INTRODUCTION

On the cusp of the fourth decade of the acquired immunodeficiency syndrome (AIDS) epidemic, the world has turned the corner; it has halted and begun to reverse the spread of human immunodeficiency virus (HIV). The question remains how quickly the response can chart a new course towards United National AIDS(UNAIDS)' vision of zero discrimination, zero new HIV infections, and zero AIDS-related deaths through universal access to effective HIV prevention, treatment, care and support. [1]

Morphology and Characteristics:

HIV is a retrovirus in the Retroviridae family, Lentivirus genus. It is enveloped, diploid, single-stranded, positive-sense RNA viruses with a DNA intermediate that causes AIDS. [2] Projecting from the envelope 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.[3]

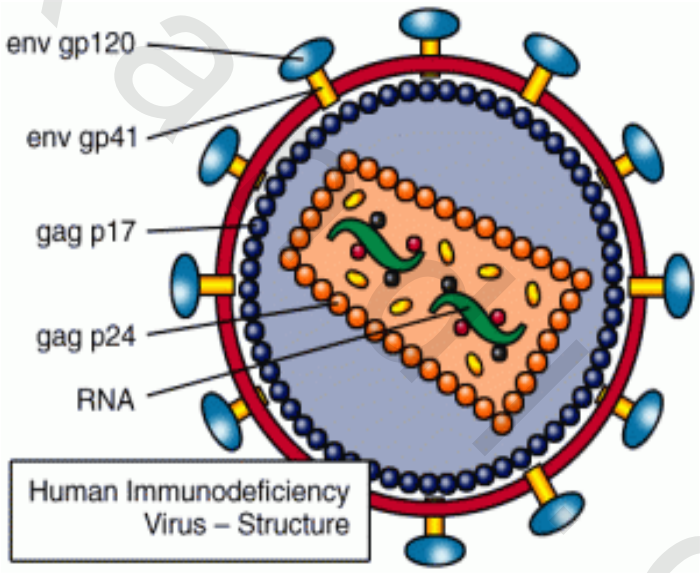

Figure (1): HIV structure. [3]

HIV divided into two major types, HIV type 1 (HIV-1) and HIV type 2 (HIV-2). [4] HIV-1 subdivided into different groups (M, O and N) and genetic subtypes. Nine subtypes are currently recognized for group M (A–K), with numerous subtypes (e.g. A1–A4) and circulating recombinant forms (e.g. CRF01_AE).[5][6]Each of these tends to be associated with a particular geographical area with less strong associations for transmission categories, rate of progression and resistance patterns. [7] HIV-2 infection differs from HIV-1 in being inherently resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and patients have lower viral loads, slower CD4 decline, lower rates of vertical transmission and 12-fold slower progression to AIDS. [8]

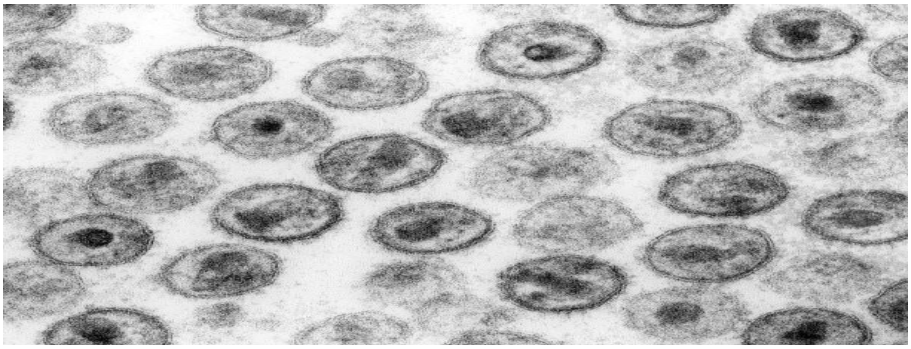

Figure (2): HIV as viewed by electron microscopy. [9]

Epidemiology:

International statistics

The AIDS epidemic is one of the most destructive health crises of modern times, ravaging families and communities throughout the world.[10] Globally, World Health Organization (WHO) and UNAIDS have estimated 35.3 (32.2–38.8) million people were living with HIV in 2013, an increase from previous years as more people are receiving the life- saving antiretroviral therapy. There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2013, down from 2.3 (2.1–2.6) million in 2005[11].

Most infection occurs in low-income countries. HIV/AIDS continued to be the leading cause of death in sub-Saharan Africa and the fourth leading cause of death worldwide. Given the nature of the epidemic and the low coverage of antiretroviral therapy (ART) in developing countries, mortality has been increasing in the past 5 years.[12]

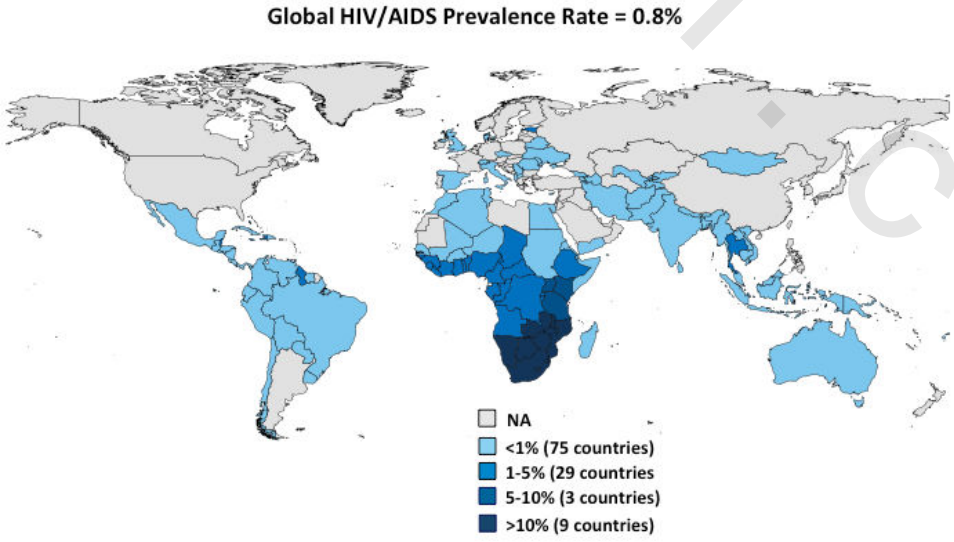

Figure (3): Adult HIV prevalence rate, 2013.[13]

HIV in Egypt:

Egypt is not spared the consequences of HIV/AIDS epidemic although still considered a low prevalence country, yet the number of discovered HIV positive persons on the increase. Egypt has low HIV prevalence among the general population (below 0.02 %) with a concentrated epidemic among men having sex with men (MSM)) (Cairo 5.4% and Alex 6.9%) and injecting drug users (IDUs)(Cairo 7.7% and Alex 6.7%) as detected by the latest biological/behavioral surveillance survey completed in 2010. [14]

HIV and AIDS estimates (2013) [15]

Number of people living with HIV	6,500 [4,300 - 10,000]
Adults aged 15 to 49 prevalence rate	<0.1% [<0.1% - <0.1%]
Adults aged 15 and up living with HIV	6,300 [4,100 - 9,900]
Women aged 15 and up living with HIV	1,400 [<1,000 - 2,100]
Children aged 0 to 14 living with HIV	N/A
Deaths due to AIDS	<500 [<200 - <1,000]

Modes of Transmission:

