Study of Self-reported Adverse drug reactions and Factors influencing it among HIV/AIDS patients on Antiretroviral therapy

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INTRODUCTION

- Acquired immunodeficiency syndrome (**AIDS**) caused by Human immunodeficiency virus (**HIV**) is a major global health problem.
- According to HIV sentinel surveillance (2012-13), the HIV prevalence in the general population was **0.35%**.
- Less than **1%** prevalence among Antenatal Clinic (**ANC**) attendees during **2012-13**.

- Prevalence of antenatal cases were highest in Nagaland **(0.88%)** followed by Mizoram **(0.68%)** and Manipur **(0.64%).** [1]

- People living with HIV/AIDS (**PLHA**) in India were **20.89** lakh in 2011.

- India ranks **third** highest (PLHA), after South Africa and Nigeria (UNAIDS Report on the Global AIDS epidemic **2010**). [2]

- ART with potent combination of drugs reduced the rates of hospitalization, opportunistic infection and mortality to HIV infection.

- First patient was started on free ART on 1st April **2004**.

- March 2013: **18.13** lakhs PLHA registered at the **400** ART Centre functioning all around the country.

- Currently near **6.5** lakhs are on first line ART. [3]

- Effective ART improved the pattern of morbidity, mortality and pattern to a chronic manageable infection.
- Clinical benefits of HAART, increased survival and longevity in HIV patients.
- Anti-retrovirals (ARVs), like chronically administered drugs, reported to have ADRs with higher occurrences at the beginning of ART. [4, 5]
- Studies also showed that ADRs could be a source for new co-morbidities and hospital admission. [6, 7]

- ADRs varies from mild gastrointestinal disturbance to serious adverse effects including hematological disorders, hepatotoxicity and lactic acidosis.

- **ADRs is the most important limiting factor** that compromises patient compliance and adherence.

- ADRs become a concern and public health problem particularly in developing nations as adequate drug toxicity monitoring and reporting schemes barely existed.

- Lack of ADR monitoring and reporting system underestimates the burden of ART associated ADRs.

- ADRs has considerable influence on treatment adherence, treatment outcomes and treatment options.

- Hence this study was conducted to evaluate the self-reporting of ADR and factors influencing it among HIV/AIDS infected individuals.

OBJECTIVES

- To know socio-demographic and clinical characteristics among patients on HAART.
- To know the reasons for missing ART dose.
- To know the pattern of self-reported ADRs.
- To know the association between selected variables and adverse drug reactions to ART.

MATERIALS AND METHODS

- Ethical clearance for the study was taken from Institutional Ethics Committee of RIMS college before starting the study.
- **Study Design:** Cross-sectional, observational study
- **Study Period:** between **December 2013** to **November 2014.**
- **Sample size:** Two hundred and seventy (**270**) cases was decided to be minimum study sample.
- The **study population** comprised patients treated at ART center, RIMS teaching Hospital, Raichur, Karnataka.

INCLUSION CRITERIA

- All patients of either sex
- HIV infected patients on ART.
- Having been on ART for minimum of 6 months.
- Age more than or equal to 18 years
- Patients who are willing to provide informed consent

EXCLUSION CRITERIA

- HIV infected person not on ART
- Having been on ART for less than 6 months
- Age less than 18 years
- Not willing to provide consent

- Adult AIDS Clinical Trials Group (**AACTG**), semi structured questionnaire was adopted, which was pre structured and pre tested containing questions to collect data on :

- Socio-demographic profile

- Self-reported ADRs

- Reasons for missing dose

- Variables related to ART medication, laboratory values, clinical staging and CD4 cell count were obtained from patient treatment records.

STATISTICAL ANALYSIS

- All the parameters were analyzed by using computer software SPSS 17.0 version.
- Proportions were used in this study.
- Logistic regression analysis were used to determine the associations of dependent variables.
- P value of ≤ 0.05 was considered statistically significant.

