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Review Article

Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome: What is the Least a General Medicine Trainee Should Know

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Abstract

Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have been a global health issue in developed countries. It has significant complications that lead to its morbidities and mortality. It has a substantial impact on the quality of life and the health economy. In addition, there is no cure, which makes it a lifelong disease. However, with the advances in healthcare and new medications, the disease can be controlled. HIV is on the rise in Pakistan and isn't a rare disease anymore. There are many factors which can be reasons for this endemic disease, including globalisation and travelling. However, many local factors also contribute to its spread, such as blood transfusions, needle sharing, and IVDU, razors and needle sharing by barbers and quacks respectively, & changing sexual preferences and practices. Therefore, our trainees should know the main points of the disease. The review has avoided going into the molecular or microbiological details of the virus or the disease, as that can distract them from knowing the bare minimum clinically essential information, and it is also beyond the scope of those who are not in ID or Microbiology training.

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Introduction

HIV is on the rise in Pakistan and isn't a rare disease anymore. Therefore, our trainees should know the main points. Due to social stigmata and its consequences, reporting is an issue and exact incidence & prevalence is under reported. Its associated comorbidities need long term follow up and multimodality treatment. HIV is an RNA virus. It has a diploid genome that is composed of two molecules of RNA. From RNA, it makes its DNA (Reverse Transcription). Normally, we make RNA from the DNA (Transcription). This virus makes DNA from its RNA (Reverse Transcription). HIV has three important enzymes, which are important to remember as these are the therapeutic targets.[1] Reverse Transcriptase. It synthesizes dsDNA from viral RNA[2] Integrate the enzyme. This is to integrate the viral genetic material into the human DNA, which will then make viral proteins.[3] Protease Enzyme. This is for the final modification of the viral proteins. The HIV has a capsule that has a lipid bilayer. The capsule has a glycoprotein P24, which is a receptor binder. This glycoprotein-24 is important as it's one of the diagnostic tests for HIV. The receptor for HIV is the CD4 protein present on the T Helper cells and macrophages. Other proteins of the virus are gp 120 & gp 41.[1,2]

PATHOGENESIS OF HIV & AIDS

Mode of transmission

- Sexual Transmission through sexual secretions. The passive partner is at greater risk due to prolonged exposure to the secretions and the likelihood of mucosal injury as well. More common in homosexual men.
- Bloodborne: it's due to transfusions. Also common in IV drug abusers
- Vertical Transmission. A pregnant female may have a chronic disease, and 33 to 50

percent of children get affected if not treated. This percentage is reduced to 10 percent if the mother is treated during pregnancy with HAART.[3,4]

How does HIV decrease CD-4 cell count?

CD-4 T-Cells (also named as Helper T cells) are part of the immune system that decide which limb of the immune system is to be activated, either B cells, T Cells, or both. CD-4 cells are the chief regulators and controllers of the immune system. Reducing the CD-4 cells is the reason for the severe immunodeficiency syndrome. Various stages and the treatment plans for HIV cases are based on the CD-4 cell counts.[3,4]

- HIV enters the CD4 cells and stops all the functions of the CD4 cells by incorporating its nuclear material into the CD4 cell DNA, which is paralysed.
- It also fuses multiple CD4 cells, reducing their number.
- When the virus is about to leave the cell, it causes the cell to rupture, thus further decreasing the CD4 count.

How does HIV virus crosse the blood-brain barrier?

The Virus also binds to Macrophages, thus getting access to multiple tissues. This is known as the Trojan Horse Phenomenon.

Diagnosis of HIV

After a person has been exposed to the virus, it takes 4 to 5 days to be present in the blood. So, the PCR should be done after 1 week.

