“STUDY OF METABOLIC SYNDROME IN HIV - POSITIVE PATIENTS IN A TERTIARY HOSPITAL”

REG NO. BG0111002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka
In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"STUDY OF METABOLIC SYNDROME IN HIV POSITIVE PATIENTS IN A TERTIARY HOSPITAL"** is a bonafide research work done by **CANDIDATE REG NO. BG0111002.**

Dr. V. A. Kothiwale **MD, Ph.D**
Professor and Head,
Department of Medicine,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. A. S. Godhi **MS,FICS**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

%	-	Percentage
µ	-	Micro
3TC	-	Lamivudine
AACE	-	American Association of Clinical Endocrinologists
AIDS	-	Acquired Immunodeficiency Syndrome
AMA	-	American Medical Association
APC	-	Asia Pacific Criteria
ART	-	Antiretroviral therapy
ARV	-	Antiretroviral
ATP	-	Adult Treatment Panel
AZT	-	Zidovudine
BMI	-	Body mass index
BP	-	Blood pressure
CAD	-	Coronary Artery Disease
CCR	-	Chemokine receptor
CDC	-	Centers for Disease Control and Prevention
CI	-	Confidence interval
Cms	-	Centimeters
CNS	-	Central nervous system
CRP	-	C-reactive protein
CSF	-	Cerebrospinal fluid
CVD	-	cardiovascular disease
CXCR	-	Chemokine-related receptor
DBP	-	Diastolic blood pressure

DF	-	Degree of freedom
DHSS	-	Department of Health and Human Services
DM	-	Diabetes Mellitus
DNA	-	Deoxyribonucleic acid
EFV	-	Efavirenz
EGIR	-	European Group for the Study of Insulin Resistance
EIA	-	Enzyme immunoassay
ELISA	-	high-sensitive enzyme-linked immunoabsorbent assay
FBS	-	Fasting blood glucose
FDA	-	Food and drug administration
FPG	-	Fasting plasma glucose
FTC	-	Emtricitabine
GALT	-	Gut-associated lymphoid tissue
GI	-	Gastrointenstinal
HAART	-	Highly active antiretroviral therapy
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus
HDL-C	-	High density Lipoprotein Cholesterol
HIV	-	Human Immunodeficiency Virus
HOMA IR	-	Homeostasis model assessment of insulin resistance
HOMA	-	Homeostasis model assessment
Hs-CRP	-	High sensitivity C-Reactive protein
HTN	-	Hypertension
IDF	-	International Diabetes Federation
IFG	-	Impaired fasting glucose

IGR	-	Impaired glucose regulation
IGT	-	Impaired glucose tolerance
IL	-	Interleukin
Kg	-	Kilogram
Kg/m^2	-	Kilogram per meter square
L	-	Litre
LDL	-	Low density lipoprotein
MeTS	-	Metabolic syndrome
mg	-	Milligrams
mg/dL	-	Milligrams per deciliter
min	-	Minute
mL	-	Milli litre
mm Hg	-	Millimeters of mercury
mmol	-	Millimole
MTCT	-	mother-to-child transmission
NCEP	-	National cholesterol education programme
NCEP-ATP III	-	2003 National Cholesterol Education Program Adult Treatment Panel III
NFHL	-	Nutrition for Healthy Living
NHANES	-	National Health and Nutrition Examination Survey
NHLBI	-	National Heart, Lung, and Blood Institute
NIH	-	National Institutes of Health
NPDR	-	Non proliferative diabetic retinopathy
NVP	-	Nevirapine
OGTT	-	Oral glucose tolerance test

OR	-	Odds ratio
PCR	-	Polymerase chain reaction
PI	-	Protease inhibitor.
PVD	-	Peripheral vascular disease
RNA	-	Ribonucleic acid
SAT	-	Subcutaneous abdominal tissue
SBP	-	Systolic blood pressure
SC	-	Subcutaneous
SD	-	Standard deviation
T2DM	-	Type 2 diabetes mellitus
TDF	-	Tenofovir
TG	-	Triglycerides
TNF	-	Tumor necrosis factor
U.S.	-	United States
UNAIDS	-	United Nations Programme on HIV/AIDS
USPSTF	-	U.S. Preventive Services Task Force
VAT	-	Visceral adipose tissue
VLDL	-	Very low density lipoprotein
WC	-	Waist circumference
WHO	-	World Health Organization
WHR	-	Waist hip ratio
µg/min	-	Microgram per minute
µU/L	-	Microunit per litre

ABSTRACT

Background and objectives

There has been a decline in morbidity and mortality since the introduction of highly active antiretroviral therapy (HAART) for HIV. However, evidence suggests emergence of a number of metabolic derangements. The present study was carried out to find out the prevalence of metabolic syndrome in HIV patients and to assess the clinical and laboratory profile of these patients.

Methodology

This one year cross sectional study was conducted during the period of January 2012 to December 2012 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 75 HIV positive patients were studied. The diagnosis of metabolic syndrome was done according to NCEP ATP III criteria.

Results

In the present study, majority (76%) of the patients were males. Most of the patients (37.33%) were aged between 41 to 50 years and the mean age was 42.03±10.35 years. Antiretroviral treatment was present in 62.67% of the patients. The body mass index in 33.33% patients was between 25 to 29.99 Kg/m^2 with mean being 24.17±3.60 Kg/m^2. Pallor was present in 53.33% and clubbing, edema and icterus was noted among 5.33% patients each. Crepitations (4%) and decreased air entry (4%) were noted in respiratory system. The CNS examination (4%) revealed ataxia (1.33%), nystagmus (1.33%) and neck rigidity (1.33%) while per abdominal findings revealed hepatomegaly (2.67%). The

fasting blood sugar levels in 16% of the patients were ≥ 110 mg/dL. Abnormal high density lipoprotein was noted in 81.33% patients and abnormal triglyceride levels were noted in 49.33% patients.

Conclusion and interpretation

The prevalence of metabolic syndrome was 21.33%. Among these, three components were present in 14 (87.5%) patients and four components in two (12.50%). Statistically significant association was found between metabolic syndrome and ART treatment, waist circumference, raised blood pressure levels and body mass index.

Keywords

Antiretroviral therapy; Human immunodeficiency virus; Metabolic syndrome;

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Chapter 1

Introduction

INTRODUCTION

The Human Immunodeficiency Virus (HIV) targets the immune system and weakens people's surveillance and defense systems against infections and some types of cancer. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immunodeficiency results in increased susceptibility to a wide range of infections and diseases that people with healthy immune systems can fight off. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which can take from 2 to 15 years to develop depending on the individual. AIDS is defined by the development of certain cancers, infections, or other severe clinical manifestations.[1]

HIV continues to be a major global public health issue, having claimed more than 25 million lives over the past three decades. There were approximately 34 [31.4–35.9] million people living with HIV in 2011. Sub-Saharan Africa is the most affected region, with nearly 1 in every 20 adults living with HIV. Sixty nine per cent of all people living with HIV are living in this region. HIV infection is usually diagnosed through blood tests detecting the presence or absence of HIV antibodies. There is no cure for HIV infection. However, effective treatment with antiretroviral drugs can control the virus so that people with HIV can live healthy and productive lives. In 2012, more than 9.7 million people living with HIV were receiving antiretroviral therapy (ART) in low- and middle-income countries.[1]

The Government of India estimates that about 2.40 million Indians are living with HIV (1.93 - 3.04 million) with an adult prevalence of 0.31% (2009). Children (<15 years) account for 3.5% of all infections, while 83% are the in age group 15-49 years. Of all HIV infections, 39% (930,000) are among women. India's highly heterogeneous epidemic is largely concentrated in only a few states in the industrialized south and west, and in the north east. The four high prevalence states of South India (Andhra Pradesh – 500,000, Maharashtra – 420,000, Karnataka – 250,000, Tamil Nadu – 150,000) account for 55% of all HIV infections in the country. West Bengal, Gujarat, Bihar and Uttar Pradesh are estimated to have more than 100,000 people living with HIV/AIDS each and together account for another 22% of HIV infections in India.[2]

Behaviours and conditions that put individuals at greater risk of contracting HIV include having unprotected anal or vaginal sex; having other sexually transmitted infection such as syphilis, herpes, chlamydia, gonorrhoea, and bacterial vaginosis; sharing contaminated needles, syringes and other injecting equipment with drug solutions used while when injecting drugs; blood transfusions, medical procedures that involve unsterile cutting or piercing; and accidental needle stick injuries, among health workers as well as parent to child transmission.[1]

HIV can be suppressed by combination ART consisting of three or more antiretroviral (ARV) drugs. ART does not cure HIV infection but controls viral replication within a person's body and allows an individual's immune system to strengthen and regain the capacity to fight with infections. With ART, people living with HIV can have longer asymptomatic and healthy lives.[3]

There is over 30-fold increase in the number of people receiving ART in developing countries between 2003 and 2012, and close to a 20% increase in just one year (from 8 million in 2011 to 9.7 million in 2012).[1] The introduction of ART has resulted in significant reduction in mortality and morbidity of these patients. However, its prolonged usage has brought with it some metabolic abnormalities which need evaluation.[4]

However, highly active antiretroviral therapy (HAART) in HIV infection produces a spectrum of metabolic complications, including dyslipidemia, insulin resistance, and changes in body fat compartmentalization (peripheral lipoatrophy and central fat accumulation). Several studies have described and characterized the lipid and metabolic abnormalities associated with lipodystrophy, noting many similarities with the metabolic syndrome.[5-8]

The early natural history of HIV lipodystrophy,[6] poor responses to peroxisome proliferator–activated receptor-γ agonists and fibrates,[9,10] and the impact of HAART on molecular processes in lipid, insulin, and glucose metabolism is also reported.[11]

The metabolic effects of HAART in contributing to increased risk of premature and accelerated atherosclerosis in HIV infection are recognized.[12-15]

The metabolic syndrome is a term used to describe a cluster of risk factors for cardiovascular disease (CVD) such as, high triglycerides, low high-density lipoprotein (HDL), hypertension, hyperglycemia and abdominal obesity.[16]

Metabolic syndrome has been identified as a significant and multifaceted risk factor for CVD by the U.S. National Cholesterol Education Program Adult Treatment Panel III (ATPIII) report.[17] Metabolic syndrome encompasses disturbances in glucose, insulin, and lipid metabolism, associated with abdominal obesity.[18] Metabolic syndrome doubles coronary heart disease mortality, after adjustment for age, sex, cholesterol level, physical activity, and smoking.[19] In the Kuopio Ischemic Heart Disease Risk Factor Study, men with metabolic syndrome had a threefold increase in coronary death, after adjusting for age, low density lipoprotein (LDL) cholesterol, smoking, and family history.[20]

Metabolic syndrome affects 24% of the adult population in the U.S.[21] The International Diabetes Federation (IDF) recently published its universal classification,[22] which permits epidemiological study across different populations, using evidence-based abdominal obesity cutoffs that are sex and ethnicity specific.

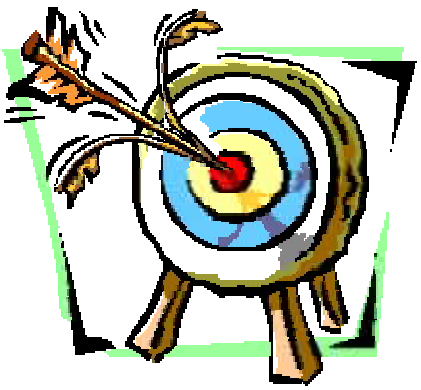
Metabolic syndrome prevalence in HIV-infected patients receiving HAART is unclear.[24] The drugs implicated in the treatment of HIV include nucleoside reverse transcriptase inhibitors (major components of first-line therapy in India) and also protease inhibitors (components of current second-line therapy in India). With the alteration in insulin sensitivity, dysglycemia, dyslipidemia, hypertension, and body fat abnormalities, there are concerns about the long-term risks of ART.[25]

In India, there is genetic predisposition to insulin resistance and cardiovascular risk,[26,27] this impact may be significant.

Considering the above facts, the present study was undertaken to assess the prevalence of metabolic syndrome in HIV patients and to find out the clinical and laboratory profile of HIV positive patients with metabolic syndrome so as to identify the risk factors in time and to prevent further complications.

Chapter 2

Objectives



OBJECTIVES

The objectives of the present study were;

Primary

To find out the prevalence of metabolic syndrome among HIV patients.

Secondary

To study the clinical and laboratory profile of HIV positive patients with metabolic syndrome.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Human immunodeficiency virus

Human immunodeficiency virus is a blood-borne, sexually transmissible virus. The virus is typically transmitted via sexual intercourse, shared intravenous drug users, and mother-to-child transmission (MTCT), which can occur during the birth process or during breastfeeding.

Two distinct species of HIV (HIV-1 and HIV-2) have been identified, and each is composed of multiple subtypes, or clades. All clades of HIV-1 tend to cause similar disease, but the global distribution of the clades differs. This may have implications on any future vaccine, as the B clade, which is predominant in the developed world (where the large pharmaceutical companies are located), is rarely found in the developing countries that are more severely affected by the disease.

HIV-2 carries a slightly lower risk of transmission, and HIV-2 infection tends to progress more slowly to acquired AIDS. This may be due to a less-aggressive infection rather than a specific property of the virus itself. Persons infected with HIV-2 tend to have a lower viral load than people with HIV-1,[28] and a greater viral load is associated with more rapid progression to AIDS in HIV-1 infections.[29] HIV-2 is rare in the developed world. Consequently, most of the research and vaccine; drug development has been (perhaps unfairly) focused on HIV-1.

History

HIV-1 probably originated from one or more cross-species transferred from chimpanzees in central Africa.[30] HIV-2 is closely related to viruses that infect sooty mangabeys in western Africa.[31] Genetically, HIV-1 and HIV-2 are superficially similar, but each contains unique genes and its own distinct replication process.

Timeline of HIV

- **1959** - The first known case of HIV in a human occured in a person who died in Congo, and was later confirmed to have HIV infection from his preserved blood samples.[32] The authors of the study did not sequence a full virus from his samples, hence stated that "attempts to amplify HIV-1 fragments of >300 base pairs were unsuccessful ... However, after numerous attempts, four shorter sequences were obtained"; these represented small portions of two of the six genes of the complete HIV genome.[33]

- June 28, in New York City, Ardouin Antonio, a 49-year-old Jamaican-American shipping clerk died of *Pneumocystis carinii* pneumonia, a disease closely associated with AIDS. Gordon Hennigar, who performed the postmortem examination of the man's body, found "the first reported instance of unassociated *Pneumocystis carinii* disease in an adult" to be so unusual that he preserved Ardouin's lungs for later study. The case was published in two medical journals at the time, and Hennigar has been

quoted in numerous publications stating that he believed Ardouin probably had AIDS.[34]

- **1960s** – The HIV-2, a viral variant found in West Africa, was thought to have been transferred to people from sooty mangabey monkeys in Guinea-Bissau during that period.[34]

- **1964** - Jerome Horwitz of Barbara Ann Karmanos Cancer Institute and Wayne State University School of Medicine synthesized AZT under a grant from the US National Institutes of Health (NIH). AZT was originally intended as an anticancer drug.[34]

- **1966** - Genetic studies of the virus indicated that HIV first arrived in America, infecting one person in Haiti. as many of the Haitians were working in Congo, providing the opportunity for infection.[34]

- **1968** - The disease spread from the 1966 American strand, but remained unrecognized for another 12 years.[34]

- **1969** - A St. Louis teenager, identified as Robert Rayford, died of an illness that baffles his doctors. Eighteen years later, molecular biologists at Tulane University in New Orleans test samples of his remains and find evidence of HIV.[34]

- 1975 - In the residents of Africa certain reports of wasting and other symptoms in patients were later seen who were later determined to have AIDS.[34]

- 1976 - Norwegian sailor Arvid Noe died and was later determined that he contracted HIV/AIDS in Africa during the early 1960s.[34]

- 1977 - Danish physician Grethe Rask died of AIDS contracted in Africa. A San Francisco prostitute gave birth to the first of three children who were later diagnosed to have AIDS. The children's blood was tested after their deaths and revealed an HIV infection. The mother died of AIDS in May 1987 and her test results showed HIV infection.[34]

- 1978 - A Portuguese man known as Senhor José (English: Mr. Joseph) dies; he was later confirmed as the first known person with HIV-2 infection. It is believed that he was exposed to the disease in Guinea-Bissau in 1966.[34]

- 1979 - An early case of AIDS in the United States was of a female baby born in New Jersey in 1973 or 1974. She was born to a sixteen-year-old girl, an identified drug-injector, who previously had multiple male sexual partners. The baby died in 1979 at the age of five. Subsequent testing on her stored tissues confirmed that she had contracted HIV-1.[34]

Since the discovery of the first AIDS case in the United States in 1981, HIV/AIDS has become a major worldwide health problem. There were an estimated 740,000 people living with HIV/AIDS in China by the end of 2009.[35]

Epidemiology

Worldwide

According to recent World Health Organization statistics (WHO) HIV continues to be a major global public health issue, having claimed more than 25 million lives over the past three decades. There were approximately 34 [31.4–35.9] million people living with HIV in 2011. Sub-Saharan Africa is the most affected region, with nearly 1 in every 20 adults living with HIV. Sixty nine per cent of all people living with HIV are inhabitants of this region.[1]

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS),[36] in 2008 approximately 33.4 million people worldwide (1% of the global adult population aged 15-49 y) were infected with HIV, reporting a decline from the data obtained in 2006 (39.5 million reported at that time). UNAIDS estimates that 2.7 million people were newly infected with HIV and that 2 million people died from AIDS in 2008, both the statistics showing a slight decline over the time.

The vast majority of infections remain in sub-Saharan Africa, where 5.2% of the population is thought to be infected. Between 2004 and 2006, the prevalence of HIV infection in central, eastern Asia and Eastern Europe increased by 21%. During this period, the number of new HIV infected persons aged 15 to 64 years rose by 70% in Eastern Europe and central Asia.

The infection rates in many developed countries remain stable, and some developing countries have achieved significant gains in controlling and even

reversing the effects of the HIV epidemic. However, this is partially due to the deaths in HIV-infected people, together with simultaneous prevention of new infections. As India, for example, has used a national prevention campaign focusing on high-risk populations that can prevent about 100,000 new HIV infections occurring over a period of 5 years has been implemented, with increasing results been seen in areas with higher levels of investment.[37] These figures together show that global HIV infection is in a state of flux.

Racial, sexual, and age-related differences in incidence

In the United States, the rate of HIV infection is highest in blacks (83.7 cases per 100,000 population). The prevalence is also high among Hispanic persons (29.3 per 100,000 population). These increased rates are due to socioeconomic factors rather than genetic predisposition.

In the developed world, HIV infection is much more common in males. In 2009, males accounted for about 76% of all diagnoses of HIV infection among adults and adolescents in the US.[38] Among heterosexuals, females are more likely to acquire HIV infection from an infected male than a male is from an infected female, but a large proportion of infections in males are due to homosexual contact, with or without injection drug use. Males are also more likely to acquire HIV infection from injection drug use alone.

Males were also more likely to acquire HIV infection through contaminated blood products for treatment of hemophilia before universal testing of the blood supply was instituted. The risk of HIV exposure from factor VIII concentrates has been virtually eliminated by viricidal treatment of plasma-

derived factor VIII concentrates, as well as the introduction of recombinant factor VIII concentrates and the gradual elimination of albumin from the production process used for these products.

In the developing world, HIV infection is equally common in males and females. The primary route of HIV transmission in the developing world is heterosexual contact.

Young adults tend to be at a higher risk of acquiring HIV, typically through high-risk activities such as unprotected sexual intercourse or intravenous drug use. In 2009 in the US, the largest percentage (15% of all diagnoses) and the highest rate (36.9 per 100,000 population) were in persons aged 20–24 years.[38]

Indian scenario

The Government of India estimates that about 2.40 million Indians are living with HIV (1.93 - 3.04 million) with an adult prevalence of 0.31% (2009). Children (<15 yrs) account for about 3.5% of all the infections, while 83% are the in the age group of 15-49 years. Of all HIV infections, 39% (930,000) are among women. Making it India's highly heterogeneous epidemic that is largely concentrated in only a few states in the industrialized south and west, and in the north east.[2]

The four high prevalence states of South India (Andhra Pradesh – 500,000, Maharashtra – 420,000, Karnataka – 250,000, Tamil Nadu – 150,000) account for about 55% of all HIV infections in the country. West Bengal,

Gujarat, Bihar and Uttar Pradesh are estimated to have more than 100,000 PLHA each and together account for another 22% of HIV infections in India.[2]

Transmission

HIV infection can be transmitted through:

- Unprotected sexual intercourse with an infected partner;
- Injection or transfusion of contaminated blood or blood products;
- Sharing unsterilized injection equipment that has been previously used by someone who is infected;
- Maternofetal transmission (during pregnancy, at birth, and through breastfeeding).[39]

The risk of occupational HIV transmission from contaminated needles to healthcare workers was found to be 0.3% (in case series performed prior to the availability of potent anti retroviral therapy).[39]

Risk factors

Behaviours and conditions that put individuals at greater risk of contracting HIV include:

- Having unprotected anal or vaginal sex;
- Having another sexually transmitted infection such as syphilis, herpes, chlamydia, gonorrhoea, and bacterial vaginosis;
- Sharing contaminated needles, syringes and other injecting equipment and drug solutions when injecting drugs;

- Receiving unsafe injections, blood transfusions, medical procedures that involve unsterile cutting or piercing; and
- Experiencing accidental needle stick injuries, including among health workers.

Pathophysiology

HIV produces cellular immune deficiency characterized by the depletion of helper T lymphocytes ($CD4^+$ cells). The loss of $CD4^+$ cells results in the development of opportunistic infections and neoplastic processes.

