A GUIDE TO

HIV Care Services

AND

Management of Opportunistic Infections

2022
Edition

World Health Organization

National STD/AIDS Control Programme
SRI LANKA

A Guide to HIV Care Services and Management of Opportunistic Infections

2022 Edition

National STD /AIDS Control Programme, Ministry of Health, Colombo, Sri Lanka

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Director's Message

The NSACP has undertaken the salient task of achieving "ending AIDS by 2030" along with other global stakeholders. As the main governmental institution which is responsible for the national response to HIV in Sri Lanka, the NSACP conducts curative and preventive services to the community while giving special emphasis to the key groups in the country. Furthermore, it gives the necessary guidance and support to other stakeholders to reach the goal of ending AIDS.

During 2021, 419 people living with HIV (PLHIV) were registered in the HIV care services. These PLHIV consisted of males, females, and transgender people. A total of 329 were newly commenced on ART during the year 2021. ART services were scaled up to 31 out of 41 STD clinics in the country. NSACP provides necessary technical support, training and prepares national guidelines for management of STI and HIV. In order to maintain quality HIV care services, HIV care and treatment unit of NSACP ensures that the guidelines are updated regularly to include new research evidence.

This publication "A guide to HIV care services and management of Opportunistic Infections" is the second edition of the previous guideline published in 2017. As the director NSACP I am grateful to all the contributors for the commitment and dedication in updating this guideline. The financial and technical support provided by the Ministry of Health and World Health Organization (WHO) is also highly acknowledged.

Dr. Rasanjalee Hettiarachchi

Director

National STD/AIDS Control Programme

Forward

We are delighted to publish the second edition of the "guideline for the management of Opportunistic Infections and HIV". The first edition of this was published in 2017. Presently medical science is advancing at such a speed that existing knowledge keeps constantly changing. Unless we keep ourselves updated regularly, we will soon find ourselves outdated. Therefore, the objective of publishing this second edition was to update the current management of opportunistic infections and HIV in par with the rest of the world.

This work is targeted at providing up to date knowledge to consultant Venereologists, physicians & other consultants from different fields, post graduate trainees in Venerology & other fields and medical officers in Venereology.

In this current edition some new chapters are added, such as other infections associated with HIV, HIV and cardiovascular diseases/ Diabetes mellitus/ hypertension/ dyslipidaemia, HIV and bone, HIV associated neurological conditions Psychiatric Aspects of HIV Infection and AIDS, HIV and liver diseases HIV associated haematological conditions, herpes groups of viruses, substance misuse and HIV, Vaccination Guidelines and TB/ HIV reporting and recording. We had the opportunity of obtaining services of eminent consultants from respective areas in writing up the respective chapters.

This product is a result of the hard work of many people. I would take this opportunity to thank the WHO for funding, Director NSACP for the guidance, Dr Piyumi Perera, Dr Nalaka Kulathunge, Dr Kanchana Wirasinghe and Dr Sachni Mendis for their untiring efforts in producing this guideline.

Dr Himali P Perera

Consultant Venerologist

Ex-Co Ordinator HIV care and Treatment

Contents

Pyrexia of Unknown Origin (PUO)

Dr. Jayadarie Ranatunaga

Introduction

HIV-related PUO is defined as a pattern of fever with temperature >38.3 ^{0}C on several occasions over 4 weeks or more for out-patients or more than 3 days in the hospital, in which the diagnosis remains uncertain after an initial diagnostic workup, including at least 2 days of incubation of microbiological cultures for in-ward patients.

1. It is a common clinical manifestation in HIV-positive patients with severe immunosuppression. The probability of infection being the cause increases with a decreasing CD4 count.
2. Fever is rarely the effect of HIV itself.
3. Actively looking for a cause for fever is advised. The possibility of multiple infections is high.

Some common facts to be borne in mind:

1. Even in the era of HAART, tuberculosis and lymphoma continue to be significant causes of PUO.
2. But when the population on ART ages, multisystem diseases should be considered in the differential diagnosis.
3. Fever may develop due to immune reconstitution syndrome after ART due to an underlying infection.
4. Fever may be the first symptom of underlying diseases such as PJP, Cryptococcal disease, HSV, Syphilis or Infective endocarditis.
5. Fever and personality change may be seen in Cryptococcal meningitis, HSV and VZV infections.
6. Another less common infection for prolonged fever with low immunity is Bartonella infection. *Bartonella quintana* or *Bartonella henselae* are two varieties of it.

Common causes of PUO in PLHIV

But are not limited to,

- **Infections** - TB, MAC, PJP, Cryptococcal infections, Hep B and C, CMV, HSV, Toxoplasmosis, Histoplasmosis, Endocarditis, Salmonellosis and Shigellosis, Visceral Leishmaniasis, Malaria, Melioidosis, Leptospirosis
- **Malignancies** - Lymphomas, KS, Multi-system Castleman's syndrome
- **Multisystem diseases** - Connective tissue disorders (e.g., SLE, Rheumatoid disease)
- **Rheumatic diseases**-Vasculitis, Sarcoidosis
- **IRIS** - MAC, TB, Cryptococcus, Viral Hepatitis
- **Other** - Drug-induced, multiple aetiologies may exist in a single patient.

Clinical evaluation

A detailed history including the duration and development of symptoms from all major systems, including constitutional symptoms.

Travel and residence history, contact history of any disease specially TB, vaccination and prophylactic treatment history, other medications, recreational drug use, previous infections and treatment history, occupational history, sexual history with any related symptoms suggestive of a STI, and family history should be obtained.

Documentation of temperature and fever pattern is very important. Thorough general and systemic examination should be carried out with special emphasis on rashes, lymphadenopathy, signs of arthritis, new or changing cardiac murmurs, hepatosplenomegaly, abdominal tenderness fundoscopy and neurological deficits focusing on differential diagnosis and should be examined and observed regularly as new clinical features may develop.

Investigations may include,

- FBC with Differential Count, CD4 count
- LFT, RFT, LDH
- CRP/ESR
- Chest X-ray, USS abdomen and pelvis
- Microscopy - sputum, urine, stools
- Culture - Blood, sputum, urine, stools (including mycobacterial and fungal cultures)
- Leptospirosis Ab test
- Typhoid Ab test
- GeneXpert for TB, Mantoux test, ADA, HRCT
- Molecular studies for viruses depending on the availability.

- Syphilis serology, Cryptococcal Antigen
- Hepatitis screening, CMV and Toxoplasma antibodies
- Blood films for malaria
- ANA, Rh Factor
- 2D Echo if endocarditis suspected.
- Melioidosis Ab
- Arterial blood gases if indicated.

If this diagnostic workup does not give a diagnosis, depending on the clinical features and initial test results may need invasive investigations like,

- Bronchoscopy and BAL
- Upper/lower GI endoscopy
- Cytology/Histology from lymph Nodes, liver, bone marrow, lung (pleural). (When pathological samples are taken, one sample should be sent to microbiology and the other for histopathology with good history)
- Lumbar Puncture and CSF examination
- CT/MRI of chest, abdomen, pelvis and brain

Management should be done according to the diagnosis.

References

1. British HIV Association guidelines for the treatment of opportunistic infections in HIV seropositive individuals. HIV Medicine. British HIV Association Guidelines. United Kingdom. 2011; 9

Cryptococcal Infection

Dr. Nalaka Abeygunasekara

Introduction

The most common presentation of cryptococcal disease is cryptococcal meningitis and less common presentations include pulmonary disease, skin, lymph node and bone involvement. Cryptococcal disease is far less common among children than adults. Most HIV-associated cryptococcal infections are caused by Cryptococcus neoformans. Overall, 90% of cryptococcal cases in people with HIV are observed in patients who have CD4 cell counts <100 cells/μL.

Clinical presentation

In HIV-infected patients, cryptococcosis commonly presents as subacute meningitis or meningoencephalitis with fever, malaise and headache. Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms such as lethargy, altered mental status, personality changes, and memory loss that are usually a result of increased intracranial pressure.

Isolated pulmonary infection is also possible. Symptoms and signs include cough and dyspnoea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation. Skin lesions may show umbilicated skin lesions that mimic those seen with molluscum contagiosum.

Diagnosis

- Serum cryptococcal antigen (CrAg)
- India ink stain of CSF
- CSF cryptococcal antigen
- Cryptococcal culture of CSF

- CSF cryptococcal PCR
- HIV-positive patients who have a CD4 cell count <100 cells/μL, need to be screened for serum cryptococcal antigen prior to ART initiation or re-initiation.

Treatment

Treatment of cryptococcal neurological disease consists of 3 phases: induction, consolidation and maintenance.

Induction

Preferred therapies	Alternative therapies
• **Liposomal amphotericin B** 3-4mg/kg IV daily + **Flucytosine** 25 mg/kg orally 6hrly for two weeks. • **Amphotericin B deoxycholate** 0.7mg - 1 mg/kg IV daily + **Flucytosine** 25 mg/kg orally 6hrly for one week followed by **Fluconazole** 1200mg orally daily for one week. • **Amphotericin B deoxycholate** 0.7mg - 1 mg/kg IV daily + **Flucytosine** 25 mg/kg orally 6hrly for two weeks.	• Amphotericin B lipid complex 5 mg/kg IV daily + Flucytosine 25 mg/kg orally 6hrly for two weeks. • Amphotericin B deoxycholate 0.7mg - 1 mg/kg IV daily + Fluconazole 1200mg orally/IV daily for two weeks • Flucytosine 25 mg/kg orally 6hrly + Fluconazole 1200mg orally/IV daily for two weeks. • Liposomal Amphotericin B 3–4 mg/kg IV daily + Fluconazole 1200 mg orally daily/IV for two weeks. • Liposomal Amphotericin B 3–4 mg/kg IV daily for two weeks. • Amphotericin B deoxycholate 0.7mg - 1 mg/kg IV daily for two weeks. • IV/Oral Fluconazole 1200mg daily for two weeks (if unable to use amphotericin).

If not improved clinically or remain clinically unstable, may need to continue induction therapy until the CSF culture is negative.

Consolidation

Commence after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture at the end of two weeks)

- **Fluconazole** 800mg orally once daily for 8 weeks.

Maintenance

- **Fluconazole** 200mg orally (for at least one year).

Stopping maintenance therapy

Maintenance therapy can be stopped, once the following criteria are fulfilled:

- Completed initial (induction, consolidation) therapy, and at least 1 year of maintenance therapy
  and
- Remain asymptomatic from cryptococcal infection.
  and
- CD4 count ≥100 cells/μL for ≥3 months and suppressed HIV RNA in response to effective ART.