The transmission of HIV is a function both of where the virus appears in the body and how it is shed. The presence of HIV in genital secretions and in blood, and to a lesser extent breast milk, is significant for spread of HIV. However, the appearance of HIV in saliva [16], urine, tears, and sweat is of no major clinical or social importance, as transmission of HIV through these fluids does not routinely occur, primarily because of the low concentration of HIV in these fluids[17]. Though infectious particles of HIV are frequent in cerebrospinal fluid, contact with this fluid in daily life is extremely rare.[18]

1) **Sexual transmission:** HIV is primarily a sexually transmissible disease. Homosexual, bisexual, and heterosexual transmission all can occur.[19] Worldwide, heterosexual transmission accounts for the majority of cases of HIV infection.[20] The risk of transmission influenced by factors such as multiple partners, co-existent other sexually transmitted infections [21], genetic factors, male circumcision,[22] and stage of HIV disease. [23]

2) **Parenteral transmission:** Parenteral exposure to blood and blood products is the most highly efficient method of HIV transmission—from 67% to over 90%.[24,25] The primary risk group for HIV transmission via blood exposure is IUD sharing infected needles. Less common practices of blood co-mingling, or use of instruments such as tattoo needles not properly disinfected, also carries a potential risk for HIV infection. Health care workers with percutaneous exposures to HIV-containing blood have an average rate of infection of only 0.3%.[25-27] In recent years, the estimated risk of infection due to blood or blood products transfusion has decreased sharply because improvements in test sensitivity have reduced infectious window periods.[28]

3) **Mother to child transmission:** HIV infection can also be acquired as a congenital infection perinatally or in infancy through breast milk. In the absence of breast-feeding, intrauterine transmission accounts for 25 to 40% of infection.[29] Breast-feeding substantially increases the risk of HIV transmission from mother to child to be at least 16% and prolonged breast-feeding nearly doubles the overall infant HIV infection rate and in 29% with acute maternal HIV infection. [30]

Pathophysiology:

The HIV life cycle is complex. [31] In the early steps, HIV gains access to cells without causing immediate lethal damages but the entry process can stimulate intracellular signal cascades, which in turn might facilitate viral replication.[32,33] The two molecules on the HIV envelope, the external glycoprotein (gp120) and the transmembrane protein (gp41), form the spikes on the virion's surface.[34] During the entry process, gp120 attaches to the cell membrane firstly by binding to the CD4 receptor. Subsequent interactions between virus and chemokine co-receptors (eg, CCR5, CXCR4) trigger irreversible conformational changes.[34,35] The actual fusion event takes place within minutes by pore formation[35,36] followed by releases the viral core into the cell cytoplasm. After the core disassembles, the viral genome is reverse transcribed into DNA by the virus' own reverse transcriptase enzyme.[31] Related yet distinct viral variants can be generated during this process since reverse transcriptase is inherently error-prone, resulting in a high rate of HIV mutation, which can rapidly lead to viral resistance in those on treatment. Once integrated into the cellular DNA the provirus resides in the nucleus of infected cells and can remain quiescent for extended periods of time. [31]

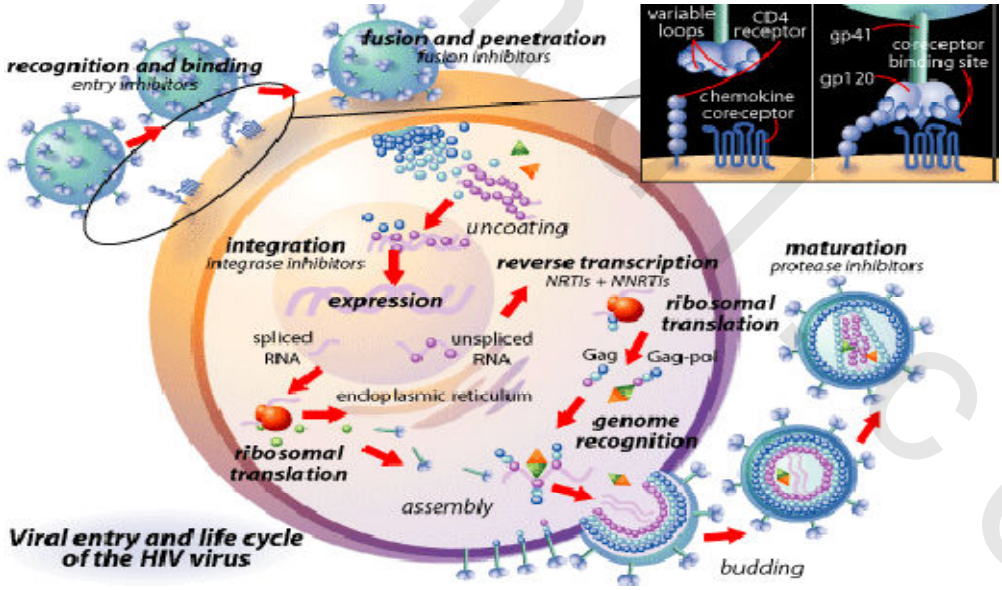

Figure (4): The life cycle of HIV and its mechanism of infection. [7]

Within a few weeks of infection there is initial peak of plasma viremia reaches 10^5–10^7 copies per milliliter, lasts approximately 2–3 weeks, and then drops to a steady state level of viral replication, "viral set point" within 4–6 months after infection. The rate of viral RNA decline and the viral RNA in plasma vary among infected individuals in a wide range.[37] The immune control is thought to be dependent on killer T cells and neutralising

antibodies. Depending on how effective this control is, the viral load is known as the set point and this is thought to be prognostic of natural history outcomes for the infected person. Infection by HIV is characterized by several effects on the host immune system. B cells decline in number and function and, because of the toxicity of HIV antigens, cytokine regulation is distorted causing a decrease in CD4+ T-cells. [38]

Natural history

The typical course of HIV infection can be described in three phases:

1) The primary infection phase, which is associated with a massive increase in viral load followed by a decrease to a viral load set-point following the initiation of antiviral immune responses.

2) the asymptomatic or chronic phase, which is associated with a gradual increase in viral load from primary infection set-point concurrent with a gradual, but irreversible decrease in CD4 T-cell numbers.

3) The symptomatic phase or AIDS, associated with the terminal failure of the immune system and disease. [39,40]

On average, there is a period of 8 to 10 years from initial infection to clinical AIDS in adults, though AIDS may be manifested in less than two years or be delayed in onset beyond 10 years. About 10% of persons will rapidly progress to AIDS in 2 to 3 years following HIV infection, while about 10% have not progressed to AIDS even after 10 years. [41]

