

## EVALUATION OF THE ADVERSE REACTIONS OF ANTIRETROVIRAL DRUG REGIMENS IN A TERTIARY CARE HOSPITAL IN KOLKATA: A PROSPECTIVE OBSERVATIONAL STUDY

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### ABSTRACT

#### BACKGROUND

The introduction of Highly Active Antiretroviral Therapy (HAART) has led to a significant decrease in AIDS-related mortality and morbidity. However, adverse reactions to these drugs, being inevitable, have led to major obstacles in its success, especially in developing nations like India. Moreover, the latest changes made by W.H.O. in the treatment guidelines of ART naive patients would expectedly lead to changes in the Adverse Drug Reaction (ADR) patterns as well. Hence, this study aimed at evaluating the ADRs of currently prescribed ART regimens in a tertiary care hospital in Kolkata (WB).

#### METHODOLOGY

168 ART naive patients enrolled initially were studied prospectively over a period of 1 year; each patient being followed up individually for 6 months. All patients were asked to visit the ART centre once a month or whenever they developed any symptom. They were screened clinically and investigated suitably by the physician according to the latest NACO guidelines.

#### RESULTS

Majority were males (56%) with an M:F ratio of 1:0.774; 93.3% patients belonging to the 15-49 yrs. age group. TDF+3TC+EFV (56%) was the commonest 1<sup>st</sup> line regimen prescribed. 76.6% patients experienced ADRs. Total 184 ADRs were noted, of which, GIT contributed the most (27.17%). Majority (66.67%) of neurological ADRs was contributed by neuropsychiatric manifestations. Rash (10.3%) was the commonest cutaneous ADR. Anaemia (13.6%) was the commonest haematological ADR with a statistically significant female preponderance. Most ADRs were grade 1 (63.04%). Majority ADRs were "possible" (65.76%) while 34.24% were "probable" by Naranjo scale. Maximal ADRs (48.37%) were noted from patients under AZT+3TC+NVP regime. IRIS was observed as a paradoxical reaction to ART in 10% cases.

#### CONCLUSION

It should not be forgotten that ADRs are the inevitable consequence of pharmacotherapy. Hence, proper implementation of current protocols designed for screening of patients especially during the initial months of therapy may help in earlier detection of ADRs and thus help in preventing serious/life threatening consequences.

#### KEYWORDS

HAART, ADR, NACO, IRIS, NARANJO.

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**INTRODUCTION:** HIV-AIDS, a global pandemic of the recent times accounts for 35.2 million people living with HIV (PLHIV), 2.3 million people newly infected and 1.6 million killed by it-according to WHO 2012.<sup>(1)</sup> India now is in 3<sup>rd</sup> position in the world with 2.4 million (2009) people living with the disease of which 90% cases belonging to 15-49 years age group.<sup>(2)</sup> West Bengal belongs to group II

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(moderate prevalence-concentrated epidemic) with 50734 cumulative number of HIV positive patients in the Integrated Counseling and Testing Centre (ICTC)s of which Kolkata contributes 26516.<sup>(3)</sup>

Treatment of HIV infection (and its complications) is complex, lifelong, needs expertise, strong motivation and commitment of patient and is expensive too. But, the prevalence and mortality has declined steadily after 2004 when NACO rolled out free combination of Antiretroviral Therapy (ART) to the eligible registered patients. Antiretroviral Therapy (ART) is only 27 years old and still evolving. Apart from the 3 newly introduced classes of drugs like fusion inhibitor (Enfuvirtide), CCR5 entry inhibitor (Maraviroc) and integrase inhibitor (Raltegravir), the "backbone" of ART has always been the NRTIs (nucleoside reverse transcriptase inhibitors-Zidovudine, Lamivudine,

Stavudine, etc.), the NNRTIs (non-nucleoside reverse transcriptase inhibitors) - Nevirapine, Efavirenz, the NtRTI (non-nucleoside reverse transcriptase inhibitors) - Tenofovir and PIs (Protease inhibitors) - Saquinavir, Ritonavir, Nelfinavir, etc. Hence, understanding the biology of HIV infection and availability of these highly potent drugs has mandated the "Highly Active Antiretroviral Therapy" (HAART) with a combination of 3 drugs; monotherapy (practiced previously) is now contraindicated<sup>(4)</sup> due to the fear of developing resistance. According to the WHO recommended ARV treatment schedule (June 2013), also adopted by NACO, thereafter, the preferred first line regimen for "treatment naive" (untreated) patients is Tenofovir + Lamivudine + Efavirenz.<sup>(5,6)</sup>

Adverse Drug Reactions (ADRs), the inevitable consequence of pharmacotherapy<sup>(7)</sup> is defined by WHO as "any response to a drug, which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function." ADRs are higher in patient groups on multiple interacting medications like HIV/AIDS patients.

