halibet hospital were found to be highly prevalent. Furthermore, CD4 count below 200, was identified as a major risk factor that predisposes patients to ADRs. This is burdensome to resource constrained countries such as Eritrea who have limited drug options and high HIV prevalence, therefore these findings will help patients and healthcare professionals understand the nature as well as seriousness of these ADRs and identify the risks involved with ART medications which can help minimize ART associated ADRs early on.

Keywords: Anti-retroviral medications, Adverse drug reaction, Nature, Prevalence, Seriousness, Risk factors

* Correspondence: Liduhg@gmail.com
Asmara College of Health Sciences, P.O box – 1833, Asmara, Eritrea

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
Highly Active Anti-Retroviral Therapy (HAART) has made a significant change in the lives of people living with HIV (PLWH) in decreasing AIDS-related deaths and improving quality of life [1]. Despite their remarkable contribution, these drugs have been associated with serious adverse drug reactions (ADRs) that may lead to drug resistance and switching of anti-retroviral therapy (ART) regimen [2, 3] and emergence of new comorbidities which may lead to decreased adherence consequently leading to virological failure [4, 5]. It has been elucidated that the type of ART regimen influences the timing, nature and duration of ADRs [6, 7]. Furthermore, the occurrence of ADR might be higher in developing countries due to higher prevalence of concomitant conditions, overstretched healthcare systems and economic constraints that would hamper close follow up of patients on HAART [8–10]. Moreover, age, gender and the disease itself have been identified as risk factors for ADRs of HAART in different countries. [6, 11].

Limited study has been conducted on the adverse effect of ART in Sub-Saharan countries, such as Eritrea, despite having high prevalence of HIV. A five-month prospective study conducted in Eritrea by Russom et al. 2017 [12] aimed at measuring ADR related hospital admissions in all Eritrean hospitals showed first line ART drugs (Zidovudine/lamivudine and Tenofovir/lamivudine) to be among the top three drugs implicated in causing ADR related deaths. The study further added that ART associated anemia accounted for 20.8% of the ADR related deaths which could have easily been prevented by appropriate laboratory monitoring. Despite the above facts, no study has been conducted so far in Eritrea to evaluate the safety of ART. The aim of this study was, therefore, to determine the prevalence, nature, seriousness and risk factors of adverse reactions of antiretroviral drugs.

Methods
Study design and setting
This was a retrospective, historically longitudinal, descriptive study conducted in all eligible patients treated with ART in Halibet national referral hospital. Longitudinal data (drug and medical history) of patients compiled between September 2005 and December 2016 in the ART clinic was abstracted from patients’ clinical cards. The HIV clinic in Halibet hospital as part of the infectious clinic gives an outpatient services to 1242 adult patients, above 18 years of age, that come from different parts of the country.

Source and study population
The study population was PLWH/AIDS who were attending Halibet national referral hospital’s ART clinic between 2005 and December 2016. The source population covers all HIV patients in the country as the hospital provides services to all patients coming from different parts of the country. Patient cards that were hard to assess were excluded from this study since the information they presented was not enough to be evaluated. Furthermore, patients aged 60 years and above were also excluded from the study as they may have different co-morbidities and are likely to take multiple drugs which would make the causality assessment more challenging.

Exposure definition
Once a patient is diagnosed with HIV, he/she may start on HAART. HAART refers to the combination of three or more antiretroviral drugs for the treatment of HIV infection. The patients may start therapy regardless of their CD4 count under the new ART guidelines. Once patients decide to start ART, they begin with standard first-line HAART regimen which for an adult includes Atripla (Tenofovir/Emtricitabine/Efavirenz), Tenofovir/Lamivudine+Nevirapine, Zidovudine/Lamivudine+Nevirapine, Zidovudine+Lamivudine+Efavirenz, Abacavir+Lamivudine+Efavirenz, Abacavir+Lamivudine+Nevirapine. Patients who develop resistance to these first-line regimens(clinical failure, immunological failure and virological failure) move to a boosted protein inhibitor (PI) and two nucleoside reverse transcriptase inhibitor (NRTI) combinations as they are preferred strategy for second-line ART. In case of TDF +3TC or FTC based first-line regimen failure, AZT + 3TC or FTC based first-line regimen failure, AZT + 3TC+ ATV/r are used. For AZT + 3TC based first-line regimen failure, TDF + 3TC/FTC + ATV/r and TDF + 3TC/FTC + LPV/r are used as second-line regimens respectively. Since these are combination drugs, they do not use weight-based regimen and the same doses are given to all patients deemed as adults. In case of ADRs, specific or symptomatic relief may be given to alleviate the encountered ADRs and in severe cases the drug may be withdrawn.