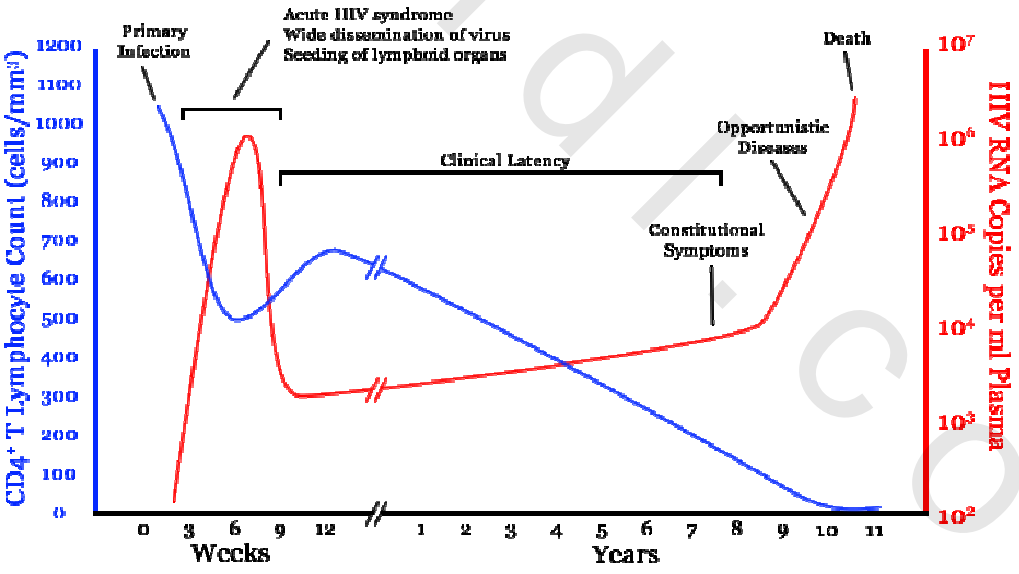

Figure (5): Timeline of CD4 T-cell and viral-load changes over time in untreated human immunodeficiency virus (HIV) infection. [42,43]

Clinical manifestations:

HIV infection is characterized by three phases;

1) **Primary HIV infection**: defined as the time period from initial infection with HIV to the development of an antibody response. The acute viral syndrome of primary HIV infection (sometimes referred to as "seroconversion illness") with symptoms resembling those of mononucleosis appear within days to weeks following exposure to HIV. Symptoms may be mild or severe and may last from a few days to several weeks, with the average duration being 14 days. The most common presenting symptom is fever, seen in over 75% of patients. Other commonly reported symptoms include fatigue, lymphadenopathy, headache, and rash. The rash, which is present in 40-80% of cases, is maculopapular in character and involves the trunk. [44,45] Primary HIV infection in children is usually accompanied by one or more of the following: mononucleosis-like syndrome, dermatitis, or generalized lymphadenopathy. [46]

2) **Clinical asymptomatic:** The HIV infection then becomes clinically "latent." During this phase, the infected persons appear in good health, can be variable--from as short as 18 months to over 15 years. This latent period lasts, on average, from 8 to 10 years**.**

3) **Clinical AIDS:** The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/mm^3 (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. [47]

HIV Classification: CDC and WHO Staging Systems.[47]

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and for providing 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 WHO Clinical Staging and Disease Classification System.

CDC Classification System for HIV Infection

The CDC disease staging system assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. (see Table 1).

Table (I) CDC Classification System for HIV-Infected Adults and Adolescents

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) 200-499 cells/µL	A2	B2	C2
(3) <200cells/µL	A3	B3	C3

*** Category B:** HIV infection with symptoms that are directly attributable to HIV infection (or a defect in T-cell–mediated immunity) or that are complicated by HIV infection. These include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)

- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving two or more episodes or at least one dermatome
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5ºC) or diarrhea lasting >1 month
- Peripheral neuropathy

#Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis, esophageal, bronchi, trachea, or lungs
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- HIV Encephalopathy
- Herpes simplex: chronic ulcers (>1 month), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- Mycobacterium avium complex (MAC) or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis(TB), 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 caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for ≥1 month) or chronic weakness and documented fever for ≥1 month[47]

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

The WHO classification based on the clinical assessment of the HIV/AIDS patients.

Table (II): WHO Clinical Staging of HIV/AIDS for Adults and Adolescents[48]

Primary HIV Infection
• Asymptomatic • Acute retroviral syndrome
Clinical Stage 1
• Asymptomatic

• Persistent generalized lymphadenopathy
Clinical Stage 2
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrheic dermatitis • Fungal nail infections
Clinical Stage 3
• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) • Persistent oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/µL) • Chronic thrombocytopenia (platelets <50,000 cells/µL)

Table (II): cont,

Clinical Stage 4
• HIV wasting syndrome, as defined by the CDC (see Table 1, above) • *Pneumocystis* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) • Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma

- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal *Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Opportunistic infections

All HIV-infected persons are at risk for illness and death from opportunistic infections and neoplastic complications as a consequence of the inevitable manifestations of AIDS. [49]

In the following review the most imported opportunistic infection and neoplastic lesion will be highlighted.

Candidiasis

Epidemiology

Oropharyngeal candidiasis is (OPC) the most commonly reported opportunistic infection observed in HIV/AIDS patients. The majority of infection is caused by *Candida albicans*. In this setting, *C. albicans* resistance has been accompanied by a gradual emergence of non-albicans Candida species, particularly *C. glabrata*, as a cause of refractory mucosal candidiasis, particularly in patients with advanced immunosuppression.[50] The occurrence of oropharyngeal candidiasis is recognized as an indicator of immune suppression, and these are most often observed in patients with CD4+ counts <200 cells/mm^3. [51,52]

Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular chelosis is also noted on occasion and might be caused by Candida.[53]

Diagnosis

Diagnosis of oropharyngeal candidiasis is usually clinical and based on the appearance of lesions. If laboratory confirmation is required, a scraping for microscopic examination for yeast forms using gram stain or a potassium hydroxide (KOH) preparation provides supportive diagnostic information. Cultures of clinical material identify the species of yeast present.[54]

Prophylaxis:

Candida organisms are common commensals on mucosal surfaces in healthy persons.[55] No measures are available to reduce exposure to these fungi. fluconazole can reduce the risk for mucosal candidiasis among patients with advanced HIV disease. However, routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable mortality, ART reduces the frequency of mucosal candidiasis. Refractory cases of mucosal candidiasis typically resolve when immunity improves in response to ART. [56,57]

Treatment: [58]

Oral Therapy*:*

1. Fluconazole 100 mg PO once daily for 14 days[59] or single dose of 750 mg. [60]
2. Itraconazole oral solution 200 mg PO daily, *or*
3. Posaconazole oral solution 400 mg PO BID once, then 400 mg daily**.** [61]

Topical Therapy:

1. Clotrimazole troches 10 mg PO 5 times daily, or
2. Miconazole mucoadhesive buccal tablet 50 mg: Apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet).[62]
3. Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily**.** [58]

Mycobacterium tuberculosis

Epidemiology

WHO estimates that TB is the cause of death for 13% of persons with AIDS.[63] TB disease can develop immediately after exposure (primary disease) or after reactivation of latent TB infection (LTBI) (reactivation disease). Primary disease accounts for one third or more of cases of TB disease in HIV-infected populations. Unlike other AIDS-related OIs, CD4+ count is not a reliable predictor of increased risk for TB disease in HIV-infected persons.[64]

Clinical Manifestations

Persons with LTBI are asymptomatic and are not infectious. The presentation of active TB disease is influenced by the degree of immunodeficiency.(65) CD4 cell counts >350 cells/mm3, HIV-related TB clinically resembles the disease seen in HIV-uninfected patients. Most patients have disease limited to the lungs, and common chest radiographic manifestations include upper lobe fibro nodular infiltrates with or without cavitations'. Extra pulmonary disease is more common in HIV infected individuals than in those who are uninfected, regardless of CD4 cell counts, although clinical manifestations are not substantially different from those described in HIV-uninfected individuals. TB must be considered in disease processes involving any site in the body, but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.(66,67)

In patients with advanced HIV disease, the chest radiographic findings of pulmonary TB are markedly different than those in patients with less severe immunosuppression. Lower lobe, middle lobe, interstitial, and miliary infiltrates are common and cavitation is less common. Intrathoracic lymphadenopathy is common, with mediastinal involvement seen more often than hilar adenopathy. Even with normal chest radiographs, patients with HIV infection and pulmonary TB may test positive on acid-fast bacilli (AFB) sputum smears and cultures, particularly if they have cervical node involvement.(67,68)

The greater the degree of immunodeficiency, the higher the likelihood of extrapulmonary TB, such as lymphadenitis; pleuritis; pericarditis; and meningitis, all with or without pulmonary involvement, and in most TB patients with CD4 cell counts <200 cells/mm^3 TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.(67)

Histopathological findings also are affected by the degree of immunodeficiency. Patients with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or may be completely absent.(69)

After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection.(70,71)

Diagnosis

Diagnosis of Latent Tuberculosis Infection (LTBI)

Testing for LTBI at the time of HIV diagnosis should be routine .Diagnosis of LTBI can be accomplished with one of two approaches: (71-73)

1- Tuberculin skin test (TST) (positive ≥5 mm of induration at 48–72 hours).