- Antibodies may appear after 4 to 6 weeks. False positive antibodies of HIV are likely in autoimmune diseases, malignancies causing immune stimulation, some infections, or vaccines. False negative HIV antibodies are possible in the very early stage of the infection (first few weeks) or advanced AIDS when the immune system can't make antibodies.
- P24 is a viral antigen and becomes positive early in the disease course. It's more useful than serology as it becomes positive in 1-2 weeks, but it's not as sensitive as PCR. However, the antigen level may fall during the seroconversion phase. p-24 antigen can also be negative in the early few weeks or with effective HAART therapy suppressing the virus.
- PCR-RNA is more reliable than antibodies or antigens. It becomes positive after a week, and the result is not affected by confounding factors such as immunodeficiency. Quantitative PCR also helps detect viral load.
- HIV & STDs (Sexually Transmitted Diseases): The risk of other STDs also increases, such as Chlamydia, gonorrhoea, HPV, and HCV.[5]

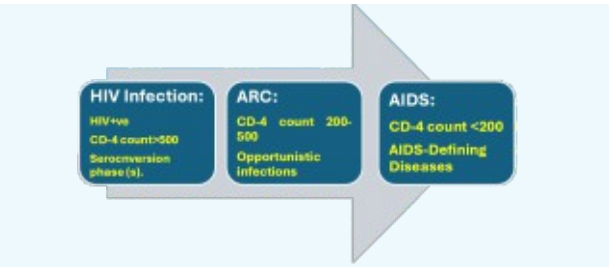
Clinical Manifestations & Disease Course

Seroconversion / acute phase:

1. Seroconversion: Acute response of the body to the virus is an inflammatory response that causes fever, weight loss, anorexia, general lymphadenopathy, mucosal ulceration, and cutaneous ulceration. Viremia is usually suppressed after a few weeks. In the seroconversion phase of some diseases, symptoms appear the same and are due to an inflammatory response.
2. The disease continues to progress unless treated.
3. The patient may have multiple relapses of illness resembling the seroconversion phase due to recurrent fights of the immune system with the replicating virus.
4. The HIV patient then enters ARC (AIDS-related complex) and finally into AIDS.[4,5,6]

CD-4 count & stages of HIV infection

1. HIV positive: The patient has HIV, but the CD-4 count is above 500. Normal CD4 cell count is 500- 1500.
2. ARC (AIDS-Related Complex): HIV: A person with a CD-4 count less than 500 is ARC (AIDS-Related Complex).



Flowsheet showing the natural course of the disease in HIV & AIDS.

AIDS: HIV positive with a CD-4 count of 200 or less is AIDS. It is also AIDS when the AIDS defining diseases start to appear in an HIV positive case (independent of the CD-4 count).[4,5]

Aids-related complex (ARC) & infections: When the CD4 count is between 200 and 500 but less than 500 in a patient with HIV, it's called ARC. This is when the opportunistic infections become prevalent and virulent. [4,5.,6] A few examples of opportunistic or disseminated infections in ARC cases are:

Table 1: *AIDS defining diseases*

Body Part Involved	Diseases
Brain	Cerebral toxoplasmosis, B-cell primary brain lymphoma, HIV encephalitis or HIV related Dementia
Retinal Diseases	CMV retinitis, Toxoplasma chorioretinitis
Lungs	Pneumocystis (PJP) pneumonia
Abdominal Diseases	CMV Colitis, CMV Nephritis, CMV Hepatitis, MAC infections: Ileocolic region infections due to Mycobacterium avium and other atypical mycobacteria, Isospora and microsporia-related chronic diarrhea
Invasive Fungal Infections	Candida in the small gut and brain, Invasive Histoplasmosis
Cancers	Non-Hodgkin Lymphoma, Burkitt Lymphoma, Cervix: Invasive Cervical Cancer, Kaposi's Sarcoma is a sarcoma of blood vessels

- Disseminated Herpes zoster
- Disseminated TB

Aids-defining diseases[8-14]**:** AIDS affects almost all organs of the body. Presence of any of these diseases in anyone with HIV positive is considered to have AIDS (independent of CD-4 count). That's why these are called AIDS-Defining Illnesses: (Positive HIV status is an essential requirement).