Virology of HIV

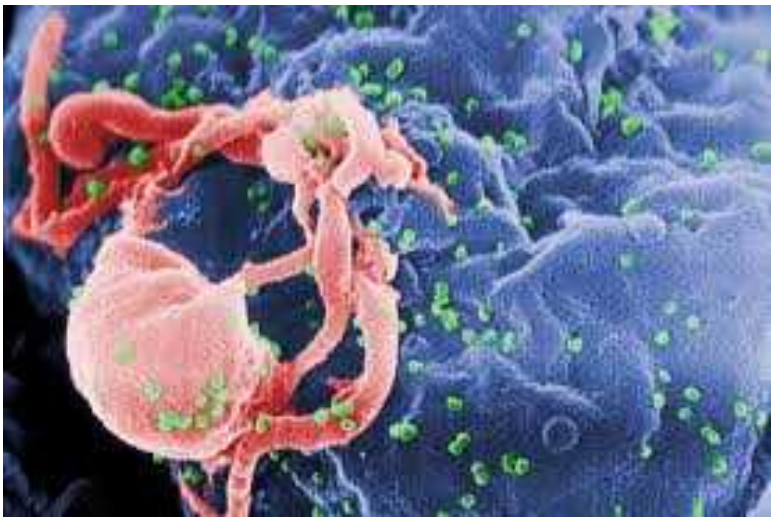


Figure 1. Scanning electron micrograph of HIV-1 budding (in green) from cultured lymphocyte

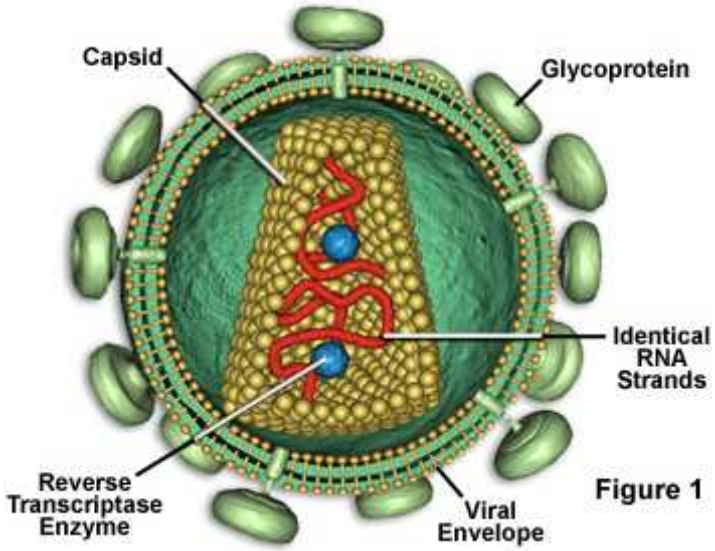


Figure 2. Human immunodeficiency virus anatomy

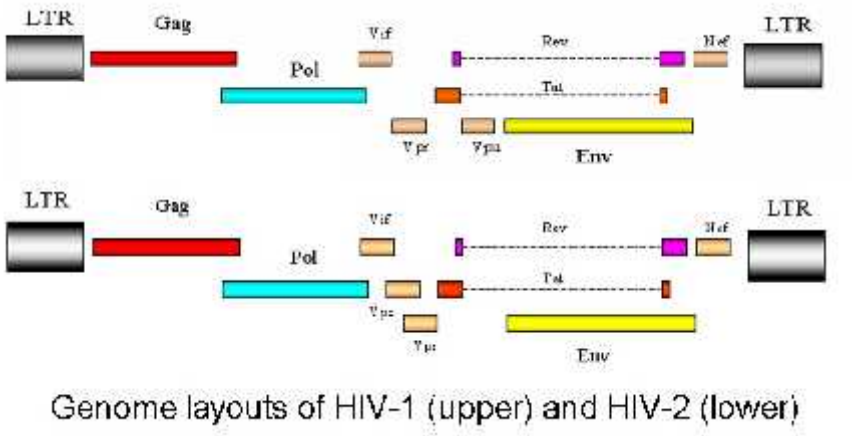
HIV-1 and HIV-2 are retroviruses in the Retroviridae family, *Lentivirus* genus. They are enveloped, diploid, single-stranded, positive-sense ribonucleic acid (RNA) viruses with a deribonucleic acid (DNA) intermediate, which is an integrated viral genome (a provirus) that persists within the host-cell DNA.

HIV contains 3 species-defining retroviral genes: *gag*, *pol*, and *env*. The *gag* gene encodes group-specific antigen; the inner structural proteins. The *pol* gene encodes polymerase; it also contains integrase and protease (the viral enzymes) and is produced as a C-terminal extension of the Gag protein. The *env* gene encodes the viral envelope the outer structural proteins responsible for cell-type specificity. Glycoprotein 120, the viral-envelope protein, binds to the host $CD4^+$ molecule.

HIV-1 has 6 additional accessory genes: *tat*, *rev*, *nef*, *vif*, *vpu*, and *vpr*. HIV-2 does not have *vpu* but instead has the unique gene *vpx*. The only other virus known to contain the *vpu* gene is simian immunodeficiency virus in

chimpanzees (SIV_{cpz}), which is the simian equivalent of HIV.[30,40] Interestingly, chimpanzees with active HIV-1 infection are resistant to the disease.[41]

The accessory proteins of HIV-1 and HIV-2 are involved in viral replication and may play a role in the disease process.[42,43] The outer part of the genome consists of long terminal repeats (LTRs) that contain sequences necessary for gene transcription and splicing, viral packaging of genomic RNA, and dimerization sequences to ensure that 2 RNA genomes are packaged.



Genome layouts of HIV-1 (upper) and HIV-2 (lower)

Figure 3. Genome layout of human immunodeficiency virus (HIV)–1 and HIV-2

The dimerization, packaging, and gene-transcription processes are intimately linked; disruption in one process often subsequently affects the another. The LTRs exist only in the proviral DNA genome; the viral RNA genome contains only a part of each LTR, and the complete LTRs are re-created during the reverse-transcription process prior to integration into the host DNA.

The biologic basis for AIDS

The specific details of the disease process that leads to AIDS are not fully understood despite considerable progress in the virology of HIV and the immunology of the human host, much of which has been driven by the urge to understand AIDS better.[44,45]

There is a specific decline in the $CD4^+$ helper T cells, resulting in inversion of the normal CD4/CD8 T-cell ratio and dysregulation of B-cell antibody production.[45,46] Immune responses to certain antigens begin to decline, and the host fails to adequately respond to opportunistic infections and normally harmless commensal organisms. Because the defect preferentially affects cellular immunity, the infections tend to be nonbacterial (fungal, viral).

The pattern of opportunistic infections in a geographic region reflects the pathogens that are common in that area. For example, persons with AIDS in the United States tend to present with commensal organisms such as *Pneumocystis* and Candida species, homosexual men are more likely to develop Kaposi sarcoma because of co-infection with HHV8, and tuberculosis is common in developing countries.

Gut-associated lymphoid tissue (GALT) plays a role in HIV replication.[47] Although the portal of entry for HIV infection is typically through direct blood inoculation or exposure of the virus to genital mucosal surfaces, the GI tract contains a large amount of lymphoid tissue, making this an ideal site for HIV replication.

GALT has been shown to be a site of early viral seeding and establishment of the proviral reservoir. This reservoir contributes to the difficulty of controlling the infection, and efforts to reduce the levels of HIV provirus through sustained antiretroviral therapy (alone or in combination with interleukin-2 activation of resting HIV-infected T cells) have consistently failed.[48]

A feature of HIV replication in GALT is that it is compartmentalized, even among different areas of the gut.[49] Measurements of $CD4^+$ T cells in GALT show relatively less reconstitution with antiretroviral therapy than that observed in peripheral blood.[50] At least one report has suggested that early treatment may result in better GALT $CD4^+$ T-cell recovery,[50] but clinical data generally argue against early initiation of therapy, which has not been shown to improve long-term survival.

In addition, HIV replication can be detected even in patients with supposedly suppressed replication, as judged by plasma viral load measurements. $CD8^+$ killer T-cell responses to HIV occur in GALT and do not decline with antiviral therapy as much as peripheral measurements do.[51] These findings underscore the limitations of peripheral measurements in what is really a central viral replication.

One theory for the discrepancy between GALT and blood measurements is that ongoing viral replication in the lymphoid tissue, and the resulting immune activation, may actually hamper efficient $CD4^+$ T-cell replenishment.[52]

Studies of T-cell–replication kinetics have revealed that untreated HIV infection is characterized by rapid T-cell turnover due to a defect in T-cell replication from the thymus.[52] These changes can be reversed with effective long-term antiviral therapy,[53] suggesting that they are due to a direct effect of the virus or are a feature of the immune response against HIV.

It is known that normal cell cycling is necessary to produce a normal cytokine profile[54] and that HIV causes cell-cycle arrest.[55] Whether this is the exact mechanism is unresolved. However, analysis of the cytokine levels in HIV infected, uninfected, and HAART-treated patients show that cytokines involved in T-cell homeostasis were definitely affected, and the therapy partially corrected these defects. In particular there were decreased levels of IL-7, IL-12, IL-15 and FGF-2, and increased tumor necrosis factor (TNF) alpha and IP-10.[56]

Several of the HIV proteins directly affect T-cell function, either by disrupting cell cycling or by down-regulating the CD4 molecule. The loss of T cells is clearly a primary issue, as the T-cell repertoire narrows in terms of which antigens the immune system will recognize and respond to. Antiretroviral therapy is able to reverse these changes,[57] but the degree of reversal is decreased if therapy is initiated very late in the infection and is further decreased when therapy is initiated when CD4 T-cell counts are 200/µL and below.

Direct cytotoxic effects of viral replication are likely not the primary cause of CD4 T-cell loss. A significant bystander effect[58] is likely to be secondary to T-cell apoptosis as part of immune hyperactivation in response to the chronic infection. Infected cells may also be affected by the immune attack.

One interesting issue is that the co-receptor usage of the virus strains tends to change over time. The initial infection nearly always involves a strain that uses the chemokine receptor 5 (CCR5), which is found on macrophages and dendritic cells, as a co-receptor with CD4. People who are homozygous for deletions in the *CCR5* gene (ie, CCR5-delta32) tend to be resistant to infection,[59] and those with heterozygosity for the polymorphism tend to show slower progression of disease.[60]

Over the time, the receptor usage shifts to chemokine-related receptor (CXCR4) and other related receptors found on $CD4^+$ T cells. These virus strains are more likely to cause cell fusion (syncytia formation). This trend is far from absolute but does correlate in many people with disease progression.[61]

A single case report detailed a possible cure resulting from stem-cell transplantation in a CCR5-delta32 homozygous donor (performed to treat acute myelocytic leukemia). Although this important finding is unlikely to impact routine management of HIV infection, it does suggest that reconstitution of a host immune system with a population of mutant cells is a possible avenue of research to explore.[62]

Regardless of the cause for the disruption, a loss of thymic replacements in the face of an induced state of immune activation and T-cell loss seems to be a key component of the mechanism by which HIV narrows the T-cell repertoire and progresses to AIDS.[62,63]

Visible effects of HIV infection come in the form of disrupted lymph-node architecture. This disruption is temporal, and at one point, lymph-node

biopsy was considered as a form of staging the disease.[64] The disruption of the follicular dendritic network in the lymph nodes and subsequent failure of normal antigen presentation are likely contributors for the disease to process.

HIV replicates in activated T cells (its promotor contains a nuclear factor kappa B [NF-kappa-B]–binding region, the same protein that promotes other proteins in activated T cells and macrophages), and activated T cells migrate to the lymph nodes. As such, much of the viral replication occurs outside the peripheral blood, even though serum viral load is still a useful surrogate marker of viral replication.

As mentioned above, with regards to GALT, HIV infection may be compartmentalized; specifically, areas of immune-privilege may occur such as in the testes and central nervous system where not only will there be differences in HIV pseudospecies but also different degrees of antiretroviral drug penetration. There is evidence that even with good peripheral control of HIV, the virus may still be detectable in the cerebrospinal fluid (CSF) and semen of some infected patients.[65]

Phases of HIV infection

Clinical HIV infection undergoes 3 distinct phases: acute seroconversion, asymptomatic infection, and AIDS.

Acute seroconversion

Animal models show that Langerhans cells are the first cellular targets of HIV, which fuse with $CD4^+$ lymphocytes and spread into deeper tissues. In

humans, there is rapid occurrence of plasma viremia with widespread dissemination of the virus which is observed 4-11 days after mucosal entrance of the virus.

There is no fixed site of integration, but the virus tends to integrate in areas of active transcription, probably because these areas have more open chromatin and more easily accessible DNA.[66] This greatly complicates eradication of the virus by the host, as latent proviral genomes can persist without being detected by the immune system and cannot be targeted by antiretrovirals.

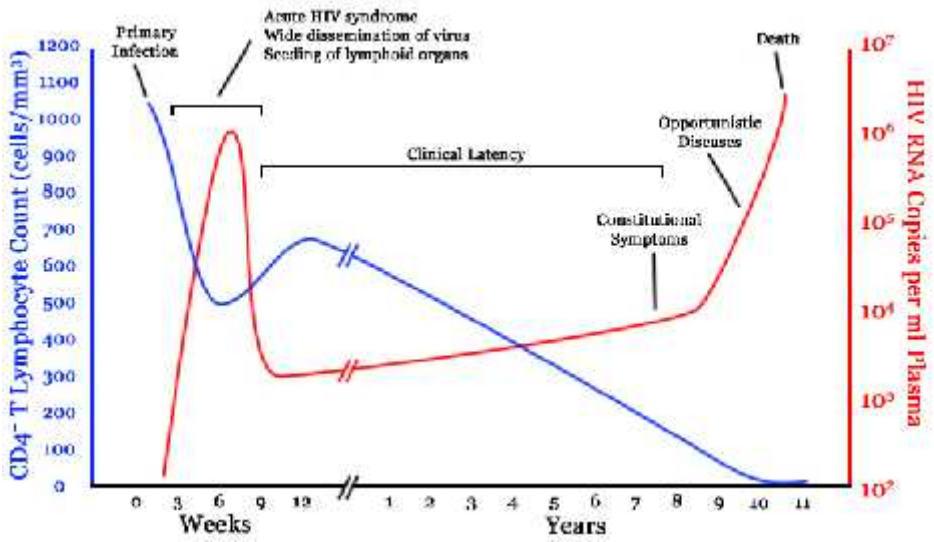


Figure 4. Timeline of CD4 T-cell and viral-load changes over time in untreated human immunodeficiency virus infection.[44]

During this phase, the infection is established and a proviral reservoir is created.[67] This reservoir consists of persistently infected cells, typically macrophages, and appears to steadily release the virus. Some of the viral release replenishes the reservoir, and some go on to produce more active infection.

The proviral reservoir, as measured by DNA polymerase chain reaction (PCR), seems to be incredibly stable. Although it does decline with aggressive antiretroviral therapy, and the half-life is such that eradication is not a viable expectation.

The size of the proviral reservoir correlates to the steady-state of the viral load and is inversely correlated to the anti-HIV $CD8^+$ T-cell responses. Aggressive early treatment of acute infection may lower the proviral load, but generally, treatment in newly infected (postseroconversion) patients yields no long-term benefit.

At this point, the viral load is typically very high, and the $CD4^+$ T-cell count drops precipitously. With the appearance of anti-HIV antibodies and $CD8^+$ T-cell responses, the viral load drops to a steady state and the $CD4^+$ T-cell count returns to levels within the reference range, although slightly lower than before the infection.

Seroconversion may take a few weeks, up to several months. Symptoms during this time may include fever, flulike illness, lymphadenopathy, and rash. These manifestations develop in approximately half of all people infected with HIV.

Asymptomatic HIV infection

At this stage of the infection, persons infected with HIV exhibit few or no signs or symptoms for a few years to a decade or more. Viral replication is clearly ongoing during this time,[68] and the immune response against the virus is

effective and vigorous. In some patients, persistent generalized lymphadenopathy is an outward sign of infection. During this period, the viral load, if untreated, tends to persist at a relatively steady state, but the $CD4^+$ T-cell count steadily declines. This rate of decline is related to, but not easily predicted by, the steady-state of viral load.

No firm evidence has shown that the initiation of therapy early in the asymptomatic period is effective. However, very late initiation is known to result in a less effective response to therapy and a lower level of immune reconstitution.

AIDS

When the immune system is damaged enough that significant opportunistic infections begin to develop, the person is considered to have AIDS. For surveillance purposes in the United States, a $CD4^+$ T-cell count less than 200/µL is also used as a measure to diagnose AIDS, although some opportunistic infections develop when $CD4^+$ T-cell counts are higher than 200/µL, and some people with CD4 counts under 200/µL may remain relatively healthy.

Many opportunistic infections and conditions are used to mark when HIV infection has progressed to AIDS. The general frequency of these infections and conditions varies from rare to common, but all are uncommon or mild in immunocompetent persons. When one of these is unusually severe or frequent in a person infected with HIV and no other causes for immune suppression can be found, AIDS can be diagnosed.[69]

Immunologic control of HIV

The primary mechanism for immunologic control of HIV appears to be CD8+ cytotoxic T-cells. T-cell responses are correlated with the steady-state of viral load and hence, the rate of progression.[70] Cellular immunity is apparently responsible for some multiple-exposed, but uninfected individuals.[71]

Although antibodies against HIV can be detected, it is clear that they are not sufficiently neutralizing to assist with immunologic control of the infection.

The role of NK (Natural Killer) cells may be important in the initial control of HIV. Escape mutations have been detected, implying that immunologic pressure on HIV exists from NK cells.[72]

Opportunistic infections and conditions

Even after starting therapy and with effective suppression of viral load, patients with persistently low CD4 counts remain at high risk for opportunistic infections. In general, all patients remain at a relatively high risk for opportunistic infections and other AIDS-related events for the first 6 months of antiretroviral therapy.[73] An observational study of 20,730 HIV patients in Uganda found that, among patients with more than six months of follow-up after the initiation of antiretroviral therapy, the pre-therapy CD4 cell count was still predictive of mortality.[74]

Although malaria is not typically considered an opportunistic infection, its incidence was found to be significantly higher among children in Tanzania who were perinatally infected with HIV than those without HIV infection.[75] This was

true for physician-diagnosed clinical malaria, probable malaria involving laboratory testing for parasitemia as well as malaria that was confirmed by blood smear.

There also appears to be an increased rate of anal cancer in high-risk groups (in particular, men who have sex with men). This is not very surprising considering the link between anal cancer and human papillomavirus (HPV), and the fact that cervical cancer, also caused by HPV, is considered as an AIDS-defining condition.[76]

HIV Encephalopathy is a severe condition usually seen in end-stage disease. Milder cognitive impairments may exist with less advanced disease. For example, one study found significant deficits in cognition, planning, coordination and reaction times in HIV-infected compared to uninfected children, effects that were more pronounced in those with higher viral loads.[77]

WHO clinical staging system for HIV infection and HIV related disease

World Health Organization has developed a clinical staging system (originally for prognosis), based on clinical criteria. The definition of symptoms, signs and diseases is according to clinical judgement. Clinical condition or performance score, whichever is the higher, determines whether a patient is at clinical stage 1, 2, 3 or 4. Clinical stage is important as a criterion for starting antiretroviral (ARV) therapy.[78]

WHO clinical staging system for HIV infection :

Primary HIV infection	• Asymptomatic • Acute retroviral syndrome
Stage 1	• Asymptomatic • Persistent generalized lymphadenopathy
Stage 2	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infections
Stage 3	• Unexplained severe weight loss (>10% of presumed or measured) • Unexplained chronic diarrhoea for longer than one month • Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month) • Persistent oral candidiasis • Oral hairy leukoplakia • PulmonaryTB(current) • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre) or chronic thrombocytopaenia (<50 × 109 per litre)
Stage 4	• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Disseminated mycosis (coccidiomycosis or histoplasmosis) • Recurrent non-typhoidal Salmonella bacteraemia • Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV associated tumours • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV associated nephropathy or symptomatic HIV associated cardiomyopathy[22]

Diagnosis

Screening for human immunodeficiency virus (HIV) infection is paramount, since infected individuals may remain asymptomatic for years while the infection progresses. Serologic tests are the most important studies in the evaluation for HIV infection.

Secondary testing that may be performed to assist with diagnosis or staging includes viral culture, lymph node biopsy, proviral DNA polymerase chain reaction (PCR) and genotyping of viral DNA/RNA.

Staging of HIV disease is based partially on clinical presentation, but other laboratory tests like CD4 count can help in deciding whether to initiate or to modify treatment.

Baseline laboratory studies for other infections (eg, tuberculosis) are important in the initial workup of a patient with newly diagnosed HIV infection. In addition, baseline levels of factors that may be affected by antiretroviral therapy (eg, lipids) should be measured.

Screening for HIV Infection

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians should screen for HIV in all adolescents and adults at an increased risk for HIV infection, including all pregnant women.[79]

The Centers for Disease Control and Prevention (CDC) recommends HIV screening for patients in all health-care settings, after the patient is notified that

testing will be performed unless the patient declines (opt-out screening). The CDC recommends that persons at high risk for HIV infection to be screened for HIV at least annually.[80]

Citing the benefits of early diagnosis and treatment and the failure of risk-based screening to identify a substantial proportion of HIV-infected patients early in the disease, the American College of Physicians recommends that clinicians shall adopt to routine screening for HIV and encourage all patients to be tested.[81]

HIV Testing

HIV infection is usually diagnosed through detection of antibodies to the virus. Production of these antibodies usually begins three to eight weeks after infection. The period following infection but before antibodies become detectable is known as the "window period". Diagnosis of HIV infection is also possible through detection of the virus (p24 antigen, nucleic-acid based tests or culture).[39]

HIV antibody tests

The most widely available method of identifying HIV-infected individuals is the detection of HIV antibodies in serum or plasma samples. The two main methods of testing for HIV antibodies are as follows.[39]

The enzyme immunoassay (EIA)

Enzyme immunoassays are probably the most efficient tests for testing large numbers of samples per day, as in large blood banks or for surveillance studies.[39]

Simple/rapid tests

Several antibody tests can equal the performance of EIA and do not need special equipment or highly trained staff. These tests are considered rapid if they take less than 10 minutes and simple if they take longer.[39]

There are four types of assays: agglutination, comb/dipstick, flow through membrane and lateral flow membrane. In most formats, the appearance of a clearly visible dot or line indicates a positive result. Many of the tests have an internal control sample, which validates each test run.[39]

A high-sensitive enzyme-linked immunoabsorbent assay (ELISA) should be used for screening. Most ELISAs can detect HIV-1 types M, N, and O and HIV-2.

A positive ELISA result should be followed with confirmatory testing in the form of one or more Western blot assays or similar specific assay. Specific diagnostic criteria vary by test. Results are typically reported as positive, negative, or indeterminate.