As mentioned earlier, introduction of HAART has led to a significant decline in AIDS related mortality and morbidity, but unfortunately, ~25% of all patients discontinue their initial HAART regimen due to treatment toxicity, etc. within first 8 months of therapy.<sup>(8,9)</sup> While the development of new ART agents continues, it is highly prudent to maximise the effectiveness of currently available treatments, which includes proper evaluation (identification and understanding) of the adverse drug effects.

Firstly, it is a matter of common sense that the risk of drug-specific adverse effects will vary from drug to drug, class to class and patient to patient. Previously, the most preferred 1st line HAART regimen for ART naive patients was zidovudine + lamivudine + nevirapine.<sup>(4)</sup> But from June 2013, WHO has modified it to tenofovir + lamivudine + efavirenz. Hence, it is logical to expect a change in the pattern of ADRs in the ART naive patients, thereafter.

Secondly, it is important to note that the first 6 months of ART are very crucial<sup>(6)</sup> mainly due to four reasons: (i) Early drug toxicities including the most serious ones like nevirapine-induced rash, Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and zidovudine-induced anaemia typically appear in the first few months of starting ART; (ii) mortality due to ART is higher in this phase as compared to later on; (iii) CD4 counts show a marked rise from their baseline values in majority of patients indicating immune recovery (iii) Immune Reconstitution Inflammatory Syndrome (IRIS), which is considered a marker of ART success, also typically appears in this phase.

Thirdly, as the WHO's modification in the treatment guidelines of ART naive patients is very recent, there would be an obvious need for research and information regarding the toxicity profile of the patients on this relatively newer regimen.

Hence, this study aims at evaluating the adverse reactions of the currently prescribed ART regimens in a

tertiary care hospital in West Bengal during the first 6 months of treatment.

**AIMS AND OBJECTIVES:** To evaluate the adverse drug reactions of antiretroviral regimens currently prescribed for the treatment naive HIV-positive patients attending the ART Centre of R.G. Kar Medical College and Hospital, Kolkata, under the following criteria:

- Onset.
- Organ system involved.
- Incidence and frequency of occurrence.
- ART regimen involved.
- Severity.
- Causality.
- Distribution over male and female patients.

#### **MATERIALS AND METHODS:**

##### **Study Setting:**

- Data collection: ART Centre (Dept. of Medicine); RGKMC and H.
- Data processing/analysis: Dept. of Pharmacology; RGKMC and H.

**Study Duration:** One year (June 1, 2014 - May 31, 2015).

**Study Type:** Prospective, observational, cross-sectional.

**Study Population:** All HIV-positive patients attending the ART Center of RGKMC and H during the study period.

**Sample Size Calculation:** Considering the constraints of a single investigator study, it was decided that the sample size of the present study would be calculated on the basis of a similar study done by Anwikar et al<sup>(10)</sup> with an ADR prevalence (P) of 12.36%.

##### **Estimated Sample Size (N) = Z<sup>2</sup> PQ/L<sup>2</sup>**

Z = 1.96 for 95% CI; P = 12.36; Q = 100-P = 87.64; Precision (L) = 5%.

Using the above expression and setting the above values; N=168.

**Mode of Sampling:** Purposive.

##### **Study Variables:**

- Sociodemographic (Age, sex, height, weight, educational, occupation, marital status, mode of transmission).
- Disease related (WHO clinical stage, CD4 count, baseline investigations).
- Therapy related (1st line ART regimen, CPT, ATT, change of regimen).
- ADR related (frequency, organ system involved, distribution overtime, severity, causality).

**Plan of Study:**

- Only HIV positive, treatment-naive (and eligible for 1st line ART) patients who were 18 years and above were selected after taking informed consent and necessary clearance from Institutional Ethics Committee (IEC).
- Baseline data was collected on a predesigned pre-coded standardised form (based on the "white card" issued by NACO, Dept. of AIDS Control, MOHFW, GOI, Sept. 2010).
- Follow up: Each patient was followed up once every month for 6 months; data regarding ADRs, change in ART regimen, change in WHO clinical stage, other concomitant drugs, CD4 count (at 6 months) with other relevant laboratory parameters (Hb, ALT, etc.) were recorded on the same case report form under the section.
- Causality assessment was done by NARANJO adverse drug reaction probability scale.<sup>(11)</sup>
- Severity grading was done by "Division of AIDS Table for grading the Severity of Adult and Paediatric Adverse Events, December 2004."<sup>(12)</sup>

**Data Analysis:** GraphPad Prism (Version 5.00, 2007) software was used for statistical analysis.

- Descriptive data was expressed in percentages (%).
- Fisher's exact test was used for categorical data (2 groups).
- To show difference between 2 paired groups, paired t-test (for parametric data) and Wilcoxon's matched pair test (for nonparametric data) were used.
- Association between 2 variables were analysed by Pearson's (for parametric data), Spearman's (for nonparametric data) and Risk Ratio (RR) and Odd's Ratio (OR) (for categorical data).

