TO STUDY THE THERAPEUTIC RESPONSE FOLLOWING HIGHLY ACTIVE ANTIRETRO VIRAL THERAPY

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Certificate

This is to certify that the dissertation entitled

" THERAPEUTIC RESPONSE FOLLOWING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY " is the bonafide original work of **Dr.A.VENI**, in partial fulfillment of the requirements for M.D. Branch-1 (General Medicine) Examination of the Tamil Nadu DR.M.G.R.Medical University to be held in March 2010.

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DECLARATION

I **Dr. A.VENI**, solemnly declare that dissertation titled, **"THERAPEUTIC RESPONSE FOLLOWING HIGHLY ACTIVE ANTIRETRO VIRAL THERAPY"** is a bonafide work done by me at Annal Gandhi Memorial Hospital during 2007-2009 under the guidance and supervision of my unit Chief Prof Dr**.S.PANNEER SELVAM, M.D**.,HOD /PROFESSOR of Medicine.

The dissertation is submitted to the Tamilnadu **Dr.M.G.R Medical University,**towards the partial fulfillment of requirement for the award of M.D. Degree (Branch-I) in General Medicine.

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INTRODUCTION

AIDS – the acquired immuno deficiency syndrome called slim disease is a fatal illness caused by a retrovirus known as human immuno deficiency virus which breakdown the body's immune system leaving the victim Vulnerable to a host of life threatening opportunistic infections, neurological disorders or unusual malignancy. Strictly speaking the term AIDS refers only to the last stage of the HIV infection.[5]

The human immunodeficiency virus (HIV) infection has spread worldwide, with various adverse health and economic implications, particularly in the developing world. Unless a cure is found or life prolonging therapy can be made more widely available, the majority of people will remain suffering the profound impacts the disease has on their quality of life.[56]

Globally, 33 million people were estimated to be living with HIV/AIDS in 2007. The number of HIV-positive TB cases and deaths were estimated at 1.39 million cases (15% of all incident cases) and 0.48 million deaths, which was 24% of the estimated two million HIV deaths in 2007.[10,21]

In India, the 2006 estimates suggested that

national adult HIV prevalence in India was approximately 0.36 per cent, amounting to 2.34 million (ranging between 2 and 3.1 million) people living with HIV and AIDS.Even going by the conventional figure of 40% of the Indian population infected with *Mycobacterium tuberculosis*, it is estimated that not less than one million persons with HIV are co-infected with TB.

Considering the fact that the lifetime risk of developing TB disease is between 50-60%, India is likely to have not less than one lakh patients, needing treatment for both HIV and TB simultaneously at any given point of time. Free Anti-Retroviral Therapy (ART) was introduced in India in April, 2004, as a component of care, support and treatment, in National AIDS Control Program(NACP).

The concept of managing HIV disease in India till that time was to treat the opportunistic infections, as and when these were identified. Initiation of ART reduces risk of further HIV-related morbidity and mortality. ART reduces the incidence of TB even in high TB prevalence countries.[21]

MILESTONES IN THE HISTORY OF HIV [14,4]

1. 1981- First report of AIDS case
2. 1983 – HIV identified
3. 1985 – AZT entered phase I, II trials
4. 1986 – HIV 2 identified, AZT showed survival benefit in AIDS Patients
5. 1987 - AZT for Therapy
6. 1995 – Double nucleoside combination
7. 1996 – Protease Inhibitor, NNRTI introduced
8. 1997 – Concept of full HIV suppression
9. 1998 – Dramatic reduction in AIDS related morbidity and mortality
10. 2001 – Inexpensive ART available in resource poor country
11. 2004 – During April Government of India initiated supply of free ART to HIV Patients.

AIM OF THE STUDY

1. **To study the clinical response to highly active antiretroviral therapy (HAART)**
2. **To study the Immunological response to highly active antiretroviral therapy (HAART)**
3. **To study the functional status improvement to highly active antiretroviral therapy (HAART)**
4. **To study the prevalence of HIV and TB co-infection**

Review of literature

Introduction

No other disease in history has been studied so extensively in a short period as AIDS. The first documented evidence of the disease appeared in United States in 1981, followed by reports from other parts of the world. HIV entered India a few years later. The first case of AIDS was reported in 1986. [5] Antiretroviral therapy for treatment of Human Immuno deficiency Virus type 1 (HIV-1) infection has improved steadily since the advent of combination therapy in 1996. More recently, new drugs have been approved, offering added dosing convenience and improved safety profiles, while some previously popular drugs are being used less often as their drawbacks become better defined.[36]

AGENT FACTOR

When the Virus was first identified it was called Lymphadenopathy associated Virus, then renamed as Human T cell lymphotropic virus III. In May 1986, the international committee on the

taxonomy gave it a new name: Human immune deficiency virus (HIV) [5]

STRUCTURE[42]

Belongs to the lentivirus subgroup of the family retroviridae. HIV is a spherical envelop virus about 90-120nm in size. Nucleocapsid has an outer icosahedral shell and an inner cone shaped core, enclosing the ribonucleo proteins. The genome is diploid, Composed of two identical Single stranded, positive sense. RNA copies . In association with Viral RNA, the reverse transcriptase enzyme, Which is a characteristic feature of retroviruses.

VIRAL GENES AND ANTIGENS [42]

The genome of HIV contains the three structural genes, gag, pol and env characteristics of all retroviruses as well as other nonstructural and regulatory genes specific for the virus.

MAJOR ANTIGEN OF HIV

A. **Envelope Antigens**:

Spike Antigen – gp 120 (Principle envelope Antigen)

Transmembrane pedicle protein – gp 41

B. **Shell Antigen**:

Nucleocapsid protein - P – 18

C. **Core Antigens**:

Principle Core Antigen –P24

Other Core Antigen - P15, P55

D. **Polymerase Antigens** :

P31, P51, P66

STAGES OF VIRAL REPLICATION [12,8]

STAGES	STEPS IN REPLICATION	DRUG TARGETS
1	Attachment to CD4 receptor	----------
2	Binding to co-receptor CCR5 or CXCR4	CCR5/CXCR4 receptor inhibitors
3	Fusion	Fusion inhibitors
4	Reverse Transcription	Nucleoside and non-nucleoside Reverse transcriptase inhibitors
5	Integration	Integrase inhibitors
6	Transcription	----------
7	Translation	----------
8	Cleavage of polypeptides and assembly	Protease inhibitors
9	Viral release	----------

EPIDEMIOLOGY: [3,38,44]

India has the World's largest population suffering from AIDS after South Africa and Nigeria. HIV infection in India declined drastically in recent years from 5.5m in 2005 to below 2.5million in 2007.

Nationwide HIV Prevalence rate among adults stood at 0.34% in 2007.Main factor which contributed to India's large HIV infected population are extensive labor migrate, low literacy level.

1. World

Global summary of the AIDS. Epidemic as on Dec 2007

Numbers of people living with HIV - 2007.

