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Clinical, Immunological and Virological Profile of Patients with HIV Infection on Second Line Antiretroviral Therapy

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Abstract
Background and Objectives: *The goal of antiretroviral therapy is to maximally and durably inhibit viral replication. Objectives of this study were –*

- *To study the various clinical features of patients on second line anti retroviral therapy.*
- *To study the immunological and virological profile of these patients.*
- *To study various factors determining the initiation of second line ART*

Material and Methodology: *Retrospective analysis of 30 HIV patients on second line Antiretroviral Therapy was done. Clinical examination and various immunological profiles like CD4 count, CD8 count and virological profiles like viral load and viral resistance testing were noted if done. Details of therapy in terms of drugs, schedule, adverse effects etc. were noted.*
Results: *Majority of patients had BMI in the normal range. Mean CD4 cell count increased from 114/mm3 at start of first line therapy to 168/mm3 at start of second line therapy. Immunological failure was the reason to switch to second line therapy in 63.33% patients. The most common second line regimen followed was Tenofovir + Abacavir + Lopinavir + Ritonavir, in 73.33% of patients, but it showed a high incidence of minor adverse effects. Viral load was estimated in 50% patients of which 36.67% patients had >20,000 HIV virus copies/ml. Tuberculosis was the main opportunistic infection encountered.*
Analysis and Discussion: *Second line antiretroviral therapy has changed the prognosis of HIV infected patients who have first line regimen failure. The switch to second line treatment was relatively slow, due to CD4 cell count being used as the main criteria to switch therapy. This study highlights the importance of assessing viral load to monitor any early virological failure of first line ART to switch early to second line therapy. The response to therapy was good in terms of clinical and immunological parameters.*
Keywords: *HIV, Antiretroviral therapy, CD4 cell count*

I. Introduction

In the past 25 years or so, no disease has endangered and taken away as many lives of human beings and their resources as AIDS. AIDS is, in fact, rewriting medical history as humankind's deadliest scourge. HIV/AIDS is the fourth leading cause of death worldwide, killing more than 2.1 million people in 2007. This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to life threatening opportunistic infections, neurological disorders or certain unusual malignancies.

The AIDS Epidemic, since its discovery in 1981, is spreading all over the world breaking all social, cultural and geographical barriers. In 2007, it was estimated by WHO that 33.2 million people lived infected with the HIV virus worldwide. [1]

In the absence of antiretroviral therapy, the median time of progression from HIV infection to AIDS is nine to ten years, and the median survival time after developing AIDS is only 9.2 months.[2] Although treatments for AIDS and HIV can slow the course of the disease, there is currently no vaccine or cure. Current treatment for HIV infection consists of 'highly active antiretroviral therapy', or HAART introduced in 1996. [3]

Current optimal HAART regimens consist of combinations of at least three drugs belonging to at least two classes of antiretroviral agents, typically of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI). The main parameters to recommend initiating treatment are viral load, rapidity in CD4 decline, and patient readiness. [4]

The goal of antiretroviral therapy is to maximally and durably inhibit viral replication so that the patient can attain and maintain effective immune response towards potential microbial pathogens so that there is improvement in the patient's quality of life, reduction in complications, and reduction of HIV viremia below the limit of detection. Many HIV-infected individuals have experienced remarkable improvements in their general health and quality of life, which has led to the plummeting of HIV-associated morbidity and mortality. [5]

Although access and efficacy of first line therapy is reasonably well-established, there is a substantial and unacceptable mortality rate in the first six months after initiation of antiretroviral therapy, particularly in those with low CD4 cell counts and late stage disease. Failure of first line therapy is inevitable in a proportion of

patients due to the likely emergence of high-level resistance during first line therapy. Many studies to date have confirmed the use of second line regimens when HIV RNA assay show virological failure of first line therapy.

The goal of second line therapy is to retard clinical progression of the disease rather than complete suppression of viraemia. The time of switching is dictated by treatment failure, and this can be measured in three ways: clinically, by disease progression and WHO staging; immunologically, using trends in CD4 counts over time, and virologically, by measuring HIV viral loads (plasma HIV-1 RNA levels).

The new second-line regimen has to involve drugs that retain activity against the patient's virus strain and should ideally include a minimum of three active drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success and minimize the risk of cross-resistance. The basic principle is ideally to support the chosen boosted PI with a dual NRTI backbone composed of two unused NRTIs. [6]

The data regarding various aspects of second line antiretroviral therapy is sparse due to non-availability, cost and complexities of second line regimen in a resource-limited country like India and hence, this study was undertaken.

Treatment

There is no specific treatment either for HIV infection or the immunodeficiency caused by it. Palliative treatment of the symptoms and cure of the opportunistic infections were the only options available. Now various categories of Anti-Retro Viral drugs (ARVs) are available. These drugs can only contain the infection but not cure the disease.

Antiretroviral agents are drugs which act at various stages of the life cycle of HIV in the body and work by interrupting the process of viral replication. Theoretically, ARV drugs can act in any of the following ways during different stages of viral replication [11].

- Block viral RNA cleavage and inhibit the enzyme reverse transcriptase (reverse transcriptase inhibitors)
- Block the enzyme, integrase, which helps in the incorporation of the proviral DNA into the host cell chromosome (integrase inhibitors)
- Block the RNA so as to prevent viral protein production.
- Block the enzyme protease (protease inhibitors)
- Inhibit the budding of virus from host cells.
- Block binding of HIV to target cell (fusion inhibitors)

The currently available agents target the virus mainly by inhibiting the enzymes reverse transcriptase (RT inhibitors) and protease (protease inhibitors), and thus prevent fusion of the virus with CD4 cells (fusion inhibitors).

