PREVALENCE OF DYSLIPIDEMIA IN PEOPLE LIVING WITH HIV/AIDS ON ANTI-RETROVIRAL THERAPY IN A TERTIARY CARE CENTRE IN CHENNAI – A CROSS SECTIONAL STUDY

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
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DECLARATION

I, Dr. R.Pavithra, solemnly declare that this dissertation titled "**PREVALENCE OF DYSLIPIDEMIA IN PEOPLE LIVING WITH HIV/AIDS ON ANTI-RETROVIRAL THERAPY IN A TERTIARY CARE CENTRE IN CHENNAI – A CROSS SECTIONAL STUDY**" is a bonafide work done by me at Government Stanley Hospital, Chennai, during February to July 2021 under the guidance and supervision of Prof. Dr. S.M.Sujatha M.D., Government Stanley Hospital, Chennai. I also declare that this bonafide work or a part of this work was not submitted by me or any other for award degree or diploma to any other university, board either in India or abroad.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University towards fulfilment of university regulations for the award of **M.D. degree (Branch-I) in General Medicine**.

Date: **Signature of the candidate**

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This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of M.D. degree

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NOMENCLATURE

ABBREVIATIONS AND ACRONYMS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
HAART	Highly Active Anti-Retroviral Therapy
c ART	combined Anti-Retroviral Therapy
PLHA	People Living With HIV/AIDS
ELISA	Enzyme Linked Immuno-Sorbent Assay
UNAIDS	Joint United Nations Program on HIV/AIDS
IDU	Injection Drug Users
NACO	National AIDS Control Organisation
NACP	National AIDS Control Program
CDC	Centers for Disease Control and Prevention
gp	glycoprotein
CNS	Central Nervous System
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
pol	polymerase
env	envelope protein
vif	viral infectivity factor
vpu	viral protein U
nef	negative effector
vir	viral protein R
rev	regulator of viral gene expression
tat	transcriptional activator

mg	milligram
pg	picogram
dl	deciliter
ml	milliliter
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	Non- Nucleoside Reverse Transcriptase Inhibitors
PI	Protease Inhibitors
AZT	Zidovudine
d4T	Stavudine
3TC	Lamivudine
TDF	Tenofovir
NVP	Nevirapine
EFV	Efavirenz
DTG	Dolutegravir
RTV	Ritonavir
LPV	Lopinavir
ATV	Atazanavir
HDL	High Density Lipoprotein
ATBCA 1	ATP Binding Cassette Transporter A
TGL	Triglyceride
LDL	Low Density Lipoprotein
TC	Total Cholesterol
SREBP 1	Sterol Regulatory Enhancing Binding Protein 1
PPARγ	Peroxisome Proliferator Activated Receptor γ
CVD	Cardiovascular Disease
BMI	Body Mass Index
DAD	Data collection on Adverse events of Anti-HIV Drugs study group
SMART	Strategies for Management of Antiretroviral Therapy

TLR	Toll-Like Receptor
LPS	Lipopolysaccharides
SLE	Systemic Lupus Erythematosus
RA	Rheumatoid Arthritis
ACS	Acute Coronary Syndrome
START	Strategic Timing of Anti-retroviral Treatment study
AACTG	Adults AIDS Clinical Trials Group

SYMBOLS

Δ	delta
γ	gamma
μ	micro

TABLE OF CONTENTS

INTRODUCTION

Acquired Immune Deficiency Syndrome was first recognised in the United States in 1981. Human Immunodeficiency Virus was isolated in 1983 and by the year 1984, it was demonstrated clearly to be the causative agent of AIDS. In 1985, Enzyme Linked Immunosorbent Assay (ELISA), a sensitive method was developed and this led to the appreciation of evolution of HIV epidemic in US and other developed nations and ultimately among developing nations throughout the world.

It is considered to be a chronic disease necessitating long term management that requires Highly Active Anti-Retroviral Therapy (HAART). The introduction of HAART has led to prolong the lives of people living with HIV/AIDS. Morbidity and mortality of these individuals remain elevated compared to general population. Therefore the management of comorbidities remain more important in these individuals.

Although the benefits of antiretroviral therapy have revolutionized the care of HIV patients, increasingly severe treatment-associated metabolic side effects have been observed. Among them dyslipidemia, insulin resistance and overt diabetes mellitus, which are well-known risk factors for cardiovascular disease. The dyslipidemia promotes atherosclerosis and results in increased cardiovascular mortality. HIV infection, HAART, chronic immune activation can all alter the lipid profile and other metabolic parameters. This study focuses on relationship of altered lipid profile with patients on antiretroviral therapy in a tertiary care centre in Chennai.

AIM AND OBJECTIVES

AIM

To study the prevalence of dyslipidemia in people living with HIV/AIDS on Highly Active Anti-Retroviral Therapy for atleast 3 months duration and longer

OBJECTIVE

PRIMARY

To study the fasting lipid profile of people living with HIV/AIDS on HAART in a tertiary care centre in Chennai

SECONDARY

To determine the prevalence of dyslipidemia in PLHA to specific anti-retroviral agents used

To assess the cardiovascular risk and dyslipidemia in PLHA on HAART and to decide on lipid lowering medications

REVIEW OF LITERATURE

EPIDEMIOLOGY

AIDS is a global pandemic with cases reported from every country. An estimated 36.7 million individuals were living with HIV, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) at the end of 2016(1). An estimated 95% of people living with HIV reside in low- & middle- income countries; ~50% are women, and 2.1 million are children <15 years(1). The global prevalence has increased >4fold since 1990, reflecting the combined effects of high rates of new infections and the life-prolonging impact of antiretroviral therapy. The majority of new HIV infections are due to heterosexual transmission. Members of certain high-risk populations are highly affected. Sex workers, IV drug abusers, transgenders, prisoners, men who have sex with men accounted for 34% of all new HIV infections.

Between 2000 and 2016, the estimated annual number of new HIV infections fell by 40% globally(1). These reductions reflect progress with HIV prevention efforts and the increased provision to HIV-infected people of ART, which makes them much less likely to transmit the virus to sexual partners. From 2010 to 2016, there was a 47% reduction in HIV infections among children <15 years, which is due to the increasing availability of antiretroviral medications to prevent the transmission of HIV from mother to child(1).

In Asia, an estimated 5.1 million people were living with HIV at the end of year 2016. HIV prevalence is highest in the Southeast Asian countries. However, populations of many Asian nations are large that even low infection and seroprevalence rates result in large numbers of people living with HIV. So, 3 populous countries—China, India and Indonesia— account for around three-quarters of all people living with HIV in the region. Although the HIV epidemic in Asia has long been concentrated among specific populations—sex workers and their clients, men who have sex with men and IDUs—it is expanding to the heterosexual partners of those most at risk(1).

FIGURE 197-8 Estimated number of adults and children living with HIV infection as of December, 2016. Total: 36.7 million (30.8 million–42.9 million). *(From Joint United Nations Programme on HIV/AIDS [UNAIDS].)*

Global distribution of HIV infection by population(1):

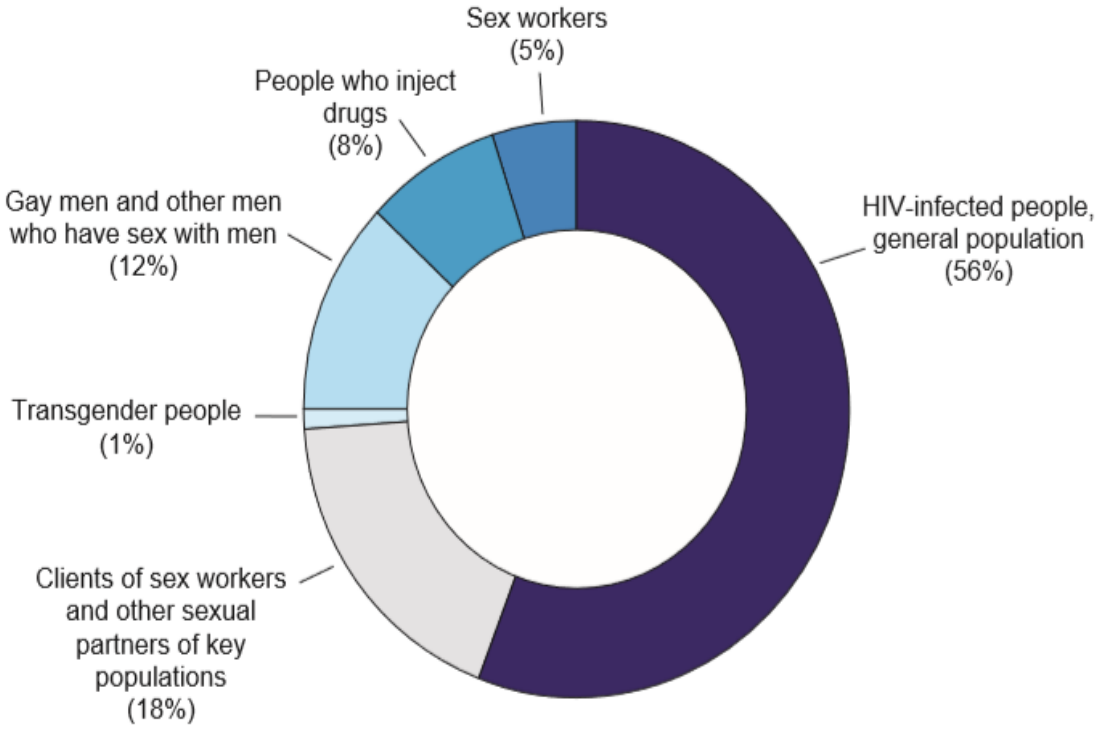


FIGURE 197-11 Global distribution of new HIV infections by population. Data for 2015. *(From UNAIDS.)*

India(2) has a low HIV prevalence of 0.22%. Even with this low prevalence, India has the 3rd highest burden of HIV in the world with an estimated value of 2.14 million people living with HIV/AIDS. The 1st few cases of HIV were detected among the female sex workers in Chennai, Tamil Nadu, in 1986, followed by reports from other parts of the country. By the year 1987, ≈135 cases were reported in the country. Out of them, 14 had already progressed to AIDS. By 2006, it was estimated to be around 5.6 million cases in the country, mainly in the states of Maharashtra, Andhra Pradesh, Karnataka, Tamil Nadu, Manipur & Nagaland(2).

NATIONAL RESPONSE TO HIV EPIDEMIC(2)

The 1st phase of the National AIDS Control Program (NACP) was started in 1992 and lasted till 1999. This was followed by NACP-II (2000-2005), NACP-III (2006-2011), and NACP-IV(2012-2017). The anti-retroviral therapy (ART) was introduced in the later phase of NACP-II (2004). NACP-IV aims at improving the integration and mainstreaming of HIV care in general health system.

DEFINITION(1)

The current CDC classification for HIV infection and AIDS categorizes the patients based on the clinical conditions associated with HIV infection together with the level of CD4+ T lymphocyte count. Advanced HIV disease (AIDS) is classified as stage 3 if one or more specific opportunistic illness has been diagnosed.

TABLE 197-1 CDC Stage 3 (AIDS)-Defining Opportunistic Illnesses in HIV Infection
Bacterial infections, multiple or recurrent[a]
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive[b]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,[b] disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV

[a]Only among children age <6 years. [b]Only among adults, adolescents, and children age ≥6 years.

Source: MMWR 63(RR-03), April 11, 2014.

WHO Clinical Staging in Adults, Adolescents & Children(2)

Table 3: WHO Clinical Staging in Adults, Adolescents and Children

Adults and adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (Sinusitis, Tonsillitis, Otitis Media, Pharyngitis) • Herpes Zoster • Angular Cheilitis • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Seborrhoeic Dermatitis	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (Otitis Media, Otorrhoea, Sinusitis, Tonsillitis) • Herpes Zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Extensive wart virus infection • Extensive Molluscum Contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of the presumed or measured body weight) • Unexplained chronic diarrhoea for more than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent Oral Candidiasis • Oral Hairy Leucoplakia (OHL) • Pulmonary Tuberculosis • Severe bacterial infections (such as Pneumonia, Empyema, Pyomyositis, bone or joint infection, Meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, Gingivitis or Periodontitis • Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 109/l) and/or chronic thrombocytopaenia (<50 x 109/l)	• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) • Persistent Oral Candidiasis (after the first 6 weeks of life) • Oral Hairy Leucoplakia (OHL) • Lymph node Tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial Pneumonia • Acute necrotizing ulcerative gingivitis or Periodontitis • Unexplained anaemia (<8 g/dL), neutropenia (<0.5 x 109/l) or chronic thrombocytopaenia (<50 x 109/l) • Symptomatic Lymphoid Interstitial Pneumonitis • Chronic HIV-associated lung disease, including Bronchiectasis

Clinical stage 4	
• HIV wasting syndrome • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial Pneumonia • Chronic Herpes Simplex infection (orolabial, genital or anorectal of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system Toxoplasmosis • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated non-tuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis • Chronic Isosporiasis • Disseminated mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin) • Symptomatic HIV-associated nephropathy or cardiomyopathy • Recurrent septicaemia (including non-typhoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial infections (such as Empyema, Pyomyositis, bone or joint infection, Meningitis, but excluding Pneumonia) • Chronic Herpes Simplex infection (orolabial or cutaneous of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) • Central nervous system Toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated nontuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis (with diarrhoea) • Chronic Isosporiasis • Disseminated endemic mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis, Penicilliosis) • Cerebral or B-cell non-Hodgkin Lymphoma • HIV-associated nephropathy or cardiomyopathy
a) In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used. b) For children younger than 5 years, moderate malnutrition is defined as weight-for-height <–2 z-score or mid-upper arm circumference ≥ 115 mm to < 125 mm. c) Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America. d) For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 z-score; and severe acute malnutrition is either weight for height <–3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.	

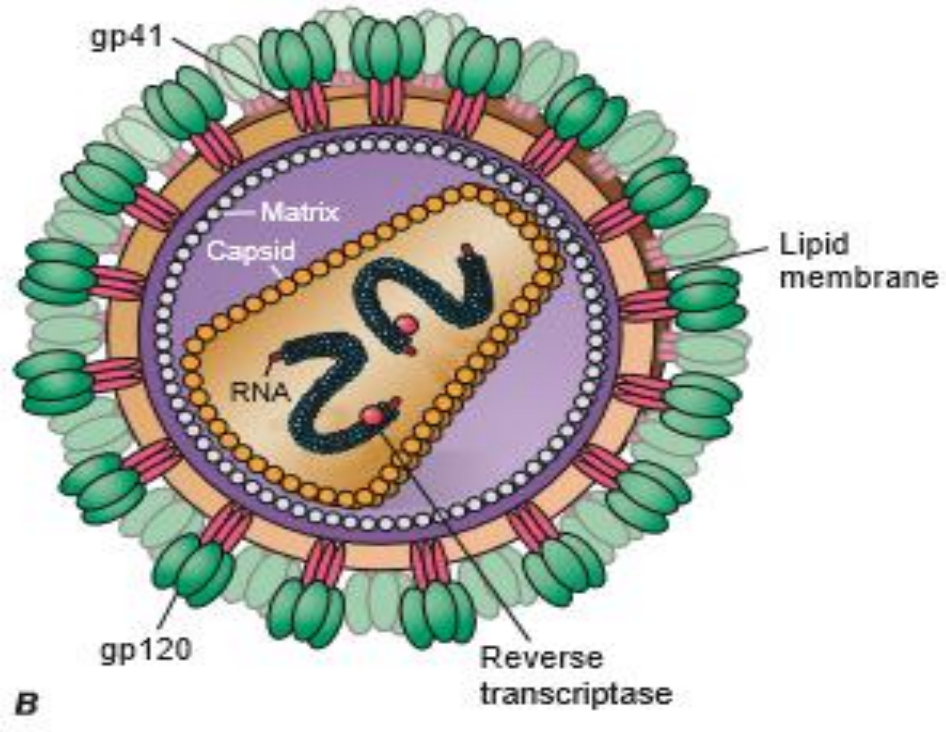
Source: Adapted from WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, World Health Organization, 2007 (www.who.int/HIV/pub/guidelines/ HIVstaging150307.pdf).

ETIOLOGY

Human Immunodeficiency Virus is the etiologic agent of AIDS. It belongs to the family of Retroviridae; and the subfamily of lentiviruses. HIV-1 and HIV-2 cause cytopathic effects either directly or indirectly. HIV-1 is the most common cause of HIV disease throughout the world. It comprises several subtypes. The currently defined groups of HIV-1 are M, N, O & P(1). The HIV-2 groups A through H are derived from a nonhuman primate reservoir. The HIV-1 viruses came from gorillas or chimpanzees. HIV – 2 from sooty mangabeys. HIV-1 M group viruses are responsible for the AIDS pandemic. The HIV – 1 group O and HIV – 2 viruses cause much more localised epidemics. This HIV – 2 is concentrated more in West African people.

MORPHOLOGY

The HIV virion has an icosahedral structure. There are numerous external spikes formed by two major envelope proteins - the external gp120 and the transmembrane gp41(1). It has 2 copies of positive sense single-stranded RNA which are tightly bound to nucleocapsid proteins p7, and enzymes needed for the development of virion such as reverse transcriptase, ribonuclease, proteases and integrases. This is further surrounded by the envelope. The envelope exists as a trimeric heterodimer. The virion buds from the surface of the infected cell and incorporates the lipid bilayer of various cellular proteins of the host.



LIFE CYCLE OF HIV

HIV infects the CD4 cell, resulting in the following sequence of events.

Stage 1:

This begins with engagement of the viral gp120 and the CD4 cell receptor which results in a conformational change in gp120.

Stage 2:

Then it permits interaction with one of two chemokine co-receptors (CXCR4 or CCR5).

Stage 3:

This is followed by membrane fusion and cellular entry involving gp41. The

monocyte, macrophages, follicular dendritic cells and microglial cells in the CNS also express the CD4 cell receptor and they are permissive to infection.

Stage 4:

After penetrating the cell, uncoating occurs. Then, a copy of DNA is transcribed from the RNA genome by the reverse transcriptase enzyme which is carried by the infecting virion. The process of Reverse transcription is error-prone and multiple mutations arise with ongoing replication.

Stage 5:

This DNA is transported into the nucleus where it gets integrated randomly within the host cell genome via integrase enzyme. Integrated virual DNA is called proviral DNA.

Stage 6:

When host cell is activated, this DNA copy is used as a template to transcribe new RNA copies.

Stage 7:

These are processed and exported from the nucleus, the viral mRNA then translated into viral peptide chains. These form new viral structural proteins and viral enzymes such as the reverse transcriptase and protease. Then they migrate to the cell surface.

Stage 8:

There, they assembled using the host cellular apparatus to produce infectious viral particles.