Total	:	33.2million
Adults	:	30.8million
Women	:	15.4million
Children	:	2.5million

People newly infected with HIV in 2007

Total	:	2.5million
Adults	:	2.1million
< 15 years	:	4, 20,000

AIDS Death in 2007

Total	:	2.1 million
Adults	:	1.7million
< 15 yrs	:	3, 30,000

2**. In India**

2.4 million people living with HIV / AIDS

Adults HIV prevalence 0.34% (0.25% - 0.43%)

Among PLHA 39% were females 3.5% were children

Based on Sentinel Surveillance data, HIV prevalence in adults population classified into 3 groups of states in the country.[5]

Group I: High prevalence state: Includes Maharashtra, TamilNadu, Karnataka, Andhra Pradesh, Manipur and Nagaland where the HIV infection has crossed 5% in high risk groups and ≥ 1% in antenatal women.

Group II: Moderate Prevalence State: Includes Gujarat, Goa, Pondicherry where HIV infection has crossed 5% or more among high risk groups but the infection is below 1% in antenatal women.

Group III: Low prevalence States: Includes remaining states where the HIV infection in any of the high risk groups is still less than 5% and < 1% in Antenatal women.

Annual Sentinel Surveillance [5,30]

In India, the districts have been classified according to the epidemiological and Vulnerability criteria using the Sentinel Surveillance data for the last 3 years.

Categories of Districts

A - > 1% ANC prevalence in district in anytime of the sites in the last 3 years

B- < 1% ANC, >5% prevalence in High risk groups (HRG).

C- < 1% ANC, <5% HRG with known hot spots

D- < 1% ANC, <5% in HRG with no known hot spots.

HRG (High Risk Groups) – STD Population, Female sex workers

MSM -men having sex with men

IDU - Intra Venous drug users

ANC : Antenatal clinic

Hot spots: Migrants, Truckers, Large aggregation of factory workers, Tourists.

A recent study published in the British medical journal "The Lancet" in (2006) reported an approximately 30% decline in HIV infections among young women aged 15 to 24 years attending prenatal clinics in selected southern states of India from 2000 to 2004 where the epidemic is thought to be concentrated. The authors cautiously attribute observed declines to increased condom use by men who visit commercial sex workers and cite several pieces of corroborating evidence.

MODES OF TRANSMISSION :[44]

The modes of transmission of HIV are sexual (man to man, Heterosexual and oral), parenteral (blood or blood product recipients, injection drug users and those experiencing occupational injury) and vertical route.

CLINICAL FEATURES [34,35,38]

- **Asymptomatic HIV** (clinical latency)
  - Patient often unaware of infection
  - Immune system able to control virus to limited extent
  - Able to transmit HIV to others

- **Symptomatic HIV**
  - Minor to moderately severe symptoms

- Recurrent symptoms

- **AIDS**
  - Severe immunosuppression associated with opportunistic infections or malignancies

- **Without antiretroviral treatment**
  - 30% will develop AIDS in 3 years
  - 90% will develop AIDS within 10 years

Acute Retroviral Syndrome

Fever-96%	**Myalgias-54%**	**Hepatosplenomegaly-14%**
Adenopathy-74%	**Diarrhea-32%**	**Weight loss-13%**
Pharyngitis-70%	**Headache-32%**	**Thrush-12%**
Rash-70%	**Nausea&vomiting-27%**	**Neurologic symptoms-12%**

BASELINE EVALUATION [51]

A standard clinical and laboratory evaluation is recommended

prior to initiation of ART. It is intended to establish the baseline status

for future comparison, individualizing ART according to patient's clinical status and preferences, and ruling out active OIs.

History

Points to be elicited in history taking:

1. HIV specific symptoms- present and past
2. Genital ulcers and other sexually transmitted diseases
3. Personal history- smoking, alcohol, drugs
4. Past history of any coronary artery disease
5. High risk behavior- partner's HIV sero-status if known
6. Women- gynaecological history, past pregnancies, contraception
7. Family history of coronary disease, hypertension, diabetes and hyperlipidemia
8. Treatment history: any past or current use of ARVs (useful for designing ART regimen), sexual partners ARV use, ARV use during pregnancy.

Physical examination

A routine physical examination is essential prior to initiating ART. Following evaluation is recommended:

1. Body weight, height, Body Mass Index

2. Temperature/Lymph-node

3. Dermatological/Oral cavity: oral candidiasis, oral hairy leukoplakia

4. Systemic examination

Laboratory evaluation

The purpose of baseline laboratory evaluation is to stage HIV disease, rule out concomitant infections and determine baseline safety parameters. The following tests are recommended:

1. Confirm HIV infection : A pre-requisite prior to ART initiation, it also is needed to rule out HIV-2 infection. Nonnucleoside reverse transcriptase inhibitor's (NNRTIs) have no activity against HIV-2.

2. Specific investigations to rule out OIs

3. CD4 counts : Estimated by flow-cytometry. Alternative low cost technologies are becoming available, however further evidence is needed to recommend its routine use in clinical practice.

4. CBC : Baseline Hemoglobin and WBC counts are needed to monitor hematological toxicity on Zidovudine (ZDV).

5. LFTs : Necessary to find evidence of hepatitis, particularly when NVP use is contemplated.

6. Urine routine: To evaluate proteinuria and sugar (necessitate

estimation of blood glucose)

7. Creatinine : Dose of some nucleoside reverse transcriptase inhibitors (NRTIs) has to be adjusted according to creatinine clearance.

8. HBsAg : To rule out concomitant hepatitis B infection, this can influence choice of ARV regimen. Additionally, abrupt stopping of anti-HBV drugs like lamivudine and tenofovir is not recommended in patients with chronic hepatitis B coinfection since it may result in hepatitis B flare.

9. Chest X-ray : To rule out TB or other pulmonary infection.

Antiretroviral Drugs approved for use [1,7]

NRTI	NNRTI	PI	Entry inhibitor
Zidovudine(ZDV)	Nevirapine(NVP)	Saquinavir(SQV)	Enfuvirtide(T-20)
Stavudine(d4T)	Efavirenz(EFV)	Indinavir (IDV)	**Nucleotide RTI**
Lamivudine (3TC)	Delavirdine	Ritonavir(RTV)	

tenofovir(TDF)

Didanosine(ddI) (DLV) Nelfinavir(NFV **CCR 5**

Antagonist

Zalcitabine(ddC) Lopinavir(LPV/r) Maraviroc

Abacavir(ABC) Amprenavir(APV)

Emtricitabine(FTC) Fos-amprenavir(FPV)

Integrase Inhibitors Tiprinavir(TPV)

Raltegravir Atazanavir(ATV)

Dosage of antiretroviral drugs used in the first-line ART regimens [7,27]

Drug	**Dosage**
1. Zidovudine (AZT)	300 mg twice daily
2. Lamivudine (3 TC)	150 mg twice daily
3. Nevirapine (NVP)	200 mg twice daily, except for the first 2 weeks
4. Efavirenz (EFV)	600 mg once daily
5. Stavudine (d4T)	30 mg twice daily

Medical eligibility to start ART: [6,47]

1. If CD4 testing available:

1. CD4 < 200 at any WHO clinical stage

2. WHO clinical stage 4 : No matter of CD4 count
3. WHO clinical stage 3 : Consider ART if CD4, < 350 and initiate if CD4 < 200cells/mcl.
4. WHO clinical stage 1 & 2: CD4 < 200cells/mcl

2. IF CD4 testing not available:

WHO clinical stage 3 & 4.