RESULTS

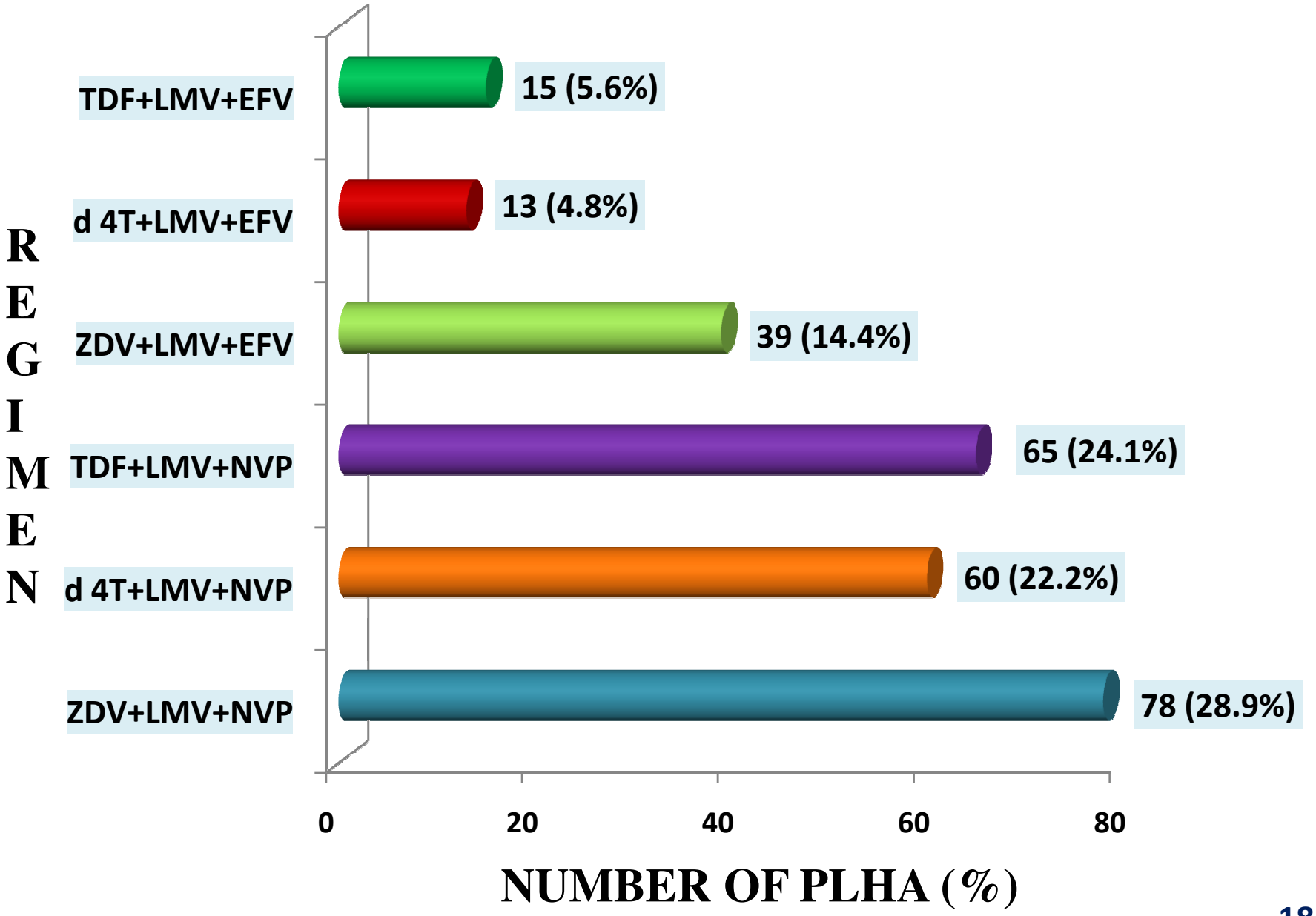
- A total of **270** participants were enrolled in the study.

Descriptive analysis of socio-demographic, clinical variables of the participants on HAART.

	VARIABLES	n (%)*,N=270
SOCIO-DEMOGRAPHIC	Education (primary and above)	190 (70.4)
	Work status (Employed)	235 (87)
	Age (≤40 years)	135 (50)
	Gender (male)	142 (52.6)
	Marital status (married)	181 (67)
	Place of residence (rural)	194 (71.9)
CLINICAL	Duration on ART (≤ 2 years)	185 (68.5)
	Current CD4 level (cells/mm^3)	
	101-200	10 (3.7)
	201-350	75 (27.8)
	> 350	185 (68.5)

* frequency and proportions, total number of participants (N = 270)

