Review Of Literature

REVIEW OF LITERATURE

EPIDEMIOLOGY OF HIV/AIDS

AIDS has killed more than 25 million people between 1981 and 2007, and an estimated 33.2 million people worldwide live with HIV as of 2007, making it one of the most destructive epidemics in recorded history. Despite recent, improved access to antiretroviral treatment and care in many regions of the world, the AIDS epidemic claimed an estimated 2 million lives in 2007, of which about 270,000 were children.

The epidemic of AIDS, sweeping the world cuts across the conventional boundaries of nationality, sex and age. HIV, the Human Immunodeficiency Virus, a retrovirus which causes AIDS has infected millions of people worldwide in developed as well as developing countries. It has become truly global in scope, sparing none of continents.

The number of AIDS cases gives a foretaste rather than a true reflection of health crisis. The real measure of epidemic is the number of people infected with HIV infection. Among the special features of HIV infection are that once infected, it is probable that a person will be infected for life. The spectrum of HIV infection varies from acute sero-conversion illness associated with early infection to the full blown AIDS.

The HIV/AIDS is pandemic at present and continues to expand relentlessly. Its magnitude has increased over hundred fold since AIDS was discovered in 1981. The HIV pandemic is reaching new communities and countries round the world in some areas with great rapidity and reported from areas which had been left relatively untouched.

Significant gains in preventing new HIV infections are being seen in a number of countries most affected by the AIDS epidemic. This is according to a new report released by UNAIDS.[1]

Certain countries which are seeing changes in sexual behaviour followed by declines in the number of new HIV infections. This includes increasing condom use among young people with multiple partners and that young people are waiting longer to have sexual intercourse in some of the most heavily affected countries.

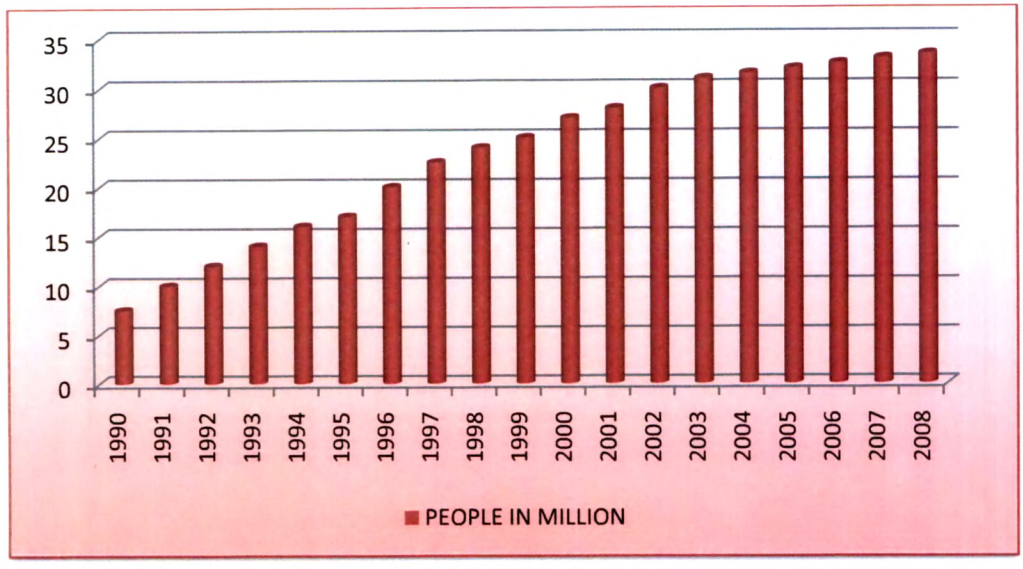
Despite the decline in new HIV infections the AIDS epidemic is far from over and that rates of new HIV infections are rising in many countries. AIDS also continues to be the leading cause of death.

AIDS is a long-term issue requiring a response grounded in evidence and human rights and one that requires strong leadership and sustained financing.

The UNAIDS report clearly shows that stronger measures are needed to turn the epidemic around and that 'knowing your local epidemic' remains critical to an effective response.

GLOBAL SCENARIO

The rising trend of prevalence of HIV/AIDS after identifying the first case in 1981 which reaches approximately to 31.1-35..8 million in 2008.



Trend and number of people living with HIV/AIDS,WHO statement 2008[1]

A global view of HIV infection, 2008 (WHO statement) [1]

Global summary of HIV/AIDS epidemic , December 2008			
Number of people living with HIV/AIDS in 2008	Total	33.4 million	31.1-35.8 million
	Adult	31.3 million	29.2-33.7 million
	Women	15.7 million	14.2-17.2million
	Children <15 yr	2.1 million	1.2-2.9 million
People newly infected in 2008	Total	2.7 million	2.4-3 million
	Adult	2.3 million	2.0-2.6 million
	Children <15y	430,000	240,000-610,000
AIDS death in 2008	Total	2.0 million	1.7-2.4 million
	Adult	1.7 million	1.4-2.0 million
	Children <15y	280,000	150,000-410,000

INDIAN SCENARIO

Since the human immunodeficiency virus (HIV) was found in Chennai in 1986, India has had an AIDS epidemic. India is one of the largest and most populated countries in the world. India has a population of 1.1 billion people — one sixth of the world's population — and is home to perhaps one of every eight people with HIV infection Of this number, it is estimated that around 2.4 million Indians are currently living with HIV, Of these, an estimated 39% are female and 3.5% are children. [1]

HIV emerged later in India than it did in many other countries. Infection rates soared throughout the 1990s, and today the epidemic affects all sectors of Indian society, not just the groups – such as sex workers and truck drivers – with which it was originally associated.

The History of HIV/AIDS in India

At the beginning of 1986, despite over 20,000 reported AIDS cases worldwide[2], India had no reported cases of HIV or AIDS.[3] There was recognition, though, that this would not be the case for long, and concerns were raised about how India would cope once HIV and AIDS cases started to emerge. One report, published in a medical journal in January 1986, stated:

"Unlike developed countries, India lacks the scientific laboratories, research facilities, equipment, and medical personnel to deal with an AIDS epidemic. In addition, factors such as cultural taboos against discussion of sexual practices, poor coordination between local health authorities and their communities, widespread poverty and malnutrition, and a lack of capacity to test and store blood would severely hinder the ability of the Government to control AIDS if the disease did become widespread.[4]

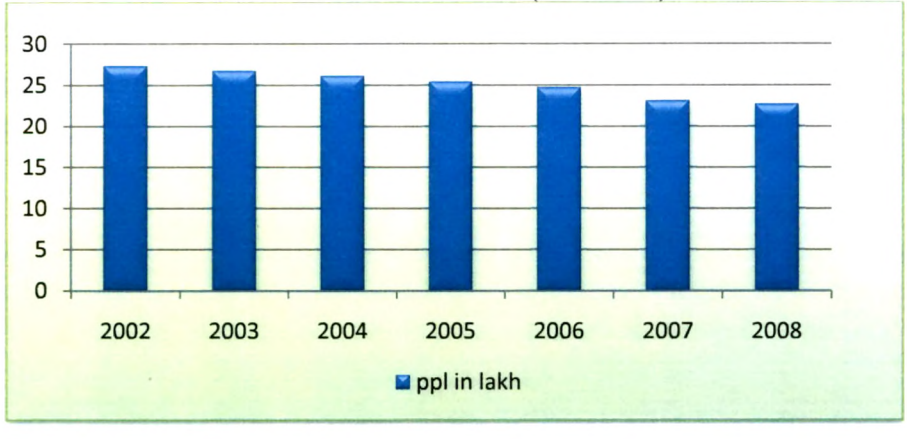
Current estimates

In 2006 UNAIDS estimated that there were 5.6 million people living with HIV in India, which indicated that there were more people with HIV in India than in any other country in the world[1]. However, NACO disputed this estimate, and claimed that the actual figure was lower[5]. In 2007, following the first survey of HIV among the general population, UNAIDS and NACO agreed on a new estimate – between 2 million and 3.6 million people living with HIV. The figure was confirmed to be 2.4 million in 2008.[1, 6]

In terms of AIDS cases, the most recent estimate comes from August 2006, at which stage the total number of AIDS cases reported to NACO was 124,995. Of this number, 29% were women, and 36% were under the age of 30. These figures are not accurate reflections of the actual situation though, as large numbers of AIDS cases go unreported.[7]

Overall, around 0.3% of India's population is living with HIV. While this may seem a low value, India's population is vast, and so the actual number of people living with HIV is remarkably high. There are so many people living in India that a mere 0.1% increase in HIV prevalence would increase the estimated number of people living with HIV by over half a million. (Fig. 2)

Estimated Number of People living with HIV/AIDS in India(till 2008)