3. Post exposure prophylaxis: [2]

1. A Combination of 2 nucleoside reverse transcriptase inhibitor for 4 weeks duration for less severe exposure.
2. A combination of 2 nucleoside reverse transcriptase inhibitor plus a 3rd drug (protease inhibitor) for 4 weeks duration for more severe exposure.
3. **Selecting the Regimen:** [6,16,18]

As a general rule should not initiate ART during a severe acute opportunistic infection or other severe illness.

1. If the patient on ATT - Efavirenz based regimen
2. Is there Anaemia - <8gm% - Stavudine based regimen
3. If there is Jaundice or known liver disease?

   Non nevirapine based regimen
4. If the patient is diabetic (or) heart diseases? Individualized according to patient's condition

Goal of ART [2,6,15,48]

1. **Clinical Goals**: Prolongation of life and Improvement in quality of life
2. **Virological Goals**: Greatest possible reduction in viral load for as long as possible
3. **Immunological Goals**: Immune reconstitution that is both quantitative and qualitative
4. **Therapeutic Goals**: Rational sequencing of drugs in a fashion that achieves clinical, Virological and Immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence.
5. **Reduction of HIV transmission in individuals**: Reduction of HIV transmission by suppressing the viral load.

Adherence to ART:

- 95 % Adherence : less than **3 doses** missed /month
- 80 – 95% Adherence**: 3-12 doses** missed/month
- <80% Adherence**: ≥ 12 doses** missed /month

LABORATORY MONITORING OF PATIENT'S WITH HIV INFECTION DURING TREATMENT

1.CD4 + T cell count

2. HIV RNA determinations

3. HIV resistance testing

4. TB / HIV co- infection assessment

Treatment failure: [9,19]

1. Increased viral load-**Virological failure**
2. decreased CD4 count -**Immunological failure**
3. Increased opportunistic infection- **Clinical failure**

Pulmonary TB

This is **most common form of TB disease**. The presentation depends on the degree of immunosuppression:

In patients with **mild immunosuppression**, chest X-ray (CXR) typically shows upper lobe and/or bilateral infiltrates, cavitation, pulmonary fibrosis and shrinkage. The clinical picture often resembles post-primary pulmonary TB (PTB), and the sputum smear is usually positive.

In **severely immune suppressed** patients, the features of the disease are atypical, resembling those of primary TB. The sputum

smear can often be negative and CXR shows interstitial infiltrates, especially in the lower zones, with no features of cavitation and fibrosis. Unilateral or bilateral infiltrates are seen more often in the lower lobes than in the upper lobes and typical cavities are seen in only 25% of patients.

In persons with **advanced HIV infection**, disseminated and extrapulmonary TB are more common. The most common forms are lymphadenitis, pleural effusion, pericarditis, miliary disease and meningitis. The **most important symptoms** are: cough lasting longer than 3 weeks and not responding to the usual antibiotic treatment, purulent/blood-stained sputum, evening fever, night sweats and weight loss.

Diagnostic tests:

Sputum examination:

Microscopic examination of sputum stained by the Ziehl–Neelsen (ZN) methodis the diagnostic test of choice. A PTB suspect should submit three sputum samples for microscopy.At first visit, the patient should provide an on-the-spot sputum sample. Give the patient a sputum container to take home for an early morning sample on the following day (that is, on day 2). An inpatient can provide two early morning sputum samples.

Radiological examination:

The classical pattern seen on CXR in TB is upper lobe infiltrates with cavitation. However, in severe immunosuppression, the affected region is mostly extrapulmonary in the form of hilar adenopathy and pleural effusion. There may be upper zone infiltrates or a military pattern, and atypical lower zone infiltration of the lung fields as described above. Cavitation may not be seen in patients with severe immune suppression. It is not possible to make a confirmed diagnosis of TB based on the X-ray picture alone.

Purified protein derivative (PPD) test:

PPD is likely to be positive at higher CD4 counts. As the count falls to less than 100 cells/mm3 it may become negative. It has no diagnostic significance.

Fine-needle aspiration cytology (FNAC):

An FNAC from a lymph node may show AFB in patients with HIV infection.

Other tests:

An **ultrasonography** of the abdomen may show enlarged intra-abdominal lymph nodes and multiple hypoechoic lesions in organs such as the spleen or liver.

Lumbar puncture (LP):

Done in suspected cases of TB meningitis may have a turbid or viscous appearance, with 100–300 lymphocytes/ mm3, 0–200 polymorphs/mm3, 0.5–3 g/litre of protein, and half the blood value of glucose.

CT scan

can pick up brain tuberculomas, hydrocephalus or enhancement of the basal meninges.

Bone marrow biopsy and culture

may demonstrate the presence of the organisms.

Treatment

Standard Directly observed treatment, Short-course (DOTS) regimens are to be followed

according to the RNTCP programme in India. The patient should be referred to a DOTS centre for antituberculosis therapy (ATT). The regimens used for the treatment of pulmonary and

extrapulmonary tuberculosis are same in both HIV-positive and -negative individuals. Around 6–8 months of treatment appears to be sufficient for extrapulmonary disease at many sites. Twelve months of therapy is recommended for miliary TB, bone or joint disease and tubercular meningitis. Persistently positive sputum culture after 2–3 months of therapy suggests the possibility of drug-resistant TB or non-compliance with therapy.

Revised National Tuberculosis Control Programme (RNTCP)

Treatment regimens followed vary according to the type of patient (whether the patient is a new case of TB or one who has been treated for TB previously), severity of illness and response to treatment.

Category I – Regimen used: 2(EHRZ)3 , 4 (HR)3

This regimen is recommended in patients with new sputum smear-positive TB, seriously ill smear-negative TB, seriously ill extrapulmonary TB, and all new TB patients who voluntarily disclose their HIV status.

Category II – Regimen used : 2 (SEHRZ)3/1(EHRZ)/5 (EHR)3

This regimen is recommended in patients with previously treated smear-positive TB (including relapse, failure and treatment after default).

Category III – Regimen used: 2(HRZ)3/4(HR)3

This regimen is recommended in patients with new smear-negative TB, extrapulmonary TB and those who are not seriously ill.

In all categories,

treatment is given **in two phases.**

The first or **intensive phase** consists of treatment lasting for 2–3 months. In the intensive phase, three to five anti-TB drugs are administered depending on the category of treatment prescribed and all the thrice-weekly doses are given under direct observation.

This is followed by the **continuation phase**, which lasts for 4–5 months. In the continuation phase, the number of anti-TB drugs administered is reduced to two or three drugs depending on the regimen prescribed and only the first dose of the week is given under direct supervision and the remaining two doses in the week are self-administered.

E (ethambutol), H (isoniazid), R (rifampicin), Z (pyrazinamide) and S

(streptomycin).