Outcome definition
This study’s primary outcome measures were the nature of ADRs encountered, their prevalence, seriousness as well as the possible risk factors that predispose patients to ADRs.

Sampling, study instruments and data collection approach
A sample that would ideally be representative of the patients in Halibet National referral hospital was taken. This sample was calculated using the following formula:
Initial sample size \( \frac{Z^2pq}{e^2} = 384.16 \)

Adjusted to the population size (population correction factor) \( n = \frac{N}{1 + \frac{n}{N}} = 293 \).

Where \( p = \) prevalence of ADR = 0.05.

\( q = \) complement of \( p = 1 - 0.05 \).

\( Z = \) parameter of the confidence interval = 1.96.

\( e = \) margin of error = 0.05.

\( N = \) population size = 1242.

Three hundred nine patients were taken as sample to further decrease the margin of error.

This sample was taken from the population by selecting every fifth card from the 1242 cards that were alphabetically ordered to ensure randomness. Data collection tools developed by the Eritrean Pharmacovigilance Centre for conducting similar studies were used to capture data. Demographic information of all the eligible patients attending the ART clinic during the study period was documented using a ‘Patient Listing Form’. It was used to capture demographic information of the patients regardless of their adverse drug reaction status including age, sex, number of drugs taken, availability of co-morbidities, CD4 count and so on. The second data collection tool was a comprehensive and well-structured tool for those with ADRs aimed at collecting patient demographic information, reaction details and drug details on both suspected and concomitant drugs including those taken for longer period of time to manage ADRs. Furthermore, detailed information of ADRs manifested during treatment including type of ADR, date reaction started, date reaction stopped, therapy started and stopped, dechallenge and rechallenge information, seriousness of the reactions, reaction outcome, information on other possible alternative cause(s) or explanations, management taken and treatment provided whenever available was recorded.

For the purpose of this study, the definition of an ADR was based on the one developed by the World Health Organization (WHO) [13] WHO has defined an ADR as a noxious, unintended drug reaction that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy. Depending on the definition used, therapeutic failure, overdose or poisoning and drug abuse was excluded from the study.

**Case assessment**

Causality assessment was performed for all suspected ADRs using Naranjo probability scale [14]. The Naranjo ADR probability scale is a tool developed to assess the probable causal associations between the suspected drug(s) and the ADRs encountered. It consists of a series of 10 questions which are believed to be among the main features of causality including whether the event is documented, plausible temporal association, dechallenge and rechallenge information, likelihood of alternative causes, dose-response relationship, presence of objective evidence, history of similar problems before with the same or similar medications and so on. The questions are answered as either “Yes”, “No”, or “Do not know”. Different values are allocated for each question according to its importance as –1, 0, +1 or +2. Based on the total score, assessors categorize the likelihood of drug-reaction relationship as “Certain”, “Probable”, “Possible” or “doubtful/unlikely”.

Seriousness of the identified suspected ADRs was determined according to the definition of the ICH E2A guideline [15]. According to the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Resulted in death,
- Is life-threatening,
- Required hospitalization or resulted in prolongation of existing hospitalization,
- Resulted in persistent or significant disability/incapacity,
- Caused congenital anomaly/birth defect or
- Medically important event or reaction that required medical/surgical intervention to prevent serious outcome.

**Data processing and statistical analysis**

Data was captured into computer using an entry program developed with CSPro version 6.3.2 software package. All questionnaires were entered twice; that is 100% verification was done to eliminate keying errors during entry. Data was edited during and after data entry using CSPro and Statistical Package for Social Science version 20 (SPSS-20). Both descriptive and analytical analysis was carried out on the data using SPSS. Both univariate and multivariate analysis were carried out to measure the association of some potential risk factors and ADRs. Results were presented as percentage and frequencies as appropriate. To test statistical significance, 95% confidence intervals and/or \( P \)-value were used. A \( P \)-value < 0.05 was regarded as being statistically significant.

**Results**

Three hundred and nine (309) patients, 64.1% females and 35.9% males, were included in this study (Table 1). Of the 309 patients, 62.8% experienced at least one ADR. 128 (64.6%) of these patients were females while 66 (59.5%) were males. 44.3% of them experienced at least three ADRs with similar male to female ratio. Of these, 29.8% were found to be serious. Gastrointestinal upset (19.5%) were the most frequently reported ADR.
followed by non-specific symptoms (11.2%), hypersensitivity reactions (10%) and lipodystrophy (9.8%) (Fig. 1). Lipodystrophy (32.8%) followed by peripheral neuropathy (22.4%) and anemia (16%) were among the frequently reported serious reactions (Fig. 2).