**Inclusion Criteria:**

- Age: 18 years and above.
- Treatment naive patients eligible for 1st line ART (According to NACO guidelines, 2013).

**Exclusion Criteria:**

- Treatment experienced (Already on ART regimen) patients.
- Critically ill patients.
- Pregnant females.

**Data Archiving:** Archiving of study documents was done by the principal investigator at the Dept. of Pharmacology.

**RESULTS AND ANALYSIS:**

- A total of 168 eligible patients were enrolled during the study period of which 18 were lost in follow up; hence, 150 patients were available for final analysis. Out of them, 84 (56%) were males, 65 (43.3%) were females (M:F ratio=1:0.774) and 1 (0.67%) belonged to the transgender - transsexual (TG-TS) category.

- One hundred forty (93.3%) patients belonged to the age group of 15-49 yrs. of which 77 (55%) were males, 62 (44.3%) were females [55 (84.6%) of reproductive age group (15-45 yrs.)] and 1 (100%) was a transgender-transsexual. Mean age (yrs.) = 35±10 SD.

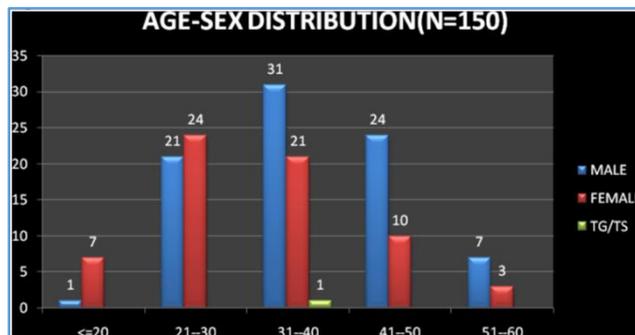


Figure 1

The commonest route of transmission was heterosexual contact 138 (92%) followed by homosexual contact 5 (3.33%), transfusion of blood and blood products 3 (2%) and injectable drug use 2 (1.33%); 2 (1.33%) were unknown.

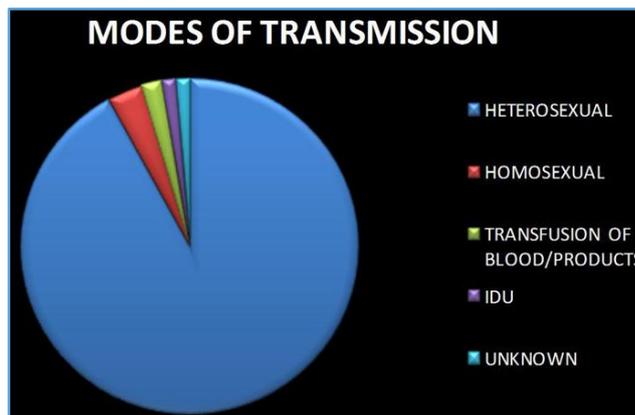


Figure 2

Ninety eight (65.33%) patients belonged to WHO clinical stage I.

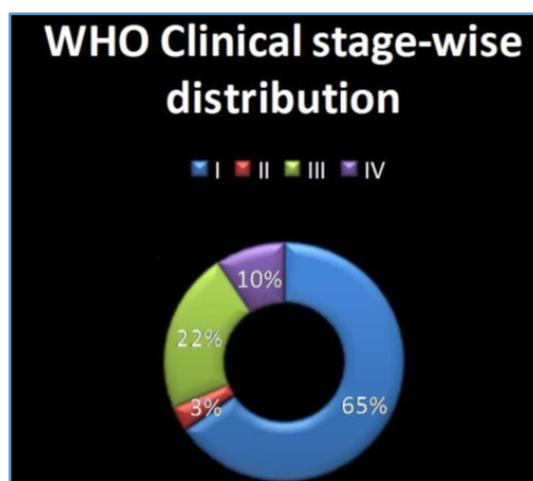


Figure 3

- The mean CD4 count (at baseline) was found to be 212±112 SD; majority (25.33%) patients having values in the 301-350 range. The mean CD4 count (after 6 months of ART) was found to be 303±137 SD ( $p < 0.0001$ ).
- Among the 1st line ART regimens, the most common one prescribed was TDF+3TC+EFV (56%); followed by AZT+3TC+NVP (28.57%). D4T+3TC+NVP (2.28%) was the least prescribed.

