



**DRUG UTILIZATION STUDY AND ADVERSE DRUG REACTION OF ANTI
RETROVIRAL DRUGS AMONG HIV INFECTED PATIENTS IN AN ART CENTER**

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ABSTRACT

Objective: To i) Evaluate the drug utilization pattern of antiretroviral drugs in Human immunodeficiency virus infected patients and ii) Monitor adverse drug reactions associated with anti-retroviral drugs. **Materials and Methods:** A retrospective observational study was carried out by collecting the data of HIV infected patients visiting ART center of Civil Hospital, Belagavi for a period of six months. The detailed data from case file was collected and noted in a proforma. Simple descriptive statistics was used for analysis. **Results:** The total numbers of patients were 230. Of which majority were males 122(53.04%). Most common age group affected were 30-45years 92(40%) and common risk factor being heterosexual group 197(85.65%). Occurrence of HIV was more among illiterates (33.91%) and agricultural laborers (13.4%). CD4 count was done prior to ART, most of the patient 93(40.43%) showed less than 200 cells/ μ L. The most commonly prescribed ART regimen was combination of Tenofovir +Lamivudine +Efavirenz 177(76.96%) and among NRTI 460(45.9%), lamivudine was commonly prescribed 230(22.95%). The concomitant medication prescribed was antibacterial agents 251(25.05%) and others were hematinics (3%). The most common adverse drug reaction was anemia due to drug zidovudine. Tuberculosis was the common opportunistic infection among the patients. **Conclusion:** Anti-retroviral drugs utilized in our study was in accordance with national guidelines and rational. Incidence of ART associated ADRs were less and more frequent only in patients with prolonged treatment.

KEYWORDS: Drug utilization, antiretroviral drugs, adverse drug reaction.

INTRODUCTION

HIV is a major global public health issue. It having infected 74.9 million humans and caused 32 million deaths so far. In 2018, 37.9 million people living with HIV, 1.7 million people becoming newly infected and 770 000 died of it. By the end of June 2019, 24.5 million people were accessing antiretroviral therapy globally.^[1] In India 2100000 were living with HIV of which 56% were accessing antiretroviral therapy.^[2]

HIV infection and AIDS are both caused by human retrovirus. This virus is transmitted primarily by sexual contact, by blood, blood products, body secretions and from infected mothers to infants intrapartum, perinatally or via breast milk.^[3] Once infected the virus remains in the body lifelong. The risk of developing AIDS increases with time.

Profound immunodeficiency associated with HIV infection or AIDS occur primarily from gradual depletion of CD4 T cells or helper T cells which eventually results in development of opportunistic infections. They also infect B cells, macrophages and nerve cells. There is reduction in cellular immunity.

Alteration in T cell function which is responsible for development of neoplasia, opportunistic infection. Production of antibodies to HIV will be too few and are ineffective against HIV.^[4]

Drugs available for HIV treatment belongs to classes of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors, CCR5 co-receptor antagonist and HIV integrase strand transfer inhibitors. The goal of therapy is to suppress virus replication as much as possible for as long as possible. The current standard of care is to use at least three drugs simultaneously for the entire duration of treatment. The expected outcome of initial therapy in a previously untreated patient is an undetectable viral load (plasma HIV RNA < 50 copies/mL) within 24 weeks of starting treatment. A minimum of three antiretroviral agents are required to guarantee effective long-term suppression of HIV replication without resistance. In treatment-naïve patients, a regimen containing a NNRTI plus two NRTIs is as effective as a regimen containing an additional nucleoside.^[5]

National AIDS Control Organization provides prevention, support, care and treatment to HIV patients in India through ART centers.^[6] Adopting changing trends in pharmacotherapy of HIV/AIDS in the world and rational use of drugs are some of the measures to treat it more effectively.

Drug utilization studies are powerful exploratory tools to ascertain role of drugs in society. These studies help to evaluate changing pattern of drug use, compliance with national guidelines and rational use of drugs.^[7] Several utilization studies are periodically conducted across the world, including India. This study was conducted to evaluate the utilization pattern and monitor the adverse drug reactions of oral antiretroviral drugs in our ART center.