Other considerations

- Measures to decrease intracranial pressure should be used for patients with raised intracranial pressure or patients with signs of increased intracranial pressure (confusion, blurred vision, papilledema, lower extremity clonus etc). Drainage of CSF via lumbar puncture is recommended. Remove 20–30 ml of CSF daily until symptoms and signs improve with normalising the pressure (<20 cm H_2O in lying position). Corticosteroids and mannitol are not recommended.
- Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances and anaemia. Pre-infusion administration of 500 ml to 1000 ml of normal saline appears to reduce the risk of nephrotoxicity. Potassium supplements will prevent possible hypokalaemia.
- ART administration should be considered between 4 and 6 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions.
- Some patients with cryptococcal meningitis experience persistent or recurrent symptoms. The most common causes are raised intracranial pressure, sub optimal therapy/non-

adherence to therapy, development of IRIS and presence of other concomitant illnesses (such as viral, bacterial or tuberculous meningitis).

- An estimated 10%-50% of HIV infected patients with cryptococcal meningitis experience IRIS typically occurring 3–12 weeks after initiating ART. Appropriate management of IRIS is to continue both ART and antifungal therapy and reduce elevated intracranial pressure, if present. In patients with severe symptoms of IRIS, some specialists recommend a brief course of steroids.
- Treatment of non-CNS, extra pulmonary and diffuse pulmonary disease is the same as CNS disease.
- For localised non-meningeal disease or only focal pulmonary infiltrates, fluconazole 400-800 mg/day for ten weeks followed by fluconazole 200 mg/day for four months combined with effective ART is recommended.
- Patients with isolated serum Cr Ag positivity (where cryptococcal meningitis has been excluded by CSF assay) needs to be treated with fluconazole 800 mg/day for two weeks, followed by consolidation and maintenance as for treatment of CNS disease.
- Amphotericin B therapy can be given to pregnant women. However, exposure to flucytosine and fluconazole during pregnancy has been associated with an increased risk of birth defects in animal studies and some uncontrolled human studies. Therefore, the use of flucytosine and fluconazole in pregnant women should be evaluated on an individual basis, considering the benefits and potential harm.

References

1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centres for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Management of Cryptococcosis, 2022; H-I
2. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV infected adults, adolescents and children. World Health Organization. March 2018.

Toxoplasmosis

Dr. Nalaka Abeygunasekara

Introduction

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease usually occurs because of the reactivation of latent tissue cysts. Clinical disease is mostly seen among the patients with CD4 less than 200 cells/µl.

Clinical presentation

Among patients with HIV, the most common clinical presentation of *T. gondii* infection is a 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. In the absence of treatment, disease progression results in seizures, stupor and coma.

Retinochoroiditis and pneumonia can occur but rare.

Diagnosis

Contrast enhanced CT scan of brain – shows multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated oedema. Sometimes, it can manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions.

- MRI scan of brain – more sensitive than CT scan
- Toxoplasma antibodies - negative serology make toxoplasmosis unlikely.
- CSF toxoplasma PCR – if LP is safe and feasible, but low sensitivity.
- Brain biopsy (CT guided needle biopsy) - indicated for patients who fail to respond to therapy.

Treatment

Acute therapy - for at least 6 weeks (extend the duration if clinical or radiologic response is poor at the end of 6 weeks).

Preferred therapy	Alternative therapy
• **Pyrimethamine** 200mg oral loading dose then 50-75mg once a day + **Sulfadiazine** 1–1.5 g 6hrly	• **Pyrimethamine** 200mg oral loading dose then 50-75mg once a day + **Clindamycin** 600 mg orally 6 hourly or • **TMP-SMX** (TMP 5 mg/kg and SMX 25 mg/kg) IV or orally bd

Chronic maintenance therapy After completion of the acute therapy (at least for 6 weeks), all patients should be continued on chronic maintenance therapy as outlined below till immune recovery.

Preferred therapy	Alternative therapy
• **Pyrimethamine** 25–50mg orally daily + **Sulfadiazine** 2000–4000mg orally daily (in 2 to 4 divided doses)	• **Clindamycin** 600mg orally 8hrly + **Pyrimethamine** 25–50 mg orally daily or • **TMP-SMX** 960 mg bd

Discontinuing chronic maintenance therapy

Successfully completed initial therapy, remains asymptomatic and CD4 count >200 cells/μL for >6 months in response to ART.

Other considerations

- Folinic acid 15 mg/day or leucovorin 10–25 mg/day reduces the likelihood of development of hematologic toxicities associated with pyrimethamine therapy.
- Initiate ART within 2 to 3 weeks after commencing specific therapy for toxoplasmosis.
- Patients with toxoplasmosis should be monitored closely for drug adverse events and clinical and radiologic improvement.

- Anticonvulsants should be administered to patients with seizures and continued at least through the period of acute treatment.
- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated oedema; discontinue as soon as clinically feasible. However, corticosteroid use can lead to further immunosuppression.
- IRIS associated with TE has been reported but appears to be rare.
- Toxoplasma-seropositive patients who have CD4 counts <100 cells/µL should receive primary prophylaxis against toxoplasmic encephalitis (oral cotrimoxazole 960mg daily). This can be stopped once CD4 count >200 cells/µL for >3 months in response to ART or if CD4 count is 100-200 cells/µL and HIV RNA levels remain below limits of detection for at least 3-6 months in response to ART.
- Treatment of pregnant women with TE should be as same as in non-pregnant adults. Although pyrimethamine has been associated with birth defects in animals, human data have not suggested an increased risk for defects, therefore, it can be administered to pregnant women after the first trimester. Similarly, sulfadiazine appears safe in pregnancy.
- Ocular Toxoplasmosis - Ocular infection gives rise to a spectrum of disease. However, it is rare among patient with AIDS. The hallmark of ocular toxoplasmosis is necrotizing retinochoroiditis (chorioretinitis). Symptoms include pain and redness of the eye, photophobia, blurring of vision etc. Toxoplasma infection can lead to retinochoroiditis and uveitis in affected individuals.
- The diagnosis of ocular toxoplasmosis is made by ophthalmic examinations and a variety of clinical presentations that are consistent with *T. gondii* infection of the eye. Treatment includes pyrimethamine and sulfadiazine. Steroids are indicated if the associated inflammation is severe.

References

1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centres for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Management of toxoplasma gondii encephalitis, CDC guideline, 2022; AA-1
2. Medscape international, 2021, Ocular toxoplasmosis: overview, https://emedicine.medscape.com/article/2044905-overview
3. Park YH, Nam HW. Clinical features and treatment of ocular toxoplasmosis. Korean J Parasitol. 2013 Aug;51(4):393-9. doi: 10.3347/kjp.2013.51.4.393. Epub 2013 Aug 30. PMID: 24039281; PMCID: PMC3770869.

Pneumocystis Pneumonia

Dr. Chandrika Jayakody

Introduction

Pneumocystis carinii pneumonia (PCP) is caused by the fungus *Pneumocystis jirovecii*. Approximately ninety percent of the PCP cases are seen among patients with a CD4 count less than 200 cells/µl. Other factors associated with a higher risk of PCP in the pre-ART era included, non-adherence to prophylaxis, oral thrush, oral hairy leukoplakia, unintentional weight loss, recurrent bacterial pneumonia, previous episodes of PCP and higher plasma HIV RNA levels.

Clinical presentation

The most common manifestations of PCP are sub-acute onset of progressive exertional dyspnoea, fever, malaise, non-productive cough, and chest discomfort that worsens within days to weeks. In mild cases, pulmonary examination usually is normal at rest and with exertion; tachypnoea, tachycardia and diffuse crepitations may be observed. Wheezing and signs of focal consolidation or pleural effusion are less common presentations.

Diagnosis

- Chest X ray typically demonstrates diffuse, bilateral, symmetrical interstitial infiltrates emanating from the hilar in a butterfly pattern. (Characteristically sparing the apices and costophrenic angle). In early stages, chest radiograph may be normal. Atypical presentations also occur such as lobar consolidation, pneumatoceles, pneumothorax etc. However, pleural effusion and lymphadenopathy are rare. If present, consider an alternative diagnosis.
- HRCT of chest shows patchy ground-glass attenuation. Negative HRCT scan make the diagnosis of PCP highly unlikely.

- Definitive diagnosis is by demonstrating the organisms in broncho-alveolar lavage fluid, induced sputum or histopathologic or cytopathologic demonstration of organisms in tissue. Demonstrate organisms with silver stain or immunofluorescence.
- PCR has increased sensitivity, but reduced specificity compared to visualization since PCR cannot distinguish colonization and the diseases.

Oxygen saturation of <94% indicates moderately severe or severe disease.

Treatment

For moderate to severe PCP - Total duration of treatment is 21 days.

Preferred Therapy	Alternative Therapy
• **TMP-SMX**: TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given 8hrly. May switch to oral therapy after clinical improvement	• **Pentamidine** 4 mg/kg IV once daily infused over at least 60 minutes or • **Primaquine** 30mg orally once daily + **Clindamycin** IV 600mg 6hrly

For mild to moderate PCP - Total duration of treatment is 21 days

Preferred Therapy	Alternative Therapy
• **TMP-SMX**: (TMP 15–20 mg and SMX 75–100 mg) /kg/day given orally in 3 divided doses or • **TMP-SMX** –3 SS tablets tds	• **Dapsone** 100 mg orally daily + **TMP** 15 mg/kg/day orally (3 divided doses) or • **Primaquine** 30 mg orally daily + **Clindamycin** orally 600mg 8hrly or • **Atovaquone** 750 mg orally bd

Adjunctive Corticosteroids

Corticosteroid therapy is necessary for moderate to severe PCP.

prednisolone should be started as early as possible within 72 hours of PCP therapy and continue for 21 days.

- 40mg bd for 5 days
- 40mg daily for 5 days
- 20mg daily for 11 days

Secondary Prophylaxis

Secondary prophylaxis should be started after completing the treatment for acute condition with 3 weeks of therapy and continue till immune recovery.

- **TMP-SMX** - 1 DS tablet orally daily

or

- **Dapsone** 100 mg orally daily

or

- **Pentamidine** aerosol 300mg nebulization once a month

Primary Prophylaxis

PCP prophylaxis should be used in all HIV-seropositive individuals with severe or advanced HIV clinical disease (WHO Stage III or IV) and or with CD4 cell count ≤ 350 cells/µl.