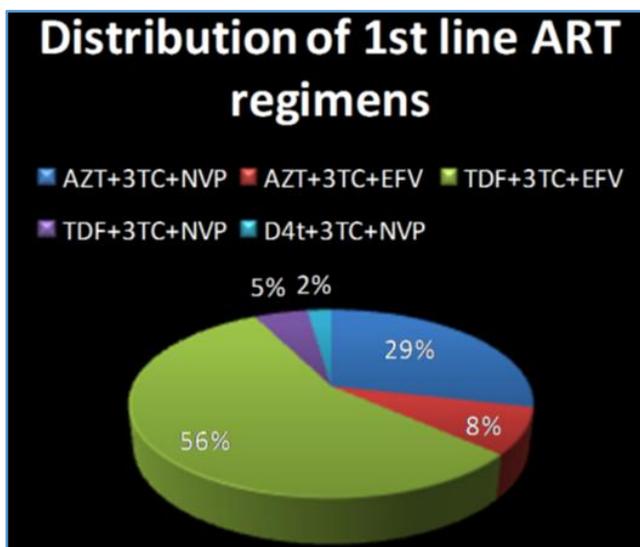


Figure 4

- Out of the 150 patients receiving ART, 30 (20%) were also receiving Antitubercular Treatment (ATT), 94 (62.67%) were under Co-Trimoxazole Prophylaxis Therapy (CPT) and 29 (19.33%) were receiving both.
- A total of 115 (76.67%) patients experienced ADRs; comprising 59 (51.3%) males and 55 (47.8%) females. Among the various age groups, majority ADRs were seen in the 21-40 years group - 76 (66.1%). Thirty five (23.33%) patients did not experience any ADR; of which, 25 (71.4%) were males and 10 (28.6%) females.

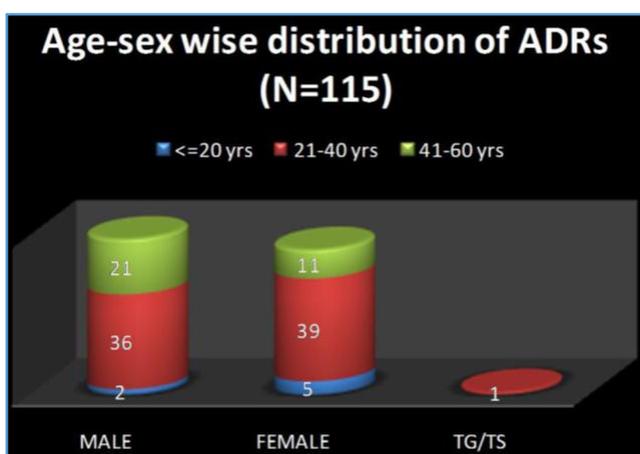


Figure 5

A total of 184 ADRs of which 88 (47.82%), 95 (51.63%) and 1 (0.54%) were seen in males, females and TG-TS respectively were observed in the entire study period. The system wise distribution was as follows: Gastrointestinal system - 50 (27.17%), nervous system 42 (22.82%), skin - 38 (20.65%), haematopoietic system - 28 (15.22%), hepatobiliary - 9 (4.89%), musculoskeletal - 8 (4.34%) and others 9 (4.89%).

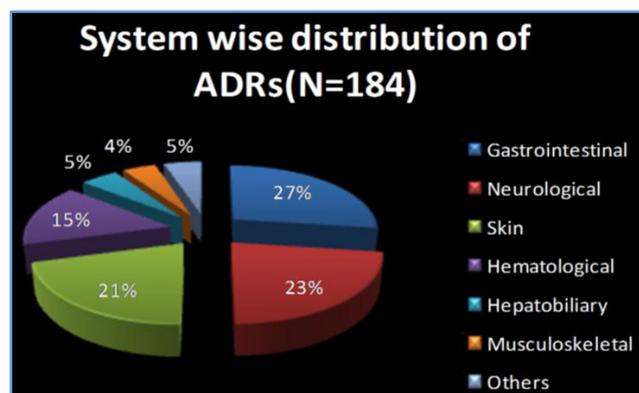


Figure 6

- Pertaining to the GI tract, 50 ADRs were observed; 22 (44%) in males and 28 (56%) in females [also see table]; diarrhoea 19 (38%) was the most common.
- Within the nervous system, 42 ADRs were seen; 23 (54.76%) in males and 19 (45.24%) in females [also see table 2]; neuropsychiatric symptoms (drowsiness, depression, insomnia, vivid dreams, hallucinations, nightmares, etc.); 28 (66.67%) was the commonest cluster of AEs noted. Only one (2.38%) case of peripheral neuropathy was noted. Suicidal tendency 2 (4.76%) and peripheral neuropathy were the two reasons for changing the ongoing ART regimen.
- Thirty eight cutaneous ADRs were seen; 23 (60.52%) in males, 14 (36.84%) in females and 1 (2.63%) in TG-TS. Rash 19 (50%) was the commonest, majority 12 (63.15%) of which were "mild" (grade 1), mostly seen in efavirenz-containing regimens. Four (21.05%) were "severe" (grade 3) and one (5.2%) was SJS (grade 4). Nevirapine was suspected for all these four cases, hence replaced by efavirenz subsequently. One case of grade 2 rash was attributed to lamivudine. Incidence of rash was slightly greater in males [see table 2]. Hyperpigmentation (nail/skin/mucosa) was the next common ADR - 13 (34.2%).
- From the haematopoietic system, 28 ADRs were noted; 6 (21.4%) in males and 22 (78.6%) in females. Anaemia 25 (89.3%) was the commonest AE with statistically significant ( $p < 0.0001$ ) female preponderance [See table 2]. Among these, 7 (28%) were grade 3 (Hb 6.5-7.4 g/dL) and 2 (4%) were grade 4 (Hb < 6.5 g/dL).
- From the hepatobiliary system, 9 ADRs were noted; 6 (66.67%) in males and 3 (33.33%) in females.