2- Interferon-gamma release assays (IGRAs) for detection of LTBI. Current evidence suggests that IGRAs have higher specificity (92%–97%) than TST (56%–95%). (74)

Diagnosis of Active Tuberculosis

The evaluation of suspected HIV-related TB should include a chest radiograph.

Sputum samples for AFB smear and culture should be obtained from patients with pulmonary symptoms and chest radiographic abnormalities. A normal chest radiograph does not exclude the possibility of active pulmonary TB when suspicion for disease is high, sputum samples should be obtained. Obtaining three unique specimens, preferably in the morning of different days, increases the yield for both smear and culture. [68,75]

Prophylaxis:

Indications:

a. Screening tests for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB.

b. Close contact with a person with infectious TB, regardless of screening test result.

Preferred Therapy (Duration of Therapy = 9 Months):

a. Isoniazid (INH) 300 mg PO daily + pyridoxine 25 mg PO daily[76] or

b. INH 900 mg PO BIW (by directly observe therapy DOT) + pyridoxine 25 mg PO daily[77]

Alternative Therapies:

a. Rifampin (RIF) 600 mg PO daily x 4 months[78] or

b. Rifabutin (RFB)(dose adjusted based on concomitant ART) x 4 months

Treatment of active TB:

- Empiric treatment should be initiated in HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB.
- DOT is recommended for all patients requiring treatment for HIV-related TB.

1. Intensive Phase (2 Months)

a. Daily therapy (5–7 days per week) given DOT.
b. INH + (RIF or RFB) + pyrazinamide (PZA), ethambutol (EMB); if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

2. Continuation Phase (For Drug Susceptible TB)

a. INH + (RIF or RFB) daily (5–7 days per week) or TIW [79][80][81]

3. Total Duration of Therapy:

a. Pulmonary, drug-susceptible TB—6 months
b. Pulmonary TB & positive culture at 2 months of TB treatment—9 months
c. The total duration of therapy should be based on number of doses received, not on calendar time. [82]

4. For Drug-Resistant TB

a. Empiric Therapy for Suspected Resistance to Rifamycin +/- Resistance to Other Drugs: INH + (RIF or RFB) + PZA + EMB + (moxifloxacin or levofloxacin) + (an aminoglycoside or capreomycin)
b. Therapy should be modified based on drug susceptibility results
   - Resistant to INH: (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months
   - Resistant to Rifamycins +/- Other Antimycobacterial Agents: Therapy and duration of treatment should be individualized based on drug susceptibility, clinical and microbiological responses.[83]

ART must be started during TB treatment, yet starting ART very early in the course of TB therapy increases pill burden, potential drug toxicity and the risk of TB immune reconstitution inflammatory syndromes (IRIS).[84]

Toxoplasmic Encephalitis

Toxoplasmic encephalitis (TE) is caused by the protozoan Toxoplasma gondii. *Toxoplasma gondii* is an obligate intracellular protozoan of worldwide distribution and is a major opportunistic pathogen in immunocompromised hosts. TE occurs almost due to reactivation of latent tissue cysts. Primary infection occasionally is associated with acute cerebral or disseminated disease.[85,86]

Epidemiology

Seroprevalence of *Toxoplasma* antibodies varies among different geographic locales, with a prevalence of approximately 11% in the United States, versus 50% to 80% in certain European, Latin American, and African countries.[86,87] The advent of HAART has resulted in a reduction in the incidence of CNS disorders especially TE compared with the pre-HAART years in patients with advanced immunosuppression who were seropositive for T. gondii and not receiving prophylaxis with drugs against the disease. Clinical disease is rare among patients with CD4 T lymphocyte (CD4) cell counts >200 cells/ mm^3. Patients with CD4 counts <50 cells/ mm^3 are at greatest risk .Primary infection occurs after ingestion of cysts or oocysts.[88,89]

Clinical Manifestations

Toxoplasmic encephalitis (TE) is the most common cause of focal brain lesion (FBL) in HIV/AIDS individuals with profound immune deficiency. The most common clinical presentation is focal encephalitis with headache, confusion, or motor weakness and fever. Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms. Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement are rare in patients with AIDS. [90,91]

Diagnosis

HIV-infected patients with TE are almost seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies. Anti-toxoplasma immunoglobulin M (IgM) antibodies usually are absent. Quantitative antibody titers are not useful for diagnosis.[92]

Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI and detection of the organism in a clinical sample. Imaging studies of the brain will typically show multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema. Toxoplasmosis also can manifest as a single brain lesion or diffuse encephalitis. MRI has sensitivity superior to that of CT studies for radiological diagnosis of TE. [93]

Detection of the organism requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Lumbar puncture should be performed for T. gondii polymerase chain reaction (PCR). Detection of T. gondii by PCR in CSF has high specificity (96%–100%), but low sensitivity (50%), especially once specific anti-toxoplasma therapy has been started.[93,94]

The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leucoencephalopathy (PML). Less common causes of focal neurologic disease in patients with AIDS include mycobacterial infection (especially TB); fungal infection, such as cryptococcosis, Chagas' disease and pyogenic brain abscess, particularly in IUDs.[93]

Prophylaxis

HIV patient should be tested for IgG antibody to Toxoplasma soon after they are diagnosed with HIV.

A- Indications for Initiating Prophylaxis:

- Toxoplasma IgG positive patients with CD4 count <100 cells/mm3
- Toxoplasma seronegative patients should have toxoplasma serology retested
- If CD4 count declines to <100cells/mm3 for seroconversion.

