DISSERTATION ON

EARLY OUTCOMES OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV IN RESOURCE CONSTRAINT SETTINGS

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CERTIFICATE

This is to certify that this dissertation entitled **"EARLY OUTCOMES OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV IN RESOURCE CONSTRAINT SETTINGS"** submitted by **Dr. AMARNATH. K. A** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2009 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

Additional Professor,
Institute of internal medicine,
Madras Medical College,
Government General Hospital,

Director,
Institute of Internal Medicine,
Government General Hospital,
Chennai – 600 003.

Dean,
Madras Medical College,
Government General Hospital,
Chennai – 600 003.

DECLARATION

I solemnly declare that the dissertation titled **"EARLY OUTCOMES OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV IN RESOURCE CONSTRAINT SETTINGS "** is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2007-2008 under the guidance and supervision of Prof.D.RAJASEKARAN, M.D.

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

Place:

Date:

Dr. AMARNATH .K . A
M.D. General Medicine
Postgraduate Student,
Institute of Internal Medicine,
Madras Medical College,
Chennai.

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CONTENTS

INTRODUCTION

Human immunodeficiency virus (HIV) infection /Acquired Immunodeficiency Syndrome is a global pandemic, with cases reported from virtually every country. While initially limited, infection with the HIV has literally exploded over the past two decades to become the worst epidemic of the twentieth century. With more than 35 million fatalities, the AIDS epidemic now ranks alongside the influenza pandemic of the early 1900s and the Bubonic plague of the fourteenth century in terms of fatalities.[9] Unfortunately, the epidemic continues to spread relentlessly into new areas and to consolidate in many other locations. It is caused by a lenti virus human immunodeficiency virus. It was first recognized in USA in 1981 and the virus was first isolated in 1983. It has spread all over the world and by the end of 2007, 33.2 million individuals were living with HIV infection according to WHO- UNAIDS.[7]

More than 95% of people living with HIV/AIDS reside in developing countries mainly in African and asian continents. More than two thirds, approximately 22.5 million people were living in sub-Saharan Africa. In Asia, an estimated 4.9 million people were living with HIV at the end of 2007 of which 2.4 million people were living in India alone.

Highly Active Anti Retroviral Therapy is a novel treatment available since 1996, and has dramatically changed the evolution of HIV infection, with marked

improvement in survival and quality of life in developed countries where it was initially used. As a result, the gap between outcomes for HIV-infected persons in the rich developed world and the poor developing world began to widen. The need to close the treatment gap was declared a global public health emergency by WHO in 2003. The "3 by 5" initiative, launched by UNAIDS and WHO in December 2003, was a global strategy to provide antiretroviral therapy to people in developing countries. From then on HAART became available in resource poor countries.

HIV infection was first detected in India in 1986, among female sex workers in Chennai. From then on infection rates soared throughout the 1990s, and today the epidemic affects all sectors of Indian society, not just select groups. In 1987 a National AIDS Control Programme was launched to co-ordinate national responses. In 1992 the government set up NACO (National AIDS Control Organisation), to oversee the formulation of policies, prevention work and control programmes relating to HIV and AIDS. NACO launched the Highly Active Anti Retroviral Therapy (HAART), in the form of fixed drug combinations on April 2004, and was available in eight government hospitals through out the country, including Chennai. Though ART was available since 2004 in India, there are very few reports studying the efficacy of HAART, its adverse effects in our population, adherence of our population to therapy, and other factors.

ART centre was set up at our hospital in 2005, and is fully functional since then, catering to the needs of HIV patients. We report the outcomes of newly diagnosed, ART naive HIV patients started on HAART between January 2007 to December 2007.

Aims and Objectives

1. To analyse the early clinical outcomes of antiretroviral-naïve adults in a public sector ART programme in resource limited setting.
2. To study the trends of cd4 counts, weight, haemoglobin with treatment.
3. To determine risk factors, causes of death among patients accessing ART.
4. To analyse the adverse effect profile of ART.
5. To analyse the trend of opportunistic infections after starting ART.
6. To analyse the adherence to ART in public care settings.

REVIEW OF LITERATURE

The acquired immunodeficiency syndrome (AIDS) was first recognized among homosexual men in the United States in 1981 [1]. While initially limited, infection with the human immunodeficiency virus (HIV) has literally exploded over the past two decades to become the worst epidemic of the twentieth century.

ORIGIN OF THE HIV EPIDEMIC

Molecular phylogenetic studies suggest that HIV evolved from simian immunodeficiency virus (SIV), which has been found in two of four subspecies of chimpanzees in the Cameroon [2]. Several lines of evidence support zoonotic transmission of primate lentiviruses into humans [3]. Similarities in viral genome between SIV and HIV, prevalence in the natural host, geographic association between the animal reservoir and emergence of human cases, plausible route of transmission. The Pan troglodytes troglodytes species of chimpanzees has been established as the natural reservoir of HIV-1 and the most likely source of original human infection. HIV-2 is more closely related phylogenetically to the simian immunodeficiency virus (SIV) found in sooty mangabeys than it is to HIV-1 [1].

HIV-1 has evolved into groups M, N, and O; M ("Main") is considered the pandemic strain and comprises the vast majority of strains of HIV. [3,4] Viruses from group M are subsequently divided into ten distinct subtypes (A to J). Group O ("Outlier") represents far fewer strains from Cameroon, Gabon, and Equatorial

Guinea. Group N ("non-M/non-O") is represented by very few isolates and has only been documented in Cameroon. Studies have been performed to ascertain the origins of HIV infection. In an extensive field study, SIV-specific antibodies and nucleic acids were assayed in urine and fecal samples collected from the forest floor in the Cameroon.[5] Through sequence analysis, the origins of pandemic (group M) and nonpandemic (group N) HIV could be traced to distinct, geographically isolated chimpanzee communities. The origin of group O HIV is still unknown. Direct evidence of simian-to-human transmission is still missing, but is inferred by the known practice of hunting chimpanzees for food ("bushmeat"), particularly in western Africa.[3] Unlike other more readily transmitted zoonoses, important viral adaptations may have been required for HIV to infect humans. These adaptations may have included the acquisition of viral regulatory genes such as vpu, vif, nef, and tat, and structural genes, gag and env.[2] Although infected chimpanzees develop high levels of viremia, they do not have evidence of immune activation, T cell depletion, or clinical disease.[2] However, SIV can cause AIDS after cross-species transmission from asymptomatic African sooty mangabeys to Asian macaques.[6]

WORLDWIDE STATISTICS

As of December 2007, 33.2 million people were estimated to be living with HIV/AIDS, and more than 35 million had died since the beginning of the epidemic.

[7] Of the 33.2 million, 22.5 million were living in sub-Saharan Africa alone, where the adult prevalence rate is 5.0 percent. More than half of those living with HIV/AIDS are women. It is estimated that 15 million children have been orphaned by the premature death of both parents due to AIDS, placing enormous responsibilities on communities, and 2 million children are living with HIV/AIDS. In terms of the recent growth of the epidemic, an estimated 2.7 million people became newly infected with HIV in 2007, including 370 000 children under age 15, many of whom became infected by perinatal transmission.[7] An additional 2.1 million people died due to AIDS in 2007, including 330,000 children. Each day more than 6800 people become newly infected with HIV with increasing numbers among young adults, women, and children; and more than 5700 people die from AIDS each day. Young people, 15–24 years of age account for 45% of all new HIV infections in adults. Over 1,150 children become infected daily as a result of mother-to-infant transmission, despite data that antiretroviral drugs given at the time of delivery and to the infant after birth can largely prevent this.[8] Unfortunately, antiretroviral prophylaxis to prevent mother-to-child transmission reaches only 10 percent or less of affected mothers.[8] Of the 370 000 infants and children infected with HIV in year 2007, 70 percent were born in sub-Saharan Africa, 25 percent in southeast Asia, and the remainder in Latin America and the

Caribbean. With escalation of the epidemic in southeast Asia and eastern Europe, these numbers are only likely to increase.[7]

Sub-Saharan Africa — Approximately 10 percent of the world population lives in sub-Saharan Africa, but the region is home to approximately 67 percent of the world population living with HIV infection.[9]All countries in this region have an HIV seroprevalence rate that is above 5 percent, with some as high as 25 percent.[9]

Asia — Of the 4.5 million HIV-infected persons living in Asia, more than half live in India.[9] The estimates for India are based primarily on anonymous testing data from public clinics for prenatal care and for patients with other STDs.[9] Approximately 85 percent of HIV transmission in India is thought to be through sexual contact. In China, the government estimates that over one million people are infected with HIV, which represents an HIV prevalence of approximately 0.05 percent of the general population.[11] Among new HIV infections in China, 49 percent are caused by drug use and approximately 50 percent by sexual transmission.