Brain Lymphoma, TB & Toxoplasma & AIDS: Toxoplasmosis is a parasitic infection that makes cysts and calcified nodules. It becomes reactivated when immunity is severely low in an AIDS case (CD4 count<100). In immunocompetent individuals, the infection is usually asymptomatic or presents as an acute febrile illness with lymphadenopathy and splenomegaly. B-cell primary brain lymphoma is also common in AIDS patients. Reactivation of pulmonary or extrapulmonary TB is also very common in immunocompromised cases.

- B-cell Lymphoma and Toxoplasmosis affect mainly the periventricular area and form nodules, which are local accumulations of cells. They are deep-seated in the brain and hence taking a biopsy is very difficult.
- Contrast-enhancing CT is used to help in diagnosis, but both the lymphoma and toxoplasma have contrast-enhancing peri-ventricular lesions. ICP may be raised. Toxoplasma causes large (often >2cm in size) multiple lesions in the deeper brain and involves the basal ganglia, thalamus, corticomedullary junction, and peri-ventricular parts of the brain.
- Brain tuberculosis can also cause various contrast-enhancing lesions, which are often larger than 2 cm and also share a similar location. TB recurrence is more common in endemic areas and may have pulmonary lesions as well. TB usually causes irregularly thickened and irregularly enhancing lesions. TB lesions are hypointense on T2 MRI and iso or hypointense on T1 MRI, whereas toxoplasma lesions are often hyperintense on MRI.
- There may be no positive finding in CSF (it is usually bland) as the infection may or may not extend to CSF.
- Treatment for toxoplasmosis is by Pyrimethamine plus Sulfadiazine. Usually, a 3-week trial of this treatment is given: if there is a positive response, then the diagnosis is considered to be Toxoplasmosis. Ninety-five percent are treated effectively. In case there is no response to treatment, then it is most likely B-cell Lymphoma and warrants lesion biopsy.[8,9,10]

Cryptococcal meningitis: Cryptococcus is a yeast (fungi) with a capsule. The main source is the environment, soil, and eucalyptus trees. It causes chronic meningitis, which affects the meninges at the base of the skull. Basal meningeal diseases affect cranial neuropathy & CSF flow may also be blocked through cisterns, which causes Hydrocephalus. Basal meningitis may also affect the Circle of Willis, which is present at the base of the skull, thus causing a stroke, which may be an initial presentation of the disease.

- Cryptococcal pneumonia is also common in these cases.
- Cryptococcal antigen in the CSF and blood is helpful. India-ink stain is used for its capsule.
- Lipophilic Amphotericin B and flucytosine are used initially, and then fluconazole for

oral treatment.[10]

CMV infections in AIDS: CMV reactivation or new infection in AIDS cases is common when the CD-4 count is below 100, or especially when it's below 50.

- CMV causes a capillary endothelial infection, causing ischemic cotton wool spots. There may be retinal exudates, bleeding, or retinal Ischemia. Retinal Toxoplasmosis causes infection of the retina and choroid & toxoplasma cysts may be present in the retina.
- CMV-related Hepatitis, colitis, &/or nephritis are also common. These occur mostly when the CD-4 count is well below 100.

PJP Pneumonia in AIDS:

- PJP. It causes atypical bilateral fungal pneumonia. The interstitium of the alveoli is infected & thickened (interstitial pneumonitis). Because of wall thickening of the alveoli, the oxygen exchange is affected, which leads to high A-a gradient & hypoxemia (low PaO2, low oxygen saturation).
- Hypoxemia: Oxygen saturation doesn't drop below 95% as long as PaO2 is not below 60-80 mm Hg. Therefore, even normal SpO2 doesn't exclude hypoxemia. This fact is based on the Oxygen-Dissociation Curve, which indicates that Hb is 95% saturated at a PaO2 of 60-80 mm Hg. The first thing to change, when oxygen is deficient, is a drop in PaO2. SpO2 below 95% is a marker of hypoxemia. If the hypoxemia is due to alveolar disease or alveolar capillary disease, then the first thing to change is an increase in A-a gradient, even before a drop in PaO2.
- Lung infiltrates may have a wide differential, and the absence of typical clues for infections may delay the diagnosis.
- PJP is a fungal infection. It is stained with silver. It has a saucer plate appearance.
- Prophylaxis & Treatment is sulfamethox-azole-pyrimethamine (Septran, Bactrim). The dose is higher in treatment than that used for prophylaxis.[11,12]

AIDS & abdomen:

- There is often chronic diarrhea & weight loss due to chronic infection of the ileocecal region by MAI, Isospora, etc. Stool culture and intestinal biopsies help in diagnosis.