METHODS

This retrospective observational study was conducted in the tertiary care government hospital, ART center, BIMS, Belagavi over a period of six months from January to June 2019. The study was approved by institutional ethical committee. Patient records which included demographic data, anthropometry, investigation results, drug regimen and adverse drug reactions of all patients receiving anti-retro viral therapy were included

in the study irrespective to age and sex. Patients having treatment modification due to immunological failure, pregnant women and lactating mothers and patients with comorbid conditions were excluded from the study. The data collected was tabulated in a specially designed proforma in MS excel and analyzed using descriptive statistics and the results were presented by percentage.

RESULTS

The total number of HIV patients included in our study was 230. Age of the patients varied from 5 months to 66 years, among these 122 (53.04%) were males, 107(46.5%) were females and 1(0.46%) transgender. In age group, the most common to be infected were of 30-45years 92 (40%), then 45-60years 59(25.7%) followed by 15-30years 57(24.78%), 1-15 years 14(6.09%) and 1(0.43%) patient less than 1 year.

Entry point of 111 (48.26%) patients to ART center was from various outpatient departments of BIMS while 82(35.65%) patients directly walked into the ART center is shown in Table 1. Among the risk factors who developed HIV were heterosexuality 197(85.65%) was the most common, then mother-child 20(8.69%) followed by blood transfusion in 3(1.3%) this is shown in Figure 1.

Table 1: Entry point to ART center.

Entry point	No of patients (n=230)	Percentage (%)
Direct walk in	82	35.65
Inpatient	16	6.96
Outpatient	111	48.26
Private Practitioner	10	4.35
Others	11	4.78

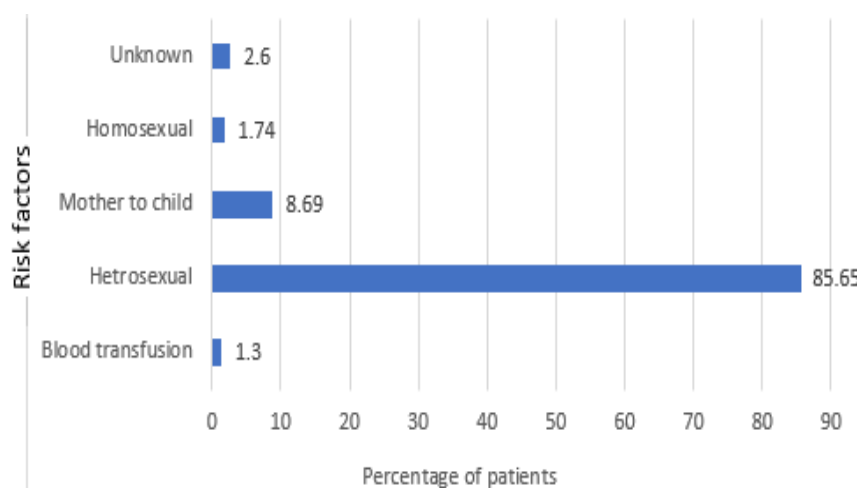


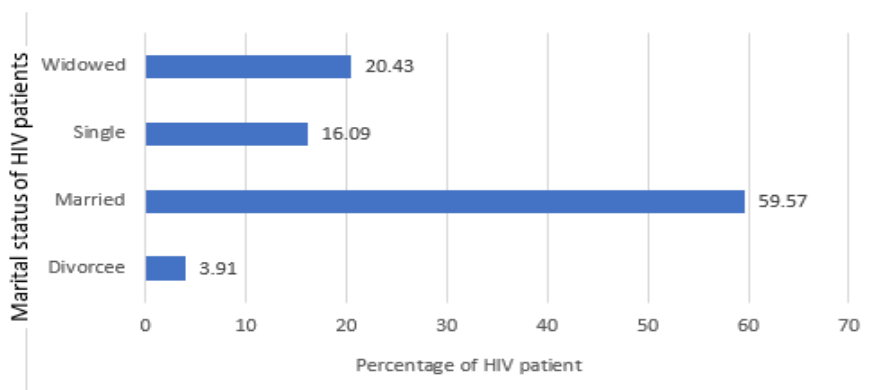
Fig 1: Risk factors for the development of HIV.