TMP-SMX is the drug of choice. Although other drugs may have similar efficacy against PCP, they do not provide the additional protection provided by TMP-SMX against other infections and some are not as effective at low CD4 T-cell counts.

The preferred regimens are the same as above.

The prophylaxis should be continued till CD4 count increases to >350 cells/µl for >3 months following ART. However, discontinuation can be considered if the CD4 count is 100-200 cells/µl and HIV RNA remains below the limits of detection for at least 3-6 months.

Other considerations

ART should be initiated, when possible, within 2 weeks of diagnosis of PCP.

References

1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centres for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Management of pneumocystis pneumonia, CDC guideline, 2022; W1
2. British HIV Association guidelines for the treatment of opportunistic infections in HIV seropositive individuals. HIV Medicine. British HIV Association Guidelines. United Kingdom. 2011; 3.4

Tuberculosis

Dr. R. Asha Samaranayake

Introduction

HIV and Tuberculosis (TB) form a lethal combination of HIV-TB co-infection where each accelerating the other's progress. The intersection and syndemic interaction between HIV and TB epidemics have deadly consequences around the world. Among PLHIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death for HIV-associated mortality, accounting for one of every five HIV-related deaths.

Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19. However, some developed countries with low incidence and prevalence have begun to investigate measures to eliminate TB.

In the view of global TB irradiation strategy by WHO; the Stop TB by 2035, the WHO has identified scaling up of joint TB/HIV interventions, and management of comorbidities. A strengthening joint TB and HIV programming is highlighted. The “one-stop shop” integrated TB/HIV service model is promoted for universal access to TB/HIV interventions. These include HIV testing and counselling to all presumptive and diagnosed TB patients; systematic screening for PL HIV; ART and TB preventative therapies (TPT). In addition, an improvement in TB infection control in health-care facilities providing services to PL HIV is highlighted too.

Prevention of TB

According to Centers for Disease Control and Prevention (CDC), the specific actions in TB prevention includes.

a. Screening patients for active tuberculosis and tuberculous infection.

b. Providing rapid diagnostic services.

c. Prescribing appropriate curative and preventive therapy.

d. Maintaining physical measures to reduce microbial contamination of the air.

e. Proper isolation of persons with, or suspected of having, infectious tuberculosis.

f. Screening health-care-facility personnel for tuberculous infection and tuberculosis.

g. Promptly investigating and controlling outbreaks.

h. TPT for PLHIV and defined risk groups.

HIV-TB Co-Infection

What HIV does to TB?

Mycobacterium tuberculosis primarily infects macrophages, which require CD4+ T cells to augment intracellular clearance of microbial pathogens. It is, therefore, the integrity of both the number and quality of intact CD4 cells are important in this process. In HIV, as both the quality and the quantity of the CD4 cells are affected.

Therefore, HIV infection is one of the most important risk factors for reactivation of TB from latent TB to active TB (HIV increases the risk of latent TB reactivation by 20-folds.). In addition, presence of HIV increases the susceptibility MTB infection or re-infection and also increases progression of both primary and secondary TB causing more deadly disease. In PLHIV risk of TB is increased by 2-5 folds in early HIV-1 infection and by more than 20-folds in advanced HIV-1 disease. The risk of TB remains increased by approximately four folds in PLHIV on antiretroviral therapy (ART).

Although infection with TB in HIV occurs across any level of CD4 counts, with low counts below 200/mm3, it can produce more deadly disease like disseminated TB, central nervous system TB and its complications. Systemic spread of MTB with more severe disease can happen in both primary progressive and secondary progressive diseases in PLHIV. This kind of severe systemic disease is seen in PLHIV who are not on treatment or poor responders to ART, especially infants and children. Severe infection causes either granulomas or naked bacilli to spread by blood stream causing very severe generalized disease, like miliary TB or even causing deadly TB sepsis.

What TB does to HIV?

At the cellular level, the pro-inflammatory response to MTB may exacerbate HIV disease progression by increasing virus propagation by, increased transcription, and increased cell to cell virus transmission.

In addition, M. tuberculosis infection also has a negative impact on the immune response to HIV, accelerating clinical progression from HIV infection to AIDS. In addition, HIV–TB co-infected patients have been found to be at higher risk of new additional opportunistic infections and mortality than HIV-infected patients without TB with the same CD4 count.

HIV-TB Co-Infection

A. Active TB

B. Latent TB

MTB is an intracellular parasite that mainly attacks macrophages and inhibits their apoptosis and many other host defensive immunological steps owing to its immune evasion properties. Therefore, once infected, MTB can become a long-term infection in humans, causing a continuous spectrum of metabolic bacterial activity, and antagonistic immunological responses. This leads to a spectrum of pathological changes and clinical manifestations. The clinically visible active TB therefore will be representing just a tip of an ice burg, where major part of TB infected people will lay under the water, as latent TB and other sub clinical states.

Active TB Infection

Symptomatic disease with actively reproducing metabolically active MTB is seen usually with positive imaging.

Latent TB infection (LTB)

It is a result of both the host immune integrity and immune evasion by MTB.

The host immune reaction is at primary infection is characterized by activation of α/β T-cell receptor-positive lymphocytes, recently recruited immature macrophages, and strongly enhanced M. tuberculosis antigen-specific Th1 responses, with large amounts of locally secreted IFN-γ, and some neutrophils. The main immune requirements for maintain latent TB state without reactivation to active TB are recognized as numbers and function of CD4+ and CD8+ T cells, levels of tumour necrosis factor-α (TNF-α), and IFN-γ and IL-12 receptors.

The host immune cells (macrophage) will therefore provide a sanctuary site to viable intra cellular dormant MTB, who will remain hidden to imaging and not provoking host immunity to a level that causes any symptoms. MTB has a unique ability to produce this latent TB state by slowing down its own metabolism or by becoming metabolically inactive (dormant or at rest), and also

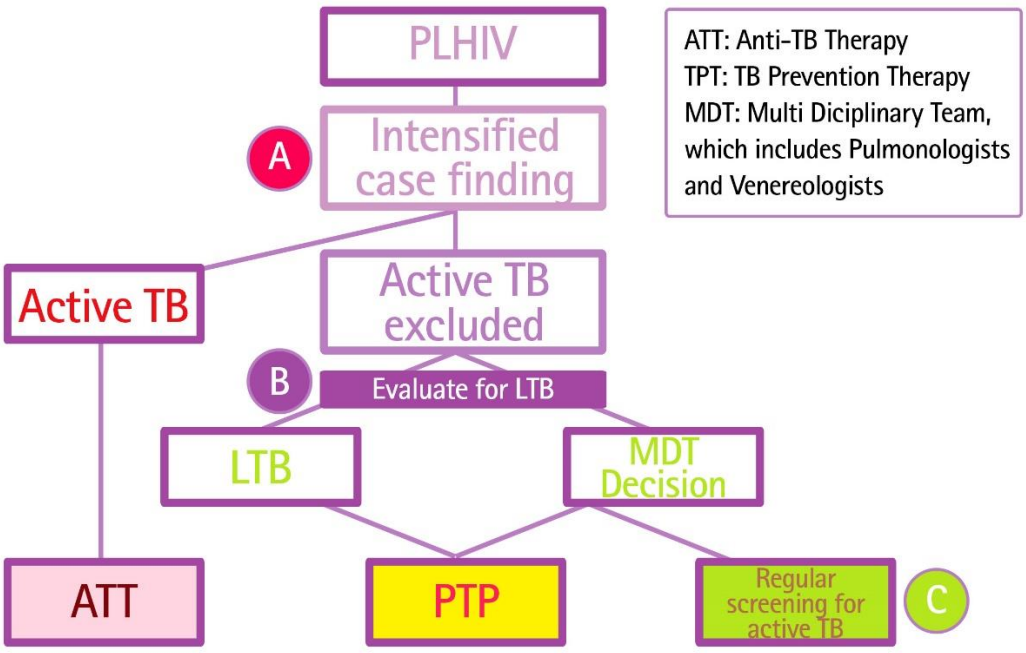
by the ability to evade host's many immune mechanisms. Thus, it remains negative at imaging, biochemical means and the host will be completely asymptomatic.

Screening and Treating TB infection in PLHIV

It is very important to screen PLHIV for LTB after excluding active TB by intensified case finding. **(Flow Chart 5-1; - Important Screening Steps in PLHIV for TB)** This is to decide on the early initiation of Anti TB Therapy (ATT) in Active TB and TB protective Therapy (TPT) to LTB, as it significantly reduces HIV/TB deadly disease outcomes according to the current evidence.