Classes of ART drugs available

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS(NRTI'S)	NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS(NNRTI'S)	PROTEASE INHIBITORS(PI'S)
Zidovudine(AZT/ZDV)*	Nevirapine(NVP)*	Saqinavir(SQV)*
stavudine(d4t)*	Efavirenz(EFV)*	Ritonavir(RTV)*
Lamivudine(3tc)*	Delavirdine(DLV)	Nelfinavir(NFV)*
Didanosine(ddl)*	FUSION INHIBITORS	Amprenavir(APV)
Zalcitabine(ddc)*	Enfuviritide(t-20)	Indinavir(INV)*
Abacavir(ABC)*	INTEGRASE INHIBITORS	Lopinavir/Ritonavir (LPV/r)*
Emtricitabine(ftc)	Raltegravir	Foseamprenavir(FPV)
NtRTI - Tenofavir(tdf)*	CCR5 ENTRY INHIBITOR	Atazanavir(ATV)*
* Available in India	Maraviroc	Tipranavir(TPV)

When several such drugs, typically three or four, are taken in combination, the approach is known as highly active antiretroviral therapy, or HAART. It is done to prevent developing resistance to antiretroviral drugs.

Viral load and CD4 cell count

Viral load and CD4 cell tests provide critical information for decisions on antiretroviral therapy (ART).

Viral load should be tested: [12]

- Before starting or changing medications. This provides a reference value;
- About 2 to 8 weeks after starting or changing medications. This shows whether the new drugs are working;
- Every 3 or 4 months. This helps make sure the medications are still working. For patients who haven't started taking medications, it helps decide when to start.

The national programme in India does not recommend routine viral load monitoring. Viral load measurement is not recommended for decision-making for the initiation or regular monitoring of ART in resource-limited settings [6].

CD4 cell counts should be done: [12]

- When someone first tests HIV-positive
- every three to four months to (1) determine when to start antiretroviral therapy in patients not being treated; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections.

WHO guideline for initiation of ART [6]

1. All Stage IV patients irrespective of CD4 count are initiated on ART
2. Patients in Stage I, II & III of the disease are put on ART based on their CD4 counts

- CD4 count < 200/ mm3 : All patients are initiated on ART irrespective of symptomatic status
- CD4 count 200 – 350/ mm3: Treatment is offered to symptomatic patients; CD4 count should not be allowed to fall < 200/mm3
- CD4 count > 350/mm3: Treatment is deferred

3. Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count [12]:

a. Pregnant women
b. Patients with HIV-associated nephropathy
c. Patients co-infected with HBV when treatment for HBV infection is indicated

Thus it is evident that all symptomatic patients require ART and in asymptomatic individuals ART should be started before the immunodeficiency becomes too severe. The following factors are to be considered before prescribing anti-retroviral for asymptomatic HIV positive people:

1. Co-morbid conditions
2. Potential adverse drug effects
3. Potential drug interactions with other medications
4. Pregnancy or pregnancy potential
5. Results of genotypic drug resistance testing
6. Gender and pretreatment CD4 T-cell count if considering nevirapine
7. Patient adherence potential
8. Convenience (e.g., pill burden, dosing frequency, and food and fluid considerations)

Goals of therapy

The currently available ARV drugs cannot eradicate the HIV infection from the human body. This is because a pool of latently infected CD_4 cells is established during the earliest stages of acute HIV infection and persists within the organs/cells and fluids (e.g., liver and lymphoid tissue) even with prolonged suppression of plasma viraemia to <50 copies/ml by antiretroviral therapy.

The goals of therapy are as follows: [10]

- Clinical goals: Prolongation of life and improvement in quality of life
- Virological goals: Greatest possible reduction in viral load for as long as possible
- Immunological goals: Immune reconstitution which is both quantitative and qualitative
- Therapeutic goals: Rational sequencing of drugs in a fashion that achieves clinical, virological and immunological goals while maintaining treatment options, limiting drug toxicity and facilitating adherence
- Reduction of HIV transmission in individuals: Reduction of HIV transmission by suppression of viral load.

The following tools are suggested to help achieve these goals:

- Selection of Initial Combination Regimen
- Pretreatment Drug Resistance Testing
- Improving Adherence

Recommended first line antiretroviral regimen [6]

- Zidovudine(300 mg BD) + Lamivudine(150 mg BD) + Nevirapine(200 mg BD)
- Zidovudine(300 mg BD) + Lamivudine(150 mg BD) + Efavirenz(600 mg OD)
- Stavudine(30 mg BD) + Lamivudine(150 mg BD) + Nevirapine(200 mg BD) or Efavirenz(600 mg OD)
- Tenofovir(300 mg OD) + Lamivudine(150 mg BD) + Efavirenz(600 mg OD)
- Zidovudine(300 mg BD) + Lamivudine(150 mg BD) + Tenofovir(300 mg OD)

Adverse effects of the ART drugs

Antiretroviral therapy can have a wide range of adverse effects on the human body. Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy. Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV. Several uncommon but more serious adverse effects associated with antiretroviral therapy, including AZT-associated anemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity and NNRTI-associated hypersensitivity reactions. These side effects are treated according to accepted therapy for these conditions in patients not receiving HAART. The adverse effects are [13]

- Gastrointestinal - abdominal pain, diarrhoea, nausea, vomiting, flatulence, hepatitis, hyperbilirubinemia, hypercholesterolemia, liver failure, alteration in taste,
- Central Nervous System related - dizziness, headache, insomnia, mental confusion, migraines, mood swings, nightmares, numbness, somnolence
- General - Steven-Johnson syndrome, xeroderma (dry skin), xerostomia (dry mouth), alopecia, anemia, hyperpigmentation, ingrown nails, lipodystrophy, malaise, myalgia, myopathy, neutropenia, aphthous ulcers, rash, renal failure

Resistance to antiretroviral therapy

When HIV multiplies, most of the new copies are mutated i.e. they are slightly different from the original virus. Some mutations keep multiplying even when the patient is taking antiretroviral drugs. When this happens, the drug will stop working. This is called "developing resistance" to the drug.

If only one ARV drug is used, it is easy for the virus to develop resistance. For this reason, using just one ARV drug (monotherapy) is not recommended. But if two drugs are used, a successful mutant would have to get around both drugs at the same time. And if three drugs are used, it's very hard for the right mutations to show up that can resist all three drugs at the same time. Using a triple-drug combination means it takes much longer for resistance to develop.

Viral resistance testing helps health care providers choose the most effective drugs. Resistance testing is recommended for patients starting therapy, when viral load is not controlled by new medications, or when it "breaks through" a regimen that used to work. The guidelines recommend resistance testing before starting antiretroviral treatment (ART). It can also make sense for people who don't need to start ART yet. This can show if the person got infected with drug-resistant virus.