Stage 9:

These viral particles bud from the cell surface and incorporating the host cell membrane as their own lipid bilayer coat, and then cell lysis occurs.

Once maturation is complete, the new infectious virion is available to infect the uninfected cells and the process continues.

Genes involved are:

All these processes are enabled by 3 important viral genes (Gag, Pol and Env), and the products of 6 regulatory genes (Vif, Vpu, Vpr, Nef, Tat and Rev).

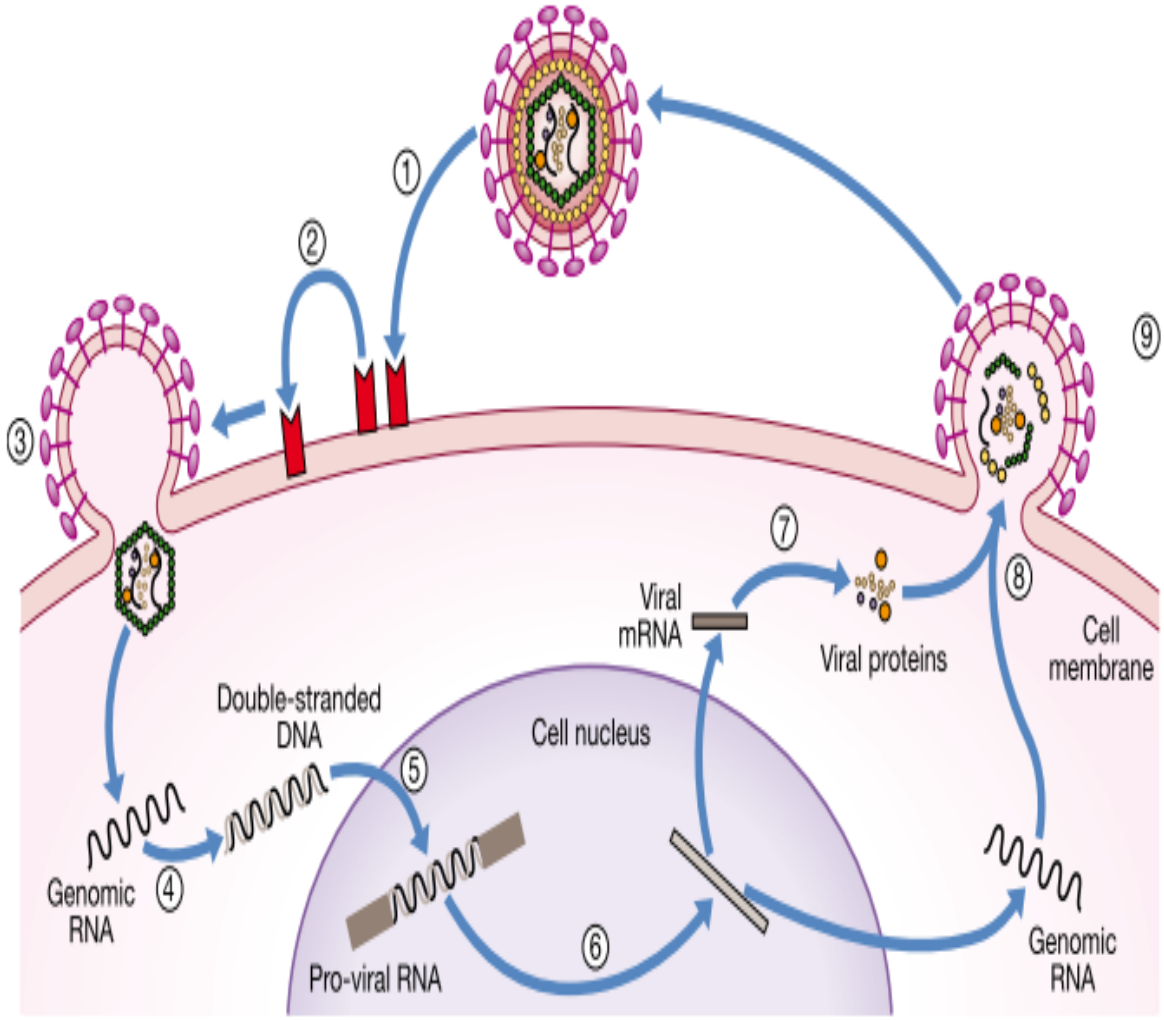


Fig. 14.2 Life cycle of HIV.

Binding of HIV with its target cell(1)

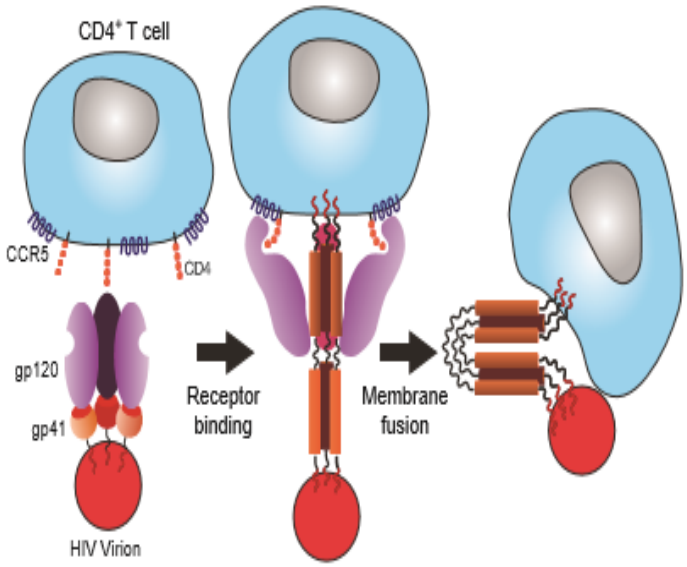


FIGURE 197-4 Binding and fusion of HIV-1 with its target cell. HIV-1 binds to its target cell via the CD4 molecule, leading to a conformational change in the gp120 molecule that allows it to bind to the co-receptor CCR5 (for R5-using viruses). The virus then frmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule. Virus-cell fusion occurs as the transitional intermediate of gp41 undergoes further changes to form a hairpin structure that draws the two membranes into close proximity (see text for details). *(Adapted from D Montefiori, JP Moore: Science 283:336, 1999; with permission.)*

TRANSMISSION

Human Immunodeficiency Virus is present in blood, semen and other body fluids like breast milk and saliva. Exposure to infected body fluid leads to the risk of acquiring infection. This is dependent on the integrity of the exposed site, the type of body fluid and the volume of body fluid and also the viral load. HIV can enter either as free virus or within cells.

The modes of spread are:

- sexual contact (includes both heterosexual and male to male)
- parenteral (blood and blood product recipients, intravenous drug abusers and those experiencing occupational injury)
- infected mothers to infants (intra-partum, perinatal period or via breast milk)

The transmission risk after exposure:

- 90% for blood and blood products
- 15–40% for the vertical route
- 0.5–1.0% for injection drug use
- 0.2–0.5% for genital mucous membrane spread
- < 0.1% for non-genital mucous membrane spread.

TABLE 197-3 Estimated Per-Act Probability of Acquiring HIV From an Infected Source, By Exposure Act

TYPE OF EXPOSURE	RISK PER 10,000 EXPOSURES
Parenteral	
Blood transfusion	9250
Needle-sharing during injection drug use	63
Percutaneous (needle-stick)	23
Sexual	
Receptive anal intercourse	138
Insertive anal intercourse	11
Receptive penile-vaginal intercourse	8
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[a]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

[a]HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Sources: CDC, *www.cdc.gov/hiv/risk/estimates/riskbehaviors.html*; P Patel: AIDS 28:1509, 2014.

PATHOPHYSIOLOGY

The hallmark of HIV disease is profound immunodeficiency(1). This is mainly due to progressive deficiency of CD4 T Helper cells which has high affinity for gp120 molecules in HIV and this occurs due to polyclonal immune activation. The two co-receptors, CCR5 and CXCR4 are essential for binding of gp120 molecule and CD4 helper T cell. After this, the configuration of gp120 is changed. Also gp41 undergoes change in configuration and establish contact with target cell membrane. Molecules of Fusion Peptides are then inserted on the exposed ends of gp41 which cause fusion of viral envelope with cell membrane. Then the viral genome enters the target cell.

When virus is non-replicating in the cell, the infected cell is unharmed. Latent virus retains its viability and it can start replicating at any opportunistic time(3).

When virus replicates, the host cell is damaged always. Direct toxicity is due to enormous replication of virus by fragmentation of the cell due to excess budding; by lysis of the infected cell due to cytotoxic proteins; and by syncytium inducing effect of the virus(3). Indirect toxicity is due to apoptosis; and by IgM and IgG antibodies and cytotoxic lymphocytes(3). When replication of the virus is not sufficient to kill the cell, it causes cell dysfunction.

Even in the absence of antiretroviral medication, a few HIV patients can maintain normal CD4 counts and low or undetectable plasma viremia. Those who have long-term viral suppression are called "elite controllers." This clinical characteristic was found to be extremely infrequent. The persistence of HIV-specific T-helper cell proliferative response distinguishes these people from regular and rapid progressors. These proliferative responses allow for continuing HIV-specific cytotoxic T lymphocyte activity and thus

containment of plasma viremia. However, it's unclear whether these HIV immune responses are the source of HIV control or the effect of it.

PATHOGENESIS OF EARLY HIV INFECTION

HIV-1 is most commonly transmitted through the anogenital mucosa.GP-120, a viral envelope protein, interacts to the **CD4 molecule** on dendritic cells. Interstitial dendritic cells are abundant in the cervico-vaginal epithelium as well as tonsillar and adenoid tissue, and they may act as first target cells in infections transmitted through genital-oral sex.

Transmission of macrophage tropic viruses rather than T cell tropic viruses is more likely in newly acquired HIV infection. Different co-receptors are involved in viral entrance into these cells. GP-120 bind to the chemokine receptor CCR5 as well as CD4 for entering into macrophages. T cell tropic viruses are labelled as X4 based on the CXCR4 receptor on these cells, whereas macrophage tropic viruses are identified as R5(4)

HIV-infected cells fuse with CD4+ T cells, causing the virus to propagate. HIV can be detected in regional lymph nodes two days after mucosal exposure and in plasma three days later. When the virus enters the bloodstream, it spreads quickly to organs like brain, spleen, and lymph nodes(4).

During the early stages of infection, the mucosa of the intestine is also a major target. In rhesus macaques, massive CD4 T-cell depletion has been demonstrated during acute infection with simian immunodeficiency virus. The studies found that CD4+ memory T cells were destroyed in a preferential manner, which could be due to direct infection or apoptosis. When compared to peripheral blood, this can result in an early and disproportionate depletion of

CD4+ T lymphocytes in the gastrointestinal tract. Microbial translocation due to alterations in the gut mucosal barrier has also been hypothesised as a possible cause of chronic immune activation.

Viremia(5) was observed between 5 and 30 days after experimental intra-vaginal simian immunodeficiency virus exposure

HIV RNA levels in humans rise rapidly from the earliest quantifiable measure to a peak level that usually corresponds to sero-conversion. A phase of low-level viremia prior to peak level viremia, on the other hand, may be more common.

The amount of HIV DNA in peripheral blood mononuclear cells can be used to assess the amount of the cellular HIV reservoir, which is seen quickly after infection. The HIV DNA level and initial CD4 cell count were found to be independent indicators of disease progression in a trial of 163 individuals who did not start antiretroviral medication immediately after diagnosis of acute infection(6).

Patients have a substantial number of susceptible CD4+ T cells and no HIV-specific immunological response when they first become infected with HIV. As a result, viral replication is fast, with plasma HIV RNA levels exceeding 10^7 copies/mL and p24 antigen levels above 100 pg/mL.

Plasma RNA levels drop with the formation of HIV specific immunity, mostly due to the emergence of virus-specific CD8+ cytotoxic T cells, and symptoms of the acute retroviral syndrome disappear. Plasma HIV RNA levels will stabilise at an individual's specific set-point within six months of infection in the absence of antiretroviral therapy.

CD4 T cells producing interferon gamma in response to HIV antigens were readily detected. But, in patients with early HIV infection who presented later in their clinical course, antigen-specific CD4+ T cells could not be readily detected. This coincided with lower frequencies of activated and proliferating T cells. This suggests apoptosis and cytopathic infection with HIV leads to their rapid decline. Regulatory T cells may also play an important role in suppressing HIV specific CD4+ T cell responses in early infection.

Genetic susceptibility:

Four single-nucleotide polymorphisms ----> CCR-5, CCR-2, MIP1A and IL2, were associated with HIV infection susceptibility in different genetic models.

The most extensively studied of these factors is the CCR5(4), a major co-receptor for HIV. CCR5 (δ) 32 is an allele which contains a 32-base pair deletion. This codes for a non-functional co-receptor. CCR5 (δ) 32 homozygotes are highly resistant to HIV infection. Those who are heterozygous for the 32-base pair deletion can acquire the HIV infection, but have a slower rate of progression.

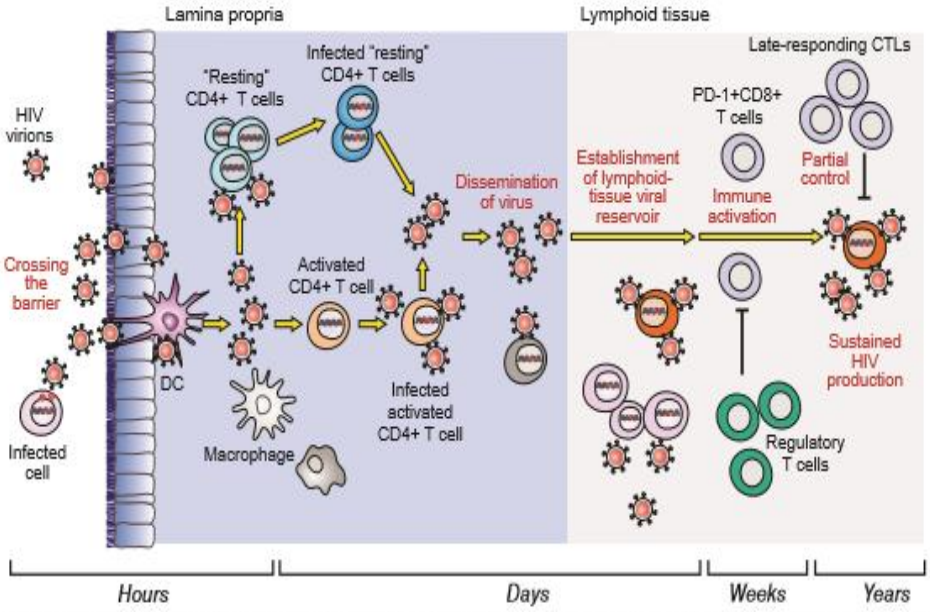


FIGURE 197-18 Summary of early events in HIV infection. See text for detailed description. CTLs, cytolytic T lymphocytes; HIV, human immunodefciency virus. *(Adapted from AT Haase: Nat Rev Immunol 5:783, 2005.)*

PERSISTENT AND CHRONIC INFECTION

Despite the strong cellular and humoral immune responses that arise after primary infection, the virus manages to evade total immune-mediated clearance, paradoxically seems to thrive on immunological activity, and is never completely eradicated from the body. Rather, a chronic infection develops and remains in the untreated patient for a median of ten years before the patient becomes clinically unwell. The characteristic of HIV illness is the emergence of a chronic, persistent infection. Virus replication may always be detected in untreated individuals during the long course of chronic infection using widely accessible tests that measure copies of virion-associated HIV RNA in plasma. Most untreated patients have viral levels that range from a few thousand to a few million copies of HIV RNA per millilitre of plasma(7).

PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION INDUCE IMMUNE DYSFUNCTION(1)

Viral replication and immune activation is persistent in HIV infection. This derives the substrates for persistent inflammation and immune activation. This occurs mainly in untreated patients. However, patients on ART also having detectable degrees of viral replication and immune activation even the viremia is better controlled with the medications.

This is reflected by excessive activation of B cells resulting in hypergammaglobulinemia; increased expression of pro-inflammatory cytokines such as IL-6; increased cell turnover; increased activation of monocytes; increased apoptosis; increased expression of cell cycle checkpoint regulators in CD4+ and

CD8+ T cells. From an immunologic point of view, chronic activation of immune cells for a prolonged period of time, result in 'functional' exhaustion of virus infected T cells. Hence, there will be inadequate response to the invading antigen as reflected by immune dysfunction.

The conditions associated with persistent inflammation and immune activation in HIV infection includes advanced age, bone fragility, neurocognitive dysfunction, cardiovascular disease, diabetes mellitus, chronic liver disease, chronic kidney disease and cancers.

ADVANCED HIV DISEASE(1)

In untreated patients or in patients in whom treatment has not adequately controlled the viral replication, the CD4+ T cell count falls below a critical level (<200/μL) and the patient becomes more susceptible to opportunistic infections.

Patients have constitutional signs and symptoms or may develop an opportunistic disease abruptly without any prodromal symptoms. The depletion of CD4+ T cells gradually progressive and unrelenting in this period. The CD4+ T cell counts in the untreated patient to drop to as low as 10/μL or even to zero. In places where cART and prophylaxis and treatment for opportunistic infections are accessible to such patients, survival is increased even in those patients with advanced HIV disease. In untreated patients who progress to the severe form of immunodeficiency usually succumb to neoplasms or opportunistic infections.

CLINICAL PRESENTATION

Acute HIV infection

- 60% patients are **asymptomatic**
- **Symptomatic infection is characterized by**
    - Fever
    - Lymphadenopathy
    - Sore throat
    - Rash
    - Myalgia/arthralgia
    - Diarrhea
    - Headache

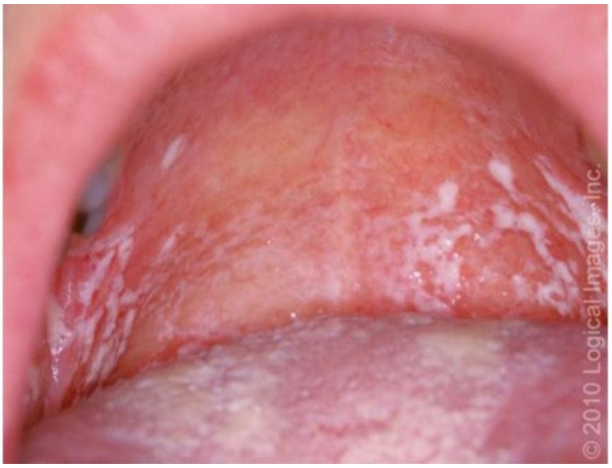
Acute HIV infection is a period of rapid viral replication and infection of CD4 cells. The plasma viral RNA level is very high. The HIV RNA levels are greater than 1 million copies/mL. The CD4 cell count can drop transiently. The presence of a prolonged symptomatic illness of >14 days during early infection correlates with more rapid progression to AIDS(8).