- Out of the 115 patients experiencing ADRs, 67 (58.26%) experienced only one ADR, 38 (56.7%) males and 29 (43.3%) females. 48 (41.7%) patients, 21 (43.75%) males and 27 (56.25%) females experienced >1 ADRs. None of the patients experienced >3 ADRs.
- At the end of 6-month follow up, it was noted that majority 112 (60.87%) ADRs [GI (39.28%), neurological (19.64%), skin (17.85%), haematological (14.28%), hepatobiliary (5.35%)] occurred within the 1st month. All ADRs related to GIT and hepatobiliary system were noted within the 1st 3 months. Least number 5 (2.71%) of ADRs were observed in the 6th month.

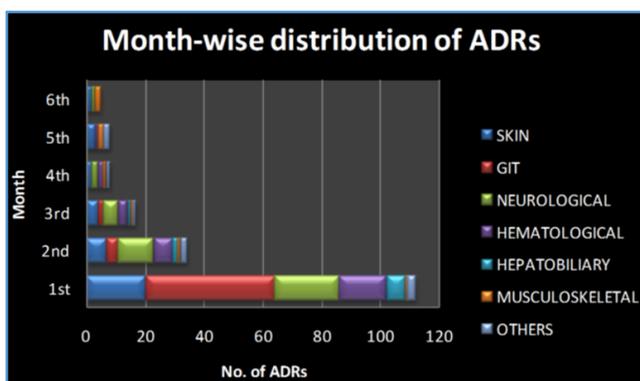


Figure 7

- Immune Reconstitution Inflammatory Syndrome (IRIS) was noted as a paradoxical reaction to ART in 15 (10%) cases; 13 (86.67%) in males and 2 (13.33%) in females occurring mostly 10 (66.66%) within the 1st 3 months of starting ART. Seven (46.67%) of those cases had a CD4 count  $\leq$ 50 cells/mm<sup>3</sup>. Tuberculosis 10 (66.67%) was the commonest IRIS followed by herpes zoster 3 (20%) and herpes simplex 2 (13.33%).
- Regarding severity of the ADRs, mostly 116 (63.04%) were "mild" (grade 1) followed by 51 (27.71%), which were "moderate" (grade 2). Twelve (6.52%) were "severe" (grade 3), which also included the sole case of peripheral neuropathy. Five (2.71%) were "potentially life threatening" (grade 4) including the case of SJS and two cases each of suicidal tendency and anaemia (Hb <6.5 g/dL). Relation between ADR severity with age and sex was not statistically significant (p=0.778 and 0.445, resp.).

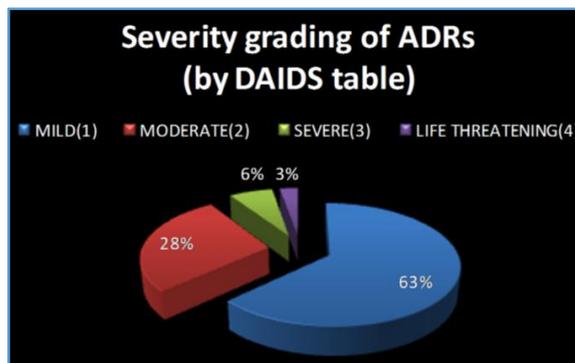


Figure 8

At completion of 6-month follow up, it was noted that maximal ADRs were reported from patients under regimen AZT+3TC+NVP - 89 (48.37%) followed by TDF+3TC+EFV-73 (39.67%).

ART REGIMEN	NO. OF PATIENTS N=150 (%)	NO. OF ADRS N=180 (%)
AZT+3TC+NVP	50 (8.57)	89 (48.37)
AZT+3TC+EFV	14 (18.66)	16 (8.69)
TDF+3TC+EFV	98 (56)	73 (39.67)
TDF+3TC+NVP	9 (5.14)	4 (2.17)
D4T+3TC+NVP	4 (2.28)	2 (1.08)

**Table 1: No. of ADRs with Respect to ART Regimens**

- Causality assessment revealed most of the ADRs to be "possible" (65.76%) while the rest being "probable" (34.24%). None of them were "highly probable" or "doubtful."

