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Original Article

Adverse drug reactions to antiretroviral treatment among people living with HIV at HIV clinic, Colombo, Sri Lanka.

Leelani I. Rajapaksa [1], Vindya R. Perera[1], Shanika H. Jayasena [1]

Abstract

Sri Lankan PLHIV are managed adhering to national antiretroviral treatment (ART) guidelines. Since 2016 all the PLHIV were offered ART irrespective of their CD4 count. Some PLHIV experience Adverse drug reactions (ADRs) which result in sub-optimal patient and programmatic outcomes. Therefore, this study was designed to determine the prevalence of ADRs and to identify the causality, severity and preventability.

A clinic based retrospective cohort study was conducted among all PLHIV registered for ART at the HIV clinic, Colombo until 31st December 2019. The data was collected on the ADRs that occurred from January 2015- December 2019. Each ADR was appraised using Naranjo's algorithm, modified Hartwig and Seigel scale, Shumock and Thornton criteria.

The cohort included 1028 patients of whom 90 (8.7%) developed ADRs. Predominant ADR were hypersensitivity reactions (32%). Evaluation of ADRs through Naranjo's scale denoted that 55 (61%) were probably and 33 (37%) were possibly due to ART. Majority of ADRs were mild 59 (65%) and 7% were severe. Only 2% of ADR were preventable. Out of all the patients exposed to the corresponding drug, percentage occurrence of ADRs were highest with atazanavir (32.5%) followed by raltegravir (9%) and efavirenz (5.9%). Majority (58.8%) of the ADRs, including all the severe ADRs occurred within 6 months of commencement of ART.

As bulk of these ADR are predictable, frequent reviews should be made especially during the first 6 months of ART initiation. Introduction of newer ART drugs (Dolutegravir) with lesser toxicity in the updated ART guidelines in 2020 will increase adherence to ART.

Key words: Adverse Drug reactions, Antiretroviral drugs, causality, severity and preventability

Affiliation: [1]National STD/AIDS Control Programme

Authors: Dr. Leelani I. Rajapaksa, MBBS, MSc, MD, Consultant Venereologist; Dr. Vindya R. Perera,MBBS, PgDVen, MD, Senior Registrar ; Dr. Shanika H. Jayasena, MBBS, PgDVen, MD, Acting Venereologist

Corresponding Author: Dr. Leelani I. Rajapaksa, Email: lilanirajapaksa2@gmail.com,

https://orcid.org/0000-0003-3547-1104

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Introduction

National STD/AIDS Control Programme Sri Lanka commenced ART programme in December 2004. By December 2019, 1771 PLHIV have been on antiretroviral therapy. People living with HIV (PLHIV) are managed at the 33 STD clinics in the country according to the national ART guidelines including appropriate treatment, contact tracing and regular follow up. In 2018, majority of PLHIV on ART (49.2%) were registered at the main HIV clinic in Colombo. (1)

Antiretroviral treatment guidelines for HIV infection was first developed in 2004 and regularly updated based on WHO recommendations. The goal of treatment is to maintain a satisfactory immune system to prevent the occurrence of opportunistic infections. All PLHIV registered for HIV care services were offered ART according to the national guidelines. TDF+FTC+EFV fixed dose combination was recommended as the preferred ART regimen in 2016 guidelines. (2) Introduction of antiretroviral treatment (ART) has led to significant reduction in morbidity and mortality related to HIV and AIDS. The response observed among PLHIV provided with ART had been encouraging improving both quality and quantity of life. (3) However, the positive response can be affected by emerging issues such as adverse drug reactions (ADRs).

Many studies have been carried out in countries with high prevalence of HIV on adverse drug reactions to ART. A prospective observational study carried out in Eastern India by Mukherjee et al among 610 PLHIV over 12 months from 2014 to 2015 revealed that Zidovudine based ART regimens had maximum ADRs. (4) Nervous system disorders were common followed by GI and metabolism disorders. EFV associated ADR has affected continuity of treatment. The study highlighted the importance of introduction of newer generation drugs with lesser toxicity.