CMV-related Hepatitis, colitis, &/or nephritis are also common. These occur mostly when the CD-4 count is well below 100.

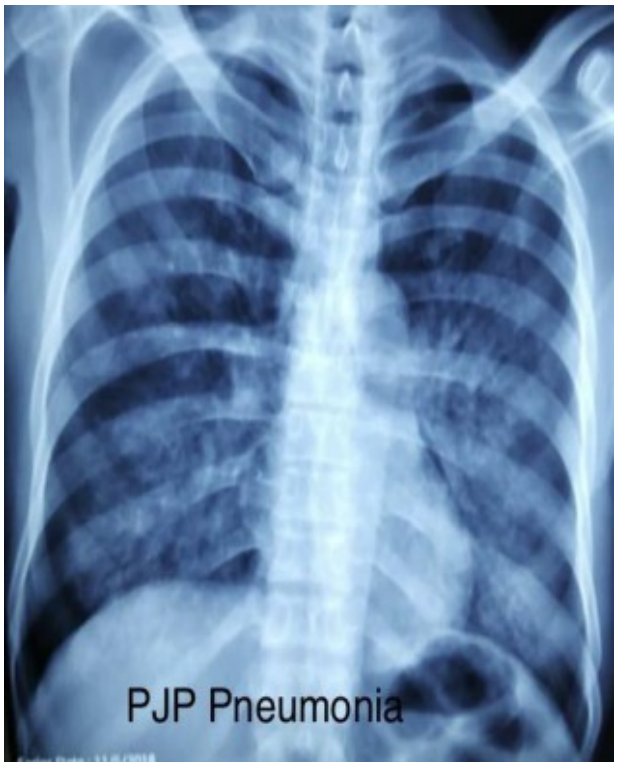


Fig 2: *Chest X-ray showing bilateral interstitial pneumonitis in a patient with AIDS and hypoxic respiratory failure.*

AIDS & Kaposi's sarcoma: It is the malignancy of venules causing nodule formation along the course of the vein(s). The blood appears blue or purple in veins. Lumen might get blocked due to filling up by the cancer cells, and the colour may become brown.

- It usually starts in the skin, lungs, liver, and/or gut. It may present as GI bleeding.
- As it originates from connective tissue, it is named Kaposi Sarcoma.
- HHV-8 commonly causes it.[13,14]

D/D of HIV & AIDS: **D/D depends on its stage:** During acute infection or seroconversion, it confuses with

- EBV (Mononucleosis)
- CMV
- Toxoplasma
- Aggressive NHL can also rarely be confused due to lymphadenopathy and splenomegaly.

During AIDS, D/D is very broad and depends on the organ we are dealing with for example, cerebral toxoplasmosis of AIDS can be confused with Primary B-cell Brain Lymphoma, fungal infections, CMV encephalitis, or other causes of multifocal contrast-enhancing cerebral lesions.[14]

HIV & AIDS treatment*[15-24]*: HIV Treatment has the following main components

- Pre-exposure Prophylaxis
- Post-exposure Prophylaxis
- Prophylaxis, treatment & monitoring for a positive case
- Preventive and protective measures

Pre-Exposure Prophylaxis: It is given to people who have a chance of getting HIV by going on vacation and having unprotected sex. Usually, one or two medications are prescribed.

Post-Exposure Prophylaxis: For possible exposure due to needle prick or unprotected sex, again, usually 2 or 3 medicines are prescribed.