The numbers before the bracket indicate the number of months for which the drugs are to be administered.

The number “3” given as a subscript after the bracket indicates that the drugs are administered thrice weekly.

Category I and Category III regimens are given for 6 months, while the Category II regimen is for 8 months.

Precautions

In HIV-infected TB patients, combining rifampicin with protease inhibitors and nevirapine has been found to decrease the levels of all the drugs, thereby decreasing the effectiveness of ART and increasing the rifampicin levels, leading to rifampicin-induced hepatotoxicity. In case ATT and ART are used together, an efaviranzbased ART regimen should be followed. If oral candidiasis is also present, administration of anti-TB drugs

together with fluconazole can also result in hepatotoxicity. Close monitoring for serum transaminases and serum bilirubin is necessary for early detection of hepatotoxicity.

Dosages

In adults, the dosages of the drugs are as follows:

Isoniazid 600 mg thrice weekly

Rifampicin 450 mg (600 mg if weight >60 kg) thrice weekly

Pyrazinamide 1500 mg thrice weekly

Ethambutol 1200 mg thrice weekly

Streptomycin 0.75 g thrice weekly (0.5 g in patients >50 years of age).

Materials & Methods

The study was conducted on 118 HIV infected adults who attended the ART centre, Annal Gandhi Memorial Hospital from August 2007 to August 2009. All patients were thoroughly evaluated by detailed history, general examination, systemic examination, appropriate Investigations as per proforma.

List of Pre and Post treatment investigation included the following.

1. Hemoglobin
2. Total and differential count
3. Erythrocyte Sedimentation Rate
4. Platelet count
5. Blood sugar
6. Blood urea
7. Serum creatinine

8. Liver function test
9. X-Ray chest PA view(If necessary)
10. Sputum for AFB (If necessary)
11. CD4 count (6 monthly)
12. Other specific test it needed.

Selection Criteria:

The following criteria are used for selection of HIV patients:

1. Patient should be more than or equal to 20 years
2. The diagnosis of HIV confirmed as per WHO criteria
3. Initiation of HAART according to WHO criteria

Exclusion criteria:

1. Patient less than 20 years
2. The patients who have already received treatment with ART outside
3. Patients who died within 6 months after initiation of HAART
4. Patients who missed more than 12 doses per month
5. Patients who lost follow up after initiation of HAART

Diagnostic criteria

For the purpose of diagnosis, three rapid HIV test kits based on different antigens / principle are to be used. Blood samples are processed for HIV. The test result may be positive, Negative (or indeterminate as described below.

Test kit 1(Micro Lisa) – Positive

Test kit 2 (In stochk) – Positive

Test kit 3 (Pareekshak) – Positive

Case reported as positive

Subjects and Methods:

This prospective study was conducted at the ART centre, Annal Gandhi Memorial Hospital, Trichy from August 2007.

118 HIV positive patients were selected as per selection criteria. 18 patients excluded subsequently since they lost follow up or poor adherence rate or died within 6 months of treatment.

Patients were enquired, regarding occupation, educational status personal history, family history and their complaints.

History was obtained in detail about the marital status and couples and couple reactivity, children status.

After receiving consent from the patients, general and systemic examinations were performed ,then laboratory investigations were done in all patients.

All patients were examined for opportunistic infections. Patient's weight was recorded during each visit. Nutritional advise was given to all patients.

Functional status obtained by history.

Clinical staging were determined by clinical examination of the patients.

All patients were subjected to relevant investigation as required.

`WHO clinical staging of HIV/AIDS for adults [6,51]

Clinical Stage 1

Asymptomatic

Persistent Generalized Lymphadenopathy

Clinical Stage 2

Moderate unexplained weight loss (under 10% of presumed or measured body weight)

Recurrent respiratory tract infections

Herpes zoster

Angular cheilitis

Recurrent oral ulcerations

Papular pruritic eruptions

Seborrhoeic dermatitis

Fungal nail infections

Clinical Stage 3

Unexplained severe weight loss (>10% of measured body weight)

Unexplained chronic diarrhea > 1 month

Unexplained persistent fever > 1 month

Persistent oral candidiasis

Oral hairy leucoplakia

Pulmonary tuberculosis

Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis)

Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis

Unexplained anemia (<8 g%), neutropenia (<500), and or chronic thrombocytopenia (<50,000)

Clinical Stage 4

HIV wasting syndrome

Pneumocystis carinii pneumonia

Recurrent severe bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal

of more than one months duration or visceral at any site)

Esophageal candidiasis

Extrapulmonary tuberculosis

Cytomegalovirus disease (retinitis or any other organ)

Central nervous system toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacterial infection

Progressive multifocal leucoencephalopathy

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated mycosis (histoplasmosis)

Recurrent septicemia

Lymphoma (cerebral or B cell Non-Hodgkins)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV associated nephropathy or cardiomyopathy

Functional status Assessment: [27]

As per NACO guidelines, functional status of the patients before, and after starting treatment was assessed and graded as WAB.

W – Working: Able to perform usual work in or out of the house, harvest, normal activities of playing

A – Ambulatory: Able to perform activities of daily living but not able to Work

B – Bedridden: Not able to perform activities of daily living

CD4 Count Analysis: [27]

The specimen were collected and analysed by the BD FACS Calibur flow cytometer (Beckton, Dickinson & Company, San jose, USA), from may 2008,PARTEC cyflow counter was used.

Highly active anti retroviral therapy was initiated if the patient meets the WHO criteria for starting treatment.

Initiation of HAART based on CD4+ count and WHO clinical stage

.Before starting ART, tuberculosis infection was specifically investigated and if found positive was treated with ATT as per RNTCP guidelines.

ART regimens used are, [27]

I. Stavudine + Lamivudine + Nevirapine

II. Stavudine + Lamivudine + Efavirenz

III. Zidovudine + Lamivudine + Nevirapine

IV. Zidovudine + Lamivudine + Efavirenz

V. Change over from one to other regimen

Treatment follow up:

After 6 months and 1 year of initiating therapy, patients were reexamined in detail for change in

1. Functional status
2. Clinical stage
3. Body weight
4. CD4 count
5. Opportunistic infections
6. Development of Side effects.