Reasons for switch to second line therapy

Antiretroviral treatment failure can be defined as a suboptimal response to therapy.

Virological failure:

- Within 6 months after starting a treatment, the viral load should drop below 400 copies. Within 1 year, it should be less than 50 copies. If the viral load does not drop this much, change the treatment.
- An increase in viral load from undetectable to detectable levels
- Plasma viral load > 10,000 copies/mL

Immunological failure

- Fall of CD4 count to pre-therapy baseline (or below)
- 50% fall from the on-treatment peak value (if known)
- Persistent CD4 levels below 100 cells/mm

Clinical failure

- New or recurrent WHO stage 4 condition, after at least 6 months of ART, with some exceptions like lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia which may not indicate treatment failure.

Second line ART

Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed (clinically, and or immunologically and or virologically). Current WHO treatment guidelines recommend that the protease inhibitor (PI) class should be reserved for second-line ART and that Ritonavir-boosted protease inhibitors (bPIs) are preferred supported by two agents from the NRTI class.

Humphreys et al from University of California found that there is insufficient evidence to evaluate second line therapies in patients who fail first line treatment. [14]

M A Boyd and D A Copper from National Centre in HIV Epidemiology and Clinical Research in Australia concluded that access to second line treatment is problematic in developing countries. [15]
Pujades Rodriguez et al from Epicentre in France found that the rate of switch to second line treatment in ART-naïve adults on NNRTI based first line ART was relatively low, with good early outcomes observed in PI based second line regimens.[16]

II. Materials And Methods

Design: Descriptive study
Type of study: Retrospective analysis of HIV patients on second line ART
Setting: Tertiary care immunodeficiency centre of academic institution
Time Horizon: 2 months

Selection Of subjects
Sample Size: Thirty (30) patients on antiretroviral therapy attending the antiretroviral treatment clinic of a tertiary care hospital were included in the study.
Method of Sampling: Convenient Sampling by the investigator
Inclusion Criteria:
1. Patients with HIV infection on second line Anti-Retroviral Therapy
2. Minimum duration of three months on second line Anti-Retroviral Therapy
3. Age > 16 years

Exclusion Criteria
1. Patients with major co-morbidities requiring acute in-hospital medical care
2. Patients with major psychiatric illness

Methodology
30 patients on second line antiretroviral Therapy attending the antiretroviral treatment clinic of a tertiary care hospital were included in the study.
1. Patients were dealt with individually in the examination room.
2. Informed consent was obtained from the patients before conducting the study using the form attached in appendix-A.
3. Demographic profile of patients such as name, age, sex, residence and socioeconomic status were noted.
4. Structured pro forma and in-depth interviews with the patients were conducted.
5. Onset and duration of HIV infection were noted.
6. Indication for which patient had been initiated on first line Anti-retroviral Therapy was noted.
7. Detailed clinical features including height, weight, vital parameters, any past or concomitant opportunistic infection were noted from the patients' clinical record. The functional status of the patient whether working, ambulatory or bedridden was noted.
8. The major body systems like central nervous, cardiovascular, respiratory, gastrointestinal were clinically examined thoroughly for any abnormality.
9. Detailed laboratory profile was recorded as under

Hematological
- Hemoglobin
- Total Leukocyte Count
- Differential Leukocyte Count

Metabolic
- Serum Bilirubin
- Serum Creatinine

Immunological
- CD4 cell count
- CD8 cell count
- CD4 : CD8 ratio

Virological
- HIV viral load, whenever feasible.

- HIV viral resistance, whenever feasible, was done at National AIDS Research Institute, Pune, Maharashtra in Drug Resistance Lab by the method of In-House Drug Resistance Assay and drug resistance analysis was done using Stanford Genotypic Resistance Interpretation algorithm.

10. The details of first line Anti-Retroviral Therapy including the drugs, dosage, date of starting and stopping were recorded.
11. The reason for switch to second line therapy was noted in code as under:

a. Clinical treatment failure
b. Immunological failure
c. Virological failure

12. Details of second line Anti-Retroviral Therapy including the drugs, dosage and date of starting were recorded.
13. Adverse effects, if any, of the therapy was noted..

Data analysis

The questionnaires were checked for completeness and the data was compiled on computer using MS EXCEL programme.

III. Observations And Results

Demographic profile of the patients

A total of 30 patients who were on second-line antiretroviral therapy and met the inclusion criteria were considered for the present study, after obtaining their informed consent. The socio-demographic profile of the respondents was as follows:

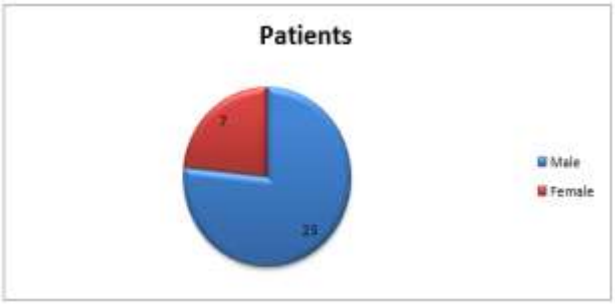
Age: The mean age of the patients was 40.33 years with standard deviation of 6.26 years with a range of 32 to 53 years. The distribution of patients according to age has been shown in table 1.

Table 1. Distribution of age groups of patients

Age Group	Frequency	Percent
< 35 yrs	9	30%
36-40 yrs	7	23.33%
41-45 yrs	7	23.33%
46-50 yrs	4	13.33%
50 + yrs	3	10%
Total	30	100.0%

Gender: Out of 30 patients undertaken for study, 23(76.67%) were male and 7(23.33%) were female as shown in fig. 1.

Fig 1. Distribution of patients according to gender



Socioeconomic status: 24(80.00%) patients were in the lower-middle class, 4(13.33%) were in the upper-middle class and 2(6.67%) of the patients were in the upper-lower class according to Kuppuswamy's scale of socioeconomic classification [17]. The distribution has been shown in table 2.