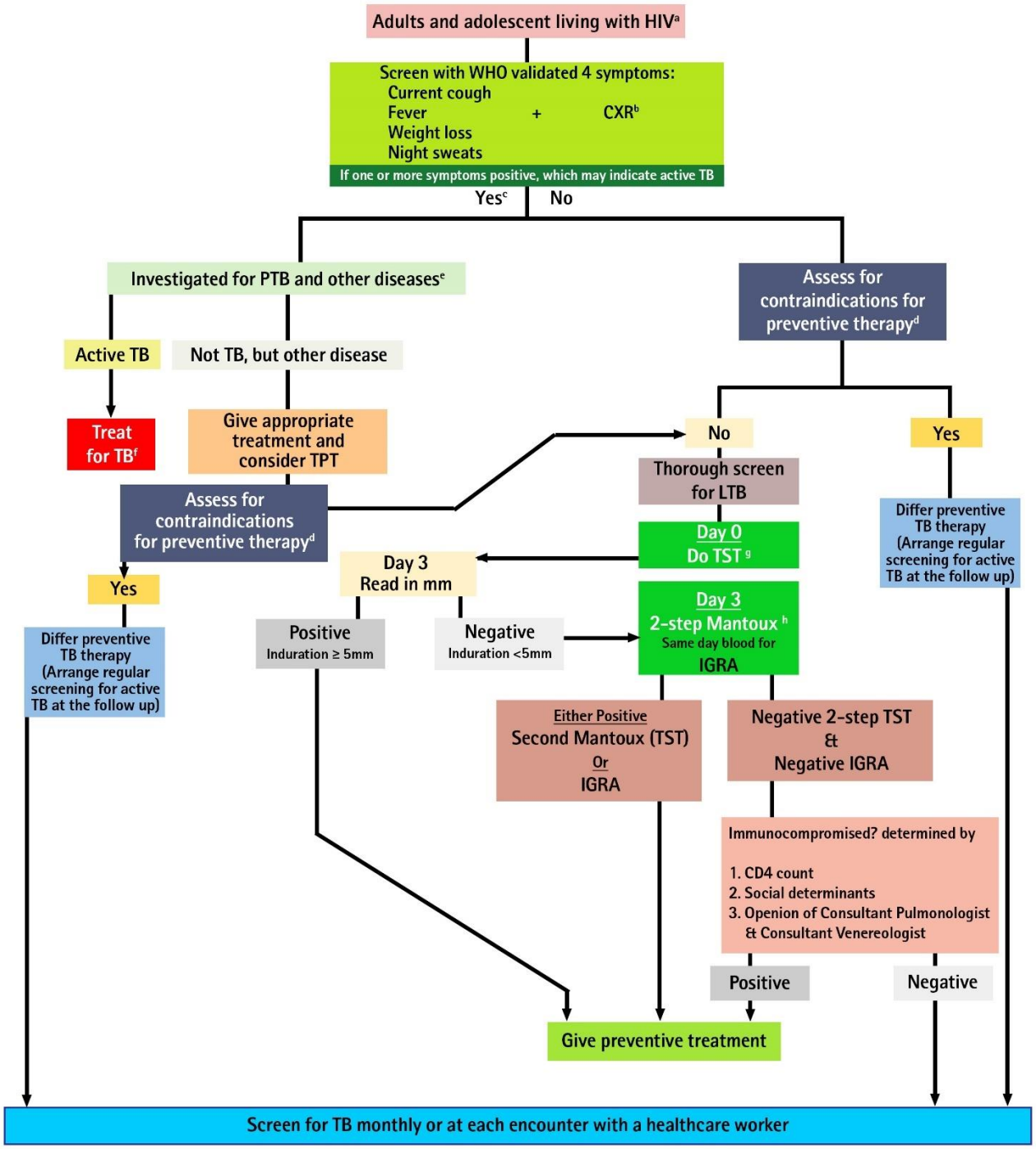
PLHIV who are excluded of having active or latent TB, should be subjected to assess the CD4 counts, social determinants (the TB burden of residential community) and final decision of TPT can be made by multidisciplinary discussion (MDT) among Consultant Pulmonologist and Consultant Venerologist. The PLHIV who are remaining needed to be screened symptomatically for active TB regularly at each clinic visit. (Also see **Flow Chart 5-2; Process of TB workup in PLHIV)**

Flow Chart 5-1; Important Screening Steps in PLHIV for TB



A. Intensified TB case finding
B. Screening for LTB
C. Regular symptomatic screening of PLHIV without Active or Latent TB for active TB

Flow Chart 5-2; Process of TB workup in PLHIV



a. Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce M. tuberculosis transmission in all settings in which care is provided.
b. Chest radiography is included into the initial screening tool / can be done if available, particularly for people living with HIV on ART. but is not required to classify patients into TB and non-TB groups.

c. Either symptoms or Xray or both are suggestive of TB or other diseases
d. Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of TB and current pregnancy should not be contraindications for starting preventive treatment.
e. Xpert MTB/RIF should be used as the initial diagnostic test for TB.
f. Resume regular screening for TB reactivation after completion of treatment for active TB disease.
g. TST of Tuberculin Skin test, also called Mantoux test once inoculated (on Day 1) intra dermally, the cutaneous induration should be measured in millimetres after 72 hours or Day 3. Is usually done in non-dominant forearm.
h. Two-Step Mantoux Test is doing a second TST after an initial negative TST reaction. Is to increase the sensitivity and to reduce false negativity, especially in HIV-infected persons by immune booster effect. The second test (Refer table 5-for other combinations) is done from 1 week to 3 weeks of the initial TST, in the same forearm.

Intensified case finding

Refer to the District Chest Clinic for TB case finding and management in following all categories of PLHIV.

A. Every newly diagnosed PLHIV

B. ALL HIV infected adults, adolescents and children living with HIV who have not undergone TB screening previously.

C. ALL HIV infected adults, adolescents and children, who are close contacts of smear positive TB patients.

Screening for active TB and case finding

The four symptoms-based screening is recommended by the current National Latent TB guidelines and WHO. (Refer; Flow Chart 5-2; Process of TB workup in PLHIV and Table 5-1; Symptom-based TB screening for PLHIV) Other screening tools are chest X-ray and sputum Gene-Xpert study.

Four Symptoms Based Screening

Symptom-based TB screening for PLHIV

PLHIV	Symptoms	Remarks
Children	Current Cough Poor weight gain* history of contact with a TB case Fever	If one or more symptoms positive which may indicate active TB disease
Adults and adolescents	Cough Fever Loss of weight Night sweats	If one or more symptoms positive which may indicate active TB disease

* "Poor weight gain" is defined as: 1. reported weight loss, or 2. very low weight (weight-for-age less than -3 z-score), or 3. underweight (weight-for-age less than -2 z-score), or 4. confirmed weight loss (>5%) since the last visit, or 5. growth curve flattening.

Chest Radiograph

In the diagnosis of pulmonary TB among PLHIV, it is important to note that, the spectrum of radiological findings varies according to HIV status and immunological status.

During the early phase of HIV when individuals are not immunosuppressed, the radiographic pattern is similar to HIV uninfected individuals with more typical lesions, such as upper lobe infiltrates with or without cavities.

Furthermore, in advance disease due to the marked immunodeficiency in PLHIV, chest X ray may give false negative findings, as well as shadows due to co-optimistic infections may give false positive findings. Therefore, it is important to be cautious when interpreting a chest X ray in advanced HIV status. Also with advancing immunosuppression, extra pulmonary involvement, intrathoracic/mediastinal lymphadenopathy, lower lobe infiltrate and miliary TB are usual featured on chest X-rays.

Gene-Xpert Study or X-pert MTB/RIF

Gene-Xpert, a cartridge based nucleic acid amplification (Real time Polymerize chain amplification) test is a widely accepted diagnostic test for Tuberculosis. This test is a rapid diagnostic test for Tuberculosis detection as well as Rifampicin resistance in direct smear negative cases.

This test in sputum is highly recommended in higher burden settings, and should utilize as an early diagnostic test, if indicated and available. This recommendation is not only due to its high sensitivity and specificity of detecting MTB in PLHIV, but also it will additionally give idea about rifampicin sensitivity, hence clue to MDR –TB.

Special consideration in screening of children for active TB

In paediatric TB, bacteriological confirmation should be sought whenever possible.

Diagnosis of latent TB

Currently, there is no universally accepted gold standard test for his purpose.

Screening for Latent TB

1. The Tuberculin skin test (TST) or Mantoux test - Is a surrogate marker of intact type IV cell mediate immune response. It involves a small injection of tuberculin (or purified protein derivative – PPD) into the skin, usually on the non-dominant forearm. After 72 hours the injection, the site is assessed and the induration, other than erythema is measured in millimetres. In immune-competent, the cut off value is taken, as 10mm, while immune-compromised like PLHIV it is 5mm or above it.
2. The Gamma Interferon (IFN-γ) Release Assays (IGRA) - When infected by MTB, the host T cells are sensitized to MTB antigens and the activated effector T cells, both CD4+ and CD8+, produce the cytokine interferon-gamma. The test stimulates the memory T cells in host's blood sample by in vitro sensitization using MTB specific antigens. There are two kinds of IGRA s in practice. They are as bellow.
    a. T-SPOT.TB – **(Detects number of spots or cells with specific INF- γ)** Uses the enzyme-linked immunospot (ELISPOT) methodology to enumerate M. tuberculosis-sensitized T cells by capturing interferon-gamma in the vicinity of T cells from which it was secreted.
    b. QuantiFERON-TB Gold - **(Detect the MTB specific quantity of INF- γ in plasma)** The QFT system uses specialized blood collection tubes, which are used to collect whole blood. Incubation of the blood occurs in the tubes for 16 to 24 hours, after which, plasma is harvested and tested for the presence of IFN-γ produced in response to the MTB specific single mixture of synthetic peptides antigens (ESAT-6, CFP-10, and TB7.7) to stimulate T cells. Although the ESAT-6 and CFP-10 antigens stimulate both CD4+ and CD8+ T cells to release IFN-γ, these two epitopes mainly stimulate CD4+ T cells.

The test requires, the collected blood specimen reach the Central Lab in Welisara within 8 hours of collection.

Future of Latent TB diagnosis

The novel skin tests: C-Tb skin test is in the pipeline. It is based on one-to-one bound two secreted MTB antigen hetero-dimeric complex called ESAT-6/CEP-10 complex.

They are,

- The ESAT-6 antigen complex: Early secreted Antigenic Target 6-kDa protein.
- CFP-10: 10 kDa secreted antigen from Mycobacterium tuberculosis.

The C-Tb skin test has similar sensitivity for active TB and latent TB compared to tuberculin skin test (TST) and QuantiFERON-TB-Gold-In-Tube (QFT). Current evidence is supporting C-Tb, as a safe and similar test-positivity rates, compared to TST and QFT, in children and HIV-infected persons with active or latent M. tuberculosis infection.

Diagnosis of Latent TB in PLHIV

Both tests; TST and IGRA are acceptable for use in PLHIV, but the possibility of false negative results should be considered. Therefore, combination of Two-step Mantoux and OGRA are recommended, if available. However, the final decision of starting TPT is by considering MDT approach by considering the CD4 cell number and social determinants.

TST: TSTs are considered positive in PLHIV if induration of ≥5 mm is present.

The Two-Step Mantoux is recommended to enhance the LTB detection reducing false negativity.

IGRA: According to current evidence T-SPOT.TB is more sensitive in detecting LTB, than QuntiFERON_TB Gold test, in PLHIV. The latter test will be available in Sri Lankan state sector soon.

Any PLHIV with reactivity on either LTB diagnostic tests, should be considered infected with M. tuberculosis.

Two-Step TST Decision Making Chart

<table>
<tr><th colspan="2">Person with unknown TST</th><th>One documented negative TST</th><th colspan="2">Properly documented results of previous two-step TST</th></tr>
<tr><td colspan="2">A two-step test is required</td><td></td><td></td><td></td></tr>
<tr><td>If both tests are negative, refer as *Person with a negative TST.</td><td>If either test is positive, refer as *Person with a positive TST</td><td>If the TST was done in the past 12 months, only a one-step test is required.
If the result is positive, refer as *Person with a positive TST.</td><td>If both tests are negative, only a one-step test is required.
If the result is positive, refer as *Person with a positive TST</td><td>If any previous test was positive, refer as *Person with a positive TST.</td></tr>
<tr><td colspan="5">*Person with a Positive TST</td></tr>
</table>

Best practice indicates that a two-step tuberculin skin test (TST) involves two tests performed within one to three weeks of each other. The second test can be completed up to one year from the first test, provided there has not been an exposure to infectious tuberculosis (TB) disease during that time period. It cannot be done less than one week from the first test.