Americas — After sub-Saharan Africa, the Caribbean has the second highest HIV seroprevalence rates in the world.[9]

Indian statistics

The 2006 estimates suggest national adult HIV prevalence in India is approximately 0.36 percent, amounting to between 2 and 3.1 million people with

an average figure of 2.5 million people living with HIV and AIDS; almost 50 percent of the previous estimate of 5.2 million. More men are HIV positive than women. Nationally, the prevalence rate for adult females is 0.29 percent, while for males it is 0.43 percent meaning, that for every 100 people living with HIV and AIDS, 61 are men and 39 women. Prevalence is also high in the 15-49 age group (88.7 percent of all infections), indicating that AIDS still threatens the cream of society, those in the prime of their working life. Adult HIV prevalence among the general population is 0.36 percent, among Injecting Drug Users (IDUs), it is as high as 8.71 percent, while it is 5.69 percent and 5.38 percent among Men who have Sex with Men (MSM) and Female Sex Workers (FSWs), respectively.[12]

MODES OF TRANSMISSION AND DYNAMICS OF THE EPIDEMIC

The major modes of HIV infection are [13, 14] :

- Sexual transmission, including via heterosexual and homosexual contact
- Parenteral transmission: predominantly among injection drug users (IDU), blood transfusions
- Perinatal transmission

HIV infection is predominantly a sexually transmitted disease (STD) worldwide. Despite the initial description of the disease among men who have sex with men (MSM) in the United States, more than 80 percent of infections occur through heterosexual transmission, throughout the world, and over 50 percent of all HIV-

infected people in the world are women.[15] In the United States, ~49% of the HIV/AIDS cases diagnosed in 2005 among adults and adolescents were attributed to male-to-male sexual contact. Heterosexual contact accounted for another 32%. The yearly incidence of new cases of AIDS attributed to heterosexual transmission of HIV is steadily increasing in the United States.[1] Worldwide, the most common mode of infection, particularly in developing countries, is clearly heterosexual transmission. Since the level of HIV infection is so high among women, the potential exists for large numbers of infected children, since infants can become infected with HIV in utero, at birth, or during breastfeeding. Mother-to-child transmission accounts for 90 percent of infection among children worldwide. In the worst-affected countries in the world, such as sub-Saharan Africa between 20 and 40 percent of pregnant women are HIV-infected, and one-third of their babies are infected.[7] IDU is fueling epidemics in central and eastern Europe and in some countries of Asia. It is also a major concern in industrialized nations and the Middle East. Within each region, each country, and each community, the HIV epidemic has established its own unique character, depending upon the time of introduction of the virus, the social fabric of that community, its culture, its sexual networks, the mobility of the people and the reaction of the government to mounting an AIDS control program.[13] Countries in sub-Saharan Africa and the Caribbean currently have the highest national rates of adult HIV prevalence.

PATHOGENESIS AND PROGRESSION OF DISEASE

HIV is a member of the lentivirus family of retroviruses. HIV appears as spherical particles that are approximately 110 nm in diameter, with knob like projections on the surface of the virus and a cone-shaped viral core.[16] The genome is organized into three major regions (gag, pol and env) and has six regulatory genes that are vital for its life cycle and pathogenicity .[17]

LIFECYCLE

In the lifecycle of HIV the first point of interaction consists of the binding of the HIV envelope surface protein gp120 with the CD4 receptor on the host cell assisted by co receptors, significantly CCR5 and CXCR4 expressed predominantly by macrophages and lymphocyte respectively, and the subsequent exposure of the other HIV envelope protein, gp41.

After the fusion of the viral and cellular membranes, the viral capsid enters the cell and the HIV reverse transcriptase enzyme converts the single stranded HIV RNA into a double stranded DNA, which then is integrated with host chromosome by the viral enzyme integrase. Cellular enzymes transcribe the provirus into mRNA which is then translated into the structural proteins or which serve as genomic RNA for progeny virus. Viral replication involve both the assembly of the viral particles, with each viral core incorporating two copies of the viral RNA genome,

and the budding and release of the virus from the cell surface mediated by HIV protease enzyme.

Disease progression

Shortly after acute HIV infection, HIV begins to preferentially destroy HIV-directed CD4+ helper T cells; this process impairs the critical interaction between host CD4+ T cells and CD8+ T cells and thus weakens the host CTL response. HIV extensively seeds lymphoid organs and the central nervous system. As a result, the infection persists, and continued rounds of replication lead to the gradual depletion of all CD4+ T cells. At the same time, a subset of activated, HIV-infected CD4+ cells returns to a quiescent state, remains latently infected.[20] The CD4+ T cell count provides an accurate way to assess the current immunologic status. The plasma HIV RNA level is strong independent predictor of the progression to AIDS in untreated HIV-infected persons.[19] In essence, the higher the HIV RNA level, the more rapidly the disease will progress.

CLINICAL FEATURES

Primary infection

Primary infection is symptomatic in 70-80% of infected individuals and usually occurs 2-4 weeks after exposure. The major clinical manifestations are fever (seen in 80% - 90%), rash (40%-80%), headache(32%-70%), lymphadenopathy (40%-

70%), pharyngitis (50%-70%) and myalgias or arthralgias (50%-70%) .[21] Acute HIV illness typically persists for less than 14 days, but some patients have had illnesses that have extended for longer than 10 weeks. The appearance of specific anti-HIV antibodies in serum takes place 3-12 weeks later, although very rarely seroconversion may take place after 3 months.

Asymptomatic stage - clinical latency

The median time of this stage is about 10 years during which HIV replication is ongoing and progressive. The rate of disease progression is directly correlated to with HIV RNA levels as stated above. Long term nonprogressors show little, if any, decline in CD+ T cell counts. During the asymptomatic phase, the average rate of CD4+ Tcells decline is 50/uL per year. When the CD4+ T cell count falls below 200/uL, the resulting immunodeficiency leads to symptomatic disease.

Symptomatic disease – AIDS

Acquired immunodeficiency syndrome (category c disease) is defined by the development of specified opportunistic infections, tumors etc.

Common AIDS defining conditions –

- Oesophageal candidiasis
- Cryptococcal meningitis
- Chronic cryptosporidial diarrhea
- CMV retinitis

- Chronic mucocutaneous herpes simplex
- Disseminated mycobacterium avium intercellulare
- Miliary or extrapulmonary tuberculosis
- Pneumocystis pneumonia
- Cerebral toxoplasmosis
- Kaposis's sarcoma
- HIV encephalopathy / PML
- Lymphoma

The listed AIDS defining conditions are as per revised CDC classification (1993) which categorizes persons on the basis of clinical conditions and CD4+ T lymphocyte counts.[22] For children less than 13 years of age, there is a modified and revised classification system for HIV infection. The WHO has also published a staging system for HIV infection. The WHO classification is an approach for use in resource limited settings and is widely used in African and Asian continents.

WHO STAGING OF HIV INFECTION

Clinical group – I

Acute HIV infection

PGL

Asymptomatic

Normal activity

Clinical group – 2 (early stage disease)

Weight loss less than 10%

Muco cutaneous problem

Herpes zoster

Recurrent URI

Normal activity

Clinical group – 3 (intermediate disease)

Weight loss less than 10%

Chronic diarrhea

Prolonged fever 1 month

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis

Severe bacterial infection

Bed ridden less than 50% of day (previous month)

DIAGNOSIS

The diagnosis of HIV infection depends upon the demonstration of antibodies to HIV infection is the ELISA, also referred to as enzyme immunoassay (EIA). This solid – phase assay is an extremely good screening test with a sensitivity of >99.5%. most diagnostic laboratories use a commercial EIA kit that contains

antigens from both HIV-1 and -2 and thus are able to detect either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensititvity to newly discovered species, such as group O viruses. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity.

The most commonly used confirmatory test is the western blot. This assay takes advantage of the fact that multiple HIV antigens of different, well characterized molecular weight elicit the production of specific antibodies. These antigens can be separated on the absis of molecular weight, and antibodies ot each component can be detected as discrete bands on the western blot.[23] A negative western blot is one in which no bands are present at molecular weights corresponding to HIV gene products.

While the western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20 – 30% may show one or more bands on western blot. While these bands are usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RNA PCR, RNA assay, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which is the product of the percent of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count (determined by WBC and differential percent) has been shown to correlate very well with the level of immunologic competence.

Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3 to 6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to most guidelines, a CD4 count <350 cells/cmm is an indication for initiating antiretroviral therapy, and a decline in CD4 cell count of >25% is an indication for considering a change in therapy.

INTRODUCTION OF ANTIRETROVIRAL THERAPY

The development of ART has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast and short lived trends. Since the introduction of zidovudine as monotherapy in 1987, the treatment options have grown rapidly. Research has unleashed an array of drugs in each of the class of drugs and newer classes of drugs are fast coming upon the horizon.

