ADVERSE DRUG REACTIONS WITH SECOND LINE ANTIRETROVIRAL DRUG REGIMEN

DR. NAVEEN POKALA *1, DR. ROHIT DIXIT2, DR. PATEL MOULIK MANUBHAI3, DR. K VIJAYAL4,

1Assistant Professor, Mamata Medical College, Khammam], Dr. Rohit Dixit 2Assistant Professor, Navodaya Medical College, Raichur, 3Assistant Professor, Mamata Medical College, Khammam, 4Rtd Professor, Gandhi Medical College, Secunderabad.
Email: naveenpokala@yahoo.com

ABSTRACT

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Because of treatment failure with first line ART, second line ART is being instituted in 10 Centers of excellence in our country, Gandhi hospital being one of them.

Aims & Objectives: The aim of this study is to gain knowledge on the profile of ADR associated with second line ARV drugs, the burden of adverse drug reactions of second line ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

Material & Methods: Institution based cross sectional study conducted using review of clinical records and follow up of adult patients started on second line ART from May 2010 to April 2011 at GANDHI Hospital. All adult AIDS patients of either sex aged greater than or equal to 20 years who were registered for second line anti-retroviral treatment at GANDHI Hospital were included in the study. The clinical records of study subjects were reviewed retrospectively for ADRs. Information on patient's details, the WHO clinical staging of the disease at the start of ART, duration of treatment, drug details, nature of the adverse drug reactions, severity, outcome, and results of investigations performed were collected using a data collection format (Annex I). Data were collected from May 2010 to April 2011.

Results: 58 cases were included in the study. 58 cases were included in the study. Among the total 58 patients who were on second line ARV drugs, ADRs were reported in 44 (75.86%) patients (Table 3). The most frequently observed ADRs were nausea (12.25%), followed by insomnia (10.29%), loss of appetite (9.31%) malaise (7.35%) and vomiting (7.35%). Out of the 44 patients who developed ADRs, 20 (45.45 %) patients were grade II, whereas grade I and III ADRs occurred in 9 (20.45%) and 15 (34.09%) of the patients respectively. Grade IV was reported in none of the patients. No ADRs were noted in 14 (24.14%) patients. Out of 44 patients who had ADRs, 32 patients (72.73%) had less than 5 ADRs and 12 patients (27.27%) had more than 5 ADRs.

Conclusion: Second line anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS. Though second line ART regimens are associated with mild to moderate ADRs, these are most effective regimens as they improved CD4 counts and reduced viral load significantly.

Keywords: NACO, HIV, Immunodeficiency, Second line, Side effects, Regimen, Reporting

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. [1]

DISEASE BURDEN

- HIV is a rapidly evolving pandemic [2] entering its third decade, with cases reported from virtually every country. At present, 33.2 million individuals were living with HIV infection (range: 30.6–36.1 million) according to the Joint United Nations Programme on HIV/AIDS (UNAIDS).
- India has the third largest number of HIV positive persons with an estimated 3.8 million infected persons. HIV prevalence is highest in Southeast Asia, with wide variation in trends between different countries. [3]
- AIDS was first recognized by the U.S. Centers for Disease Control and Prevention in 1981 and its cause HIV, identified in the early 1980s. Although treatments for AIDS and HIV can slow the course of the disease, there is no known cure or vaccine. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but these drugs are expensive and routine access to antiretroviral medication is not available in all countries.[4]

The National AIDS Control Programme (NACP), launched in 1992, has being implemented as a comprehensive programme for prevention and control of HIV/AIDS in India. NACP's Phase-III has

the overall goal of halting and reversing the epidemic in India over the five-year period (2007-2012). [5]

People Living with HIV/AIDS (PLHA): The total number of people living with HIV/AIDS (PLHA) in India is estimated at 23.9 lakh (19.3 – 30.4 lakh) in 2009. Children under 15 yrs account for 3.5 percent of all infections, while 83 percent are the in age group 15-49 years. Of all HIV infections, 39 percent (9.3 lakhs) are among women. [6]The four high prevalence states of South India (Andhra Pradesh– 5 lakhs, Maharashtra–4.2 lakhs, Karnataka–2.5 lakhs, and Tamilnadu–1.5 lakhs) account for 55 percent of all HIV infections in the country.