CHRONIC HIV INFECTION

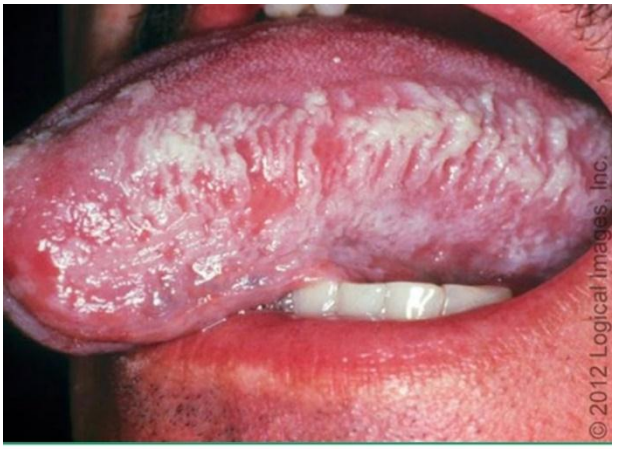
Most persons have few to no symptoms prior to development of severe immunosuppression (i.e., CD4 declines to <200 cells/microL). Some patients have nonspecific symptoms and signs like fatigue, sweats or weight loss. Some can have generalized lymphadenopathy on physical examination. This is known as **persistent generalized lymphadenopathy**(9). The enlarged lymph nodes involve at least 2 non-contiguous sites other than inguinal nodes for more than 3 to 6 months without an alternative cause. The lymph nodes are symmetrical, enlarged, painless, mobile, rubbery, and they are located in the cervical, submandibular, occipital, and axillary chains.

Some of the complications can occur at CD4 cell counts >200 cells/microL.

- Recurrent or persistent oropharyngeal or vulvovaginal candidiasis and oral hairy leukoplakia

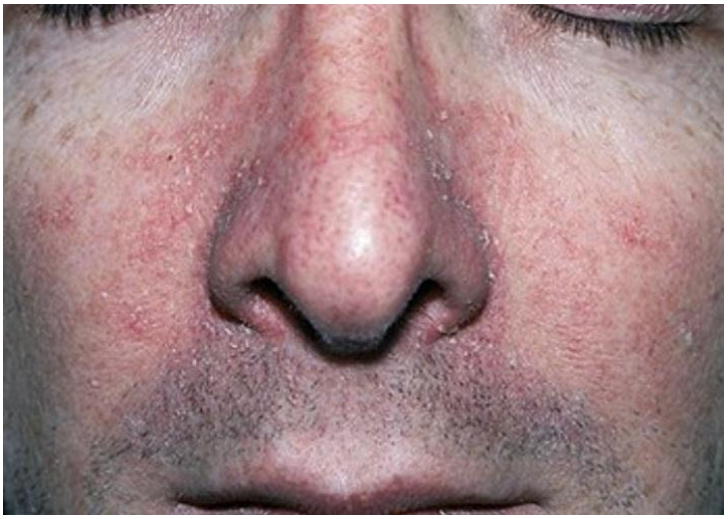


Oral Candidiasis



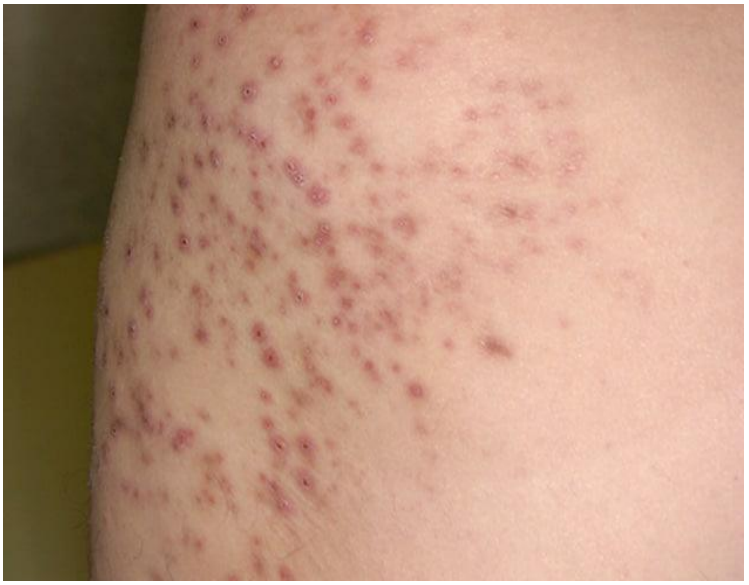
Oral Hairy Leukoplakia

- Seborrheic dermatitis



Facial redness and scale involving the nasolabial folds and central face

- Bacterial folliculitis particularly due to Staphylococcus aureus. There is high risk of acquiring CA-MRSA in HIV patients(10).



Folliculitis

- The manifestations of HSV, VZV and HPV infections are often more severe

AIDS

It is the outcome of chronic HIV infection and consequent CD4 cells depletion. It is defined as a CD4 cell count <200 cells/microL or the presence of any AIDS-defining condition regardless of the CD4 cell count.

The AIDS-defining conditions are already mentioned above in the definition part.

Additional findings in AIDS patients are

- Mucocutaneous candidiasis
- Oral hairy leukoplakia
- Seborrheic dermatitis
- Herpetic infections

All these can develop when the CD4 count is <200 cells/microL

Other **dermatologic findings** include:

- Eosinophilic folliculitis
- Xerosis
- Prurigo nodularis
- Molluscum contagiosum
- Bacillary angiomatosis
- Exacerbation of psoriasis
- Scabies infections

These skin conditions commonly occur or flare within 6 months or after initiating ART.

Hematologic alterations like (11)

- Anemia
- Leukopenia
- Lymphopenia
- Thrombocytopenia

These are found in patients with CD4 count <200 cells/microL

- Patients with Polyclonal hyper-gammaglobulinemia having an increased risk of bacterial infections occuring in late-stage HIV infection.

ANTI RETROVIRAL THERAPY

Goals of ART (2)

- **Clinical**:

  Increased survival and improvement in quality of life

- **Virological**:

  Possible sustained reduction in viral load

- **Immunological**:

  Immune reconstitution - both quantitative and qualitative

- **Therapeutic**:

  Rational sequencing of drugs

  Maintaining future treatment options

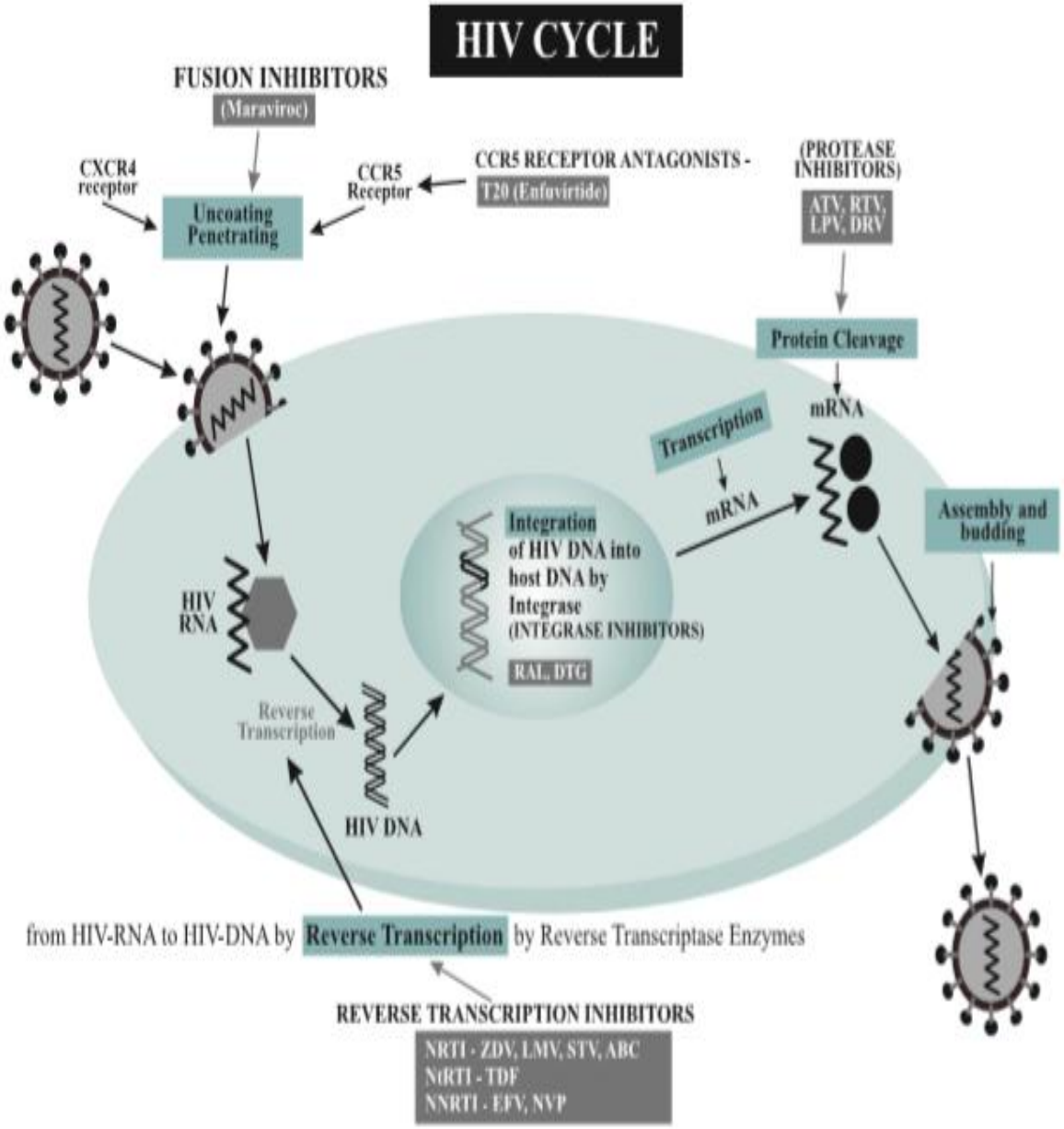
  Limiting drug toxicity

  Facilitating adherence

- **Preventive:**

  Reduction of HIV transmission by suppression of viral load

TARGETS OF ANTI RETROVIRAL THERAPY



The current **NACO guidelines (2017)** recommend to start ART for all persons diagnosed with HIV infection regardless of the CD4 count or WHO Clinical Staging or age group or population sub-groups(2)

Class of ART drugs:

Nucleoside reverse transcriptase inhibitors (NsRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Saquinavir (SQV)
Stavudine (d4T)	Efavirenz*(EFV)	Ritonavir (RTV)*
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir (NFV)
Abacavir (ABC)*	Rilpivirine (RPV)	Amprenavir (APV)
Didanosine (ddI)	Etravirine (ETV)	Indinavir (INV)
Zalcitabine (ddC)	**Integrase Inhibitors**	Lopinavir (LPV)*
Emtricitabine (FTC)	Raltegravir (RGV)*	Fosamprenavir (FPV)
Nucleotide reverse Transcriptase inhibitors (NtRTI)	Elvitegravir (EVG)	Atazanavir (ATV)*
	Dolutegravir (DTG)	Tipranavir (TPV)
Tenofovir (TDF)*		Darunavir (DRV)*
Fusion inhibitors (FI)	**CCR5 Entry Inhibitor**	
Enfuvirtide (T-20)	Maraviroc	
*Available in the national programme		

Nucleoside / Nucleotide Reverse Transcriptase Inhibitors

Mechanism

These drugs undergo intracellular phosphorylation by several host enzymes (ex: cytoplasmic or mitochondrial kinases and phosphor-transferases). The active triphosphate form, then inhibits the viral replication through competitive binding to the viral enzyme, reverse transcriptase. After the NRTI triphosphate is incorporated DNA chain elongation is terminated(12).

Adverse Events

The most common toxicity is mitochondrial toxicity. This may manifest as peripheral neuropathy, pancreatitis, lipoatrophy, lactic acidosis and hepatic steatosis

Non-Nucleoside Reverse Transcriptase Inhibitors

Mechanism

These drugs prevent HIV-1 reverse transcriptase from adding new nucleotides to the growing DNA chain. They block viral cDNA elongation at a site that is separate from the active site targeted by the NRTI class. This results in stereo-chemical change in the protein, which reduces the ability of the naturally occurring nucleosides to bind to the active site. The enzyme, reverse transcriptase becomes less flexible and DNA polymerization is inhibited. cDNA elongation is reduced which ultimately results in decline in the viral replication(13).

Adverse Events

The NNRTIs – Efavirenz and Rilpivirine can result in neurologic and psychiatric side effects. They are also associated with QT prolongation.

Integrase Inhibitors

Mechanism

After the entry of virus into CD4 T cells, viral RNA is reverse transcribed into DNA by the enzyme HIV reverse transcriptase. Then, the integrase enzyme catalyzes the process by which viral DNA is integrated into the host cell genome. This is essential for the maintenance of viral genome and viral gene expression. Integrase inhibitors target the strand transfer step of viral DNA integration. These drugs inhibit the binding of the pre-integration complex to the host cell DNA and thus ending the integration of HIV replication(14).

Adverse Events

These drugs are associated with increased weight gain compared with other agents. Insomnia and dizziness can also occur. Also, depression and suicidal ideation have been reported rarely, especially in patients with a history of psychiatric illness. Some reported small elevations in creatine phosphokinase (CPK), rhabdomyolysis, myopathy or myositis in patients taking raltegravir and dolutegravir.

Protease Inhibitors

Mechanism

Protease inhibitors competitively inhibit the cleavage of the Gag-Pol polyproteins in HIV-infected cells, thereby resulting in the production of immature virions, which are not infectious

Adverse Events

Some of the class-specific side effects are insulin resistance, hyperglycemia, diabetes(15), hepatotoxicity, hyperlipidemia(16), lipodystrophy, bleeding in patients with hemophilia and prolongation of PR interval(17)

ENTRY INHIBITORS

Mechanism

Maraviroc is the only approved CCR5 antagonist. This drug blocks the entry of CCR5-tropic viruses into the CD4 T cell. It is not commonly used for initial treatment of HIV. But, it may have a role in patients with drug-resistant virus.

Fusion inhibitors

Mechanism

These drugs bind to the envelope glycoprotein 41 to prevent viral fusion to the CD4 T cell. Enfuvirtide is the only approved fusion inhibitor. It is an injectable agent that is effective in patients who have not been exposed to this medication. However, it is difficult to administer for longer duration due to the need for twice-daily injections. This often leads to local cutaneous reactions.

HIV AND METABOLIC DISORDERS

A variety of metabolic disorders are seen in terms of HIV infection. These are due to either direct consequence of HIV infection or secondary to opportunistic infections, neoplasms or medication side effects. A syndrome named, “lipodystrophy” consisting of raised plasma triglycerides, total cholesterol, apolipoprotein B and hyperinsulinemia and hyperglycemia is seen in 33% to 75% of patients with HIV infection receiving thymidine analogues or protease inhibitors(1). Many are having truncal obesity with peripheral wasting which may develop at 6 weeks to several years following the start of ART.

The U.S. National Cholesterol Education Program Adult Treatment Panel III(18) proposed a criteria:

LDL CHOLESTEROL (mg/dl)	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high

TOTAL CHOLESTEROL(mg/dl)	
<200	Desirable
200-239	Borderline high
≥240	High

HDL CHOLESTEROL(mg/dl)	
<40 in males	Low
<50 in females	Low
≥60	High

TRIGLYCERIDES(mg/dl)	
<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

HIV per se and ART both have different implications in lipid profile. Initial concerns of increased rates of MI arising due to dyslipidaemia in HIV-infected patients on ART have been confirmed by studies such as the D:A:D study, a large, prospective, multi-cohort study that showed associations between exposure to antiretroviral therapy and an increased risk of myocardial infarction. In multivariate analyses, for every mmol/L increase in total cholesterol, the relative risk of myocardial infarction increased by a factor of 1.26(19).

A cross-sectional study was conducted in HIV infected persons above 15 years receiving first-line ART for atleast 6 months in Cameroon. The prevalence of dyslipidemia was 70.2%. Hypercholesterolemia was observed in 29.8%; one-third of them had high LDL-cholesterol. Hypertriglyceridemia was present in 51.8% of them. 18.4% of them had low HDL cholesterol levels(20).

Friis-Moller et al., conducted a large cross-sectional study and concluded increased prevalence of dyslipidemia in HIV patients treated with ART compared to healthy subjects matched for age and BMI from Framingham Heart Study(21).

Lipid abnormalities are present in untreated HIV infection, such as low high-density lipoprotein (HDL) cholesterol, low low-density lipoprotein (LDL) cholesterol with predominantly small, dense LDL cholesterol particles and hypertriglyceridemia(22). After initiation of ART, LDL and total cholesterol levels increase but HDL cholesterol levels remain low, particularly if the patient is on protease inhibitors(23).

In the Swiss HIV Cohort Study, hypercholesterolemia and hypertriglyceridemia were 1.7 to 2.3 times more common in patients taking protease inhibitors than those who are not taking them.

Thus, the HIV infection causes an atherogenic lipid profile with an increase in triglycerides, oxidized LDL cholesterol and small, dense LDL cholesterol with a reduction in HDL cholesterol. The prevalence of hyperlipidemia in HIV patients is 28% to 80% in different studies and the commonest abnormality being hypertriglyceridemia.