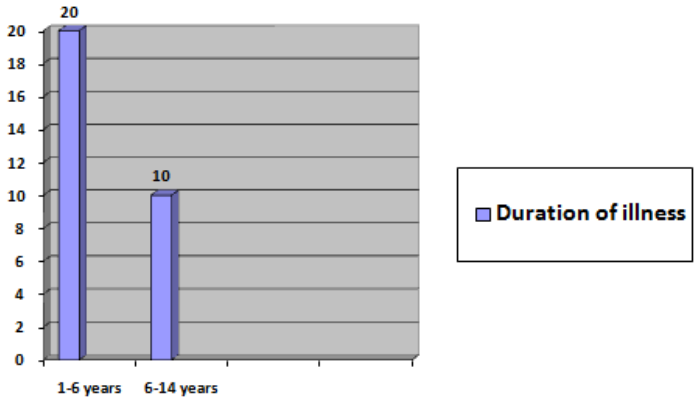
Table 2. Distribution of socioeconomic status of patients

Socioeconomic status	Frequency	Percent
Upper Lower	24	80%
Lower Middle	4	13.33%
Upper Middle	2	6.67%
Total	30	100.0%

Clinical Profile of patients

Onset and duration of illness: The onset of HIV infection in patients was in between 15 months to 164 months. The mean duration of illness was 6 years. The duration of illness has been demonstrated in fig. 2.

Fig 2. Distribution of patients according to duration of illness



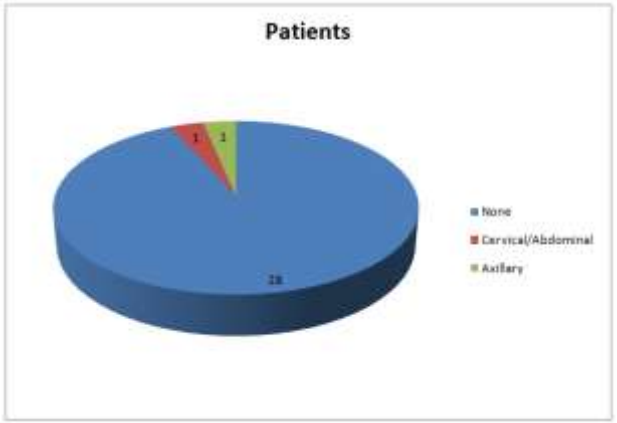
Body Mass Index: The mean body mass index of the patients was 19.77 kg/m2 with standard deviation of 2.39 kg/m2 with a range of 13.41 to 23.64 kg/m2. The distribution of patients according to age has been shown in table 3.

Table 3.

Body Mass Index	Frequency	Percent
<15	2	6.67%
15-16.99	0	0.00%
17-18.99	9	30%
19-20.99	10	33.33%
21-22.99	7	23.33%
23 and above	2	6.67%
Total	30	100.0%

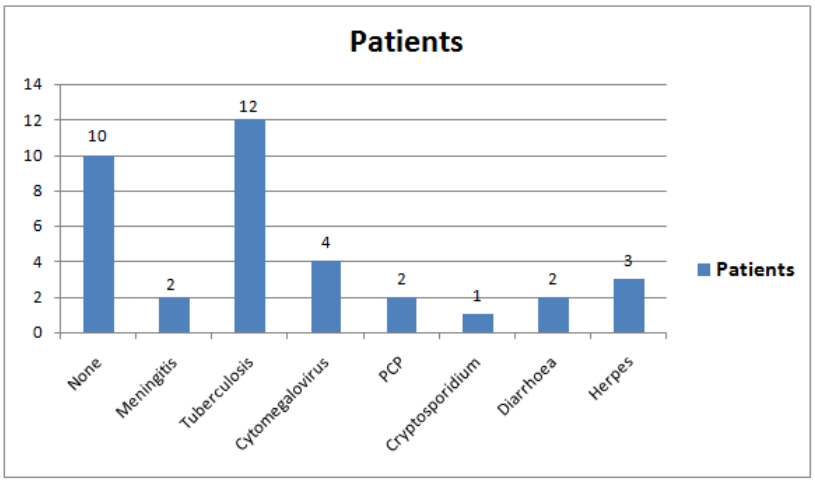
Lymphadenopathy: 28(93.33%) patients in the study had no lymph node enlargement. 1(3.33%) patient had cervical and abdominal lymphadenopathy and 1(3.33%) patient had axillary lymphadenopathy, which has been depicted in fig 3.

Fig 3. Lymphadenopathy



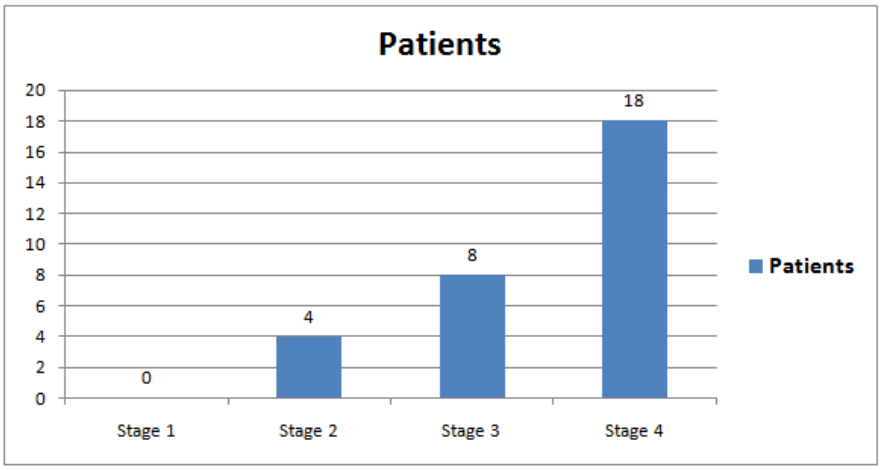
Opportunistic Infections: 10(33.33%) patients had not developed any opportunistic infections till the time of study. 2(6.67%) patient had developed Cryptococcal meningitis. 12(40%) patients had developed Tuberculosis in the course of their illness. 4(13.33%) had developed Cytomegalovirus infection, 2(6.67%) patient suffered from Pneumocystis carinii Pneumonia, 1(3.33%) from Cryptosporidium infection, 2(6.67%) from diarrhoea and 3(9.09%) from Herpes Zoster infection. Six patients had more than one opportunistic infections. This has been shown in fig 4.