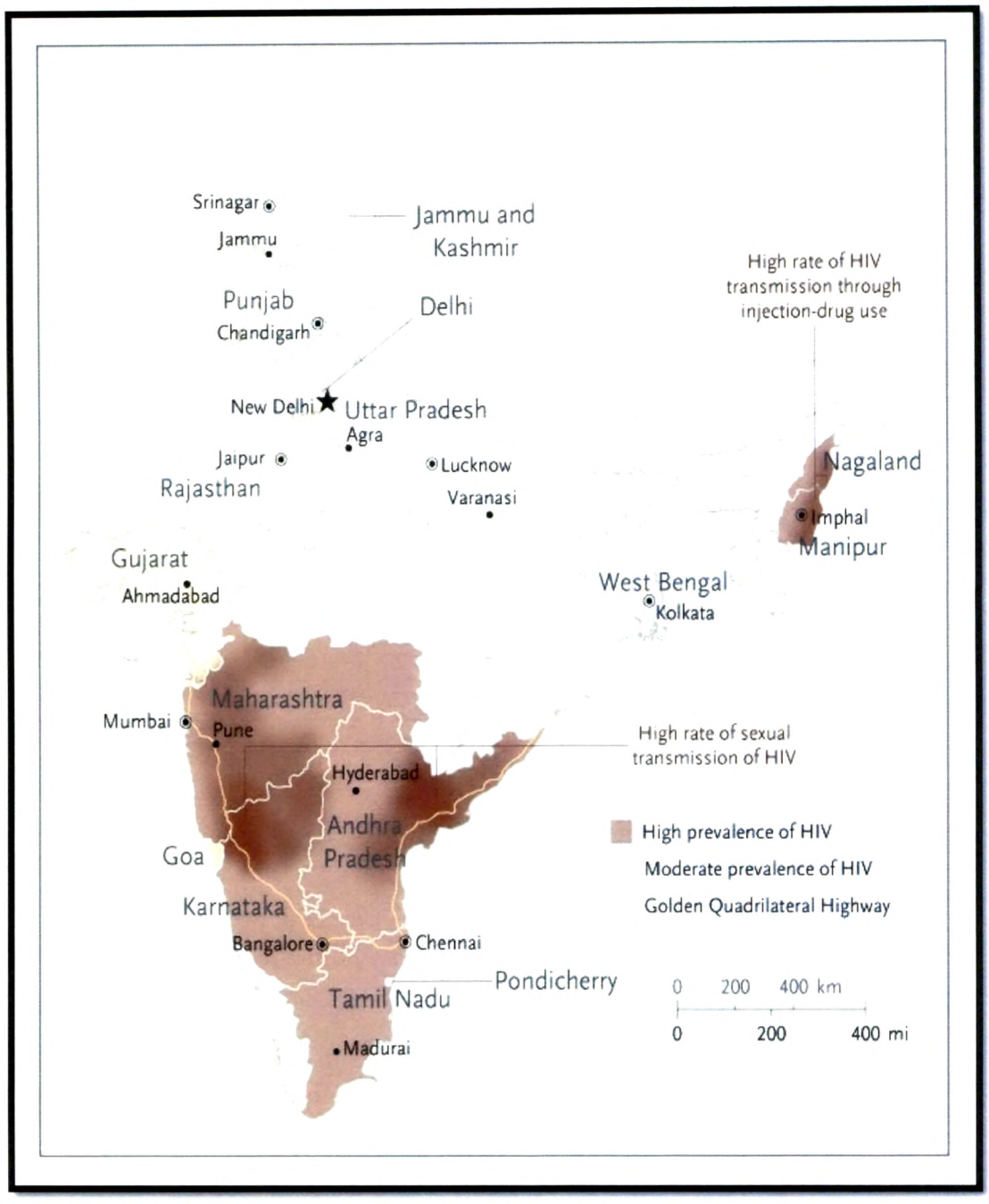


Fig. 2. HIV PREVALENCE IN INDIA

GUJARAT SCENARIO

As per the data of IDSP (Integrated Diseases Surveillance Project), Gujarat in the year 2006 about 6750 patients were diagnosed to have HIV/AIDS who were come across the medical fraternity in rural and urban areas. Among them about 355 patients were within the Vadodara urban setting which contributes about 25% of the total number of cases within the Gujarat state. Gujarat is in moderate HIV prevalence state with 6 out of 25 districts in A category and other four being in B category. The recent trend of epidemic indicates that the epidemic has moved to the generalized population as well

DATA FROM ART CENTRE , VADODARA (till nov. end 2010)

The ART center in vadodara was established on 21st January, 2009 in OPD 26 on the first floor of the common OPD building. Around 3700 patients are enrolled in the center, one of the largest in Gujarat.

	ADULT		CHILDREN<15 yr		TOTAL
	Male	Female	Male	Female	
Total no of patients enrolled	2054	1381	151	96	3691
Total no. of patients cumulative on ARV	1252	711	66	25	2056
Total no. alive on ARV	994	577	48	24	1643

Under ART centre, vadodara till nov. 2010 total 1643 patients were on ARV with total enrolement was of 3691 patients of which 247 were children < 15yrs of age .

HIV/AIDS

No other word endangers as much fear, revulsion, despair and utter helplessness as AIDS. Despite increased AIDS awareness, the terror persists.

HIV, the etiological agent of AIDS, belongs to genus lentivirus subgroups of family Retroviridae. [10] Previous names for the virus include human T-lymphotropic virus-III (HTLV-III), lymphadenopathy-associated virus (LAV), and AIDS-associated retrovirus (ARV) [11,12]

The retroviruses are RNA viruses which contain RNA directed DNA polymerase or reverse transcriptase.

HIV has two major categories: HIV-1 and HIV-2. HIV-1, which currently has about 10 subtypes, is most common worldwide and the only form found in the US. HIV-2 is less virulent and though currently confined to West Africa—it's spreading.

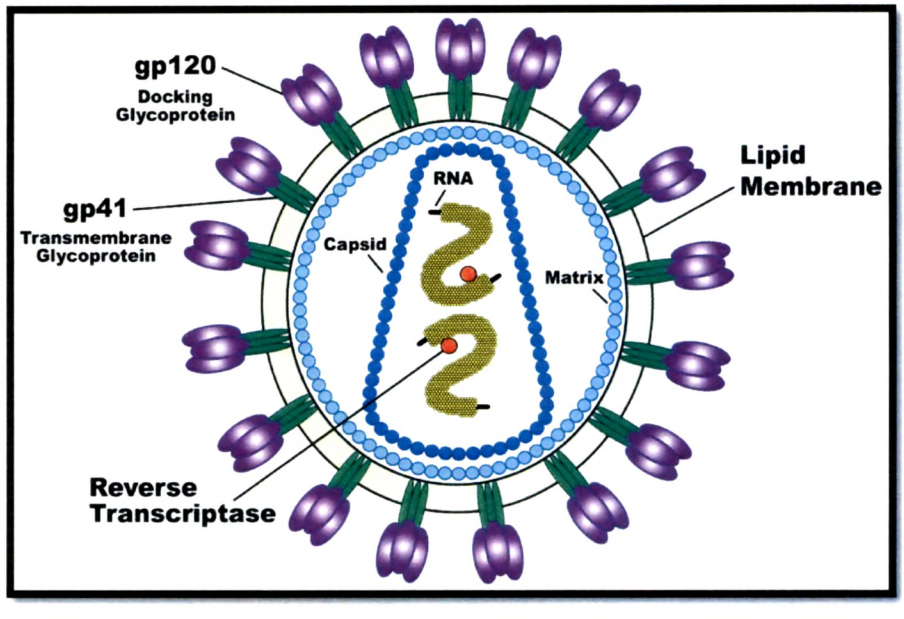
Comparison of HIV species[13]

Species	Virulence	Transmutability	Prevalence	Purported origin
HIV-1	High	High	Global	Common chimpanzee
HIV-2	Low	Low	West Africa	Sooty Mangabey

HIV (HUMAN IMMUNODEFICIENCY VIRUS)

Outside the human cell, HIV exists as roughly spherical particles (sometimes called virions). The surface of each particle is studded with lots of little spikes.

HIV particles surround themselves with a coat of fatty material known as the viral envelope (or membrane). Projecting from this are around 72 little spikes, which are formed from the proteins gp120 and gp41. Just below the viral envelope is a layer called the matrix, which is made from the protein p17. The viral core (or capsid) is usually bullet-shaped and is made from the protein p24. Inside the core are three enzymes required for HIV replication called reverse transcriptase, integrase and protease. Also held within the core is HIV's genetic material, which consists of two identical strands of RNA. [13] (Fig 3)



(Fig 3. STRUCTURE OF HIV VIRION)

The proteins gp120 and gp41 together make up the spikes that project from HIV particles, while p17 forms the matrix and p24 forms the core.

Retroviruses are the exception because their genes are composed of RNA (Ribonucleic Acid). RNA has a very similar structure to DNA. However, small differences between the two molecules mean that HIV's replication process is a bit more complicated than that of most other viruses.

HIV has just nine genes (compared to more than 500 genes in a bacterium, and around 20,000-25,000 in a human). Three of the HIV genes, called gag, pol and env, contain information needed to make structural proteins for new virus particles. The other six genes, known as tat, rev, nef, vif, vpr and vpu, code for proteins that control the ability of HIV to infect a cell, produce new copies of virus, or cause disease.

Major antigens of HIV[14, 15]