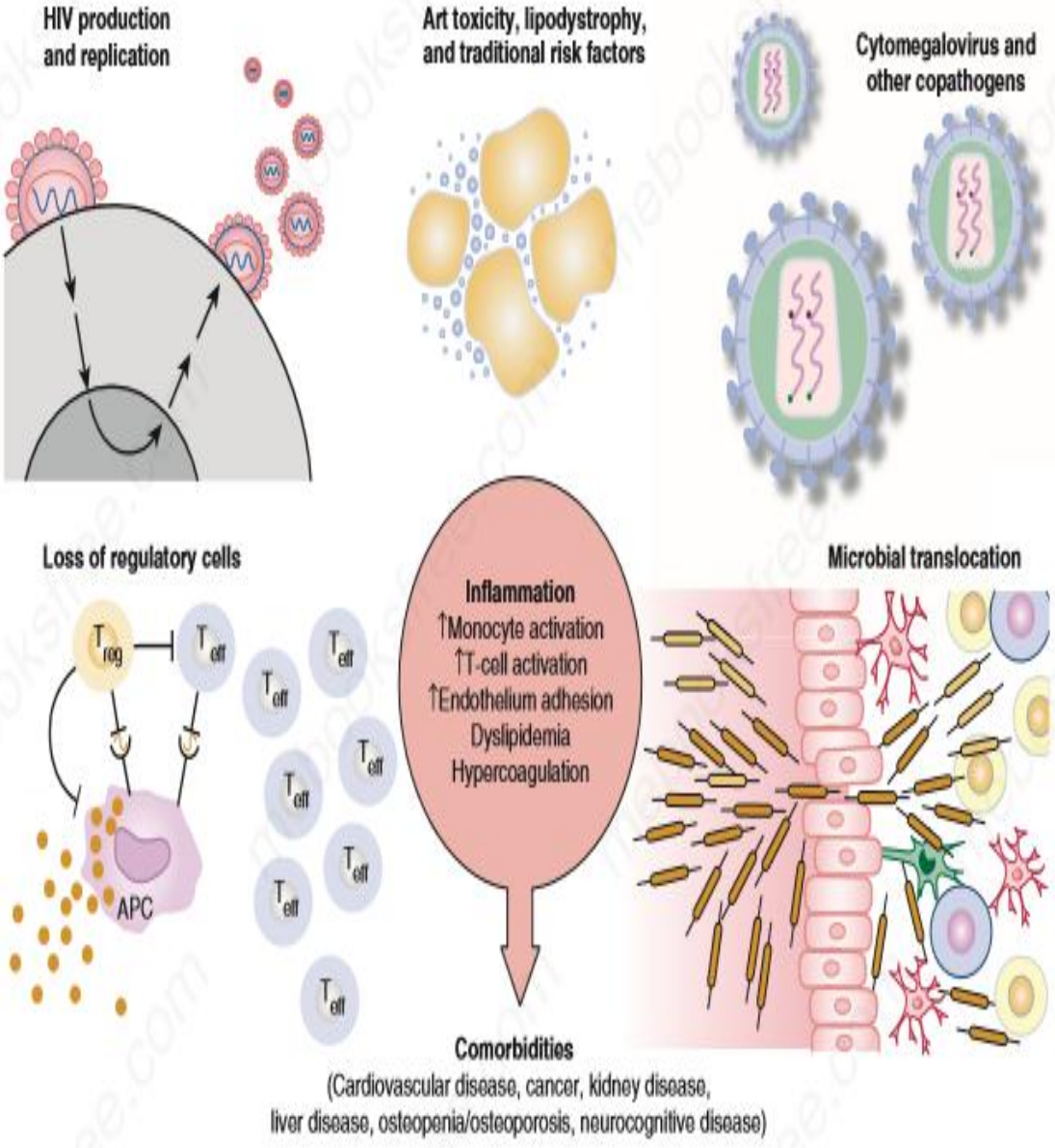
Regarding the direct effect of HIV, the low-level transcription of HIV genes may continue even after years of Anti-Retroviral Therapy. The HIV-encoded proteins - negative factor (nef) and transactivator of transcription (tat) induce inflammation and endothelial cell dysfunction. In addition to this, the HIV envelope protein gp-120 has been linked to higher endothelin-1 levels. Thus, the HIV virus itself may promote atherogenic lipid profile by releasing low levels of proteins. Most studies show that the impact of HIV on the endothelium is likely due to downstream effects of the virus, like chronic inflammation(24).

The mechanism of cardiovascular disease in HIV is multifactorial which includes

- Ongoing viral replication
- Side effects from ART
- Traditional risk factors
- Coinfection with other viral pathogens
- Immune activation
- Microbial translocation in the gut

All of these factors may increase the inflammation in the setting of treated as well as suppressed HIV disease, resulting in

- Monocyte activation
- Dyslipidemia
- Hypercoagulability
- Vascular disease function
- End-organ disease, not only in the heart but also in other systems


HIV production
and replication
Art toxicity, lipodystrophy,
and traditional risk factors
Cytomegalovirus and
other copathogens
Loss of regulatory cells
Inflammation
↑Monocyte activation
↑T-cell activation
↑Endothelium adhesion
Dyslipidemia
Hypercoagulation
Microbial translocation
APC
Comorbidities
(Cardiovascular disease, cancer, kidney disease,
liver disease, osteopenia/osteoporosis, neurocognitive disease)

HAART ASSOCIATED DYSLIPIDEMIA

HAART associated lipid abnormalities are most evident with protease inhibitors (PI), especially when they are combined with inhibitors of cytochrome p450 3A4. But other drug classes, including nucleoside reverse transcriptase inhibitors (NRTIs) may also have deleterious effects. Alterations in lipid concentration and composition are observed even with the most 'lipid friendly' ART regimens(22).

HIV protease inhibitors may promote atherosclerosis by direct cellular mechanisms which is described in experimental data from murine models. Further, there are considerable differences among the various protease inhibitors in their propensity to cause dyslipidemia(25).

The Strategies for Management of Antiretroviral Therapy (SMART) study(25) found an excessive risk of CVD in patients whose ART was interrupted when their CD4+ count reached a certain level than in patients who received continuous treatment. The reason for this finding remains unclear. It could be due to arterial inflammation, a reduction in HDL cholesterol levels or both caused by an acute increase in viral replication upon interruption of ART. The latter effect is particularly important after discontinuation of NNRTIs, since these drugs themselves cause a rise in HDL.

HDL has many anti-inflammatory & cardioprotective roles. It promotes cholesterol efflux from macrophages in the vessel wall via reverse cholesterol transport. It prevents oxidative modification of LDL. Also it supports endothelial cell repair. The cholesterol efflux capacity of HDL particles were inversely related to CVD risk and this was independent of the total HDL concentration. The anti-atherogenic role of

HDL is compromised during HIV infection and in inflammatory environments. The impairment of efficacy of reverse cholesterol transport was associated with exposure to Toll-like receptor (TLR) ligands such as lipopolysaccharide (LPS). This is particularly significant in HIV infection as the reduced gut barrier function and the increased plasma levels of microbial products have been reported in HIV positive individuals(22).

Further, the monocytes in HIV infection readily form cholesterol-laden foam cells and impaired HDL-mediated reverse cholesterol transport may be the reason for it. HIV can directly block ATP-binding cassette transporter A1 (ABCA-1) mediated cholesterol efflux to HDL particles, resulting in intracellular accumulation of lipids and enhanced foam cell formation. HIV RNA levels also correlate inversely with HDL levels. Acute inflammatory responses may similarly alter HDL levels and impair cholesterol efflux from macrophages. Low HDL levels have also been observed in individuals with acute infections, SLE and RA and cholesterol efflux is impaired in animal models of sepsis. Modulation of lipid metabolism during chronic infection may be a non-specific consequence of inflammation(22).

Most HIV drugs have the potential to increase LDL cholesterol levels. Protease inhibitors increase the triglyceride levels, with ritonavir being the worst culprit. In some cases, it may cause extreme hypertriglyceridemia with levels more than 1000 mg/dL. Nowadays, the lower doses of ritonavir used result in less hypertriglyceridemia. Increased triglyceride levels are also seen with ritonavir-saquinavir and ritonavir-lopinavir combinations. Atazanavir has less effect on triglyceride levels(26).

Second-generation protease inhibitors, the integrase inhibitor raltegravir and the entry inhibitor maraviroc, have favorable effects on lipid profiles.
Tenofovir alafenamide, a newer formulation of tenofovir disoproxil fumarate that was approved by the Food and Drug Administration (FDA) in November 2015, has been associated with higher levels of total cholesterol, LDL cholesterol and HDL cholesterol than those treated with tenofovir disoproxil fumarate(27).

Lipodystrophy:

It is a syndrome characterized by fat accumulation in the dorsocervical region and an increase in or preservation of visceral fat with subcutaneous and peripheral fat loss, resulting in relative central adiposity. This develops in 20% to 35% of patients after initiation of ART, particularly in those who have taken protease inhibitors and the nucleoside reverse-transcriptase inhibitors - stavudine and didanosine. Newer protease inhibitors such as atazanavir do not cause lipodystrophy.

In HIV patients, lipodystrophy is commonly associated with features of the metabolic syndrome. These features include insulin resistance, impaired glucose tolerance, elevated triglycerides, low HDL cholesterol levels and hypertension. The prevalence of the metabolic syndrome in HIV patients has been varied from 8.5% to 52%(28). Progression to metabolic syndrome is common in the first 3 years after initiation of ART regimen that includes stavudine or lopinavir/ritonavir, but is less common with the newer drugs. Most studies indicate that the presence of metabolic syndrome is a predictor for cardiovascular disease and death in HIV patients.

Atherosclerosis:

The older anti-retroviral drugs, may promote atherosclerosis by mechanisms in addition to dyslipidemia. Protease inhibitors induce reactive oxygen species and endothelial cell apoptosis. Nucleoside reverse-transcriptase inhibitors increase the platelet reactivity. The non-nucleoside reverse-transcriptase inhibitors cause monocytes to adhere to the vascular endothelial cell. Chronic inflammation and T-cell activation may play a central role in the development of atherosclerosis. Untreated HIV-infected persons have very high levels of T cells. Even after successful treatment with ART, higher T-cell levels persist. T-cell activation leads to increased levels of inflammatory markers, like interleukin-6, D-dimer, and high-sensitivity C-reactive protein. As reported by the Strategies for Management of Antiretroviral Therapy (SMART) Study (a study of continuous Vs. intermittent ART), these higher levels of inflammatory markers and coagulation markers are independent predictors of Cardiovascular events and fatal Cardiovascular disease in the setting of treated HIV infection.

Monocytes and macrophages are more significant in the pathogenesis of HIV disease as well as atherosclerosis. For this reason, they play a unique role in HIV-associated cardiovascular disease. Activated monocytes have been shown to accelerate the progression of carotid atherosclerosis. Monocytes from HIV patients and from patients without HIV infection but having an acute coronary syndrome (ACS) have been shown to be a pro-coagulant phenotype. This suggests another mechanism by which monocytes in HIV patients might drive atherosclerosis(29).

The CD4 count and the viral load also influence the cardiovascular risk. The CD4 count nadir predicts the subclinical carotid atherosclerosis. A low CD4 count with ART has been associated with an increased risk of cardiovascular disease. A low CD4 count was independently associated with an increased prevalence of carotid plaques in one study. This data suggests that earlier initiation of ART may be beneficial (Strategic Timing of Anti-Retroviral Treatment [START] Study). Other studies have shown that initiation of anti-retroviral therapy improves the endothelial function but does not restore it to normal. So that, higher viral loads correlate with worsened endothelial dysfunction

Atherosclerosis in HIV patients is a distinctive pathologic entity from that seen in the general population. Autopsy studies have reported that coronary atherosclerosis in young HIV patients resemble transplant vasculopathy and also it is characterized by diffuse, circumferential vessel involvement with smooth muscle proliferation mixed with enormous elastic fibres.

Also, calcification of the internal elastic media has been seen in HIV patients. The CT angiographic studies reveal that noncalcified plaques are much more common in HIV patients. These plaques are more likely to be lipid laden, inflammatory and are prone to rupture. Carotid plaque has also been found to be more common in HIV patients compared with uninfected controls in many studies(30).

Treatment of Dyslipidemia in HIV Patients:

Adult AIDS Clinical Trials Group (AACTG) and The Infectious Diseases Society of America published guidelines in 2003 for the evaluation and management of ART-related hyperlipidemia. These recommendations were based on National Cholesterol Education Program Adult Treatment Panel III guidelines. This advocated LDL cholesterol targets according to the level of cardiovascular risk based on the Framingham Risk Score predictions for 10 years.

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) produced new guidelines for the treatment of cholesterol for reducing the atherosclerotic risk in adults. This replaced the ATP III guidelines.

The ACC/AHA guidelines recommend treatment with *moderate or high-intensity statins* for

- patients with established atherosclerotic cardiovascular disease
- patients with LDL cholesterol level of 190 mg/dL or higher
- patients with diabetes who are 40 to 75 years of age and have LDL cholesterol level of 70 to 189 mg/dL
- patients with a 10-year CV risk of 7.5% or more who are 40 to 75 years of age and have LDL cholesterol level of 70 to 189 mg/dL

Some evidence suggests that these guidelines are not accurate in identifying HIV patients who should be treated with statins. Further, the compliance with guidelines appears to be suboptimal. In the HIV Outpatient Study, one fifth had a 10-year CV risk of more than 20%, yet a large percentage of at-risk patients who were eligible for treatment with Statins did not receive recommended interventions and did not reach the recommended treatment goals.

Specific drug-drug interactions are need to be considered when initiating lipid-lowering therapy in HIV patients.

Both protease inhibitors and NNRTIs can affect the cytochrome P450 isoforms. Simvastatin and Lovastatin plasma levels increase with protease inhibitor use. Thus, these statins are contraindicated with protease inhibitors due to the risk of rhabdomyolysis. Atorvastatin blood levels increase to a lesser extent only, so, it may be used at lower doses. Pravastatin and Fluvastatin are safe as they are not metabolized by CYP3A4. But their capacity to reduce LDL cholesterol levels is limited. Rosuvastatin has minimal P450 metabolism, but levels appear to be increased when it is used in combination with atazanavir/ritonavir and lopinavir/ritonavir, and so lower dose of 10mg is recommended.

The HIV guidelines in 2003, for the treatment of hyperlipidemia recommended diet and exercise interventions. This have been shown to decrease levels of total cholesterol by 11% to 25% in HIV populations.

Pravastatin of 20 to 40 mg/day or atorvastatin of 10 mg/day was recommended as starting therapy for elevated LDL cholesterol levels in patients taking any Protease inhibitor or Delavirdine. Fluvastatin of 20 to 40 mg/day was considered as an alternative second-line agent.

The European Society of Cardiology recommended that individuals with HIV and dyslipidemia needs to be treated to achieve the goal of LDL as it is defined for high-risk individuals.

Hypertriglyceridemia is common in HIV patients. This can be treated with fibrates (Gemfibrozil 600 mg twice daily or micronized Fenofibrate 54 to 160 mg once daily) when triglyceride levels are more than 500 mg/dL. Fibrates and statins have a drug-drug interactions. Hence, when combined, they should be used only at low doses.

Niacin and bile acid sequestrants are not recommended for HIV patients. Ezetimibe appears to be safe and effective when added to statin. It lowers LDL cholesterol levels modestly when used alone in HIV patients.

PCSK9 inhibitors markedly lower LDL cholesterol levels and are being investigated in clinical trials to determine whether they have a role in reducing the cardiovascular events. In a recent placebo-controlled trial, atorvastatin decreased the volume of non-calcified plaques and also decreased their high-risk features. But this drug had no impact on vascular inflammation or inflammatory markers.

MATERIALS AND METHODS

The study was conducted in the general medicine wards and ART centre of Govt. Stanley Medical College and Hospital, Chennai. It was conducted over a period of six months from February 2021 to July 2021. The study was approved by the Institutional Ethical Committee.

People living with HIV / AIDS on Highly Active Anti-Retroviral Therapy were included in this study. A total of 73 patients, both male and female, above 18 years of age, were enrolled into the study. There were 43 male and 30 female participants. The patients were included in the study group after getting informed and written consent from them.

Study type:

Cross sectional study

Study setting:

General medicine wards and ART centre in Government Stanley Hospital, Chennai

Study Population:

People living with HIV / AIDS on HAART attending ART centre and as inpatients in General Medicine wards in Government Stanley Hospital, Chennai

Inclusion Criteria:

- ✓ People living with HIV / AIDS of age > 18 years, receiving HAART for atleast 3months duration and longer

Exclusion Criteria:

- ✓ People less than 18 years of age
- ✓ People receiving ART for less than 3 months duration
- ✓ Poor compliance on ART
- ✓ People receiving lipid lowering medications
- ✓ People on long term steroid therapy or immunosuppressants
- ✓ Known cardiovascular / liver disease / renal disease / thyroid disorders / diabetes mellitus
- ✓ Pulmonary Tuberculosis
- ✓ Chronic Alcoholics
- ✓ Those who are not willing to participate in the study

After obtaining informed and written consent from the patients / attenders, detailed history regarding demographic data, duration of ART, various class of drugs, comorbid conditions and also detailed clinical examination had been done for HIV seropositive patients who attended ART clinics and who were admitted as inpatients in General Medicine wards. Under aseptic precautions, 5 ml of 12 hours fasting blood sample was collected from each of the participants. This sample was used for analysis of Blood sugar, Lipid Profile, Liver and Renal parameters. In Lipid profile, LDL is the calculated parameter using Friedewald et al formula. The data regarding routine investigations done at ART centre like CD4+ T-lymphocytes, Haemoglobin, Total WBC & ESR was collected from the patient's ART card. All these investigations were recorded.

Statistical analysis:

The collected data were entered into Microsoft Excel and statistical analysis was done using IBM SPSS statistical software. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and S.D were used for continuous variables. To find the significance in the categorical data, Chi-Square test was used. In all the above statistical tools, the probability value .05 is considered as significant level.

RESULTS

73 patients of people living with HIV / AIDS of age > 18 years, who were receiving HAART for atleast 3 months duration and longer, attending the ART centre were enrolled into the study. The following results were obtained from this study:

Table 1: Age distribution

Age distribution		
	Frequency	Percent
<= 30 yrs	14	19.2
31 - 49 yrs	51	69.9
>= 50 yrs	8	11.0
Total	73	100.0
Mean ± SD = 39 ± 9 yrs		

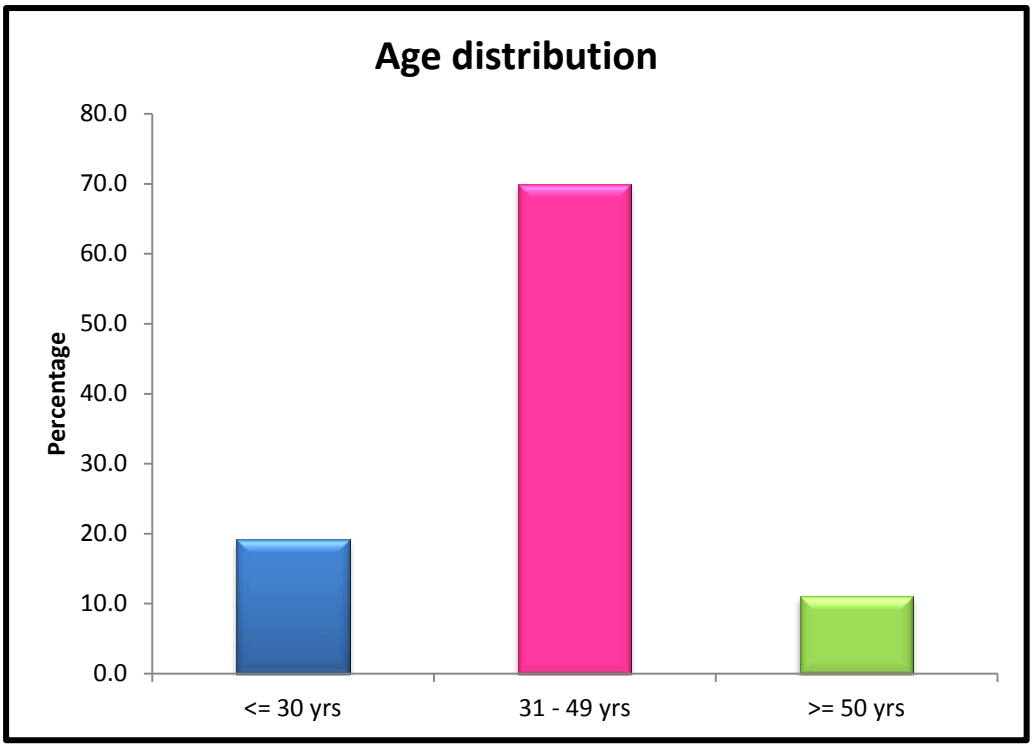


Figure 1

The above table shows Age distribution were <=30 years is 19.2%, 31-49 years is 69.9%, >50 is 11.0 %.