The Government of India on November 30, 2003 announced a plan to place 1 lakh AIDS cases in India on anti-retroviral therapy (ART) by the end of 2007 and 15-20% additional AIDS cases each year, thereafter, for a period of 5 years.

Till December 2008, 197 ART centre's have been established and 1, 99,237 persons have been put on ART in India.

The primary goals of ART are maximal and durable reduction in plasma viral load levels, restoration of immunological functions aimed at prolongation of life and improved in quality of life.

Presently there are 15, US FDA approved antiretroviral agents available in India. A combination of at least 3 agents from different classes of anti-retroviral drugs is the regimen of choice (first line ART). Because of treatment failure with first line ART, second line ART is being instituted in 10 Centers of excellence in our country,

Gandhi hospital being one of them. Antiretroviral therapy (ART) has markedly changed the pattern of infection by the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). Current ART regimens are capable of reducing viral load to undetectable levels with a consequent increase in lymphocyte T-CD4+ counts and a substantial reduction in HIV-associated morbidity and mortality **[1].** In spite of ART benefits, adverse reactions to these drugs have been pointed to as one of the main reasons for discontinuation and nonadherence to ART.

Success of the anti-retroviral treatment is highly dependent on willingness of HIV positive Individuals to adhere to complex ARV regimens**.** [7] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or treatment failure within the first 8 months of therapy**.** [8]

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients. [9, 10]Therefore, many countries have adverse drug reactions (ADR) monitoring centers, which are responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluation is made and safety measures are taken to protect the public from unnecessary harm.

The aim of this study is to gain knowledge on the profile of ADR associated with second line ARV drugs, the burden of adverse drug reactions of second line ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

MATERIAL AND METHODS

Study Subjects

Adult patients on second line ART who fulfilled the inclusion criteria of study subject.

Study Design

Institution based cross sectional study conducted using review of clinical records and follow up of adult patients started on second line ART from May 2010 to April 2011 at GANDHI Hospital C.O.E.

Sample Size: the total sample size was 58.

Inclusion and exclusion criteria

Inclusion criteria

All adult AIDS patients of either sex aged greater than or equal to 20 years who were registered for second line anti-retroviral treatment at GANDHI Hospital.

Exclusion criteria

- Patients above 60 and below 20 years of age
- Patients with known hypersensitivity reactions.
- Patients with liver failure and renal failure
- Patients with neuropsychiatric disorders
- Any patient with deliberate or unintended overdose, missing clinical record, incomplete data or those transferred in after they have been on second line ART for more than one month were excluded from the study.

Study variables

Independent
Socio-demographic variables
Clinical and laboratory state at the beginning of second line ART
Second line ART Regimen
Dependent
Frequency of ADRs
Types of ADRs
Severity of ADRs

Data Collection Procedure

The clinical records of study subjects were reviewed retrospectively for ADRs. Information on patient's details, the WHO clinical staging of the disease at the start of ART, duration of treatment, drug details, nature of the adverse drug reactions, severity, outcome, and results of investigations performed were collected using a data collection format (Annex I). Data were collected from May 2010 to April 2011.

Operational definitions

An adverse drug reaction (ADR) is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in human'.

A side effect is 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which, is related to the pharmacological properties of the drug'.

ADRS to ART and Severity grading (See Annex II)

Data Processing and Management

Data entry and analysis were done using Microsoft excel sheet and graph pad prism statistical software. Tables and graphs were used to present frequencies of adverse drug reactions (ADRs) in patients on second line ART. Associations between the independent and dependent variables were tested using OR and 95 % CI was used to measure the strength of the association between the independent and dependent variables.

Ethical Considerations

Study was started after taking approval from the institutional ethics committee of the Gandhi hospital. Informed consent of the patient was also taken. Confidentiality of the information was assured in such a way that no disclosure of any name of the patient, the health care provider or drug product in relation to the finding was made.