Active TB disease and treatment in PLHIV

In PLHIV, TB-HIV-1 co-infection modifies the natural history, clinical presentations, and the outcomes of TB.

TB is a multisystem disease which can affect any organ other than hair. Usually in HIV negative patients, about 80% will develop pulmonary TB (PTB), and 14%-20% extra pulmonary TB (EPTB). However, in HIV-TB co-infection, the percentage having EPTB will be more. Therefore, more attention is needed to diagnose EPTB among PLHIV.

In addition, advanced HIV status will predispose them to disseminated TB, CNS TB, high disease related morbidity and mortality. Above all, due to immune failure with advancing HIV, the clinical and radiological manifestations of TB will be atypical, so the diagnosis is challenging.

Treatment of Active Tuberculosis in PLHIV

Treatment of drug-susceptible TB using 6-month regimen - Recommendation by WHO and adopted by National TB guidelines, Sri Lanka. See Box 5-1

Treatment of drug-susceptible TB in PLHIV

BOX 5-1: Recommendations	Level of Evidence
1. New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.	Strong recommendation, high certainty of evidence
2. Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy***	Strong recommendation, high certainty of evidence
3. In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, *and daily dosing remains the recommended dosing frequency.*	Conditional recommendation, very low certainty of evidence
4. The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.	Conditional recommendation, low certainty of evidence
5. In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended.	Strong recommendation, high certainty of evidence

***Directly observed therapy (DOT) is recommended over self-administered therapy, as is daily therapy over intermittent therapy – both are associated with better tuberculosis outcomes.

Initiating Drug-susceptible TB treatment (Anti TB therapy-ATT) and Antiretroviral therapy (ART) in PLHIV. See Box 5-2

In the 2022 update of WHO consolidated guidelines on tuberculosis (Module 4: treatment - drug-susceptible tuberculosis treatment) the following evidence-based recommendations are published. See BOX -5-2

BOX 5-2; Initiating Drug-susceptible TB treatment (Anti TB therapy-ATT) and Highly Active Antiretroviral therapy (HAART) in PLHIV	
Recommendation	Level of Evidence
▪ It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients	Strong recommendation, high certainty of evidence
▪ HAART should be started as soon as possible after initiating active TB treatment, regardless of CD4 cell count, among PLHIV **#	*For Adults* - Strong recommendation, low to moderate certainty of evidence *For Adolescents and Children* - Conditional Recommendation based on very-low-certainty of evidence
▪ In TB Meningitis-ART should be delayed at least four weeks (and initiated within eight weeks). Corticosteroids should be considered adjuvant treatment for TB meningitis.	RC trials, found no association between immediate ART and improved survival in patients with HIV-associated TBM; moreover, the confidence interval for the hazard ratio associated with immediate ART treatment was sufficiently narrow to exclude a risk reduction of ≥20% due to immediate ART. Furthermore, immediate ART appeared to be associated with a higher frequency of severe (grade 4) adverse events, suggesting that early ART initiation may actually be detrimental in this group.
▪ Children and infants	Strong recommendation, very low certainty of evidence

** Strong recommendation, very low certainty of evidence**ART timing trials in HIV-associated tuberculosis indicate early introduction of ART improves survival in several forms of tuberculosis, especially in patients with a low CD4 T-cell count.

Except for in TB meningitis.

- Having a low CD4 count, and early initiation of HAART are both risk factors for development of paradoxical TB-Immune-reconstitution inflammatory syndrome (TB-IRIS)
- Therefore, theoretically, TB-IRIS may be observed more frequently in the future and should be anticipated. Table 5.2

According to published guidelines by the WHO, the routine co-trimoxazole prophylaxis should be given to all PLHIV (including pregnant women and infants) with active TB disease regardless of CD4 cell count.

Concerns on combining ATT and ART

- Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS)
- Drug Toxicities and interactions

TB-IRIS: Is an abnormal, excessive immune response against alive or dead Mycobacteria tuberculosis that may occur in either HIV-infected or, more rarely, uninfected patients.

WHO recommendation for the use of adjuvant steroids in the treatment of TB meningitis

- In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. (Strong recommendation, moderate certainty of evidence).

For further clarifications please refer the National Manual of TB, Sri Lanka

Currently, there are no guideline-based definitive dosage recommendations found for systemic steroids regards to TB meningitis. However, case-based decisions by neurology opinion are advised.

Initiating TPT in PLHIV

Once active TB is ruled out, combination of Two-step Mantoux and IGRA are recommended, if available to screen for LTB to decide on TB Prophylaxis Treatment (TPT). However, the final decision of starting TPT is by considering MDT approach by considering the CD4 cell number and social determinants. (Please refer Flow Chart 5-2; Process of TB workup in PLHIV, and Box 5-3).

Box 5.3: Guide to rule out active TB and to screen and initiate treatment for LTB among adults and adolescent living with HIV

1. Follow four symptoms rule and Chest Xray to exclude active TB disease.
2. Two-Step TST and IGRA will be done on patients after excluding active TB disease
3. If either of Two-Step TST/IGRA testing are positive TPT can be initiated after confirming that the liver enzyme tests after initiation of ART is not significantly elevated within 3 months of testing for LTB.
4. If TST/IGRA tests are negative a team of Consultant Pulmonologist and Consultant Venereologists will assess the patient for severe immunocompromised status based on CD4 count and clinical determinants. If the consultative team determines that the patient is severely immunocompromised and/or has poor social determinants TPT is initiated despite negative TST/IGRA testing.
5. Pregnancy is not a contraindication for TPT. All pregnant women with HIV should be evaluated for latent tuberculosis and appropriate TPT should be initiated without delay.

Box 5-4: Guide to rule out active TB and to screen and initiate treatment for LTBI among children living with HIV

1. Provide TPT for infants aged <12 months living with HIV only if particular infant has a history of household contact with a person with TB and do not have TB disease according to investigations conducted.
2. Provide TPT for children aged ≥ 12 months living with HIV, irrespective of their contact history, after ruling out active TB disease.
3. Recommend preventive treatment for children, regardless of whether they are on ART or not.
4. Provide TPT for all children living with HIV who have been successfully treated for TB only if they are living in a residential area with high TB incidence and transmission. This decision should be taken with expert opinion considering the local epidemiology of the disease, socio economic background and other relevant factors (Preventive treatment can be started immediately after the last dose of TB therapy or later, according to clinical judgment).

Tuberculosis Preventive Therapy (TPT) for PLHIV

In the Sri Lankan context, decision on TPT prophylaxis in the absence of active TB will be taken at the discretion of the Consultant Chest Physician. Bellow mentioned PLHIV without active TB should receive at least six months of TPT as a part of a comprehensive package of HIV care. TPT can be given to such individuals irrespective of the degree of immune suppression, to patients on ART, to those who have previously been treated for TB and also to pregnant women.

Adults and Adolescents Living with HIV

1. Every newly diagnosed with HIV, and ALL HIV infected adults, adolescents after excluding active TB, when their TST or IGRA became positive.
2. Every newly diagnosed with HIV, and ALL HIV infected adults, adolescents after excluding active TB, when their TST or IGRA became negative, yet their level of immune-compromised state is significantly low (enough to cause false negative TST or IGRA), as decided by clinical experts TPT is indicated.

Infants: <12 months Old Living with HIV

3. Provide TPT for infants aged <12 months living with HIV only if particular infant has a history of household contact with a person with TB and do not have TB disease according to investigations conducted.

Children aged ≥ 12 months living with HIV

4. Provide TPT for children aged ≥ 12 months living with HIV, irrespective of their contact history, after ruling out active TB disease.

For all Children Living with HIV

5. Recommend preventive treatment for children, regardless of whether they are on ART or not.
6. Provide TPT for all children living with HIV who have been successfully treated for TB only if they are living in a residential area with high TB incidence and transmission. This decision should be taken with expert opinion considering the local epidemiology of the disease, socio economic background and other relevant factors (Preventive treatment can be started immediately after the last dose of TB therapy or later, according to clinical judgment).
    - For Children and Infants, the recommended dose of isoniazid (INH) for preventive therapy in HIV co-infection is 10 mg/kg daily for 6 months (maximum 300 mg/day)
    - TB prevention therapy should be implemented for contacts of a source case and for all HIV-infected individuals over a year of age. Although infection can be identified through skin tests or interferon gamma release assays, the non-availability of these tests should not preclude prevention therapy, once active TB has been excluded. Therapeutic options have moved from isoniazid only for 6–9 months to shorter regimens. Prevention therapy after exposure to a source case with resistant TB should also be implemented but should not prevent pivotal prevention trials already under way. A microbiological diagnosis for TB remains the gold standard because of increasing drug resistance. Antiretroviral therapy for

rifampicin co-treatment requires adaptation for those on lopinavir-ritonavir, which requires super-boosting with additional ritonavir. For those with drug resistant TB, the main problems are identification and overlapping toxicity between antiretroviral and anti-TB therapy. In spite of renewed focus and improved interventions, infants are still vulnerable to TB.

Important points to consider in managing Latent TB and TPT xxx

- Testing for latent TB infection using TST or IGRAs is not an essential requirement for initiating preventive treatment in PLHIV or children aged < 5years who are close contacts of a pulmonary TB patient.
- However, based on the clinical scenario of the child, grading of sputum results of index case, period and intensity of exposure, TST may be performed as a supportive evidence of tuberculosis infection.
- At each visit to HIV clinic, Consultant Venereologists or MO/STDs should counsel them and emphasize the importance of adherence to TPT and motivate them to attend the chest clinic and HIV clinic regularly.
- Peripheral neuropathy may occur in patients with HIV infection. This can be prevented or minimized by supplementary pyridoxine 10 mg daily.
- Document compliance to TPT, duration of TPT and instructions given in each visit.
- Steps should be taken to minimize transmission of TB in HIV clinic settings.

In the management of HIV/TB co infection case by case proper documentation, and maintenance (May involve computer-based data entry) of them in a manner, by which should be transparently available to the multidisciplinary teams involved in shared care for reference is important.