- Baseline tests should be done and PCR advised at 6 weeks, 12 weeks, and 24 weeks. PCR should be negative in all these, then it's considered negative.
- Treatment for 4 to 6 weeks reduces infectivity by 90 to 95 percent.

Treatment of HIV & AIDS Cases: In case the patient is HIV positive, the treatment should be started as soon as possible.

- Check baseline CD4 count.
- HIV viral load (Quantitative PCR) to check infection burden.
- LFTs, FBC, RFTs, lipid profile, diabetes for monitoring, and side effects of the treatment.
- Patient & caregiver teaching and understanding

Benefits of Treatment: With treatment, viral replication slows down & so does the disease progression. Therefore, the following are the beneficial effects of the treatment.

- Slowing the progression from HIV to AIDS
- Decreased risk of transmission to others
- Reduced mortality and complications of HIV positive cases.
- Starting treatment is very important for a person who has an HIV-negative partner.

***Drugs used for HIV & AIDS*[18,19,20,21]**

Reverse Transcriptase Inhibitors (RTI)

1. RT inhibiting drugs are nucleoside or nucleotide reverse transcriptase inhibitors. These are direct enzyme blockers. The Nucleotide analog deceives the enzyme by resembling the nucleotides in the RNA.
2. Non-nucleoside Reverse Transcriptase inhibitors: These drugs are non-competitive inhibitors of the enzyme that induce conformation changes in Reverse Transcriptase, reducing its activity.
3. Few Examples of RT Inhibitors: Abacavir, Didanosine, Lamivudine, Tenofovir, Zidovudine. Non-nucleoside RT inhibitors are Delavirdine, Efavirenz, and Nevirapine.

Nucleoside drugs affect the rapidly dividing cells of the body. They may cause the following effects:

- Bone marrow suppression. Same effect as chemotherapy drugs, which block the DNA chain formation. Drug resistance to these drugs is because the DNA keeps repairing and changing.
- Mitochondrial DNA is also affected. It has 13 genes. It can release Mitochondrial toxins that affect neurons, muscle cells, and the intestine, and in turn, lactic acid is produced. This can cause lactic acidosis. In that case, medicine has to be stopped. Drug-drug interactions with Metformin can worsen lactoacidosis.

Special precautions

- Dose reduction is indicated in patients with renal or hepatic insufficiency.
- Due to resistance, 2 or more medicines are added along with NRTI/nNRTI.
- Abacavir is hepatotoxic and can also cause pancreatitis.
- Nevirapine can damage small bile ducts and liver cells, causing cholestasis and transaminitis.
- Lamivudine at a lower dose is given if the patient has liver injury.
- Tenofovir damages renal tubules, especially the proximal renal tubule. If GFR is less than 50, then do not give Tenofovir.
- In pregnancy, all these can be used except Efavirenz

Integrase Inhibitors: They do not allow the HIV genome to integrate into human DNA. They have the

name "Teg" in their names. Example: Ral**teg**ravir, Dolutegravir

Protease Inhibitors: They are the attachment blockers. They inhibit the maturation of new viruses. They have the name "navir" as a suffix.

- They have metabolic side effects such as worsening of diabetes, dyslipidaemia, fatty liver, neuropathic and neurotoxic effects.
- Ritonavir can boost other drugs by inhibiting cytochrome P450.
- Example: Atazanavir, Darunavir, Fosamprenavir, Lopinavir

How Drugs Are Combined: A combination of 3 medications is usually used for the treatment of HIV. **Usually 1 medicine from each group. For example:**

Emtricitabine/Lamivudine

Tenofovir

Dolutegravir

In postexposure, usually one pill once a day is advised. In pre-exposure, one pill was advised.