Description of the procedure

Fifty eight patients who are on second line ART drugs due to treatment failure of first line ART drugs have been included in the study based on inclusion and exclusion criteria. The study subjects were monitored for the adverse drug reactions for a period of 12 months. Causality assessment was done by NARANJO score and drug adherence rate calculated by pill count method.

Following parameters were monitored

Adverse effects complaints of adverse effects like nausea, vomiting ,diarrhea, abdominal discomfort, flatulence, headache, dry mouth, taste perversion, hyper pigmentation of nails, asthenia, myalgia, myopathy, insomnia, depression, fatigue, malaise, circumoral or peripheral numbness and others if any were recorded.

Vitals-pulse rate, blood pressure, respiratory rate, body weight

Systemic examination

INVESTIGATIONS

Complete blood picture, complete urinary examination, Lipid profile, Liver function tests, Blood urea, Serum creatinine, Serum electrolytes, Random blood sugar, serum amylase

CD4 count: CD4 count analysis was done by flow cytometric analysis [42] method using CD4 easy count kit (PARTEC Company).

Viral load: Viral load testing methods are three types: (1) nucleic acid amplification based tests (NATs or NAATs) (2) "Home–brew" or in-house NATs (3) non-nucleic acid-based test.

Nucleic acid-based tests (NATs) The Polymerase Chain Reaction ((PCR) method: PCR of in vitro DNA synthesis uses a DNA template, polymerase, buffers, primers, and nucleotides to multiply the HIV in the blood sample. Then a chemical reaction marks the virus. The markers are measured and used to calculate the amount of virus. PCR is used to quantify integrated DNA.

RESULTS

Socio-demographic distribution of the study population

58 cases were included in the study. The age of patients were ranging from 20–60 years. The Socio-demographic distribution of the population is as shown in Table-1. 45 patients (77.59%) were below poverty line.

Table 1: socio-demographic distribution of the study population on second line ART at GANDHI Hospital C.O.E

Variables	N (%)
Age group	
20-29	06(10.35)
30-39	28(48.27)
40-49	17(29.31)
50-60	07(12.06)

Clinical and laboratory findings of patients at the time of initiation of second line ARV drugs

At the initiation of treatment, 24 (41.38%) patients were at Clinical stage II, while 23(39.65%) at stage III, 7 (12.06%) at stage I and 4(6.9%) at stage IV (Table 2). At the initiation of treatment, 29 Patients (50%) weighed below 50 kg and 29 (50%) weighed more than 50 kg. A total of 43 (74.13%) patients had CD4 count less than 100 cell/mm³, 15 (25.87%) patients had CD4 count more than 100 cells/ mm³. A total of 34 (58.62%) patients had viral load more than 1 lakh and 24(41.38%) had less than 1 lakh viral load. Patients with NACO regimen V were 34 (58.62%) and Va were 24 (41.37%).

Table 2: Clinical and laboratory conditions of study patients at the time of initiation of second line ARV drugs at GANDHI Hospital C.O.E.

Variables	N (%)	Variables	N (%)
WEIGHT		WHO	
<50 kg	29(50)	clinical stage	
>50 kg	29(50)	Stage I	07(12.06)
CD4 count		Stage II	24(41.38)
<100	43(74.13)	Stage III	23(39.65)
>100	15(25.87)	Stage IV	04(6.9)
VIRAL LOAD		NACO regimen	
<1 lakh	24(41.38)	V	34 (58.62)
>1 lakh	34(58.62)	Va	24 (41.37)

Frequency of ADRs and severity

Among the total 58 patients who were on second line ARV drugs, ADRs were reported in 44 (75.86%) patients (Table 3). The most frequently observed ADRs were nausea (12.25%), followed by insomnia (10.29%), loss of appetite (9.31%) malaise (7.35%) and vomiting (7.35%). Out of the 44 patients who developed ADRs, 20 (45.45 %) patients were grade II, whereas grade I and III ADRs occurred in 9 (20.45%) and 15 (34.09%) of the patients respectively. Grade IV was reported in none of the patients. No ADRs were noted in 14 (24.14%) patients. Out of 44 patients who had ADRs, 32 patients (72.73%) had less than 5 ADRs and 12 patients (27.27%) had more than 5 ADRs.