Table 2 depicts education and occupation status of HIV patients, the occurrence of HIV in illiterates was more 78(33.91%) when compared to patients with college education 33(14%). Regarding occupational status 62(26.96%) were construction labourers, followed by 46(20%) housewives and 30(13.04%) agricultural labourers.

Table 2: Education and occupation of HIV patients.

Education	No of patients(n=230)	Percentage (%)
Illiterate	78	33.91
Primary school	59	25.65
Secondary school	60	26.09
College	33	14.34
Occupation status of patients		
Agricultural Cultivator/landlord	7	3.04
Agricultural labourer	30	13.04
Domestic servant	1	0.43
Gov/Pvt service	17	7.39
Hotel staff	4	1.74
Housewife	46	20
Local transport worker	5	2.17
Construction labourer	62	26.96
Retired	2	0.87
Self employed	10	4.35
Semi skilled worker	12	5.22
Skilled worker	6	2.61
Student	10	4.35
Truckdriver	1	0.43
Unemployed	17	7.39

Figure 2 shows the marital status of HIV patients in the study group. Most of the patients were married 137(59.57%) while 47(20.43%) were widowed.

**Fig 2: Marital status of HIV patients.**

Patients initial weight at the time of admission was noted, majority 91(39.57%) were of 46-60kg, 81(35.22%) of patients were 31-45kgs, 29(12.61%) weighed 61-75kgs, 12(5.22%) were 76-90kgs, 7(3.04%) patients weighed 1-15kgs and 16-30kgs, (0.87%) patients weighed 91-105kgs and 1(0.43%) patient was above 106kgs.

Majority of patients were walking 203(88.26%) at the time of admission, 24(10.43%) were bedridden and 3(1.3%) were ambulatory.

Table 3: WHO clinical staging at the time of starting ART.

WHO Clinical stage	Total no of patients(n=230)	Percentage (%)
I	4	1.74
II	208	90.43
III	10	4.35
IV	8	3.48

Table 3 shows WHO clinical staging at the time of starting ART and majority of the patients were in WHO clinical stage II (90.43%). Table 4 shows Initial CD4 count of HIV patients before starting ART in which most of the patients had initial CD4 counts less than 200 cells/ μ L 93(40.43%) and 39(16.96%) patients had CD4 count above 500 cells / μ L. All patients were prescribed with HAART regimen irrespective of CD4 count.

Table 4: Initial CD4 count of HIV patients before starting ART.

CD4 count(Cells/ μ L)	Total no of patients(n=230)	Percentage (%)
≤ 200	93	40.43
201 - 250	19	8.26
251 - 300	14	6.09
301 - 350	20	8.70
351 - 400	19	8.26
401 - 450	10	4.35
451 - 500	16	6.96
> 500	39	16.96

The prescribed drugs of antiretroviral agents from HAART regimens, which were utilized by the patients is shown in the table 5.

Table 5: Utilization pattern of different HAART regimens.

Drug regimen	No of patients(n=230)	Percentage (%)
Abacavir + Lamivudine+ Efavirenz	20	8.7
Abacavir + Lamivudine + Lopinavir/ritonavir boosted	1	0.43
Tenofovir + Lamivudine+ Efavirenz	177	76.96
Tenofovir + Lamivudine+ Nevirapine	2	0.87
Zidovudine + Lamivudine+ Nevirapine	12	5.22
Zidovudine + Lamivudine+ Efavirenz	18	7.83

Prescribing pattern of subclass of antiretroviral agents was nucleoside reverse transcriptase inhibitors (66.6%) followed by non-nucleoside reverse transcriptase inhibitors (33.18%) and protease inhibitors (0.14%). The most commonly prescribed antiretroviral agent was

lamivudine (33.33%). Ritonavir boosted lopinavir (1%) was preferred protease inhibitor. Second most common drug medication class was antibacterial agents (25.05%), cotrimoxazole (15.04%) followed by antitubercular drugs (9.88%) is shown in Table 6.