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Mycobacterium Avium Complex

Dr. R. Asha Samaranayake

Introduction

Mycobacterial disease is a major part of the spectrum of opportunistic infections (OIs) associated with HIV infection. Other than higher burden of HIV TB co-infection (Chapter 5) infections with at least 12 different Non Tuberculos Mycobacteria (NTM) have been reported in HIV scenario, and the most common is Mycobacterium avium complex (MAC). NTM are also known as mycobacteria other than tuberculosis (MOTT).

MAC infection in humans is caused by two main species: *Mycobacterium avium and Mycobacterium intracellulare*; because these species are difficult to differentiate, they are also collectively referred to as *Mycobacterium avium-intracellulare* (MAI). MAC is the atypical Mycobacterium most commonly associated with human disease.

The mode of MAC transmission is thought to be through inhalation, ingestion, or inoculation of MAC bacteria via the respiratory or gastrointestinal (GI) tract. Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.

Changing Epidemiology of MAC association with HAART

M. avium was the etiologic agent in 20% to 40% of PLHIV, who acquired disseminated MAC disease in the era prior to effective ART. The overall incidence of MAC disease among PLHIV has continued to decline in the modern ART era to current levels of <2 cases of MAC as the first opportunistic infection [OI] per 1,000 person-years.

Although the incidence of disseminated MAC disease is declining in the current ART era, there is evidence showing increased prevalence of MAC associated localized disease and pulmonary disease. In a study from an endemic area in southern Europe, mycobacteriosis was the third

cause of pulmonary infiltrates in HIV patients. This higher association may be partly due to frequent performance of TB cultures for PLHIV.

Epidemiologic studies have shown that NTM prevalence is increasing, with pulmonary disease being the most common clinical syndrome. As the prevalence of HIV infection increases due to longer life expectancies with ART, PLHIV may represent a unique cohort susceptible to NTM-related chronic respiratory illness. PLHIV may be particularly vulnerable to the consequences of NTM given their defective T cell-mediated immunity and high rates of structural lung disease. Furthermore, the emergence of chronic comorbidities in PLHIV, such as chronic obstructive pulmonary disease (COPD), may be permissive to NTM infection.

Current guidelines from the American Thoracic Society (ATS)/Infectious Diseases Society of America do not specifically address NTM in PLHIV, however, in whom diagnostic criteria and clinical outcomes may hold important consequences for differentiation between respiratory colonization, transient infection, subclinical or overt, active disease. Currently in Sri Lanka, the speciation of NTM is not available. However, according to the current evidence, MAC is the most common cause of infection by NTM in patients with AIDS. M. avium is the isolate in more than 95% of patients with AIDS who developed MAC infections.

Although ART has altered the frequency and outcome of MAC infection, it remains an important OI of AIDS.

Evidence based Risk Factors for MAC in PLHIV

- MAC disease typically occurs in PLHIV with CD4 cell counts <50 cells/mm3.
- Plasma HIV RNA levels >1,000 copies/mL.
- Ongoing viral replication despite ART.
- Previous or concurrent OIs.

Clinical Entities of MAC in PLHIV

MAC disease associated with HIV can be of three main clinical entities.

These are;

A. Disseminated multi-organ MAC infection is a common complication of late-stage HIV-1 infection. It is seen among those who are not on effective ART or poor with poor response to ART.
B. Localized disease has been reported more often in PLHIV who are having a good response to ART with immune restoration.
C. MAC associated pulmonary disease.

Symptoms and Signs of - MAC disease associated in HIV

A. Disseminated disease

Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms may include fever, night sweats, weight loss, fatigue, diarrhoea, and abdominal pain.

B. Localized disease

Organ specific focal symptoms can occur according to the organs involved.

Localized syndromes include cervical, intra-abdominal or mediastinal lymphadenitis, pneumonia, endophthalmitis, pericarditis, septic arthritis, osteomyelitis, skin or soft-tissue abscesses, palatal and gingival ulceration, bursitis, genital ulcers, or central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS).

C. HIV associated pulmonary NTM disease

The symptoms of NTM pulmonary disease are variable and nonspecific. However, virtually all patients have chronic or recurring cough. Other symptoms include sputum production, fatigue, malaise, dyspnoea, fever, haemoptysis, chest pain, and weight loss. Constitutional symptoms

are progressively more prevalent with advancing NTM lung disease. Evaluation is often complicated by symptoms caused by coexisting lung diseases, such as bronchiectasis, chronic obstructive airway disease associated with smoking.

Physical findings are nonspecific and reflect underlying pulmonary pathology, such as bronchiectasis and chronic obstructive lung disease. On chest auscultation, findings may include rhonchi, crackles, wheezes, and squeaks.

Laboratory Abnormalities

These include anaemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels. Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies.

Other laboratory abnormalities may occur with localized disease.

Diagnosis

A. Diagnosis of Disseminated MAC or Localised Disease

A confirmed diagnosis of disseminated MAC disease and local disease are based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids of involved site. [In Sri Lanka, the samples are sent to the central culture lab, as for MTB cultures through serving district TB clinic.]

When PLHIV present with lymphadenopathy it is recommended to perform TB culture to exclude MAC.

B. The Diagnostic Criteria of NTM Lung Disease

ATS/IDSA Criteria for Diagnosis of NTM Pulmonary Disease*

Adopted from An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases external icon.

Table 6-1: ATS/IDSA Criteria for Diagnosis of NTM Pulmonary Disease*

Category	Criteria
Microbiologic	▪ At least 2 separate positive cultures from sputum samples or ▪ At least 1 positive culture from a bronchoalveolar wash/lavage or biopsy or ▪ Biopsy with mycobacterial histopathologic features and at least 1 positive culture from sputum or bronchial wash
Radiographic	▪ Nodular or cavitary opacities or ▪ Multifocal bronchiectasis with small nodules
Clinical	▪ Pulmonary symptoms

A patient must fulfil criteria from all 3 categories to be diagnosed with NTM pulmonary disease.

*As both the clinical and radiological criteria are non-specific, other diagnosis causing these need to be excluded before considering these criteria for diagnosis of NTM pulmonary disease

- Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.

- Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
- Making the diagnosis of NTM lung disease does not, parse, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

Treatment

A. Disseminated disease

- ART should be started as soon as possible after the diagnosis of MAC disease, preferably at the same time as initiation of antimycobacterial therapy in people with HIV and disseminated MAC disease who are not receiving effective ART.
- If ART has already been initiated, it should be continued. The regimens should be modified when there is any potential for an adverse drug-drug interaction(s) between the antiretroviral and antimycobacterial drugs.
- Antimicrobial treatment of DMAC requires combination therapy that should include a macrolide [clarithromycin or azithromycin] and ethambutol with or without rifabutin. (Table 6-b)

Table 6-b: Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents -Disseminated Mycobacterium avium complex (MAC) disease (1)

Preventing First Episode of Disseminated MAC Disease (Primary Prophylaxis)
Primary prophylaxis is not recommended for adults and adolescents who immediately initiate ART (AII). *Indications for Initiating Primary Prophylaxis* ▪ Not on fully suppressive ART and ▪ CD4 count <50 cells/mm3 after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some people with HIV) (AI) *Preferred therapy* ▪ Azithromycin 1200 mg PO once weekly (AI), or ▪ Clarithromycin 500 mg PO BID (AI), or ▪ Azithromycin 600 mg PO twice weekly (BIII)

Alternative Therapy

- Rifabutin 300 mg PO daily (BI) (dose adjustment may be necessary based on drug-drug interactions)

Note: Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis

- Initiation of effective ART (AI)

Indication for Restarting Primary Prophylaxis

- CD4 count <50 cells/mm3 (only if not on fully suppressive ART) (AIII)

Treating Disseminated MAC Disease

Preferred Therapy

At least 2 drugs as initial therapy to prevent or delay emergence of resistance (AI)

- Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AI), or
- Azithromycin 500–600 mg (AII) plus ethambutol 15 mg/kg PO daily (AI) when drug interactions or intolerance precludes the use of clarithromycin

Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.

Alternative Therapy

Some experts would recommend addition of a third or fourth drug for people with HIV with high mycobacterial loads
(i.e., >2 log CFU/mL of blood), or in the absence of effective ART (CIII).
The Third or Fourth Drug Options May Include:

- Rifabutin 300 mg PO daily (CI) (dose adjustment may be necessary based on drug-drug interactions), or
- A fluoroquinolone (CIII) (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), or
- An injectable aminoglycoside (CIII) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily)

Chronic Maintenance Therapy (Secondary Prophylaxis)

Same as treatment regimens

Criteria for Discontinuing Chronic Maintenance Therapy (AII)

- Completed at least 12 months therapy, and
- No signs and symptoms of MAC disease, and
- Have sustained (>6 months) CD4 count >100 cells/mm3 in response to ART

Indication for Restarting Secondary Prophylaxis

- CD4 <100 cells/mm3 (AIII)

Other Considerations

- NSAIDs may be used for people with HIV who experience moderate to severe symptoms attributed to IRIS (CIII).
- If IRIS symptoms persist, a short-term course (4 weeks–8 weeks) of systemic corticosteroid (equivalent to prednisone 20–40 mg) can be used (CII).

Isoniazid and pyrazinamide are not effective for the therapy of MAC

Monitoring Patients Receiving Therapy for Disseminated MAC

Clinical manifestations of disseminated MAC such as fever, weight loss, and night sweats should be monitored regularly during the initial weeks of therapy. Microbiologic response, as assessed by blood culture every 4 weeks during initial therapy, can also be helpful in interpreting the efficacy of a therapeutic regimen.

Most patients who ultimately respond show substantial clinical improvement in the first 4-6 weeks of therapy. Elimination of the organisms from blood cultures may take somewhat longer, often requiring 4-12 weeks.

B. Localized disease

Focal MAC tends to occur at higher CD4 cell counts and in the presence of effective ART. Most clinicians would recommend a three-drug regimen for duration of at least 12 months and possibly for 24 months.

NTM Pulmonary disease

MAC Lung Disease treatment recommendations:

In Sri Lanka, the standard practice is based on British Thoracic guidelines. As a drawback we lack facilities for speciation.

- Patients respond best to MAC treatment regimens the first time they are administered; therefore, it is very important that patients receive recommended multidrug therapy the first time they are treated for MAC lung disease (A, II).
- Expert consultation should be sought for patients who have difficulty tolerating MAC treatment regimens or who do not respond to therapy (C, III)

Rifampicin 600 mg daily

and

Ethambutol 15 mg/kg daily

and

Azithromycin 250 mg daily or clarithromycin 500 mg twice daily

and

Consider intravenous amikacin for up to 3 months

or

nebulized amikacin

Duration of Pulmonary NTM infection treatment

Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

Preventing Exposure

MAC organisms commonly contaminate environmental sources of infection, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

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Cytomegalovirus (CMV)

Dr. Manjula Rajapakshe

Introduction

Cytomegalovirus (CMV) is a DNA virus in the herpes virus family that can cause disseminated or localized end-organ disease in HIV people with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV representing re-activation of latent infection but infection with a novel strain may also occur.