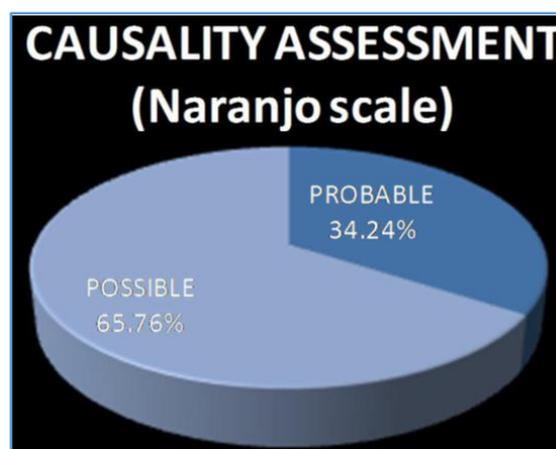


Figure 9

The distribution of various ADRs among male and female patients was as below:

ADR	Male; n (%)	Female; n (%)	Total; n (%)	P value
Anaemia	5 (5.59)	20 (30.7)	25 (16.7)	<0.0001

**Table 2: Incidence of ADRs Among the Males and Females. \*Highly Significant**

**DISCUSSION:** Males (56%) outnumbered the females (43.3%) with a male-female ratio of 1:0.774. Such male preponderance was also observed in previous studies by Ahmad et al,<sup>(13)</sup> Singh et al<sup>(14)</sup> and Joge et al.<sup>(15)</sup> In the current social scenario, females avoid medical attention fearing ostracism, gender bias, social stigma and neglect attached with HIV-AIDS, thus the lesser females attending HIV clinic.

Among the 1<sup>st</sup> line regimens prescribed (over the 6-month phase), the commonest ones were TDF+3TC+EFV (56%) followed by AZT+3TC+NVP (28.5%); PI based regimens were absent. In comparison, studies conducted by Lihite et al<sup>(16)</sup> showed most common ones to be d4T+3TC+NVP (65.3%), AZT+3TC+NVP (34%), d4T+3TC+EFV (30%); TDF+3TC+EFV (3%) being one of the least. Kumaraswamy et al<sup>(17)</sup> showed similar findings too. Such stark differences in the findings of this study in comparison to previous ones is the direct reflection of the WHO recommended ARV treatment schedule (2013),<sup>(5)</sup> which clearly states that TDF+3TC+EFV (in absence of any contraindication/unavailability) should be the preferred 1<sup>st</sup> line regimen for all adults/adolescents/pregnant, d4T should be omitted from 1<sup>st</sup> line regimens due to its well-known metabolic toxicities and PI based regimens are to be used as 1<sup>st</sup> line agents for children <3 years and as 2<sup>nd</sup> line agents for adults only.

Total 115 (76.7%) patients experienced ADRs as compared to Sharma et al<sup>(18)</sup> (71%) and Lihite et al<sup>(16)</sup> (31%). This comprised 59 (51.3%) males and 55 (47.8%) females showing higher prevalence in males. This is similar to studies by Jha et al<sup>(19)</sup> (53.5% males, 46.5% females) and Lihite et al<sup>(16)</sup> (75.26% males, 24.74% females), but different from Srikanth et al<sup>(20)</sup> (33.05% males, 41.82% females). Such sex differences in ADRs might be due to male-female disparities in BMI and fat composition, hormonal effects on drug metabolism or genetic constitutional differences at enzymatic level.

In this study, 184 ADRs were seen in 115 patients [mean ADR/patient=1.6]; similar results shown by Lihite et al<sup>(16)</sup> [1.72], Srikanth et al<sup>(20)</sup> [1.47] and Jha et al<sup>(19)</sup> [1.23], but a bit different from Sharma et al<sup>(18)</sup> [2.23]. GIT (27.17%) was the most common system involved in this study similar to Nagpal et al<sup>(21)</sup> [GIT (42.39%)] and Lihite et al<sup>(16)</sup> [GIT (31.25%)], but different from Srikanth et al<sup>(20)</sup> [skin (31.57%)], Sharma et al<sup>(18)</sup> [skin (44.4%)] and Singh et al<sup>(22)</sup> [nervous system (20.83%)]. Such differences might be due to disparities in patient profile, prescribed ART regimens and concomitant medications for treating various OI.

Pertaining to the GIT, diarrhoea (19/50=38%) was the commonest ADR found here; in comparison, gastritis was shown to be the most common ADR by Lihite et al<sup>(16)</sup> (13.13%) and Sharma et al<sup>(18)</sup> (9/18=50%). Diarrhoea was shown by them as 2% and 5.5%, resp. AZT and TDF were the suspects (in this aspect) in our study and since regimens containing these two agents were maximum, this might have been the cause of such findings in this study contrasted with other studies, which mostly contained AZT and NVP, hence

responsible for the greater incidence of gastritis in their studies.