Table 6: Utilization of concomitant drugs along with antiretroviral drugs.

Drug	No of drugs prescribed(n=1002)	Percentage (%)
1. Antiretroviral agents		
a) Nucleoside reverse transcriptase inhibitors	460	45.91
Zidovudine	31	3.09
Lamivudine	230	22.95
Tenofovir	179	17.86
Abacavir	20	2
b) Non-nucleoside reverse transcriptase inhibitors	229	22.85
Nevirapine	14	1.4
Efavirenz	215	21.46
c) Protease inhibitors	1	0.1
Lopinavir (ritonavir boosted)	1	0.1
2. Antibacterial Agents	251	25.05
a) Antitubercular drugs	99	9.88
Isoniazid	24	2.4
Rifampicin	24	2.4
Pyrazinamide	24	2.4
Ethambutol	24	2.4
Streptomycin	7	0.7
b) Other antibacterial agents	152	15.17
Co-trimoxazole	151	15.07
Amoxicillin+ Clavulanic acid	1	0.1
3. Antifungal	4	0.4
Fluconazole	3	0.3
Ketaconazole	1	0.1
4. Antiprotozoal drugs	2	0.2
Metronidazole	2	0.2

5.Steroid	2	0.2
Hydrocortisone	1	0.1
Clobetasol	1	0.1
6.Vitamins	13	1.29
Folic acid	10	1
Becosules	3	0.3
7.Haematinics	30	3
Ferrous Sulphate	20	2
Ferrous ascorbate	10	1
8.Antihistamines	3	0.3
Cetirizine	3	0.3
9.Calamine lotion	3	0.3

Table 7 depicts adverse drug reactions observed during ART therapy. Anemia was the most common adverse drug reaction.

Table 7: Adverse drug reactions with ART.

Adverse drug reaction	No of patients (n=230)
Anemia	20
Gastroenteritis	2
Rashes	3
Peripheral neuropathy	1

Figure 3 shows opportunistic infection among HIV patients. TB was the most common opportunistic infection observed.

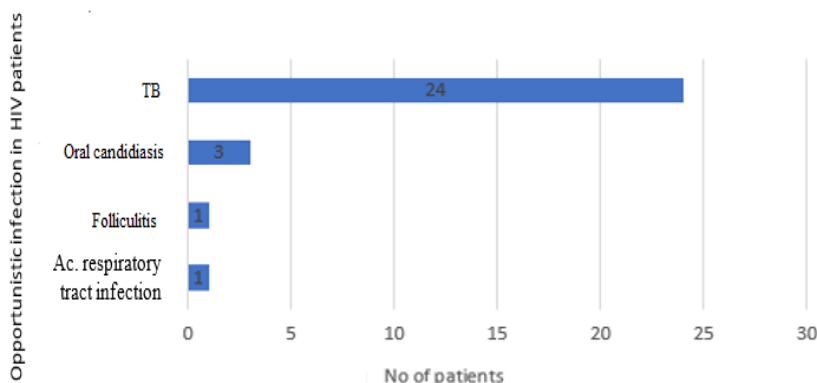


Figure 3: Opportunistic infection in HIV patients.

DISCUSSION

New antiretroviral drugs have been developed by understanding molecular biology and pathogenesis of the disease, its treatment protocols have changed the world's outlook on HIV/AIDS from a "virtual death sentence" to a "chronic manageable disease".^[8]

Our study group had patients with age ranging from 5 months to 66 years and age group 30-45years was 92(40%), this higher prevalence of HIV among the sexually active and economically productive age group. This was in accordance with other studies by Chacko Jiyo et al and Shailesh P. Parmar et al from India.^[8,9] Majority of patients were males 122(53.04%) compared to females. Similar higher HIV seropositivity among male was also seen in other studies.^[9,10]

Higher educational attainment beyond primary level being associated with reduced HIV prevalence for both males and females. Occurrence of HIV was more common among illiterates 78(33.91%) followed by patients who completed primary schooling 60(26%), same finding was seen in a study from Ugandal.^[11] Most of the patients were married 137(59.57%) which is in consonance with other studies.^[12,13] Being heterosexual 197(85.65%) was the most common risk factor among the study group followed by blood transfusion 3(1.3%) patients, finding were similar to a study done by Fehmida Visnegarwala et al.^[13]