A systematic review on ADRs effect on adherence to ART was carried out by Haochu Li et al based on 39 qualitative studies. The findings revealed the occurrence of ADRs is linked to non-adherence. This highlighted the link between EFV use and CNS toxicity and non-adherence.(5) Bhuvana et al conducted a prospective study of ADRs to antiretroviral therapy among PLHIV in a tertiary care hospital in India for 6 months in 2012.(6) Of the 158 cases evaluated, most common first line regimen was Zidovudine based and common ADRs were anaemia (55.1%) and skin rash (25.3%). Most were having severity 3 ADRs (93.0%) and 30.3% were preventable. A retrospective review of patient medical records by Teklay et al in Ethiopia from 2009 – 2011 among 403 PLHIV cases revealed that 65.5% of patients developed at least one adverse effect to ART. (6) The most common were GI and CNS symptoms. The importance of monitoring of ADRs were highlighted in the study findings.

Most of the ART drugs cause considerable ADRs resulting in poor adherence. It is important to understand the occurrence of ADRs in the local context to improve the ART programme. This was the first study carried out to understand the occurrence of ADRs among PLHIV in Sri Lanka. Objectives of the study were to evaluate the incidence of ADRs and to assess their causality, severity, preventability and determinants of ADRs and to determine the programmatic outcome of the patients who experience ADRs.

Methods

A retrospective clinic-based study was designed to evaluate the incidence of ADRs and to assess the causality, severity, preventability of the reported ADR.

The study was conducted at the main HIV clinic, Colombo which caters to 50% of PLHIV in the country. The study population was PLHIV who were registered for ART services at the HIV clinic, Colombo from December 2004 until December 2019. Paediatric patients with HIV, pregnant and lactating women and PLHIV who have not started ART were excluded.

WHO definition of ADR was adopted. All significant ADRs are reported in the “Adverse drug reactions register” from 2015. The medical officers were expected to complete the case

reporting form on suspected adverse reaction to medicines. The data was collected on the ADRs that occurred from 1st January 2015 to 31st December 2019. Necessary details of ADRs are clearly indicated in the clinical case records as well. Further all substitutions are reported in the clinic quarterly returns. This includes substitutions due to ADR, drug interactions or medical reasons. Each patient's case records were maintained in a hard file and the cover of the file carries information on changes of ARV regimen with dates. (7)

The data were gathered by the documented ADRs in the adverse drug reactions register from 2015- 2019. ADRs reported during the period were categorized using the following tools.

1. Causality – Naranjo's algorithm
2. Severity – Hartwig and Seigel scale
3. Preventability – Shumock and Thornton criteria

Causality, severity and preventability of each registered ADR was appraised using Naranjo's algorithm, modified Hartwig and Seigel scale, Shumock and Thorntom criteria, respectively. A structured data extraction format was used to collect data on socio demographic characteristics, management strategies and the final outcome. A clinic based retrospective cohort study was conducted among all PLHIV who were commenced on ART till 31st December 2019.

Structured data extraction formats were used to collect details about mild, moderate and severe ADRs, adherence issues and management strategies. Emphasis was placed on occurrence of ADRs and response to management. Clinical information was obtained from the clinical case records. The details on ART regimen and laboratory data were obtained through case records maintained at the HIV clinic. Data were collected by identified and trained data collectors who were practicing medical officers at the HIV clinic.

Essential laboratory investigations which are indicated in the guidelines for initiation and follow up of PLHIV on ART were considered to understand the severity of ADRs when necessary.

Data were analysed by the principal investigator using SPSS package.

Ethical clearance was obtained from the Ethical clearance committee of the National Hospital Sri Lanka. Permission to conduct the study was obtained from the Director and HIV care coordinator of National STD AIDS Control Programme, Sri Lanka. Data collection formats did not include personal identification details to maintain anonymity and confidentiality.

Results

The cohort included 1,028 patients of whom 90 (8.7%) developed ADRs. Three fourths were in the 31–60-year age group. Mean age was 45.7 years. There were more males (60%) than females (40%). Sinhalese were 77% followed by Tamils (15%). Most were having education up to O/L or more. Only 4% never been to school and 15% had primary education. Among those who reported ADRs age ranged from 21 to 70 years with mean age 45.2 years. Among them only 52% of persons who experienced ADRs were living with their partner.