Testing for HIV-2 should be ensured in patients from an HIV-2 endemic area or those who have indeterminate results on HIV-1 Western blot testing. Not all HIV tests include detection of HIV-2 or Group O. In New York City, 62 cases of HIV-2 were detected over an 8-year period, of which 40 were initially misdiagnosed as HIV-1.[82]

Early detection using combination screens may be more effective than simply using serology. The additional detection of p24 antigen or viral RNA may

detect a greater number of very recent infections before seroconversion occurs. This would likely result in significant reductions in transmission as well as overall health costs and healthcare burden.[83]

Treatment

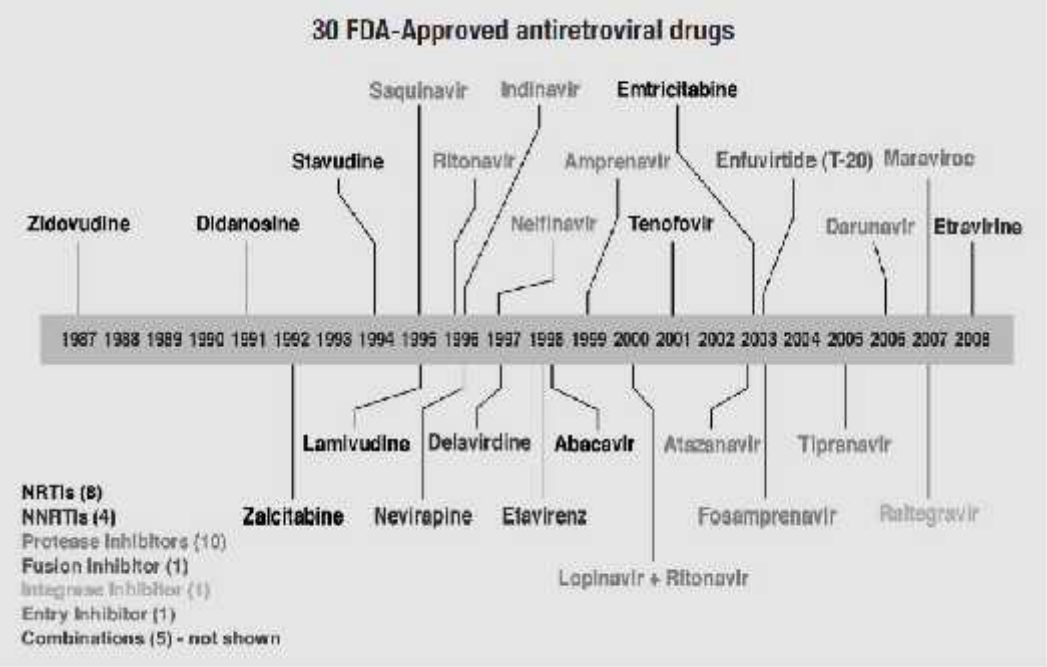


Figure 5. Antiretroviral drugs approved for HIV infection[84]

Research in the treatment of HIV infection has resulted in the development of 5 ARV drug classes: entry inhibitors, including fusion inhibitors and chemokine coreceptor (CCR) inhibitors; nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); integrase inhibitors; and protease inhibitors (PIs). With the approval of the first PIs, the treatment of HIV shifted to highly active ARV therapy (HAART). HAART refers to a combination of agents from ≥2 different ARV classes and is a standard approach for treating HIV infection today. The challenge of controlling HIV in patients with resistance to ARVs has contributed to

accelerated research in treatment with novel ARV activity. This research has led to the introduction of a CCR5 inhibitor, an integrase inhibitor, and a new NNRTI.

Currently available antiretroviral agents are classified as follows: [85]

- Nucleoside reverse transcriptase inhibitors (NRTIs).
- Non-nucleoside reverse transcriptase inhibitor (NNRTI's).
- Protease inhibitors (PI).
- Integrase inhibitors,
- Chemokine receptor antagonists and Entry (fusion) inhibitors.
- Maturation inhibitors

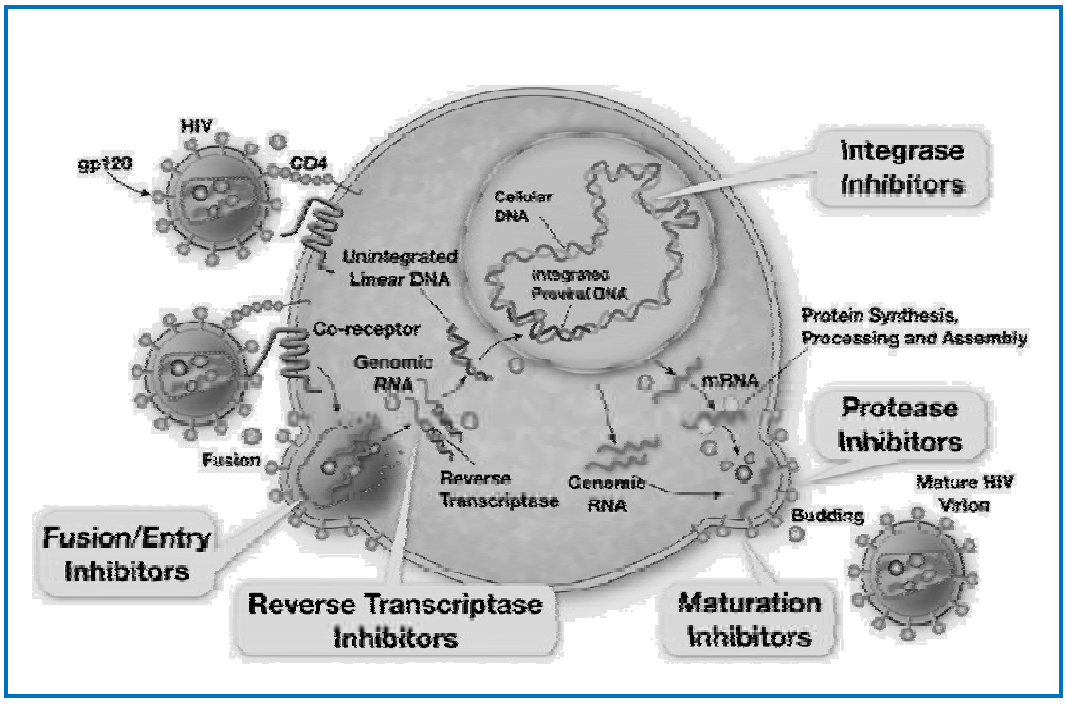


Figure 6. Targets of antiretroviral drugs in the HIV life cycle[84]

Antiretrovirals approved for use

NRTI	NNRTI	PI	Entry inhibitor	Intergrase inhibitor	Maturation inhibitors
Zidovudine	Nevirapine	Saquinavir	Enfuvirtide	Raltegravir	Bevirimat
Stavudine	Efavirenz	Indinavir	Maraviroc	Elvitegravir	
Lamivudine	Delavairidine	Ritonavir			
Didanosine	Etravirine	Lopinavir			
Zalcitabine		Atazanavir			
Abacavir		Amprenavir			
Emtricitabine					
Tenofovir					

Guidelines for the use of ARVs in adults and adolescents infected with HIV-1 were developed by the Department of Health and Human Services (DHHS) expert panel and these guidelines provide guidance to clinicians on when to initiate ARV treatment, preferred and alternative treatment choices and goals, also emphazing the use of ARVs in special population groups (eg, injection drug users, patients co-infected with hepatitis B virus [HBV] and/or hepatitis C virus [HCV]), and in the management of treatment-experienced patient. These guidelines also provide information on standard dosing for ARVs, dose adjustments for patients with renal and hepatic impairment, adverse events, and drug-drug interactions. Separate guidelines are available for the management of HIV infection in adults, adolescents, and children; the prevention of mother-to-child HIV transmission; and postexposure prophylaxis in occupational and nonoccupational settings. These guidelines focus on pertinent information regarding the treatment of adult and adolescent patients with chronic HIV-1 infection.[86]

ARV Treatment in India[87]

Regimen	National ART regimen	Preference
Regimen I	Zidovudine+Lamivudine +Nevirapine	Preferred regimen for patients with Hb >9 gm/dL
Regimen I (a)	Stavidine+Lamivudine +Nevirapine	For patients with Hb >9 gm/dL
Regimen II	Zidovudine+Lamivudine +Efavirenz	Preferred for patients on anti-tuberculosis treatment if Hb >9 gm/dL
Regimen II (a)	Zidovudine+Lamivudine +Nevirapine	Preferred regimen for patients with Hb >9 gm/dL
Regimen III	Tenofovir+Lamivudine +Nevirapine	For patients not tolerating ZDV or
Regimen III (a)	Tenofovir +Lamivudine + Efavirenz	For patients not tolerating ZDV or d4T on efavirenz regime
Regimen IV	Zidovudine+Lamivudine +Atazanavir + Ritonavir	Patient not tolerating NVP and EFV; Hb > 8 g/dL
Regimen IV	Stavidine+Lamivudine +Atazanavir / Ritonavir	For patients not tolerating NVP and EFV and Hb <8 gm/dL
Regimen V	Tenofovir +Lamivudine +Atazanavir+Ritonavir	

As of date, the FDA has approved 26 ARVs. Of this, 19 are available in India.[87]

ART Treatment guidelines

The DHHS panel strongly recommends obtaining an HIV genotypic resistance assay, which may detect baseline (ie, transmitted) viral resistance mutations and helps as a guide for the selection of ARV regimen, before ARV treatment is initiated. This recommendation was implemented after drug-resistant HIV strains (particularly strains resistant to NNRTIs) were detected in up to 15% of patients previously untreated with ARVs.[86]

The panel's recommendations regarding when to initiate ARV therapy are summarized in Table.[88] A standard ARV regimen consists of a combination of 2 NRTIs plus 1 NNRTI or a combination of 2 NRTIs plus 1 PI. In most cases, the PI is boosted with a low dose of ritonavir (100–400 mg/d) to enhance the plasma level of the PI through inhibition of the PI's metabolism via the CYP3A4 pathway. This ritonavir boosting effect also increases the threshold for resistance development and is a recommended approach for patients treated with most PIs, with the exception of nelfinavir.[86]

Recommendations for starting ARV therapy in patients chronically infected with HIV-1[88]

Clinical condition / CD4 T lymphocyte count	Recommendations
• History of AIDS defining illness such as an opportunistic infection (e.g., Toxoplasma encephalitis, pneumocystis jiroveci pneumonia) • CD4 T lymphocyte count ≤ 350 cells/mm^3 • Patients who are pregnant • Patients who are coinfected with HBV infection when HBV treatment is indicated • Patients who have HIV associated nephropathy	ARV therapy should be initiated
• Asymptomatic patients with CD4 T lymphocyte count > 350 cells/mm^3 who do not meet any of the conditions described above	The optimal time to start ARV therapy is not clearly defined. Benefits and risks of treatment initiation should be considered

Generally, in the absence of significant viral resistance at baseline, either an NNRTI- or a PI-based regimen is initiated, depending on factors such as concomitant medical conditions, pill burden, confidentiality (certain ARVs, such as ritonavir, should be refrigerated), and side effect profiles.[88]

Efavirenz is a preferred NNRTI; when this agent is combined with NRTIs, the regimen has a low pill burden. Efavirenz has been associated with CNS side effects including dizziness, drowsiness, vivid dreams, sleep disturbance, and hallucinations. In clinical trials, 53% of patients receiving efavirenz reported CNS symptoms compared with 25% of patients in the control arm. Although CNS side effects resolve over time in most patients, these potential effects should be considered before efavirenz therapy is initiated.[86]

Efavirenz is not a favorable option for pregnant women (especially during the first trimester of pregnancy) or for women of child-bearing age who are not on contraceptives, as this agent has a teratogenic potential (pregnancy category D). Nevirapine is an alternative NNRTI treatment option; however, this agent is less commonly prescribed than efavirenz in the United States because of its association with liver toxicity (particularly in patients with high pre-nevirapine $CD4^+$ T lymphocyte counts) and skin rash (including severe reactions such as Stevens-Johnson syndrome). In the PI class, the preferred agents for initial therapy include ritonavir-boosted atazanavir, ritonavir-boosted darunavir or fosamprenavir, or fixed-dose lopinavir/ritonavir.[88]

ARV components recommended for treatment of HIV-1 infection in previously untreated patients[88]

	NNRTI or PI options		Dual NRTI options
Preferred components	NNRTI Efavirenz or PI – Atazanavir + ritonavir once daily Darunavir + ritonavir once daily Fosamprenavir + ritonavir twice daily Lopinavir / ritonavir once or twice daily	Preferred components	Tenofovir/emtricitabine once daily
Alternative to preferred	NNRTI – Nevirapine Or PI – Atazanavir (Unboosted) once daily Fosamprenavir (Unboosted) once daily Fosamprenavir + ritonavir once daily Saquinavir + ritonavir twice daily	Alternative to preferred	Abacavir / lamivudine once daily for patients who test negative for HLA-B 5701 Or Zidovidine / lamivudine twice daily Or Didanosine + emtricitabine or lamivudine

- An ARV regimen is constructed by combining 1 component from column A and 1 component from B
- Efavirenz is not recommended for use during the first trimester of pregnancy or in sexually active women with child bearing potential who are not using contraception
- Nevirapine should not be initiated in women with CD4 T lymphocyte counts> 250 cells/mm^3 or in men with CD4 T lymphocyte counts > 4000 cells/mm3 because of an increased risk of symptomatic liver related events.
- Atazanavir must be boosted with ritonavir used in combination with efavirenz or tenofovir

The preferred dual NRTI to be used in combination with an NNRTI or a PI is tenofovir/emtricitabine. Alternatively, abacavir/lamivudine may be used in patients who test negative for HLA-B*5701 (abacavir hypersensitivity reaction test); zidovudine/lamivudine or didanosine EC combined with emtricitabine or lamivudine can also be used in combination with an NNRTI or a PI.[88]

The DHHS panel also addresses management of HIV infection in treatment-experienced patients who experience virologic or immunologic failure. Generally, the approach for these patients involves a detailed review of ARV treatment history, past intolerance to ARVs, historical and current resistance assay results, concomitant therapies, and medical conditions. Clinical trials of novel ARVs or treatment approaches for previously treated patients should be considered, if available. Also, when relevant and if available, therapeutic drug monitoring (TDM) for ARVs may be considered.[88]

ARV adverse events

The success of ARV therapy greatly depends on the patient's adherence to the treatment regimen. The detrimental effect of poor adherence is the emergence of viral strains that are resistant to ARVs. One of the common causes of suboptimal adherence to ARV therapy is poor tolerance of medications. Adverse events associated with ARVs can be classified as short term (GI adverse events) and long-term (changes in body fat composition).[24] Selected ARV-related adverse events are summarized in Table.

Selected ARV class – related adverse effects[88]

NRTIs	GI intolerance Peripheral neuropathy Lactic acidosis; pancreatitis Bone marrow suppression Lipoatrophy (most common with thymidine analogues stavudine and zidovudine) Renal toxicity (Tenofovir > other NRTIs)
NNRTIs	Rash Liver toxicity Dyslipidemias
PIs	GI intolerance Metabolic complications: Fat maid distribution, dyslipidemia, insulin resistance Injection site reactions GI intolerance Respiratory infections (pneumonia) Myalgias
CCR5 inhibitors	Liver toxicity GI intolerance
Integrase inhibitors	Nausea Diarrhoea Headache Pyrexia

WHO recommendations[89]

The new WHO 2013 guidelines to start ART in people living with HIV are as below;

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm3.

- ART should be initiated in all individuals with HIV with CD4 count >350 cells/mm³ and ≤ 500 cells/mm3 regardless of WHO clinical stage (strong recommendation, moderate-quality evidence). ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:

- Individuals with HIV and active TB disease (strong recommendation, low-quality evidence).

- Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease (strong recommendation, low-quality evidence).

- Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence).

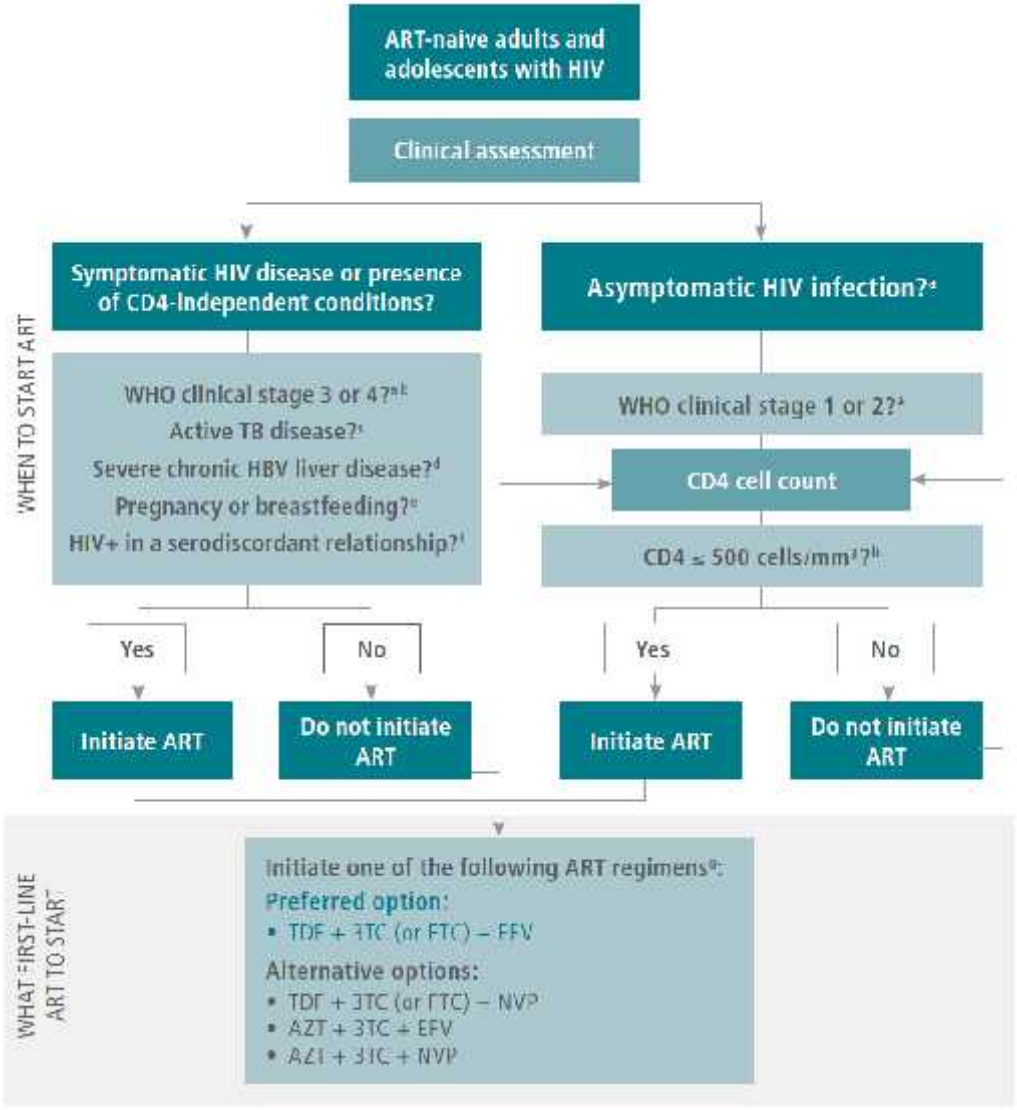


Figure 7. WHO 2013 guidelines to start ART in people living with HIV[89]

The continuing success of potent antiretroviral therapy (ART) has resulted in dramatic reductions in HIV-associated morbidity and mortality. HIV-infected individuals are now living longer. This longer life span has exposed them to the effects of aging, and other host and environmental factors known to increase the risk of obesity, diabetes, and CVD in the general population. The HIV virus itself can cause lipid abnormalities including high triglycerides and low HDL cholesterol, and the side-effects of antiretroviral medications have also been associated with metabolic and body shape changes.[90]

Metabolic syndrome

Despite abundant research on the subject of MetS, the criteria used for diagnosing MetS are different across studies, causing confusion when assessing prevalence rates across countries. To aid in the clinical practice and research of the syndrome, the WHO,[91] the EGIR,[92] the NCEP,[16] the AACE[93] and the IDF[94] have proposed different definitions.

The new IDF definition emphasizes the importance of central obesity defined by ethnic specific values. WHO,[91] the EGIR,[92] the NCEP,[16] the AACE[93] and the IDF[94] definitions of MetS are as below.

<u>WHO definition</u>[91]

Diabetes (fasting plasma glucose ≥7.0 mmol/l and/or 2-hour plasma glucose ≥11.1 mmol/l), or impaired glucose regulation (fasting plasma glucose 6.1-6.9 mmol/l and/or 2-hour plasma glucose 7.8-11.0 mmol/l), and/or insulin

resistance (below lowest quartile of glucose uptake in the euglycaemic clamp), and two or more of the following:

- Raised triglycerides (≥1.7 mmol/l or > 150 mg/dL) and/or low HDL-cholesterol (<0.9 mmol/l in men, < 1.0 mmol/l in women).
- Central obesity (waist-to-hip ratio >0.90 in men, >0.85 in women) and/or body mass index (BMI) >30 kg/m^2.
- Raised blood pressure (systolic blood pressure ≥140 mmHg / diastolic blood pressure ≥90 mmHg).
- Microalbuminuria (urinary albumin excretion rate ≥20 μg/min or albumin/creatinine ratio ≥30 mg/g).

EGIR definition for non-diabetic individuals[92]

Hyperinsulinaemia (fasting insulin concentrations in the highest quartile) and at least two of the following:

- Hyperglycaemia (fasting plasma glucose ≥6.1 mmol/l or 110 mg/dL).
- Central obesity (waist circumference ≥94 cm in men, ≥80 cm in women).
- Hypertension (systolic blood pressure ≥140 mmHg and/ diastolic blood pressure ≥90 mmHg or treated for hypertension).
- Dyslipidaemia (triglycerides >2.0 mmol/l [>178 mg/dL] or low HDL-cholesterol < 1.0 mmol/l [<39 mg/dL] or treated for dyslipidaemia).

NCEP definition[16]

Three or more of the following:

- Abdominal obesity (waist circumference >102 cm in men, >88 cm in women).
- Triglycerides ≥1.7 mmol/l (> 150 mg/dL).
- HDL-cholesterol < 1.03 mmol/l in men (< 40 mg/dL), <1.29 mmol/l in women (< 50 mg/dL).
- Systolic blood pressure ≥130 mmHg and/ diastolic blood pressure ≥85 mmHg.
- Fasting plasma glucose ≥6.1mmol/l (≥ 110 mg/dL).

AACE definition for non-diabetic individuals[93]

Two or more of the following:

- Triglycerides ≥1.7 mmol/l (≥ 150 mg/dL).
- HDL-cholesterol < 1.03 mmol/l (< 40 mg/dL) in men, <1.29 mmol/l (< 50 mg/dL) in women.
- Systolic blood pressure ≥130 mmHg and/ diastolic blood pressure ≥85 mmHg or current use of antihypertensive medications.
- 2-hour plasma glucose 7.8-11.0 mmol/l or fasting plasma glucose 6.1-6.9 mmol/l (IFG) (IFG was added in updated AACE criteria).

IDF definition[94]

Central obesity defined as ethnicity specific values of waist circumference (≥ 90cm for South Asian men and ≥80cm for South Asian women) and at least two of the following:

- Raised triglycerides levels (≥1.7 mmol/l or > 150 mg/dL), or specific treatment for this lipid abnormality.
- Reduced HDL-cholesterol (< 1.03 mmol/l in men, <1.29 mmol/l in women), or specific treatment for this lipid abnormality.
- Raised blood pressure (systolic blood pressure ≥130 mmHg and/diastolic blood pressure ≥85 mmHg), or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose (≥5.6 mmol/l), or previously diagnosed type 2 diabetes.