HIV, Pregnancy & Newborn[18,21]:

- Treatment has to be given in pregnancy to reduce vertical transmission. Still, there is a risk of 10 to 20 percent that the newborn will be positive despite the treatment.
- Every newborn whose mother is positive has to be given prophylactic treatment.
- If the mother took treatment during pregnancy and the viral load remained low in the mother, then treat the newborn only with a single drug such as Zidovudine. But if the mother did not take treatment and the viral load in the mother remained high, then a 2 to 3 medicine combination has to be advised.
- Breastfeeding is contraindicated in HIV cases.
- C-section is preferred over SVD.
- Usually, there is a 3-drug combination for the mother and 1 or 2 for the baby.

IRIS (Immune Reconstitution Inflammatory Syndrome): IRIS is a state of hyperinflammatory response that usually occurs in the first 6 months of treatment in HIV patients. Once HAART is started, and the CD4 count begins to improve, the body begins to react. The fight against the clinical and subclinical infections strengthens as immunity increases. At the start of treatment, the CD 4 count is very low or the viral load is too high. IRIS can damage the organ(s) involved. There is a diagnostic criterion for labelling IRIS

1. Inflammatory reaction comes after a few weeks of starting anti-HIV medications.
2. Evidence that the CD 4 count is improving.
3. No evidence of recurrence of any infection.
4. No worsening of the actual HIV disease.
5. HIV was not resistant to the treatment.

Prevention & treatment of IRIS:

- Precautions to be taken when the HIV viral load is too high &/or the CD4 levels are too low. Give a gap, from the start of HAART, of 8 to 12 weeks, or the gap can be as much as 6 to 8 weeks.
- Inflammation is managed by dexamethasone.
- Note: If the patient is already taking ATT for TB, then delay HAART treatment for a few weeks.[21,22,23]

Prophylaxis of various opportunistic infections in HIV & AIDS cases[21-24]

CD 4 count < 200: Coccidioidomycosis- Fluconazole or Voriconazole. Fluconazole passes the blood-brain barrier.

- PJP & Toxoplasma- Septran (Bactrim).

CD 4 count < 100: Toxoplasmosis- Sulfamethoxazole-Trimethoprim, Pentamidine, Atovaquone, or Dapsone.

CD 4 count < 50 or 100: CMV - Famciclovir or Ganciclovir (the latter is more effective). Foscarnet is nephrotoxic.

Vaccinations for HIV & AIDS cases: All inactivated vaccines are safe in these cases. These include HPV, Hep A and B, Pneumococcal, HiB, & Meningococcal, DPT, and the annual flu vaccine. Live attenuated vaccines such as MMR, BCG, and Varicella zoster can be given to those who have a CD4 count above 200.

- If the CD-4 count is less than 200, then HAART is started, and then live attenuated vaccines are given once the CD-4 count is 200 or above.
- If the CD-4 count is less than 200, there is no response to the live attenuated vaccine, and there is a high risk of infection with these live vaccines.

Precautions for HIV & AIDS cases:

- Avoid cats and bird exposure

- Avoid unprotected sex
- Avoid breastfeeding
- Avoid needle sharing, blood donations, sharing of razors, etc.

Encourage the patient to disclose his HIV status to his sex partners. If they are reluctant, then it is the responsibility of the health care worker to convey the message as it is a medicolegal issue.

Conclusion

HIV is an emerging issue globally and in our part of the world as well. Diagnosis is often delayed due to its initial non-specific clinical manifestations which is further complicated by the social stigmata attached to the disease. The disease has a progressive course with multiple complications. Treatment is available to prevent or slow down the progression, complications and associated morbidities. Treatment has many potential interactions and side effects. The disease should be managed by multimodality team including and led by infectious disease experts. Its very important for all the physicians to have knowledge about the disease as it involves almost every system.

In addition to the medical aspect of the disease, knowledge about its widespread social implications, risk to other humans and healthcare cost are of great help. Patient's and caregiver education, and counselling are essential component of the treatment. Patient's privacy and confidentiality should be maintained. However, people at risk (such as sex partners) should be informed, preferably by the patient.

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AH: Conception

JA: Design of the work

AH, JA: Data acquisition, analysis, or interpretation

AH: Draft the work

JA: Review critically for important intellectual content

All authors approve the version to be published

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