Fig 4. Opportunistic Infections



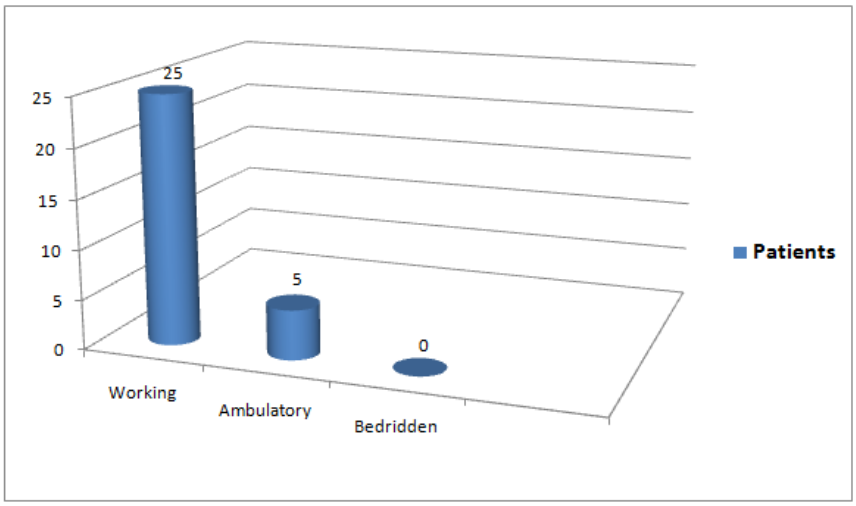
WHO Clinical Staging: 18(60.00%) patients were in stage 4 of WHO clinical staging, 8(26.67%) patients were in stage 3 and 4(13.33%) patients were in stage 2 of the disease. None (0.00%) of the patients was in stage 1. This has been depicted in fig 5.

Fig 5. WHO clinical staging



Functional Status: 25(83.33%) patients were in working condition and 5(16.67%) patients were ambulatory. None (0.00%) of the patients was bedridden.

Fig 6. Functional Status of patients



Systemic Examination: On clinical examination, the cardiovascular system, and respiratory system of all 30 patients had no detectable abnormality. 6 patients showed signs of peripheral neuropathy like tingling and numbness. In gastrointestinal system examination, 5(16.67%) patients were found to have liver enlargement. The examination of gastrointestinal system of rest 25(83.33%) patients revealed no abnormality. The details have been shown in fig 7 and fig 8.

Fig 7. Systemic Examination of patients

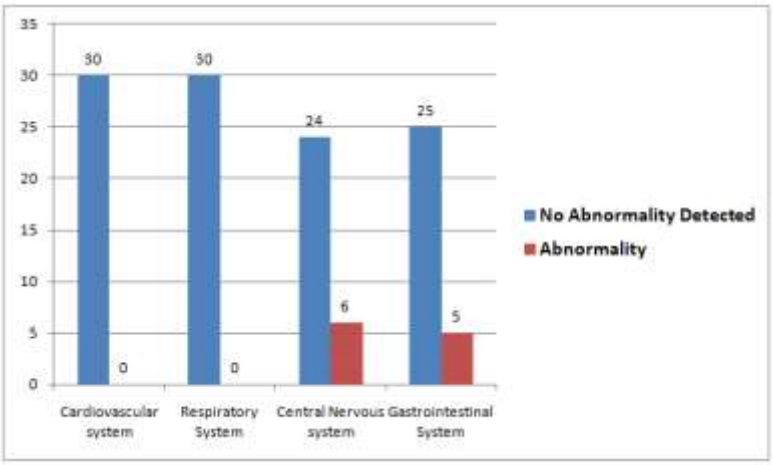
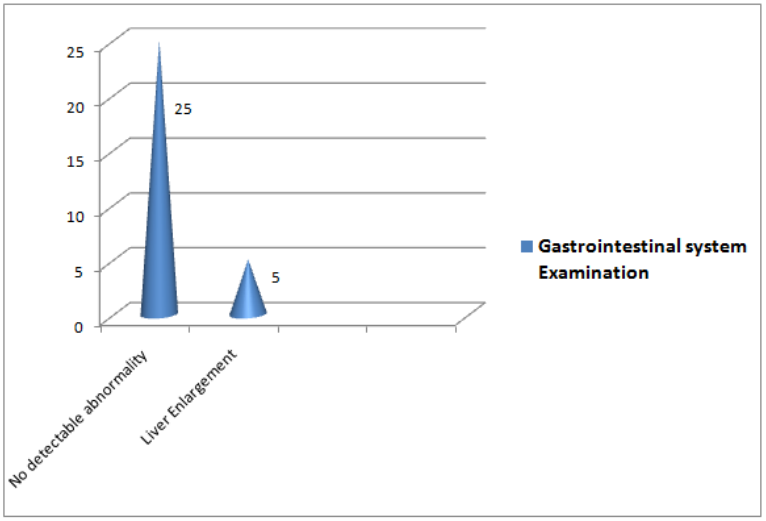


Fig 8. Gastrointestinal System Examination of patients



Laboratory Profile of Patients

Hemoglobin Estimate: The mean hemoglobin concentration of the patients was 12.43 g/dl with standard deviation of 1.5 g/dl with a range of 9.5 to 14.7 g/dl (Normal Range 13-15 g/dl for female and 14-16 g/dl for male). The distribution of patients according to hemoglobin concentration has been shown in table 4.