  If above 5.6 mmol/l, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Presentation

History

As with other diseases, careful history taking is important in metabolic syndrome. Even though the condition is diagnosed based on physical and laboratory features, it may be suspected if symptoms of any of the component

disorders are present, such as the increased hunger, thirst, or urination that may accompany hyperglycemia. Patients reporting a history of hypertension, dyslipidemia warrant screening for metabolic syndrome. Symptoms suggesting the risk of cardiovascular and other complications, such as chest pain or shortness of breath, must be investigated carefully. As lifestyle changes can ameliorate the condition, attention should be paid to the patient's dietary habits and exercise routine so that areas for improvement can be identified.

The social history is important for identifying additional risks, such as tobacco use, which may exacerbate the increased cardiovascular complications associated with metabolic syndrome. A family history should be obtained because genetics may play an important role in metabolic syndrome. This feature of the disease is under active investigation; however, currently no gene or group of genes has been implicated consistently, suggesting that the environment exerts substantial influence.[95]

Physical examination

The physical examination is crucial in patients with metabolic syndrome as the findings of elevated blood pressure and abdominal obesity are 2 of the 5 diagnostic criteria. Measurement and documentation of waist circumference is an important routine when screening for metabolic syndrome. Additionally, the examination may reveal findings reflective of the other criteria. For example, patients with insulin resistance and hyperglycemia or diabetes mellitus may have acanthosis nigricans, hirsutism, peripheral neuropathy, and retinopathy. Patients

with severe dyslipidemia may have xanthomas or xanthelasmas. The presence of arterial bruits may portend a higher risk of cardiovascular complications.

Diagnosis

Initial laboratory studies in patients suspected of having metabolic syndrome should include standard chemistry methods to assess for hyperglycemia and renal dysfunction and also lipid studies should to be done to assess for hypertriglyceridemia or low HDL levels.

If a family history of early coronary or other atherosclerotic disease is present, consider including, in addition to HDL-C,the low-density lipoprotein cholesterol (LDL-C), studies of lipoprotein(a), apolipoprotein-B100, high-sensitivity C-reactive protein (CRP), and (if the patient does not merit to the lowest LDL-C target [< 70]), then consider homocysteine and fractionated LDL-C.

In view of the various associations between metabolic syndrome and other conditions discussed, additional blood tests such as thyroid function tests and liver function tests, hb-A1C levels, and uric acid may be of a greater value and help. Hyperuricemia appears to be much more common in patients with metabolic syndrome than in the general population, and this is attributed to the inflammatory effects of metabolic syndrome.[96] Further studies should be pursued as clinical findings dictate.

Metabolic syndrome and HIV

Metabolic syndrome (MetS) is an aggregation of central obesity and metabolic abnormalities that confers an increased risk of CVD and type 2 diabetes. Since its introduction, the definition of MetS has been under scrutiny especially since it excludes known CVD risk factors such as smoking. The existence of MetS as a diagnostic entity is also controversial, and there is a limited data in HIV-infected populations.[90]

The age-adjusted prevalence of MetS in the adult US population is 34.3%[97] in HIV-infected populations, the estimated prevalence ranges from 7%–45%.[98] Data on the incidence of MetS in HIV-infected individuals receiving potent ART is limited by the cross-sectional nature of most of the studies.

A US-based HIV-infected cohort that included both treatment-experienced and treatment-naive individuals reported an incidence of 1.2 per 100 person-months,[99] and an international study of HIV-infected adults initiating ART reported an incidence of 12 per 100 person-years.[100] Most of the existing data on factors associated with MetS are from cross-sectional studies;[101] few studies have examined factors associated with MetS among ARV-naive individuals after starting potent ART.

Since the introduction of highly active antiretroviral therapy (HAART) for HIV, the decline in morbidity and mortality has been clouded by the emergence of a number of metabolic derangements. These disorders include dyslipidemia, insulin resistance, abnormalities of glucose metabolism, and changes in fat distribution. Hypertriglyceridemia, low high-density lipoprotein

cholesterol (HDL-C), insulin resistance, and increased waist circumference can occur simultaneously in HIV infection and are reminiscent of metabolic syndrome, which increases the risk of cardiovascular disease (CVD). CVD may be increased in HIV infection, and much of the increased risk may be related to components of metabolic syndrome.[102]

Recently, there has been debate over the extent to which metabolic syndrome represents a coherent syndrome with a major underlying cause, such as insulin resistance, or a group of risk factors that, when occurring together, lead to disproportionately increased risk of CVD. In the context of HIV, the individual metabolic disorders of the syndrome clearly have different identifiable causes and are not associated with one another.[102]

Prevalence of Metabolic Syndrome in HIV Infection

The prevalence of metabolic syndrome in HIV-infected people has been evaluated, but different definitions were used. Most studies found a prevalence of 11% to 26% in HIV-infected patients, with the exception of three early studies from a single group in Pavia, Italy, whose patients were all on HAART.[24,103-114] This prevalence of metabolic syndrome may be comparable or slightly less than that in the general population, at least in the United States.

Studies of the prevalence of metabolic syndrome in HIV infection

Study/year	Prevalence	Criteria	Study population	*Comments*
Gazzaruso et al./2002[110]	45.4% HIV+	NCEP-ATP III	553 Italian HIV+, all on HAART regimens not described)	
Bruno et al./2002[107]	39.8% HIV+ 6% HIV-negative controls	EGIR	201 Italian HIV+, all on HAART (regimens not described) 201 HIV-negative were matched by age and gender	*Italian HIV-negative patients in this study have an unusually low prevalence of metabolic syndrome*
Gazzaruso et al./2003[109]	33.1% HIV+ 2.4% HIV-negative controls	EGIR	287 Italian HIV+ on HAART; HIV-negative matched by age & gender	*Italian HIV-negative patients - An unusually low prevalence of MS*
Jerico et al./2005[112]	17% HIV+ overall 5.1% < 30 y 27.0% 50–59 y	NCEP-ATP III	710 HIV+, Barcelona, Spain	*Associated with stavudine and lopinavir/ritonavir*
Bonfanti et al./2006[106]	22% HIV+ 23.8% men 17.4% women	NCEP-ATP III	1243 Italian HIV+ from SIMONE multicenter study	*Associated with age, BMI, lipodystrophy, and indinavir use*
Jacobson et al./2006[111]	24% NFHL HIV+ 34% NHANES HIV-negative	NHLBI/AMA	477 HIV+ patients in NFHL Study (of US HIV+) compared with 1876 HIV-negative patients in NHANES	*Associated with lopinavir/ritonavir*
Bergersen et al./2006[103]	13.3% of all HIV+ patients; 1.8% of HAART naïve 16.4% of HAART therapy 16.0% of controls In non-overweight patients: 15% in HAART HIV+ 2% in HAART naïve 2% controls	Essentially NCEP-ATP III	357 patients: 56 HIV+ HAART naïve 207 HIV+ on HAART (regimens not described) 94 HIV-negative controls in Scandinavia	*Associated with HAART, age, and lipodystrophy*
Estrada et al./2006[108]	15.8% HIV+ on therapy 3.2% HIV-negative	NCEP-ATP III	146 HIV+ patients in Madrid, Spain 159 HIV-negative patients matched by BMI	*Associated with elevated HOMA and lipodystrophy*
Samaras et al./2007[114]	14% HIV+ 12% all men 25% all women 18% HIV+	IDF NCEP-ATP III	788 HIV+ (451 with clinical lipodystrophy) from Lipodystrophy Case Definition Cohort (international multicenter)	*Associated with PI use*
Bernal et al./2007[104]	11.4% HIV	IDF	210 HIV+ from Mediterranean Spain	*Associated with age and BMI*
Mondy et al./2007[113]	25.5% HIV+ 26.5% HIV−	NCEP-ATP III	471 HIV+ from US NHANES (2001–2002) matched for age, gender, ethnicity, tobacco use	*Associated with age, white ancestry, greater BMI, and higher CD4*
Bonfanti et al./2007[105]	*20.8% HIV+* *15.8% HIV-negative (P < 0.0001)* *22.1% HIV+* *20.5% HIV− (P < 0.0001)*	*NCEP-ATP III* *IDF*	*1243 Italian HIV+ from SIMONE* *922 HIV-negative unmatched Italian controls from PAMELA*	

Participants having 3 or more of the following criteria were defined as having the metabolic syndrome:

1. Abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women);
2. High level of fasting glucose (= 6.1 mmol/L or on antidiabetic medication);
3. Low level of high-density lipoprotein cholesterol (< 1.0 mmol/L in men and < 1.3 mmol/L in women);
4. Hypertriglyceridemia (> 1.7 mmol/L); and
5. Elevated blood pressure (≥130/≥85 mm Hg [both] or on antihypertensive medication).

A multi-center AIDS Cohort study reported a prevalence of 33% (OR=1.43, p= 0.002) among HIV-infected men in comparison to 27% among the HIV-negative controls with increased waist circumference being the most frequently occurring component in both HIV-infected and HIV- uninfected men.[115]

Another study reported prevalence of metabolic syndrome was 24% (95% CI: 21% to 28%). The most common metabolic abnormalities were low HDL (prevalence = 54%, 95% CI: 49% to 58%) and high triglycerides (prevalence = 47%, 95% CI: 42% to 51%), and the least common was high blood glucose (prevalence = 4%, 95% CI: 3% to 7%). The prevalence of high blood pressure and abdominal obesity were 33% (95% CI: 29% to 37%) and 25% (95% CI: 22% to 30%), respectively. The study also highlighted that the risk of developing metabolic syndrome was 80% higher among those with at least a 0.5-log increase in viral load in the previous six months while, the risk was two times higher in those using lopinavir/ritonavir or ddI.[99]

A study reported that, current protease inhibitors use was an independent predictor of an increased level of triglycerides only (p=0.03). Patients who had a history of stavudine use were also more likely to have higher triglyceride levels than those who had no history of stavudine use (p=0.05). Stavudine use was not associated with changes in BMI or waist circumference. Current NNRTI use and lower HIV RNA levels were found to be significant predictors of higher HDL cholesterol for both, whereas an increased duration of HIV infection was significantly associated with lower HDL cholesterol levels (p=0.05).[113]

Another study showed the prevalence of metabolic syndrome in HIV positive patients as 26.6%; 43.3% in the ART-treated group, and 10% in the ART naïve group.[116]

An Indian study showed that, 19% (according to IDF criteria) and 25% (according to NCEP III) of HIV patients on ART developed metabolic syndrome.[117]

Another study reported that, at baseline, in the HIV-positive and negative groups, respectively, 40% and 36% had IR by HOMA (>2.0), 92% and 55% had low HDL (M<40; W<50 mg/dl; p < 0.001) and 15% and 23% had high TG (>150 mg/dl), showing high frequency of metabolic syndrome among HIV-positive patients due to low HDL and high insulin resistance.[118]

A study showed prevalence of untreated HIV patients was 18% whereas in treated group it increased to 28.4% in d4T ARV sub group patients and 40% in patients treated with protease inhibitor based therapy.[119]

A study from Italy compared 1263 HIV-infected patients from the Sindrome Metabolica ONE (SIMONE) cohort to the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) cohort, a sample of the general Italian population. The group of HIV-infected patients was not matched with the healthy controls and had a higher percentage of men, lower BMI, and higher rate of smoking. By ATP III criteria, the HIV-infected patients had a higher prevalence of metabolic syndrome than the controls (20.8% vs 15.8%), but the difference was smaller using IDF criteria (22.1% vs 20.5%). The difference remained after multivariable adjustment. However, the HIV-negative cohort data was collected 10 years prior to data collection in the HIV cohort, making it likely that the prevalence of metabolic syndrome was underestimated in controls due to increase in the incidence of obesity in recent years.[105]

Three early studies[107,109,110] on populations in Pavia, Italy had reported an even higher prevalence of metabolic syndrome in HIV infection, ranging from 33.1% to 45.4%. Age and gender-matched controls were included in two of the three studies and the prevalence of metabolic syndrome in the healthy population was 2.4% and 6%, respectively, which is clearly lower than the prevalence in the general Italian population, suggesting that the controls in these studies were unusually healthy.

Characteristics of MS in HIV-infected versus control patients

The profile of metabolic syndrome differs between HIV-infected patients and the general population. As discussed in the next section, these differences can be attributed to the effects of HIV and its therapy. Although different definitions

of metabolic syndrome were used in these studies (ATP III, EGIR, NHLBI), the most commonly achieved metabolic criteria for metabolic syndrome in HIV infection were hypertriglyceridemia and low HDL-C. In contrast, the most common features contributing to metabolic syndrome in the NHANES cohort by ATP III criterion was abdominal obesity, low HDL-C, and hypertension, followed by hypertriglyceridemia. The opposite was true in HIV infection, where the least common criteria met were increased waist circumference or BMI. In studies with control groups, the HIV-infected cohorts had lower rates of abdominal obesity and BMI than control groups.[102]

Some studies[103,104,106] link the presence of metabolic syndrome in the HIV-infected population to the common factors of age, white ancestry, greater BMI, and higher homeostasis model assessment. Among the HIV-related factors, higher CD4 cell count, lipodystrophy, and use of HAART, protease inhibitors (PIs), lopinavir/ritonavir, indinavir, and stavudine have been associated with metabolic syndrome.[102]

Deconstructing Metabolic Syndrome in the Setting of HIV

A syndrome usually implies that components are associated with one another. Alternatively, the cluster of components confers a risk beyond that of the sum of individual components.

In the general population, there is some evidence for clustering of components in metabolic syndrome. For example, Reaven and others[120] have shown that insulin resistance is associated with dyslipidemia (low HDL-C and

elevated triglyceride levels), hypertension, and a predisposition toward diabetes, which predicts CVD.

Due to similar questions arising from a proposed HIV-lipodystrophy syndrome, there has been extensive research dissecting out the relationships among insulin resistance, dyslipidemia, and fat changes in HIV-infected patients. Shortly after the introduction of PIs for HIV, the term "lipodystrophy syndrome" was used to describe a constellation of symptoms that included insulin resistance, dyslipidemia (low HDL-C and higher low-density lipoprotein cholesterol [LDL-C] and triglyceride levels), increased abdominal fat, and decreased peripheral fat.[121] This syndrome had several features reminiscent of metabolic syndrome in the general population. It was rapidly attributed to PI therapy in cross-sectional cohort studies[121] despite earlier research in which individual components of the lipodystrophy syndrome occurred in the absence of PI use.[122]

However, recent studies show that these metabolic disorders are not all caused by PIs and are not always associated with one another. The presence of individual components can often be attributed to independent factors, such as specific antiretroviral drugs, HIV disease, and/or restoration of health.

HIV-related factors affecting diagnosis of MS dyslipidemia: hypertriglyceridemia and low HDL-C

Before the introduction of HAART, HIV infection was associated with dyslipidemia.[123] Early in the course of infection, HDL-C plummets to levels around 25 mg/dL. With progression of HIV, LDL-C decreases slightly. With advanced disease, such as AIDS, triglycerides and very low-density lipoprotein

cholesterol (VLDL-C) cholesterol increase. There is a strong negative correlation between HIV RNA levels and HDL-C levels.[124] The association is weaker with LDL-C levels. Only very high HIV RNA levels are associated with increased triglycerides and VLDL-C. Low CD4 cell count is associated with low HDL-C levels but not with LDL-C, VLDL-C, or triglyceride levels.

Hypertriglyceridemia is thought to be due to decreased clearance of triglycerides and, to a lesser extent, increased production of VLDL. These changes are associated with elevated levels of the cytokine interferon-α, which mediates the host response to viral infection. In contrast, interferon-α is not associated with low HDL-C.[123]

These data show clear dissociations of the contributing factors to triglycerides and HDL-C in HIV infection, although triglycerides and HDL-C are tightly linked in the general population. Indeed, in two definitions of metabolic syndrome (WHO and EGIR), the dyslipidemia criteria could even be met by either hypertriglyceridemia or low HDL-C.

The effects of HIV therapy confirm the dissociation of HDL-C and triglycerides. Early cross-sectional cohort studies suggested that PIs were associated with lower HDL-C levels, but this has not been substantiated with prospective trials. Studies in healthy volunteers show that treatment with the PIs ritonavir, lopinavir/ritonavir, indinavir, and atazanavir does not change HDL-C levels. In HIV infection, some, but not all, trials have found modest increases (13%–21%) in HDL-C levels with atazanavir, nelfinavir, indinavir, and amprenavir. The non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs

nevirapine and efavirenz also increase HDL levels. None of these drugs restores HDL-C to normal levels in those who begin therapy with HDL-C levels around 25 mg/dL.[102]

In contrast, hypertriglyceridemia is commonly caused by ritonavir-based regimens. Full-dose ritonavir, which is no longer commonly used, can cause a two- to threefold increase in triglyceride levels. When the combination of lopinavir and ritonavir was given to healthy volunteers for 4 weeks, triglyceride and VLDL-C levels increased by 83% and 33%, respectively. In the studies of metabolic syndrome in HIV-infected patients, only a ritonavir-based PI regimen has been linked with hypertriglyceridemia. Ritonavir has been shown in vitro to inhibit the degradation of apolipoprotein B and increase sterol regulatory element binding proteins in the liver, which may increase VLDL-C production.[102]

Other antiretroviral therapies, including efavirenz and the nucleoside reverse transcriptase inhibitor (NRTI) stavudine, may be associated with hypertriglyceridemia. It should be emphasized that ritonavir, efavirenz, and stavudine induce hypertriglyceridemia without the decrease in HDL-C expected from studies of hypertriglyceridemia in patients without HIV.[102]

PIs do not induce hypertriglyceridemia by inducing insulin resistance. The PI indinavir most effective in inducing insulin resistance in healthy volunteers, did not induce hypertriglyceridemia.[125] Lopinavir/ritonavir induces significant hypertriglyceridemia whereas it has a little effect on insulin resistance.[126]

Insulin resistance, glucose metabolism, and diabetes

Consistent with early studies linking insulin resistance with other components of metabolic syndrome,[120] insulin resistance or disturbances in glucose metabolism are included as criteria in each of the syndrome definitions. Insulin resistance is a required criterion in the WHO[91] and EGIR[92] definitions. Elevated glucose is required for the IDF definition.[94]

In the setting of HIV, insulin resistance has a number of causes, including antiretroviral therapy (certain PIs and to a lesser extent certain NRTIs). The mechanism of induction by these PIs is partially understood and differs from insulin resistance in the general population. HIV-related insulin resistance does not seem to be associated with other aspects of the syndrome.

The PI indinavir has the most dramatic effect on insulin-mediated glucose disposal. Indinavir given for 4 weeks to healthy normal volunteers caused a 17% decrease in insulin-mediated glucose disposal (insulin sensitivity).[125] A single dose of indinavir induced a greater (34%) decrease in insulin-mediated glucose disposal. A single dose of full-dose ritonavir, which is no longer used, decreased insulin-mediated glucose disposal by 15%; the effect of chronic administration is unknown.[102] Lopinavir/ritonavir has less of an effect on insulin sensitivity, but the magnitude of this effect is not clear. In healthy volunteers, a single dose of lopinavir/ritonavir decreased insulin-mediated glucose disposal by 13%, but 4 weeks of lopinavir/ritonavir had no effect on insulin sensitivity.[126] Several PIs (amprenavir, atazanavir, and tipranvir) have no effect on insulin sensitivity.[102]

PIs induce insulin resistance by a novel mechanism that does not resemble the insulin resistance found in patients with type 2 diabetes or obesity, which involves most aspects of insulin action. Rather, PIs acutely block transport of glucose by the insulin-sensitive glucose transporter GLUT4. In vitro studies have shown that PIs selectively inhibit glucose transport in adipocytes without affecting early insulin-signaling events or translocation of intracellular GLUT4 transporters to the cell surface.[102]

Because PIs do not block insulin signaling, they may have little effect on fatty acid (FA) metabolism. Indeed, indinavir, which induces the most insulin resistance, has no effect on FA levels, insulin suppression of FA, or triglyceride levels.[125] Lopinavir/ritonavir induces hypertriglyceridemia under conditions where insulin still fully suppresses FAs.[126] Thus, the HIV drug–specific effects do not link insulin resistance to other intermediary derangements observed in metabolic syndrome.

NRTIs, specifically stavudine, may have an effect on insulin sensitivity. Less is known about the mechanisms.[102]

There are other effects of PIs on glucose metabolism that are not fully understood. Chronic administration of indinavir induces small increases in fasting glucose and insulin levels, which are not easily attributed to an effect on GLUT4. Indinavir also increases endogenous glucose production and blunts insulin suppression of endogenous glucose production in healthy volunteers. The mechanism by which indinavir affects endogenous glucose production is not known. No other PI has been shown to increase fasting glucose.[102]

There may be other independent effects of PI on glucose tolerance. When healthy volunteers with normal glucose tolerance were given indinavir for 4 weeks, three of 10 developed impaired glucose tolerance or diabetes. Even when PIs have little or no effect on insulin-mediated glucose disposal (atazanavir/ritonavir or lopinavir/ritonavir), they may still induce deterioration in glucose tolerance. The mechanism by which PIs impair glucose tolerance is not fully understood.[102]

Fat distribution in HIV infection: implications for metabolic syndrome

All definitions of metabolic syndrome include central obesity. Central obesity is required to meet the IDF definition, which uses different waist circumferences for ethnic groups as well as for gender. An alternative view of metabolic syndrome is that visceral obesity is the driving mechanism for insulin resistance, hypertriglyceridemia, low HDL-C, and hypertension. Changes in fat distribution that occur in HIV infection were first thought to be similar, but as is discussed in the following text, the HIV-specific change may actually lead to underestimation of the prevalence of metabolic syndrome.[102]

Early after the introduction of HAART, reports appeared of facial lipoatrophy (fat loss), increased upper trunk fat (buffalo hump), lipoatrophy of the arms and legs, and abdominal obesity. They were rapidly synthesized into a single syndrome of peripheral lipoatrophy with central lipohypertrophy that was attributed to PIs.[121] Peripheral lipoatrophy was different from the cachexia previously seen in HIV infection. Many felt that the peripheral lipoatrophy

resulted in compensatory central lipohypertrophy, which would lead to metabolic syndrome with increased CVD.