Currently the following classes of medications, target HIV :

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Abacavir, didanosine, emtricitabine, lamivudine, stavudine, zidovudine , zalcitabine & tenofovir

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Nevirapine, efavirenz, delavirdine are already existing

PROTEASE INHIBITORS (PIs)

Indinavir, saquinavir, ritonavir, nelfinavir, lopiinavir plus ritonavir, atazanavir

FUSION INHIBITORS - Enfuvirtide

INTEGRASE INHIBITORS – Raltegravir

CCR5 ANTAGONISTS – Maraviroc

Newer drugs and classes of drugs that have or about to join these popular drugs are

New NRTIs – Elvucitabine, Nicavir, Racivir, Stampidine, Apricitabine, KP-1461

New NNRTIs - Etravirine, Rilpivirine

New PIs – Darunavir, Brecanavir, tipranavir

New CCR5 antagonists – Vicriviroc

New integrase inhibitors – Elvitegravir

Drugs in the pipeline include – maturation inhibitors (Bevirimat) , attachment inhibitors, entry inhibitors, anti-CD4 antibodies[28] (Ibalizumab).

Mechanism of action:

NRTIs- structurally resemble human nucleosides that HIV uses to make viral DNA. The HIV reverse transcriptase enzyme can mistakenly incorporate the synthetic nucleoside analogue into the elongating strand of viral DNA during the reverse transcriptase process; once incorporated into viral DNA, the nucleoside anaologues act as chain terminators because they lack the 3′ hydroxy group required for chain elongation.

NNRTIs – directly inhibit the proper functioning of the reverse tarnscrioptase enzyme.

PIs – selectively bind to HIV protease and prevent this enzyme from performing its normal function of cleaving viral polyprotein precursors into individual functional proteins.

FUSION INHIBITOR – works by binding to gp41 envelope protein of HIV to prevent it from mediating fusion of viral and cell membranes.

INTEGRASE INHIBITORS - HIV integrase is an enzyme which inserts viral DNA into the cellular genome through two catalytic reactions essential for viral life cycle. Integrase inhibitors act at this step and disrupt the viral replication.

CCR5 antagonists - HIV enters CD4+ T-cells via the chemokine receptor 5 (CCR5) or CXC chemokine receptor 4 (CXCR4 coreceptor). These drugs act at this step and prevent the virus from entering the cells. Viral strains from patients with early stage disease usually use CCR5 coreceptors, whereas one-half of viral strains from patients with advanced immunosuppression enter via either the CXCR4 coreceptor alone, or both ("dual/mixed" tropic viruses).Because CCR5 antagonists are not active against CXCR4 or dual-mixed tropic viruses, a pretreatment screening test should be used to assess viral tropism.[1]

HAART – IT'S IMPLICATIONS

Zidovudine (ZDV/AZT) was the first nucleoside analog to be approved for the treatment of HIV infection in 1987.[29] In the late 1980's and early 1990's, monotherapy treatment trials using nucleoside reverse transcriptase inhibitors led to only transient clinical and immunologic improvement. ZDV led to clinical benefit and immunologic improvements in patients with advanced HIV disease; while in asymptomatic disease, no benefit of early versus deferred monotherapy was seen. Two large trials (Delta trial, ACTG 175 trial) suggested that use of dual nucleoside analog therapy was superior to monotherapy in reducing the combined endpoints of declining CD4 cell counts, onset of AIDS, or death. The ACTG 320 trial was a landmark study, which proved that triple therapy with two NRTIs plus a

protease inhibitor was superior to dual NRTI therapy alone in reducing AIDS-related complications and deaths. With this major breakthrough in clinical management of HIV infection, the three-drug therapy (including two different classes of drugs) was used to lower HIV RNA below the level of detection. This approach to treatment dramatically reduced the development of drug resistance and frequently led to both durable virologic suppression and long-term clinical benefits.[30]

The term 'highly active antiretroviral therapy' or combination antiretroviral therapy (ART) gained widespread acceptance since 1996 when the new class of protease inhibitors were approved for use and is the corner stone of management of patients with HIV infection. Since then HAART has maintained itself as the first line of defence against HIV infection. Traditionally HAART consists of combination of three or more drugs in any of the following class, not necessarily in the same order: NRTI + NRTI + NRTI / NNRTI / PI. In the earlier phase HAART was shown to reduce, the incidence of AIDS defining conditions in Europe from 30.7 to 2.5 per 100 patient years between 1994 and 1998 which was replicated in USA and elsewhere. [31]

HAART adverse effects

In 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs.[26] Realization about lipodystrophy, a new term, followed by mitochondrial toxicity.[27] Reinforced the dictum: all effective drugs have side effects. The initial euphoria over eradication of viral load with HAART has turned bleak with HIV remaining detectable in latently infected cells, even after long term suppression and the most recent estimate for eradication of these cells standing at 73.3 years .[32] This has led us to coexist with the spectrum of dramatic improvement in the standard of living standard of HIV infected individuals on one hand and hitherto unheard of toxicities of associated with daily consumption of loads of drugs on a long term basis. Treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. Common side effects associated with HAART are [1]:

ZDV - Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea

ddI - Pancreatitis, peripheral neuropathy, abnormalities on liver function tests, lactic acidosis, hepatomegaly with steatosis

ddC - Peripheral neuropathy, pancreatitis, lactic acidosis, hepatomegaly with steatosis, oral ulcers

d4T - Peripheral neuropathy, pancreatitis, lactic acidosis, hepatomegaly with steatosis, ascending neuromuscular weakness, lipodystrophy.

Abacavir - Hypersensitivity reaction (can be fatal), fever, rash, nausea, vomiting, malaise, fatigue, loss of appetite.

Nevirapine - Skin rash, hepatotoxicity.

Efavirenz - Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression.

PIs - Diarrhea, nausea, headaches, hyperglycemia, fat redistribution, lipid abnormalities.

Maraviroc - Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, fever, musculoskeletal symptoms.

Raltegravir - Nausea, rash.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Following the initiation of effective ART, a paradoxical worsening of preexisting, untreated, or partially treated opportunistic infections may be noted in the form of localized lymphadenitis, prolonged fever, pulmonary infiltrates, increased intracranial pressure, uveitis, and Graves' disease. These IRISs are particularly common in patients with underlying untreated mycobacterial infections. They are seen in 10–50% of patients, depending upon the clinical setting, and are most common in patients starting therapy with CD4+ T cell counts <50 cells/cmm, high viral load who have a precipitous drop in HIV RNA levels following the initiation of HAART.[1] Signs and symptoms may appear anywhere from 2 weeks to 2 years after the initiation of HAART. Underlying mechanism appears to be related to a phenomenon similar to type IV hypersensitivity reactions and reflects the immediate improvements in immune function that occur as levels of HIV RNA drop, CD4+ cell count increase and the immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reactions while specific antimicrobial therapy takes effect. Data from resource-limited countries on TB IRIS is scarce; a rate of 8% was reported from India.[85] Crisis seem to be alarming in third world nations, where the proportion of HIV/TB IRIS is reportedly high, ranging from 11% to 43%.[86-89]

Monitoring of patients with HIV

CD4+ T Cell Counts

It is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement has been shown to correlate very well with the level of immunologic competence. CD4+ T cell measurements are performed at the time of diagnosis and every 3–6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to most guidelines, a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy. Once the CD4+ T cell count is <200/cmm patients should be placed on a regimen for P. jiroveci prophylaxis, and once the count is <50/cmm primary prophylaxis for MAC infection is indicated.

HIV RNA Determinations

Plasma HIV RNA (viral load) has become an essential component in the monitoring of patients with HIV infection. The two most commonly used techniques are the RT-PCR assay and the bDNA assay. Both assays generate data in the form of number of copies of HIV RNA per milliliter of serum or plasma. Measurements of changes in HIV RNA levels over time have been of great value in delineating the relationship between levels of virus and rates of disease

progression, the rates of viral turnover, the relationship between immune system activation and viral replication, and the time to development of drug resistance. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–6 months thereafter in the untreated patient. In general, most guidelines suggest that therapy be considered in patients with >100,000 copies of HIV RNA per milliliter. Following the initiation of therapy or any change in therapy, plasma HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. During therapy, levels of HIV RNA should be monitored every 3–4 months to evaluate the continuing effectiveness of therapy.

HIV Resistance Testing

The availability of multiple ARV drugs as treatment options has generated a great deal of interest in the potential for measuring the sensitivity of an individual's HIV virus to different ARV agents. HIV resistance testing can be done through either genotypic or phenotypic measurements These tests are quite good in identifying those ARV agents that have been utilized in the past and suggesting agents that may be of future value in a given patient. Drug resistance testing in the setting of virologic failure should be performed while the patient is still on the failing

regimen because of the propensity for the pool of HIV quasispecies to rapidly revert to wild-type in the absence of the selective pressure of ARV therapy. Resistance testing enhances the short-term ability to decrease viral load by ~0.5 log compared to changing drugs merely on the basis of drug history. In addition to the use of resistance testing to help in the selection of new drugs in patients with virologic failure, it may also be of value in selecting an initial regimen for treatment of therapy-naïve individuals. This is particularly true in geographic areas with a high level of background resistance.