In the sample more than 83% were in the WHO stage 1 or 2 at the time of reporting the ADR. CD4 count was <200 cells/µl in 21.1% and between 200-350 cells/µl in 23%. Only 28.9% had CD4 counts >500 cells/µl.

Most were on TDF+3TC+EFV (56%), TDF+FTC+ATV/r (16%) or AZT+3TC+EFV (13%) at the time of developing ADR. As shown in Figure. 1. EFV was responsible for 54% of ADRs. Atazanavir ATV/r (16%), zidovudine AZT (11%) and tenofovir TDF (8%) were other important drugs for causing ADRs.

Out of all the patients exposed to the corresponding drug, percentage occurrence of ADRs were highest with atazanavir (32.5%) followed by raltegravir (9%) and efavirenz (5.9%). From four patients who developed ADRs to raltegravir (Integrase inhibitor) 75% had a severe reaction requiring the drug to be stopped or substituted. Among those who developed ADRs 64% on atazanavir and 59% on efavirenz required withholding ART or ART substitution.

Figure 1. ARV drugs responsible for ADRs

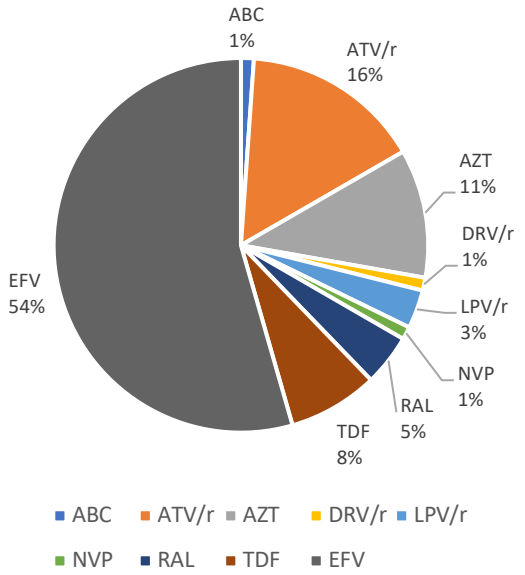


Table 1. Common adverse drug reactions and the ARV drug responsible

ADR	Severity	Drug	Num	Time since starting the drug
Hepatotoxicity	Grade 2	EFV	1	
	Grade 3,4	EFV	2	
Anaemia		AZT	2	>5 yrs
Diarrhoea		Boosted PI	3	<6 months
Vertigo		EFV	9	
nightmares		EFV	2	
Gynaecomastia		EFV	4	<6 months
Skin hypersensitivity	Grade 1,2	EFV	15	<6 months
		DRV	1	<6 months
	Grade 3	EFV	6	
		RAL	2	
		NVP	1	
	Grade 4	EFV	2	
		RAL	2	
Jaundice		ATV	11	
Cushings		LPV/r	1	
		ATV/r	1	
Lipoatrophy		AZT	6	>36 months
Hyperpigmentation		AZT	3	>48 months
Renal impairment	moderate	TDF	2	<6 months
	severe	TDF	3	>12 months
Reduced bone mineral density		TDF	2	>5 yrs

Table 1 presents some common ADRs. Predominant ADR was skin hypersensitivity reactions (32%). Most were mild to moderate reactions. However, there were four cases with severe hypersensitivity (grade 4) two each due to EFV and RAL. Vertigo, nightmares, gynaecomastia, hepatotoxicity were other important ADRs caused by EFV. Most of these ADRs occurred within first 6 months. Jaundice was due to ATV. AZT related anaemia, lipoatrophy and hyperpigmentation were reported among PLHIV on long term treatment. Renal impairment and Bone changes were observed among a few PLHIV on TDF based ART.

Majority (58.8%) of the ADRs, including all the severe ADRs occurred within 6 months of commencement of ART.

According to Naranjo's algorithm for assessing causality of the ADR (Figure 2), only 2% of ADRs were unlikely due to the identified drug as responsible and none of the reported ADR were certain. Evaluation of ADRs through Naranjo's scale denoted that 55 (61%) were probably and 33 (37%) were possibly due to the identified antiretroviral drug.