Most common ADRs were gastrointestinal (47.04%), followed by neurological (20.95%), cutaneous (8.33%) and metabolic (3.92%).Anaemia was observed in 6 patients (2.94%), renal toxicity in 3 (1.47%) patients and liver toxicity in 6 (2.94%) patients. Dyslipidemia was observed in 6 (2.94%) patients and pancreatitis in only 2 (0.98%) patients. Myalgia was observed in 9 (4.41%) patients.

Among the gastro intestinal, nausea (12.25%) was most common followed by loss of appetite (9.31%), diarrhea (6.37%) and gastritis (4.41%). Among the neurological ADRs, most common ADR was insomnia (10.29%), followed by paresthesia (3.92%) and headache (3.92%). Depression was observed in 5 (2.45%) patients. Among the cutaneous ADRs hair loss (2.94%) was most common followed by xeroderma (1.96%) and rash (1.96%). Hyperpigmentation of nails observed in 3 (1.47%) patients.

Table 3: Distribution and severity of ADRs to second line ARV drugs at GANDHI Hospital C.O.E

Variables	N (%)	Variables	N (%)
ADR		Cutaneous	
Yes	44(75.86)	Hair loss	06 (2.94)
No	14 (24.14)	Xeroderma	04 (1.96)
Types of ADR		Rash	04 (1.96)
Gastro intestinal		Hyperpigmentation of nails	03 (1.47)
Nausea	25 (12.25)		
Loss of appetite	19 (9.31)	Metabolic	06 (2.94)
Vomiting	15(7.35)	Dyslipidemia	02 (0.98)
Diarrhea	13 (6.37)	Pancreatitis	
Gastritis	09 (4.41)	Hematological	06 (2.94)
Dry mouth	08 (3.92)	Anaemia	
Change in taste perception	04 (1.96) 03 (1.47)	Renal	03 (1.47)
Oral ulcers		↑RFT	
Neurological	21 (10.29)	Hepatic	06 (2.94)
Insomnia	08 (3.92)	↑LFT	
Paresthesia	08 (3.92)	Miscellaneous	09 (4.41)
Headache	05 (2.45)	Myalgia	15 (7.35)
Depression Somnolence	02 (0.98)	Malaise	

Severity grading of these ADR is as follows. Grade I - 09 (20.45%), Grade II - 20 (45.45%), Grade III - 15 (34.09%)

The incidence of ADR in different variables is shown in Table 4.

Table 4: Incidence of ADRs in the different variables

Variables	ADR present	ADR absent	OR	95% CI	P value
Sex					
Male	31 (81.58)	07 (18.42)	2.38	0.59-9.73	0.28
Female	13 (65)	07 (35)			
Age					
<40 yrs.	25 (73.53)	09 (26.47)	0.73	0.18-2.95	0.85
>40 yrs.	19 (79.17)	05(20.83)			
Weight					
< 50kg	21 (72.42)	08 (27.58)	0.68	0.17-2.68	0.75
>50 kg	23 (79.32)	06 (20.68)			
Socio economic status					
BPL/Y	34 (75.56)	11 (24.44)			
BPL/N	10 (76.93)	03 (23.07)	0.93	0.17-4.71	0.79
CD4 count					
<100	34 (79.07)	09 (20.93)			
>100	10 (66.67)	05 (33.33)	1.89	0.43-8.29	0.53
Viral load					
< 1lakh	18 (75)	06 (25)			
>1 lakh	26 (76.5)	08 (23.5)	0.92	0.23-3.68	0.85
Regimen					
V	23 (67.65)	11 (32.35)			
Va	21 (87.5)	03 (12.5)	0.3	0.06-1.40	0.153

DISCUSSION

The selection of the existing second-line drug regimens were based on the availability of fixed-dose combinations, affordability, toxicity profile, need for laboratory monitoring, coexistent conditions (TB and hepatitis B), potential for maintenance of future treatment

options and special considerations for women of childbearing potential. These standardized simplified second line regimens have been essential in expanding access to ART in resource limited countries. If these drugs are not used appropriately, the current second-line regimen will lose its efficacy sooner than it had to. To maximize durability of second line regimen one has to deal with factors that affect the adherence of patients to ART. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

In this study the second line regimen V (TDF/3TC + LPV/r + ZDV) was prescribed in 58.62% of the cases and Va (TDF/3TC + LPV/r) was prescribed in 41.37% of cases. Regarding follow up of patients, 58 cases were still on follow up at the C.O.E.