HAART in resource poor settings

With the wide spread use of HAART, dramatic decrease in the morbidity and mortality associated with HIV infection throughout the developed world was seen. As a result, the gap between outcomes for HIV-infected persons in the developed world and outcomes for those in the developing world began to widen. It was seen that more people with HIV(> 95% of total HIV infected population) were living in developing countries and the epidemic continuing, where ART was still inaccessible due to the high cost of drugs, poverty, illiteracy and ignorance.[36] There were lot of concerns regarding the feasibility of ART programs in resource poor settings and also adherence to therapy. Providing antiretroviral therapy involves more than just dispensing of medications, and a variety of problems,

including the prevailing limitations in health infrastructure and human resources in the countries most heavily affected by the HIV/AIDS pandemic, have been mentioned as reasons to expect failure of treatment programs. [33] With all these factors, the need to close the treatment gap was declared a global public health emergency in 2003 by WHO. The "3 by 5" initiative, launched by UNAIDS and WHO in December 2003, was a global strategy to provide antiretroviral therapy to three million people living with HIV/AIDS in 50 developing countries by the end of 2005. By the end of 2005 the WHO estimated that there were just over 1.3 million people receiving antiretroviral therapy (ART) in low-income and middle-income countries, representing 20% of the 6.5 million estimated to need it. This program was subsequently replaced by The Global Fund for AIDS, Tuberculosis and Malaria as well as bilateral support like the President's Emergency Plan for AIDS Relief (PEPFAR). By the end of 2007, the number of AIDS patients receiving ARVs had risen from less than 50,000 to 2.2 million over a five-year period in low and middle income countries in sub-Saharan Africa.[7] The development of generic medications has been an important advance in making ART available in resource-poor countries.[34]

Indications for starting ART : All HIV positive persons with CD4 count less than 200 cells/cmm, irrespective of clinical stage, all HIV positive persons in stage 4

disease irrespective of CD4 count, patients in stage 3 with less than 350 cells/cmm.[35]

Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers.[36]

WHO clinical staging	CD4 testing not available	CD4 testing available
1	Do not treat **[A-III]**	Treat if CD4 count is below 200 cells/mm^3 [a] **[A-III]**
2	Do not treat [b] **[B-III]**	
3	Treat **[A-III]**	Consider treatment if CD4 count is below 350 cells/ mm^3 [a c d] and initiate ART before CD4 count drops below 200 cells/mm^3 [e] **[B-III]**
4	Treat **[A-III]**	Treat irrespective of CD4 cell count **[A-III]**

Drugs recommended : The public health approach to ART scale-up in resource-limited settings aims to support the development of treatment programmes that can reach as many people as possible. Countries are encouraged to use the public health approach to support and facilitate wider access to ART. Countries select a firstline regimen and a limited number of second-line regimens, for those individuals who cannot tolerate or fail the first-line. Firstline regimens include 2NRTI+1NNRTI. It is recommended that PIs be reserved for second-line therapy because their use in an initial treatment regimen essentially rules out second-line options in resource poor settings.[36] PIs as initial therapy with a standard dual

NRTI backbone are an option for the treatment of viral types with intrinsic resistance to NNRTIs (e.g. HIV-2). Availability of second line ART drugs are limited to few resource poor countries due to the high cost of therapy and also sophisticated laboratory monitoring (viral loads, mutation testing) .

Treatment failure: following definitions of ART failure are used [36]:

Clinical failure [a]	New or recurrent WHO stage 4 condition [b c]
CD4 cell failure [d]	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • persistent CD4 levels below 100 cells/mm³ [e]
Virological failure	Plasma viral load above10 000 copies/ml [f]

Indian scenario

The free ART initiative in India was launched on 1st April, 2004. The guide lines for ART in resource constraints settings were framed by NACO during a national consultation in january 04 and were further modified in December 2005 and 2006.[12] Indications for starting are the same as those in other resource constraint settings shown in the above table. Currently, the national programme provides the following first-line regimen drugs: stavudine (30mg), lamivudine (150mg), zidovudine (300mg), nevirapine (200mg), efavirenz (600mg) either singly or as fixed drug combinations. Recommended first-line antiretroviral regimens are:

Zidovudine + lamivudine + nevirapine → preferred first line regimen.

Zidovudine + lamivudine + efavirenz ⟶ alternate first line regimen

Stavudine + lamivudine + nevirapine / efavirenz ⟶alternate first line regimen

Tenofovir + lamivudine + nevirapine / efavirenz and zidovudine + lamivudine + tenofovir are other options available under special considerations.

Second line drugs were not available under the national programme until may 2008 in India, after which they were made available only in select larger centres.

HAART outcomes in resource poor settings:

Most of the reports/studies are from African continent and few from asian continent.

1) **Clinical outcomes :** In all studies, clinical outcomes improved with HAART.
    a) Weight gain : Among 14 studies that reported on weight trends, the weight gain ranged from 1.5–10.7 kg, showing an increase in weight with treatment. [37-51]
    b) The mortality rate ranged from 0% – 27%. [37-51, 53, 55, 57–65, 67-70]
    c) Three studies presented the probability of survival at the ends of their investigations, which ranged from 70% to 86.3%. [55, 56, 67]
    d) Adverse events to drugs occurred in 14.3%–80.2% of patients in studies. [37-40, 54, 57, 61]Three studies reported that 10%–62% of patients experienced specific types of adverse events, with dizziness, anemia, rash, neutropenia, and peripheral neuropathies occurring most frequently.

e) Opportunistic infections: Five studies reported that 5%–15% of patients had developed either CDC category C HIV-related events, AIDS-defining illnesses, or opportunistic infections generally. [38,49,51,58,60] In the latter case, the opportunistic infections that most commonly emerged were tuberculosis and candidiasis. Thirty percent of Senegalese patients taking a once-daily regimen were hospitalized for opportunistic infections. [37] Two other studies found that 5% of patients had to change treatments or withdraw from the study as a result of tuberculosis. [54, 59] One study determined that opportunistic infections decreased by 68% due to HAART.[57]

1) Laboratory outcomes :

a) CD4 cell counts : Patients were at an advanced stage of HIV at the start of therapy as indicated by initial CD4 count of less than 50 cells/cmm in many studies. Most of the studies demonstrated gain in CD4 counts. Increases in the CD4 cell count ranged from 74 to 440 cells/mm3 at the ends of studies, with median increases of 138.6 cells/mm3. [40-43,45,46, 52,55-60] Only few studies reported CD4 cell count increase of less than 100 cells/mm3 over the duration of treatment follow-up [38, 39, 44, 47, 54]

b) viral loads : Most of the studies demonstrated a decline in viral load, undetectability ranged from less than 50 to less than 500 copies/mL. In

the 21 studies that reported viral load outcomes, the percentage of patients who had viral loads that were less than the cut off values by the end of the study varied from 32% to 95%, with a median of 73% of patients achieving undetectability. [37-54, 57, 58, 61, 65–68] ART resulted in an HIV RNA viral load suppression in 60%–70% of individuals at time points up to month 18. This proportion of individuals who had viral suppression is similar to that observed in developed countries, even in clinical trials. [67,72-74]

2) Adherence to treatment: Adherence to treatment was highlighted as an issue in 10 studies. The percentage of patients who took more than 95% of treatment doses ranged from 68% to 99%.[37–39, 45, 47, 54] Oyugi et al. determined an average adherence rate of 85% using 4 different methods (pill count, self-report, visual analogue scale, and Medication Event Monitoring System technology). [40] A Nigerian study that compared cohorts aged less than 55 years with cohorts aged more than 55 years found that the older patients had an adherence rate of 91%, whereas the younger patients had a reported adherence rate of 76%. [49]

3) Retention : Eighteen studies documented retention of cohorts as ranging from 53.8% to 100% over a mean duration of follow-up of 12 months. [37–43, 46–49, 51, 53,55, 57, 59, 60, 62, 63, 65]

Conclusions : Review of studies analyzing ART programs in economically backward countries provides promising evidence for the administration of HIV treatment in resource-poor settings. Essentially all studies reported high rates of adherence and optimistic outcomes comparable to those of developed countries. [71]

Pooled data from these studies are encouraging, because ~70% of the patients had undetectable HIV viral loads (defined as an HIV RNA level of less than 400 copies/mL) at month 6 after initiation of antiretroviral therapy, and 57% at month 12. These virologic response rates approximate the rates found in similar clinical trials that, until now, have been conducted mostly in developed countries. Data also suggest that patients who received antiretroviral therapy free of charge had an almost 30% higher chance of having an undetectable HIV viral load after therapy than did patients who had to pay for all or part of their drug therapy. [75] Preliminary results show the major benefits brought by HAART in resource-poor settings, even for patients at an advanced stage of AIDS. Patients show regular attendance, and immunological and virological responses indirectly indicate a high level of individual drug adherence. Regardless of the need for operational research, these results support the belief that treating severely immunocompromised AIDS patients is feasible in various settings, including in peripheral health facilities, as has also recently been reported by Ugandan and Senegalese national initiatives.[76] Observational data presented by MSF at the International AIDS Conference in

Bangkok included findings for 112,000 adults who have been treated in 31 MSF programs in 16 resource poor countries, which demonstrated that most patients experienced a 3–5 kg weight gain and an increase of 135 cells/mL in CD4 cell counts at month 12 of antiretroviral treatment. [77] Similarly, Zhou et al. published findings from an observational cohort of antiretroviral-naive Asian patients receiving HAART and found 69% of patients showed a virologic response (i.e., had an HIV RNA load of < 400 copies/ mL) at month 6. [78] The WHO guidelines provide an appropriate framework, as reflected by the ability for the studies reviewed to employ recommended regimens and regular monitoring strategies The results demonstrated have strong implications for current treatment initiatives, including those administered by national governments and the President's Emergency Plan for AIDS Relief.