Patients with CD4 count, below 200 cells/mm3, and between 200 and 348 had a statistically higher occurrence of ADRs, 65.5 and 67.9%, respectively, ($\times 2 = 18,539, P = 0.000$). Those with CD4 count below 200 were about six times more likely to face ADRs compared to those with higher CD4 count (OR = 6.2; $p = 0.000$), and those patients with CD4 count between 200 and 349 were also about five times more likely to develop ADRs (OR = 5.1; $p = 0.001$) compared to patients with CD4 count above 349. In the regression model patients with age (35–44 years old), female gender, lower baseline body weight, and co-morbidities were tested to have statistically insignificant impact (Table 2). The regression model fitted to the data was statistically significant in predicting the likelihood of ADR among the patients ($p = 0.002 < 0.05$). Therefore the model correctly predicts the ADR status of the patients (69.6%).

In terms of time of onset of the reactions, anemia had an earlier onset with 52.2% of the reaction starting earlier than a year. Similarly, 39.55% of hypersensitivity reaction, 66.7% of hepatobiliary disorder, and 53.6% peripheral neuropathy had higher occurrence within the first year of treatment. Lipodystrophy, however, didn’t start to appear until two to three years of initiating the ART regimen (41.5%), while the rest occurred after 3 years (58.5%).

Most of the reactions were associated with stavudine and zidovudine containing HAART with 75.2 and 67.5% respectively. Tenofovir and nevirapine were similar in bringing ADRs with 54.1 and 53.5% respectively. Lamivudine is the least offending drug with 46.8%.

The causal relationship that was assessed using Naranjo probability scale in majority of the suspected adverse drug reactions cases was found to be possible 393/420. (Fig. 3).

The suspected offending drug was withdrawn in 21.1% of the cases to manage the encountered ADRs. In the rest of the cases, either management was not documented or no action was taken. Specific

---

**Table 1** Background characteristics of all patients included in study

| Patient background characteristics | Number | %   |
|-----------------------------------|--------|-----|
| Sex of the patient                |        |     |
| Male                              | 111    | 35.9|
| Female                            | 198    | 64.1|
| Broad age group                   |        |     |
| < 25                              | 16     | 5.2 |
| 25–34                             | 93     | 30.1|
| 35–44                             | 135    | 43.7|
| 45 and above                      | 65     | 21.0|
| Any co-morbidities               |        |     |
| Yes                               | 70     | 22.7|
| No                                | 239    | 77.3|
| CD4 count                         |        |     |
| Below 200                         | 197    | 63.8|
| 200–349                           | 81     | 26.2|
| 350 and above                     | 28     | 9.1 |
| Not Reported                      | 3      | 1.0 |
| Weight of patients (Kg)           |        |     |
| Below 50                          | 91     | 46.9|
| 50–59                             | 66     | 34  |
| Above 60                          | 37     | 19.1|
| Total                             | 309    | 100.0|

---

![Fig. 1](image-url) The frequency and nature of all ADRs that were seen in descending order.
treatment was given in 24% of the ADRs 29% were managed symptomatically, and 2.9% were managed both with specific treatment and symptomatically.

**Discussion**

This study found that ADR associated with ART medications are highly prevalent. This is similar with previous studies [16, 17].

GI symptoms were the most commonly reported ADRs similar to previous studies [16, 18, 19] followed by non-specific symptoms such as chills, fever, headache, hypersensitivity reactions and lipodystrophy. Furthermore, lipodystrophy which was associated primarily with Stavudine was the most serious ADR followed by peripheral neuropathy, anemia and hepatobiliary disorders. However, it is important to remember that Stavudine has been removed from ART list of medications and thus lipodystrophy is not as prevalent as it once was. Peripheral neuropathy was associated with Stavudine followed by Zidovudine and in one case by Atripla, this is an important finding because Atripla hasn’t been known to cause peripheral neuropathy and only one other study to our knowledge has similar findings [20] (Table 3).

Anemia which was mostly associated with Zidovudine was the third most serious ADR, unlike previous studies that found anemia to be the most serious ADR [12, 16, 21]. This difference could be either due to the inappropriate laboratory monitoring of the patients on HAART in Halibet hospital which undermines the real frequency or due to the nature of this study. Hepatobiliary disorder was associated with Nevirapine and to a lesser extent with Efavirenz. This was consistent with a systematic review and meta-analysis conducted by Shubber et al. [22]. Most of the ADRs (anemia, hypersensitivity reaction, hepatobiliary disorder and peripheral neuropathy) were observed within the first year of starting ART while lipodystrophy occurred within 2–3 years following commencement of the ART.