Modified Hartwig and Siegel Scale was used to categorise the severity of the ADR (Figure 3). Majority of ADRs were mild 59(65%) which means there was no need to change treatment or required no antidote or other treatment. Moderate severity (28%) either needed substitution plus other treatment with or without admission. In the sample 7% were severe implying either they needed intensive medical care, caused permanent harm to the patient or directly or indirectly lead to death.

Figure 2. Naranjo algorithm for assessing the causality of an ADR

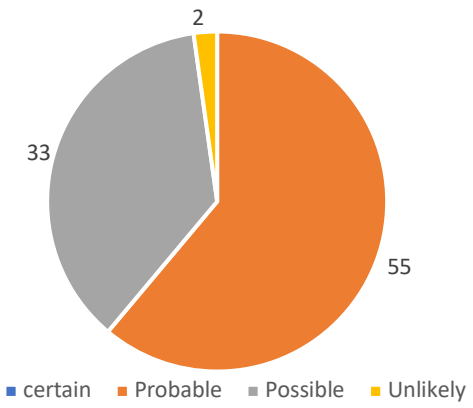
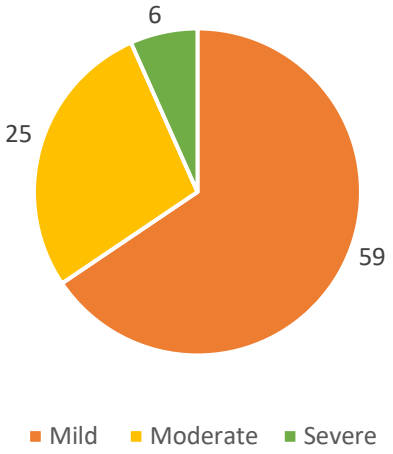


Figure 3. Severity assessment by modified Hartwig and Siegel scale

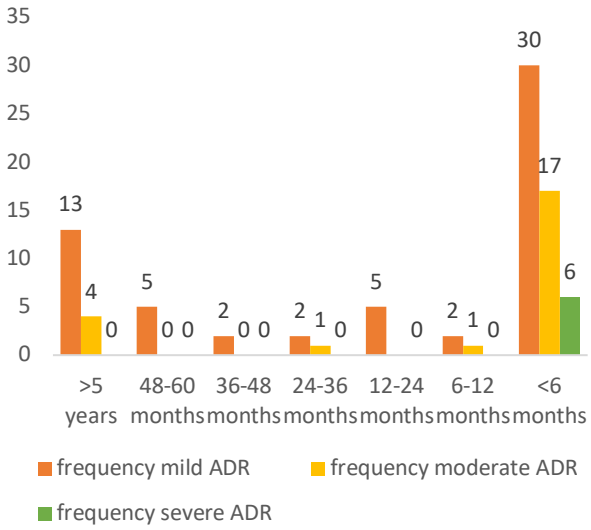


In the sample, ART regimens were substituted in 58 cases and 32 continued the same ART regimen. Majority (78%) improved following management of ADR including substitution. However, 2% showed virological failure by 2019. 3% were transferred out, 9% were lost to follow up and 8% deaths reported by 2019.

As presented in Figure 4, most of these ADRs occurred within first 6 months. Most PLHIV reported mild ADRs within 6 months. However, there were 6 cases presenting with severe ADR in the early period. PLHIV who were on ART for more than 5 years presented with ADRs mostly related to AZT with lipoatrophy and hyperpigmentation etc.

Modified schumock and Thornton preventability scale was used to assess preventability. According to the scale in the sample only 2% of ADR were preventable.

Figure 4. Time to develop ADR after starting ART



Discussion

The cohort included 1,028 patients of whom 90 (8.7%) developed ADRs. This percentage is much lower than reported in other studies. Similar study conducted by Teklay et al in Ethiopia in 2013 revealed 65.5% developing at least one ADR to ART. However, the definition of ADR is not clear in the study. (7)

Majority of the sample (83%) was asymptomatic and were in WHO stage 1 or 2 at the time of reporting the ADR indicating higher occurrence of ADRs among asymptomatic PLHIV. However, this finding has to be interpreted based on the immunity level as well. In the sample CD4 count was <350 cells/µl in 44% and only 29% had CD4 >500 cells/µl.