MATERIALS AND METHODS

Settings

ART CENTRE, Institute of internal medicine,

Madras Medical College and Government General Hospital

Chennai - 600 003.

Ethical approval

Obtained

Study duration

This study was conducted for a period of eighteen months from 1st January 2007 to June 30, 2008.

Study Design

To evaluate the effectiveness of HAART in antiretroviral-naïve adults, attending the ART centre; a single centre prospective cohort study.

Inclusion criteria

All HIV positive patients started on HAART within 2 months of diagnosis. attending ART centre from January 1st 2007.

Age > 18 yrs.

In WHO clinical stage III / stage IV or with CD4 count < 200 cells/cmm.

Patients with no history of antiretroviral therapy (ART naïve).

Exclusion criteria

All HIV positive patients not started on ART.

Patients not started on ART for more than 2 months from diagnosis.

Age < 18 yrs.

In WHO clinical stage I/II or with CD4 count > 200 cells/cmm.

On previous antiretroviral therapy at any point (non ART naïve).

Laboratory Methods

Testing for HIV 1 and 2 had been performed on each patient using ELISA technique. For those with positive results on the first ELISA test, a second more specific ELISA was used for confirmation. Western blot technique was not used for confirmation. Full blood count, blood sugar, urea, creatinine, liver function tests were done. CD4 count was performed for all HIV positive patients using flow cytometry. Chest X ray and other tests were done only when there was a clinical suspicion and not routinely.

METHODS

Study population

A total of 461 patients were enrolled for the study from the population of HIV infected patients who attended the ART clinic, Institute of Internal Medicine, from the period between 1st January 2007 to December 31st 2007.

221 patients were excluded as per exclusion criteria. The remaining 240 patients were selected for the study, who satisfied all the inclusion and exclusion criteria, were followed till june 30th 2008. Written consent was obtained from all patients participating in the study.

All patients with HIV referred to ART centre were subjected to a detailed clinical history regarding their marital status, risk factors for HIV, possible route of acquisition, history of opportunistic infections, sexually transmitted infections, previous HIV testing, medication/drug use, comorbidities like diabetes, hypertension, hepatitis B/C, history of vaccination, allergy, history of smoking/alcoholism. A thorough physical examination done for screening and clinical staging.

Initial investigations included complete blood count, renal function tests, liver function tests, CD4 count, sputum examination for TB bacilli and chest x ray for those with cough

Patients who were in stage III/IV of WHO staging and those with CD4 count less than 200 irrespective of stage were eligible for therapy. ART was started for these patients before which they were given counseling regarding the nature of the disease, need for life long therapy, effects and side effects of therapy, need for durg adherence. Consultation frequency was determined by clinical protocol; fortnightly for the first month and then monthly. They were seen more frequently if clinically

indicated. CD4 count and other investigations mentioned above were done at baseline and every six months thereafter. Standardized flow chart algorithms for the management of adverse events were in place as per NACO guidelines.

Eligible patients were started on triple therapy including 2NRTIs + 1NNRTI. Stavudine, lamivudine, nevirapine were the drugs routinely prescribed. Single-drug substitutions were permitted: zidovudine could be substituted for stavudine, and efavirenz could be substituted for nevirapine when they developed some adverse effects to routine drugs, when they were on concomitant ATT or when routine drugs were out of stock. HIV-infected adults and adolescents with pulmonary tuberculosis and a CD4 T-cell count of more than 200 per cubic millimeter were treated for tuberculosis, and initiation of antiretroviral therapy was deferred. In patients with tuberculosis who had a CD4 T-cell count less than 200 per cubic millimeter, antiretroviral therapy was initiated after the completion of two weeks of tuberculosis therapy. Second line drugs were not available at our ART centre. When patients missed 3 consecutive visits, two or more attempts were made to contact them before considering them lost to follow up. Once HAART was initiated, patients returned to the ART centre at monthly intervals for medical evaluation, adherence education, and medication refills. Adherence to therapy was checked by pill count, returning of empty contrainers and self reporting at every follow up.

Clinical services were provided at the ART centre by a team comprising of doctors, nurses and counsellers with good continuity of care. A strong patient centred approach was used to promote adherence. This included a comprehensive counseling infrastructure providing for one to one individual counselling with trained counselors.

FINANCIAL SUPPORT: nil.

CONFLICT OF INTEREST: nil.

Statistical analysis:

Data analysis was done with use of SPSS, version 10. Descriptive statistics were used to calculate the frequency, mean, median, and standard deviation. To examine the linear trend of the proportions, trend chi-square was used and to find the test of association chi-square was computed. For all normally distributed variables, Student's *t* test was used to determine the significant mean difference in various groups. Survival times were calculated from the date of the participant's initiation of ART to the last day of study follow-up for each participant. Kaplan-Meier survival analysis was performed to determine the mean and median durations of survival in relation to the demographic variables, CD4 cell count, and antiretroviral therapy. Tarone-Ware statistics were used to test the equality of the survival distributions for all of the variables. Multivariate Cox regression analyses for all factors relating to survival of patients were done.

OBSERVATION AND RESULTS

The analysis included 240 adults who were selected after considering the inclusion and exclusion criteria and started on ART. The median follow up time was ten months for all the 240 patients and 14 months for those surviving at the end of study.

Baseline characteristics

Baseline characters of 240 ART naïve patients are given in table below. More men (73.3%) than women accessed treatment. Median age of the patients was 36 years. Most (90%) were married. Predominant route of acquisition of HIV was heterosexual (97.1%). Patients began treatment with advanced disease as evidenced by low cd4 count, advanced WHO stage. The median baseline CD4 lymphocyte count was 122cells/cmm. 84 patients (35%) were in WHO stage IV, 114 patients (47.5%) were in stage III, 29 (12.1%) were in stage II, 13 patients (5.4%) were in stage I.

Antiretroviral treatment initiation

70.8% of patients were started on stavudine, lamivudine, nevirapine regimen; 17.5% started on zidovudine, lamivudine, nevirapine regimen; 10% started on stavudine, lamivudine, efavirenz regimen; 1.7% started on zidovudine, lamivudine, efavirenz regimen.

Base line characteristics of patients enrolled in the study	
Characteristic	Value
Total patients enrolled	240
Male	176 (73.3%)
Female	64 (26.7%)
Median age	36 yrs
Married	216 (90%)
Unmarried	24 (10%)
Route of acquisition of HIV	
Heterosexual	233 (97.1%)
Male having sex with male (MSM)	4 (1.7%)
Intravenous drug use (IVD)	2 (0.8%)
Blood transfusion (BT)	1 (0.4%)
WHO stage	
Stage I	13 (5.4%)
Stage II	29 (12.1%)
Stage III	114 (47.5%)
Stage IV	84 (35%)
Median body weight in kg	48 (min-max of 26 to 74)
Median body mass index	17.78 (min-max of 11.56 to 29.55)

Median CD4 cell count/cmm	122 (min-max of 5 to 495)
Median Hemoglobin in g/dl	9.5 (min-max of 5.5 to 15)
Initial ART regimen –	No. %
stavudine, lamivudine, nevirapine	170 (70.8%)
stavudine, lamivudine, efavirenz	24 (10%)
zidovudine, lamivudine, nevirapine	42 (17.5%)
zidovudine, lamivudine, efavirenz	04 (1.7%)

Survival and patient retention at the time of data analysis

At the time of analysis, of 240 patients enrolled in the study, 162 (67.5%) were still under follow up, 35 patients (14.5%) were lost for follow up and 43patients (17.9%) died. Of the 35 patients lost to follow up, 9 patients were transferred within 3 months of starting ART, 1 patient was transferred at 5 months. The whereabouts of rest 25 patients were not traceable, and were lost within 3 months after start of therapy, and it was not known if they were alive or dead at the time of analysis. The main reason for lost to follow up was their leaving the city to return to their native villages.