**Table 2** Prevalence of ADR based on background characteristics

| Background characteristics | Prevalence of ADR | Significance test (P-value) |
|----------------------------|-------------------|-----------------------------|
| Broad age group            |                   |                             |
| < 25                       | 9                 | 56.3                        |
| 25–34                      | 51                | 54.8                        |
| 35–44                      | 93                | 68.9                        |
| 45 and above               | 41                | 63.1                        |
| Sex of the patient         |                   |                             |
| Male                       | 66                | 59.5                        |
| Female                     | 128               | 64.6                        |
| Any co-morbidities         |                   |                             |
| Yes                        | 49                | 70.0                        |
| No                         | 145               | 60.7                        |
| CD4 count                  |                   |                             |
| Below 200                  | 129               | 65.5                        |
| 200–349                    | 55                | 67.9                        |
| 350 and above              | 7                 | 25.0                        |
| Not Reported               | 3                 | 100.0                       |
| Total                      | 194               | 62.8                        |

**Table 3** ADRs that were associated with specific drug combinations are shown below

| Nature                      | Drug                | %   |
|-----------------------------|---------------------|-----|
| GI upset                    | Atripla             | 32.9|
| Peripheral neuropathy       | D4T                 | 65.5|
|                            | AZT                 | 27.6|
|                            | Atripla             | 6.89|
| Anemia                      | AZT                 | 70.8|
|                            | Atripla             | 16.6|
|                            | D4T + 3TC + NVP     | 8.3 |
| Hypersensitivity reaction   | NVP                 | 61.9|
|                            | EFV                 | 23.8|
| Hepatobiliary disorder      | NVP                 | 62.5|
|                            | EFV                 | 31.25|
| Lipodystrophy               | D4T                 | 100%|
However, a study done by Shelburne et al. [30] indicates the type of drug regimen [6, 23, 24] a nature and the difference in the timing of these ADRs depends on factors that may predispose the patients to ADRs similar to antiretroviral medications including non-antiretroviral co-administered medications such as over the counter drugs and patients life style (alcoholism or smoking) were not documented in the patients’ clinical cards and thus their contribution to ADR prevalence was left unmeasured. Furthermore, co-morbidity types were not captured by our questionnaire as it lacked to address this. In addition, the findings are from a small size and from one referral hospital, hence a bigger study needs to be conducted to solidify these findings.

**Conclusion**

The findings in this study have proven that ART associated ADRs are highly prevalent and are threatening the adherence level that is much needed to ensure maximum benefit from these medications. The drugs as well as the risk factors that are mostly associated with ADR occurrence found in this study should help health professionals at all levels to foresee, identify and minimize ADR at the earliest possible time as well as to understand the need for close follow up and monitoring to avoid the occurrence of serious ADRs.

**Abbreviations**

3TC: Lamivudine; ABC: Abacavir; ADR: Adverse Drug Reactions; ART: Antiretroviral Therapy; ATRIPLA: TDF + 3TC + EFV; AZT: Zidovudine; D4T: Stavudine; EFV: Efavirenz; FTC: Emtricitabine; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immune Deficiency; ICH: International Conference on Harmonization; IRIS: Immune Reconstitution Inflammatory Syndrome; LPV/r: Lopinavir/ Ritonavir; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NVP: Nevirapine; PI: Protease Inhibitor; PLWH: People Living With HIV; TDF: Tenofovir

**Acknowledgments**

We would like to give our sincere thanks to Mr. Mulugeta Russom for his invaluable help to this work from start to finish, we also would like to acknowledge Mr. Mehari Zeregabr, Mr. Dawit Tesfai, Mr. Hagos Ahmed, Mr. Filmon Hagos, Mrs. Bissirat Fessehaye, all the staff of Halibet national referral hospital’s HIV clinic and all the staff of National Pharmacovigilance office.

**Funding**

No funding sources.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

LH and SF contributed to data collection, data interpretation and article writing. IA contributed to study design and project co-ordination. All authors reviewed the manuscript during preparation, provided feedback and approved the final manuscript.