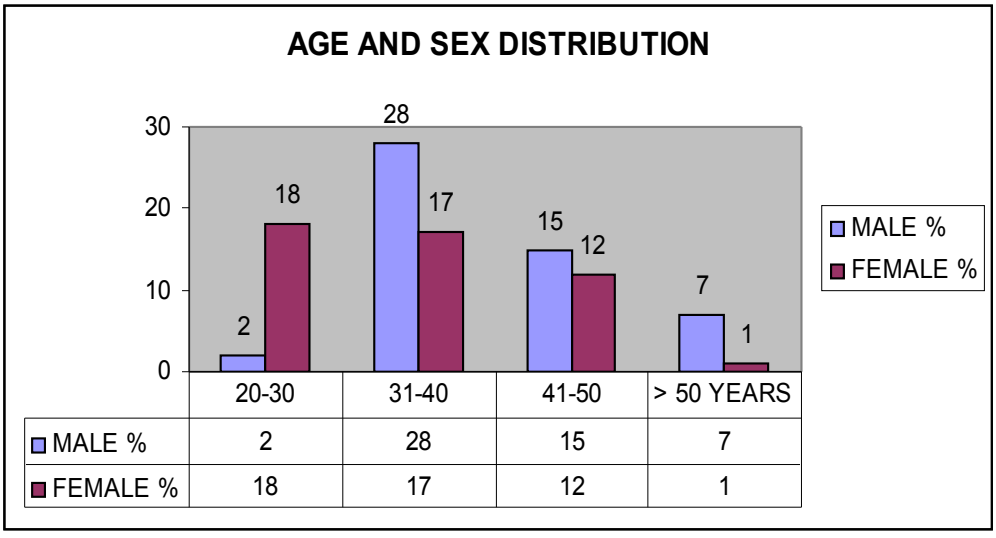
If the patient died after initiating HAART, enquiry was made into cause of death.

RESULTS AND OBSERVATIONS

This study was conducted among 118 patients attending ART centre at Annal Gandhi Memorial Hospital, Trichy with the aim of analyzing Immunological, clinical response and functional status improvement following highly active retro viral therapy. The analysis revealed the following results as found out among the study population of 100 patients.18 patients were excluded from the study because of their poor adherence rate, discontinued treatment with in 6 months starting treatment and lost follow up.

AGE/SEX DISTRIBUTIONS:

Fig - 1



When Age distribution was analyzed, most of them belonging to the reproductive age group of 20-50 years. This shows that HIV prevalence is high among 20-50 years of age groups. When sex distribution was analyzed, there was increased prevalence in males compared to females.

ENTRY POINT

Table - 1

Among our study subjects 79% entered though VCTC, 9% entered through PPTCT, 12% entered through RNTCP.

EMPLOYMENT STATUS

Table - 2

EMPLOYMENT STATUS		
SEX	**YES**	**NO**
MALE	52	28
FEMALE	0	20
TOTAL	52	48

Among our study subjects 52% were employed

MARITAL STATUS

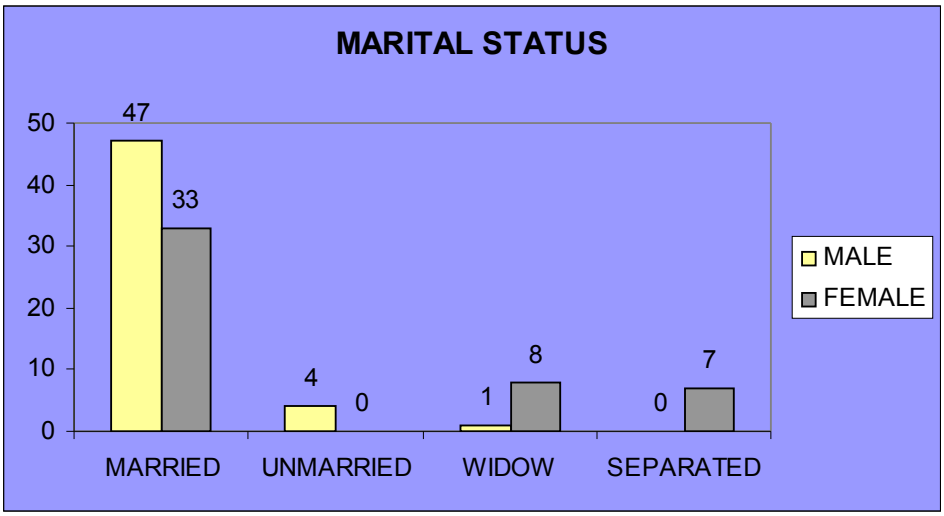


Fig – 2

When marital status was analysed most of them were married (80%)

FAMILY WISE DISTRIBUTION

Table - 3

FAMILY WISE DISTRIBUTION	
FAMILY	**PATIENTS**
WIDOWER	2
HUSBAND POSITIVE WIFE NEGATIVE(DISCORDANT)	23
HUSBAND NEGATIVE WIFE POSITIVE(DISCORDANT)	9
HUSBAND AND WIFE POSITIVE	54
NOT KNOWN	12
TOTAL	100

when analyzing family wise distribution 54% were both husband and wife positive. 32% were discordant couples. They were remained as discordant throughout the study.

OPPURTUNISTIC INFECTIONS & HIV

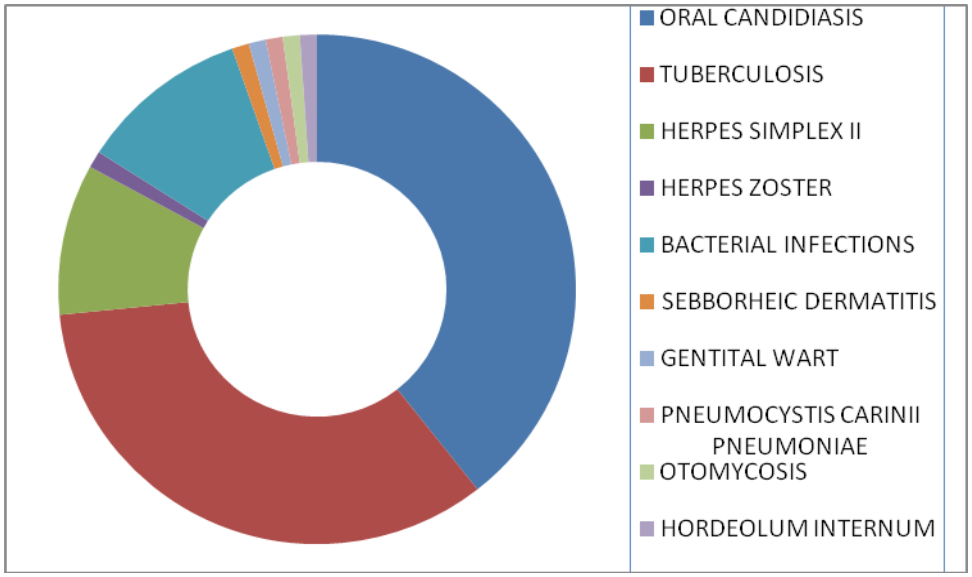


Fig – 3

When opportunistic infections were analyzed 37% of patients developed Oral Candidiasis , 32% of the individuals developed tuberculosis which includes both pulmonary and extra pulmonary tuberculosis , 10% of patients developed Recurrent bacterial infections,where as 40% not had any oppurtunistic infections.