In this study, the frequency of ADRs among patients who were on second line ARV drugs was found out to be about 75.86%. Out of the 44 patients who developed ADRs, majority 20 (45.45 %) patients were grade II, whereas grade I and III ADRs occurred in 9 (20.45%) and 15 (34.09%) of the patients respectively. Grade IV was reported in none of the patients. None of the ADRs were noted in 14 (24.14%) patients. Out of 44 patients who had ADRs, 32 patients (72.73%) had less than 5 ADRs and 12 patients (27.27%) only had more than 5 ADRs.

There was no significant association between the initial hemoglobin level of the patient at the initiation of treatment and severity of anemia. This may be due to the fact that those with low initial hemoglobin were started on regimen that doesn't have ZDV.

Duration of treatment at the time of diagnosis of ADRs was also significantly associated with the type of ADRs. Anaemia and malaise were reported throughout treatment duration. Nausea, vomiting, diarrhea, gastritis were reported at the initiation of treatment, whereas most Paresthesias, renal toxicity, raised ALT, dyslipidemias were diagnosed beyond 6 months duration. Pancreatitis which was observed in 2 cases was seen after 12 months duration of treatment.

In 58 cases, 204 ADRs were noted and types of ADRs were 24. Association of ADRs in males (81.58%) was stronger than females (65%). 41-60 years age group (79.17%) had more ADRs than 20-40 years age group (73.53%). Initial weight more than 50 kg group, had more ADRs (79.32%) than less than 50 kg weight group (72.42%). Initial CD4 count less than 100 group, had more ADRs (79.07%) than CD4 count more than 100 groups (66.67%). Viral load more than 1 lakh group had more ADRs (76.5%) than viral load less than 1 lakh group (75%) (Table 4)

Average drug adherence rate was 96% in this study. Causality assessment done by NARANJO score revealed the probable association of ADRs with second line ART.

In this study, socio-demographic and initial clinical states of patients were found to have no significant association with the development of ADRs.

CONCLUSION

Second line anti-retroviral drugs are expensive, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS. Research to improve current treatments includes decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance.

The most frequently diagnosed ADRs were nausea followed by insomnia, loss of appetite, malaise and vomiting. Out of the 44 patients who developed ADRs, majority of patients had grade II, followed by grade III and I ADRs. Grade IV was reported in none of the patients.

Most common ADRs were gastrointestinal followed by neurological, cutaneous and metabolic. None of the socio-demographic variables, the initial clinical and laboratory state were significantly associated with the development of ADRs which needs to be confirmed with further prospective study.

The type of ADRs that the patient developed was very much associated with the duration of treatment. Similarly, the severity of ADRs was also associated with type of ADRs and the duration of treatment.

Though second line ART regimens are associated with mild to moderate ADRs, these are most effective regimens as they improved CD4 counts and reduced viral load significantly.

Consequently, the following recommendations have been made based on the findings in this study:

Recommendations

Even if majority of patients tolerate second line ART regimens well, the monitoring of treatment according to the national guidelines is recommended. Patients should be routinely investigated with full blood count, liver, pancreas and renal function tests, as well as fasting cholesterol, triglycerides and glucose levels.

Patients should be evaluated and managed for opportunistic infections and adequately prepared for second line ART treatment with adherence counseling before embarking on second line ARV treatment.

Patients should be educated on the possible ADRs of second line ARV drugs

ADR monitoring should be strengthened.