A: Envelope antigens

1. Spike antigen – gp 120
2. Transmembrane pedicle antigen – gp 41

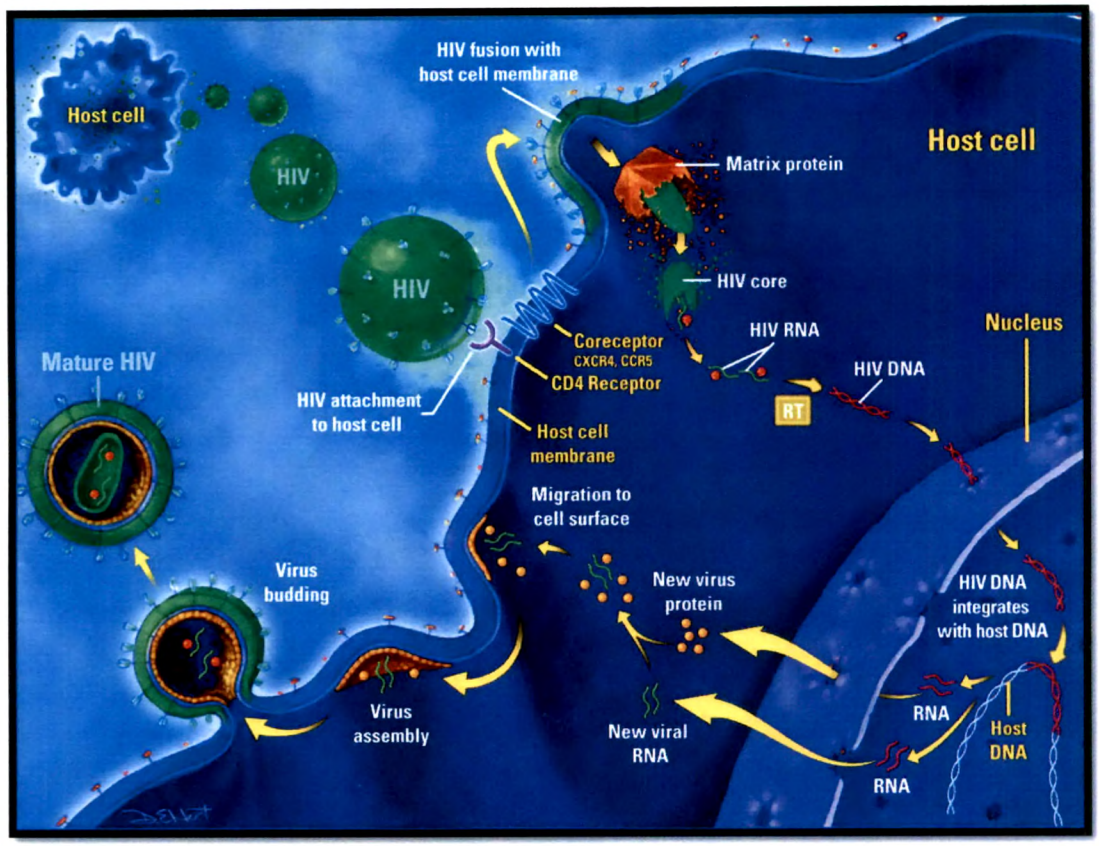
B: Shell antigen

1. Nucleocapsid protein – p 18

C: Core antigens

1. Principal core protein – p 24
2. Other core antigens – p 15 p 55
3. Polymerase antigens – p 31 p 51 p 64

LIFE CYCLE OF HIV[14, 15]



Once HIV is in the body, it targets and infects a certain type of white blood cell called a CD4 cell. HIV then takes over or "hijacks" these cells and turns them into virus factories that can produce thousands of viral copies. The steps HIV goes through to complete this process are as follows:

1. Entry

HIV enters a cell by attaching itself to specific points, called receptors, on the cell's surface. Once HIV gets inside a cell, it releases its own genetic material and enzymes.

2. Reverse Transcription

HIV's genetic material comes in a form known as RNA. The RNA contains the "instructions" that will reprogram the CD4 cell's

machinery to produce more viruses. In order to be effective, HIV's RNA must be converted into DNA. This conversion process depends on an HIV enzyme called reverse transcriptase.

3. Integration

Next, the newly copied DNA is inserted into the genetic material of the CD4 cell. This is done with the help of another HIV enzyme called integrase.

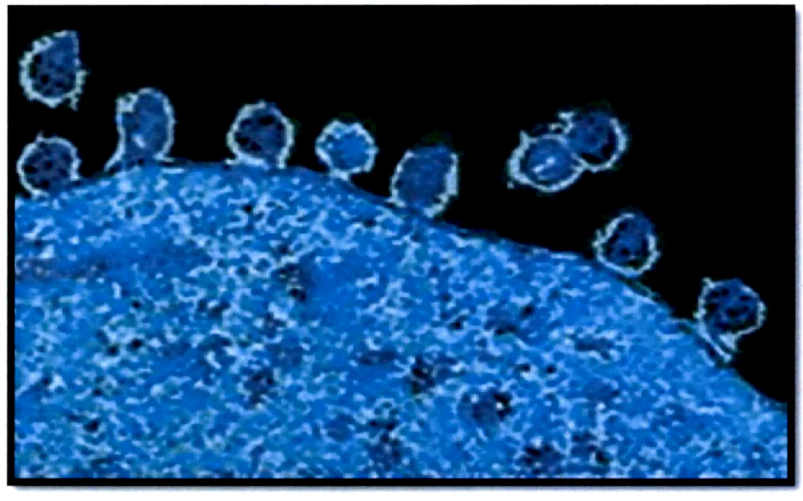
4. Cleavage

Once the virus is integrated into the CD4 cell, new HIV proteins are produced by it in the form of long chains. These chains have to be cut up into smaller pieces, and then reassembled in order to become new HIV virus. This cutting process depends on a third HIV enzyme called protease.

5. Assembly and Budding

Finally, the cut-up pieces are put together to form new virus particles, which then "bud" back out of the original CD4 cell. This new virus goes on to target and infect other cells.

HIV particles budding from an infected cell



HIV TRANSMISSION[14, 15]

HIV is a virus that is found in blood and other body fluids such as semen and vaginal fluids. It cannot live for long outside the body.

The most common ways that people become infected with HIV are:

- Having sexual intercourse with an infected partner.
- Injecting drugs using a needle or syringe that has been used by someone who is infected.

➢ Sexual Transmission

1. Unsafe sexual behaviors, both homo and heterosexual, is the predominant mode of transmission. Thus, HIV ranks as a sexually transmitted disease worldwide.
2. Though initially discovered in homosexual males, heterosexual transmission is the most common mode of infection worldwide, particularly in developing countries. Male to female transmission is 8 times more efficient than the converse – maybe due to prolonged exposure of vaginal and cervical mucosa to infected seminal fluid compared to brief exposure of male genitalia to infected vaginal fluid. Also, semen contains higher concentration of HIV than vaginal or cervical fluid.[15]

Factors associated with increased risk of transmission.

1. Anal intercourse – as the anal mucosa is thin and fragile. The risk increases if rectal ulcers are present or practices such as anal douching or insertion of hard objects or clenched first into the rectum which traumatize the rectal mucosa.
2. Presence of other STD's greatly increases both susceptibility as well as infectivity.

3. Failure to use barrier contraceptives, oral contraceptive pill usage, circumcision, alcohol consumption and illicit drug use have all been linked to increased risk of sexual transmission of HIV.

➢ **Transmission by Blood and Blood Products**

1. Intravenous drug users who share injection, paraphernalia such as needles, syringes or water for dissolving the drug or the cotton through which drugs are filtered can be exposed to HIV.
2. Any skin piercing like tattooing or acupuncture can transmit HIV.
3. Blood and blood products are capable of transmitting HIV. But hyper- immune gamma globulin, hepatitis B immune globulin, plasma derived hepatitis B and Rho immune globulin have not been associated with transmission of HIV perhaps due to inactivation of virus during processing.

➢ **Maternal-Fetal/Infant Transmission**

1. This is extremely important form of transmission of HIV infection in developing countries.
2. The two most important causes of transmission are

1) Perinatal Transmission

Risk of transmission during this period in the absence of prophylactic antiretroviral therapy ranges from 25-35% in developing countries as compared to 15-25% in industrialized countries.

Factors increasing risk of transmission

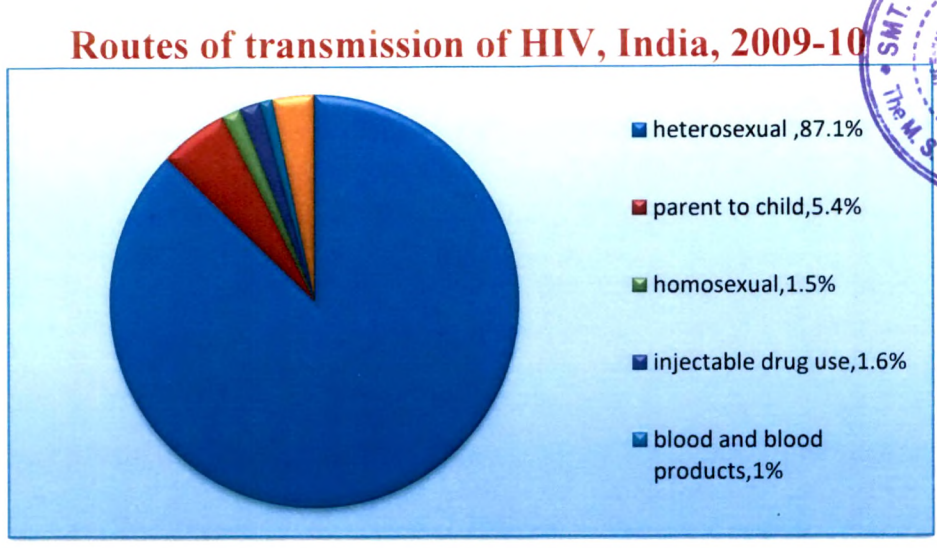
1. Inadequate prenatal care
2. Acute primary infection of HIV
3. Poor general health of mother during pregnancy, smoking and STDs
4. High risk pregnancy

2) Breast Feeding

Account for 5-15% infants become infected after delivery and are an important mode of transmission especially in developing countries where breast feeding is continued for a prolonged time. The risk is highest in early months of breast feeding. However, avoidance of breast feeding is not currently recommended in developing countries as breast milk is the only source of adequate nutrition and immunity against potentially serious infections for the infant.

Other Routes of Transmission

1. Occupational exposure – health care workers and lab personnel do face a small but significant risk of acquiring HIV infections by Needle-stick injury or injury with other sharp instruments which are contaminated with HIV positive blood – the risk is however only 0.3% compared to a risk of 6-30% following similar exposure to Hepatitis B. Rarely, exposure of mucous membranes or abraded skin to HIV infected material especially if the exposure involves prolonged contact with a large volume of blood/secretions carries a risk of transmission.
2. No convincing data exist that saliva, sweat, tears, urine, other body fluids, mosquito or other insect bites can transmit HIV infection.



DIAGNOSIS OF HIV INFECTION [13,14]

- **HIV EIA (ELIZA, enzyme linked immuno assay)**

  EIA is commonly used as a screening assay for many infectious diseases, including HIV. These assays are used because they are cheap, highly sensitive and generally amenable to automation, facilitating high-volume testing. It has shortened the 'window period', or the time from exposure to seroconversion, from up to 12 weeks or more in the early days of diagnostic testing to the current window period' of less than three weeks in most cases.

  The small disadvantage of such a highly sensitive test is that the test produces false positives, the number and type of which vary with the assay used and the HIV prevalence in the tested population.

  All HIV diagnostic laboratories must confirm repeated EIA screen-positive results by a confirmatory assay, usually with Western blot.