Of 43 deaths, 8 (18.6%) were due to pneumocystis jiroveci pneumonia, 3 (6.9%) due to cryptococcal meningitis, 11 (25.5%) due severe wasting of which 5 had

chronic diarrhoea, 13 (30.2%) died of tuberculosis of which 4 had disseminated TB, 5 had meningitis, 4 had pulmonary TB, 1 (2.3%) died of squamous cell carcinoma of lung, 1 died of HIV encephalopathy, 1 due to severe bacterial pneumonia, 3 (6.9%) died of massive haematemesis of which 1 had extrahepatic portal vein obstruction with hepatitis B, 1 had liver cirrhosis with hepatitis B and one more with hepatitis C. Factors present at baseline which were predictors of death were presence of AIDS defining illness, low CD4 count, low body mass index and low haemoglobin. Of the deaths due to HIV, 35 (81.3%) occurred within the first 3 months of starting therapy yielding an estimate of survival of 79% for all the patients followed. Eighty three patients began treatment with a CD4 count of less than 100 cells/cmm. Estimates of survival at 18 months stratified by initial cd4 lymphocyte count were 56.7% for those initiating treatment with less than 50 cells/cmm and 82.9% for those with more than 50 cells/cmm.

CD4 T cell response:

103 (42.9%) patients had CD4 count less than 100, 97 of them had CD4 count between 100 to 200 cells/cmm and 40 (16.7%) had more than 200 cells/cmm. Median CD4 count at baseline was 122, at 6 months 277 and at 12 months 338. Of the 205 patients only 3 patients had a decrease in CD4 count from baseline. Mean CD4 cell gain at 6 months was 162 cells/cmm (95% CI, 140 to 183) and gain at 12

months, from baseline was 225.7 cells/cmm (95% CI 193 to 258 cells/cmm) which was very significant (p=0.000). 32.5% of patients in <100 count group died whereas around 13% patients died in the other two groups. The proportion of patients surviving increasing significantly (p<0.005) as the cd4 count increased from baseline.

CD4 Groups	Number of Pts	Percentage
< 100	103	42.9
100 – 200	97	40.4
> 200	40	16.7
Total	240	100

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed
		Mean	Std. Deviatio	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	CD4__0 - CD4__6	-162.07	136.84	10.78	-183.37	-140.78	-15.029	160	.000
Pair 2	CD4__6 - CD4___12	-59.23	109.09	12.05	-83.20	-35.26	-4.917	81	.000
Pair 3	CD4__0 - CD4___12	-225.74	156.51	16.32	-258.15	-193.33	-13.835	91	.000

CD4_0 → CD4 count at baseline (0 months) **CD4_6 → CD4 count at 6 months**

CD4_12 → CD4 count at 12 months

CROSS TABLE

CD4 Groups	Died	Survived	Total
< 100	27 (32.5%)	56 (67.5%)	83
100 - 200	11 (12.8%)	75 (87.2%)	86
> 200	5 (13.9%)	31 (86.1%)	36
Total	43 (21%)	162 (79%)	205

Weight gain :

Of 240 patients 130 (54.2%) had BMI less than 18; 83 patients (34.6%) had BMI between 18 - 22.9 and 27 patients (11.3%) had BMI more than 23. Mean weight gain at 6 months was 3.73 kgs and mean weight gain at 12 months from baseline was 4.43 kgs with almost all patients showing an increase in weight which was statistically significant (P=0.000). 25.5% of patients died in BMI group <18 whereas that of the other two goups were 11.8% and 8% respectively, which shows that the proportion of survival is increasing as BMI increases and the linear association, is statistically significant.

Patient cohort divided into BMI Groups:

BMI Groups	Number of patients	percentage
< 18	119	49.6
18 – 22.99	83	34.6
> 23	27	11.3
Missing data	11	4.6
Total	240	100

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed
	Mean	Std. Deviat	Std. Erro Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 WT_0 - WT_6	-3.74	4.93	.37	-4.47	-3.00	-10.03	174	.000
Pair 2 WT_6 - WT_12	-.37	4.11	.45	-1.26	.52	-.823	83	.413
Pair 3 WT_0 - WT_12	-4.43	6.37	.67	-5.77	-3.10	-6.602	89	.000

WT_0 → weight at baseline (0 months) **WT_6 → weight at 6 months**

WT_12 → weight at 12 months

CROSS TABLE:

BMI Groups	died	survived	total
<18	24 (25.5%)	70 (74.5%)	94
18 – 22.99	9 (11.8%)	67 (88.2%)	76
> 23	2 (8%)	23 (92%)	25
Total	35 (17.9%)	160 (82.1%)	195

Haemoglobin response:

Of 240 patients, data was available for 201 patients, of which 14 patients were in Hb less than 7g/dl group, 109 patients were in Hb 7 to 10g/dl group and 78 patients were in Hb more than 10g/dl group. Mean gain in Hb at 6 months was 0.7g/dl and mean gain at 12 months from baseline was 1.28g/dl with almost all patients showing an increase in Hb which was statistically significant (P=0.000). 71.4% of patients died in less than 7 Hb group, and 30.3% died in Hb 7-10 group, where as none died in more than 10 Hb group, which shows that proportion of patients surviving increased as haemoglobin increased, which is statistically significant

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 HB_0 - HB_6M	-.706	1.171	033E-02	-.884	-.528	-7.815	167	.000
Pair 2 HB_6M - HB_1	-.824	.666	944E-02	-.962	-.686	-11.865	91	.000
Pair 3 HB_0 - HB_12	-1.284	1.283	.134	-1.549	-1.018	-9.595	91	.000

CROSS TABLE

Hemoglobin	died	survived	Total
< 7	10 (71.4%)	4 (28.6%)	14
7 - 10	33 (30.3%)	76 (69.7%)	109
> 10		78 (100%)	78
Total	43(21.4%)	158 (78.6%)	201

Opportunistic infections:

167 (69.58%) of total 240 patients developed one or the other opportunistic infection. Of these 167 patients, 81(48.5%) had some opportunistic infection at the time of diagnosis of HIV, 50 of whom had AIDS defining illness. The rest 86 patients (51.5%) developed some opportunistic infection after the start of ART. Of

them 27 patients developed AIDS defining illness, of which except for 3 patients, the rest(24) developed infection within 2 months of start of therapy. The most common AIDS defining infection was extrapulmonary TB, pulmonary TB was not considered as AIDS defining infection.

Tuberculosis :

66 patients (27.5%) of 240 had TB, of which 29 patients were detected to have TB at diagnosis and the rest 37 developed new onset TB during the course of therapy. Of these 37 patients, 13 patients (45.9%) developed TB within 4 months of initiation of therapy. Of the total 66 patients, 28 (42.4%) developed pulmonary TB, 33 patients (50%) developed extra pulmonary TB and 5 patients (7.5%) developed disseminated TB. Of the 66 patients who developed TB, 13 patients died, 10 were lost to follow up and the rest were declared cured.15 patients (22.7%) of 66 had features suggestive of immune reconstitution inflammatory syndrome in the form of worsening of symptoms like increase in size of lymph nodes, increase in fever and cough, though it was not severe enough to warrant stopping of ART.

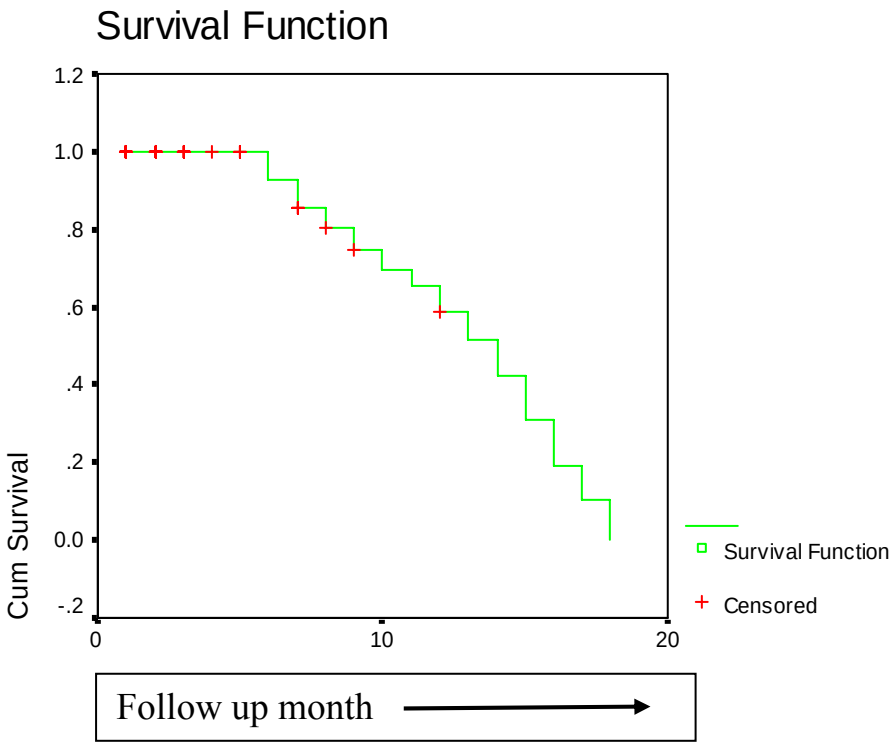
First line medication changes and toxic effects :

28 patients (11.6%) of a total of 240 started on ART, changed their initial regimen. Of them 15 patients (53.5%) changed as they developed new onset TB, 12 patients (42.8%) changed their initial regimen as they developed adverse reaction to ART. Nevirapine was the drug which caused most adverse effects, mainly skin rash,