REFERENCE

1. Sepkowitz KA. "AIDS-the first 20 years". N.Engl. J.Med 2001; 344(23): 1764–72.
2. Kallings LO. "The first postmodern pandemic: 25 years of HIV/AIDS". J Intern Med 2008; 263 (3): 218–43.
3. Anthoni S. Fauci, H. Clifford lane. Harrison's Principles of Internal Medicine 17th edition, chapter Human Immune Deficiency virus disease; AIDS and related disorders, Pg. 1146-47.
4. Palella, F. J. Jr, Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman and D. J., Holmberg, S. D. "Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators". N. Engl. J. Med 1998; 338 (13): 853–860.
5. Naco.gov.in [Internet]. National AIDS Control Organisation, Ministry of Health and Family Welfare. Annual report 2010-11. Available from http://www.naco.gov.in/upload/REPORTS/NACO%20Annual%20Report%202010-11.pdf
6. K. Sujatharao. Towards containing HIV/AIDS epidemic in India: policies under national AIDS control programme phase III(2007-12), vol 107, no 05, journal of the Indian medical association May 2009 Pg. 274.
7. Adriana Ammassari, Maria Paola Trotta, Rita Mul et al. Correlates and Predictors of Adherence to HAART. JAIDS 2002:31: S123-S127.
8. V Montessori et al. Adverse effects of antiretroviral therapy for HIV infection. Canadian Medical Association Journal 2004; 170 (2): 229-238.
9. Adverse Drug reaction Reporting Guideline, Drug Administration and Control Authority, 2003
10. Aidsmap.com [Internet]. HIV & AIDS: Sharing knowledge and saving lives. Monitoring Drug Side Effects. Available from http://www.aidsmap.com/Side-effects/page/1254858/
11. Kahn, J. O. and walker, B.D. Acute Human Immunodeficiency Virus type 1 infection. N. Engl. J. Med. 1998; 331 (1): 33–39.
12. Ho, D. Time to hit HIV, early and hard. N. Engl. J. Med. 1995; 333(7):450-451.
13. Joseph T. Dipiro, Robert L.Talbert, Gary C.Yee, Gary R. Matzke Barbara G. Well, L. Michael Posey. Human immunodeficiency virus infection. In: Joseph p Dipiro editor. Pharmacotherapy, A Pathophysiological approach, 7th edition. 2009. Pg. 2067.

14. H.L.Sharma, KK Sharma. HIV and Anti-retroviral Drugs. In: H.L Sharma, editor. Principles of pharmacology, 1st edition. New Delhi: Paras Publishers 2007. Pg. 810-811.

15. Cdc.gov [internet]. Center for disease control and transmission [Updated on 2013, 18th December] Available from http://www.cdc.gov/hiv/basics/transmission.html

16. Anthoni S. Fauci, H. Clifford lane. Human immune deficiency virus disease; AIDS and related disorders. In: Dan Longo, editor. Harrison's Principles of Internal Medicine 17th edition 2011. Pg. 1137-39.

17. Smith D, Richman D, Little S. HIV Super infection. Journal of Infectious Diseases 2005; 192(3):438–44.

18. Cdc.gov [Internet]. Center for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. Available from http://www.cdc.gov/mmwr/PDF/RR/RR4719.pdf

19. Anthoni S. Fauci, H. Clifford lane. Human immune deficiency virus disease; AIDS and related disorders. In: Dan Longo, editor. Harrison's Principles of Internal Medicine 17th edition 2011. Pg. 1837-39.

20. Barr SD, Smiley JR, Bushman FD. The interferon response inhibits HIV particle production by induction of TRIM 22. PLoSPathog 2008; 4(2):1-2.

21. Panacos Pharmaceuticals. "Clinical Trial: Phase 2 Safety and Efficacy Study of Bevirimat Functional Monotherapy in HIV Treatment Experienced Patients for 2 Weeks". ClinicalTrials.gov. Retrieved 2007-08-28.

22. Laurence Brunton, Keith Parker, Donald Blumenthal, Lain Brunton, Goodman & Gilman's Manual of Pharmacology & Therapeutics, 11thEdition, Charles Flexner, Ch. Antiretroviral Agents And Treatment Of HIV Infection Pg. 1274.