Pertaining to the nervous system, neuropsychiatric manifestations (28/42=66.6%) was the commonest cluster of ADRs followed by headache (13/42=30.95%). Only one case of peripheral neuropathy was noted. These findings were very different from most of the other studies especially Singh et al,<sup>(22)</sup> Anwikar et al<sup>(10)</sup> and Sharma et al<sup>(18)</sup> who reported peripheral neuropathy as the most common ADR involving the nervous system, incidence of headache and neuropsychiatric manifestations were rare. Such stark differences in results yielded by this study as compared to others can be attributed to 2 obvious factors: (i) Rare inclusion of d4T, the well-known causative of peripheral neuropathy in the regimens of this study. (ii) Abundance of EFV-containing regimens, which is the prime offender behind the neuropsychiatric manifestations. Two cases of suicidal tendency were noted for which EFV had to be replaced with NVP. Fumaz et al<sup>(23)</sup> and Subbaraman et al<sup>(24)</sup> have also reported similar kinds of ADRs with EFV usage.

Among the cutaneous ADRs, rash (19/38=50%), including 4 cases of grade 3 and one case of grade 4 (SJS) was the commonest finding. This resembles most of the other studies especially Sharma et al<sup>(18)</sup> who noted rash (12/40=30%) including 3 cases of SJS and Lihite et al<sup>(16)</sup> who found rash (32/38=84.2%) including 2 cases of SJS. Like in these studies, all grade 3 and 4 rashes were suspected to be due to NVP in this study, which were subsequently replaced by EFV. But, most of the rashes were grade 1 and 2 for which EFV was suspected responsible except one which was attributed to 3TC. Modak et al<sup>(25)</sup> had reported 3 unusual cases of grade 4 rash with 3TC managed by its withdrawal. Prevalence of rash was slightly greater in males [Table 2], but Rather et al<sup>(26)</sup> found higher prevalence in females (p=0.049). Hyperpigmentation (nail/skin/mucosa) (13/38=34.2%) was the next common finding in this study supported by Sharma et al<sup>(18)</sup> (16/40=40%), but opposed by Lihite et al<sup>(16)</sup> (1/38=2.6%). AZT was considered responsible for such ADRs.

Regarding haematopoietic system, anaemia (25/28=89.3%) was the most common ADR with a much higher female prevalence (80%), difference being statistically highly significant (p<0.0001). Similar results were shown by Sharma et al<sup>(18)</sup> (62%), Rather et al<sup>(26)</sup> (58.6%), but none of these were statistically significant. Like all other studies, AZT was the prime suspect behind anaemia and hence in grade 3 and 4 cases was replaced mostly by TDF and sometimes by d4T. Since AZT is one of the most common components of the 1<sup>st</sup> line regimens (75/150=50% in this study), it could hence be responsible for such higher frequency of anaemia (25/184=13%) among the ADRs. Such female preponderance could be due to nutritional deficiency, menses, pregnancy, use of IUCDs, presence of recurrent infections like UTI, etc.

At the end of 6-month follow up, it was noted that majority 112 (60.87%) ADRs occurred within the 1<sup>st</sup> month of ART exposure followed by 34 (18.47%) within the 2<sup>nd</sup> month. Anwikar et al<sup>(10)</sup> in their study noted similar results

stating NVP-induced rash and SJS developed within first month of treatment followed by anaemia, hepatitis and gastritis, which developed within 6 months after initiation of ART.

Immune Reconstitution Inflammatory Syndrome (IRIS) was noted as a paradoxical reaction to ART in 15 (10%) cases occurring mostly 10 (66.66%) within the 1<sup>st</sup> 3 months of starting ART. Tuberculosis 10 (66.67%) was the commonest IRIS followed by Herpes zoster 3 (20%) and Herpes simplex 2 (13.33%). Similar results were achieved by Sharma et al<sup>(18)</sup> (22.2%). IRIS reflects the body's ability to mount an inflammatory response associated with immune recovery. ART partly restores protective pathogen-specific immune responses leading to atypical inflammatory manifestations to concurrent infective/non-infective conditions like TB, MAC and CMV. In my study, all cases of IRIS were managed conservatively without stopping ART.