Table 2: Gender distribution

Gender distribution		
	Frequency	Percent
Male	43	58.9
Female	30	41.1
Total	73	100.0

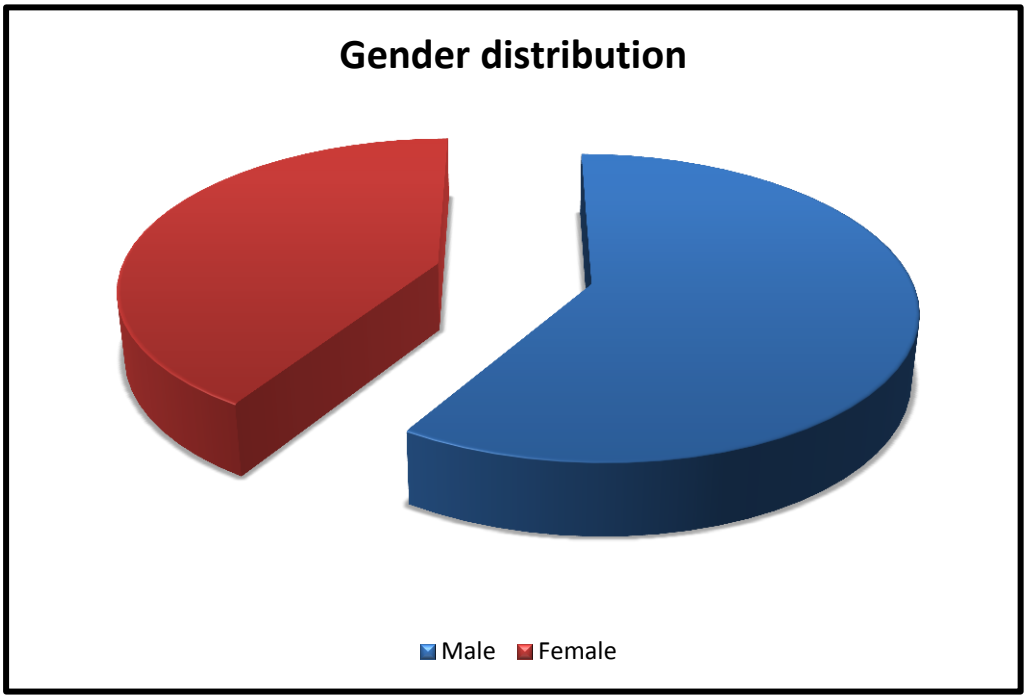


Figure 2

The above table shows Gender distribution were Female is 41.1%, Male is 58.9%.

Table 3: Distribution of Duration of illness

Duration of illness		
	Frequency	Percent
<= 1 yr	6	8.2
> 1 to < = 5 yrs	33	45.2
> 5 to < =10 yrs	15	20.5
Above 10 yrs	19	26.0
Total	73	100.0

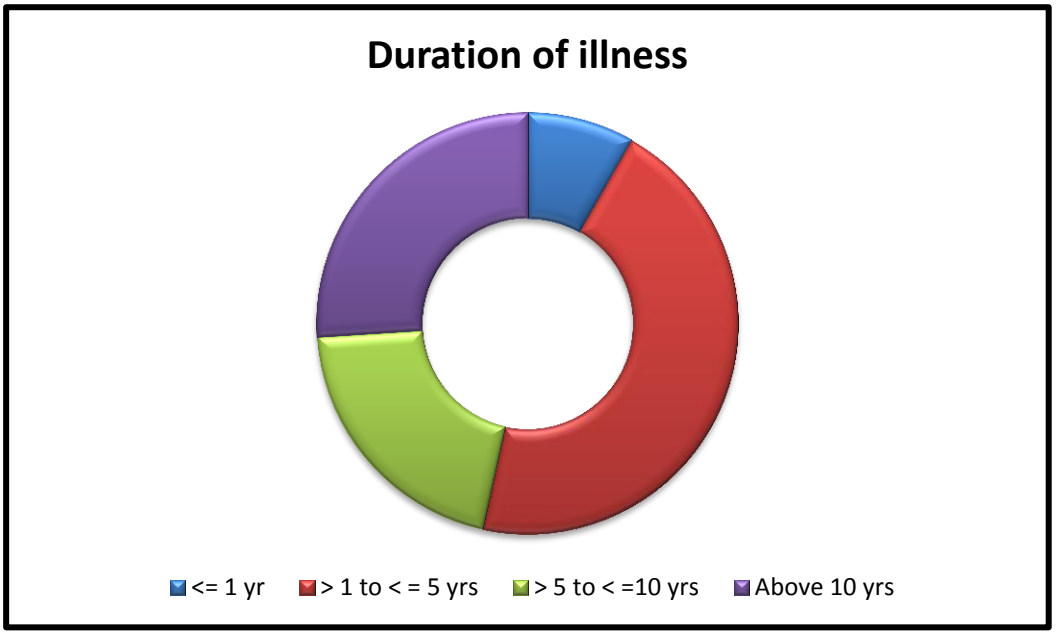


Figure 3

The above table shows Duration of illness distribution were <=1 year is 8.2%, >1 to <=5 years is 45.2%, >5 to <=10 years is 20.5, >10 years 26.0%.

Table 4: Distribution of Duration of ART

Duration of ART		
	Frequency	Percent
<= 1 yr	6	8.2
> 1 to < = 5 yrs	35	47.9
> 5 to < =10 yrs	18	24.7
Above 10 yrs	14	19.2
Total	73	100.0

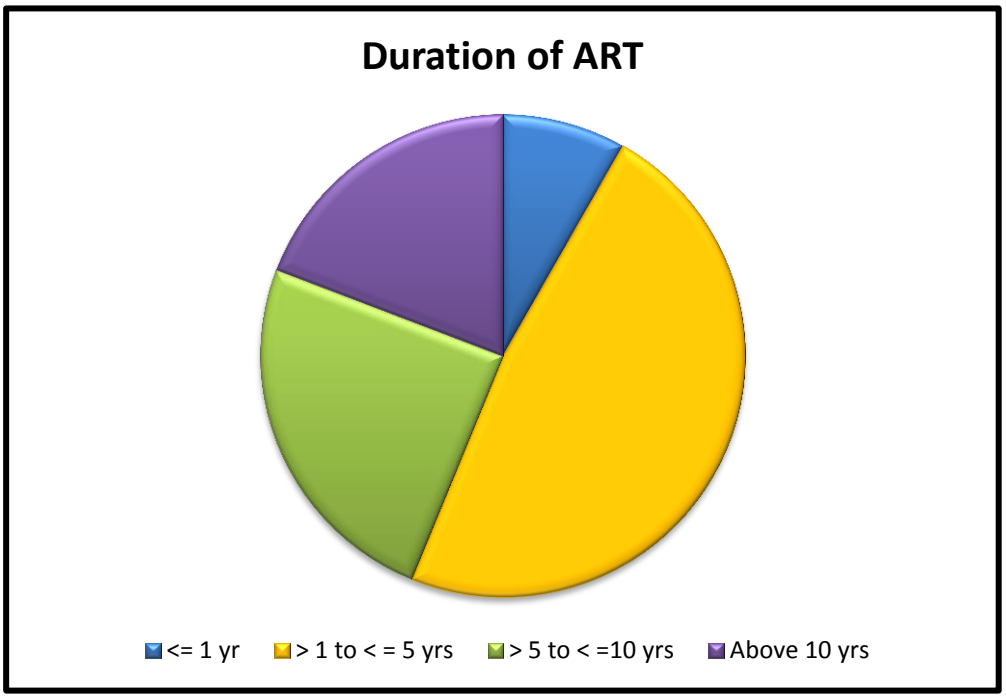


Figure 4

The above table shows Duration of ART distribution were <=1 year is 8.2%, >1 to <=5 years is 47.9%, >5 to <=10 years is 24.7, >10 years 19.2%.

Table 5: Distribution of Class of ART

Class of ART		
	Frequency	Percent
TLATV/R	1	1.4
TLD	8	11.0
TLD+DTG	1	1.4
TLE	46	63.0
TLLPV/RTV	2	2.7
TLN	2	2.7
ZLEFV	1	1.4
ZLN	12	16.4
Total	73	100.0

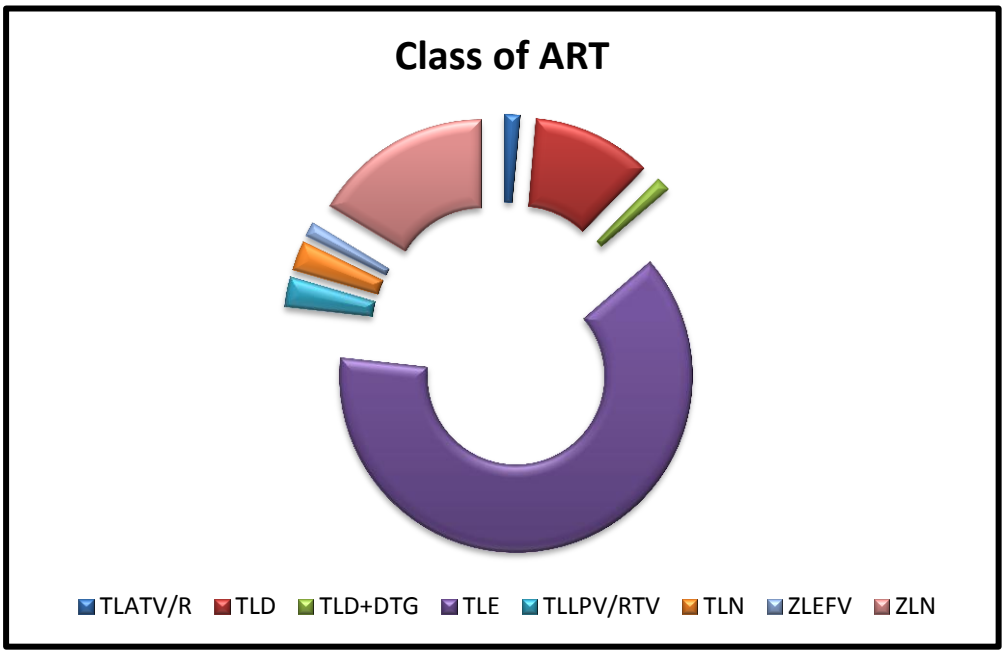


Figure 5

The above table shows Class of ART distribution were TLATV/R is 1.4%, TLD is 11.0%, TLD+DTG is 1.4%, TLE is 63.0%, TLLPV/RTV is 2.7%, TLN is 2.7%, ZLEFV is 1.4%, ZLN is 16.4%.

Table 6: Distribution of BMI

BMI		
	Frequency	Percent
Underweight	12	16.4
Healthy	37	50.7
Overweight	21	28.8
Obese	3	4.1
Total	73	100.0

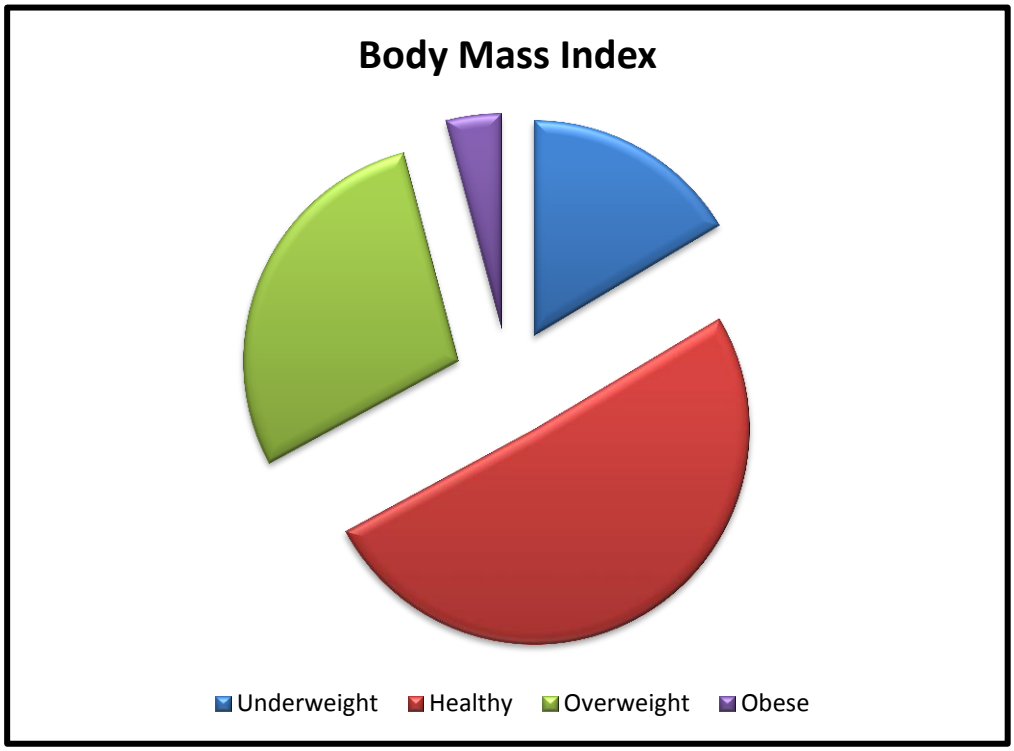


Figure 6

The above table shows BMI distribution were Underweight is 16.4%, Healthy is 50.7%, Overweight is 28.8%, Obese is 4.1%.

Table 7: Distribution of CD4

CD4		
	Frequency	Percent
> 500	46	63.0
Mild deficiency	9	12.3
Abnormal	10	13.7
Severe	8	11.0
Total	73	100.0

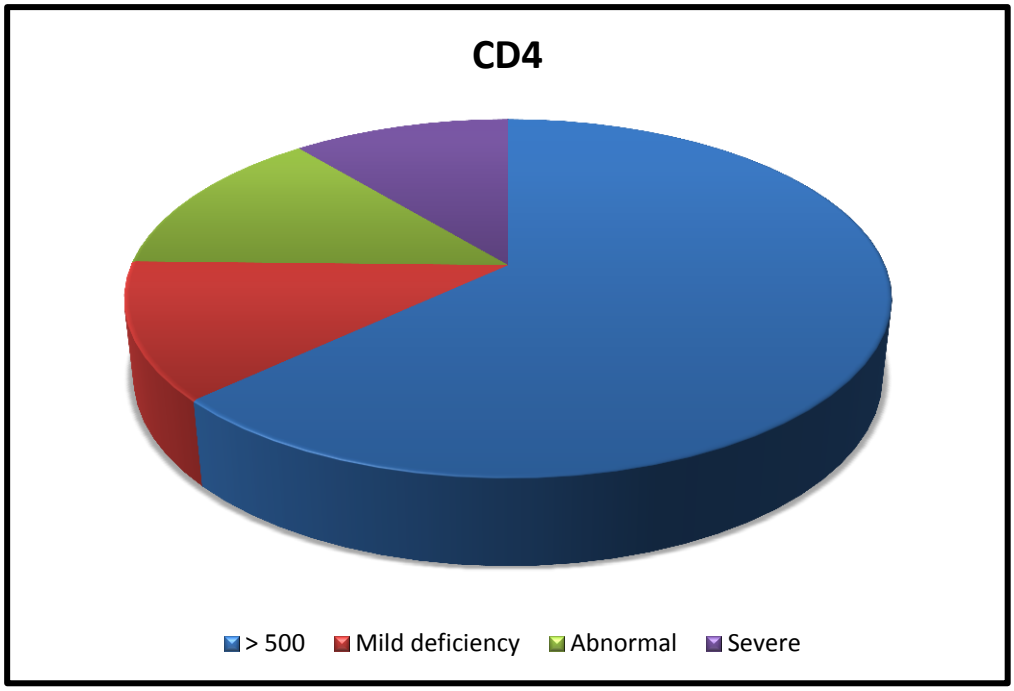


Figure 7

The above table shows CD4 distribution were > 500 is 63.0%, Mild deficiency is 12.3%, Abnormal is 13.7%, Severe is 11.0%.

Table 8: Distribution of TGL

TGL		
	Frequency	Percent
Normal	33	45.2
Borderline high	20	27.4
High	20	27.4
Total	73	100.0

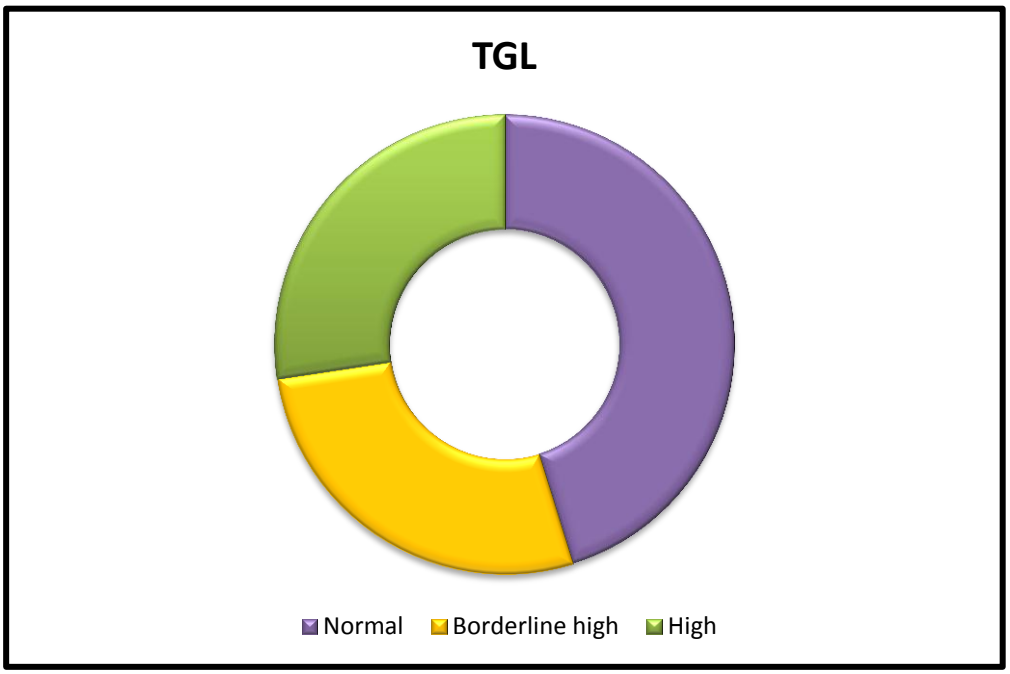


Figure 8

The above table shows TDL distribution were Normal is 45.2%, Borderline high is 27.4%, High is 27.4%.