- **p24 antigen**

  p24 antigen tests are also EIA-based and use antibody to capture the disrupted p24 antigen from patient serum. Positive results that

are repeatable must be confirmed with a neutralization procedure. In rare instances, the p24 antigen can be detected before HIV antibody in newly infected individuals.

This test is useful for specimens from patients that are high risk and symptomatic but HIV EIA-negative, or for specimens that are EIA-positive but Western blot-negative or -indeterminate.

- **Western blot**

The Western blot is an immunoblot that allows for the characterization of antibodies to each viral protein. Generally, a specimen must show a positive reaction with a minimum of one core band and one envelope band to be judged positive by Western blot.

Specimens that have bands present but do not fulfill the criteria for positivity are called Western blot indeterminate, and a follow-up specimen should be requested, usually collected three to four weeks after the initial specimen. In follow-up, patients will either show a definitive pattern indicating that they have seroconverted or will demonstrate the same banding pattern as previously observed. In the latter circumstance, the vast majority of these patients are HIV-negative and have nonspecific antibody. In these cases, if the patient is considered to be at risk or is particularly anxious, a qualitative PCR may be recommended to confirm that the patient is truly HIV-negative.

While the Western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a

poor screening test, Because these indeterminate banding patterns may be seen in patients who are not infected.

The test is also much more labour intensive and costly than EIA tests and does not allow for the efficient processing of large numbers of specimens.

- **Qualitative PCR**

PCR is a method that amplifies viral nucleic acid to allow for its detection in patient specimens. It is a particularly specific and sensitive test which can pick up very small numbers of viral particles. PCR is very useful in the diagnosis of HIV infection in babies born to infected mothers. Babies will carry maternal antibody up to approximately 15 months of age and, therefore, the antibody test is not a reliable indicator of infection in these children.

PCR may also be useful in resolving indeterminate Western blot results and testing immunocompromised individuals who may not mount an antibody response.

- **Quantitative RNA PCR and genotyping**

Quantitative RNA PCR must only be used to monitor HIV-positive individuals before or during antiretroviral therapy. It is used in conjunction with CD4 counts and general clinical assessments to ascertain when therapy should be started. It is also used to help determine the patient's response to therapy. Genotyping is used to monitor the development or presence of drug resistance in patients

before or during therapy. It is also used to assist physicians in their choice of antiretroviral drug combinations for the patient.

It should not be used as a diagnostic test for HIV because false positives and false negatives can occur in these circumstances

Characteristics of Tests for Direct Detection of HIV[14]

Test	Technique	Sensitivity	Cost/Test
Immune complex–dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients; detects down to 15 pg/mL of p24 protein	$1–2
HIV RNA by PCR	PCR amplification of cDNA generated from viral RNA (target amplification)	Reliable to 40 copies/mL of HIV RNA	$75–150
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Reliable to 50 copies/mL of HIV RNA	$75–150
HIV RNA by NucliSens	Isothermic nucleic acid amplification with internal controls	Reliable to 80 copies/mL of HIV RNA	$75–150

CLINICAL MANIFESTATIONS

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic to advanced disease with varieties of opportunistic infections and malignancies. It is preferable to adopt the concept that HIV disease is manifested in various stages. As mentioned above active virus replication and progressive immunologic impairment occur throughout the course of HIV infection and so HIV disease actually progresses even during the clinically latent stage.

WHO case definition for HIV infection [16, 17, 18, 19]

Adults and children 18 months or older

HIV infection is diagnosed based on:

Positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics; and/or;

Positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination.

Children younger than 18 months:

HIV infection is diagnosed based on:

Positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth. Positive HIV antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age.

Criteria for diagnosis of advanced HIV (including AIDS) for reporting[16, 17, 18, 19]

Clinical criteria for diagnosis of advanced HIV in adults and children with confirmed HIV infection:

Presumptive or definitive diagnosis of any stage 3 or stage 4 conditions.

and/or;

Immunological criteria for diagnosing advanced HIV in adults and children five years or older with confirmed HIV infection:

CD4 count less than 350 per mm^3 of blood in an HIV-infected adult or child. and/or;

Immunological criteria for diagnosing advanced HIV in a child younger than five years of age with confirmed HIV infection:

%CD4+ <30 among those younger than 12 months;

%CD4+ <25 among those aged 12–35 months;

%CD4+ <20 among those aged 36–59 months.

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and for providing clinicians and patients with important information about HIV disease stage and clinical management. Two major classification systems currently are in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System.

The CDC disease staging system (last revised in 1993) assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions.

The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms.

In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2005) can be used readily in resource-

constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The WHO system classifies HIV disease on the basis of clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings, and by clinicians with varying levels of HIV expertise and training

WHO clinical staging of established HIV infection[16, 17, 18, 19]

HIV-associated symptoms	WHO clinical stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

WHO immunological classification for established HIV infection[16, 17, 18, 19]

HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (%CD4+)	12–35 months (%CD4+)	36 –59 months (%CD4+)	>5 years (absolute number per mm^3 or %CD4+)
None or not significant	>35	>30	>25	> 500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

WHO CLINICAL STAGING FOR ADULTS AND ADOLESCENTS: PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV/ AIDS- RELATED CLINICAL EVENTS[16, 17, 18, 19]

CLINICAL EVENT	PRESUMPTIVE DIAGNOSIS	DEFINITIVE DIAGNOSIS
PRIMARY HIV INFECTION		
Asymptomatic		Detectable core P24 antigen and high blood HIV RNA, profound temporary lymphopenia and other transient blood abnormalities may occur. Not usually HIV antibody-positive until after symptoms. Seroconversion from HIV Ab negative to Ab-positive.
Acute Retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin manifestations.	
CLINICAL STAGE 1		
Asymptomatic.	No HIV-related symptoms reported and no signs on examination	Not required
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for three months or more	Can be confirmed by histology
CLINICAL STAGE 2		
Unexplained moderate weight loss (<10% of bodyweight)	Reported unexplained involuntary weight loss in pregnancy, failure to gain weight	Documented weight loss <10% of body weight

Recurrent presumed bacterial RTI (≥2 in any 6 month period)	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillopharyngitis without features of viral infection (such as coryza or cough)	Culture of suitable body fluid
Herpes zoster	Painful rash of small fluidfilled blisters in distribution of a nerve supply, can be hemorrhagic on erythematous background, and does not cross midline. Current or in the last two years. Severe or frequently recurrent herpes zoster is usually associated with more advanced HIV disease.	Clinical diagnosis
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responds to antifungal treatment but may recur. Also common in nutritional deficiency, e.g. of B vitamins.	Clinical diagnosis
Recurrent oral ulceration (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey Pseudomembrane	Clinical diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked postinflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin	Clinical diagnosis

Fungal nail infections of fingers	Fungal paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails. Also common in uninfected adults. Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Fungal culture of the nail or nail plate scrapings.
CLINICAL STAGE 3		
Unexplained severe weight loss (>10% of body weight	Reported unexplained involuntary weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m2; in pregnancy, the weight loss may be masked	Documented loss of more than 10% of body weight
Unexplained chronic diarrhea for longer than one month	Chronic diarrhea (loose or watery stools three or more times daily) reported for longer than one month	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than one Month	Fever or night sweats for more than one month, either ntermittent or constant with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination; malaria must be excluded in malarious areas	Documented fever >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection

Persistant oral candidiasis	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudo membranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off	Clinical diagnosis
Pulmonary tuberculosis (current)	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; PLUS EITHER positive sputum smear; OR negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitations, pulmonary fibrosis shrinkage. No evidence of extrapulmonary disease	Isolation of M. Tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms)
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and severe PID)	Fever accompanied by specific symptoms or signs that localize infection and response to appropriate antibiotic	Isolation of bacteria from Appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odor and rapid loss of bone and/or soft tissue	Clinical diagnosis

Unexplained anemia (<8g/dl), neutropenia (<1000/mm3) or thrombocytopenia (<50 000/ mm3) for more than one month	No presumptive clinical Diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or antihelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Childhood Illness guidelines or other relevant guidelines·
CLINICAL STAGE 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5; PLUS EITHER unexplained chronic diarrhea (loose or watery stools three or more times daily) reported for longer than one month; OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas	Documented weight loss (>10% of body weight); PLUS EITHER two or more unformed stools negative for pathogens; OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND No evidence of bacterial pneumonia; bilateral	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue

	crepitations on auscultation with or without reduced air entry	
Recurrent bacterial pneumonia; (this episode plus one or more episodes in last six months	Current episode plus one or more previous episodes in the past six months; acute onset (<2 weeks) of severe symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray; response to antibiotics	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology
Esophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidacies	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology
Extra-pulmonary tuberculosis	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary Tuberculosis	M. tuberculosis isolation or compatible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray)

Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology
Cytomegalo virus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, hemorrhage and necrosis	Compatible histology or Cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction).
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on Neuroimaging (computed tomography or magnetic resonance imaging
HIV encephalopathy	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging)
Extra-pulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Confirmed by CSF microscopy (India ink or Gram stain). Serum or CSF CRAG-positive or culture-positive

Disseminated nontuberculous mycobacteria infection	No presumptive clinical Diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs
Progressive multifocal Leuko-encephalopathy (PML)	No presumptive clinical Diagnosis	Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid
Candidiasis of trachea, bronchi, Lungs	No presumptive diagnosis	Confirmed by symptoms, clinical signs suggestive of organ involvement and/or macroscopic appearance at bronchoscopy. Histology or cytology, or microscopy of specimen from tissue.