Regarding severity of the ADRs, mostly 116 (63.04%) were "mild" (grade 1). Twelve (6.52%) were "severe" (grade 3), which also included the sole case of peripheral neuropathy. Five (2.71%) were "potentially life threatening" (grade 4) including the case of SJS and two cases each of suicidal tendency and anaemia (Hb <6.5 g/dL). In this context, different studies yielded different results: Singh et al<sup>(22)</sup> 26.58% (grade 3 and 4), Anwikar et al<sup>(10)</sup> 8.77% (mild), 77.19% (moderate), 14.02% (severe). Such disparities in findings might be due to patient profile, presence of other comorbidities and also due to the scale used for assessment (Modified Hartwig and Siegel scale, WHO scale, DAIDS table, etc.). In this study, mild-to-moderate ADRs were managed conservatively. In the case of peripheral neuropathy, d4T was replaced by TDF. The case of SJS was immediately hospitalised, ART was stopped and after recovery changed to EFV-based regimen. The cases with suicidal tendency were counselled properly, then their regimens were changed to TDF+3TC+NVP. Cases with grade 4 anaemia (Hb<6.5 g/dL) were given blood transfusion and their regimens were then changed to TDF+3TC+EFV. Here, we did not find any statistically significant relation of severity with age ( $p=0.778$ ) and sex ( $p=0.445$ ).

Causality assessment revealed majority of ADRs to be "possible" (65.8%) and the rest "probable" (34.2%); very similar to Lihite et al<sup>(16)</sup> [possible (63.75%) and probable (36.25%)]; but different from Jha et al<sup>(19)</sup> [probable (66.04%) and possible (33.96%)], Nagpal et al<sup>(21)</sup> [probable (6.63%) and possible (93.3%)] and Anwikar et al<sup>(10)</sup> [probable (3.5%) and possible (96.5%)]. Confounding factors, inter-reviewer variability and scale used might be the reasons behind such different results.

Maximal ADRs were reported from patients under regimen AZT+3TC+NVP - 89 (48.37%); 15 (16.85%) belonging to grade 3 and 4. Similar results were achieved by Lihite et al.<sup>(16)</sup> The next regime with the most ADRs was TDF+3TC+EFV-73 (39.67%) of which only 2 (2.73%) belonged to grade 4. Important to note was that d4T+3TC+NVP was the least common regimen prescribed - 4 (2.66%) and 2 (0.01%) ADRs were noted under it both (100%) of them belonging to grade 3. This further supports

the latest recommendations of W.H.O.<sup>(5)</sup> regarding phasing out of d4T from 1<sup>st</sup> line ART regimens. Regimens were changed due to development of ADRs for a total of 25 times during the 6-month follow-up phase of which TDF+3TC+EFV was the commonest one (17/25=68%) to have replaced the previous regimen; different from the study by Manickum et al<sup>(27)</sup> where AZT+3TC+NVP/EFV was the commonest regimen to replace the former. Hence, my observations were in accordance to the latest recommendations of W.H.O.<sup>(5)</sup>

Certain characteristic adverse reactions like lipodystrophy, dyslipidaemia, drug-induced hyperglycaemia, nephrotoxicity and bone mineral toxicity were not seen in this study. This finding is different from other studies like those conducted by Rather et al<sup>(26)</sup> - hypertriglyceridemia (15.2%); Lihite et al<sup>(16)</sup> - facial lipodystrophy (1.25%) and Sharma et al<sup>(18)</sup> - lipodystrophy (9%), hyperlipidaemia (3.5%), lactic acidosis (0.7%), which either had been carried out for longer durations or were retrospective. Furthermore, Krishna et al<sup>(28)</sup> reported a case of renal failure in a patient receiving TDF-based regime for 6 years. Patel et al<sup>(29)</sup> noted albuminuria and glycosuria in a patient on TDF-based regime for 1 year. Such ADRs were absent in this study because our follow up period was only of 6 months, hence only the short-term (<1 month) and medium term (1-6 months) toxicities could be detected.

**CONCLUSION:** Although, over the past 35 years HIV/AIDS has emerged as a major public health problem, the inception and evolution of HAART has revolutionised its management. On one hand, it has proved to be highly efficacious, while on the other, it has brought along its burden of adverse drug reactions, which is a substantial cause of morbidity in HIV infected patients. Anaemia was the most common ADR; females being significantly more likely to develop anaemia. Hence, recommendations should be made for interventions aiming at prevention and mitigation of such female preponderance. Data generated from this study combined with other similar studies conducted at various centres over West Bengal and India might help in formulating institution specific and national guidelines, respectively, regarding therapy of HIV/AIDS. It must also be remembered that ADRs are the inevitable consequence of pharmacotherapy. Hence, meticulous implementation of current protocols designed for regular screening of patients especially during the initial months of therapy may help in earlier detection of ADRs and thus help in preventing serious or life threatening consequences. In addition, patients along with their supportive family members or adherence monitors should be educated about adverse effects and taught how to recognise them in order to facilitate early management on need.

Last, but not the least, needless to say, more research is required to develop cost-effective patient-specific investigations and algorithms for prediction of ADRs of the currently prescribed regimens along with generation of more efficacious yet less toxic drugs.

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