Table 9: Distribution of Cholesterol

Cholesterol		
	Frequency	Percent
Desirable	56	76.7
Borderline high	14	19.2
High	3	4.1
Total	73	100.0

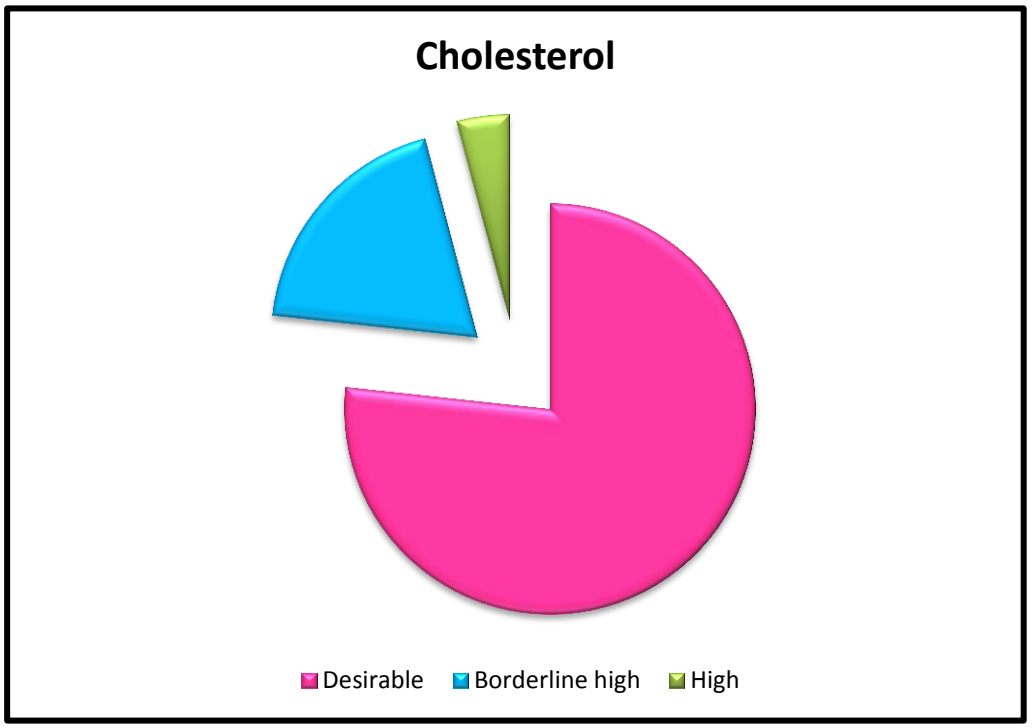


Figure 9

The above table shows Cholesterol distribution were Desirable is 76.7%, Borderline high is 19.2%, High is 4.1%.

Table 10: Distribution of HDL

HDL		
	Frequency	Percent
Low	41	56.1
Normal	32	43.9
Total	73	100.0

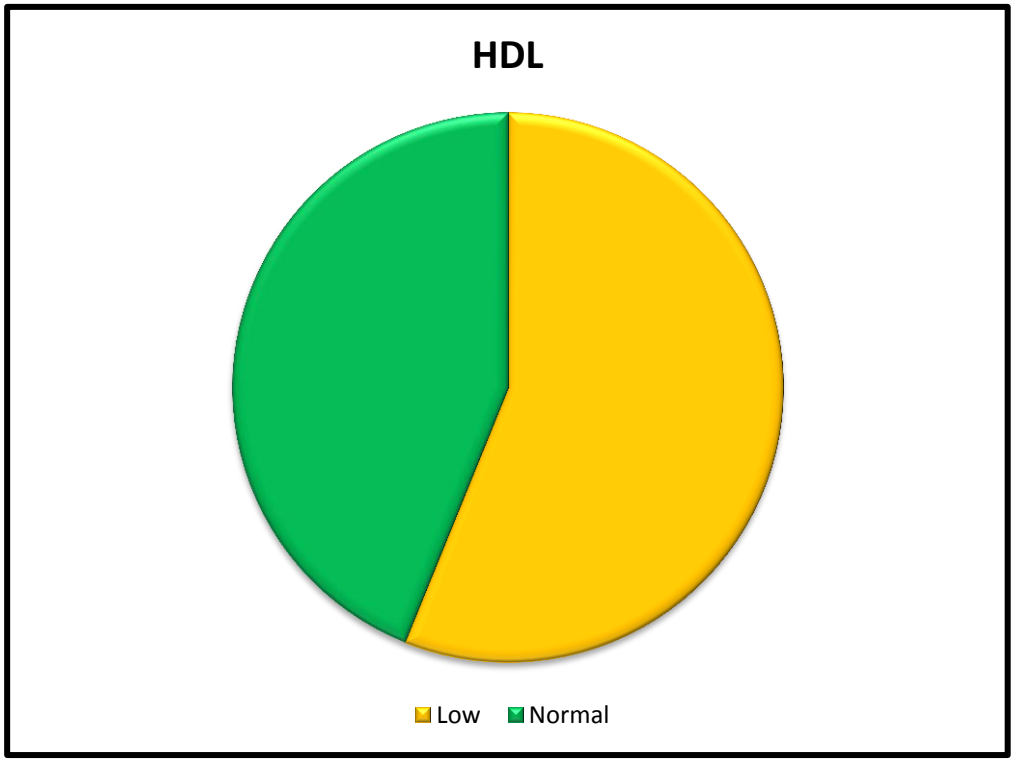


Figure 10

The above table shows HDL distribution were Low is 56.1%, Normal is 43.9%.

Table 11: Distribution of LDL

LDL		
	Frequency	Percent
Optimal	38	52.1
Near optimal	20	27.4
Borderline high	12	16.4
High	2	2.7
Very high	1	1.4
Total	73	100.0

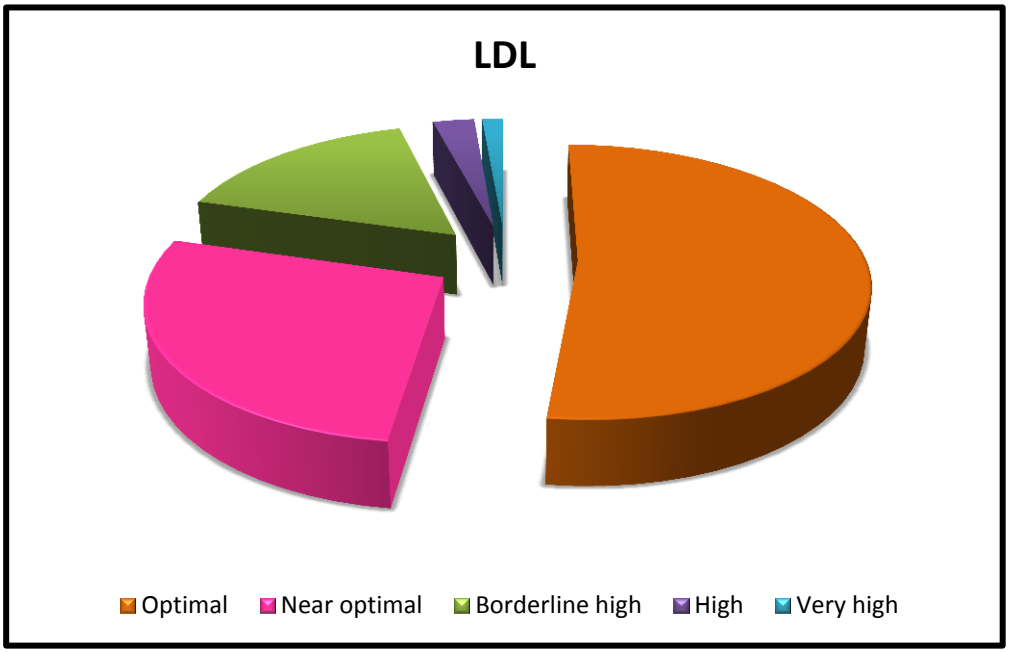


Figure 11

The above table shows LDL distribution were Optimal is 52.1%, Near optimal is 27.4%, Borderline high is 16.4%, High is 2.7%, Very High is 1.4%.

Table 12: Distribution of Dyslipidemia

Dyslipidemia		
	Frequency	Percent
Present	55	75.3
Absent	18	24.7
Total	73	100.0

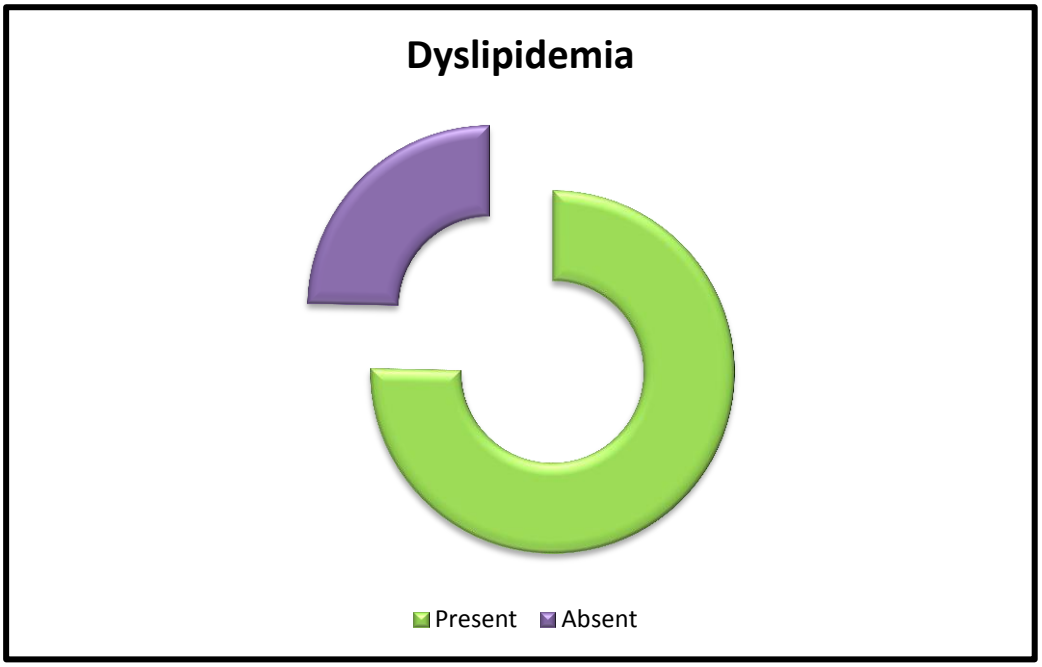


Figure 12

The above table shows Dyslipidemia distribution were Present is 75.3%, Absent is 24.7%.

Table 13: Comparison of Age with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ2 - value	p-value
			Present	Absent			
Age	<= 30 yrs	Count	7	7	14	7.760	0.021 *
		%	12.7%	38.9%	19.2%		
	31 - 49 yrs	Count	43	8	51		
		%	78.2%	44.4%	69.9%		
	>= 50 yrs	Count	5	3	8		
		%	9.1%	16.7%	11.0%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
* Statistical Significance at p < 0.05 level							

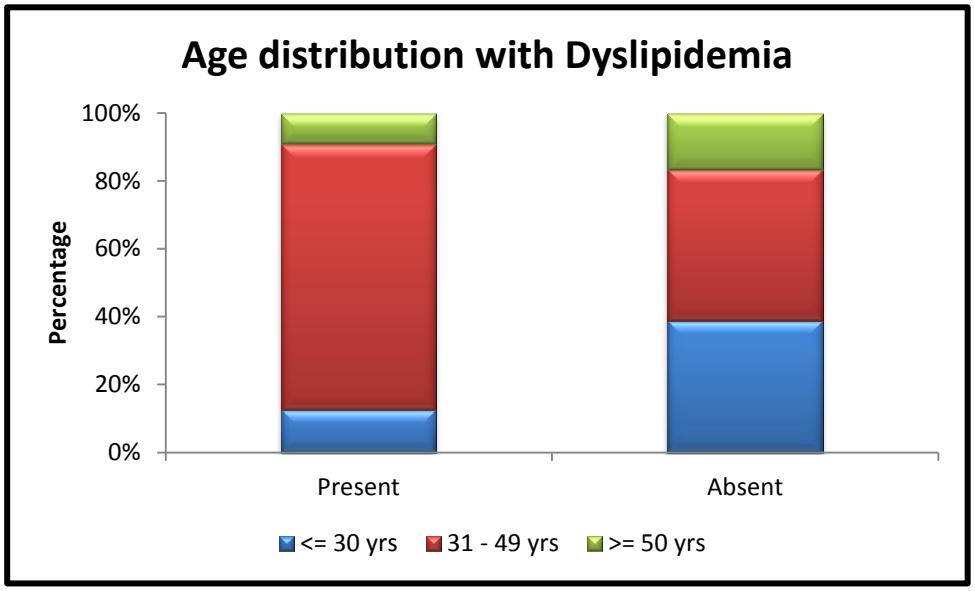


Figure 13

The above table shows comparison between Age with Dyslipidemia by Pearson's Chi-square test were $\chi 2=7.760$, $p=0.021<0.05$ which shows statistical significant association between Age and Dyslipidemia.

Table 14: Comparison of Gender with Dyslipidemia by Pearson's Chi-Square test χ

			Dyslipidemia		Total	χ 2 - value	p-value
			Present	Absent			
Gender	Male	Count	30	13	43	1.751	0.186 #
		%	54.5%	72.2%	58.9%		
	Female	Count	25	5	30		
		%	45.5%	27.8%	41.1%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

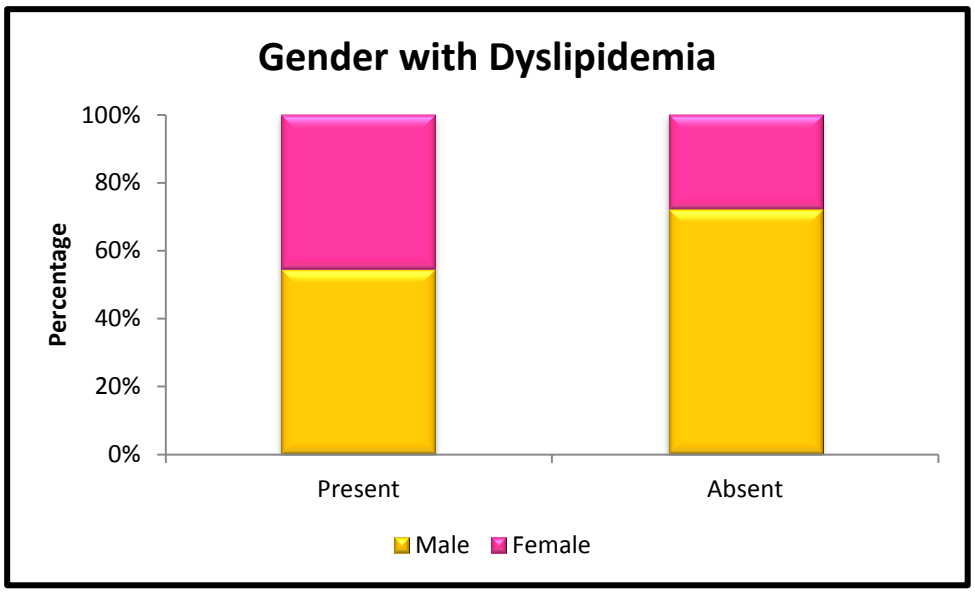


Figure 14

The above table shows comparison between Gender with Dyslipidemia by Pearson's Chi-square test were $\chi 2=1.751$, $p=0.186>0.05$ which shows no statistical significant association between Gender and Dyslipidemia.

Table 15: Comparison of Duration of illness with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ2 - value	p-value
			Present	Absent			
Duration of illness	<= 1 yr	Count	4	2	6	0.673	0.880 #
		%	7.3%	11.1%	8.2%		
	> 1 to < = 5 yrs	Count	24	9	33		
		%	43.6%	50.0%	45.2%		
	> 5 to < =10 yrs	Count	12	3	15		
		%	21.8%	16.7%	20.5%		
	Above 10 yrs	Count	15	4	19		
		%	27.3%	22.2%	26.0%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

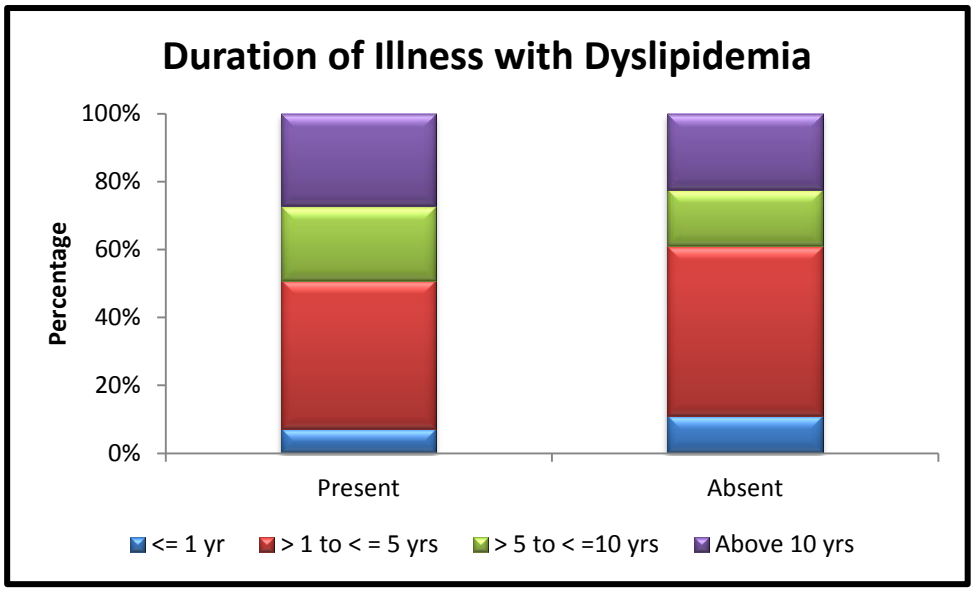


Figure 15

The above table shows comparison between Duration of illness with Dyslipidemia by Pearson's Chi-square test were $\chi 2=0.673$, $p=0.880>0.05$ which shows no statistical significant association between Duration of illness and Dyslipidemia.