Regimens prescribed to respondents


REGIMEN
TDF+LMV+EFV
d 4T+LMV+EFV
ZDV+LMV+EFV
TDF+LMV+NVP
d 4T+LMV+NVP
ZDV+LMV+NVP
15 (5.6%)
13 (4.8%)
39 (14.4%)
65 (24.1%)
60 (22.2%)
78 (28.9%)
0
20
40
60
80
NUMBER OF PLHA (%)

Reasons for missing ART doses

REASONS FOR MISSING ART DOSE	NUMBER OF RESPONSES (N=50)*
• Simply forgot	35 (70%)
• Side effects	17 (34%)
• Change in routine	12 (24%)
• Busy with other things • Was away from home	10 (20%)
• Felt depressed • Couldn't pick up medicine • Had to take other medication • Ran out of medicine	5 (10%)
• Fell asleep • Felt sick	3 (6%)

* Shows the reasons for missing ART/doses (N=50)

Most common self-reported adverse drug reactions of antiretroviral therapy

ADVERSE EFFECTS	n* (%), N=270
• Burning sensation in stomach	40 (14.8)
• Anemia	35 (13.0)
• Fatigue	30 (11.1)
• Itching and rash	20 (7.4)
• Nausea and vomiting • Numbness • Headache	15 (5.6)
• Anorexia • Insomnia	10 (3.7)
• Lipodystrophy	06 (2.2)

*frequency and proportions, total number of participants (N = 270)

Logistic regression analysis of selected variables and adverse drug reactions to ART

		Total (N)*	Self-reported ADRs**	OR (95% CI)***	P value
Age	≤ 40 years	192	21 (10.9)	1	0.004
	>40 years	78	19 (24.4)	2.975 (1.408, 6.283)	
Gender	Male	142	21 (14.8)	1	0.336
	Female	128	19 (14.8)	1.478 (0.667, 3.276)	
Education	Illiterate	80	7 (8.8)	1	0.086
	Literate	190	33 (17.4)	3.172 (0.850,11.830)	
Employment	Unemployed	35	4 (11.4)	1	0.317
	Employed	235	36 (15.3)	2.306 (0.449, 11.856)	

* frequency that refers to the total number of patients (N = 270).

** Number and proportion of patients self-reporting adverse drug reactions.

*** Values represent odds ratio (OR) at 95% confidence interval.

		Total (N)*	Self-reported ADRs**	OR (95%CI)***	P value
Duration on ART	≤2 years	185	33 (17.8)	1	0.028
	>2 years	85	7 (8.2)	0.364 (0.148, 0.898)	
Current CD4 level	≤350	85	12 (14.1)	1	0.476
	>350	185	28 (15.1)	1.329 (0.608, 2.904)	
Current ART regimen	AZT based	117	14 (12)	1	0.189
	Non-AZT based	153	26 (17)	1.639 (0.784, 3.427)	
Adherence	Yes	220	30 (13.6)	1	0.150
	No	50	10 (20)	1.891 (0.795, 4.497)	

* frequency that refers to the total number of patients (N = 270).

** Number and proportion of patients self-reporting adverse drug reactions.

*** Values represent odds ratio (OR) at 95% confidence interval.

DISCUSSION

- The present study showed that

- The most common reasons for missing ART dose in this study was **simply forgetting** (70%).

- This was consistent to study done by Alexander M et al, [8] Heckman BD et al. [9]

- Our findings show that about **14.8%** patients on HAART, reported at least one ADR.

- Consistent with findings done by Henry Namme Luma et al, [10] which reported at-least one ADR among **19.5%** of patients on HAART in 2012.

- Lower than reported in urban Kenya [11] in 2007 where HAART-related ADRs were present in **20.6%** of patients.

- This difference may be explained by the lack of uniformity in the reporting style of ADRs across settings even though all of the patients in these settings are on similar FDC generic drugs.

- However, regional or ethnic susceptibilities to ADRs might also explain this difference

- In our study, the most common reported ADRs were from **gastrointestinal system**, which is in agreement with previous study done by de Padua CA M et al. [12]

- On the contrary, Luma et al [10] and Singh et al, [13] reported that about a fifth of patients on ART developed **peripheral neuropathy**.

- Occurrence of ADR was higher in patients **>40 years** of age (24.4%) compared to those **<40years** of age (10.9%) and was statistically significant.