Chronic Cryptosporidiosis (with diarrhea lasting more than one month	No presumptive Diagnosis	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool
Chronic Isosporiasis	No presumptive Diagnosis	Identification of Isospora
Disseminated mycosis (Coccidiomycosis or Histoplasmosis)	No presumptive Diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent non-typhoid Salmonella bacteraemia	No presumptive Diagnosis	Blood culture
Lymphoma (cerebral or B-cell non-Hodgkin)	No presumptive Diagnosis	Histology of relevant specimen or, for central nervous system tumors, neuroimaging techniques
Invasive cervical carcinoma.	No presumptive Diagnosis	Histology or cytology
Atypical disseminated Leishmaniasis	No presumptive Diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen
Symptomatic HIV-associated nephropathy	No presumptive clinical Diagnosis	Renal biopsy
Symptomatic HIV-associated Cardiomyopathy	No presumptive clinical Diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by Echocardiography

CDC Classification System for HIV-Infected Adults and Adolescents[16, 17, 18, 19]

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B Symptomatic Conditions,#* not A or C	C AIDS-Indicator Conditions*
(1) ≥500 cells/μL	A1	B1	C1
(2) 200-499cells/μL	A2	B2	C2
(3) <200 cells/μL	A3	B3	C3

For symptomatic conditions, see Table 2

* For AIDS-indicator conditions, see Table 3

Table 2 CDC Classification System: Category B Symptomatic Conditions[16, 17, 18, 19]

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria:

a) They are attributed to HIV infection or are indicative of a defect in cell-mediated immunity.

b) They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

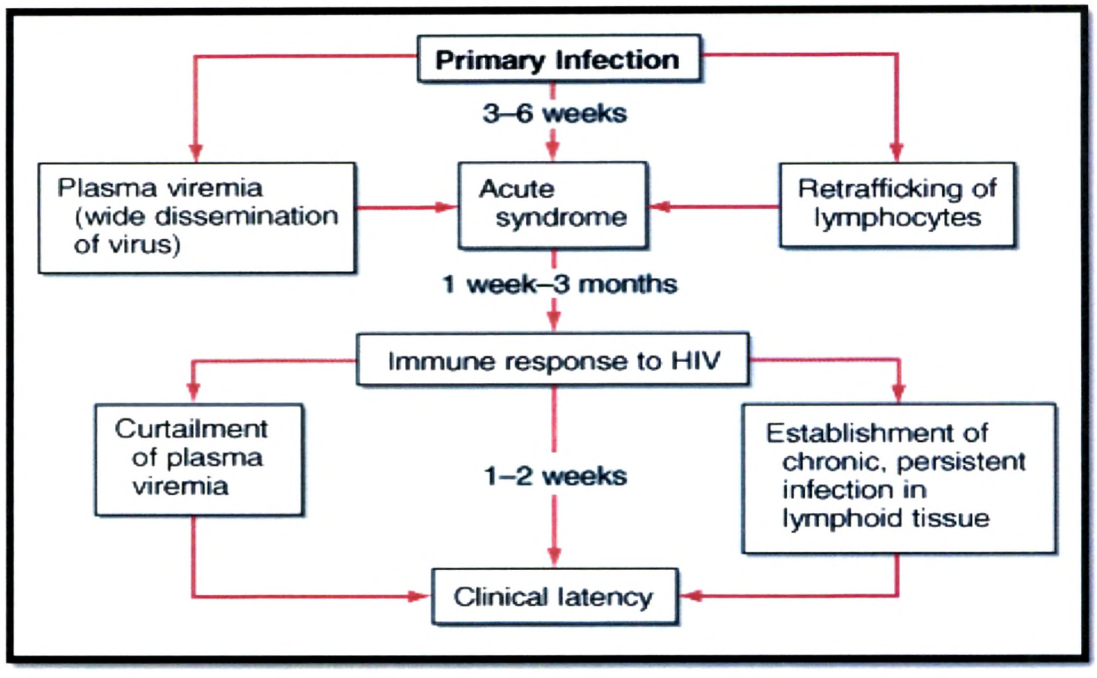
- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or frequent, or poorly responsive to therapy.
- Pelvic inflammatory disease (PID) , particularly if complicated by tuboovarian abscess
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Hairy leukoplakia, oral
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting >1 month
- Listeriosis
- Peripheral neuropathy
- Herpes zoster (shingles), involving ≥2 episodes or ≥1 dermatome

Table 3 CDC Classification System: Category C AIDS-Indicator Conditions[16, 17, 18, 19]

- Bacterial pneumonia, recurrent (≥2 episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1-month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex (MAC) or M kansasii , disseminated or extrapulmonary
- Mycobacterium tuberculosis (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci (formerly carinii) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

CLINICAL STAGING OF HIV/AIDS[15]

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is best to regard HIV disease as beginning at the time of primary infection and progressing through various stages.



- **ACUTE PRIMARY INFECTION**

Defined as mononucleosis like syndrome, with or without aseptic meningitis, associated with sero-conversion for HIV antibody. Antibody sero-conversion is required as evidence of initial infection, current viral isolation procedures are not adequately sensitive to be relied on for demonstrating the onset of infection.

*About 50-70% patients experience this stage.

*Also named as ACUTE RETROVIRAL SYNDROME (Table 4)

*Occurs 3-6 wks post-exposure

*Lasts for 1 to several wks and subsides with development of immunity.

*Most recovers spontaneously and progress while CD4+ count may be normal or decreased.

*10% progresses with fulminant course.

TABLE 4: ACUTE HIV SYNDROME

Clinical Findings in the Acute HIV Syndrome	
General	**Neurologic**
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	**Dermatologic**
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

- **ASYMPTOMATIC HIV INFECTION–CLINICAL LATENCY**

Although the length of time from initial infection to the development of clinical disease varies greatly, the median time for untreated patients is ~10 years. HIV disease with active virus replication is ongoing and progressive during this asymptomatic period.

The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA in plasma progress to symptomatic disease faster than do patients with low levels of HIV RNA.

During the asymptomatic period of HIV infection, the average rate of CD4+ T cell decline is ~50/μL per year. When the CD4+ T cell count falls to <200/μL, the resulting state of immunodeficiency is severe enough to place the patient at high risk for opportunistic infection and neoplasms, and hence for clinically apparent disease.

- **SYMPTOMATIC DISEASE**

Symptoms of HIV disease can appear at any time during the course of HIV infection. Generally speaking, the spectrum of illnesses that one observes changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in patients with CD4+ T cell counts <200/μL. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/μL and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity.

While the causative agents of the secondary infections are characteristically opportunistic organisms such as P. jiroveci, atypical mycobacteria, Cytomegalovirus (CMV), and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens.

In general, a key element of treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication through the use of combination ARV therapy and instituting primary and secondary prophylaxis for opportunistic infections as indicated.

CARDIOVASCULAR SYSTEM AND HIV PATHOGENESIS[19,20,21,22]

➢ INTRODUCTION

Studies published over the past 3 years have tracked the incidence and course of human immunodeficiency virus (HIV) infection in relation to cardiac illness in both children and adults.These studies show that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high-risk groups to target for early intervention and therapy.

Cardiovascular manifestations of HIV have been altered by the introduction of highly active antiretroviral therapy (HAART) regimens. On one hand, HAART has significantly modified the course of HIV disease, lengthened survival, and improved the quality of life of HIV-infected patients. On the other hand, the early data have raised concerns that HAART is associated with an increase in both peripheral and coronary arterial diseases. The HAART-associated changes are relevant only to the minority of HIV-infected individuals worldwide who have access to HAART. Thus, studies conducted before HAART became available remain globally applicable.

➢ DILATED CARDIOMYOPATHY

HIV disease is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9 in 1000 before the introduction of HAART. The importance of cardiac dysfunction is demonstrated by its effect on survival in acquired immunodeficiency syndrome (AIDS). Median survival to AIDS-related

death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart as shown by echocardiography at a similar infection stage. The unadjusted hazard ratio for death in HIV-related cardiomyopathy compared with idiopathic cardiomyopathy is 4.0; the ratio adjusted after multivariate analysis is 5.86. In the multicenter Pediatric Pulmonary and Cardiovascular Complications of HIV study (P^2C^2 HIV), children with vertically transmitted HIV infection (median age 2.1 years) had a 5-year cumulative survival of 64% . Mortality was higher in children with baseline depressed left ventricular fractional shortening or increased left ventricular dimension, thickness, mass, wall stress, heart rate, or blood pressure. Decreased left ventricular fractional shortening and increased wall thickness were also predictive of survival after multivariate adjustment.

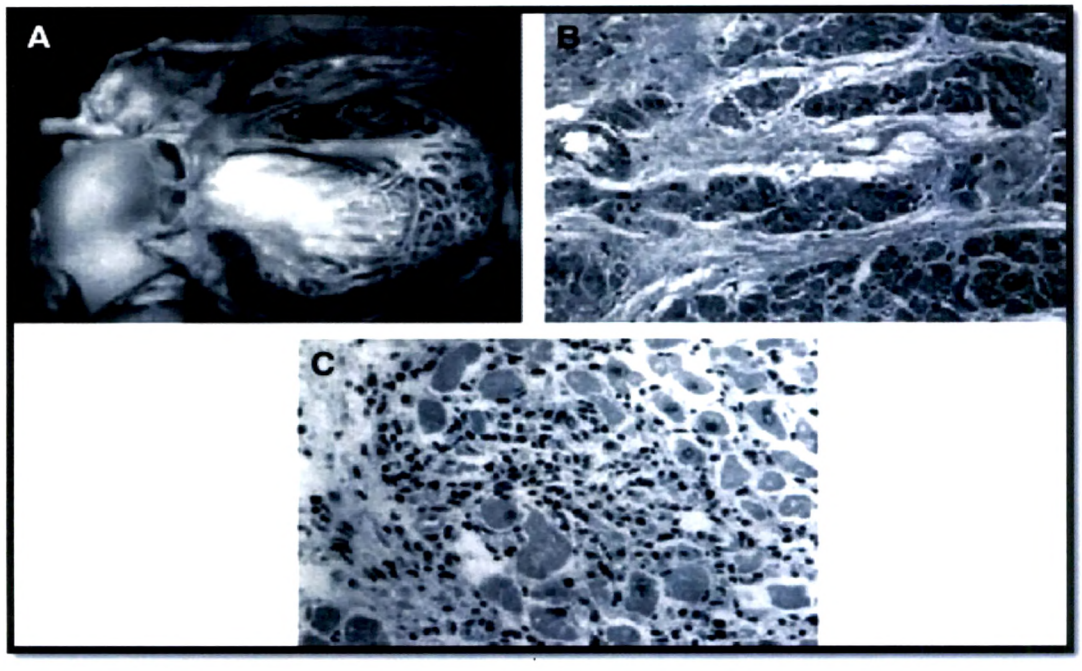
Principal HIV-Associated Cardiovascular Abnormalities