End-organ disease caused by CMV occurs in patients with advanced immunosuppression, typically those with CD4 count <50 cells/µl who are not receiving, adherent to, or responding to antiretroviral therapy (ART).

Clinical Manifestations

Retinitis

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients. It occurs as unilateral disease in many patients at presentation, but disease ultimately is bilateral in most patients in the absence of therapy or immune recovery.

Peripheral retinitis (not involving the macula or optic disc) may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Posterior retinal lesions, especially those impinging on the macula or optic disc are associated with decreased visual acuity or central field defects. Delay in diagnosis and treatment can lead to retinal detachment and blindness.

Colitis

Usual presenting features are weight loss, fever, anorexia, abdominal pain, diarrhoea, and malaise. In the colon (especially in the cecum), CMV can produce perforation and present as an acute abdomen. Haemorrhage and perforation can be life-threatening complications.

Oesophagitis

Occur in a small percentage. It presents with odynophagia, nausea, and occasionally mid epigastric or retrosternal discomfort as well as fever.

CMV neurologic disease

This includes CMV dementia, ventriculoencephalitis, and polyradiculomyelopathies.

Patients with dementia caused by CMV encephalitis typically have lethargy, confusion with or without fever.

Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death.

CMV polyradiculomyelopathy or transverse myelitis causes a Guillain-Barre-like syndrome characterized by radicular back pain, urinary retention, and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks causing loss of bowel and bladder control and flaccid paraplegia. Spastic myelopathy and sacral paraesthesia can occur.

Pneumonitis

In contrast to other conditions with severe immunosuppression such as solid organ and stem-cell transplant patients, CMV pneumonitis is uncommon in people with HIV. It can present with fever, cough or dyspnoea.

Diagnosis

The diagnosis of CMV end-organ disease is typically made on the basis of the clinical presentation and, when possible, evidence of the virus in tissue.

Retinitis

Retinitis can be clinically diagnosed with 95% Positive Predictive value (PPV) based on the recognition of characteristic retinal changes observed during an ophthalmoscopic examination performed by an experienced ophthalmologist. The characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal haemorrhage. The most typical feature is the lesion border, which has tiny dry-appearing, granular, dot-like "satellites" at the interface between infected and normal retina. Movement of lesion borders occurs at variable rates in different directions, causing a characteristic "brushfire" pattern.

Detection of CMV DNA in CSF or vitreous or aqueous humor specimens is highly suggestive that CMV is the cause of ocular disease, however, failure to detect CMV DNA in vitreous specimens does not rule out the presence of CMV retinitis. A response to empiric anti-CMV therapy also can be an important diagnostic indicator.

PCR of aqueous or vitreous humor specimens for other pathogens like herpes simplex virus, varicella zoster virus, and Toxoplasma gondii in addition to CMV can be useful in establishing the diagnosis when the diagnosis is unclear.

Colitis and Oesophagitis

In colitis, computed tomography (CT) may show colonic thickening or colonic mass. Usually, diagnosis of colitis is based on demonstration of mucosal ulcerations on endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions on haematoxylin and eosin stains.

Similarly, CMV oesophagitis is diagnosed by the presence of ulcers of the distal oesophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.

Culturing CMV, or detection of CMV DNA by PCR, from a biopsy or cells brushed from the colon or the oesophagus is insufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes, because a substantial number of patients with low CD4 cell counts may shed CMV and have positive cultures in the absence of clinical disease.

CMV neurologic disease

It is usually diagnosed with a compatible clinical syndrome, and the presence of CMV PCR in CSF or brain tissue often evaluated by PCR.

In addition, following features in CSF and imaging can be seen.

a. Encephalitis

CSF typically demonstrates lymphocytic pleocytosis (a mixture of neutrophils and lymphocytes), low-to-normal glucose levels, and normal- to-elevated protein levels

b. Ventriculoencephalitis

Periventricular enhancement of CT or MRI is highly suggestive of CMV ventriculoencephalitis rather than HIV-related neurologic disease.

c. Polyradiculopathy

The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100 to 200 neutrophils/µl and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Pneumonitis

The diagnosis of CMV pneumonitis is difficult and requires consistent clinical and radiological findings (i.e., fever, cough or dyspnoea and diffuse pulmonary interstitial infiltrates), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis like TB and PCP. Detection of CMV in the lungs in the absence of these criteria typically represents shedding, rather than clinical disease.

CMV (PCR) is detected frequently in the bronchoalveolar lavage (BAL) as a bystander and has not been shown to have diagnostic value in people with HIV.

CMV detection by antigen, PCR and culture

Blood tests to detect CMV by antigen detection, culture, or PCR are not recommended for diagnosis of CMV end-organ disease because of their PPV in people with advanced AIDS. CMV viremia can be detected by PCR, antigen assays, or culture and is often present in end organ disease. A negative serum or plasma PCR assay does not rule out CMV end-organ disease. CMV viremia may be present in the absence of end-organ disease in people with HIV with low CD4 cell counts. Even though a viral load more than 10^{4-5} is considered as high, there is no specific cut off value defined for HIV positive patients.

CMV PCR can be particularly useful in assessing CSF or vitreous or aqueous humor specimens; a positive result is highly suggestive that CMV is the cause of end organ disease.

CMV antibodies

The presence of serum antibodies to CMV, itself, does not establish the presence of CMV disease, because a large proportion of the general population has been exposed to CMV and is seropositive. An active CMV infection (primary or reactivated) is suggested if there is a 4-fold increase in IgG between the first and second sample. However, a negative immunoglobulin G (IgG) antibody level indicates that CMV is unlikely to be the cause of the disease process.

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/µl. Valganciclovir primary prophylaxis is not recommended to prevent CMV end-organ disease in people with HIV, even among patients who have CMV viremia.

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy.

Treatment

Retinitis

CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of retinal disease. The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications; prior exposure to anti-CMV drugs; and on the location of lesions.

Oral valganciclovir, intravenous (IV) ganciclovir, or IV ganciclovir induction followed by oral valganciclovir maintenance are first-line therapies for treating CMV retinitis. Although IV foscarnet, and IV cidofovir are also effective treatments for CMV retinitis, substantial toxicities, including nephrotoxicity, make these less-preferred options.

- Given the evident benefits of systemic therapy in preventing contra lateral eye involvement, reducing CMV visceral disease, and improving survival, treatment should include systemic therapy whenever feasible.

Immunoreconstitution Uveitis (IRU)

IRU, an ocular form of IRIS presumed to be an adverse immunologic reaction to CMV, is characterized by inflammation in the anterior chamber or vitreous body in the setting of immune recovery after initiation of ART and manifests symptomatically with decreased vision and/or floaters. IRU usually is observed in patients with a substantial rise in CD4 cell count in the first

4 to 12 weeks after initiation of ART. Careful ophthalmological monitoring is needed for early identification of IRU following treatment. Ocular complications of IRU include macular oedema and development of epiretinal membranes, which can cause loss of vision.

Treatment of IRU usually consists of periocular/ intravitreal/ oral administration of corticosteroid therapy. While a short course of corticosteroids is preferred, experts also recommend anti-CMV therapy to prevent CMV reactivation following corticosteroid treatment.

Treatment in different types of retinitis is given in below table

Initial Therapy Followed by Chronic Maintenance Therapy - For Immediate Sight threatening Lesions (within 1,500 microns of the fovea)

Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily, or
- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily, or
- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily, with or without
- Intravitreous injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady-state intraocular ganciclovir concentrations are achieved.

Note: IV ganciclovir can be switched to oral valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.

Alternative Therapy

- Intravitreous injections as listed above
  plus, one of the following systemic therapies:
- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h, or
- Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4g).

Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/kL, a calculated creatinine clearance ≤5 mL/min or a urine protein ≥100 mg/kL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised

Note: This regimen should be avoided in patients with Sulfa allergy because of cross-hypersensitivity with probenecid.

For Peripheral Lesions

- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily for the first 3–6 months until ART-induced immune recovery

Immune Reconstitution Uveitis (IRU)

- Minimizing lesion size by treating all CMV retinitis lesions until there is immune recovery may reduce the incidence of IRU.
- IRU might develop in the setting of immune reconstitution.

Treatment of IRU

- Periocular or intravitreal corticosteroid or a short course of systemic steroid.

Stopping Chronic Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3–6 months, and lesions are inactive, and with CD4+ count >100 cells/μL for 3–6 months in response to ART
- Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 cell count increase, anatomic location of the lesions, vision in the contra lateral eye, and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution.

Reinstituting Chronic Maintenance for CMV Retinitis

- CD4 count <100 cells/μL (AIII)

CMV neurological disease

Therapy for well-documented neurologic disease also has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, some experts would initiate therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach. The optimal duration of therapy has not been established and should be decided by the specialists based on clinical improvement.

Managing CMV Neurological Disease

- Doses are the same as for CMV retinitis.
- Treatment should be initiated promptly.
- Combination of ganciclovir IV plus foscarnet IV to stabilize disease and maximize response.
- Optimal duration of therapy has not been established.
- The role of oral valganciclovir has not been established.
- Optimize ART to achieve viral suppression and immune reconstitution.

Colitis or esophagitis

For patients who have colitis or esophagitis, anti-CMV therapy for 21 to 42 days or until signs and symptoms have resolved is generally recommended. IV ganciclovir generally is the therapy of choice and can be switched to oral valganciclovir once the patient can tolerate and absorb oral medications. Foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment-limiting or in cases of ganciclovir-resistant virus. Oral valganciclovir can be used in patients with mild disease.

Managing CMV Esophagitis or Colitis

- Doses are the same as for CMV retinitis.

Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy.

Alternative Therapy

- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h —for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance.

or

- Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption

Duration of Anti-CMV Therapy

- 21–42 days or until signs and symptoms have resolved.

Note: Maintenance therapy is usually not necessary but should be considered after relapses.

CMV Pneumonitis

Experience treating well-documented CMV pneumonia in patients with HIV infection is limited. Treatment with IV ganciclovir or, alternatively, with foscarnet, is logical. The optimal duration

of therapy has not been established and should be decided by the specialists based on clinical improvement.