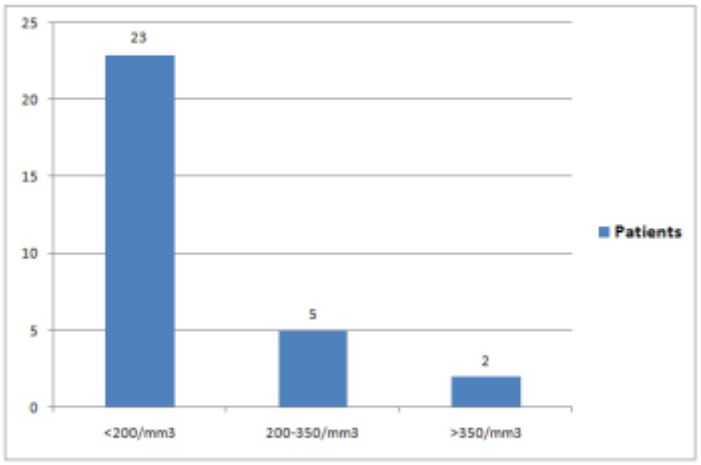
Table 4 Hemoglobin concentration in patients

Hemoglobin Concentration (g/dl)	Frequency	Percent	
9-10.99	5	16.67%	
11-12.99	13	43.33%	
13-14.99	12	40%	
Total	30	100.0%	

Immunological Profile of Patients

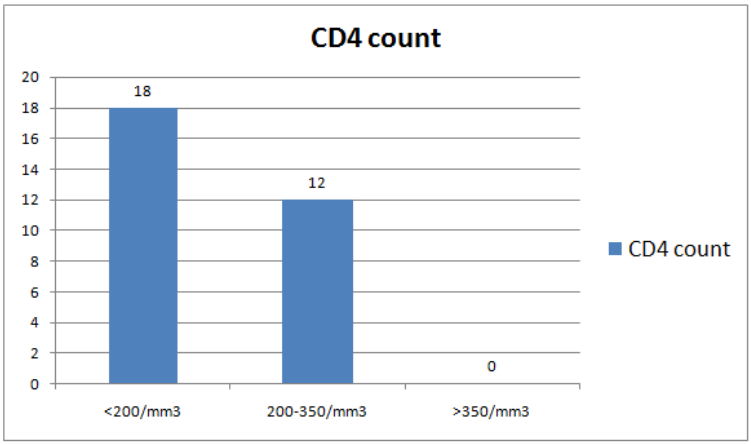
CD4 Cell Count at start of first line therapy: The mean CD4 cell count of the patients was 114/mm3 with with a range of 7/mm3 to 388/mm3. 2 patients had CD4 cell count >350/mm3, 5 patients had CD4 cell count between 200 to 350/mm3 and 23 patients had CD4 cell count less than 200/mm3. This has been depicted in fig 9.

Fig 9. CD4 cell count of patients at start of first line therapy.



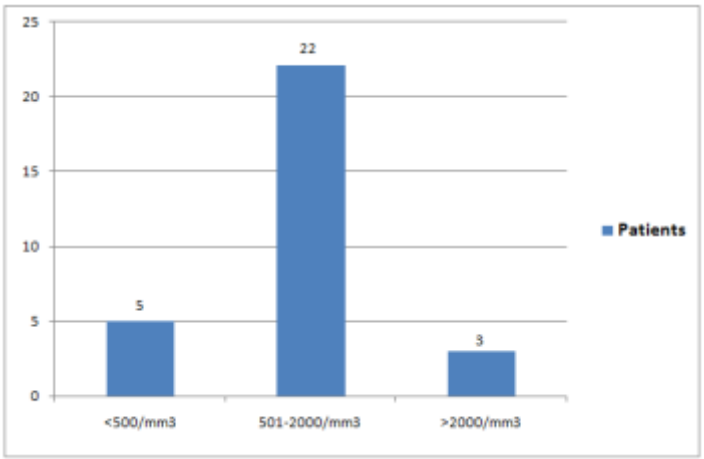
CD4 Cell Count at start of second line therapy: The mean CD4 cell count of the patients was 168/mm3 with a range of 82/mm3 to 276/mm3. None of the patients had CD4 cell count >350/mm3, 12 patients had CD4 cell count between 200 to 350/mm3 and 18 patients had CD4 cell count less than 200/mm3. This has been depicted in fig 10.

Fig 10. CD4 cell count of patients at start of second line therapy.



CD8 Cell Count: The mean CD8 cell count of the patients was 814/mm3 with standard deviation of 622/mm3 with a range of 102/mm3 to >2000/mm3. 3 patients had CD8 cell count >2000/mm3, 22 patients had CD8 cell count between 501-2000/mm3 and 5 patients had CD8 cell count less than 500/mm3. The details have been shown in Fig 11.

Fig 11. CD8 cell count of patients

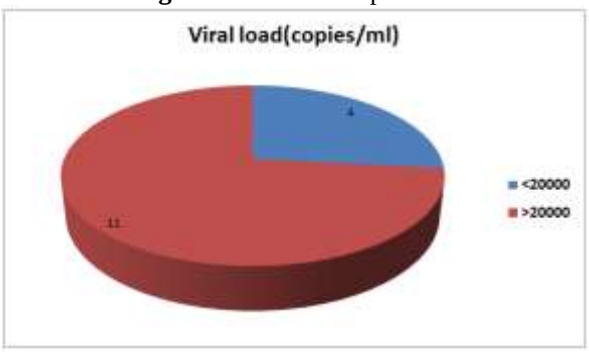


CD4: CD8 ratio: The mean CD4:CD8 ratio of the patients was 0.33 with standard deviation of 0.19 with a range of 0.06 to 0.61.

Virological Profile of Patients

HIV Viral Load at start of second line therapy: Viral load could be estimated only in 15 patients. Out of 15 patients, 11 had viral load of >20,000 copies/ml and 4 had <20,000 copies of HIV virus/ml, as shown in fig 12.

Fig 12. Viral Load of patients



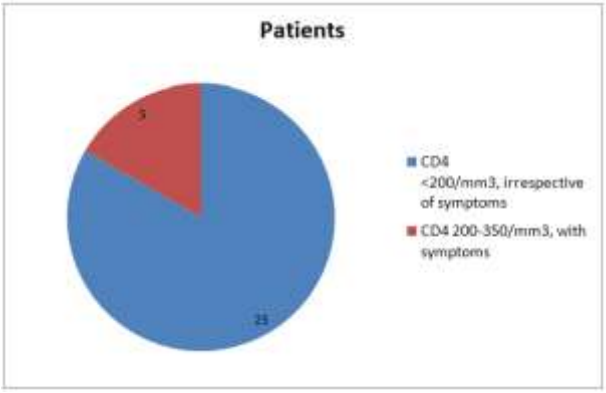
HIV Viral Resistance Testing: Genotypic viral resistance could be done in only 7 patients. The profile of resistance is given in **table 5** below.