In our study all the patients received anti-retroviral drugs irrespective of CD₄ count unlike the older studies.^[9] Earlier anti-retroviral drugs were started only on patients having CD₄ count less than 350cells/mm³ whereas in the

recent guidelines all patients diagnosed with HIV infection is given anti-retroviral drugs irrespective of CD₄ count. This explains higher proportion of antiretroviral drugs usage in this study this is in accordance with the latest national guideline by NACO in 2018.^[5]

ART regimen includes use of a treatment combination, which contains two NRTIs and one NNRTIs, preferably. NRTI remain the backbone of ART and most preferred drugs and prescribed in our study and various other studies.^[14,15] Protease inhibitors or NNRTIs based are not used commonly as PIs are more prone for more drug interactions, intolerance or adverse effects and NNRTI based regimes has higher rate of immunologic failure.^[16] The most common ART regimen prescribed was the combination of tenofovir with lamivudine and efavirenz (76.96%) followed by abacavir with lamivudine and efavirenz (8.7%). The above findings are in accordance with guidelines, which recommend tenofovir with lamivudine and efavirenz as the first choice.^[5] This was similar to another study by Hasabi *et al*^[10] but differ from Parmar *et al* study, in which zidovudine with lamivudine and nevirapine were among commonly prescribed regimen.^[9] Thus in our study zidovudine usage was less, to avoid its well recognized toxicities including lactic acidosis, lipodystrophy, anemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, skin and nail pigmentation.

In our study, usage of tenofovir (17%) based regimes was higher compared to previous studies.^[9,17] these findings are similar to some studies done.^[14,15] The study by Sujata Sapkota *et al*, have used zidovudine based regimen.^[18] This difference in prescribing rates of various regimes may be due to a different guideline in their country. In the other studies, NRTI lamivudine(22.95%) was commonly used followed by tenofovir(17.86%).^[16,17] Higher usage of lamivudine can be due to its good safety profile and its ability to restore susceptibility to zidovudine and tenofovir.^[4] Usage of tenofovir and efavirenz was higher in our study because of their convenient dosage schedule. Whereas PI was ritonavir boosted lopinavir (0.1%), similar to previous similar studies.^[4,8]

Antibacterial agents (25.05%) were the second most common class of drugs prescribed. The most common antibacterial agent used was co-trimoxazole (15.07%), followed by antitubercular agents (9.88%). These findings are in consonance with other studies.^[9,19] Use of co-trimoxazole is justifiable as it is recommended for chemoprophylaxis against pneumocystis jiroveci infection. and tuberculosis (TB) is the leading opportunistic disease and cause of death in patients with HIV infection.^[20,21] Given the high rates of TB-HIV co-infection, higher usage of antitubercular agents is justifiable. Similar to other study, the third most commonly prescribed drug class in this study was

vitamins namely folic acid and vitamin B complex tablets followed by haematinic drugs.^[8,19]

Of 230 patients, 26(11%) developed ADRs in six months of follow-up. Overall, 20 (76.92%) of ADRs were reported by patients on AZT and the commonest ADRs reported was anemia, similar finding was observed by Mukherjee *et al*.^[22] Human Immunodeficiency viruses are the causative agents in AIDS, but morbidity and mortality in AIDS cases result from opportunistic infections. In this study, among all opportunistic infections, tuberculosis (77.41%) was most common followed by oral candidiasis (9.67%) and gastroenteritis (6.45%). The findings are similar with other studies.^[9,13] Majority of studies globally have also found tuberculosis as most common opportunistic infection among HIV infected patients.^[20,21]

CONCLUSION

Anti-retroviral drugs utilized in our study were in accordance with national guidelines and rational approach to prescribing pattern. This study provides a baseline data regarding the demographic data, prescribing pattern, ADRs and opportunistic infections in HIV positive patients registered at our ART center. Incidence of ART associated ADRs are reduced as the patients were periodically monitored. Occurrence of ADR was more frequent only in patients with prolonged treatment.

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