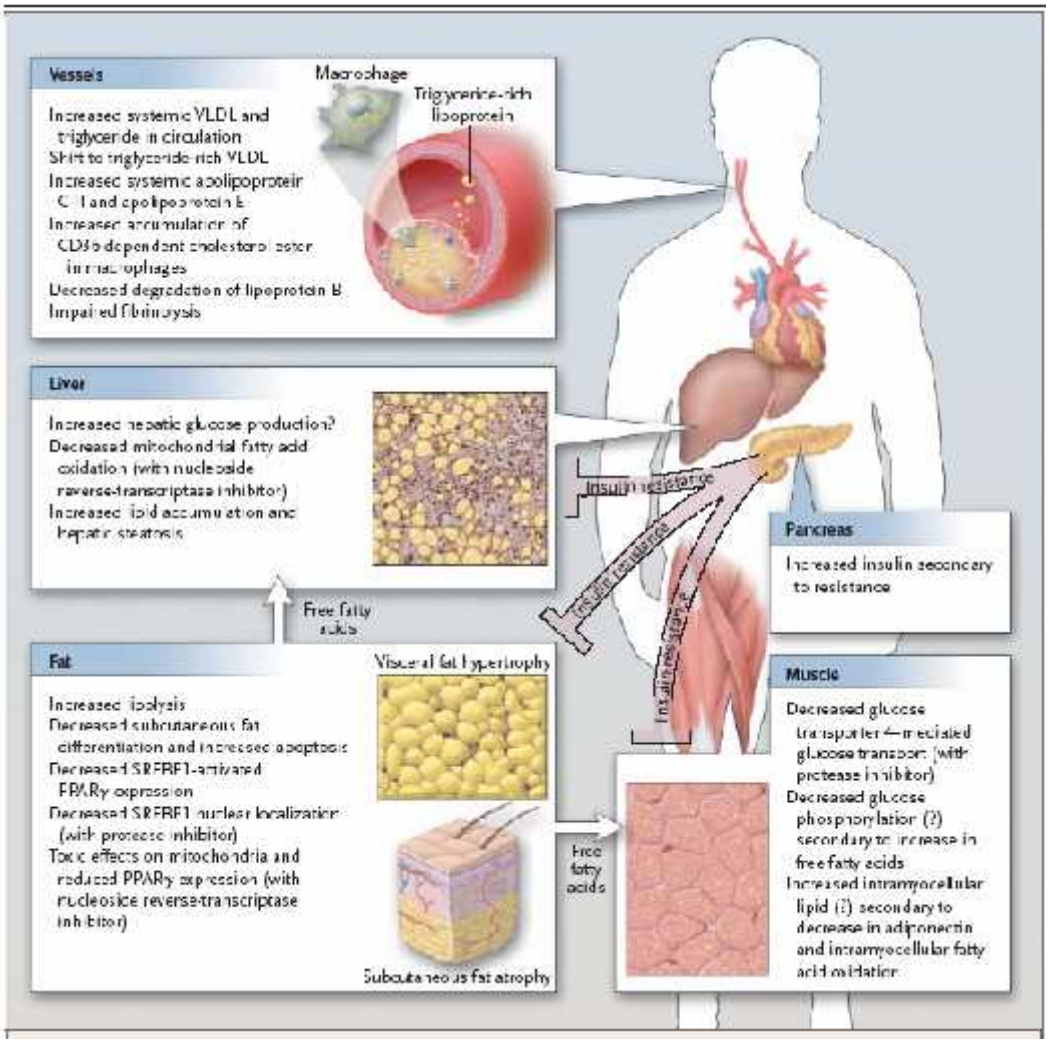


Figure 8. Potential mechanisms for MS in HIV positive patients receiving ART

Because patients with both lipoatrophy and central obesity looked so striking, a link was presumed. Diagnosis of HIV-associated lipodystrophy was based on clinical criteria, not measurements. Those criteria initially only looked for peripheral lipoatrophy or central lipohypertrophy (unidirectional clinical scales), presuming the link.

More recent studies objectively assessed fat with bidirectional scales and clinical measurements. These studies found that the HIV-specific lesion was subcutaneous lipoatrophy, with the upper trunk least affected. Lipoatrophy was mostly associated with thymidine analogue NRTI drugs, especially stavudine. PIs, and to a lesser extent NNRTIs, may contribute. Visceral fat levels were found to be independent of subcutaneous fat (not inversely increased) and not affected by those drugs. The major determinants of visceral fat were restoration to health, age, male gender, and white ancestry.[102]

While the leg was the depot most affected by lipoatrophy, lower trunk (abdominal and back) subcutaneous adipose tissue was another site greatly affected by lipoatrophy. Hence, it is not proper to use the term central lipohypertrophy, because only visceral fat is not affected by lipoatrophy. The lipoatrophy of abdominal and leg subcutaneous fat has great importance for the diagnosis of metabolic syndrome. Diagnostic criteria use waist circumference or WHR for central obesity. Waist circumference includes abdominal subcutaneous fat as well as visceral fat. If waist circumference is a surrogate for visceral fat, then the loss of abdominal subcutaneous fat might miss visceral obesity in HIV-infected patients with lipoatrophy.[102]

Even the use of WHR is problematic. With HIV-associated lipoatrophy, patients can have loss of hip fat that causes an increase in WHR without increased visceral fat. Although severe congenital and acquired lipoatrophy patients without HIV have metabolic disorders, the metabolic disorders are more severe than those seen in HIV, which mostly has less lipoatrophy.[102]

Abdominal subcutaneous lipodystrophy explains why HIV-infected patients less frequently meet the waist circumference criteria for metabolic syndrome. Lipoatrophy also leads to lower BMI, so substituting BMI does not help. Nevertheless, despite the lower waist circumference and BMI of HIV-infected patients compared with controls, BMI remains a strong quantitative predictor of metabolic syndrome in several studies.[111-113]

Thus, the parameters for waist and hip circumference need to be recalibrated for HIV, similar to what is done for gender and ethnicity in the IDF definition.[111-113] However, HIV-associated lipoatrophy is not universal, so a simple recalibration is not likely to work.

Associations of body fat with metabolic parameters

Because of HIV lipodystrophy, the correlation between individual body fat depots and metabolic disturbances has been studied in detail with comparisons to controls. However, it should be noted that the metabolic effects described here for specific antiretroviral drugs occur before any change in body composition and are independent of the associations with body fat depots using multivariable analysis in cross-sectional studies.[102]

Increased visceral fat is associated with insulin resistance, higher triglycerides, and lower HDL-C in both HIV-infected and control men and women. There is little difference in the effect in HIV-infected and control populations.[102]

Upper-trunk fat is a strong independent predictor of insulin resistance in HIV-infected and control patients and of triglyceride levels in control and, to a lesser extent, HIV-infected women. In contrast, the amount of trunk fat is not associated with HDL-C, emphasizing that each metabolic parameter may have different contributors.[102]

On the other hand, leg fat seems protective. More leg fat is associated with lower triglycerides in control and HIV-infected men and women. Although there is little difference in the association of the amount of fat with triglycerides in HIV-infected patients compared with controls, there is a high prevalence of lipoatrophy in HIV due to thymidine-based NRTI, contributing to the hypertriglyceridemia of HIV infection. There is no apparent association of leg fat with low HDL-C or insulin resistance.[102]

Hypertension

There are very few studies of hypertension in the HIV-infected population and little evidence for a significant increase compared with controls. Prospective studies of PIs or NRTIs in healthy volunteers, including those that are associated with induction of hypertriglyceridemia or insulin resistance, did not find increases in blood pressure.[125,126] However, blood pressure rises when HIV-infected patients are treated with effective antiretroviral therapy. No specific antiretroviral drug has been linked to hypertension, but, as in control populations, age and BMI are linked to hypertension.[102]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on HIV positive patients during the period of January 2012 to December 2012.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2012 to December 2012.

Place

The present study was conducted in Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching tertiary care hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

HIV positive patients admitted in the wards of Medicine Department or attending the Medicine were studied.

Sample size

A total of 75 HIV positive patients were selected for the study.

Sampling procedure

Based on the convenient Sample method, the sample size was calculated using the following formula

$n = 4 p q / d^2$

Where, p = Prevalence

q = 100-p (%)

d = Absolute error considered as 10%

Considering the above formula the sample size was calculated as 75 patients. Every consecutive patient fulfilling the selection criteria was enrolled.

Selection criteria

Inclusion

- Age more than 18 years.
- HIV positive patients (HIV status was confirmed by voluntary counselling and testing centre) on ART.
- HIV infected ART naïve patients.

Exclusion

- HIV patients with preexisting;
    - Diabetes mellitus
    - Hypertension
    - Dyslipidemia
    - Coronary artery disease
- Patients on exogenous insulin therapy and on medications

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the purpose of study and a written informed consent was obtained to participate in the study before enrollment (Annexure I).

Method of collection of data

Before the enrollment, demographic data such as age, sex and occupation were recorded. Patients were interviewed and the details about HIV infection such as duration and treatment were noted. A thorough physical examination was conducted for anthropometry (including height, weight, waist circumference), vitals (pulse rate, blood pressure and respiratory rate) and systemic examination was carried out. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The selected patients underwent the following investigations.

- Fasting glucose.
- Lipid profile – Total cholesterol, HDL, LDL and triglycerides.

Outcome variables

Body mass index

A thorough clinical examination was conducted. Height and weight was recorded and body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index was classified using WHO criteria as below.[127]

Classification	BMI (Kg/m^2)
Underweight	< 18.5
Normal range	18.5 to 24.99
Overweight	≥ 25.00
Pre obese	25.00 to 29.99
Obese	≥ 30.00

Waist circumference

The waist circumference was measured using a standard measuring tape in Cms. Waist circumference of ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches (female) was considered as abnormal.[16]

Fasting blood sugar

Assessment of fasting blood sugar was carried out based on OGTT. After an overnight fast, blood samples were drawn from each patient. Following this, 75 g glucose was administered, and at two hours another blood sample was drawn and blood glucose levels, both fasting and post glucose load were estimated and the following criteria for OGTT results was used.

- Two-hour postload glucose less than 140 mg/dL (7.8 mmol/L) = normal glucose tolerance
- Two-hour post load glucose:140–199 mg/dL (7.8–11.1 mmol/L) = IGT (impaired glucose tolerance).
- Two-hour postload glucose ≥ 200 mg/dL (11.1 mmol/L) = provisional diagnosis of diabetes.

Lipid profile

Total cholesterol, triglycerides, HDL, LDL levels were noted and the findings were recorded.

Metabolic syndrome

The diagnosis of metabolic syndrome was done according to NCEP ATP III criteria.[16]

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and

proportions and comparison was done using chi-square test (With Yates correction). The continuous data was expressed as mean ± standard deviation (SD) and comparison was done by two sample 't' test with unequal variance. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

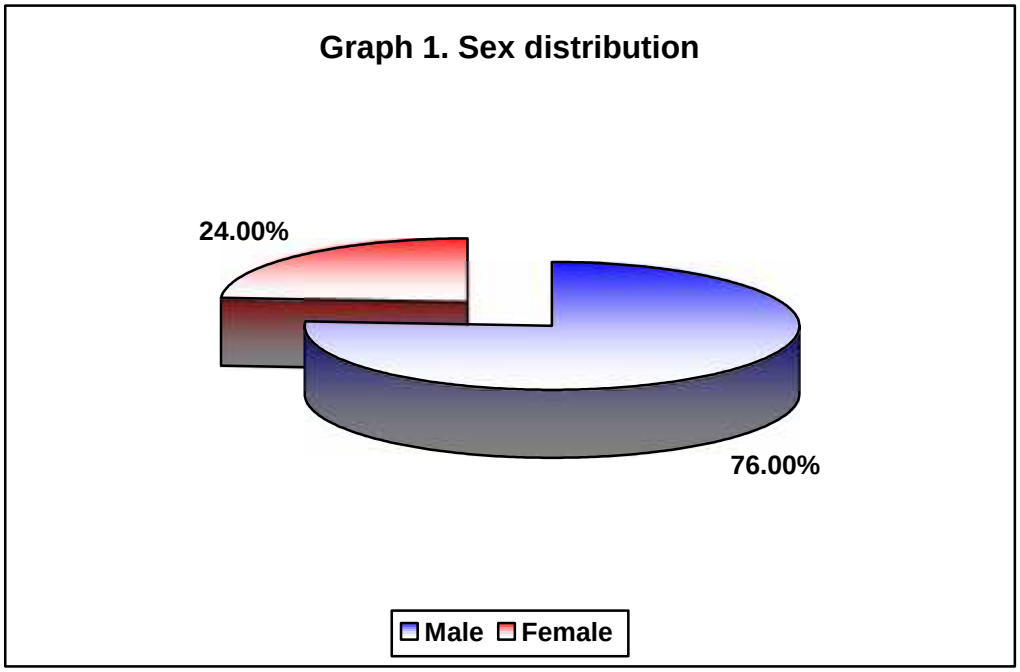
RESULTS

This one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2012 to December 2012. A total of 75 HIV positive patients were studied.

The data obtained was coded and entered into the Microsoft excel spreadsheet and master chart was prepared (Annexure III). The data was analysed and the final observations and results were tabulated as below.

Table 1. Sex distribution

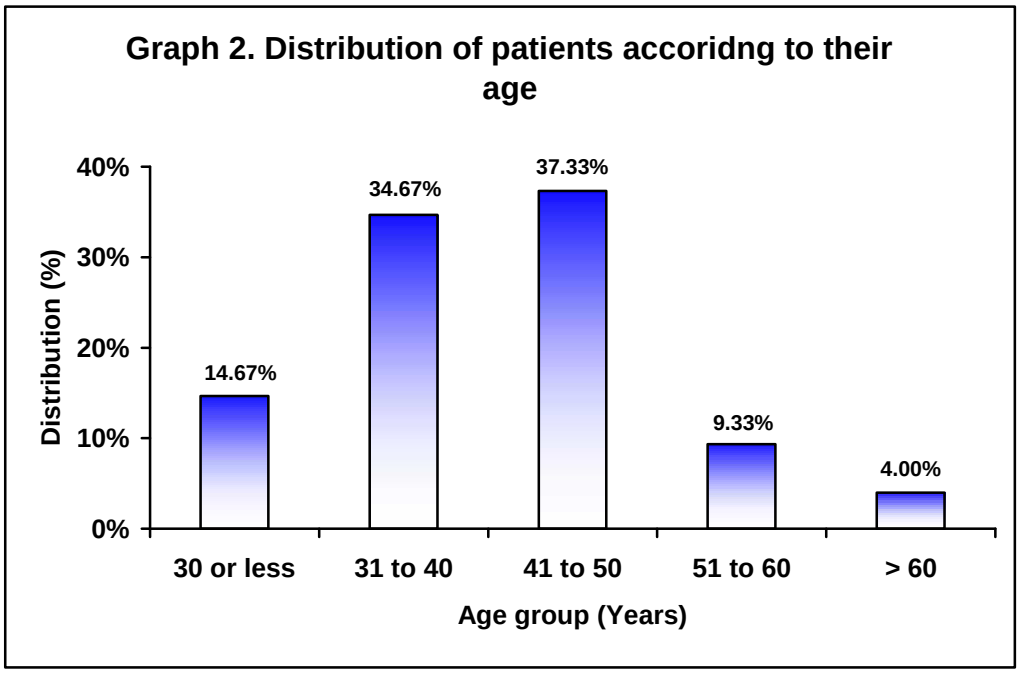
Sex	Distribution (n=75)	
	Number	**Percentage**
Male	57	76.00
Female	18	24.00
Total	**75**	**100.00**



The analysis of this study shows that, majority (76%) of the patients were males and 24% were females. The male to female ratio was 3.16:1.

Table 2. Distribution of patients according to their age

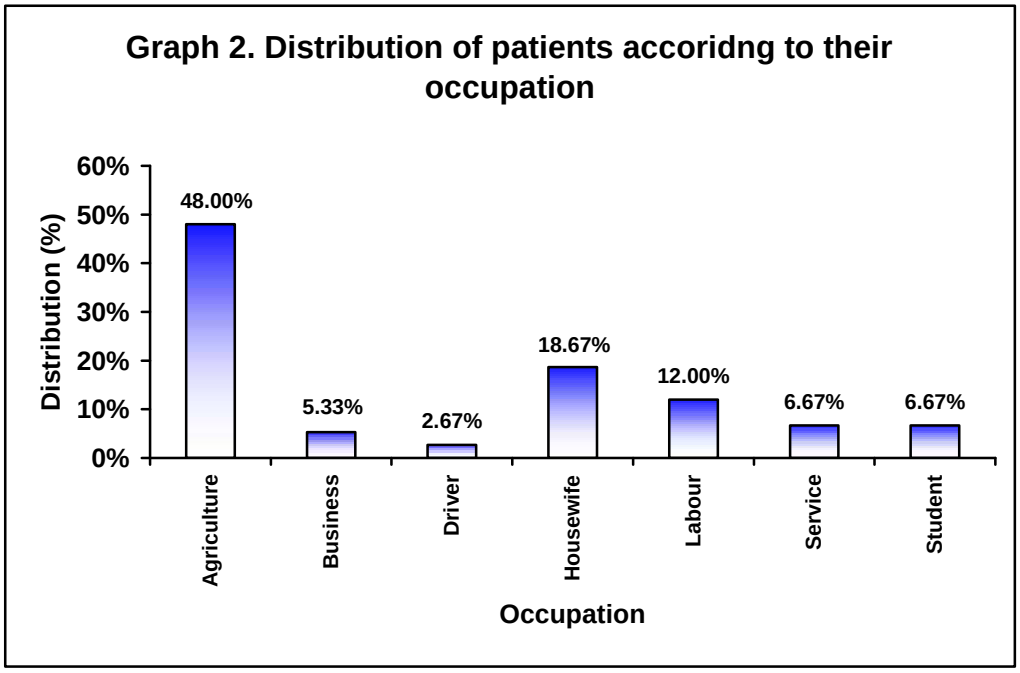
Age group (Years)	Distribution (n=75)	
	Number	**Percentage**
30 or less	11	14.67
31 to 40	26	34.67
41 to 50	28	37.33
51 to 60	7	9.33
> 60	3	4.00
Total	**75**	**100.00**



In this study, the age distribution showed that most of the patients (37.33%) were aged between 41 to 50 years followed by 31 to 40 years (34.67%). The mean age of the study population was 42.03 ± 10.35 years.

Table 3. Distribution of patients according to their occupation

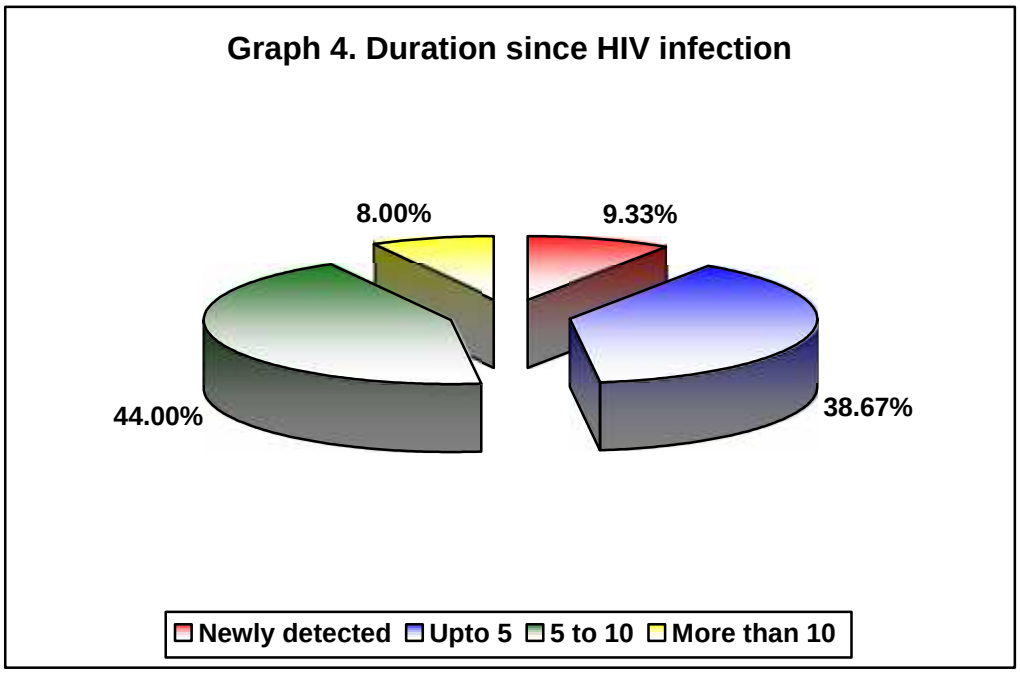
Occupation	Distribution (n=75)	
	Number	**Percentage**
Agriculture	36	48.00
Business	4	5.33
Driver	2	2.67
Housewife	14	18.67
Labour	9	12.00
Service	5	6.67
Student	5	6.67
Total	**75**	**100.00**



In the present study, most of the patients had agriculture(48%) as their occupation and 18.67% were housewives.

Table 4. Duration since HIV infection

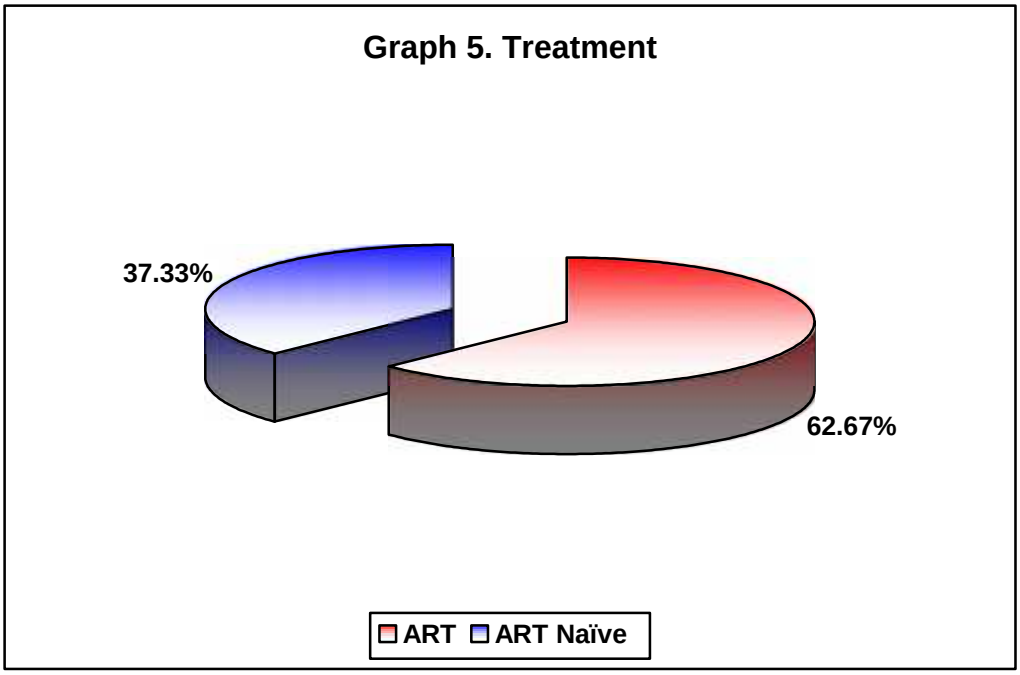
Duration	Distribution (n=75)	
	Number	Percentage
Newly detected	7	9.33
Upto 5	29	38.67
5 to 10	33	44.00
More than 10	6	8.00
Total	**75**	**100.00**



In this study, 44% of the patients had been detected to have the disease since five to ten years and 38.67% patients had been diagnosed to have HIV since five years. The mean duration of the disease was 6.46 ± 3.26 years.