ARV drug	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Lamivudine	R	R	R	S	R	R	R
Zidovudine	R	R	S	R	R	S	R
Abacavir	R	S	S	R	S	S	S
Stavudine	R	R	R	R	S	S	R
Tenofovir	S	S	S	S	R	S	S
Nevirapine	S	R	S	R	S	R	S
Efavirenz	S	R	S	R	S	R	S
Indinavir	S	S	S	S	R	S	S
Ritonavir	S	S	S	S	R	S	S
Lopinavir	S	S	S	S	R	S	S

Details of Therapy

Indication for first line therapy: 25(83.33%) patients had been started on first line antiretroviral therapy due to their CD4 cell count being less than 200/mm3, irrespective of their symptomatic status. 5(16.67%) patients had been indicated first line therapy due to their CD4 cell count between 200-350/mm3 and having symptomatic illness. This has been depicted in fig 13.

Fig 13. Indications for first line therapy



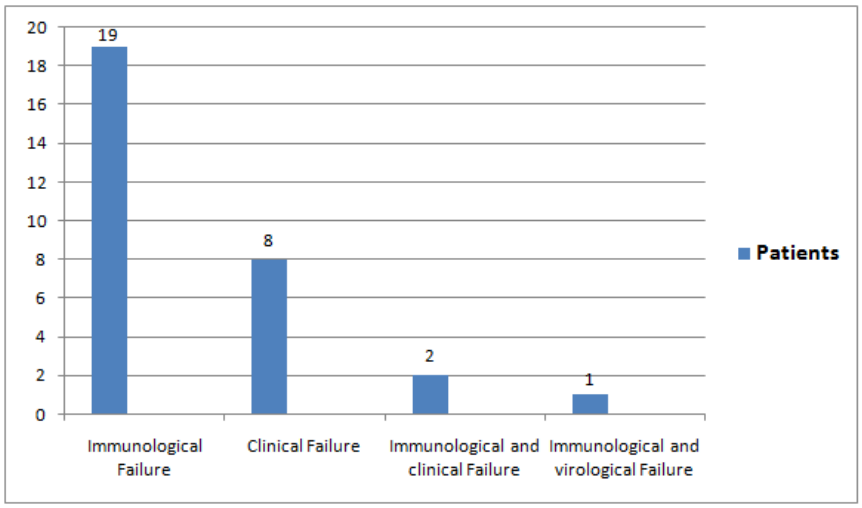
Details of first line antiretroviral therapy: All 30 patients had been started on first line antiretroviral therapy with 2 Nucleoside Reverse Transcriptase Inhibitors(NRTIs), out of Zidovudine, Lamivudine or Stavudine, and 1 Non-Nucleoside Reverse Transcriptase Inhibitor(NNRTI), either Nevirapine or Efavirenz. Other drugs e.g. antimicrobials for prophylaxis against infections and multivitamins were continued as per schedule, as shown in table 6.

Table 6. First line antiretroviral drugs

NRTI	NtRTI	NNRTI
Lamivudine	Tenofovir	Nevirapine
Zidovudine		Efavirenz
Stavudine		

Reason for switch to second line therapy: 19(63.33%) patients had been switched to second line therapy due to immunological failure, 8(26.67%) patients had been switched to second line therapy due to clinical treatment failure, 2(6.67%) patients had been switched due to both immunological and clinical treatment failure and 1(3.33%) patient had been transferred to second line therapy due to both immunological and virological failure. The details are shown in fig 14.

Fig 14. Reason for switch to second line therapy



Details of second line therapy: On switching to second line antiretroviral therapy, the drug regimens followed were as under in table 7:

Table 7. Second line ART regimens

Patients	Regimen
22	Tenofovir + Abacavir + Lopinavir + Ritonavir
1	Zidovudine + Lamivudine + Lopinavir + Ritonavir
3	Zidovudine + Lamivudine + Saquinavir + Ritonavir
2	Stavudine + Lamivudine + Indinavir + Ritonavir
2	Tenofovir + Abacavir + Efavirenz

Other drugs e.g. Antitubercular Therapy (ATT) or antimicrobials for prophylaxis against infections and multivitamins were continued as per schedule,as shown in table Adverse effects of second line drugs: 13 patients did not experience any side-effect of antiretroviral drugs. 10 patients experienced side-effects pertaining to central nervous system like headache, dizziness, memory loss and delusions etc. 2 patients developed loose motions, 1 patient developed numbness in his left arm, 1 patient had generalised pruritus and 1 patient had weight loss and anorexia due to therapy. 1 patient had burning sensation during urination and 1 patient developed diminution of vision. The adverse effects experienced by patients have been shown in table 8.

Table 8. Adverse effects of antiretroviral therapy experienced by patients

Adverse Effects of therapy	**Frequency**	**Percent**	
None	13	43.33%	
CNS Effects	10	33.33%	
Loose Motions	2	6.67%	
Numbness	1	3.33%	
Generalised pruritus	1	3.33%	
Weight loss and anorexia	1	3.33%	
Urinary irritation	1	3.33%	
Diminution of vision	1	3.33%	
Total	30	100.0%	

IV. Discussion

General

In our study, 30 patients were included. Mean age of patients was 40.33 years. Except for 6.67% of patients, who were in upper middle strata, others had relatively lower socioeconomic status including 13.33% who were in lower middle strata. The patients were thus similar in general demographic profile.

The distribution of patients according to gender revealed that only 23.33% of patients under study were female, thus reflecting low access of females to antiretroviral care due to social, economic and cultural disparities in the society, specifically they had poor access to HIV care and treatment due to poor literacy, lack of transportation, social stigma attached with HIV-infected female and lack of awareness about the disease.

Clinical, Immunological and Virological Profile

Mean duration of illness of patients was 6 years, but 33.33% patients had been infected with HIV since 6-14 years, thus showing reduced mortality after second line antiretroviral therapy.

Only 6.67% patients had body mass index (BMI) less than 17, with no patient in the overweight category. Majority of patients had BMI in the normal range (18.50-24.99).