Type	Possible Causes and Associations	Incidence
Dilated cardiomyopathy	Infectious: HIV, toxoplasma gondii, coxsackievirus group B, Epstein-Barr virus, cytomegalovirus, adenovirus	15.9 patients in 1000 asymptomatic HIV-infected persons before the introduction of HAART.3
	Autoimmune response to infection	
	Drug related	
	Cocaine, possibly nucleoside analogues, IL-2, doxorubicin, interferon	
	Metabolic/endocrine	
	Nutritional deficiency/wasting: selenium, B12, carnitine	
	Thyroid hormone, growth hormone	
	Adrenal insufficiency, hyperinsulinemia	
	Cytokines	
	TNF-α, nitric oxide, TGF-ß, endothelin-1	
	Acquired immunodeficiency	
	HIV viral load, length of immunosuppression	
Coronary heart disease	Protease-inhibitor-induced metabolic and coagulative disorders; arteritis	Mostly limited to case reports after the introduction of protease inhibitors containing HAART
Systemic arterial hypertension	HIV-induced endothelial dysfunction; vasculitis in small, medium, and large vessels in the form of leukocytoclastic vasculitis; atherosclerosis secondary to HAART; aneurysms of the large vessels such as the carotid, femoral, and abdominal aorta with impairment of flow to the renal arteries; PI-induced insulin	20%–25% of HIV-infected persons before the introduction of HAART.[29] Up to 74% in HIV-infected persons with HAART-related

	resistance with increased sympathetic activity and sodium retention	metabolic syndrome[30]
Pericardial effusion	Bacteria Staphylococcus, Streptococcus, Proteus, Nocardia, Pseudomonas, Klebsiella, Enterococcus, Listeria	11% per year in asymptomatic AIDS patients before the introduction of HAART[15]
	Mycobacteria Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Mycobacterium kansaii	
	Viral pathogens HIV, herpes simplex virus, herpes simplex virus type 2, cytomegalovirus	
	Other pathogens Cryptococcus, toxoplasma, histoplasma	
	Malignancy Kaposi's sarcoma Malignant lymphoma	
	Capillary leak/wasting/malnutrition	
	Hypothyroidism	
	Prolonged acquired immunodeficiency	
HIV-associated pulmonary hypertension	Recurrent bronchopulmonary infections, pulmonary arteritis, microvascular pulmonary emboli due to thrombus or drug injection, plexogenic pulmonary arteriopathy, mediator release from endothelium	1/200 of HIV-infected persons before the introduction of HAART[1]
AIDS-related tumors	Kaposi's sarcoma Non-Hodgkin lymphomas	12%–28% of AIDS patients before the introduction of HAART[1,6] Mostly limited to case reports before the introduction of HAART

❖ Myocarditis :

Myocarditis and HIV-1 myocardial infection are still the most studied causes of dilated cardiomyopathy in HIV disease. HIV-1 virions appear to infect myocardial cells in patchy distributions without a clear direct association between HIV-1 and cardiac myocyte dysfunction. It is unclear how HIV-1 may enter CD4-receptor-negative cells such as myocytes. Reservoir cells (ie, dendritic cells) may play a pathogenic role in the interaction between HIV-1 and the myocyte and in the activation of multifunctional cytokines (ie, tumor necrosis factor-α [TNF-α], interleukin [IL]-1, IL-6, IL-10) that contribute to progressive and late tissue damage.



HIV-related cardiomyopathy. (A) The heart is enlarged, principally from vascular dilatation, and there is mild hypertrophy with diffuse endocardial fibrous thickening. Histologic examination (B) may reveal myocyte hypertrophy with increased interstitial collagen or (C) evidence of myocarditis with lymphocytic infiltrate and myocyte necrosis

❖ **Autoimmunity:**

Cardiac-specific autoantibodies (anti-α myosin autoantibodies) have been reported in up to 30% of patients with HIV-associated cardiomyopathy.The finding supports the theory that cardiac autoimmunity plays a role in the pathogenesis of HIV-related heart disease and suggests that cardiac autoantibodies may be markers of left ventricular dysfunction in HIV-positive patients with previously normal echocardiographic findings.

❖ **Relationship to encephalopathy:**

Several studies have reported that patients with encephalopathy were more likely to die of congestive heart failure than were patients without encephalopathy.The reservoir cells in the myocardium and the cerebral cortex, which are not susceptible to treatment, may hold HIV-1 on their surfaces for extended time periods and may chronically release cytotoxic cytokines, contributing to progressive and late tissue damage in both systems independently of HAART regimens.

❖ **Nutritional deficiency:**

Nutritional deficiencies are common in HIV infection, particularly in late-stage disease, and may contribute in inducing ventricular dysfunction independently of HAART regimens. Deficiencies of trace elements have been associated directly or indirectly with Cardiomyopathy. Selenium replacement may reverse cardiomyopathy and restore left ventricular function in nutritionally depleted patients.Levels of vitamin B_{12}, carnitine, and growth and thyroid hormone may also be altered in HIV disease; all have been associated with left ventricular dysfunction.

❖ **Drug cardiotoxicity:**

Studies on transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication.

Lactic acidosis related to mitochondrial dysfunction may further contribute to myocardial cell dysfunction. Other nucleoside reverse transcriptase inhibitors, such as didanosine and zalcitabine, do not seem either to promote or to prevent dilated cardiomyopathy.

➢ **PERICARDIAL EFFUSION**

The prevalence of pericardial effusion in asymptomatic AIDS patients has been estimated at 11% before the introduction of HAART. HIV infection should be included in the differential diagnosis of unexplained pericardial effusion or tamponade. Pericardial effusion in HIV disease may be related to opportunistic infections or to malignancy, but most often a clear pathology is not found.The effusion may be part of a generalized serous effusive process also involving pleural and peritoneal surfaces. This "capillary leak" syndrome is likely related to enhanced cytokine expression in the later stages of HIV disease. Pericardial effusion spontaneously resolves in up to 42% of patients.

Pericardiocentesis is currently recommended only in large or poorly tolerated effusions, for diagnostic evaluation of systemic illness, or in the presence of cardiac tamponade.Mortality remains increased in HIV-infected patients who develop an effusion, even if the effusion resolves over time. The effects of HAART therapy on pericardial effusion are largely unexplored.

➢ ENDOCARDITIS

The prevalence of infective endocarditis in HIV-infected patients is similar to that in patients of other risk groups, such as intravenous drug users. Estimates of endocarditis prevalence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs independently of HAART regimens.

Right-sided valves are predominantly affected, and the most frequent agents are Staphylococcus aureus (>75% of cases), Streptococcus pneumoniae, Haemophilus influenzae, Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans.Patients with HIV have presentations and survival from infective endocarditis similar to those without HIV (85% v/s93%).

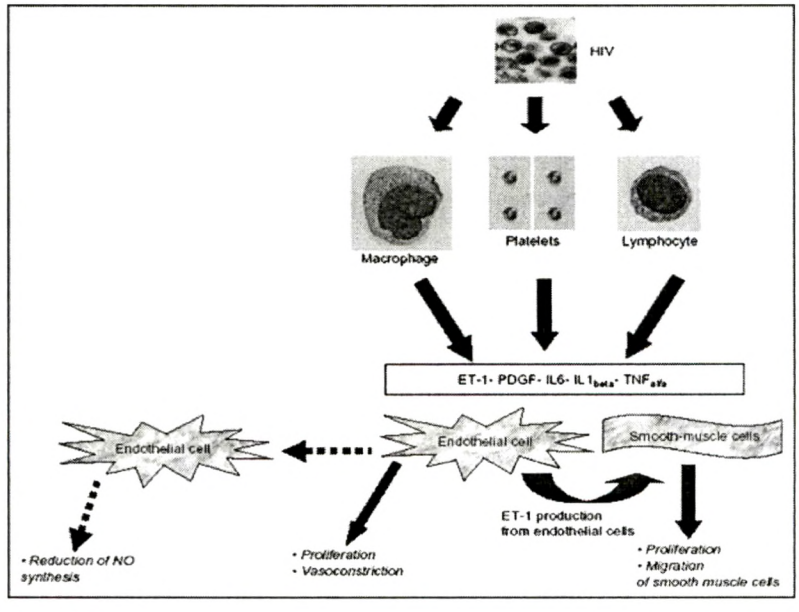
Patients with late-stage HIV disease, however, have about a 30% higher mortality with endocarditis than asymptomatic HIV-infected patients, which may be related to the degree of immunodeficiency. Surgical management is indicated in selected patients, especially when valvular dysfunction resulting in acute heart failure becomes intractable to medical therapy.

Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, occurs in 3% to 5% of AIDS patients, mostly in patients with HIV-wasting syndrome.It is characterized by friable endocardial vegetations, affecting predominantly the left-sided valves and consisting of platelets within a fibrin mesh with few inflammatory cells. Systemic embolization from marantic endocarditis is a rare cause of death in AIDS patients in the HAART era.

➢ HIV ASSOCIATED PULMONARY HYPERTENSION

The pathogenesis of primary pulmonary hypertension in HIV infection is multifactorial and poorly understood. Primary pulmonary hypertension has been found in hemophiliacs receiving lipophilized factor VIII, intravenous drug users, and patients with left ventricular dysfunction, obscuring any relationship with HIV-1. HIV-1 is frequently identified in alveolar macrophages on histology. These macrophages release TNF-α, oxide anions, and proteolytic enzymes in response to infection. Clinical symptoms and outcomes of patients with right ventricular dysfunction are related to the degree of pulmonary hypertension, varying from a mild asymptomatic condition to severe cardiac impairment with cor pulmonale and death. Activation of α-1 receptors and genetic factors (increased frequency of HLA-DR6 and DR52) have also been hypothesized in the pathogenesis of HIV-associated pulmonary hypertension.