There is a possibility that other pathologies or drugs could cause these effects. Naranjo scale was used to identify the causality. Evaluation of ADRs through Naranjo's scale denoted that 55 (61%) were probably and 33 (37%) were possibly due to ART. Only 2% were unlikely and none of the reported ADR were certain.

Mean age of the sample who experienced ADRs was 45 years and 59% were >40 years indicating occurrence of ADRs in the aged population. There were more males (60%) than females (40%). According to the Annual report 2019 of the NSACP male to female ratio of PLHIV on ART was 2:1 and the study findings reveal that more females report ADRs. Ethnic representation and educational levels were compatible with the diagnosed PLHIV in the country.

EFV was responsible for 54% of ADRs. Atazanavir ATV/r (16%), zidovudine AZT (11%) and tenofovir TDF (8%) were other important drugs for causing ADRs. According to the Annual report 2018, EFV based regimens were used by 85% of PLHIV. On further scrutiny, out of all PLHIV exposed to the corresponding drug, percentage occurrence of ADRs were highest with atazanavir (32.5%) followed by raltegravir (9%) and efavirenz (5.9%).

Predominant ADR was skin hypersensitivity reactions (32%) mostly due to EFV. Most were mild to moderate reactions. CNS and hepatotoxicity were other important ADRs caused by EFV. CNS symptoms due to EFV were significant and could affect adherence. Jaundice was reported due to ATV. Anaemia is a common problem among women in the general population in Sri Lanka. However, AZT related anaemia, lipoatrophy and hyperpigmentation were reported among PLHIV on long term treatment. As the country is experiencing high prevalence of renal problems among the general population attention was paid to renal impairment linked to TDF. There were only a few cases of renal impairment and bone changes which can be linked to TDF. This has to be interpreted with caution as most of the sample started or changed to TDF based ART regimen within the last few years and did not have long-term exposure.

Comparison with other studies conducted globally is difficult as they were conducted in different time periods. The study conducted in Eastern India by Mukherjee et al (2014-2015) revealed AZT to cause maximum ADRs. This was before introducing the WHO recommendation to identify TDF+FTC+EFV as the preferred choice. However, EFV associated ADRs were identified as affecting adherence to treatment. Bhuvana et al in 2012 revealed similar findings with AZT related anaemia and skin rash. Haochu et al carried out a systemic review of 39 qualitative studies and presented the link between EFV and CNS toxicity and non-adherence. (4-6)

Severity of the ADR was assessed using the Hartwig et al. scale which categorized ADRs into seven levels and simplified into three categories as mild, moderate and severe. Majority of ADRs were mild or moderate. However, there were 7% who required intensive medical care or ADR directly or indirectly led to death. In the sample 64% on atazanavir and 59% on efavirenz required withholding ART or ART substitution. From four patients who developed ADRs to raltegravir (Integrase inhibitor) 75% had a severe reaction requiring the drug to be stopped or substituted.

Severe ADRs may have contributed to outcomes death and virological failure in 8% and 2% respectively. In the sample 8% deaths were reported, and some may be linked to ADRs. Further 9% of the sample was lost to follow up and 2% had virological failure. The bitter experience of ADRs may have affected the adherence among these PLHIV. Based on these findings among PLHIV who experienced ADRs during the period close to 20% have experienced a negative outcome. However, these percentages were much lower than reported elsewhere. Bhuvana et al in the study conducted in India in 2012 among PLHIV 93% presented with severity 3 ADRs.

According to Modified Shumock and Thornton criteria only 2% of ADRs were preventable. Main HIV clinic, Colombo provide specialist services with well trained staff. This may have led to satisfactory screening before starting ART. The study conducted by Bhuvana et al. revealed a higher figure with 30% identified as preventable.

Conclusion

With initiation of ART to all PLHIV increasing rates of ARDs can be witnessed hindering desired outcomes. As bulk of these ADR are predictable, frequent reviews should be made especially during the first 6 months of ART initiation. There should be intensive monitoring for ADRs especially during the first 6 months of ART initiation. Patient education on ADR associated with ART and introduction of newer ART drugs (Dolutegravir) with lesser toxicity in ART guidelines updated in 2020 will increase adherence to ART

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