1. **Preferred Regimen**: TMP-SMX 1 DS PO daily

2. **Alternative Regimens***:*
   a. TMP-SMX 1 DS PO TIW, *or* TMP-SMX SS PO daily, *or*
   b. Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, *or*
   c. (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, *or*
   d. Atovaquone 1500 mg PO daily, *or*
   e. (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily

B- Indication for Discontinuing Primary Prophylaxis*:*

- CD4 count >200 cells/mm^3 for >3 months in response to ART**.**

Treating Toxoplasma gondii Encephalitis

1. **Preferred Regimen**:

   a. Pyrimethamine 200 mg PO once, followed by dose based on body weight:

   b. Body weight ≤60 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

   c. Body weight >60 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

2. **Alternative Regimens**:

   a. Pyrimethamine plus leucovorin plus clindamycin 600 mg IV or PO q6h; *or*

   b. TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO)

Chronic infectious Diarrhea:

Diarrhea remains a common problem in HIV infected patients despite HAART. Gastrointestinal opportunistic infections are common causes of diarrhea in patients with advanced AIDS and are caused by a variety of definable pathogens typically occurring in HIV-infected patients with CD4+ counts <200 cells/ mm^3. However, diarrhea may affect patients at all stages of HIV infection and have multiple causes, including noninfectious causes such as HAART, HIV enteropathy, HIV-associated malignancies, and pancreatitis.[95,96]

A wide range of pathogens may give rise to diarrhea, including bacteria, viruses, mycobacteria and parasites, which involving the small and/or the large bowel. Classical parasites in HIV/AIDS include *Cryptosporidium parvum, Isospora belli, Microspora spp, Cyclosora spp, Entamoeba histolytica and Giardia lamblia*.[97]

Systemic infections could occur when the pathogen disseminates from the gut, as in some cases of bacterial infections e.g. Salmonella. [98]

The most common cause of chronic diarrhea among patients with AIDS is infection with *Cryptosporidium parvum*.[99,100] Clinically, HIV Patients with cryptosporidiosis may be asymptomatic or have profuse, cholera-like watery diarrhea, weight loss, abdominal pain, nausea, and vomiting. Fever is present in approximately one-third of patients and malabsorption is common.[101,102] The diagnosis of cryptosporidiosis is made with microscopic identification of the oocysts in stool or tissue with acid-fast stains or direct immunofluorescence is considered as gold standard for stool examination. Antigen-detection by ElIZA is useful, with sensitivity reported ranging from 66% to 100%. Molecular methods such as PCR are even more sensitive. Cryptosporidium is confined to the brush border of enterocyte.[103] As there is no specific treatment the main stay of treatment is by initiation or optimizing ART for immune restoration and elevation of CD4 count >100 cells/mm^3.[104]

In the pre ART era, reported prevalence rates of microsporidiosis varied between 2% and 70% among HIV-infected patients with diarrhea, but incidence of microsporidiosis has

declined with the widespread use of effective ART.[101] Clinically, patients with microsporidiosis have profuse watery diarrhea, weight loss, and abdominal pain, but no fever or loss of appetite.[102] The diagnosis of microsporidiosis is made by stool examination with chromotrope and chemofluorescent stains and they are often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy may be useful.[103] as no specific treatment is available,therefore treatment with ART enables a patient's own defenses to eradicate *microsporidia*, and immune restoration (an increase in CD4 count to >100 cells/ mm^3).[104]

Isosporiasis is a chronic diarrheal illness in AIDS patients, caused by the protozoan *Isospora belli*.[105] It occurs worldwide but predominantly in tropical and subtropical regions.[106] Infection with I. belli may be asymptomatic or expressed as a mild self-limiting diarrhea lasting for 6 weeks to 6 months or as a Persistent diarrhoea indistinguishable from that caused by *Microsporidia spp and C. parvum*. Vomiting, headache, fever and malaise may also be present and dehydration follows when diarrhea is severe. In AIDS cases, extraintestinal infections can occur, although they are rare.[102] Diagnosis of isosporiasis can be carried out by the demonstration of I. belli oocysts in stool by wet mount smear examination, formalin-ether concentration methods or acid fast stain. With acid fast stain, oocysts appear red in colour. It is quite possible to have a positive biopsy but it is not easy recover the oocysts in the stool because of the small number of the organisms present. A highly sensitive and specific method for diagnosis is PCR. [103]

Cyclospora cayetanensis is a coccidian protozoan most commonly found in developing regions of the world. However outbreaks of cyclosporiasis have been reported from North America and Europe.[101] Generally, patients are presented with a rapid-onset, self-limiting diarrhea. With progressive immune suppression ($CD4^+$ T cell counts of <200 cells/ mm^3in HIV-infected individuals) prolonged carriage occurs, resulting in frequent severe relapses which may last from 4 to 7 weeks.[104] Diagnosis of *Cyclospora* oocysts in stool samples is carried with special stains such as modified acid-fast auramine or modified iron-hematoxylin. Other methods used are autofluorescence under UV epifluorescence and PCR. Histopathological examination of jejunal biopsy specimens from infected individuals showed mild to moderate acute inflammation of the lamina propria and surface epithelial disarray. Cyclosporosis in patients can be treated effectively with a 10-day course of trimethoprim-sulfamethoxazole.[107]

An infection with the following pathogenic enteric parasites generally occurs in both immunocompetent and immunosupressant patients. Although greater rates of carriage of some of these pathogens (i.e., *Entamoeba histolytica*) are associated with HIV-infected patients, this probably reflects the higher opportunity acquisition risk secondary to various sexual practices rather than the immune deficiency per se.[101]

Entamoeba histolytica is a nonflagellated amoeboid protozoan parasite. *Entamoeba* histolytica is an invasive pathogen and the causative agent of amoebiasis, with approximately 50 million cases acquired annually in the developing world.[108] *Entamoeba histolytica* acquisition is via the fecal-oral route. In confined populations e.g. MSM carriage rates are significantly higher than in the general population once the organism has been established secondary to various oral-anal sexual practices.[109] As the risks for HIV acquisition and parasite acquisition in these environments overlap, apparent associations between E. histolytica and immunosuppression exist. However, Entamoeba infection was

found to be more prevalent in HIV-negative than in HIV-positive MSM with diarrhea.[110] Generally, when clinical symptoms develop they are limited to the gastrointestinal tract. However, the likelihood of developing invasive amoebiasis is increased in the presence of HIV infection, with higher rates of amoebic colitis and amoebic liver abscesses reported.[111] The diagnosis can be made by stool examination either wet mount or after being stained by iron hematoxylin or Ziel-Neelsen stain but cannot differentiate between Entamoeba spp so we can use antigen capture and antibody-detecting ELIZA or PCR for differentiation.[112] Drug treatments for amoebiasis include paromomycin, diloxanide furoate, and iodoquinol. These drugs are all effective at treating luminal amoebiasis, although they are ineffective against invasive amoebiasis.[113] Nitroimidazole derivatives such as metronidazole, secnidazole, tinidazole, and ornidazole are effective for treatment of invasive amoebiasis though less effective against luminal disease .For treatment of luminal and extraintestinal amoebiasis, a 5-day course of metronidiazole plus a 10-day course of diloxanide furoate or a 7- to 10-day course of paromomycin for the treatment of invasive amoebiasis.[113,114]

Giardia lamblia is a common flagellated protozoan parasite with a worldwide distribution. Infections occur in both developed and developing regions of the world.[115] An Australian study found that HIV-infected patients were as likely to have Giardia as HIV-negative MSM. This suggests that, sexual practices lead to higher Giardia carriages rates.[116] Symptoms of giardiasis in HIV-infected individuals appear to be similar to those of giardiasis in HIV-negative individuals, with asymptomatic infection occurring commonly in the presence of HIV.[117] With progressive immunosuppression following reduced $CD4^+$ counts, the risk of symptomatic *Giardia* infections is increased. Despite this, giardiasis is not considered a major cause of enteritis in HIV-infected patients. [118] Diagnosis of Giardia infection can be made microscopically by identification of cysts and trophozoites in stained or unstained fecal smears.[97] Antigen assays are 85% to 98% sensitive and 90% to 100% specific.[119] A number of PCR assays are also available for the detection of *Giardia* in stool specimens.[112,120] Giardia infection can be treated with metronidiazole, tinidazole, nitrazoxamide, and ornidazole. [113,121,122]