Epoprostenol therapy is generally limited to seriously ill patients because of its cost and the need for continuous intravenous infusion with an associated risk of infection. Effects of HAART regimens on the clinical course of HIV-associated pulmonary hypertension are unknown.



➢ VASCULITIS AND CORONARY ARTERY DESEASE

A wide range of inflammatory vascular diseases, including polyarteritis nodosa, Henoch-Schönlein purpura, and drug-induced hypersensitivity vasculitis, may develop in HIV-infected individuals. Kawasaki-like syndrome— and Takayasu's arteritis have been also described.

Before the introduction of HAART, coronary heart disease in HIV infection had been postulated to be linked to cytomegalovirus or HIV-1 itself, even though controversy remains and the association between viral infection and coronary artery lesions is not clear.—Acute coronary syndromes may be observed with increasing frequency among HIV patients receiving therapy with protease inhibitors as part of HAART regimens. Protease inhibitors are designed to target the catalytic region of HIV-1 protease. This region is homologous with regions of 2 human proteins that regulate lipid metabolism, cytoplasmic retinoic-acid binding protein 1 and low-density lipoprotein-receptor-related protein. It has been hypothesized, although without strong experimental support, that this homology may allow protease inhibitors to interfere with these proteins, which may be the cause of the metabolic and somatic alterations that develop in protease inhibitors-treated patients (ie, dyslipidemia, insulin resistance, increased C-peptide levels, and lipodystrophy). Recent data indicate that dyslipidemia may be, at least in part, caused either by protease inhibitors-mediated inhibition of proteasome activity and accumulation of the active portion of sterol regulatory element-binding protein-1c in liver cells and adipocytes or to apo-CIII polymorphisms in HIV-infected patients. Endothelial dysfunction has been recently described in protease inhibitors recipients, further supporting the idea of increased risk of coronary artery disease in these patients.

The patients with preexisting cardiovascular risk factors or a family history of cardiovascular disease may have a higher risk of developing acute coronary syndromes. Data on the incidence of coronary artery disease among HIV-infected subjects receiving protease inhibitors, however, are largely limited to case reports, and controlled prospective studies are lacking.

➢ HYPERTENSION AND COAGUABLE DISORDERS

The prevalence of hypertension in HIV disease has been estimated to have been about 20% to 25% before the introduction of HAART. Recent reports indicate that elevated blood pressure may be related to protease inhibitor-induced lipodystrophy and metabolic disorders, especially fasting triglyceride, with a prevalence of hypertension in up to 74% of patients with HAART-related metabolic syndrome. HIV-infected patients, especially those with fat redistribution, may develop coagulation abnormalities such as increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or a deficiency of protein S. These abnormalities have been associated with documented thromboses involving both veins and arteries and seem to be related to protease inhibitor-containing HAART.

➢ COMMON HIV THERAPIES AND HEART

In AIDS patients with Kaposi's sarcoma, reversible cardiac dysfunction was associated with prolonged, high-dose therapy with interferon-α. Doxorubicin, which is used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin's lymphoma, has a dose-related effect on dilated cardiomyopathy, as does foscarnet sodium when used to treat cytomegalovirus esophagitis. Cardiac arrhythmias have been described with the administration of amphotericin B, ganciclovir, trimethoprim-sulfamethoxazole, and pentamidine. The principal cardiovascular actions/interactions of common HIV therapies are reported in Table 2.

Table 2. Cardiovascular Actions/Interactions of Common HIV Therapies

Class	Drugs	Cardiac Drug Interactions	Cardiac Side Effects
Antiretroviral			
Nucleoside Reverse Transcriptase Inhibitors (RTI)	Abacavir (Ziagen), zidovudine (AZT, Retrovir)	Dipyridamole	Lactic acidosis (rare), hypotension, skeletal muscle myopathy, (mitochondrial dysfunction hypothesized, but not seen clinically)
Nonnucleoside RTI	Delavirdine (Rescriptor), efavirenz (Sustiva), nevirapine (Viramune)	Warfarin (class interaction), calcium channel blockers, ß-blockers, quinidine, steroids, theophylline	Delavirdine can cause serious toxic effects if given with antiarrhythmic drugs and myocardial ischemia if given with vasoconstrictors
Protease inhibitors	Amprenavir (Agenerase), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase, Fortovase)	All are metabolized by cytochrome p-450 and interact with: sildenafil, amiodarone, lidocaine, quinadine, warfarin, statins Calcium channel blockers, ß-blockers (1.5–3x increase), prednisone, quinine, theophylline (decrease concentration)	Implicated in premature atherosclerosis, dyslipidemia, insulin resistance, and lipodystrophy/lipoatrophy

Anti-infective			
Antibiotics	Erythromycin, clarithromycin	Cytochrome p-450 metabolism and drug interactions	Orthostatic hypotension, ventricular tachycardia, bradycardia, QT prolongation
	Rifampicin	Reduces therapeutic effect of digoxin by induction of intestinal P-glycoprotein	
	Trimethoprim/sulfamethoxazole (Bactrim)	Increases warfarin effects	Orthostatic hypotension, QT prolongation
Antifungal agents	Amphotericin B	Digoxin toxicity	Hypertension, renal failure, hypokalemia, thrombophlebitis, angioedema, dilated cardiomyopathy, arrhythmias.
	Ketoconazole, itraconazole	Cytochrome p-450 metabolism and drug interactions; increases levels of sildenafil, warfarin, statins, nifedipine, digoxin	
Antiviral agents	Foscarnet, ganciclovir	Zidovudine	Reversible cardiac failure (dose-related effect), electrolyte abnormalities, ventricular tachycardia (QT prolongation), hypotension
Antiparasitic	Pentamidine (intravenous)		Hypotension, arrhythmias (torsade de pointes, ventricular tachycardia), hyperglycemia, hypoglycemia, sudden death Note: Contraindicated if baseline QTc>0.48

➢ CARDIAC INVOLVEMENT IN AIDS RELATED TUMOURS

Retrospective autopsy studies in the pre-HAART period estimated the prevalence of cardiac Kaposi's sarcoma in AIDS to be from 12% to 28%. Cardiac Kaposi's sarcoma is not usually obstructive or associated with clinical cardiac dysfunction, morbidity, or mortality. Malignant lymphoma involving the heart is infrequent in AIDS. Lymphomatous infiltration may be diffuse or may result in discrete isolated lesions, which are usually derived from the Burkitt or immunoblastic type B cells. The prognosis of patients with HIV-associated cardiac lymphoma is generally poor, although clinical remission has been observed with combination chemotherapy. The introduction of HAART may lead to a reduction in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin lymphomas. The fall may be attributable to the improved immunologic state of the patients and the prevention of opportunistic infections (human herpes virus-8 and Epstein-Barr virus) known to play a pathogenic role in these neoplasms

RENOVASCULAR SYSTEM AND HIV PATHOGENESIS[38,39,40,41]

➢ INTRODUCTION

Human immunodeficiency virus (HIV) infection is associated with several different types of renal disease. The most common clinical entity encountered in children and adults is known as HIV-associated nephropathy (HIVAN), a disease that leads to progressive renal damage, urine protein loss, and sometimes end-stage renal disease. HIVAN is often characterized by **collapsing focal segmental glomerulosclerosis** on renal biopsy, but children sometimes demonstrate clinical signs of HIVAN without underlying focal segmental glomerulosclerosis. Other less common renal manifestations of HIV infection are HIV-related immune complex glomerulonephritis and membranous nephropathy.

Though present in up to 10% of adults, HIVAN is an unusual feature of childhood HIV infection. The incidence of HIV-associated kidney disease in children is estimated at between 2% and 5% and at up to 15% in populations of African descent. Risk factors for HIVAN include high viral load, low CD4+ T-lymphocyte cell counts, and longstanding HIV disease. Many centers do not routinely perform renal biopsies on patients (adult or child) with HIV and elevated urine protein (proteinuria), and therefore the true prevalence of HIVAN is not known. Though HIVAN is believed to be the most common form of kidney disease in HIV-infected adults of African descent, biopsy data have confirmed HIVAN in only about half of suspected cases. Available data from kidney biopsy series suggest that the most common diagnoses encountered among HIV-infected individuals are the following:

- Focal segmental glomerulosclerosis, thought to be due to the direct pathogenic effect of HIV in the kidney
- Immune complex glomerulonephritis, related to the deposition of antigen–antibody complexes
- Membranous nephropathy, usually related to ongoing hepatitis B or C infection

Other non-HIVAN disorders of the kidney that sometimes occur in HIV-infected patients include

- Acute renal failure resulting from hypotension or infection,
- Drug-induced kidney disease (e.g., aminoglycosides, amphotericin B, some antiretroviral [ARV] drugs), and
- Postinfectious glomerulonephritis due to bacterial infection.

➢ ACUTE RENAL FAILURE ,FLUID AND ELECTROLYTE DISTURBUCES

Acute Renal Failure

Mild ARF, defined as a peak serum creatinine >=2.0 mg/dL, has been reported to occur in up to 20% of hospitalized HIV-infected patients. This percentage compares to an incidence rate of 4-5% in hospitalized non-HIV-infected patients. The two most common causes of ARF in this population are dehydration and acute tubular necrosis (ATN). A study of kidney biopsy specimens in HIV-infected patients with severe ARF not thought to be due to pre-renal causes or ATN reported the following distribution of renal lesions: 53% hemolytic uremic syndrome; 40% ATN either of ischemic-toxic origin or due to rhabdomyolysis; 26% obstructive renal failure that was either extrinsic, drug-induced ; 23% HIV-associated nephropathy; 3% acute interstitial nephritis; and 6% various glomerulonephritides.

Common causes of **ATN** include sepsis, hypotension, and medications commonly used in the treatment of HIV-related infections such as aminoglycosides, pentamidine, acyclovir, foscarnet, amphotericin, tenofovir, adefovir, and cidofovir.