- Not consistent with ADR studies done in Nigeria where ADR was higher in patients **<44 years** of age (72.2%) compared to those **>44 years** of age (19.6%). [14]

- Patients on ART for a relatively **longer duration** reported higher adverse drug reaction which was significant statistically similar to study done by Edwin Mu nene. [15]

- Contrary to study by Henry Namme Luma, [10] where it was not significant statistically.

- Consistent with findings by Eluwa et al, [5] which reported that gender was not significantly associated with ADRs.

- Literate, married, urban patients, those with CD4 count > 350, those on Non-AZT based regimen and those who are non-adherent to ART regimen showed higher rate of adverse events but this difference was statistically not significant which is consistent to study done by Tadesse et al. [16]

LIMITATIONS

- We measured adverse drug reactions of respondents to ART by self-report, which may be subject to recall bias and underestimate results.
- Study is cross-sectional and thus causal relationship cannot be definitively determined.
- Further studies of the similar kind with larger sample size and multiple centres will strengthen our findings and will help the physician in India in choosing the HAART regimen & taking into consideration the factors which influences it.

CONCLUSION

- Antiretroviral therapy is becoming increasingly effective but also increasingly complex.

- ADRs are one of the common occurrences among patients on ART.

- **14.8%** patients on HAART, reported at least one ADRs and most common being **gastrointestinal symptoms.**

- Significant associations were found between ADRs with patients aged **more than 40 years** and patients on ART for **less than 2 years**.

- This results points at the importance of understanding the adverse effects to ART and factors influencing it. Hence, counseling regarding the same can lead to better adherence and outcome of the therapy.

REFERENCES

1. HIV Sentinel Surveillance 2012-13: A Technical brief. [Online] 2012 Jan ; Available from URL: http://www.naco.gov.in

2. Department of AIDS Control, Ministry of Health & Family Welfare: Annual report 2012-13. [Online] ; Available from URL: http://www.naco.gov.in

3. Antiretroviral therapy guidelines for the use of antiretroviral therapy for HIV-1 infected adults and adolescents May 2013. [Online]; Available from URL: http://www.naco.gov.in

4. de Padua Menezes CA, Cesar CC, Bonolo PF, Acurcio FA, Guimaraes MDC: High incidence of adverse reactions to initial antiretroviral therapy in Brazil. Braz J Med Biol Res 2006; 39(4):495–505.

5. Eluwa GI, Badru T, Akpoigbe KJ: Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. BMC Clin Pharmacol 2012;12:7.

6. Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI: Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. Br J Clin Pharmacol 2008;65(3):396–406.

7. Pulagam P, Rajesh R, Vidyasagar S, Varma D: Assessment of hematological adverse drug reactions to antiretroviral therapy in HIV positive patients at Kasturba Hospital Manipal. BMC Infect Dis 2012;12(1):55.

8. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. [Online]. 2009 Dec 1; Available from URL: http://www.aidsinfo.nih.gov

9. Heckman BD, Catz SL, Heckman TG, Miller JG, Kalichman SC. Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. AIDS Care 2004 Feb;16(2):219–230.

10. 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. Pan African Medical Journal. 2012;12:87

11. Hawkins C, C Achenbach, W Fryda, D Ngare, and R Murphy. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. Journal of acquired immune deficiency syndromes. 2007;45(3):304-10

12. de Padua CA M, Cesar CC, Bonolo PF, Acurcio FA, Guimaraes MC: Self-reported adverse reactions among patients initiating antiretroviral therapy in Brazil. BJID 2007;11(1):20–26.

13. Singh H, Dulhani N, Tiwari P, Singh P, Sinha T: A prospective, observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. Indian J Pharmacol 2009;41(5):224–226.

14. Kenneth A. Agu, Azuka C. Oparah. Adverse drug reactions to antiretroviral therapy: Results from spontaneous reporting system in Nigeria. Perspectives in Clinical Research. 2013;4:2

15. Edwin Mu nene and Bjo rn Ekman. Does duration on antiretroviral therapy determine health-related quality of life in people living with HIV? A cross-sectional study in a regional referral hospital in Kenya. Glob Health Action 2014;7:23554

16. Tadesse WT, Mekonnen AB, Tesfaye WH and Tadesse YT. Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. BMC Pharmacology and Toxicology 2014;15:32

Thank you