ART REGIMEN

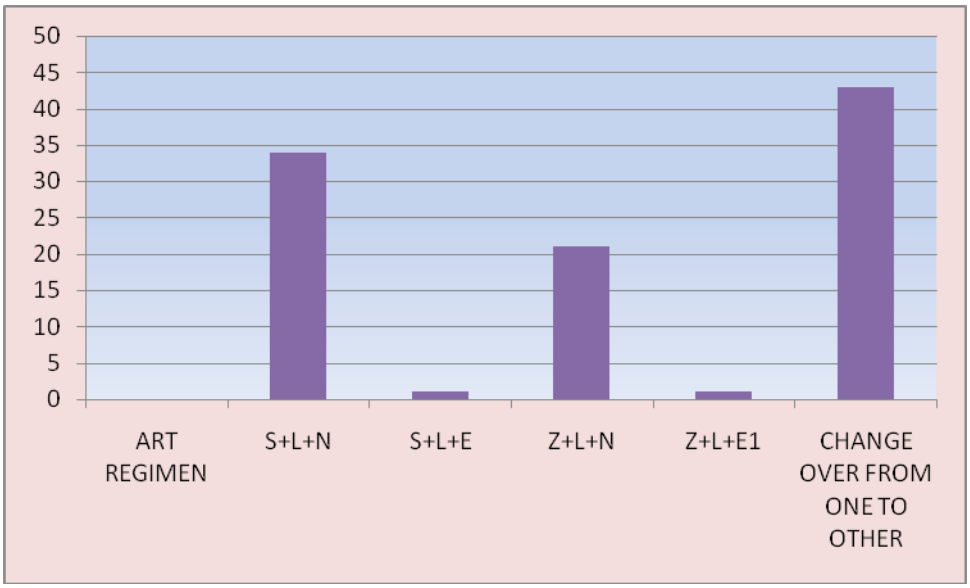


Fig –4

In this study population most of the patients received I &III regimen. Change over from one regimen to other regimen was mainly due to Nevirapine rash and due to initiation of ATT.

TUBERCULOSIS &HIV CO INFECTION

Table - 4

Significantly higher numbers of HIV patients eligible for receiving ART are also suffering from TB need an anti TB treatment. Significant number of patients referred from RNTCP for screening found to have HIV.

TUBERCULOSIS & INITIAL CD4 COUNT

Table - 5

TUBERCULOSIS & INITIAL CD4 COUNT	
CD4 COUNT	PERCENT
<100	15
100 TO 200	12
200 TO 300	4
> 300	1
TOTAL	32

Incidence of tuberculosis more common in HIV patients who had CD4 count of less than 200 per mcl.

EXTRAPULMONARY TUBERCULOSIS & INITIAL CD4 COUNT

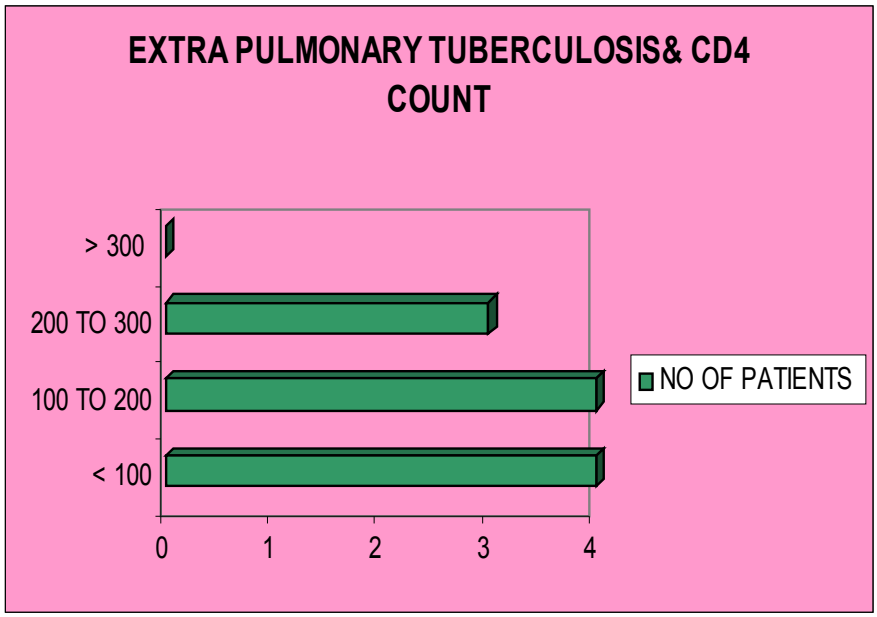


Fig - 5

Incidence of extra pulmonary tuberculosis more common in HIV patients who had CD4 count of less than 200 per mcl

WEIGHT INCREMENT

Table-6

WEIGHT INCREMENT		
WEIGHT (KG)	**MALE**	**FEMALE**
0 – 5	30	25
6 -10	11	16
11-15	5	1
≥ 16	1	2
≤ 0	5	4
TOTAL	52	48

Table – 7

PAIRED "T" TEST:						
Pair	Paired Differences					Significance (2 tailed) p value
	Mean	S.D	S.E. of mean	99% confidence interval of the difference		
				Lower	Upper	
PRE ART WEIGHT POST ART WEIGHT	4.59	4.675	0.4675	3.39	5.79	< 0.001

The change in weight after treatment as calculated by paired “T” test is statistically significant with P value < 0.001 (99% confidence interval)

The sex does not has any influence on the weight increment . Average increment of weight in this study was 5kg.

Table-8

Table - 10

PAIRED "T" TEST:						
Pair	Paired Differences					Significance (2 tailed) p value
	Mean	S.D	S.E. of mean	99% confidence interval of the difference		
				Lower	Upper	
PRE ART CD4 / POST ART CD4	220.7	158.45	15.85	199.9	261.5	< 0.001

The change in CD4 count after treatment as calculated by paired “T” test is statistically significant with P value < 0.001 (99% confidence interval)

Table - 11

WHO STAGE IMPROVEMENT

Table - 12

WHO STAGE IMPROVEMENT						
STAGE	PRE ART (O) MONTH		6TH MONTH OF ART		12TH MOHTH OF ART	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
I	3	7	42	45	47	47
II	2	1	3	2	2	0
III	38	31	6	1	0	0
IV	9	9	1	0	3	1
TOTAL	52	48	52	48	52	48

The WHO clinical stage improvement after treatment as evidenced by transition in clinical staging is statistically significant with P value < 0.001.