Acute interstitial nephritis has been found in 13% of autopsies done in patients with renal dysfunction, and an inciting agent is usually not identified. Nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole, and rifampin are often used in HIV-infected patients and are known to cause acute interstitial nephritis. In addition, there have been case reports of interstitial nephritis in patients taking indinavir or ritonavir.

Obstruction should also be considered as a cause of ARF. Sulfadiazine crystal formation causing tubular obstruction, and sulfadiazine stones causing ureteral obstruction, have been reported in volume-depleted, HIV-infected patients. Acyclovir can also cause crystalluria and ARF, and dose adjustments should be made in patients with preexisting chronic kidney disease to avoid neurotoxicity.

Roughly 4% of patients receiving the protease inhibitor indinavir may develop nephrolithiasis. Symptomatic urinary tract disease, including nephrolithiasis with renal colic, flank pain without evidence of stones, dysuria, or urgency, has occurred in 8% of patients taking the drug. Asymptomatic indinavir crystalluria is found in 20% of patients and leukocyturia in 25-35% of patients receiving indinavir at the normal dose, and the drug should not be discontinued for asymptomatic crystalluria .

➢ GLOMERULAR RENAL DISEASE

HIV ASSOCIATED NEPHROPATHY

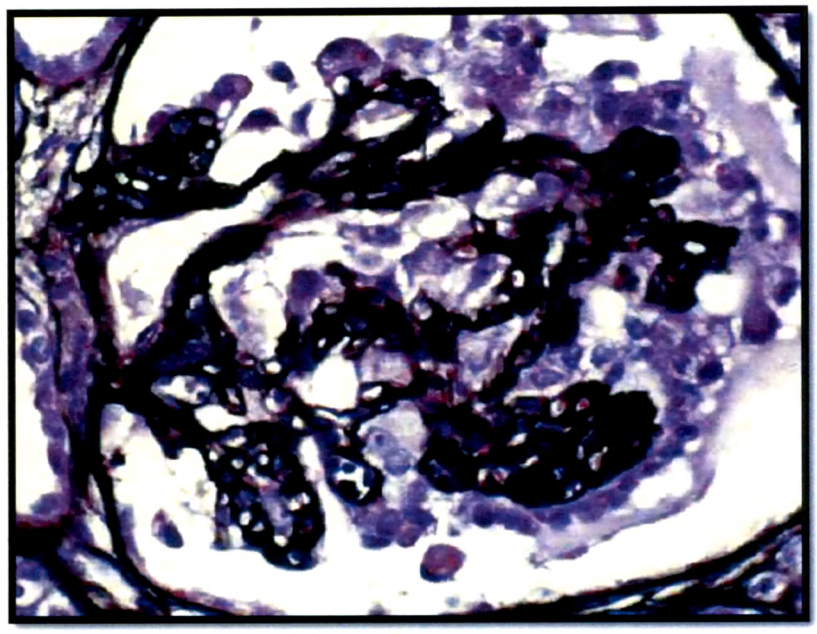
Diagnosis

HIV-associated nephropathy (HIVAN), formerly known as AIDS-associated nephropathy, is characterized by the following findings:

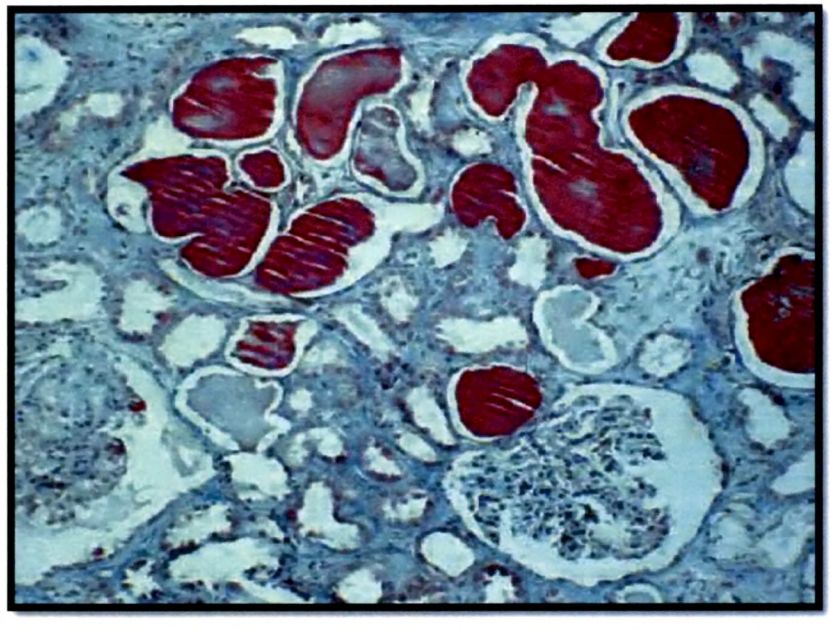
- Nephrotic range proteinuria (Urine dipstick for protein above 1+ or a urinary protein creatinine clearance ratio greater than 0.1 for more than 2 months without acute infection)
- Azotemia
- Enlarged kidneys on ultrasonographic images
- Normal pressure
- Focal segmental glomerulosclerosis (FSGS) on renal biopsy findings

Histopathology

HIVAN is associated with characteristic glomerular, tubulointerstitial, and ultrastructural lesions. The most consistent findings include collapsing focal segmental glomerular sclerosis, cystic tubular dilatation, interstitial edema, cellular infiltrates, and dilated tubules filled with pale-staining amorphous casts. Immunofluorescence is nonspecific. Electron microscopy often reveals tubuloreticular inclusions in endothelial cells, and nuclear bodies also are noted frequently. The ultrastructural changes are not unique to HIVAN, as they are also seen in idiopathic focal segmental glomerulosclerosis, heroin nephropathy, and as a rare complication of bisphosphonate therapy.



Glomerulus from a patient with HIV nephropathy. There is absence of capillary loops, the collapse of matrix with no adhesions (even though there is global sclerosis), and very conspicuous hypertrophied epithelial cell



This section shown in the trichrome stained section , there is microscystic dilation of tubules.

Pathogenesis

The pathogenesis of HIVAN has been studied intensely over the past 15 years, and the accumulated data in humans and animal models provide substantial evidence that HIVAN is caused by direct HIV infection in renal tissue. Early studies using in situ hybridization to a cDNA nucleic acid probe found the HIV genome in tubular and glomerular epithelial cells in patients with HIVAN. Patients with immune-mediated glomerulonephritis and HIV-infected patients with no renal disease had less cellular involvement. More sensitive polymerase chain reaction (PCR) techniques detected DNA from the HIV genome in all renal cell types except interstitial cells in HIV-infected patients with proteinuria, but the HIV DNA was also present in kidney tissue from HIV-infected patients without renal disease.

The important role of HIV viral products in the pathogenesis of HIVAN has been demonstrated in studies using transgenic mice containing a noninfective HIV construct encoding the envelope glycoproteins gp41 and gp120 but lacking the gag and pol genes. These mice develop a renal syndrome closely resembling HIVAN.This transgenic mouse model was also used to confirm that the renal disease develops from factors intrinsic to the kidney vs systemic factors related to HIV infection.In this study, kidneys were cross-transplanted between normal and transgenic mice. HIVAN then developed in the transgenic kidneys transplanted into the nontransgenic littermates, whereas the normal kidneys remained disease free when transplanted into the transgenic littermates. This study provided evidence that HIVAN is caused by a direct effect of HIV gene expression rather than the systemic effects of HIV infection. This model also demonstrated that the HIV transgene is expressed in renal glomerular and tubular epithelial cells, and

that transgene expression in renal epithelial cells was required for the development of the HIVAN phenotype.

Several studies have failed to demonstrate renal expression of CD4 and chemokine coreceptors required for HIV entry into cells. Therefore, the mechanism for HIV infection of the kidney remains elusive. However, studies in humans have confirmed the presence of HIV in renal epithelial cells and the ability of HIV to generate full-length mRNA in the kidney. The kidney also appears to be a reservoir for HIV. Despite undetectable viral levels in the serum, a case report described a patient who continued to express HIV in renal epithelial cells as determined by RNA in situ hybridization. Active replication of HIV may occur in renal epithelium despite well-controlled HIV infection, possibly producing HIV strains in the kidney microenvironment that differ from HIV circulating in the blood. This suggests that the kidney may serve as a viral reservoir harboring HIV strains that have evolved under tissue-specific selection pressures.

Clinical Course and Treatment

In the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents , the U.S. Department of Health and Human Services now includes a diagnosis of HIVAN as an indication for ART, regardless of CD4 count. Other treatment options that may influence the course of HIVAN include angiotensin-converting enzyme inhibitors (ACEIs) and corticosteroids administered before dialysis or kidney transplantation.

Antiretroviral Therapy

The original case reports of HIVAN described a rapid and inexorable progression to End stage renal disease(ESRD) over a period of weeks to months. However, after highly active ART came into use, several dramatic reports of renal recovery among these patients emerged in the medical literature. In one study, a patient with HIVAN and dialysis-dependent renal failure became dialysis free after 15 weeks of ART. Repeat renal biopsy revealed significant histologic recovery from fibrosis with only infrequent glomeruli showing mild collapse and minimal fibrosis. Since then, a growing number of studies has helped establish ART as a first-line treatment for HIVAN.

The effect of ART on kidney disease progression has been characterized primarily by observational studies. A cohort of 53 patients with biopsy-proven HIVAN from the Johns Hopkins renal clinic was found to have better renal survival when treated with ART compared with patients who did not receive ART (adjusted hazard ratio: 0.30; 95% CI: 0.09-0.98).

Angiotensin-Converting Enzyme Inhibitors

Both ACEIs and angiotensin II receptor blockade have inhibited the development and progression of HIVAN in animal models.Two prospective studies support the use of ACEI for the treatment of HIVAN.

Steroids

Evidence supporting the use of steroids for the treatment of HIVAN is also based on observational data. The use of steroids should be considered for patients with a documented rapid deterioration in kidney function despite ART