The spectrum of bacterial pathogens causing diarrhea in HIV-infected patients is similar to the normal host. Rates of Gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population but decline when patients are on ART.[98,123,124] One of the most frequently identified pathogens is Salmonella. The risk of bacterial diarrhea varies according to CD4 count and is greatest in individuals with clinical AIDS and/or <200 CD4 cells/mm^3.[98] Clinically, salmonella may be Self-limited gastroenteritis or severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; and Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal illness. The diagnosis made by stool and blood culture.[125] All HIV-infected patients with salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia in these patients.[126]

Preferred Therapy for Salmonella Gastroenteritis With or Without Bacteremia is Ciprofloxacin.[127] Alternative Therapy: Levofloxacin, Moxifloxacin, Trimethoprim/ sulfamethoxazole, Ceftriaxone and Cefotaxime

Duration of Therapy for Gastro enteritis without Bacteremia

- If CD4 count ≥200 cells/mm^3: 7–14 days
- If CD4 count <200 cells/mm^3: 2–6 weeks[128]

Duration of Therapy for Gastroenteritis with Bacteremia

- If CD4 count ≥200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present)
- If CD4+ count <200 cells/mm^3: 2–6 weeks [93]

Kaposi sarcoma:

Kaposi sarcoma (KS) is the most common malignancy seen in the setting of HIV infection.[129] KS is a connective tissue cancer caused by human herpes virus 8 - now called Kaposi's sarcoma-associated herpesvirus (KSHV).[130] The malignant lesion is characterised by neoplastic cells and abnormally growing blood vessels. The prevalence of KS was as high as 30% among patients with AIDS before the advent of effective antriretroviral therapy (ART). Today the incidence of KS in the United States remains approximately 3-fold higher than before the HIV pandemic, and notably KS incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[131,132] KS is described most frequently among HIV-infected persons with more advanced immunosuppression (CD4 cell counts <200 cells/ mm^3), although they can occur at any CD4 cell count.[133]

Clinical Manifestations

KS manifestations vary widely, Skin lesions may be nodular, papular or blotchy; they may be red, purple, brown or black. Lesions can also be seen under or on mucous membranes, with similar characteristics. The most common sites include the mouth, nose and throat. Usually painless - but may become painful if inflamed or swollen. [134] Intraoral lesions are common and visceral dissemination can occur, occasionally without the presence of skin lesions. Lesions involve internal organs, eg lungs (leading to dyspnoea), gastrointestinal tract (it can cause fatal bleeding) and lymphatics, resulting in lymphoedema.[135]

Diagnosis

The diagnosis can depend on clinical manifestation of characteristics lesions but definitive diagnosis is based on biopsy features with the presence of spindle cells and vascular structures with a characteristic pattern of clefting (vascular slits). Detection of the latency-associated nuclear antigen (LANA) from the virus also confirms the diagnosis.[136-138]

Preventing

Because the strongest risk factor for the development of KS in HIV-positive individuals is a low CD4 cell count, early initiation of ART is likely to be the most effective measure for the prevention of KS.[139]

Treatment

The major treatment goals for Kaposi's sarcoma include symptom palliation, shrinkage of tumour to alleviate oedema, management of organ compromise and psychological stress, prevention of disease progression, and cure. Treatment decisions depend on the presence and extent of symptomatic and extracutaneous sarcoma, the HIV-1 viral load, and the host status (CD4 count and overall medical condition).[136]

HAART:

Most, if not all, patients with Kaposi's sarcoma should receive antiretroviral treatment. Effective antiretroviral regimens are associated with both a reduction in the incidence of AIDS-related sarcoma and a regression in size and number of existing lesions.[136,139]

Local treatment:

For relatively mild and limited KS, local treatment options such as local radiation therapy, cryosurgery, laser surgery, excisional surgery and electrocauterization. Radiotherapy has become the most important therapy in the local treatment of KS. Intralesional injections of vinblastine, vincristine and interferon-alpha (INF-α) have been reported to be effective treatments. The only side-effects were local pain and skin irritation.[140]

Systemic treatment:

For more severe and aggressive KS, systemic chemotherapy with agents such as liposomal anthracyclines (doxorubicin and daunorubicin; first-line) and paclitaxel (second-line) is usually the mainstay of treatment. Other chemotherapeutics include vinorelbine, interferon-a, and interleukin-12.[141]

Effective suppression of HIV replication with ART in HIV-infected patients with KS may prevent KS progression or occurrence of new lesions, and because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS.[93]

The specific Diagnosis for HIV

HIV infection is identified either by the detection of HIV-specific antibodies in serum or plasma or by demonstrating the presence of the virus by nucleic acid detection using PCR , p24 antigen testing or, rarely these days, by growing virus in cell culture. Antibody testing is the method most commonly used to diagnose HIV infection. [142]

For detection of antibody:

A- ELISA: this test is most widely used for screening people with HIV. Because of its high sensitivity, it is suitable for testing large number of samples. [143]

Generation

1. First generation - whole viral lysates
2. Second generation - recombinant antigen

3. Third generation - synthetic peptide

4. Fourth generation - antigen + antibody (Simultaneous detection of HIV antigen and antibody) - HIV duo[144]

Antibody can be detected in a majority of individuals within 6-12 weeks after infection using the earlier generation of assays. But it can be detected within 3-4 weeks when using the newer third generation ELISA. Due to their ability to detect p24 antigen, the fourth-generation ELISA will be of value in detecting early infection. The window period can be shortened to two weeks using p24-antigen assay. As per National HIV testing policy, two ELISA using different principles are required to diagnose HIV infection (in clinical setting). [143]

ELISA tests are usually the first HIV screening tool. A positive ELISA test result is usually observed within 3-6 weeks following infection. Very rarely, antibodies may develop up to 12 weeks after infection. Beyond the window period, ELISA tests are rarely false negative. This means if the patient has a negative test result, and is beyond the window period after the last potential exposure, the test is truly negative. [145]

False-positive ELISA results can occur in the presence of other auto-antibodies, hepatic disease, influenza vaccination and an acute viral infection, as well as from laboratory errors of procedure and specimen handling. For these reasons, positive ELISA results should always be followed by confirmatory tests.[145]

B- Rapid tests

These are tests that can yield results in < 30 min.[146] The results are read by naked eye. When performed correctly, these are accurate and have wide utility in a number of testing situations. Application includes emergency room and smaller blood banks.[147]

Disadvantages:

1- Subjective interpretation

2- Difficult to read if the laboratorian is color blind

Advantages:

1- Rapid HIV assays have proven particularly useful for testing pregnant women in labor who have not received prenatal care.[148]

2- It is helpful in detecting HIV-2 infection which cannot be detected by ELISA.[149]

C- Confirmatory tests:

Western Blot (WB)

It is a more specific assay. In this antibodies against numerous proteins are detected.

1. Env (gp160, gp120, and gp41)
2. gag (p55, p24, and p17)
3. Pol (p66, p51, and p31)

If the sample has antibodies, colored bands will appear wherever human IgG binds to the viral protein on the strip. In the absence of colored bands, WB is interpreted as negative.

Interpretation

- Negative - no bands
- Positive - various criteria
- Intermediate - bands present but doesn't satisfy the criteria[143]

D- Viral Detection:

P24 Antigen, PCR, Virus culture.

Indication

1. Acute HIV infection i.e. during window period.
2. Indeterminate serology
3. Neonatal infection because diagnosis is difficult due to presence of maternal antibodies.