**Ethics approval and consent to participate**

Ethical approval was obtained from the Health Research Ethics and Protocol Review Committee (HREPRC) of Eritrea. As this was a retrospective study, informed consent was not obtained from patients and waived by HREPRC. All ethical and professional considerations were followed and particular attention was paid to keep patient details in strict confidence. Data was analyzed and disseminated anonymously.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 19 September 2018 Accepted: 24 April 2019
Published online: 06 May 2019

References

1. Anwikar SR, Bandekar MS, Smarti B, Pazare AP, Tatke PA, Kshirsagar NA. HAART induced adverse drug reactions: a retrospective analysis at a tertiary referral health care center in India. Int J Med. 2011;16:63–9.

2. Vo TT, Ledergerber B, Keiser O, Hirschel B, Funier H, Battice G, et al. Swiss HIV cohort study. Durability and outcome of initial antiretroviral treatments received during 2000 – 2005 by patients in the Swiss HIV cohort study. J Infect Dis. 2008;197:1685–94.

3. Tenores study group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multi-Centre retrospective cohort study global epidemiology. Lancet Infect Dis. 2016;16:565–75.

4. Domingo P, Lozano F. Management of antiretroviral drug toxicity. Enferm Infec Microbiol Clin. 2011;29(7):535–44.

5. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating adults and pregnant women living with HIV. Geneva: WHO; 2016.

6. Masenyetse LJ, Manda SO, Mwhambi HG. An assessment of adverse effect experiences of antiretroviral therapy in two hospitals in South Africa. AIDS Research and Therapy. 2015;12(6):1–8.

7. Coror C. Antiretroviral therapy adverse drug reaction and their management. CME. 2011;29(6):234–7.

8. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effect of highly active antiretroviral therapy in developing countries. Clin Infect Dis. 2007;45:1093–101.

9. KPMG. The State of Healthcare in Africa. KPMG Africa Limited; 2012 p. 4–51.

10. Ofotokun I, Pomeroy C. Sex difference in adverse effect to ART drug. Int AIDS S US. 2003;11(2):55–67.

11. Russom M, Tesfai D, Elias M, Teklai M, Bahta I, Ahmed H, et al. Adverse drug reaction to antiretroviral therapy during the early ART period at a tertiary hospital in Ghana. Pan African Med J. 2014;18(25).

12. Patil PT, Pawar MP, Halasawadkhar NR, Shinde MP, Kumbhar AV, Rathod MS. Current pattern of adverse drug reactions to antiretroviral therapy in antiretroviral therapy Centre attached to a government medical college of Maharashtra, India. Retrospective study. JBCP. 2016;5(6):2438–43.

13. Bartlett J. Severe liver toxicity in patients receiving two nucleoside analogues and a nonnucleoside reverse transcriptase inhibitor. [Abstract 19. In: 8th conference on retroviruses and opportunistic infections. Chicago, IL, 2001.]

14. Arpadi SM, Cuff PA, Horlick M, Wang J, Kotler DP. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ lymphocyte count and CD4+/lymphocyte percentage at baseline and use of protease inhibitors and stavudine. J Acquir Immun Defic Syndr. 2001;27:30–4.

15. Lichtenstein KA, Delaney KM, Ammon C, Ward DJ, Moorman AC, Wood KC, Holberg SD. Incidence of and risk factors for lipodystrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. J Acquir Immun Defic Syndr. 2003;2:48–56.

16. Shebume SA, Vinnesanwala F, Darcourt J, Graviss EA, Giordano TP, White AC, Hamill RJ. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 2005;19:399–406.

17. Luma HN, Doualla MS, Choukem SP, Temfack E, Ashuntantang G, Joko HA, et al. Adverse drug reactions of highly active antiretroviral therapy (HAART) in HIV infected patients at the general hospital, Douala, Cameroon: a cross sectional study. The Pan African Med J. 2012;12:87.

18. Subber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Thery F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: systematic review and meta-analysis. AIDS. 2013;27(9):1403–12.

19. Eron JJ, Benoit SL, Jemsek J, MacArthur RD, Santana J, Quinn JB, et al. Treatment with lamivudine, zidovudine, or both in HIV positive patients with 200 to 500 CD4 cells per cubic millimeter. N Engl J Med. 1995;333:1662–9.

20. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skest D, Stanford J, et al. Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, Indinavir plus Zidovudine and lamivudine. N Engl J Med. 1999;341:1865–73.

21. Lartery M, Asante-Quashie AK, Karu E, Ganu V, Nequaaye A. Adverse drug reaction to antiretroviral therapy during the early ART period at a tertiary hospital in Ghana. Pan African Med J. 2014;18(25).

22. Prosperi MC, Fabbiani M, Fanti L, Zaccarelli M, Colaligi M, Mondi A, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug related adverse event in HIV-infected patients: a retrospective cohort study. Bio Med C. 2012;2:2961–11.