An overwhelming majority (93.33%) of patients did not have any lymph node enlargement. However one patient had both cervical and abdominal lymphadenopathy and one patient had enlarged axillary lymph nodes.

66.67% of patients had been attacked with opportunistic infections. Tuberculosis was the commonest opportunistic infection, accounting for 60% of all opportunistic infections. Six patients had more than one opportunistic infections, validating that opportunistic infections in HIV patients, reduce the immunity further.

Majority of patients (86.67%) were in stage 3 and stage 4 of HIV, according to WHO clinical staging of HIV/AIDS, thus indicating the need to administer second line treatment. Staging is a useful approach in studies of progression to symptomatic HIV disease in resource-limited setting.

None of the patients was bedridden. Only 16.67% of patients were ambulatory but not in full functional capacity and majority (83.33%) in working condition. This points towards improvement in functional status and quality of life due to therapy.

On clinical examination of various body systems, most of the patients were found to be normal. 6 patients had signs of peripheral neuropathy and 5 patients had liver enlargement of varying degree, which might be due to drug toxicity. This is because of excellent functional and clinical recovery that occurs on institution of ART along with prompt and comprehensive treatment of opportunistic infections.

Laboratory findings of the patients revealed that 16.67% of patients had hemoglobin concentration <11 g/dl.

Mean CD4 cell count increased from 114/mm3 at start of first line therapy to 168/mm3 at start of second line therapy. This indicates late induction of first line therapy but early detection of first line failure by CD4 cell count.

Viral load was estimated in only 50% of cases due to high cost of investigations and lack of access to specialized laboratory services. At the time of starting second line therapy, out of 15 patients in whom viral load was estimated, 11 had done >20,000 copies of HIV virus/ml.

A sizeable number (83.33%) of patients were started on first line antiretroviral therapy due to low CD4 cell count, irrespective of their symptomatic status. It suggests that there was delay and inaccessibility to approach antiretroviral care, till the immunodeficiency became too severe, since the patients were unaware of the infection as is the usual scenario in India.

The first line regimen for antiretroviral treatment consisted of 2 NRTIs and 1 NNRTI in all 30 patients, which is the preferred first line regimen according to WHO and National AIDS Control Organization guidelines.

HIV viral resistance testing was done in only 7 patients. In Western countries viral resistance testing is done prior to initiation of first line therapy. However in a resource-limited setting like India, due to expense, non-availability and inaccessibility of viral resistance testing, it is done only in selected patients. The resistance of these patients revealed that majority of patients (64.28%) were resistant to NRTI as they form the initial backbone ART in India, due to easy availability, low pill burden and having relatively low toxicity.

Switch to second line regimen was made in all 30 patients due to failure of first line regimen. In the present study, 63.33% patients had been switched due to immunological failure and 26.67% had clinical treatment failure as the reason. 2 patients had both immunological and clinical failure and only one patient was switched to second line regimen due to immunological and virological failure.

Normally virological failure is the earliest and most accurate to detect by HIV RNA assay, followed by immunological failure and lastly by clinical treatment failure, as manifested. However in a developing country like India, due to high cost, ignorance, inaccessibility and non-availability of antiretroviral care, in general settings, clinical failure is detected first followed by CD4 count and lastly the virological failure by HIV RNA assay. But with widespread availability of CD4 cell count estimation by National AIDS Control Organization

(NACO) affiliated centers and Antiretroviral Centers of the medical colleges CD4 cell count is being increasingly used to determine the immunological failure, which is being taken as the major criteria for switching to second line therapy.

This is reflected in this study also, where majority (63.33%) of patients have been started on second line therapy due to immunological failure. In few cases where viral load was estimated, 1 patient was switched to second line therapy due to both immunological and virological failure.

Possible reasons of first line treatment failure might be:

- Incomplete adherence
- Intolerance to therapy due to adverse effects
- Pharmacokinetic issues like Poor understanding of the details of the medication regimen
- Failure to access antiretroviral care
- Low literacy level
- Since in India, viral resistance testing is not done before the initiation of first line regimen due to non-availability, inaccessibility and high expense, possibly in few patients HIV virus might not have been susceptible to the drugs administered in the first line therapy itself.

On switching to second line antiretroviral therapy, the most common drug regimen followed was Tenofovir + Abacavir + Lopinavir + Ritonavir, in 73.33% of patients, in accordance with the viral resistance testing studies, good outcomes, low toxicity and high compliance. 3 patients were administered Zidovudine + Lamivudine + Saquinavir + Ritonavir. 2 patients were prescribed the regimen Tenofovir + Abacavir + Efavirenz.

The various adverse effects experienced by majority (56.67%) of patients. Most of the adverse effects were central nervous system related like headache, dizziness, delusions etc. experienced by 10 (33.33%) patients. 2 patients complained of loose motions due to drugs. Other adverse effects experienced were numbness, pruritus, burning sensation during urination, weight loss and diminution of vision, each complained by 1 patient. In comparison with first line antiretroviral therapy, the second line regimens are more complex due to high pill burden and large number of drug interactions. We did not encounter significant metabolic abnormalities like hyperglycemia, dyslipidemia as the mean duration of second line ART was too small.

V. Conclusion

- Second line antiretroviral therapy has changed the prognosis of HIV infected patients who have first line regimen failure.
- There was delay and inaccessibility in starting antiretroviral therapy due to ignorance, high cost and non-availability. Access to second line ART regimens is relatively limited in developing countries like India.
- The switch to second line treatment was relatively slow, due to CD4 cell count being used as the main criteria to switch therapy. Viral load was done in only selected cases due to high cost, inaccessibility, non-availability of required laboratory services. This study highlights the importance of assessing viral load to monitor any early virological failure in patients on first line ART to switch early to second line therapy. Until viral load testing is widely available, cheap and done regularly, it would not be possible to detect first line ART failure early. Till then, CD4 cell count should be used as a guiding factor to detect early first line ART failure.
- The most common second line regimen followed by patients is Tenofovir + Abacavir + Lopinavir + Ritonavir, but it shows a high incidence of minor adverse effects. The response to therapy was good in terms of clinical and immunological parameters.
- Viral Resistance testing revealed resistance to NRTI in 64.28% and NNRTI in 42.85% and PI in 14.28% cases.

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