Table 5. Treatment

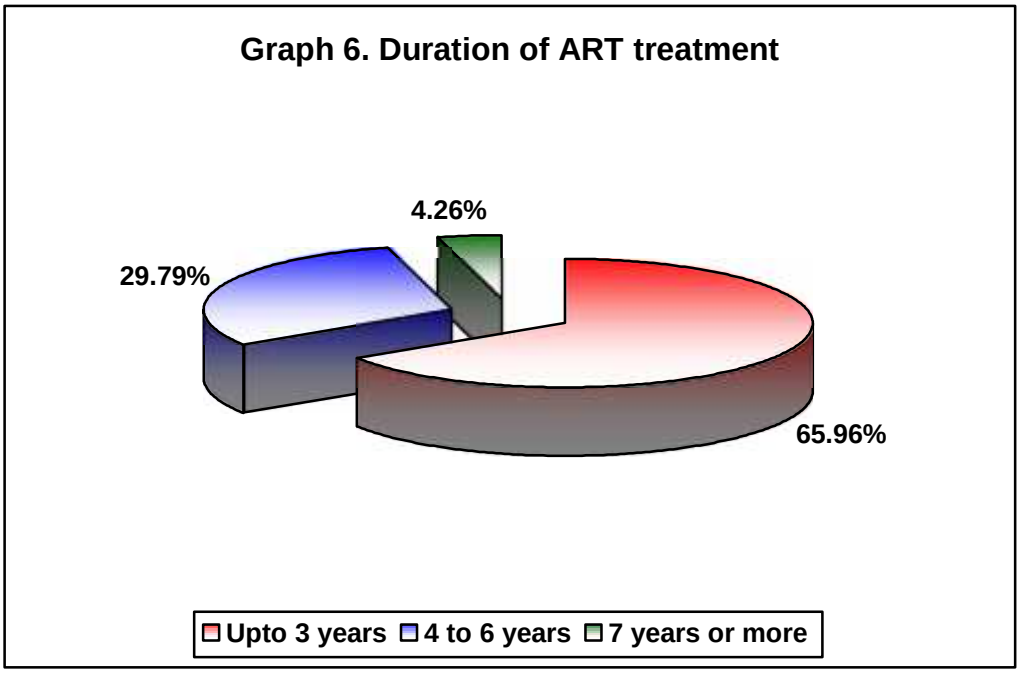
Treatment	Distribution (n=75)	
	Number	**Percentage**
ART	47	62.67
ART Naïve	28	37.33
Total	**75**	**100.00**



In the present study among the 75 patients, 62.67% of the patients were on ART treatment, while 37.33% were ART naïve.

Table 6. Duration of ART treatment

Duration	Distribution (n=47)	
	Number	Percentage
Upto 3 years	31	65.96
4 to 6 years	14	29.79
7 years or more	2	4.26
Total	**47**	**100.00**

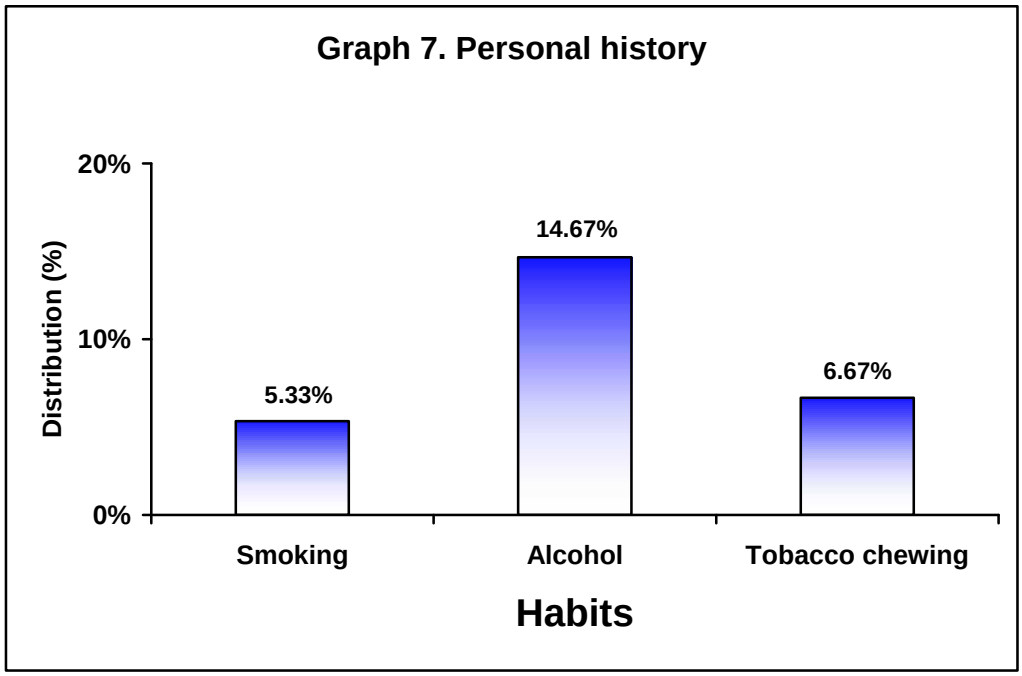


In this study, among the 47 patients on ART treatment, 65.96% were on ART since a period of three years or less and 29.79% of patients were on ART since four to six years.

Table 7. Personal history

Habits	Distribution (n=75)	
	Number	Percentage
Smoking	4	5.33
Alcohol	11	14.67
Tobacco chewing	5	6.67

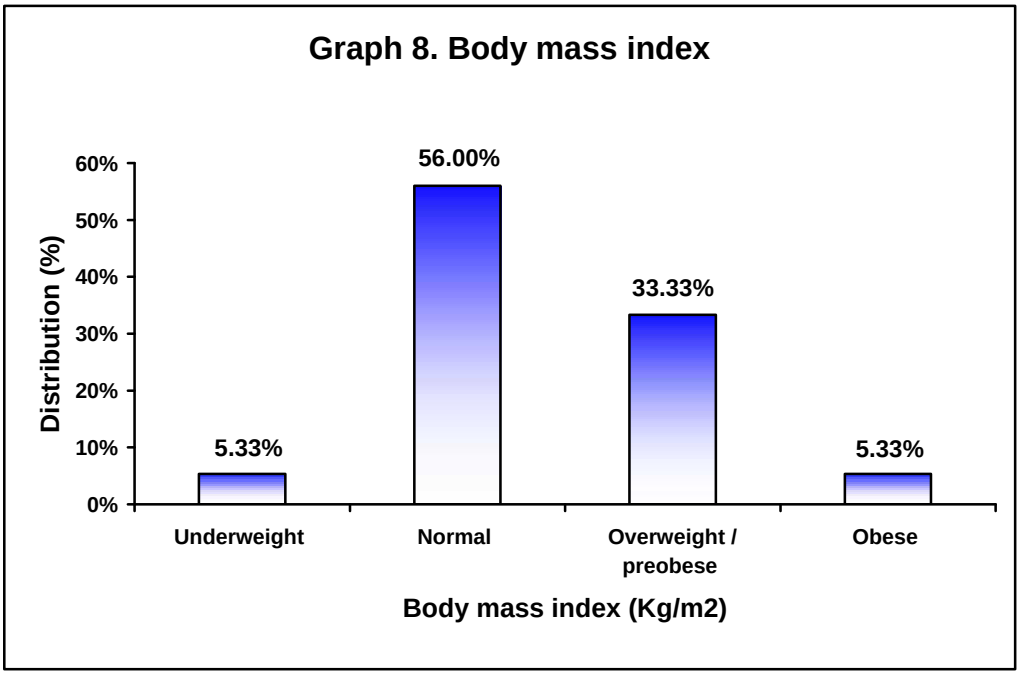
Multiple findings hence total not shown



In the present study, 14.67% of them were alcoholics, 6.67% were tobacco chewers and 5.33% were smokers.

Table 8. Body mass index

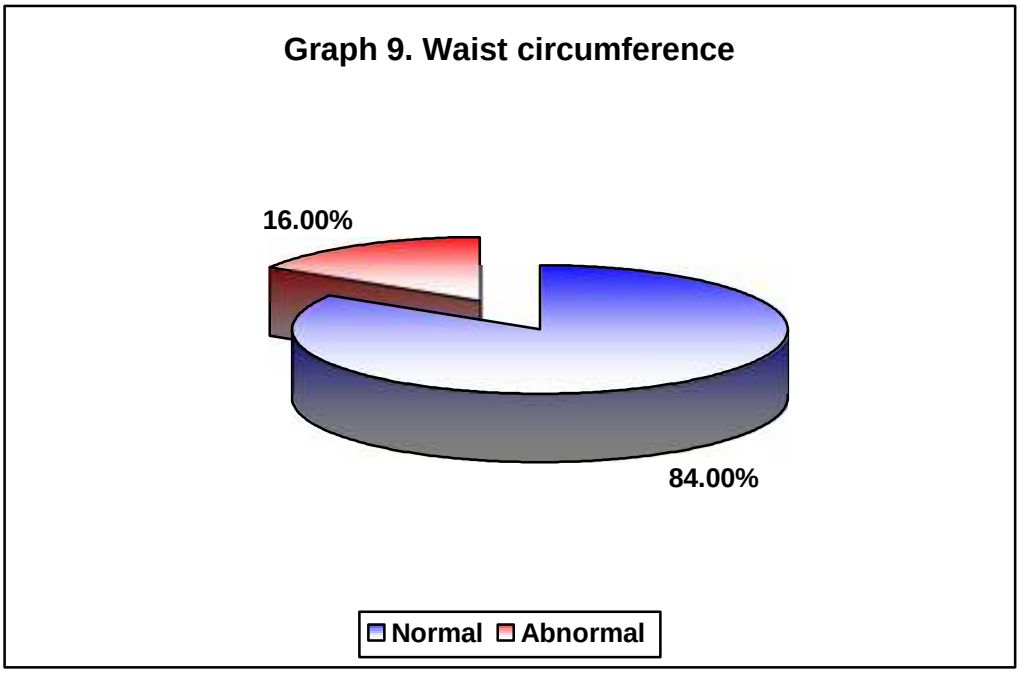
Body mass index (Kg/m^2)	Distribution (n=75)	
	Number	**Percentage**
Underweight (<18.5)	4	5.33
Normal (18.5 to 24.99)	42	56.00
Overweight / preobese (25.00 to 29.99)	25	33.33
Obese (30.00 or more)	4	5.33
Total	**75**	**100.00**



In the present study, 5.33% of patients had a BMI less than 18.5 Kg/m^2 (Underweight) and 33.33% had a BMI between 25 to 29.99 Kg/m^2 (Overweight / preobese), while 5.33% had a BMI of 30 or more (Obese). The mean body mass index was 24.17 ± 3.60 Kg/m^2.

Table 9. Waist circumference

Findings	Distribution (n=75)	
	Number	Percentage
Normal (< 102 men; < 88 women)	63	84.00
Abnormal	12	16.00
Total	**75**	**100.00**

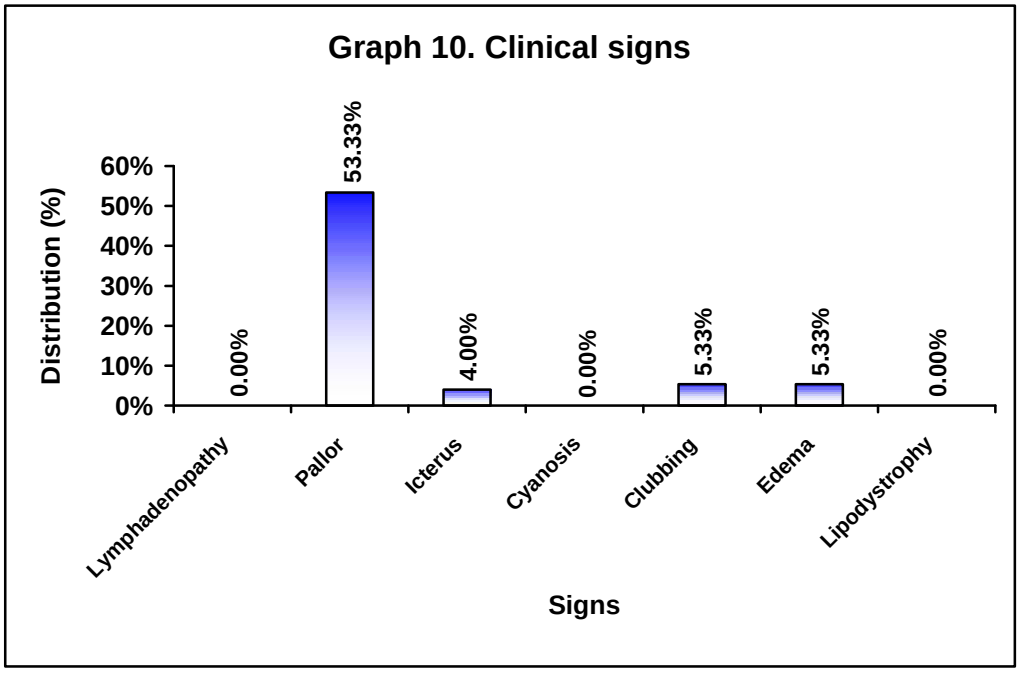


In the present study, 16% of the patients had a waist circumference of more than 102 cms among males and more than 88 Cms among the females which was considered as abnormal according to the criteria used in the study. The mean waist circumference was 90.25 ± 9.56 Cms.

Table 10. Clinical signs

Signs	Distribution (n=75)	
	Number	Percentage
Lymphadenopathy	0	0.00
Pallor	40	53.33
Icterus	3	4.00
Cyanosis	0	0.00
Clubbing	4	5.33
Edema	4	5.33
Lipodystrophy	0	0.00

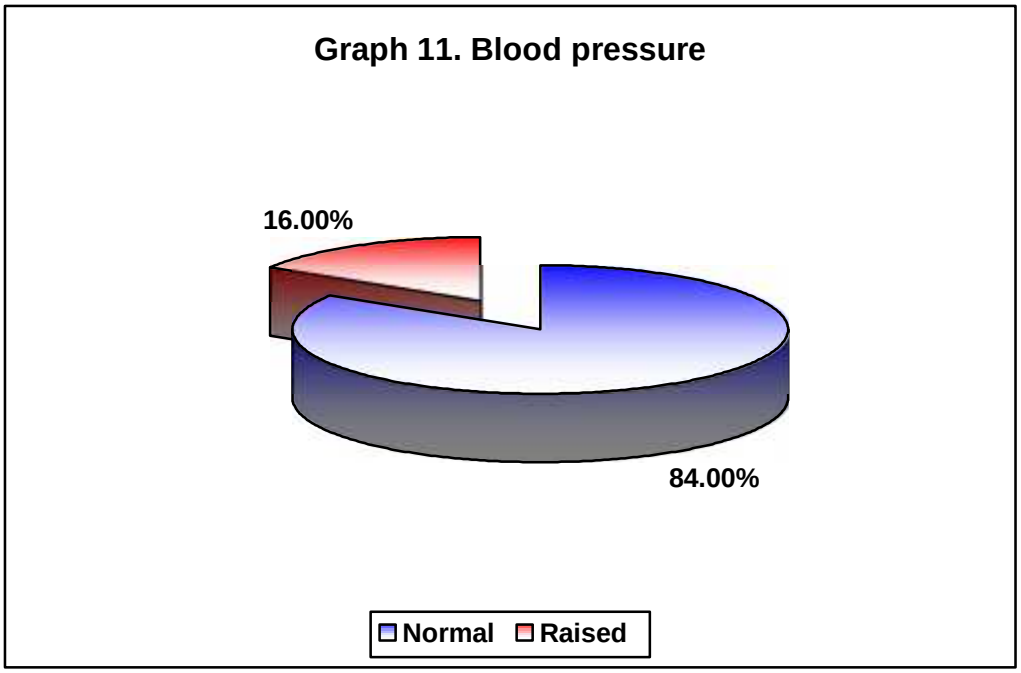
Multiple findings hence total not shown



In the present study, pallor was present in 53.33% while clubbing, edema and icterus were noted amongst 5.33% each.

Table 11. Blood pressure

Blood present	Distribution (n=75)	
	Number	Percentage
Normal	63	84.00
Raised	12	16.00
Total	**75**	**100.00**



In the present study, raised blood pressure levels > than 130 / 85 mm Hg were noted in 16% of the patients. The mean SBP was 119.09 ± 16.77 mm Hg and mean DBP was 77.57 ± 10.52 mm Hg.

Table 12. Systemic examination findings

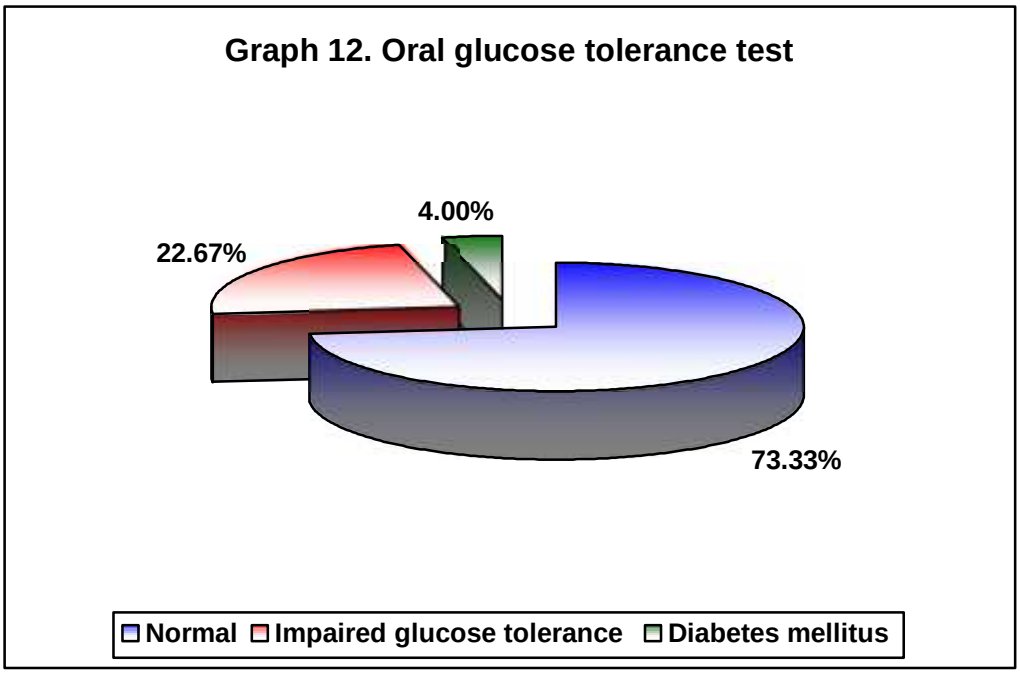
System	Distribution (n=75)	
	Number	**Percentage**
Respiratory system	6	8.00
Cardiovascular system	0	0.00
Per abdomen	2	2.67
Central nervous system	3	4.00

Multiple findings hence total not shown

In this study, 4 % of the patients had respiratory system findings such as crepts and decreased air entry each. 4.00% of the patients had positive CNS examination findings such as ataxia (1.33%), nystagmus (1.33%) and neck rigidity (1.33%) while 2.67% had hepatomegaly on per abdominal examination.

Table 13. Oral glucose tolerance test

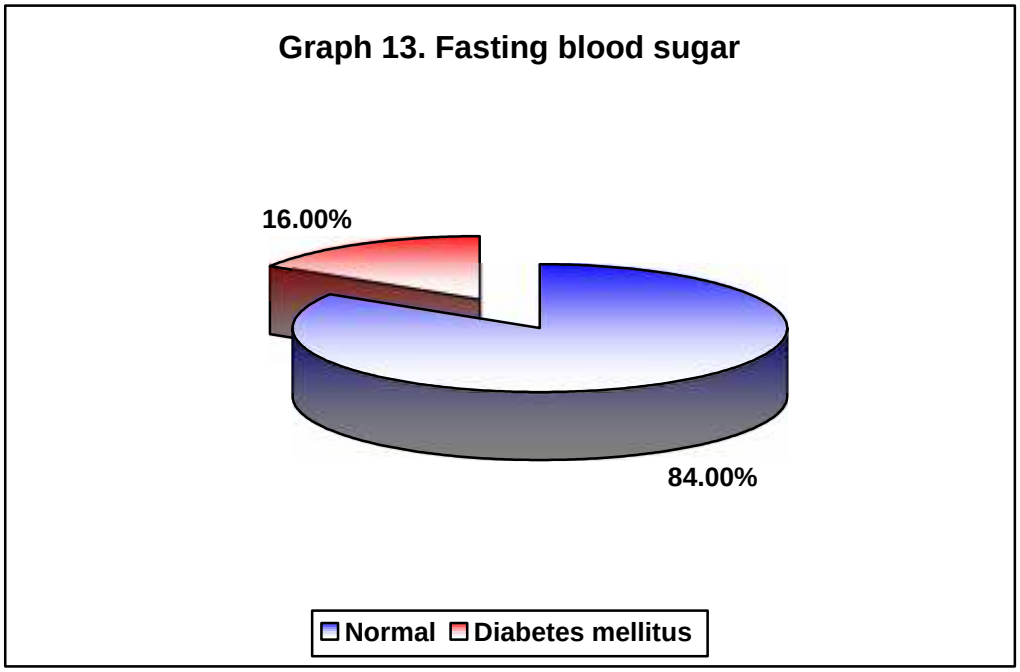
Findings	Distribution (n=75)	
	Number	**Percentage**
Normal	55	73.33
Impaired glucose tolerance	17	22.67
Diabetes mellitus	3	4.00
Total	**75**	**100.00**



In the present study, 22.67% of the patients had impaired glucose tolerance using the OGTT and 4% of the patients had OGTT values in the diabetic range. The mean OGTT levels were 121.31 ± 36.94 mg/dL.