Table 16: Comparison of Duration of ART with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ 2 - value	p-value
			Present	Absent			
Duration of ART	<= 1 yr	Count	4	2	6	1.229	0.746 #
		%	7.3%	11.1%	8.2%		
	> 1 to < = 5 yrs	Count	25	10	35		
		%	45.5%	55.6%	47.9%		
	> 5 to < =10 yrs	Count	15	3	18		
		%	27.3%	16.7%	24.7%		
	Above 10 yrs	Count	11	3	14		
		%	20.0%	16.7%	19.2%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

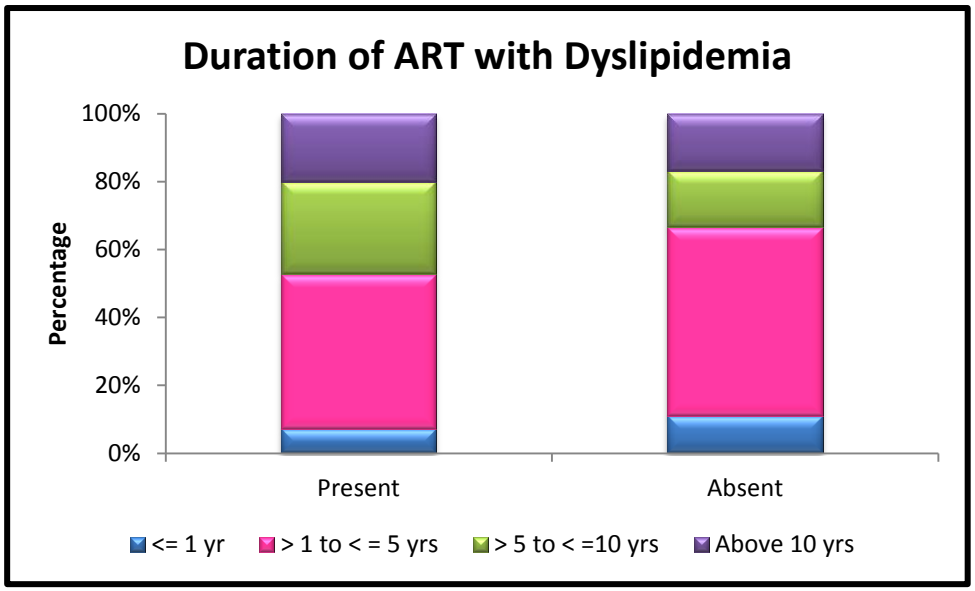


Figure 16

The above table shows comparison between Duration of ART with Dyslipidemia by Pearson's Chi-square test were $\chi 2=1.229$, $p=0.746>0.05$ which shows no statistical significant association between Duration of ART and Dyslipidemia.

Table 17: Comparison of Class of ART with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ 2 - value	p-value
			Present	Absent			
Class of ART	TLN	Count	1	1	2	3.501	0.835 #
		%	1.8%	5.6%	2.7%		
	ZLEFV	Count	1	0	1		
		%	1.8%	0.0%	1.4%		
	ZLN	Count	8	4	12		
		%	14.5%	22.2%	16.4%		
	TLD	Count	7	1	8		
		%	12.7%	5.6%	11.0%		
	TLE	Count	34	12	46		
		%	61.8%	66.7%	63.0%		
	TLATV/R	Count	1	0	1		
		%	1.8%	0.0%	1.4%		
	TLLPV/RTV	Count	2	0	2		
		%	3.6%	0.0%	2.7%		
	TLD+DTG	Count	1	0	1		
		%	1.8%	0.0%	1.4%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

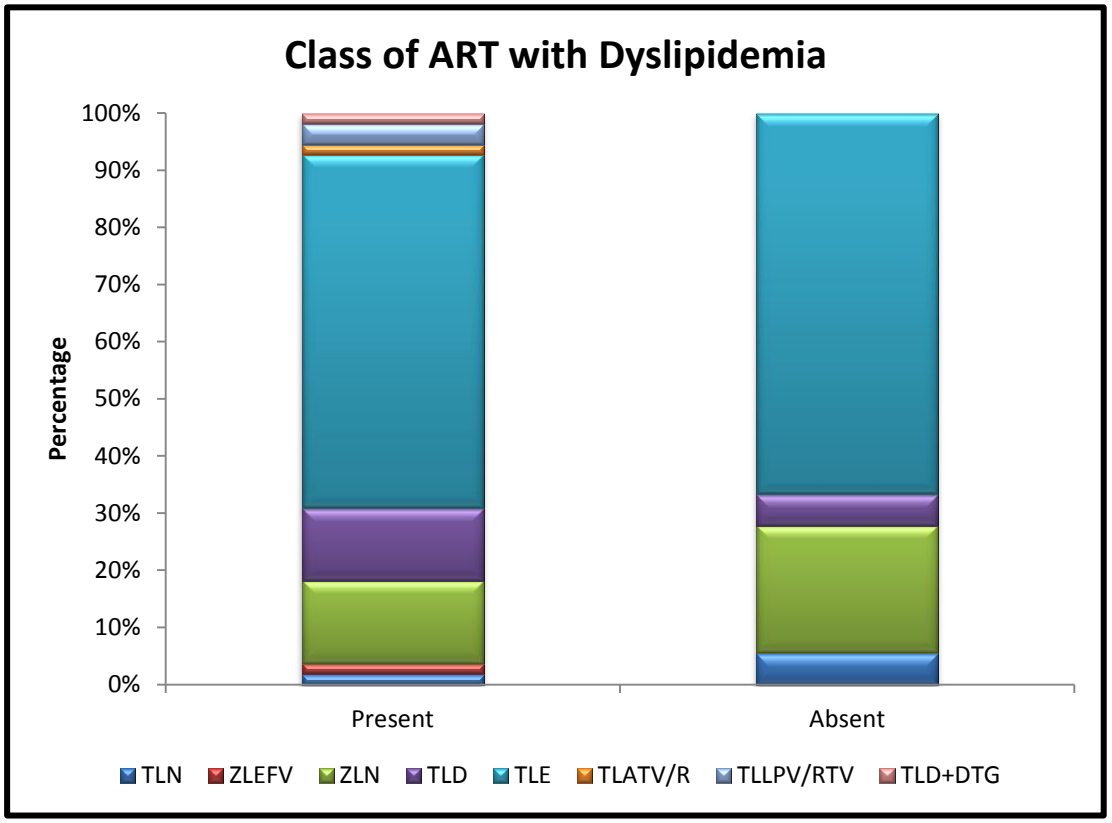


Figure 17

The above table shows comparison between Class of ART with Dyslipidemia by Pearson's Chi-square test were $\chi 2=3.501$, $p=0.835>0.05$ which shows no statistical significant association between Class of ART and Dyslipidemia.

Table 18: Comparison of BMI with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ 2 - value	p-value
			Present	Absent			
BMI	Underweight	Count	7	5	12	3.583	0.310 #
		%	12.7%	27.8%	16.4%		
	Normal	Count	31	6	37		
		%	56.4%	33.3%	50.7%		
	Overweight	Count	15	6	21		
		%	27.3%	33.3%	28.8%		
	Obese	Count	2	1	3		
		%	3.6%	5.6%	4.1%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

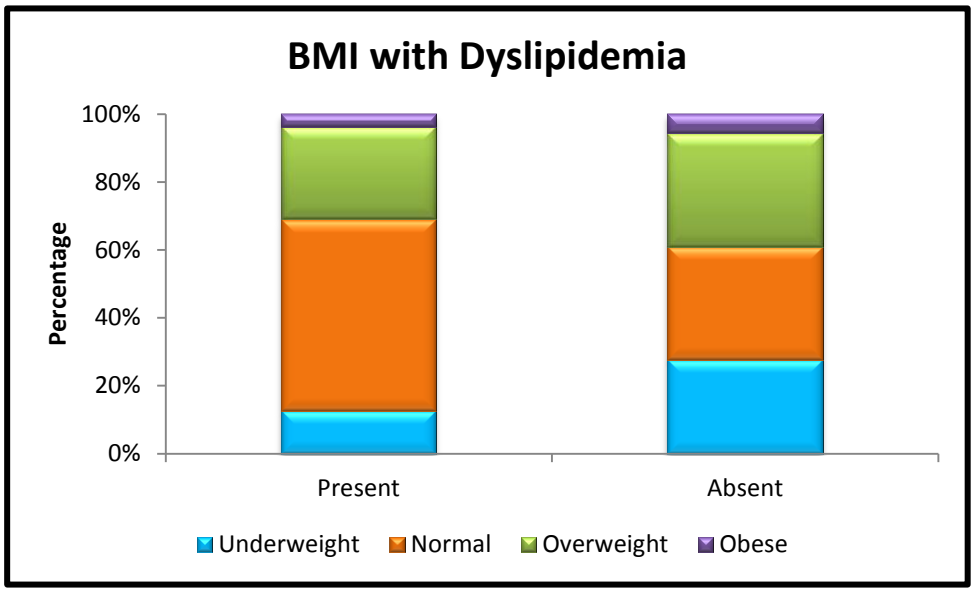


Figure 18

The above table shows comparison between BMI with Dyslipidemia by Pearson's Chi-square test were $\chi 2=3.583$, $p=0.310>0.05$ which shows no statistical significant association between BMI and Dyslipidemia.

Table 19: Comparison of CD4 with Dyslipidemia by Pearson's Chi-Square test

			Dyslipidemia		Total	χ 2 - value	p-value
			Present	Absent			
CD4	> 500	Count	33	13	46	7.249	0.064 #
		%	60.0%	72.2%	63.0%		
	Mild deficiency	Count	8	1	9		
		%	14.5%	5.6%	12.3%		
	Abnormal	Count	10	0	10		
		%	18.2%	0.0%	13.7%		
	Severe	Count	4	4	8		
		%	7.3%	22.2%	11.0%		
Total		Count	55	18	73		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

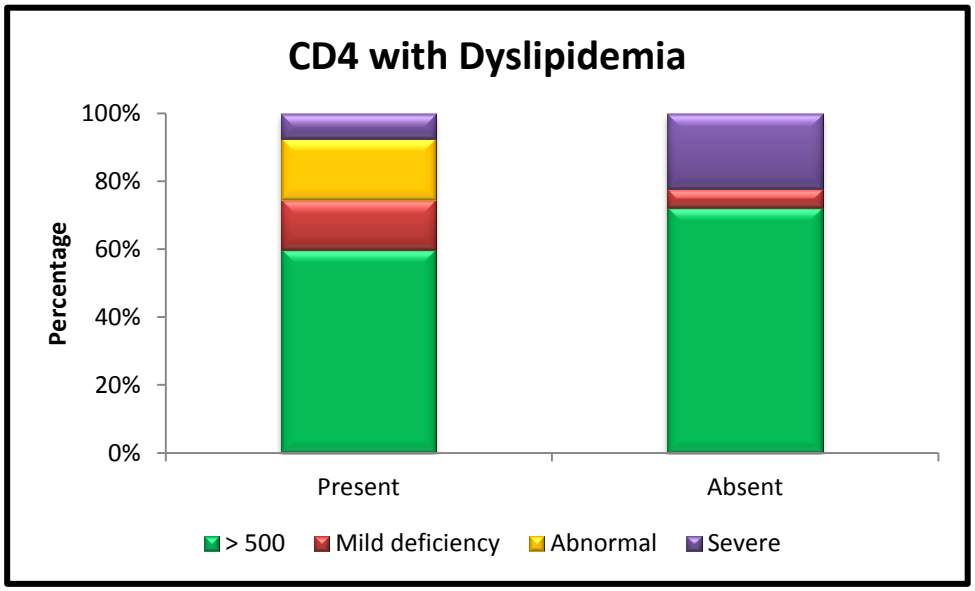


Figure 19

The above table shows comparison between CD4 with Dyslipidemia by Pearson's Chi-square test were $\chi 2=7.249$, $p=0.064>0.05$ which shows no statistical significant association between CD4 and Dyslipidemia.

Table 20: Distribution of Class with ART with Outcomes

			TGL		Cholesterol		HDL	LDL		
			Borderline high	High	Borderline high	High	Low	Borderline high	High	Very high
Class of ART	TLN	Count	0	1	1	0	1	0	0	0
		%	0.0%	5.0%	7.1%	0.0%	2.4%	0.0%	0.0%	0.0%
	TLD	Count	1	3	1	2	4	0	2	0
		%	5.0%	15.0%	7.1%	66.7%	9.8%	0.0%	100.0%	0.0%
	TLE	Count	13	14	10	1	26	10	0	1
		%	65.0%	70.0%	71.4%	33.3%	63.4%	83.3%	0.0%	100.0%
	ZLEFV	Count	0	0	0	0	1	0	0	0
		%	0.0%	0.0%	0.0%	0.0%	2.4%	0.0%	0.0%	0.0%
	ZLN	Count	5	1	1	0	6	1	0	0
		%	25.0%	5.0%	7.1%	0.0%	14.6%	8.3%	0.0%	0.0%
	TLATV/R	Count	0	0	0	0	1	0	0	0
		%	0.0%	0.0%	0.0%	0.0%	2.4%	0.0%	0.0%	0.0%
	TLLPV/RTV	Count	0	1	0	0	2	0	0	0
		%	0.0%	5.0%	0.0%	0.0%	4.9%	0.0%	0.0%	0.0%
	TLD+DTG	Count	1	0	1	0	0	1	0	0
		%	5.0%	0.0%	7.1%	0.0%	0.0%	8.3%	0.0%	0.0%
Total		Count	20	20	14	3	41	12	2	1
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

The above table shows the distribution of Class of ART with TGL,LDL,HDL and Cholesterol

Table 21: Descriptive Statistics

Descriptive Statistics					
	N	Minimum	Maximum	Mean	SD
Duration of illness	73	.4	17.0	6.3	4.4
Duration of ART	73	.4	17.0	6.0	4.3
Height/cms	73	137.0	178.0	158.1	8.6
Weight/Kgs	73	37.0	91.0	57.4	12.6
BMI	73	16.0	34.2	22.9	4.3
CD4	73	27.0	1458.0	607.8	333.9
TGL	73	52.0	486.0	169.2	82.1
Cholesterol	73	76.0	272.0	172.1	41.0
HDL	73	24.0	59.0	42.4	7.5
LDL	73	30.0	205.0	96.4	39.1

The above table shows Descriptive Statistics of Duration of illness, Duration of ART, Height/cm, Weight/Kg, BMI, CD4, TGL, Cholesterol, HDL, LDL.

DISCUSSION

With improving longevity after the advent of ART in HIV patients, non-AIDS conditions are now accounting for the majority of deaths among individuals receiving ART and the Cardiovascular disease has become an increasingly important problem in this population. The mechanism of CV disease in these patients are known to be multifactorial, in that the side-effects of HAART plays a significant role.

Demographics:

The age distribution among the study population was 19.2% under 30 years, *69.9% in 31 to 49 years group* and 11% above 50 years. A similar study done by comparison of serum lipid profile in HIV positive patients on ART with ART Naïve patients in Karnataka had age distribution among ART group of 39 ± 6 years(29).

There were more *male patients (58.9%)* compared to females (41.1%) among our study population.

Duration and Class of ART:

The distribution of duration of ART among the study population was 8.2% in <= 1 year, *47.9% in > 1 to <= 5 years*, 24.7% in > 5 to <= 10 years and 19.2% in > 10 years. This is similar to the study of V et al., in which the average duration of ART was 2 years(31).

The distribution of class of ART includes 63% of the study population were on TLE regimen (Tenofovir, Lamivudine, Efavirenz); 16.4% were on ZLN regimen (Zidovudine, Lamivudine, Nevirapine) and 11% were on TLD regimen (Tenofovir, Lamivudine, Dolutegravir). Prevalence of dyslipidemia was 75.3% in patients taking ART in our study. When it was compared with the class of ART, there were no statistically significant association between

the two. This finding is similar to the study done in Cameroonian population by Pefura Yone et al.,(32)

Body Mass Index:

Though our study had 50.7% population with normal BMI, 28.8% (n=21) came under overweight category and 4.1% (n=3) came under the obese category; Among them, 27.3% (n=15) and 3.6% (n=2) had dyslipidemia. This showed that increased BMI was associated with dyslipidemia in all these patients taking ART.

CD4 Count:

There was no statistical significance observed between CD4 count and dyslipidemia

Lipid Profile:

Our study showed *54.8% had triglyceride levels of >=150 mg/dL*;

23.3% had total cholesterol >=200 mg/dL;

5*6.1% had low levels of HDL*;

20.5% had LDL cholesterol levels >=130 mg/dL;

Outcome:

This study was done to determine the prevalence of dyslipidemia in people living with HIV / AIDS on HAART for atleast 3 months duration and longer in a tertiary care centre in Chennai.

So, ***the prevalence of dyslipidemia is 75.3% in patients taking Anti-Retroviral Therapy*** in our study. High triglyceride levels and low HDL levels were found predominantly in our patients which was similar to the observations of Pujari et al., who conducted a similar study in population of Western India with special mention to first-line ART(33).

Though the patients studied here were mostly taking TLE regimen followed by ZLN regimen and TLD regimen, the presence of dyslipidemia was not statistically significant with the class of drugs used.

Many previous studies have documented the role of protease inhibitors in lipid profile alterations. It was evident from our study that significant alterations of lipid profile can occur in patients on NRTI's, NNRTI's or combination of both or Integrase inhibitors.

Some patients were changed from one regimen to another in the recent one year which would have more impact on the lipid profile as these patients were exposed to multiple class of drugs than others.

Since, the lipid abnormalities accelerate the progression of cardiovascular disease, these patients should further be assessed for other CV risk factors and they should be the target for risk reduction.

SUMMARY

- The Age distribution were <=30 years is 19.2%, 31-49 years is 69.9%, >50 is 11.0 %.
- The Gender distribution were Female is 41.1%, Male is 58.9%.
- The Duration of illness distribution were <=1 year is 8.2%, >1 to <=5 years is 45.2%, >5 to <=10 years is 20.5, >10 years 26.0%.
- The Duration of ART distribution were <=1 year is 8.2%, >1 to <=5 years is 47.9%, >5 to <=10 years is 24.7, >10 years 19.2%.
- The Class of ART distribution were TLATV/R is 1.4%, TLD is 11.0%, TLD+DTG is 1.4%, TLE is 63.0%, TLLPV/RTV is 2.7%, TLN is 2.7%, ZLEFV is 1.4%, ZLN is 16.4%.
- The BMI distribution were Underweight is 16.4%, Healthy is 50.7%, Overweight is 28.8%, Obese is 4.1%.
- The CD4 distribution were > 500 is 63.0%, Mild deficiency is 12.3%, Abnormal is 13.7%, Severe is 11.0%.
- The TGL distribution were Normal is 45.2%, Borderline high is 27.4%, High is 27.4%.
- The Cholesterol distribution were Desirable is 76.7%, Borderline high is 19.2%, High is 4.1%.
- The HDL distribution were Low is 56.1%, Normal is 43.9%.
- The LDL distribution were Optimal is 52.1%, Near optimal is 27.4%, Borderline high is 16.4%, High is 2.7%, Very High is 1.4%.
- The Dyslipidemia distribution were Present is 75.3%, Absent is 24.7%.