23. Joseph T. Dipiro, Robert L.Talbert, Gary C.Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey, pharmacotherapy, a pathophysiological approach, 7th edition Peter L Anderson, Thomson Kakuda and Courtney V Fletcher, Ch129. Human immunodeficiency virus infection Pg. 2065.

24. K.D.Tripathi. Essentials Of Medical Pharmacology 6th Edition, Ch. 58 Anti-Viral Drugs Pg. 776.

25. D.Bachani, B.B.Rewari, Antiretroviral Therapy: Practice Guidelines and National ART ProgrammeVol 107, No 05, Journal of the Indian Medical Association May 2009 Pg. 312.

26. NACO Guidelines on Rollout of Second Line Art Nov 2008(DRAFT) Table 6 NACO Second Line Regimen Pg. 23.

27. Montessori, V., Press, N., Harris, M., Akagi, L., Montaner, J. S. Adverse effects of antiretroviral therapy for HIV infection." CMAJ 2004; 170 (2): 229–238.

28. Bertram G Katzung, Basic And Clinical Pharmacology 9th Edition, Sharon Safrin, Ch. 49 Antiretroviral agents Fig 49-4 Pg. 813.

29. Who.int [Internet]. WHO Model List of Essential Medicines Available from whqlibdoc.who.int/hq/2005/a87017_eng.pdf

30. Laurence Brunton, Keith Parker, Donald Blumenthal, Lain Brunton, Goodman and Gilman's Manual Of Pharmacology & Therapeutics, 11th Edition, Charles Flexner, Ch. Antiretroviral agents and treatment of HIV Infection Pg. 1283

31. P N Bennett, M J Brown, Clinical Pharmacology 9th Edition, Zidovudine Adverse effects Ch. 14 Viral, Fungal, Protozoal, and Helminthic Infections Pg. 260

32. Bertram G Katzung, Basic and Clinical Pharmacology 9th Edition, Sharon Safrin, Ch. 49 Antiretroviral agents Pg. 815.

33. P N Bennett, M J Brown, Clinical Pharmacology 9th Edition, Zidovudine Adverse effects Ch.14 Viral, Fungal, Protozoal, and Helminthic Infections Pg. 260.

34. Anthoni S. Fauci, H. Clifford lane. Human immune deficiency virus disease; AIDS and related disorders. In: Dan Longo, editor. Harrison's Principles of Internal Medicine 17th edition 2011. Pg. 1837-39.

35. Laurence Brunton, Keith Parker, Donald Blumenthal, Lain Brunton, Goodman and Gilman's Manual of Pharmacology & Therapeutics, 11thEdition, Charles Flexner, Ch. Antiretroviral agents and treatment of HIV Infection Pg.1291.

36. Anthoni S. Fauci, H. Clifford lane. Human immune deficiency virus disease; AIDS and related disorders. In: Dan Longo, editor. Harrison's Principles of Internal Medicine 17th edition 2011. Pg. 1337-39.

37. Anthoni S. Fauci, H. Clifford lane. Human immune deficiency virus disease; AIDS and related disorders. In: Dan Longo, editor. Harrison's Principles of Internal Medicine 17th edition 2011. Pg. 1927-33.

38. K.D.Tripathi, Essentials of Medical Pharmacology 6th Edition, Anti-Viral Drugs Pg.774.

39. Bertram G Katzung, Basic And Clinical Pharmacology 9th Edition, Sharon Safrin, Ch. 49. Antiretroviral agents Pg. 1142-43.

40. Knoll B, Lassmann B, Temesgen Z. Current status of HIV infection: a review for non-HIV-treating physicians. Int J Dermatol 2007; 46 (12): 1219–28.

41. Anthoni S. Fauci, H. Clifford lane Harrison's Principles of Internal Medicine 17th edition, chapter human immune deficiency virus disease; AIDS and related disorders, Pg. 1202-03.

42. Greve, B.et al.. "A New No-Lyse, No-Wash Flow-Cytometric Method for the Determination of CD4 T cells in Blood Samples", Transfuse Med Hemoth 2003; 30: 8-13.