Table 14. Fasting blood sugar

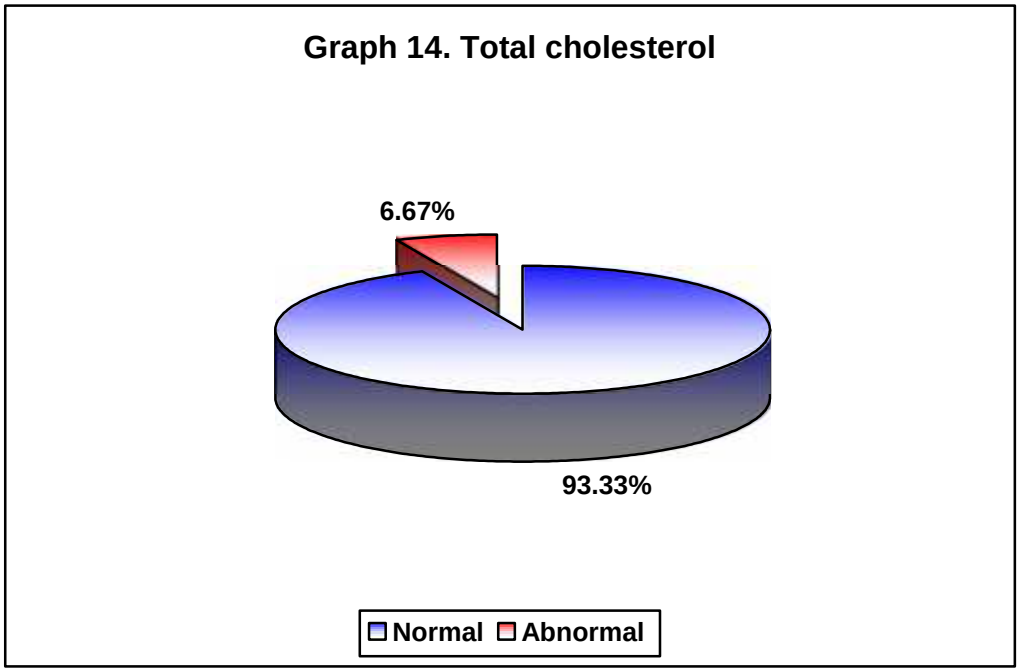
Findings	Distribution (n=75)	
	Number	**Percentage**
Normal (<110 mg/dL)	63	84.00
Impaired (≥110 mg/dL)	12	16.00
Total	**75**	**100.00**



In this study, 16% of the patients the had impaired fasting blood sugar levels. The mean fasting blood sugar levels were 88.27 ± 22.32 mg/dL.

Table 15. Total cholesterol

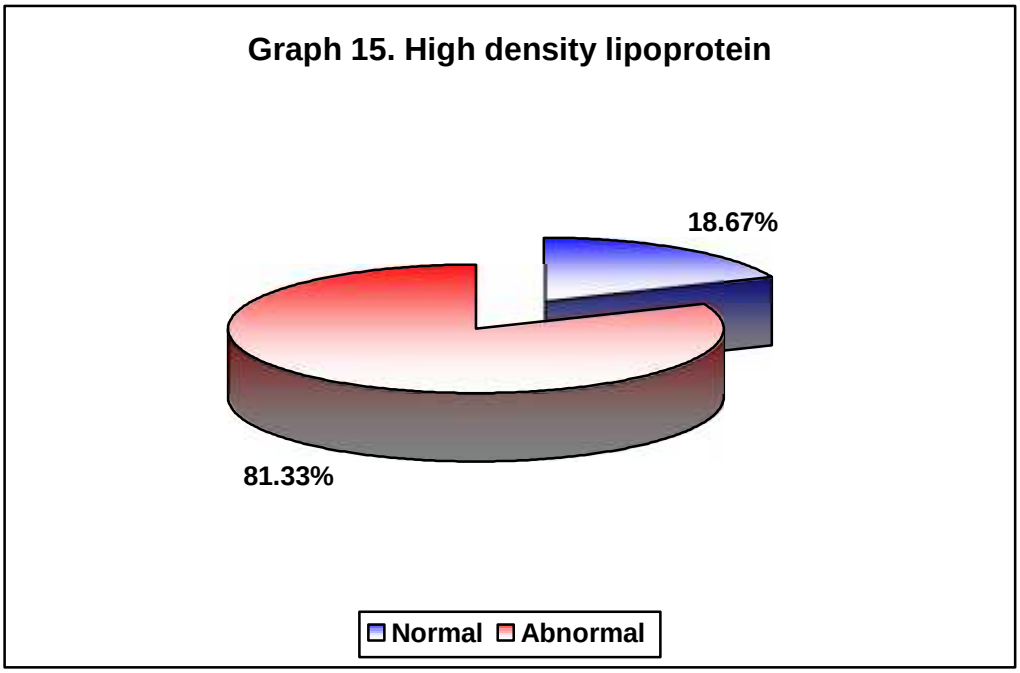
Findings	Distribution (n=75)	
	Number	**Percentage**
Normal (<200 mg/dL)	70	93.33
Abnormal (≥200 mg/dL)	5	6.67
Total	**75**	**100.00**



In the present study, 6.67% of the patients had abnormal total cholesterol levels . The mean total cholesterol levels were 151.87 ± 30.17 mg/dL.

Table 16. High density lipoprotein

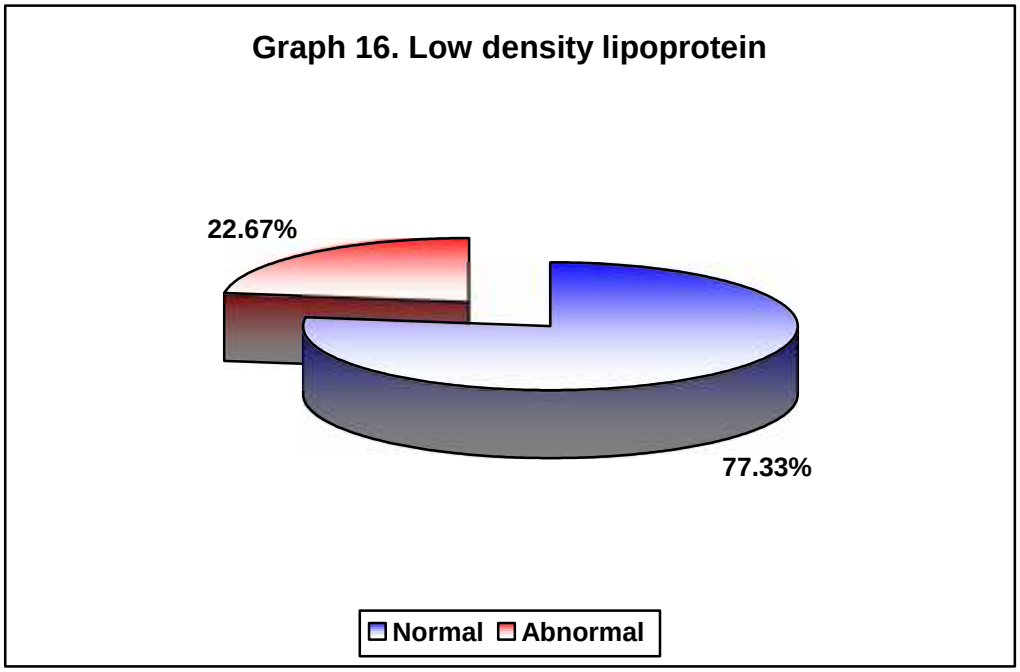
Findings	Distribution (n=75)	
	Number	**Percentage**
Normal (>40 men;>50 mg/dL women)	14	18.67
Abnormal (<40 men;≤50 mg/dL women)	61	81.33
Total	**75**	**100.00**



In this study, 81.33% (HDL <40 men;≤50 mg/dL women) had abnormal high density lipoprotein(HDL) levels . The mean high density lipoprotein levels were 32.72 ± 15.46 mg/dL.

Table 17. Low density lipoprotein

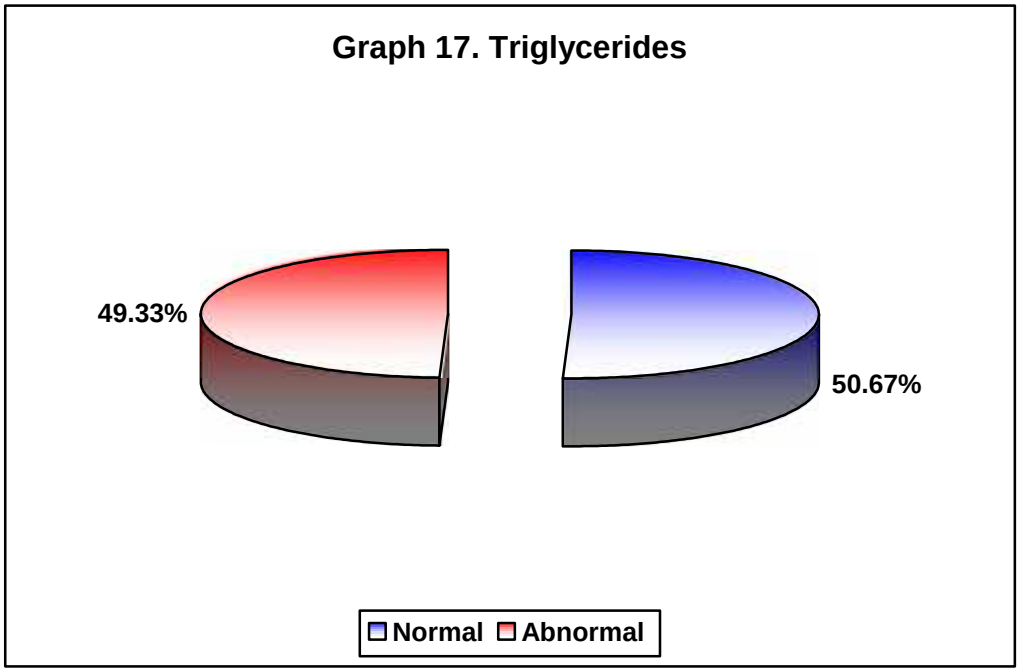
Findings	Distribution (n=75)	
	Number	**Percentage**
Normal (< 100 mg/dL)	58	77.33
Abnormal (≥100 mg/dL)	17	22.67
Total	**75**	**100.00**



In the present study, 22.67% had abnormal low density lipoprotein levels (≥100 mg/dL). The mean low density lipoprotein levels were 82.80 ± 25.75 mg/dL.

Table 18. Triglycerides

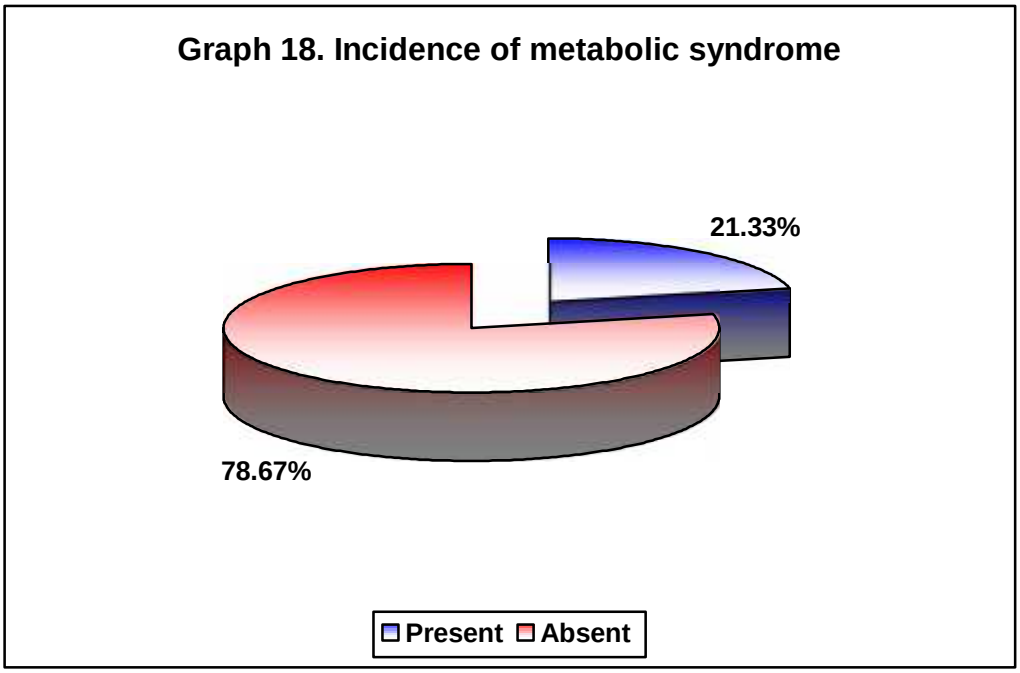
Findings	Distribution (n=75)	
	Number	Percentage
Normal (<150 mg/dL)	38	50.67
Abnormal (≥150 mg/dL)	37	49.33
Total	**75**	**100.00**



In this study, 49.33% of the total patients had abnormal triglyceride levels (≥150 mg/dL) and the mean triglyceride levels of 148.99 ± 53.62 mg/dL.

Table 19. Incidence of metabolic syndrome

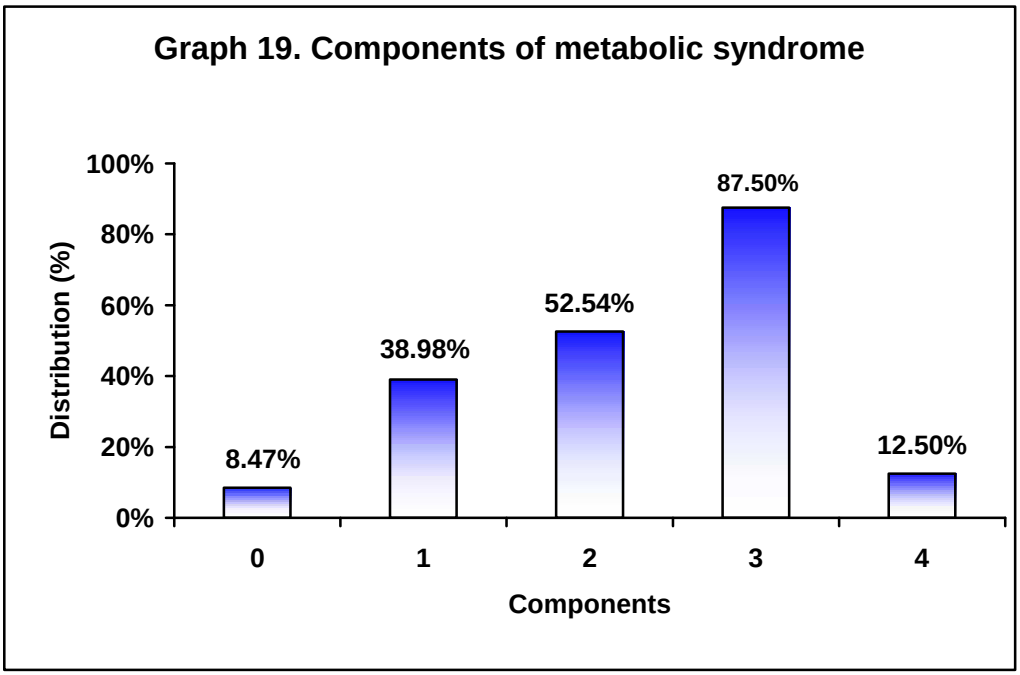
Metabolic syndrome	Distribution (n=75)	
	Number	**Percentage**
Present	16	21.33
Absent	59	78.67
Total	**75**	**100.00**



In the present study, of the total 75 patients, 21.33% patients had metabolic syndrome.

Table 20. Components of metabolic syndrome

Metabolic syndrome	Components	Distribution (n=75)	
		Number	Percentage
Absent (n=59)	0	5	8.47
	1	23	38.98
	2	31	52.54
	Total	*59*	*78.67*
Present (n=16)	3	14	87.50
	4	2	12.50
	Total	*16*	*21.33*
Total	**Total**	**75**	**100.00**



In this study, of the 21.33% patients with metabolic syndrome, 87.5% patients had satisfied three criteria for metabolic syndrome whereas 12.50% of the patients had satisfied four criteria.

Table 21. Association of metabolic syndrome with sex

Sex	Metabolic syndrome				Total	
	Present		Absent			
	Number	%	Number	%	Number	%
Male	10	17.54	47	82.46	57	100.00
Female	6	33.33	12	66.67	18	100.00
Total	**16**	**21.33**	**59**	**78.67**	**75**	**100.00**

x^2 (with Yate's correction) =1.200 **p=0.273**

In the present study, of the 16 patients with metabolic syndrome, 17.54% were males, while 33.33% were females. However this difference was not statistically significant (p=0.273).

Table 22. Association of metabolic syndrome with ART

ART	Metabolic syndrome				Total	
	Present		Absent			
	Number	%	Number	%	Number	%
ART	14	29.79	33	70.21	47	100.00
ART Naïve	2	7.14	26	92.86	28	100.00
Total	**16**	**21.33**	**59**	**78.67**	**75**	**100.00**

x^2=5.361 **p=0.021**

In this study of the total 47 patients on ART, metabolic syndrome was seen in 29.79% of the patients which was statistically significant with a p value of 0.021.

Table 23. Association of metabolic syndrome with abdominal obesity

Metabolic syndrome	Abdominal obesity				Total	
	Present		Absent			
	Number	%	Number	%	Number	%
Present	9	56.25	7	43.75	16	100.00
Absent	3	5.08	56	94.92	59	100.00
Total	**12**	**16.00**	**63**	**84.00**	**75**	**100.00**

x^2 (with Yate's correction) =20.858 **p<0.001**

In the present study, of the 12 patients with abnormal waist circumference, 56.25% of them had metabolic syndrome (p<0.001) which was statistically significant.

Table 24. Association of metabolic syndrome with triglyceride levels

Metabolic syndrome	Triglycerides				Total	
	< 150 mg/dL		> 150 mg/dL			
	Number	%	Number	%	Number	%
Present	10	62.50	6	37.50	16	100.00
Absent	27	45.76	32	54.24	59	100.00
Total	**37**	**49.33**	**38**	**50.67**	**75**	**100.00**

x^2=1.411 **p=0.235**

In this study, of the 16 patients with metabolic syndrome, 37.50% of the patients had raised triglycerides whereas in the patients without metabolic syndrome, raised triglycerides were noted in 54.24% of the patients. However this difference was statistically not significant (p=0.235).

Table 25. Association of metabolic syndrome with high density lipoprotein

Metabolic syndrome	High density lipoprotein				Total	
	Abnormal		Normal			
	Number	%	Number	%	Number	%
Present	15	93.75	1	6.25	16	100.00
Absent	46	77.97	13	22.03	59	100.00
Total	**61**	**81.33**	**14**	**18.67**	**75**	**100.00**

x^2 (with Yate's correction) =1.157 **p=0.151**

In the present study, of the total 61 patients with abnormal high density lipoprotein levels, 93.75% of the patients had metabolic syndrome while in 77.97% of the patients metabolic syndrome was absent. This difference was statistically not significant (p=0.151).

Table 26. Association of metabolic syndrome with blood pressure

Metabolic syndrome	Blood pressure				Total	
	Raised		Normal			
	Number	%	Number	%	Number	%
Present	11	68.75	5	31.25	16	100.00
Absent	1	1.69	58	98.31	59	100.00
Total	**12**	**16.00**	**63**	**84.00**	**75**	**100.00**

x^2 (with Yate's correction) =37.268 **p<0.001**

In this study, total 12 patients had raised blood pressure levels. Of which 68.75% had metabolic syndrome which was statistically significant (p<0.001).

Table 27. Association of metabolic syndrome with fasting blood glucose

Metabolic syndrome	Fasting blood glucose				Total	
	≥ 110 mg/dL		< 110 mg/dL			
	Number	%	Number	%	Number	%
Present	5	31.25	11	68.75	16	100.00
Absent	7	11.86	52	88.14	59	100.00
Total	**12**	**16.00**	**63**	**84.00**	**75**	**100.00**

x^2 (with Yate's correction) =2.225 **p=0.136**

In this study, of the 16 patients with metabolic syndrome, 31.25% had fasting blood sugar ≥ 110 mg/dL whereas 68.75% of the patients had fasting blood sugar levels < 110 mg/dL. This difference was statistically not significant (p=0.136).

Table 28. Sexwise comparison of HDL levels in patients with metabolic syndrome

Sex	High density lipoprotein (mg/dL)				Total	
	Abnormal		Normal			
	No	%	No	%	No	%
Male	9	90.00	1	10.00	10	100.00
Female	6	100.00	0	0.00	6	100.00
Total	**15**	**93.75**	**1**	**6.25**	**16**	**100.00**

In the present study of the 16 patients with metabolic syndrome, nine (90%) males and all females (100%) had abnormal high density lipoprotein levels.

Table 29. Sexwise comparison of triglyceride levels in patients with metabolic syndrome

Sex	Triglycerides (mg/dL)				Total	
	Abnormal		Normal			
	No	%	No	%	No	%
Male	6	60.00	4	40.00	10	100.00
Female	4	66.67	2	33.33	6	100.00
Total	**10**	**62.50**	**6**	**37.50**	**16**	**100.00**

In this study, among the patients with metabolic syndrome, 60% of males and 66.67% of females had abnormal triglyceride levels as compared to 40% of males and 33.33% of females.

Table 30. Sexwise comparison of waist circumference levels in patients with metabolic syndrome

Sex	Waist circumference				Total	
	Abnormal		Normal			
	No	%	No	%	No	%
Male	7	70.00	3	30.00	10	100.00
Female	2	33.33	4	66.67	6	100.00
Total	**9**	**56.25**	**7**	**43.75**	**16**	**100.00**

In the present study, waist circumference abnormalities in those who had metabolic syndrome were present among 70% of males and 33.33% of females as compared to 30% and 66.67% respectively.

Table 31. Sexwise comparison of patients on ART with metabolic syndrome

Sex	ART Treatment				Total	
	Present		Absent			
	No	%	No	%	No	%
Male	9	90.00	1	10.00	10	100.00
Female	5	83.33	1	16.67	6	100.00
Total	**14**	**87.50**	**2**	**12.50**	**16**	**100.00**

In this study of the 16 patients with metabolic syndrome, nine (90%) were males and five (83.33%) were females on ART whereas one male (10%) and a female (16.67%) were ART naïve.