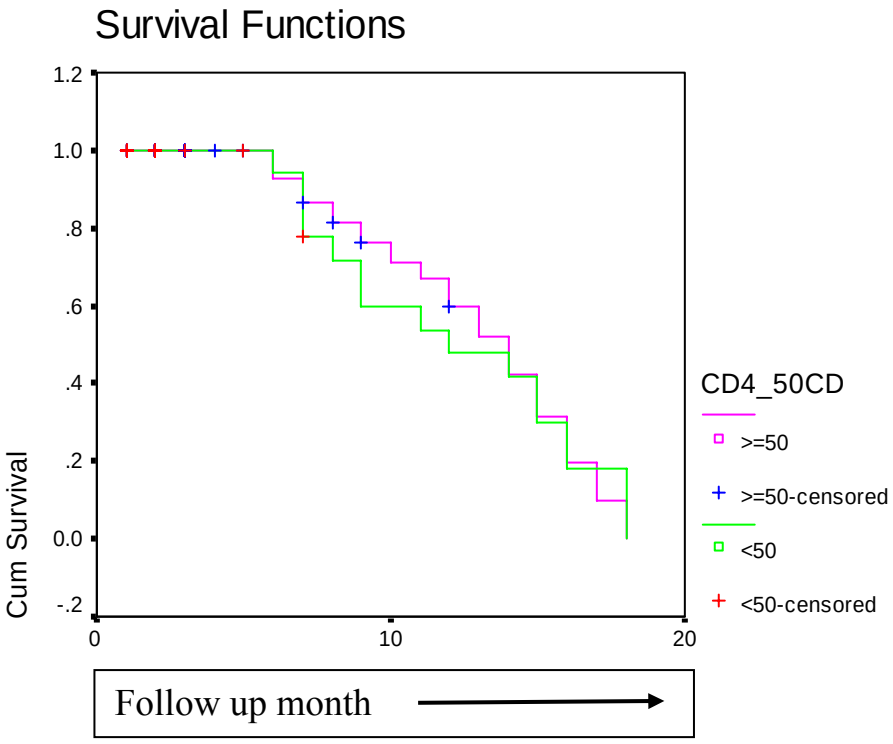
which 6 patients developed of which 2 had grade III reaction and the rest grade II; 3 patients developed severe anaemia (grade III) and 1 patient developed severe vomiting (grade III) after being started on zidovudine and 2 patients developed peripheral neuropathy induced by stavudine. ; 1 patient (3.5%) on zidovudine based regimen changed, as he developed severe anaemia (drug induced) and new onset TB. 67.8% of patients changed their initial regimen, within 3 months of the start of therapy.

Kaplan meire survival analysis :

The median survival time for all patients under follow up was 14 months (95% CI 13 – 15) as shown below in the fig.



The mean survival time for the patients who had cd4 <50 at the baseline was 12 months (95% CI 10 - 14); in case of cd4>50, mean survival time was 13 months (95% CI 12 - 14), and there was no statistically significant difference in the survival distribution (p>0.05) which is shown in the fig. below.



Adherence to therapy :

More than 95% of patients who were under follow up until till the end of study took more than 95% of doses, which was confirmed by self reporting and pill count

at the each visit, which implies a very high adherence to therapy. Most common reason for non-adherence was due to them going out of station for work.

Multivariate analysis:

There was no significant($p>0.05$) association b/w gender, age group, WHO staging, cd4 counts, and survival on multivariate analysis.

The odds ratio of mortality was 1.3 times higher in cd4 <100 group compared to the group who had cd4>200 and this is the same for the cd4 group 100 to 200, which is not statistically significant.

Discussion :

HIV infection/AIDS is a global pandemic, with cases reported from every country throughout the world with about 35 million deaths already and 33 million infected individuals. HAART is a novel treatment available since 1996, which has dramatically changed the evolution of HIV infection. With the introduction of this therapy HIV has been changed from a fatal condition to a chronic manageable illness. In developed countries, marked advances in HIV antiretroviral therapy have resulted in significant increase in the survival rate and quality of life of HIV-infected individuals. As a result, the gap between outcomes for HIV-infected persons in the rich developed world and the poor developing world began to widen. The need to close this treatment gap was declared a global public health emergency by WHO in 2003. The "3 by 5" initiative, launched by UNAIDS and WHO in December 2003, was a global strategy to provide antiretroviral therapy to people in developing countries. From then on HAART became available in resource poor countries. The early outcomes of HAART in our population in this study are as follows:

More men (73.3%) than women accessed treatment and median age of the patients was 36 years which is similar to a number of studies in resource poor settings,[37,43,44,84] Patients began treatment with advanced disease as evidenced by

low cd4 count, advanced WHO stage. The median baseline CD4 lymphocyte count was 122cells/cmm and 82.5% of the study population was in stage III and IV disease. 70.8% of patients were started on stavudine, lamivudine, nevirapine regimen; 17.5% started on zidovudine, lamivudine, nevirapine regimen; 10% started on stavudine, lamivudine, efavirenz regimen; 1.7% started on zidovudine, lamivudine, efavirenz regimen.

Survival outcomes:

Of 240 patients enrolled in the study, 162 (67.5%) were alive and 43patients (17.9%) died. Factors present at baseline which were predictors of death were presence of AIDS defining illness, low CD4 count, low body mass index and low haemoglobin. Of the deaths due to HIV, 35 (81.3%) occurred within the first 3 months of starting therapy yielding an estimate of survival of 79% for all the patients followed. Estimates of survival at 18 months stratified by initial cd4 lymphocyte count were 56.7% for those initiating treatment with less than 50 cells/cmm and 82.9% for those initiating treatment with more than 50 cells/cmm. These results are comparable with data from observational settings in both developed and developing countries. In spite of differences in reporting, patients in this study initiated therapy with almost same stage of disease as other studies,[37,84] and using survival as an endpoint, have responded to treatment at least as well, as them.[37,84]The median survival time of patients with cd4 count less than 50

cells/cmm of 12 months in this study is similar to that seen in other studies. [81] Survival outcomes in this study are just lower to those reported for patients initiating ART with low cd4 lymphocyte counts in two observational studies in Canada and the USA,[80]although the observation periods for these cohorts include years where dual therapy was provided and also the patient cohort was in a better stage compared to the present study. The difference in survival between those starting treatment with cd4 counts of less than 50 cells/cmm and more than 50 cells/cmm was not significant in this study, indicating the high efficacy of HAART in our population. This shows that all cohorts of patients should be treated, even though the cohort of patients with very low cd4 counts is usually severely sick. This finding has implications in resource poor settings, as until now opportunity of getting ART was given to the one with relatively higher cd4 counts whose prognosis was considered better than to those with very low cd4 counts. This stratification of survival by a cd4 lymphocyte count of 50 cells/cmm was motivated by the potential to compare to other studies that have used these categories.

Mortality :

81.3% of deaths occurred within 3 months of starting therapy, which is similar to that in other such studies[37,84] in both developed and developing countries. This high rate of death immediately following the start of ART was seen in highly

immunocompromised patients with very low cd4 counts, presence of opportunistic infections, low BMI, low haemoglobin. Tuberculosis (30.2%), severe wasting with chronic diarrhoea(25.5%), pneumocystis jiroveci pneumonia(18.6%) accounted for ~75% of total deaths similar to other studies in resource poor settings.[39,41,43] Most of the deaths occurred in the first three months of start of therapy as was seen in other studies.[38-52,] The occurrence of a number of deaths very soon after initiating treatment is most likely due to the extreme disease advancement of many patients by the time they were able to access treatment. The relatively short period between ART initiation and new OI development suggests that OIs were a result of immune reconstitution or, in case of TB, relatively insensitive baseline screening methods. Additionally OIs may have developed before the full effects of ART could be attained in this immunocompromised population. Innovative approaches are required to prevent, diagnose and manage opportunistic infections effectively in this population.

CD4 lymphocyte counts :

CD4 lymphocyte gains were impressive, a mean gain of 162 cells/cmm at 6 months and 225 cells/cmm at 12 months from baseline, was similar to or better than a number of studies[37,39,41-44,46,82] in both developed and resource poor countries. The cd4 cell gain was almost equal or more in cohort of patients with cd4 count less than 50 cells/cmm than those with more than 50cells/dl. This

finding is unlike most other studies which showed that cd4 cell gain was less in patients with severe immunosupression and similar to study by lawn et al.[91] Those with baseline CD4 cell counts <50 cells/µl had a higher rate of cd4 cell gain compared to rates among those with higher baseline CD4 cell counts in the first 6 months after start of ART and had similar gain of cd4 cells in the next 6 months. Kaufmann *et al.* found that CD4 cell increases in the first year of ART were similar comparing those with baseline counts <100 cells/µl with those with counts 100–199 cells/µl. The immunological response to ART among those with low CD4 cell counts was excellent with the proportion of patients with a CD4 cell count <100 cells/µl decreasing from 104 (43%) at baseline to just 7 (6%) at 6 months. This shows the higher efficacy of HAART in our patient population which is reflected by higher immunological recovery.