- The Age with Dyslipidemia by Pearson's Chi-square test were $\chi 2=7.760$, $p=0.021<0.05$ which *shows statistical significant association* between Age and Dyslipidemia.

- The Gender with Dyslipidemia by Pearson's Chi-square test were $\chi 2=1.751$, $p=0.186>0.05$ which shows no statistical significant association between Gender and Dyslipidemia.
- The Duration of illness with Dyslipidemia by Pearson's Chi-square test were $\chi 2=0.673$, $p=0.880>0.05$ which shows no statistical significant association between Duration of illness and Dyslipidemia.
- The Duration of ART with Dyslipidemia by Pearson's Chi-square test were $\chi 2=1.229$, $p=0.746>0.05$ which shows no statistical significant association between Duration of ART and Dyslipidemia.
- The Class of ART with Dyslipidemia by Pearson's Chi-square test were $\chi 2=3.501$, $p=0.835>0.05$ which shows no statistical significant association between Class of ART and Dyslipidemia.
- The BMI with Dyslipidemia by Pearson's Chi-square test were $\chi 2=3.583$, $p=0.310>0.05$ which shows no statistical significant association between BMI and Dyslipidemia.
- The CD4 with Dyslipidemia by Pearson's Chi-square test were $\chi 2=7.249$, $p=0.064>0.05$ which shows no statistical significant association between CD4 and Dyslipidemia.

CONCLUSION

1. The prevalence of dyslipidemia in our study is 75.3% in patients taking Anti-Retroviral Therapy for atleast 3 months duration and longer
2. 56.1% had low levels of High Density Lipoprotein; 54.8% had higher triglyceride levels
3. The study population had statistically significant association for age group between 31 and 49 years, whom in general also associated with significant alteration in lipid profile. This emphasizes that people living with HIV / AIDS on HAART also needs to be screened for CV risk factors in this age group
4. The prevalence of dyslipidemia in people living with HIV / AIDS taking Anti-Retroviral Therapy for atleast 3 months duration and longer was 75.3% which reflected the effect of ART on lipid profile
5. There was no statistical significance of dyslipidemia with gender, CD4 cell count, class of ART or duration of ART
6. This study to determine the prevalence of dyslipidemia in patients with different class of ART, including newer regimen, reflected the effect of change of regimen in association with lipid profile is well documented, which may act as a base to future investigational studies
7. We conclude that people living with HIV / AIDS on HAART have high prevalence of Lipid abnormalities and they should be screened for dyslipidemia and this should be appropriately managed to reduce the Cardiovascular risk

LIMITATION

There were few limitations in this study which includes the sample size of the study population was relatively small in comparing with similar studies. There were no comparison group in this study. Serial testing of lipid profile had not been done which would accurately determine the relationship between duration of ART and the alteration in lipid profile.

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PROFORMA

Sl.No.

Name:

Age:

Sex:

Address:

Contact No:

Hospital No:

Occupation:

Duration of Illness:
(HIV/AIDS)

Duration of ART:

Class of ART drugs:

Past History:

Condition	Yes	No	If yes, Specify
Diabetes			
Hypertension			
CAD			
Chronic Liver / Renal disease			
Pulmonary Tb			
Thyroid disease			
Long standing steroid / immunosuppressants			

Personal History:

	Yes	No	If yes, duration
Smoking			
Alcohol			

General Examination:

Vitals:

BP	PR	SPO2	RR

Height	Weight	BMI

Built
Pallor
Icterus
Clubbing
Pedal edema
Oral candidiasis
Herpes zoster
Subcutaneous Lipoatrophy / Central fat accumulation (Buffalo hump)

Systemic Examination:

CVS

RS

P/A

CNS

Investigations:

Hemogram :

TC	
DC	
Hb	
PCV	
Platelets	
ESR	

RFT:

Sugar	
Urea	
Creatinine	

LFT:

Total bilirubin	
Direct bilirubin	
SGOT	
SGPT	
ALP	
Total protein	
Albumin	

ECG:

CXR:

ELISA for HIV:

CD4 Counts:

FASTING LIPID PROFILE:

TGL	
Total Cholesterol	
HDL	
LDL	

MASTER CHART

	AGE		SEX		DURATION OF ILLNES		DURATION OF		CLASS OF ART	COMORBIDS/SMO	Y/N	HT/WT	BMI		CBC/RFT/LFT/ECG/CXR	CD4		TGL		CHOL		HDL		LDL	
1	36	2	F	2	11	4	11	4	ZLN		N	158/46	18.4	1	WNL	197	4	100	1	108	1	58	4	30	1
2	46	2	M	1	2	2	2	2	TLE		N	164/91	33.8	4	WNL	421	2	219	3	166	1	45	3	77	1
3	57	3	M	1	10	3	10	3	ZLN (9) TLD (1)		N	178/51	16.1	1	WNL	523	1	59	1	107	1	46	3	49	1
4	20	1	M	1	17	4	17	4	ZLN (16) TLD (1)		N	142/51	25.3	3	WNL	479	2	52	1	76	1	50	3	45	1
5	48	2	F	2	9	3	9	3	TLE		N	147/74	34.2	4	WNL	1051	1	186	2	122	1	35	2	50	1
6	49	2	M	1	3	2	3	2	TLE		N	166/78	28.3	3	WNL	587	1	218	3	132	1	36	1	52	1
7	47	2	M	1	15	4	15	4	TLN (14) TLATV/R (1)		N	152/51	22.1	2	WNL	210	3	100	1	140	1	34	1	86	1
8	40	2	M	1	2	2	2	2	TLE		N	169/72	25.2	3	WNL	945	1	75	1	184	1	56	3	113	2
9	47	2	F	2	10	3	10	3	TLE		N	144/47	22.7	2	WNL	1285	1	114	1	184	1	56	4	105	2
10	25	1	F	2	12	4	12	4	TLLPV/RTV		N	162/47	17.9	1	WNL	513	1	281	3	135	1	36	2	43	1
11	40	2	F	2	1	1	1	1	TLD		N	152/58	25	3	WNL	999	1	486	3	199	1	34	2	68	1
12	48	2	F	2	12	4	12	4	TLE (10) TLD (2)		N	160/66	25.8	3	WNL	1029	1	166	2	125	1	36	2	66	1
13	52	3	F	2	1.5	2	1.5	2	TLE		N	152/45	19.5	2	WNL	486	2	234	3	132	1	55	4	30	1
14	35	2	M	1	Jän.00	4	####	###	TLE		N	158/54	21.6	2	WNL	67	4	171	2	199	1	48	3	117	2
15	45	2	F	2	6	3	6	3	TLE(5) TLD(9mo)		N	150/56	24.9	2	WNL	691	1	319	3	202	2	38	2	100	2
16	40	2	F	2	13	4	13	4	ZLN(12) TLD(1)		N	148/43	19.6	2	WNL	627	1	196	2	171	1	38	2	94	1
17	43	2	M	1	13	4	13	4	ZLN(12) TLD(1)		N	160/69	27	3	WNL	704	1	166	2	111	1	24	1	54	1
18	18	1	F	2	13	4	13	4	ZLN(12) TLD(1)		N	154/38	16	1	WNL	624	1	134	1	134	1	38	2	69	1
19	32	2	M	1	6	3	6	3	TLE		N	170/51	17.6	1	WNL	432	2	217	3	145	1	52	3	50	1
20	41	2	F	2	14	4	14	4	TLD		N	164/75	27.9	3	WNL	384	2	215	3	263	3	41	2	179	4
21	38	2	F	2	10	3	10	3	ZLN(9) TLD(1)		N	154/53	22.3	2	WNL	1027	1	112	1	177	1	38	2	116	2
22	34	2	M	1	2	2	2	2	TLD		N	165/69	25.3	3	WNL	845	1	129	1	252	3	50	3	176	4
23	19	1	M	1	2	2	2	2	TLE		N	152/41	17.7	1	WNL	749	1	100	1	151	1	48	3	83	1
24	35	2	F	2	11	4	11	4	TLLPV/RTV		N	152/37	16	1	WNL	873	1	102	1	185	1	40	2	125	2
25	39	2	F	2	5mo	1	5mo	1	TLD		N	156/53	21.8	2	WNL	116	4	121	1	140	1	42	2	74	1
26	42	2	M	1	2	2	2	2	TLE		N	152/61	26.4	3	WNL	27	4	157	2	210	1	39	1	140	3
27	33	2	F	2	2	2	2	2	TLE		N	161/74	28.5	3	WNL	1276	1	186	2	237	2	58	4	142	3
28	35	2	M	1	11	4	10	3	TLE		N	160/58	22.7	2	WNL	236	3	157	2	224	2	39	1	154	3
29	41	2	F	2	2	2	2	2	TLD		N	155/45	18.7	2	WNL	640	1	180	2	162	1	47	2	79	1
30	23	1	F	2	2.5	2	2.5	2	TLD		N	154/48	20.2	2	WNL	548	1	279	3	188	1	59	4	73	1
31	54	3	F	2	10	3	10	3	ZLEFV		N	153/45	19.2	2	WNL	1023	1	122	1	168	1	40	2	104	2
32	47	2	M	1	2	2	2	2	TLE		N	159/52	20.6	2	WNL	439	2	314	3	152	1	30	1	59	1
33	43	2	M	1	11	4	11	4	TLE		N	151/45	19.7	2	WNL	323	3	201	3	194	1	38	1	116	2
34	43	2	M	1	13	4	9	3	TLE		N	151/58	25.4	3	WNL	67	4	171	2	199	1	48	3	117	2
35	40	2	M	1	2	2	2	2	TLE		N	164/57	21.2	2	WNL	27	4	117	1	160	1	52	3	85	1
36	47	2	F	2	9	3	9	3	TLE		N	148/43	19.6	2	WNL	279	3	168	2	148	1	47	2	67	1
37	30	1	M	1	4	2	4	2	TLE		N	172/84	28.4	3	WNL	964	1	142	1	151	1	42	3	81	1
38	32	2	M	1	3	2	3	2	TLE(2.8) TLD(4mo)		N	154/58	24.5	2	WNL	900	1	272	3	138	1	49	3	35	1
39	34	2	M	1	11	4	11	4	ZLN		N	155/63	26.2	3	WNL	796	1	103	1	112	1	47	3	44	1
40	23	1	M	1	1	1	1	1	TLE		N	154/46	19.4	2	WNL	597	1	101	1	157	1	43	3	94	1
41	45	2	M	1	9	3	9	3	ZLN		N	149/41	18.5	2	WNL	209	3	186	2	166	1	44	3	85	1
42	28	1	M	1	3	2	3	2	TLE		N	158/48	19.2	2	WNL	796	1	479	3	197	1	30	1	71	1
43	45	2	M	1	2.5	2	2.5	2	TLE		N	156/55	22.6	2	WNL	629	1	96	1	117	1	42	3	56	1
44	31	2	F	2	7	3	3	2	TLE		N	155/50	20.8	2	WNL	209	3	163	2	176	1	40	2	103	2

45	45	2	M	1	7	3	7	3	ZLN(6.5) TLD(6mo)	N	170/84	29	3	WNL	443	2	254	3	239	2	38	1	150	3
46	28	1	F	2	3	2	3	2	TLE	N	149/43	19.4	2	WNL	649	1	89	1	161	1	52	4	91	1
47	30	1	M	1	3	2	3	2	TLE	N	175/54	17.6	1	WNL	39	4	97	1	102	1	46	3	37	1
48	40	2	M	1	7	3	7	3	TLE(6.3) DTG/LPVr(9mo)	N	164/50	18.6	2	WNL	295	3	235	3	180	1	36	1	97	1
49	44	2	M	1	10	3	10	3	ZLN(9) TLD(1)	N	168/82	29.1	3	WNL	543	1	168	2	143	1	41	3	68	1
50	54	3	F	2	9	3	9	3	TLE	N	149/58	26.1	3	WNL	1013	1	97	1	186	1	52	4	115	2
51	50	3	M	1	4	2	4	2	TLE	N	158/68	27.2	3	WNL	606	1	128	1	186	1	45	3	115	2
52	36	2	M	1	1	1	1	1	TLE	N	151/64	28.1	3	WNL	579	1	169	2	207	2	36	1	137	3
53	40	2	M	1	11	4	11	4	ZLN	N	168/52	18.4	1	WNL	386	2	148	2	171	1	38	1	103	2
54	62	3	M	1	5	2	5	2	TLE(4) TLD(1)	N	165/75	27.5	3	WNL	842	1	215	3	204	2	31	1	130	3
55	28	1	M	1	5	2	5	2	TLE(4) TLD(1)	N	164/48	17.8	1	WNL	732	1	68	1	135	1	36	1	85	1
56	38	2	F	2	4	2	4	2	TLE(3) TLD(1)	N	146/44	20.6	2	WNL	438	2	139	1	211	2	39	2	144	3
57	24	1	M	1	4	2	4	2	TLE(3) TLD(1)	N	168/50	17.7	1	WNL	136	4	94	1	136	1	48	3	69	1
58	28	1	F	2	1	1	1	1	TLE	N	156/55	22.6	2	WNL	857	1	174	2	180	1	44	2	101	2
59	37	2	F	2	11	4	5	2	TLN	N	150/75	33.3	4	WNL	562	1	132	1	195	1	50	4	119	2
60	33	2	F	2	11	4	6	3	TLE	N	137/44	23.4	2	WNL	1040	1	122	1	183	1	46	2	113	2
61	47	2	M	1	11	4	11	4	TLE	N	150/51	22.7	2	WNL	800	1	100	1	186	1	34	1	132	3
62	40	2	F	2	4	2	4	2	TLE(3.4) TLD(7mo)	N	159/51	20.2	2	WNL	656	1	66	1	107	1	48	2	46	1
63	59	3	M	1	2	2	2	2	TLE	N	174/72	23.8	2	WNL	329	3	133	1	205	2	36	1	142	3
64	42	2	M	1	8 mo	1	8 mo	1	TLD	N	160/57	22.3	2	WNL	803	1	99	1	177	1	46	3	111	2
65	50	3	F	2	9	3	9	3	TLN(6) TLD(3)	N	156/62	25.5	3	WNL	687	1	239	3	204	2	32	2	124	2
66	37	2	F	2	2	2	2	2	TLE	N	174/73	24.1	2	WNL	1276	1	188	2	231	2	34	2	159	3
67	41	2	M	1	2	2	2	2	TLE	N	169/70	24.5	2	WNL	645	1	308	3	217	2	37	1	118	2
68	36	2	M	1	4	2	4	2	TLE	N	166/60	21.8	2	WNL	1458	1	237	3	210	2	31	1	132	3
69	34	2	F	2	4	2	4	2	TLE	N	148/38	17.3	1	WNL	247	3	158	2	134	1	42	2	60	1
70	37	2	M	1	4	2	4	2	TLE	N	167/69	24.7	2	WNL	724	1	202	3	158	1	38	1	80	1
71	26	1	M	1	2	2	2	2	TLD	N	166/57	20.7	2	WNL	986	1	144	1	230	2	42	3	159	2
72	42	2	M	1	3	2	3	2	TLE	N	165/73	26.8	3	WNL	220	3	112	1	272	3	45	3	205	5
73	39	2	M	1	2	2	2	2	TLD+DTG	N	159/62	24.5	2	WNL	532	1	174	2	214	2	43	3	136	3

KEY

1) **Age** (years)
   ≤30 - 1
   31 – 49 - 2
   ≥50 - 3

2) **Sex**
   Male - 1
   Female - 2

3) **Duration of ART**
   >3 months to <1 year - 1
   >1 year to ≤5 years - 2
   >5 years to ≤10 years - 3
   >10 years - 4

4) **BMI** (kg/m^2)
   Below 18.5 - 1
   18.5 to 24.9 - 2
   25 to 29.9 - 3
   30 and above – 4

5) **LDL** (mg/dL)
   <100 - 1
   100 to 129 - 2
   130 to 159 - 3
   160 to 189 - 4
   ≥190 - 5

6) **TGL**(mg/dL)
   <150 - 1
   150 to 199 - 2
   200 to 499 - 3
   ≥500 - 4

7) **HDL** (mg/dL)
   Male
   <40 - 1
   Normal - 3
   Female
   <50 - 2
   Normal - 4

8) **Total Cholesterol** (mg/dL)
   <200 - 1
   200 to 239 - 2
   ≥240 - 3

9) **CD4 Count** (cells/cu.mm)
   >500 - 1
   350 to 499 - 2
   200 to 349 - 3
   <200 - 4

INFORMED CONSENT

PREVALENCE OF DYSLIPIDEMIA IN PEOPLE LIVING WITH HIV/AIDS ON ANTI-RETROVIRAL THERAPY IN A TERTIARY CARE CENTRE IN CHENNAI – A CROSS SECTIONAL STUDY

Place of study: Government Stanley Hospital, Chennai- 600001

நான் ..... இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போதுஇ சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றிநான் அறிந்துள்ளேன்.

நான் எந்தவொருவேளையிலும் ஆய்வில் இருந்து திரும்பமுடியும்இ அதன்பின்னர்இ நான் வழக்கம் போல் மருத்துவசிகிச்சை பெறமுடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்குஎடுத்து பணம் எதையும் பெறமுடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லைஇ

என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்ககூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்யபோகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல்ரேகை:	கையொப்பம் /விரல்ரேகை:
தேதி	தேதி

ஆராய்ச்சியாளராக கையொப்பம் மற்றும் தேதி

INFORMED CONSENT

PREVALENCE OF DYSLIPIDEMIA IN PEOPLE LIVING WITH HIV/AIDS ON ANTI-RETROVIRAL THERAPY IN A TERTIARY CARE CENTRE IN CHENNAI – A CROSS SECTIONAL STUDY

Place of study: Government Stanley Hospital, Chennai- 600001

I ……. have been informed about the details of the

study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

ETHICAL COMMITTEE CERTIFICATE

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI -01
INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK	: "PREVALENCE OF DYSLIPIDEMIA IN PEOPLE LIVING WITH HIV AIDS ON ANTI RETROVIRAL THERAPY IN A TERTIAY CARE CENTRE IN CHENNAI - A CROSS SECTIINAL STUDY"
PRINCIPAL INVESTIGATOR	: DR. R. PAVITHRA
DESIGNATION	: PG IN GENERAL MEDICINE
DEPARTMENT	: DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 17.02.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

12/2/21
MEMBER SECRETARY,
IEC, SMC, CHENNAI.