WHO STAGE IMPROVEMENT

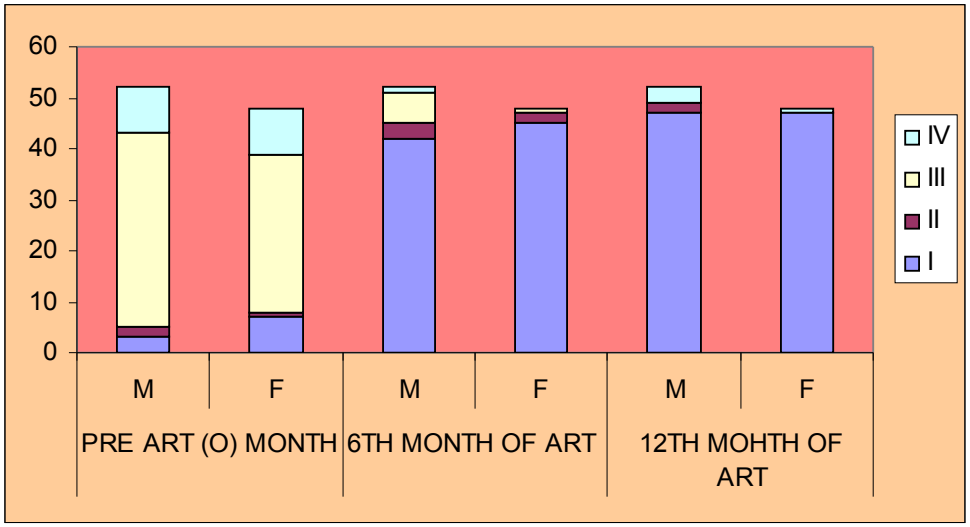


Fig-6

FUNCTIONAL STATUS IMPROVEMENT

Table -13

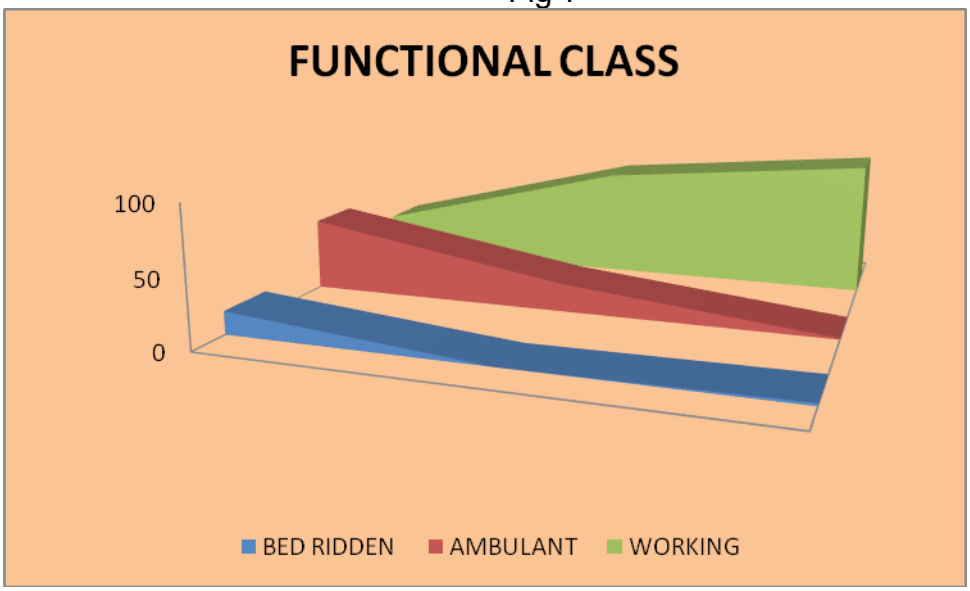
FUNCTIONAL STATUS CLASS						
CLASS	PRE ART (O) MONTH		6TH MONTH OF ART		12TH MOHTH OF ART	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
BED	12	5	0	0	1	1

RIDDEN						
AMBULANT	27	26	14	7	0	1
WORKING	13	17	38	41	51	46
TOTAL	52	48	52	48	52	48

Prior to ART 30% of the patient under working category, after 1 year of ART 97% of patients came under working category. There was a significant improvement in functional status of the patients after starting treatment.

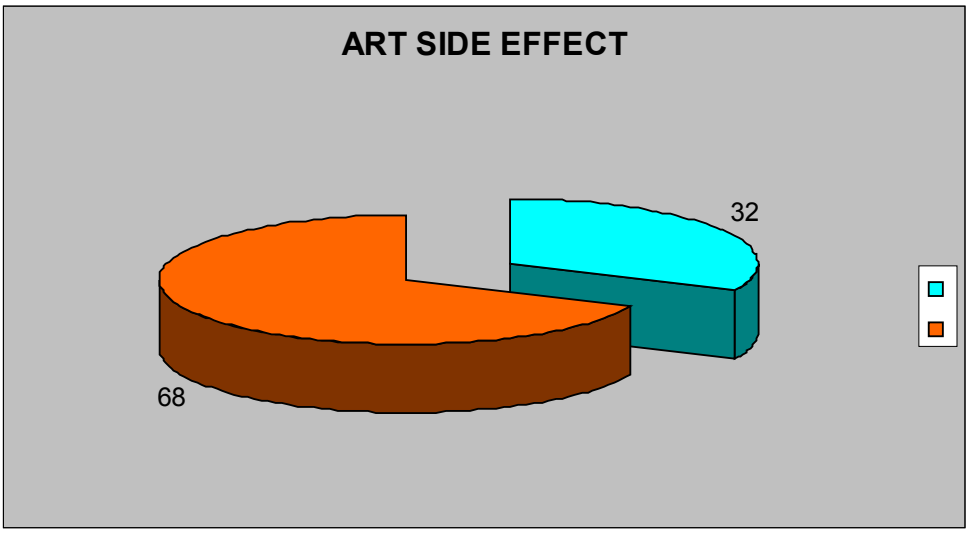
FUNCTIONAL STATUS IMPROVEMENT

Fig-7



ART SIDE EFFECT

Fig-8



32% of the patients experienced side effects of ART. Common side effect observed in this study were rash, anemia, nausea vomiting.

ANALYSIS AND DISCUSSION

1. AGE AND SEX DISTRIBUTION:

In this study, the age of the patients varies from 20 years to 75 years. The study group comprised 52 males and 48 females.

Majority of patients belonged to the most productive age group

of 20-40 years (80%) FIG – 1. As per the census regarding age distribution of AIDS cases in India, majority of HIV infections (92%) are in age group of 20-50 years. The predominance of the males over the females is similar to the census statistics of AIDS cases in India.

2. ENTRY POINT: (TABLE-1)

In this study, 87% patients entered via VCTC (ICTC)

3. EMPLOYMENT AND RISK OF HIV (Table-2)

In this study, employed patients (58%) have acquired the disease. Migrant youth are particularly vulnerable to HIV, as they may face repeated risks of HIV Infections. In this study population high prevalence of HIV observed among drivers and constructional workers.

4. FAMILY WISE DISTRIBUTION: (Table-2, Fig-3)

In this study, the majority of patients belonged to married category (80%). The widow population contributed to 9% of cases.

In nearly, 54 out of 80 couples both husband and wife positive. This gives importance of preventive measures aimed at preventing the transmission between the couples through education and adoption of safe sexual practices.

5. HIV AND OPPORTUNISTIC INFECTION: (Fig-3)

In this study most common opportunistic infection observed are oral candidiasis, tuberculosis ,recurrent bacterial infection, Herpes simplex-II.

Opportunistic infections were significantly reduced after highly active antiretroviral therapy. This is statistically significant with P value < 0.001.

6. WEIGHT INCREMENT FOLLOWING HAART: (Table-6,7,8)

In this study, the average pre-ART weight is 49.94kg which increased to 54.53kg after ART. So an average of 5kg increases in weight is seen among the study group. On analyzing statistically with paired "T" test, showed a high statistical significant with P value < 0.01. 4% of patients declined in weight after ART. However, majority showed an increment of 4.6kg after one year of ART.