Treatment change and toxicity:

28 patients (11.6%) of a total of 240 started on ART, changed their initial regimen. Of them 15 patients (53.5%) changed as they developed new onset TB, 12 patients (42.8%) changed their initial regimen as they developed adverse reaction to ART. Nevirapine was the drug which caused most adverse effects, mainly skin rash, which 6 patients developed, followed by zidovudine.The rates of treatment change due to adverse events were uniformly low and lower than those published for other cohorts.[37,48,83] This is a reflection of the incidence of severe adverse events in

general, and demonstrates that they are very less and with standardized regimens, monitoring and clinical management algorithms as in this study, ART can be safely used in resource constrained settings. The most common contraindication resulting in a treatment change was in patients who developed tuberculosis after starting ART and who were switched from nevirapine to efavirenz, due to concerns about the co-administration fo nevirapine with rifampicin.

Adherence :

The adherence to ART in this study was >95% for more than 95% of patients of all those under follow till the end of study, which is higher than most cohorts in western countries and comparable to most other studies in resource poor settings.[37-40,41,45,46,54,82]This shows that our patient population take their drugs regularly and are more adherent to therapy and also with effective counseling this can further be improved. Most common cause for non-adherence was due to patients going out of station for work (drivers), followed by forgetfulness.

Some of the studies undertaken in resource poor settings and developed nations are summarized in table below, which helps in comparision of our study to other similar such studies:

Reference	Country, year	Study population	Duration of treatment	CD4 cell count/cmm	Mortality	Weight trend kgs	Toxicity event
[37]	Senegal 2003	40 ART-naive patients	15 M	Mean↑ at15M +199	0%	Mean↑ at15M 5.1±5.3	19 cases
[39]	Malawi 2004	141 pts	6 M	Median↑ 6M +92 for 46 pts	27%	Mean↑ at 6M +5.7	4 cases
[41]	Malawi 2005	1266 pts 96.8% ART naive	>6 M	NR	12.9%	NR	NR
[43]	Uganda 2005	200 ART-naive pts	6 M	NR	3%	NR	NR
[44]	Kenya 2003	217 pts	24 M	Median↑at 12M +74	11%	NR	NR
[46]	S.Africa 2004	287 ART-naive pts	Median, 13.9 M	Mean↑ +134 6M +184 12M +220 18M +288 24M	13.7%	Mean↑ at 12M +9	

[48]	Cameroon 2003	117 pts ART naive	Median, 10.5M	Median↑ +250 12M	7.7%	Median BMI, 23 0M 25 12M	39 cases
[50]	Nigeria 2004	219 pts	12 months	Mean↑ 106 <55yr 78 >55yr	NR	Mean↑ +8<55yr +5>55yr	Seen in >55yr
[52]	Cote d'Ivoire 2003	101 pts	Median, 17M	Median↑ +115 12M	9.9%	Mean↑ 21M 3.4	10 cases
[60]	Botswana 2004	146 Pts	Median, 13.5M	Mean↑ +249 12M	Probability survival at 12M 0.7	Mean↑ 12M 11	NR
[90]	AVANTI 2 Europe Australia Canada 2000	52 Pts	Median, 52 weeks	Mean↑ +178 52wks	0%	NR	46/52 (88%)
	PRESENT STUDY	240 pts	Median, 10M	Mean↑ +226 12M	17.9%	Mean↑ 12M 4.43	12 cases

LIMITATIONS OF THIS STUDY :

There were significant limitations to our study. Because this study was observational, not all patients were equal in terms of time in the study, therapy, follow up. The period of follow up of patients in this study was 18 months and consisted of small number of patients, which could be limitation for identifying significant factors for the outcome. The survival analysis and the cox regression analysis are time dependent. Since the follow up time was only 18 months, it may not support fully to identify the real risk factors. Selection bias was present as newly diagnosed adult patients were only considered. The primary data for diagnosis and ART management were determined through physician reporting in a clinical record; therefore, there were potential inaccuracies or omissions in these data. Additionally, no other source of records was used for comparison.

CONCLUSIONS

1. The early clinical outcomes of patients with HIV in our cohort had improved on HAART similar to other studies, showing the efficacy of HAART in our population.

2. Clinical outcomes like CD4 count, weight gain, haemoglobin showed a significant increase from baseline in our patients on HAART, showing the overall improvement of our population with ART.

3. Adverse events to ART drugs was seen in 5% of patients, which was very low compared to other studies, showing that our patients tolerate ART drugs well.

4. 75.6% of opportunistic infections after start of ART were seen within the first 4 months; after which their incidence reduced, implying that the full effect of antiretroviral drugs starts around this time.

5. Adherence to ART was more than 95% in more than 95% of patients under follow up, which is better than that seen in developed countries, which shows that our population is more adherent to therapy.

6. 81.4% of deaths occurred within 3 months of start of therapy in our cohort, showing the advanced stage of presentation of these patients to hospital, and death before ART could take full effect.

In conclusion HAART proved to be effective in our cohort of patients and our findings support the ongoing feasibility of ART roll out in resource poor settings. Widespread voluntary HIV testing and counselling should be encouraged to allow HAART initiation before the development of severe immune suppression. Free access to HAART, as in this study is also important as programmes in which patients had to pay for their treatment have shown higher rates of mortality.[75,79] The findings in this study provide encouragement to those seeking to provide similar services in resource poor settings where HIV morbidity and mortality are high.

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ABBREVIATIONS

3TC lamivudine

ABC abacavir

AFB acid-fast bacilli

AIDS acquired immunodeficiency Syndrome

ALT alanine aminotransferase

ART antiretroviral therapy

ARV antiretroviral

AST aspartate aminotransferase

ATV atazanavir

AZT zidovudine (also known as ZDV)

BMI body mass index

CD4 count CD4+ T-lymphocyte

CMV cytomegalovirus

CTX co-trimoxazole

CXR chest X-ray

d4T stavudine

ddI didanosine

DNA deoxyribonucleic acid

DOT directly observed therapy

EFV efavirenz

EIA enzyme immunoassay

EPTB extrapulmonary tuberculosis

FBC full blood count

FDA Food and Drug Administration (USA)

FDC fixed-dose combination

FPV fos-amprenavir

FTC emtricitabine

GDG Guidelines Development Group

GI gastrointestinal

Hb haemoglobin

HBV hepatitis B virus

HCV hepatitis C virus

HDL high-density lipoprotein

HIV human immunodeficiency virus

HSV herpes simplex virus

IDU injecting drug user

IDV indinavir

INH isoniazid

IRIS immune reconstitution inflammatory syndrome

LDH lactic dehydrogenase

LPV lopinavir

MTCT mother-to-child transmission (of HIV)

NAM nucleoside/nucleotide analogue Mutation

NFV nelfinavir

NNRTI non-nucleoside reverse transcriptase inhibitor

NRTI nucleoside reverse transcriptase inhibitor

NVP nevirapine

OHL oral hairy leukoplakia

OI opportunistic infection

OST opioid substitution treatment

PCP Pneumocystis pneumonia

PGL persistent generalized lymphadenopathy

PI protease inhibitor

PML progressive multifocal leukoencephalopathy

PMTCT prevention of mother-to-child transmission (of HIV)

/r low-dose ritonavir

RBV ribavirin

RNA ribonucleic acid

RT reverse transcriptase

RTI reverse transcriptase inhibitor

RTV ritonavir

SJS Stevens-Johnson syndrome

SQV saquinavir

STI sexually transmitted infection

TB tuberculosis

TDF tenofovir disoproxil fumarate

TENS toxic epidermal necrolysis

TLC total lymphocyte count

VL viral load

UNAIDS Joint United Nations Programme on HIV/AIDS

USA United States of America

WBC white blood cell count

WHO World Health Organization

HAART OUTCOMES IN HIV : PROFORMA

Name:

Age:

Sex:

Education :

Occupation:

Married Y/N:

Hiv status : Date of initial detection,

CDC stage,

Status of spouse

Route of acquisition: heterosexual, homosexual, iv drug use, blood transfusion

H/O opportunistic infections: past and present

Co morbidities: Diabetes, hypertension, congestive heart failure, hepatitis B/C

H/O Smoking, alcoholism

Drugs on use: ART, ATT, antibiotics – cotrimoxazole, quinolones, fluconazole

For pt newly started on ART: Regimen

For pt on follow up : new complaints, new OI, adherence to drugs

EXAMINATION

Height	weight	BMI
Pulse	BP (upper limb)	
CVS RS	Abd	CNS

INVESTIGATIONS :

CBC: Hb, TC, DC, ESR, PCV, PLTS

Renal Function Test: sugar, urea, creatinine, Na, K

Liver function tests:

CD4 COUNT

Sputum examination for TB bacilli : if indicated

CXR: if indicated

USG abdomen: if indicated

Date	Weight	CD4 count	HB	OI	Adherence
0 M					
6 M					
12 M					
18 M					