Table 32. Comparison of continuous variables among patients with and without metabolic syndrome

Variables	Metabolic syndrome				t value	p value
	Present (n=16)		Absent (n=59)			
	Mean	SD	Mean	SD		
Age (Years)	40.80	14.02	42.30	9.23	0.499	0.619
Duration of HIV (Years)	7.50	3.73	6.10	3.09	1.450	0.152
Body mass index (Kg/m^2)	26.90	3.80	23.40	3.17	**3.802**	**<0.001**
Pulse rate (bpm)	86.10	12.29	85.50	10.23	0.193	0.847
Respiratory rate (bpm)	13.60	1.66	13.90	1.45	0.645	0.521
Total cholesterol (mg/dL)	147.00	32.03	153.10	29.78	0.725	0.471
LDL (mg/dL)	83.10	29.66	82.70	24.86	0.057	0.955
OGTT (mg/dL)	121.90	27.04	121.10	39.38	0.077	0.939

In this study, a significant positive relationship was found between body mass index and metabolic syndrome. The mean body mass index in patients with metabolic syndrome was 26.90 ± 3.80 kg/m^2 compared to 23.40 ± 3.17 kg/m^2 in patients without metabolic syndrome which was statistically significant ($p<0.001$). However, no statistical significance was observed between the two groups in regards with the age, duration of HIV disease, pulse rate, respiratory rate, total cholesterol, low density lipoprotein and oral glucose tolerance test ($p>0.050$)

Table 33. Comparison of metabolic syndrome components in patients with and without metabolic syndrome

Components	Metabolic syndrome				t value	p value
	Present (n=16)		Absent (n=59)			
	Mean	SD	Mean	SD		
Waist circumference (Cms)	97.70	11.34	88.20	7.96	**3.856**	**0.005**
Systolic blood pressure (mm Hg)	135.60	15.04	114.60	14.30	**5.157**	**<0.001**
Diastolic blood pressure (mm Hg)	87.20	10.37	74.90	8.97	**4.701**	**<0.001**
Fasting blood sugar (mg/dL)	96.20	21.09	86.10	22.32	1.631	0.107
High density lipoprotein (mg/dL)	27.20	19.19	34.20	14.11	1.613	0.111
Triglycerides (mg/dL)	184.50	79.21	139.30	40.01	**3.170**	**0.022**

The comparison of mean values of various components of metabolic syndrome in either of the groups are as shown in Table 29. It was observed that, waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides were significantly raised in patients with metabolic syndrome ($p<0.050$) but, the fasting blood sugar and high density lipoprotein were comparable.

Chapter 6

Discussion

DISCUSSION

Since the introduction of highly active antiretroviral therapy (HAART) for HIV, the decline in morbidity and mortality has been superceeded by the emergence of a number of metabolic abnormalities. These disorders include dyslipidemia, insulin resistance, abnormalities of glucose metabolism, and changes in fat distribution. Hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), insulin resistance, and increased waist circumference can occur simultaneously in HIV infection and are reminiscent of metabolic syndrome in the general population.[102]

The association of insulin resistance with low HDL-C levels, elevated triglyceride levels, and hypertension was proposed by Reaven in 1988 as "Syndrome X" and later as "insulin resistance syndrome." He noted that patients with this cluster of abnormalities are at higher risk for CVD.[120]

The term "metabolic syndrome" came into common use when the World Health Organization (WHO)[91] and the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program proposed criteria[16] by which to identify patients at higher risk for CVD. MetS increases the risk of cardiovascular disease. CVD may be increased in HIV infection, and much of this increased risk may be related to components of metabolic syndrome.[102]

Recently, there has been debate over the extent on which metabolic syndrome represents a coherent syndrome with a major underlying cause, such as insulin resistance, or a group of risk factors that, when occurring together, leading to disproportionately increased risk of CVD. Considering the above facts, the

present study was undertaken to find out the prevalence of metabolic syndrome in HIV patients and to assess the clinical and laboratory profile of these patients.

This one year cross sectional study was conducted during the period of January 2012 to December 2012 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 75 HIV positive patients were studied.

In this study, of the 75 patients studied 16 had metabolic syndrome and the prevalence of metabolic syndrome was 21.33%. Out of the 16 (21.33%) patients with metabolic syndrome, 14 (87.5%) patients were found to have three components of metabolic syndrome whereas two patients (12.50%) had four components. Large differences in prevalence of the metabolic syndrome in HIV-infected individuals have been published. Studies on adults living with HIV in the United States have reported the prevalence of MetS between 24–26%,[98,113] 18% in Australia,[114] and 17% in Spain.[112] Studies from other parts of the world have reported prevalence rates of 17%–18% on larger HIV populations using NCEP–ATP III criteria.[112,114] In India, a similar study[116] from Karnataka, India reported the prevalence of metabolic syndrome in HIV-positive patients as 26.6% whereas, a study[118] from Chennai reported a prevalence rate of 11.5% in HIV-positive groups. A recent study[128] from Allahabad, India reported prevalence of MetS as 20%. The prevalence rate found in the present study was similar to that of a recent study[128] from Allahabad and appears to be similar to a study[116] from Karnataka.

In the present study, males (76%) outnumbered females (24%) with male to female ratio was 3.16:1. Similar distribution was reported in a recent study from Allahabad, India, out of 70 cases, 71.4% were males and 28.6% were females. In this study, of the 16 patients with metabolic syndrome, 10 (17.54%) were male compared to 6 (33.33%) females. However this difference was statistically not significant (p=0.273) suggesting poor association between metabolic syndrome and sex. Similar findings were observed in a study[116] from Bangalore, India which reported that, majority of patients with metabolic syndrome were males (12 out of 16).

In this study, more than one third (37.33%) patients were aged between 41 to 50 years and 31 to 40 years (34.67%). A study[128] from Allahabad, India reported most of the cases in age group of 30 to 45 years (82.9%). In the present study, the mean age of the study population was 42.03 ± 10.35 years. However, the mean age in those with (40.80 ± 14.02 years) and without (42.30 ± 9.23 years) metabolic syndrome was comparable (p=0.619). These findings suggest that, metabolic syndrome was independent of age. A study[116] from Bangalore, India on 30 patients each, ART treated and ART naïve reported the mean as 41.63 ±10.94 and 40.6 ± 9.48 years respectively.

In this study, 44% of the patients presented with duration of HIV Since five to ten years and 38.67% patients had HIV since five years. The mean duration of the disease was 6.46 ± 3.26 years. The mean duration of the disease in patients with metabolic syndrome was slightly higher (7.50 ± 3.73 versus 6.10 ± 3.09 years) compared to those without metabolic syndrome but the difference was statistically not significant (p=0.152) suggesting that duration of the HIV

disease did not influence the metabolic syndrome. A study[116] from Bangalore, India on 30 patients each, ART treated and ART naïve reported mean duration of HIV as 53.3 ±27.76 months and 17.20 ± 9.18 months respectively.

Since the advent and adequate administration of ART significant mortality and morbidity has declined. In the present study, 47 (62.67%) patients were on ART treatment out of which 65.96% had been receiving the treatment for a duration of three years or less and 29.79% since four to six years. It was observed that, significantly higher number of patients had metabolic syndrome who were on ART (29.79%) (p=0.021) suggesting positive association of ART treatment with metabolic syndrome. Many metabolic abnormalities in adults living with HIV have been attributed to antiretroviral therapy. A study[103] form Norway reported a higher prevalence of MetS in HAART treated compared with HAART-naïve patients. A study[116] from Bangalore, India reported significantly higher (43.3%) prevalence of metabolic syndrome in HIV-positive patients in the ART-treated group, compared to ART naïve group (10%) (p=0.028) but in contrast, a study[128] from Allahabad, India reported 19.1% of patients with MetS were on HAART and 21.7% were not on HAART. Similarly, another study[129] reported no differences in the prevalence between HIV infected women naïve to antiretrovirals with those taking HAART. A community based cross-sectional study[130] reported that, compared adults living with HIV that were naïve or were taking antiretrovirals for at least two years, the odds of having MetS in those taking HAART was not significant (OR:1.17, 95%CI; .65–2.15, P5.62). Findings of the present study were in accordance with the results of study done at Bangalore[116] and a study by Norway.[103]

Although obesity is not among the components of the MetS, it has become an important health problem among females and males living with HIV. Before the introduction of HAART, elevated BMI was associated with a slower progression from HIV infection to AIDS; whereas now, elevated BMI is associated with high cholesterol, triglycerides, glucose, and insulin resistance.[98,131] In the present study, almost one third patients (33.33%) were overweight (BMI between 25 to 29.99 Kg/m^2). In a study[116] from Bangalore, of the 60 patients studied, two patients with metabolic syndrome had BMI more than 25 and none in the patients was obese with BMI above 30. The mean body mass index in this study was 24.17 ± 3.60 Kg/m^2. The comparison of mean body mass in index in patients with (26.90 ± 3.80 Kg/m^2) and without (23.40 ± 3.17 Kg/m^2) metabolic syndrome showed significantly higher body mass index in patients with metabolic syndrome ($p<0.001$). These findings suggest that, higher body mass index among HIV patients is significantly associated with higher risk of metabolic syndrome.

In the present study, 53.33% of patients had pallor and a small proportion of patients (5.33% each) presented with clubbing, edema and icterus. On systemic examination, crepts (4%) and decreased air entry (4%) were noted in respiratory system. The CNS examination (4%) revealed ataxia (1.33%), nystagmus (1.33%) and neck rigidity (1.33%) while per abdominal findings revealed hepatomegaly (2.67%). No statistically significant association was observed between metabolic syndrome and different clinical signs and symptoms studied. This could be attributed to two aspects that are, majority of the patients in this study were on ART and next being smaller sample size.

All definitions of metabolic syndrome include central obesity. Central obesity is required to meet the IDF definition, which uses different waist circumferences for ethnic groups as well as for gender. In the present study, 16% of the patients had abnormal waist circumference (> 102 cms among males and > 88 Cms among females) and significantly higher number of patients (56.25%) with abnormal waist circumference had metabolic syndrome ($p<0.001$). The mean waist circumference was 90.25 ± 9.56 Cms. The mean waist circumference in patients with metabolic syndrome (97.70 ± 11.34 Cms) was significantly high (88.20 ± 7.96 Cms) ($p=0.005$). These findings suggest that, the presence of abnormal waist circumference in patients with HIV is significantly associated with metabolic syndrome. A study from Bangalore reported significantly higher mean Waist circumference (82.7 ± 11.88 Cms) in patients with ART compared to (76.7 ± 9.64 Cms) ART naïve patients ($p=0.036$). In contrast a study[128] from Allahabad, India reported waist circumference was not increased in any case of HIV with metabolic syndrome. Increased waist circumference was also reported in 12.5% of cases in a study.[23] Presence of increased waist circumference was seen in 30.7% and 37.8% of cases in other studies.[110,113]

In the present study, raised blood pressure levels (≥ 130/85 mm Hg) was noted in 16% of patients and significantly higher proportion of patients with raised blood pressure (68.75%) had metabolic syndrome ($p<0.001$). The mean SBP was 119.09 ± 16.77 mm Hg and mean DBP was 77.57 ± 10.52 mm Hg. The comparison of mean systolic (135.60 ± 15.04 versus 114.60 ± 14.30 mm Hg) and diastolic blood pressure (87.20 ± 10.37 versus 74.90 ± 8.97 mm Hg) significantly higher values in patients with metabolic syndrome ($p<0.001$). There are very few

studies of hypertension in the HIV-infected population and little evidence for a significant increase compared with controls. However, blood pressure rises when HIV-infected patients are treated with effective antiretroviral therapy. No specific antiretroviral drug has been linked to hypertension, but, as in control populations, age and BMI are linked to hypertension.[102] A study[114] stated the proportion of patients with hypertension increased from 15.9% at entry level to 54.5% of those under follow up over 6 years. Hypertension was present in 31.4% in HIV-infected cohort in another study[113] while another study[110] reported hypertension among 42.3% HIV patients.

Consistent with early studies linking insulin resistance with other components of metabolic syndrome, insulin resistance or disturbances in glucose metabolism are included as criteria in each of the syndrome definitions. Insulin resistance is a required criterion in the WHO and EGIR definitions. Elevated glucose is required for the IDF definition.[102] In the present study, 22.67% of patients had impaired glucose tolerance on OGTT and 4% of patients had diabetes mellitus. The mean OGTT levels were 121.31 ± 36.94 mg/dL.

In our study, of the 16 patients with metabolic syndrome, 5 (31.25%) had fasting blood sugar ≥ 110 mg/dL whereas 11 (68.75%) had < 110 mg/dL fasting blood sugar levels. This difference was statistically not significant (p=0.136). The mean fasting blood sugar levels were 88.27 ± 22.32 mg/dL. The fasting blood sugar levels in HIV patients with metabolic syndrome were slightly high (96.20 ± 21.09 mg/dL) compared to those who did not have metabolic syndrome (86.10 ± 22.32 mg/dL) but this difference was statistically not significant (p=0.107). In a study[128] from Allahabad, India FBG ≥100 mg/dl was present in 28.6% cases, out

of whom 27.7% were on HAART and 30.4% were not on HAART (p=0.8089). A study[23] reported raised FBG in 11.5% of the cases while another study[110] reported the same in 24.0% of the cases. In the setting of HIV, insulin resistance has a number of causes, including antiretroviral therapy (certain PIs and to a lesser extent certain NRTIs). The mechanism of induction by these PIs is partially understood and differs from insulin resistance in the general population. HIV-related insulin resistance does not seem to be associated with other aspects of the syndrome. However the present study did not analyse the association of individual ART drugs due to the smaller sample size.

HDL-C in other inflammatory diseases may be more atherogenic than levels indicate. For example, inflammatory HDL-C is less active at preventing LDL-C oxidation and at removing cholesterol from macrophage foam cells. Indeed, inflammatory HDL may recruit macrophages to the vessel intima and may actually load macrophages with cholesterol.[102] In the present study, abnormal low density lipoprotein (≥100 mg/dL) was noted in 22.67% patients. The mean low density lipoprotein levels were 82.80 ± 25.75 mg/dL. No statistically significant difference was observed in patients with (83.10 ± 29.66 mg/dL) and without (82.70 ± 24.86 mg/dL) metabolic syndrome (p=0.955). and in our study, abnormal high density lipoprotein (≤40 men; ≤50 mg/dL women) was noted in 61 (81.33%) patients. Of these, 15 (93.75%) had metabolic syndrome whereas metabolic syndrome was absent in 46 (77.97%). However, this difference was statistically not significant (p=0.151). The mean high density lipoprotein levels were 32.72 ± 15.46 mg/dL. The mean high density lipoprotein levels were low in patients with metabolic syndrome (27.20 ± 19.19 versus 34.20

± 14.11 mg/dL) but the difference was statistically not significant. In a study[128] from Allahabad, India HDL cholesterol values were low in 50% cases, out of whom 55.3% were on HAART and 39.1% were not on HAART (p=0.2035). Another study[23] demonstrated low HDL levels in 35.63% cases while other studies reported 43.5%[113] and 52.4%[110] cases to have low HDL in HIV-infected patients.

In this study, abnormal triglyceride levels (≥150 mg/dL) were noted in 49.33% patients. Of the 16 patients with metabolic syndrome higher number of patient (62.50%) had raised triglyceride levels compared to those who did not had metabolic syndrome (45.76%) but the difference was statistically not significant (p=0.235). The mean triglyceride levels were 148.99 ± 53.62 mg/dL. The mean triglyceride levels in patients with metabolic syndrome were significantly high (184.50 ± 79.21 versus 139.30 ± 40.01 mg/dL; p=0.022). These findings suggest that raised triglyceride levels among HIV patients significantly predict the risk of metabolic syndrome among HIV patients. A study[128] from Allahabad, India reported 42.9% cases had TG ≥150 mg/dl, out of whom 44.7% were on HAART and 39.1% were not on HAART (p=0.6894). Several other studies have also reported raised triglycerides in 43.1%,[23] 44%[113] and 59.3%[110] cases Hypertriglyceridemia is thought to be due to decreased clearance of triglycerides and, to a lesser extent, increased production of VLDL. These changes are associated with elevated levels of the cytokine interferon-α, which mediates the host response to viral infection. In contrast, interferon-α is not associated with low HDL-C.[102]

In the present study, abnormal (≥200 mg/dL) total cholesterol levels were noted in 6.67% of patients. The mean total cholesterol levels were 151.87 ± 30.17 mg/dL. The total cholesterol in patients with metabolic syndrome was 147.00 ± 32.03 mg/dL compared to 153.10 ± 29.78 mg/dL in those without metabolic syndrome.

In this study, of the 16 patients with metabolic syndrome, abnormal high density lipoprotein levels were observed in nine (90%) males and all the females (100%) whereas 60% of males and 66.67% of females had abnormal triglyceride levels. With regards to waist circumference, abnormalities were seen in 70% of the males and 33.33% of the females. Though, ART treatment was seen as a significant risk factor associated with metabolic syndrome, sex distribution was almost comparable in those on ART [nine (90%) males and five (83.33%) females]. However association could be found due to the smaller sample size and these findings could not be compared with other studies due to the scarcity of data.

Overall, the present study showed there is an increase in metabolic syndrome in patients with HIV especially in those who are on ART. The limitations of the study were smaller sample size which limited the study from determining association between other constraints such as type of ART drug and prevalence of metabolic syndrome and its components and clinical features. Further studies with large sample size with comparative study design are warranted to explore the epidemiology of metabolic syndrome in patients with HIV.

Chapter 7

Conclusion

CONCLUSION

The present study showed that the prevalence of metabolic syndrome was 21.33% in HIV patients. Of the 16 (21.33%) patients with metabolic syndrome, 14 (87.5%) had satisfied four components of metabolic syndrome whereas two patients (12.50%) had satisfied two components. Of the 47 patients with ART, significantly higher number of patients (29.79%) had metabolic syndrome.

Pallor was the commonest symptom of presentation and was observed in 53.33% of patients whereas clubbing, edema and icterus were noted among 5.33% patients each. On systemic examination, crepitations (4%) and decreased air entry (4%) were present in respiratory system. The CNS examination (4%) revealed ataxia (1.33%), nystagmus (1.33%) and neck rigidity (1.33%) while per abdominal findings revealed hepatomegaly (2.67%).

Significant association was found between metabolic syndrome and ART treatment, waist circumference, raised blood pressure levels and body mass index whereas no statistically significant association was found between metabolic syndrome and sex, age, triglycerides, high density lipoprotein and fasting blood sugar.

Chapter 8

Summary

SUMMARY

The present study was aimed to find out the prevalence of metabolic syndrome in HIV patients and to assess the clinical and laboratory profile of these patients.

This one year cross sectional study was conducted during the period of January 2012 to December 2012 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 75 HIV positive patients were studied.

In the present study, majority (76%) of the patients were males. Most of the patients (37.33%) were aged between 41 to 50 years and the mean age was 42.03 ± 10.35 years. Agriculture was the occupation among 48% of the patients. 44% of the patients presented within the duration of five to ten years of HIV and the mean duration of HIV was 6.46 ± 3.26 years and 62.67% of the patients were on ART treatment. The body mass index in 33.33% patients was between 25 to 29.99 Kg/m^2 and the mean body mass index was 24.17 ± 3.60 Kg/m^2. Pallor was present in 53.33% whereas clubbing, edema and icterus were noted among 5.33% patients each. In this study, crepts (4%) and decreased air entry (4%) were noted in respiratory system. The CNS examination (4%) revealed ataxia (1.33%), nystagmus (1.33%) and neck rigidity (1.33%) while the per abdominal findings revealed hepatomegaly (2.67%).

Impaired glucose tolerance on OGTT was noted in 22.67% of patients with mean OGTT levels of 121.31 ± 36.94 mg/dL. The fasting blood sugar levels in 16% of the patients were more than or equal to 110 mg/dL and mean fasting

blood sugar levels were 88.27 ± 22.32 mg/dL. Abnormal high density lipoprotein (<40 men;≤50 mg/dL women) was noted in 81.33% patients and mean high density lipoprotein levels were 32.72 ± 15.46 mg/dL. Abnormal triglyceride levels (≥150 mg/dL) were observed in 49.33% patients with mean triglyceride levels of 148.99 ± 53.62 mg/dL.

The prevalence of metabolic syndrome in HIV positive patients was 21.33%. Of the 16 (21.33%) patients with metabolic syndrome, three components were present in 14 (87.5%) patients and two patients (12.50%) had four components. Statistically significant association was found between metabolic syndrome and ART treatment, waist circumference, raised blood pressure levels and body mass index whereas no statistically significant association was found between metabolic syndrome and sex, age, triglycerides, high density lipoprotein and fasting blood sugar.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"STUDY OF METABOLIC SYNDROME IN HIV POSITIVE PATIENTS IN A TERTIARY HOSPITAL"

Objective and purpose of the study

This research is intended to find the prevalence of metabolic syndrome in HIV positive patients and also to assess clinical and laboratory profile. The principal investigator of the study is Dr. **** ******* under the guidance of Dr. ***** ******** Professor, Department of Medicine, J. N. Medical College, Belgaum. Your co-operation will be of great help to HIV patients with metabolic syndrome in future.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood samples and undergo other necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations which may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment like other patients.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant you may call Chairman, J.N.M.C Ethical Committee for Human Research phone number 0831-2471350. In case of the queries during study or in future you may contact following person

Dr. ***** ********,**
Investigator,
Post Graduate Student
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Dr. **** ********
Chief investigator,
Professor of Medicine,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Dr. **** **********
Professor and Head,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Dr. *** **********
Chairman I.E.C.
Professor and Head,
Department of Pathology,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____ Signature or _____
Thumb print

Name of the Witness _____ Signature _____

Name of the Investigator _____ Signature _____

Date: **Place:**

Dr. **** **********
Professor of Medicine,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Dr. *** *******
Post Graduate Student
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010

Annexures

Annexure II

ANNEXURE II – PROFORMA

"STUDY OF METABOLIC SYNDROME IN HIV POSITIVE PATIENTS IN A TERTIARY HOSPITAL"

Patient Name: IP/OP number:

Age: Sex:

Date of admission: Date of discharge:

Address: Occupation:

Chief complaints

Past History

Diabetes mellitus: Hypertension:

Coronary artery disease: Dyslipidemia:

Course and status of HIV infection

Date of diagnosis: Duration of ART:

Personal history

Smoking :

Alcohol intake :

Tobacco chewing :

Any other :

Family History

GENERAL PHYSICAL EXAMINATION

Built and nourishment:			Height	:
Weight	:		BMI	:
Waist circumference	:			
Skin fold thickness	:			
Biceps	:	1-	2-	Average:
Triceps	:	1-	2-	Average:
Subscapular	:	1-	2-	Average:
Lymphadenopathy	:		Pallor	:
Icterus	:		Cyanosis	:
Clubbing	:		Edema	:
Lipodystrophy	:			

Vital Signs

Temperature	:		Pulse rate	:
Blood pressure	:	SBP -	DBP	
Respiratory rate	:			

SYSTEMIC EXAMINATION

Respiratory system :

CVS :

Per abdomen :

CNS :

INVESTIGATIONS

Fasting blood glucose :

OGTT post 75 ml glucose 2 hours RBS:

ECG :

Lipid profile:

HDL cholesterol

Triglycerides

LDL Cholesterol

Total Cholesterol

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
A	-	Ataxia
Ag	-	Agriculture
ART	-	Antiretroviral therapy
BP	-	Blood pressure
Bpm	-	Beats per minutes
BS	-	Business
Cm	-	Centimeter
CPT	-	Crepts
DC	-	Decreased air entry
dL	-	Deci litre
DV	-	Driver
F	-	Female
HEPT	-	Hepatomegaly
HIV	-	Human immunodeficiency virus
HW	-	House wife
Kg	-	Kilogram
LB	-	Labour
M	-	Male
mg	-	Milli gram
mm Hg	-	Millimeter of mercury
N	-	Normal

ND	-	Newly detected
NR	-	Neck rigidity
PS	-	Private service
ST	-	Student