Disadvantage

Repeat tests needed for confirmation
Expensive

P24 Antigen

The antigen test detects HIV free antigen (p24) in the serum. Unfortunately, this test has a low sensitivity and not routinely recommended. The reason for the lack of sensitivity of this test is that the free antigen (p24) in serum may be complexed with p24 antibody. Antigens although transient can appear as early as two weeks after infection and lasts 3-5 months, so this method can shorten the window period by one week.[150]

PCR

In this the target HIV RNA or proviral DNA is amplified enzymatically *in vitro* by chemical reaction. It is an extremely sensitive assay because a single copy of proviral DNA can be amplified. Qualitative PCR is useful for diagnostic purposes. Three different techniques namely RT-PCR, nucleic acid sequence based amplification (NASBA) and branched-DNA (b-DNA) assay have been employed to develop commercial kits. These kits shorten the window period between infection and detectability to about 12 days.[143,146]

MOHP Protocol for HIV Testing

For diagnosis of HIV infection in Egypt, the following steps should be followed:

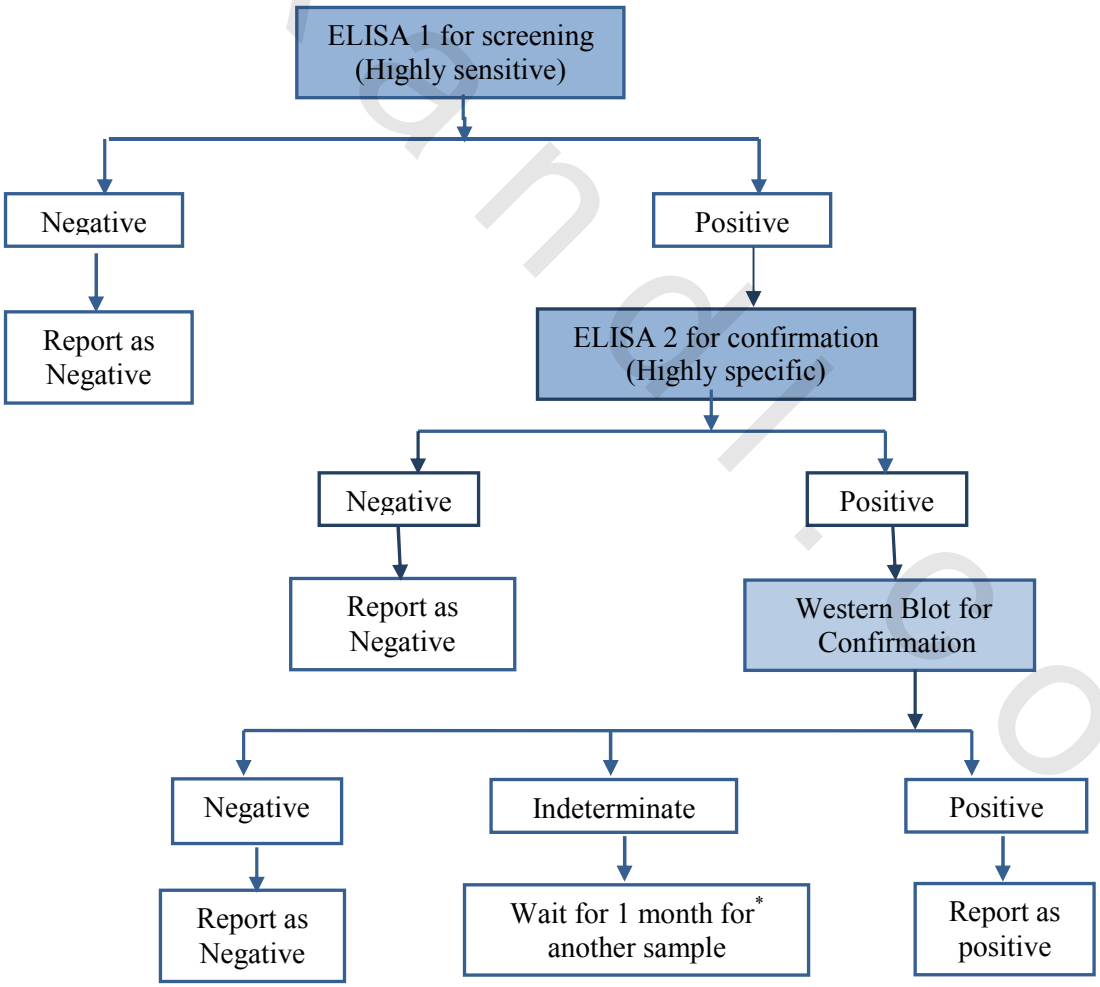

Figure (6): Scheme MOHP Protocol for HIV Testing, * If still indeterminate, repeat after 6 months then after 12 months. If still indeterminate report as negative[151]

Laboratory Testing for Initial Assessment and Monitoring While on ART:

A number of laboratory tests are important for initial evaluation of HIV-infected patients upon entry into care, during follow-up (if ART has not been initiated), and before and after the initiation or modification of therapy to assess virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs.(152)

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of ARV drug regimens: Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN), and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses **,**Fasting blood glucose and serum lipids(152) and Two surrogate markers are routinely used to assess the immune function and level of HIV viremia: CD4 count and plasma HIV RNA (viral load).(153) Resistance testing should be used to guide selection of an ARV regimen, a viral tropism assay should be performed before initiation of a CCR5 antagonist (154) and HLA-B*5701 testing should be performed before initiation of abacavir (ABC). (155)

CD4 T-Cell Count:

CD4 count serves as the major laboratory indicator of immune function in patients who have HIV infection.

- **Use of CD4 Count for Initial Assessment.** The CD4 count is one of the most important factors in determining the urgency of ART initiation and the need for prophylaxis for opportunistic infections. All patients at entry into care should have a baseline CD4 count.(156)

- **Use of CD4 Count for Monitoring Therapeutic Response.** An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50 - 150 cells/mm^3 per year, generally with an accelerated response in the first 3 months of treatment. Subsequent increases in patients with good virologic control average approximately 50 -100 cells/mm^3 per year until a steady state level is reached. Patients who initiate therapy with a low CD4 count or at an older age may have a blunted increase in their counts despite virologic suppression.(157,158)

Frequency of CD4 Count Monitoring.

In untreated patients, CD4 counts should be monitored every 3 to 6 months to determine the urgency of ART initiation. In patients on ART, the CD4 count is used to assess the immunologic response to ART and the need for initiation or discontinuation of prophylaxis for opportunistic infections. The CD4 count response to ART varies widely, but a poor CD4 response is rarely an indication for modifying a virologically suppressive antiretroviral regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 cell count provides limited information, thus, for the patient on a suppressive regimen whose CD4 cell count has increased well above the threshold for opportunistic infection risk, the CD4 count can be measured less frequently than the viral load. In such patients, CD4 count may be monitored every 6 to 12 months, unless there are changes in the patient's clinical status.(157,159,160)

Factors that affect absolute CD4 count.