7. ART REGIMENS: (Fig-4)

Patients taken regimen I accounts for 34% and regimen III accounts for 21%. The change in regimens regimen V accounts for 43%

This is due to the substitution of Efavirenz for Nevirapine in cases of intolerance to the latter or if patients are receiving rifampicin containing anti-TB treatment.[32]

In this study the stavudine based ART regimen is often preferred to zidovudine based ART while on initiation because of co-existence of anemia in many patients making them unsuitable for zidovudine based regimen. Success rate in I & III regimen is same.

8. TB AND HIV COINFECTION IN RELATION TO CD4

COUNT:

In this study, pulmonary TB (21% of patients) and Extra pulmonary TB (11% of patients) were diagnosed. They were the second most common opportunistic infection among HIV patients, next to oral candidiasis.

These patients were initially started on ATT and ART started subsequently after 2 weeks to 2 months as soon as TB treatment is tolerated. Both pulmonary and Extra pulmonary tuberculosis frequently occurs in patients with CD4 count less than 200 cells/ mcl. (table-4,5,Fig-5)

9. FUNCTIONAL STATUS IMPROVEMENT FOLLOWING HAART:

The functional status of an individual is divided into three grades according to NACO, Ministry of Health and Family welfare, Government of India.

In this study, there is an improvement in functional status level in response to ART as evidenced by an increase in patients belonging to “W” class from 30% to 79% after 6 months of treatment, 97% came under working category after 1 year of treatment. This change in class is statistically significant with “P” value < 0.01. At the end of 1 year 97% in working status 2% bed ridden, 1% ambulant. (Table-13, Fig-7).

10. WHO CLINICAL STAGE IMPROVEMENT FOLLOWING HAART:

In this study there is marked clinical improvement after ART. This reflected by the following observations.

There is an increase in clinical stage I, from 10% to 87% and clinical stage II from 3% to 5%.

The clinical stage II increase is mainly due to the patients who had improved in the clinical status from stage III to stage II.

Most important observation is the decrease in stage III from 69% to 7% after treatment. Decrease in stage IV from 18% to 1%. At the end of 1 year 94% of patients in stage I, 2% in stage II. The changes are statistically significant with P value < 0.01. (table-12,Fig-6)

11. IMMUNE RECONSTITUTION FOLLOWING HAART:

Goals of highly active antiretroviral therapy are reduction in plasma RNA levels and the immune reconstitution (Increasing the number of CD4 count and a favourable clinical outcome) [33,37,50]

In this study, the mean CD4 count has increased from baseline 81 cells /mcl to 189 cell /mcl after 6 months of ART.

The average increase in CD4 count was 108 cells /mcl.

The statistical analysis done using paired “T” test showed a

statistical significant, with P value < 0.001.

7% of patients showed a decline in CD4 count after treatment.

26% showed a 200 – 299 cells /mcl increment in CD count

14% showed a 100 – 199 cells /mcl increment in CD count

15% showed a 300 - 399 showed a 100 – 199 cells / mcl increament in CD count

11% showed a >400 cells /mcl increment in CD count (table-9,10,11)

Immunological failure according to WHO in this study was seen in 7% of patients.

Average CD4 count improvement is - 81 cells /mcl after 6 months,

108 cells /mcl after 12 months

Study by Kilaru KR el al (2006) had Immunological success around 80% [29,23,26]

Study by Smith CJ et al (2004) [39,46] demonstrated a median CD4 increase of 114 cells / mcl and Immunological success in 84% patients.

Vajpayee et al [45] showed an increase of CD4 count from a median

179 cells / mcl to 256 cells / mcl after HAART for a period of 6 months.

Institute for infections and tropical diseases, clinical centre of

Sesbia, Belgeade, and Montenegro, study result showed rise in CD4 count to atleast 200 cells per mcl.

LP Jacobson, JP phar, TE yamashita – Department of epidemiology, Johnsphopkins university Bloomberg school of public health – 2004, Multicentre AIDS cohort study which show that CD4 cell count, history of antiretroviral therapy, age at the time of initiation are independent determinants of response.[54,11,43]

lise p. jacobson, john p.phair and traci e. yamashita cohort study showed that CD4 cell count and history of ART at the time of initiation are independent determinants response.[55]

Response to HAART [52,53,13,17]

IMPACT OF HAART ON PATIENTS

As per patient's statement:

I was afraid that I would leave my family soon because I was too sick. But now after being started on ART I could feel the difference myself. Now I feel healthier and able to go to work and earn money for my family and me. I am happy and confident that I can live longer and be with my family for at least 10-15 more years.

Before ART I was roaming about doing nothing, but now after ART I got back my appearance and personality as before. Now I am going to work in manner. I am very much confident now.

I never expected that I will live. CD4 testing was done for me and ART were given. If ART is not inverted, mud would have eaten my body. Now I am doing so well with ART drugs. This is actually my rebirth.

Therapeutic response following highly active antiretroviral therapy

Conclusion:

1. **Majority of HIV patients belongs to reproductive age group.**
2. **Institution of HAART was associated with weight gain and decrease in opportunistic infection.**
3. **A high rate of immunological response was observed following HAART.**
4. **The Immunological and clinical response to HAART in HIV infected Tuberculosis patients were similar to those of Non-Tuberculosis patients.**
5. **Institution of HAART was associated with functional status improvement and mental well being.**
6. **32%of patients had HIV and Tuberculosis as a co-infection. In which 21% having pulmonary Tuberculosis, 11%having extrapulmonary Tuberculosis.**

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PROFORMA

TO STUDY THE THERAPEUTIC RESPONSE FOLLOWING HIGHLY ACTIVE ANTI RETROVIRAL THERAPY-AGM HOSPITAL,

1. Name : ART NO:
2. Age :
3. Sex : M/F
4. Address :
5. Date confirmation HIV+ test :
6. Place of HIV test:
7. Entry point :a) VCTC b)RNTCP c) O.P/I.P d) Others
8. Occupation :

9 .Education :

12.complaints:

13.Clinical stage assessment: (with available investigation in our hospital)

Systemic examination:

Respiratory system :

Cardiovascular system :

Abdomem :

Central nervous system:

WHO clinical stage :

14.Antiretroviral Treatment (Summary)					
Treatment started	SUBSTITUTION within 1st line, SWITCH to 2nd line, STOP, RESTART				
❑ STV+LMV+NVP ❑ STV+LMV+EFV ❑ ZDV+LMV+NVP ❑ ZDV+LMV+EFV ❑ Others	Date	Substitution Switch/ Stop	Reason	Date restart	New regime

17.Patient’s follow up :

Patient's follow up
18.Pre and post treatment investigation

HB	:	gms%
TC	:	cells/mm3
DC	:	P L E
ESR	:	mm/hr
Platelet count	:	lakhs/mm3
Blood Sugar	:	mg/dl
Blood urea	:	mg/dl
Serum creatinine	:	mg/dl
LFT: Sr bilirubin	:	mg/dl
SGOT	:	U/L
SGPT	:	U/L
CxR	:	
Sputum for AFB	:	

19.Others if needed :

20.Conclusion :