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4+ T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy or co-infection with human T-lymphotropic virus type I (HTLV-1)[161] may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 count without changing the CD4 percentage. In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.[162]

Management:

ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV disease into a chronic, manageable condition. [163]

The goals of ART include the following:

1. Prolong and improve the quality of life for people living with HIV/AIDS.[164]
2. Restore and preserve immunologic function.[165]
3. Maximally and durably suppress plasma HIV viral load.[166]
4. Prevent HIV transmission.[167]

Table (III): Antiretroviral Groups: [151]

Nucleoside reverse transcriptase Inhibitors (NsRTIs)	Nucleotide reverse transcriptase inhibitors (NtRTIs)	Nonnucleosidereverse transcriptase inhibitors (NNRTIs)	Protease Inhibitors (PIs)	Entry Inhibitors
Zidovudine (ZDV, AZT) Didanosine (ddI) Stavudine (d4T) Lamiduvine (3TC) Abacavir (ABC)	Tenofovir disoproxil fumarate (TDF)	Nevirapine (NVP) Efavirenz (EFZ)	Saquinavir (SQV) Ritonavir (RTV) (as Pharmacoenhancer) Indinavir (IDV) Nelfinavir (NFV) Lopinavir/ritonavir (LPV/r)	T-20

When to start ART:

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level.[167]

Table (IV): Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children according to WHO 2013 recommendation.[168]

Population	Recommendations
Adults and adolescents (≥10 years)	**Initiate ART if CD4 cell count ≤500 cells/mm3** • **As a priority**, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm3
	Initiate ART regardless of WHO clinical stage and CD4 cell count • Active TB disease • HBV coinfection with severe chronic liver disease • Pregnant and breastfeeding women with HIV • HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)
Children ≥5 years Old	**Initiate ART if CD4 cell count ≤500 cells/mm3** • **As a priority**, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm3
	Initiate ART regardless of CD4 cell count • WHO clinical stage 3 or 4 • Active TB disease
Children 1–5 years Old a	**Initiate ART in all regardless of WHO clinical stage and CD4 cell count** • **As a priority**, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤750 cells/mm^3 or <25%, whichever is lower
Infants <1 year old a	**Initiate ART in all infants regardless of WHO clinical stage and CD4 cell count**

What ART regimen to start with (first-line ART)

An initial ARV regimen generally consists of two NRTIs in combination with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an INSTI, or a CCR5 antagonist (namely maraviroc [MVC]). In clinical trials, NNRTI-, PI-, INSTI-, or CCR5 antagonist-based regimens have all resulted in HIV RNA decreases and CD4 cell increases in a large majority of patients.[169-171,173] Using simplified, less toxic and more convenient regimens

as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years.[173,174] For children younger than three years, a PI-based regimen is the preferred approach[168] (Table V).

Table (V): Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children[168]

First-line ART	Preferred first-line Regimens	Alternative first-line Regimens a b
Adults(including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF + 3TC (or FTC) +EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (orNVP)
Children 3 years to less than 10 years and adolescents <35 kg	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC or AZT + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine which ARV regimens should be switched in case of treatment failure. Before 2010, WHO guidelines on ARV recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings.

The 2010 WHO guidelines recommended that countries consider phasing viral load testing to monitor the response to ART and use a viral load threshold above 5000 copies/ml in an adherent person with no other reasons for an elevated viral load (such as drug interactions, poor absorption and undercurrent illness). However, most ARV programs in resource-limited settings still do not have access to viral load testing and continue to rely on clinical and immunological monitoring. The main rationale for recommending viral load monitoring as the preferred approach compared with immunological and clinical monitoring is to provide an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation

of drug-resistance mutations and improving clinical outcomes. Measuring viral load can also help to discriminate between treatment failure and non-adherence.[168]

What ARV regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age.[168]

Table (VI): Summary of preferred second-line ARV regimens for adults, adolescents, pregnant women and children[168]

Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC +LPV/r AZT + 3TC +ATV/r	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	**If a NNRTI-based first-line regimen was used**		ABC + 3TC +LPV/r	ABC + 3TC + LPV/r TDF + 3TC (or FTC) + LPV/r
	If a PI-based First-line regimen was used	**<3 years**	No change from first line regimen in use	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

Prevention:

HIV prevention based on ARV drugs

1- Oral pre-exposure prophylaxis

Oral pre-exposure prophylaxis of HIV (PrEP) is the daily use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of daily oral PrEP have shown evidence of effectiveness with serodiscordant heterosexual couples[175], men and transgender women who have sex with men [176], high risk heterosexual couples [177], and people who inject drugs [178][179]

2- ART for prevention among serodiscordant couples

People with HIV in serodiscordant couples who start ART for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner. HIV-positive partners with a CD4 count ≥350 cells/mm3 in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners.[180]

3- Post-exposure prophylaxis for occupational and non-occupational exposure to HIV

Post-exposure prophylaxis is short-term ART to reduce the likelihood of acquiring HIV infection after potential exposure either occupationally or through sexual intercourse.

Within the health sector, post-exposure prophylaxis should be provided as part of a comprehensive package of universal precautions that reduces the exposure of personnel to infectious hazards at work. The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure. The choice of post-exposure prophylaxis drugs should be based on the country's first-line ART regimen for HIV. A recent recommendation relates specifically to post-exposure prophylaxis in the case of sexual assault. [181]

Management of exposure to HIV

Perform a baseline HIV test on the exposed HCW using a rapid antibody test. It is also recommended to perform a complete blood count (CBC) and liver and renal function tests.

Determine if the exposure is considered low-risk or high-risk for HIV infection.

The following situations are considered high-risk exposure:

- Exposure to a large amount of blood
- Blood coming in contact with cuts and open sores on the skin
- Blood visible on a needle that caused a needle-stick injury
- Exposure to blood from someone who is HIV positive[151]

Table (VII): Post-Exposure Prophylaxis Regimens [151]

Regimen Category	Application	Drug Regimen
Basic	Low risk exposure	4 weeks of both: – Zidovudine 600 mg daily in divided doses (i.e., 300 mg twice daily) and – Lamivudine (150 mg twice daily)
Expanded	High risk exposure	Basic regimen and Nelfinavir 1250 mg twice daily

4- Combination HIV prevention:

People's HIV prevention needs change during their lifetime, and a combination approach helps people to access the types of interventions that best suit their needs at different times. Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of the following.

Other biomedical interventions that reduce HIV risk practices and/or the probability of HIV transmission per contact event, including the following:

- **Male and female condoms**. Male condoms reduce heterosexual transmission by at least 80% and offer 64% protection in anal sex among men who have sex with men [182], if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect [183].

- **Needle and syringe programmes** are highly associated with a reduction in HIV transmission through injecting drug use [184].

- **Opioid substitution therapy with methadone or buprenorphine** is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behavior and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART [185].

- **Voluntary medical male circumcision** reduces acquisition of infection and the risk of acquisition for men by up to 66% and offers significant lifelong protection [186].

Behavioral interventions reduce the frequency of potential transmission events, including the following.

- **Targeted information and education**. Programs that use various communication approaches – for example, school-based sex education, peer counseling and community-level and interpersonal counseling – to disseminate behavioral messages designed to encourage people to reduce behavior that increases the risk of HIV and increase the behavior that is protective.[168]

- **Structural and supportive interventions** affect access to, uptake of and adherence to behavioral and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reform, measures to reduce stigma and discrimination, the promotion of gender equality and prevention of gender-based violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.[168]

Egypt is a country where HIV is of low prevalence among the general population with a concentrated epidemic among high risk population. HIV has high incidence of opportunistic infections among HIV patients. There is insufficient recent data about the incidence of opportunistic infections in HIV patients. Therefore this study was conducted to define clinical presentations of some of the common opportunistic infections i.e. candidiasis, pulmonary TB, toxoplasmic encephalitis, infectious diarrhea and Kaposi sarcoma, and their relation to CD4 count in HIV patients treated in Alexandria Fever Hospital.