Managing Well-Documented CMV Pneumonitis

- Doses are the same as for CMV retinitis.
- Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable.
- The role of oral valganciclovir has not been established.
- The optimal duration of therapy has not been established.

Monitoring of Response to Therapy and Adverse Events

Indirect ophthalmoscopy of both eyes through dilated pupils should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment to evaluate efficacy of treatment, identify second eye involvement in cases of unilateral disease, and to detect IRU or such complications as retinal detachment.

Frequency of ophthalmologic follow-up can be decreased to every 3 months for patients who have experienced immune recovery (CD4+ count >100 cells/μL for ≥3 months). However, clinicians should be aware about the possibility of lesion reactivation and retinal complications with immune reconstitution.

Adverse effects of ganciclovir/valganciclovir include anaemia, neutropenia, thrombocytopenia, nausea, diarrhoea, and renal dysfunction. In patients receiving ganciclovir or valganciclovir, complete blood counts and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy.

Adverse effects of foscarnet include nephrotoxicity and electrolyte abnormalities; seizures that occur characteristically in the context of renal insufficiency; and anaemia. Genital ulcers also can occur in those who are incontinent to urine due to the toxic effects of excreted drug on exposed skin. For patients receiving foscarnet, serum electrolytes (including potassium, magnesium, calcium, and phosphorus) and renal function should be measured at least twice weekly during induction and at least weekly during maintenance therapy. Complete blood counts should be monitored weekly.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and low intraocular pressure. The risk of severe renal injury from IV cidofovir can be reduced by pre-hydration and oral probenecid before cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion. Drug administration is contraindicated if renal dysfunction or substantial proteinuria is detected.

Anti-retroviral treatment

As CMV replication usually declines within 1 to 2 weeks after anti-CMV therapy is initiated, it is justifiable to initiate ART no later than 1 to 2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV.

Immune reconstitution inflammatory syndrome (IRIS) from CMV may occur in patients who have active retinitis (and those who have had CMV retinitis in the recent or distant past) and neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, most experts would not defer initiation of ART for more than 2 weeks, although clinical judgement based on individual cases is needed.

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Progressive Multifocal Leukoencephalopathy (PML)

Dr. Nimali Jayasuriya

Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the reactivation of the endemic JC virus (a polyomavirus). Entry point of the virus is thought to be via the respiratory or oral route, and it becomes latent in the kidneys, lymphoreticular tissues, and brain.

The primary infection is asymptomatic. It can be reactivated with viral replication in the settings of immune suppression, resulting in dissemination to the brain. The cardinal pathological feature is demyelination of white matter due to viral DNA replication and is irreversible. Unlike some of the other CNS opportunistic infections that are prevented when CD4 cell counts are maintained above 100 to 200 cells/µL, PML can still appear in such patients.

Clinical presentation

PML manifests as focal neurological deficits, including behavioural, speech, cognitive, motor, and visual impairment, usually with insidious onset and steady progression. Because demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Aphasia, hemi-paresis, hemi-sensory deficits, ataxia, and loss of vision are common presentations. Head tremor is a less common presentation. Gait abnormalities occur in up to 65% patients and cognitive dysfunction is seen in up to 30% people. Seizures develop in nearly 20% of PML patients. Headache and fever are not characteristic features of PML.

Diagnosis

PML can be diagnosed either histopathologically or clinically including radiological and virological evidence.

- Magnetic resonance imaging (MRI) of brain
  Typically seen as multifocal, asymmetric periventricular and subcortical involvement with little or no mass effect or enhancement.
- JC virus detection by PCR in CSF
- Brain biopsy

Differential diagnosis

1. Multiple sclerosis

   Early in the disease MS and PML may appear similar. Periventricular location or well-defined borders favour new MS lesions

2. HIV encephalopathy

   Often diffuse white matter disease, with atrophy, symmetric, spares the subcortical U-fibres.

3. Posterior reversible encephalopathy syndrome (PRES)
   - Differing clinical history (e.g., hypertension)
   - Can involve both grey and white

4. Acute disseminated encephalomyelitis (ADEM)
   - Differing clinical history (e.g., recent infection/vaccination)
   - Can involve both grey and white matter lesions usually enhancing lesions.

5. Cerebral toxoplasmosis:
   - Usually, ring enhancing lesions

6. HIV CNS lymphoma:
   - Usually, ring enhancing lesions

Establishing the diagnosis with clinical, radiographic, and laboratory data

Certainty of PML diagnosis	Compatible Clinical Features	Compatible Image Findings	CSF JCV PCR
Definite	+	+	+
Probable	+	-	+
	-	+	+
Possible	+	+	- /or not done
	-	-	+
No PML	-	-	-
	+	-	-
	-	+	-

Treatment

No specific therapy exists for PML. The main approach to treatment is antiretroviral therapy (ART) to reverse the immunosuppression that interferes with the normal host response to this virus. ART should be started as soon as PML is diagnosed. Treatment response should be monitored with clinical examination and MRI. Neuroimaging can be repeated 6 to 8 weeks after ART initiation.

PML-IRIS

PML-Immune Reconstitution Inflammatory Syndrome has been reported to occur within the first weeks to months after initiating ART. Clinical and radiographic features are different from classical PML. Clinical course is more rapid with oedema and mass effect. Neuro imaging shows contrast enhancement. High-dose glucocorticoid therapy have been used empirically to treat this with reported benefits.

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HIV Associated Other Infections

Dr. Sachini Mendis

Bartonellosis

Epidemiology

Bartonella species cause infections that include cat scratch disease (CSD), retinitis, trench fever, relapsing bacteraemia, culture-negative endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis. The latter two manifestations occur almost exclusively in individuals who are immunocompromised. This occurs often in the latent infection, in patients with median CD4 T lymphocyte (CD4 cell) counts less than 50 cells/µl.

In patients with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year, with bacillary angiomatosis (BA) lesions and intermittent bacteraemia.

Clinical Manifestations

Bartonella lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. Bacillary angiomatosis represents a hematogenous disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany it. This infection is a major cause of unexplained fever in patients with advanced HIV and should be considered in the differential diagnosis of patients with CD4 counts less than 100 cells/µl and fever. Bartonella is a frequent cause of culture-negative endocarditis in immunocompetent and immunocompromised humans.

Diagnosis

This can be confirmed by histopathologic examination of biopsied tissue. These lesions are characterized by vascular proliferation, and a modified silver stain (such as Warthin-Starry stain)

usually demonstrates numerous bacilli. Histological features reveal innumerable gram-negative bacilli featuring intra- and extracellular distribution. Warthin-Starry silver staining will show small dark staining bacteria and electron microscopic findings include pleomorphic bacilli with a trilaminar wall. Tissue gram staining and acid-fast staining are negative. By the time Bartonella infection is suspected in patients with late-stage HIV infection, they usually have been infected with Bartonella for months or even >1 year. However, as many as 25% of Bartonella culture-positive patients never develop antibodies in the setting of advanced HIV infection.

Treatment

All patients with HIV and Bartonella infection should receive antibiotic treatment. No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in patients with HIV.

Special Consideration with regard to starting ART

The potential exists for immune reconstitution inflammatory syndrome (IRIS) in association with bartonellosis and antiretroviral therapy (ART) in persons with HIV. In ART-naive patients, ART generally can be initiated at the same time as Bartonella-directed treatment; however, patients with Bartonella CNS or ophthalmic lesions probably should be treated with doxycycline and a rifamycin class antibiotic for 2 to 4 weeks before instituting ART.

Long-term suppression can be discontinued after the patient has received at least 3–4 months of therapy and when the CD4 count remains >200 cells/μl on effective ART for ≥6 months. Some specialists would discontinue therapy only if the Bartonella titres also have decreased fourfold.

Preferred Therapy for Cat Scratch Disease, Bacillary Angiomatosis, Peliosis Hepatis, Bacteraemia, and Osteomyelitis:

- Doxycycline 100 mg PO or IV every 12 hours

  or

- Erythromycin 500 mg PO or IV every 6 hours

For Infections Involving the CNS:

- Doxycycline 100 mg PO or IV every 12 hours +/– Rifampin 300 mg PO or IV every 12 hours

For Confirmed Bartonella Endocarditis:

- Doxycycline 100 mg IV 12h + Rifampin 300 mg IV or PO every 12 hours for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months

  or

- Doxycycline 100 mg IV q12h + Gentamicin 1 mg/kg IV every 8 hours for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours

Coccidioidomycosis

Coccidioidomycosis is caused by either of two soil-dwelling dimorphic fungi: Coccidioides immitis and Coccidioides posadasii. The risk of developing symptomatic coccidioidomycosis after infection is increased in patients with HIV who have CD4 T lymphocyte counts < 250 cells/µL.

Clinical Manifestations

Four common clinical syndromes of coccidioidomycosis have been described as focal pneumonia, diffuse pneumonia, extrathoracic involvement, including meningitis, osteoarticular infection, and other extrathoracic sites.

In patients with HIV, lack of viral suppression and CD4 count of less than 250 cell/µL are associated with an increased severity of the presentation of coccidioidomycosis. Patients present with symptoms that include cough, fever, and pleuritic chest pain, However, coccidioidomycosis may present with hilar or mediastinal adenopathy, upper lobe infiltrates, nodules, and peripheral blood eosinophilia. Diffuse pneumonia and the extrathoracic disease usually occur in more immunocompromised patients. The diffuse pulmonary disease presents with fever and dyspnoea with a diffuse reticulonodular pattern on chest imaging, and in some instances may be difficult to distinguish clinically from Pneumocystis pneumonia.

Diagnosis

The diagnosis of coccidioidomycosis is based on serology, histology, culture, and clinical presentation. Culture of the organism from clinical specimens or by demonstration of spherules on histopathological examination of infected tissue confirms the diagnosis. In disseminated disease, cultures of bone marrow are frequently positive. Bone marrow trephine and culture should be performed if disseminated disease is suspected. Consideration should be given to testing serum Histoplasma antigen to follow the response to therapy in disseminated disease.

Definitive diagnosis involves the culture of the organism from sputum, broncho-alveolar lavage (BAL), or a biopsy specimen which can take up to 4 weeks for growth or identification of the yeast on a biopsy specimen or body fluid. In disseminated disease, cultures of bone marrow are frequently positive and blood cultures may also be diagnostic. Patients with disseminated histoplasmosis may have very high LDH levels (4600 IU/L). Diagnosis of CNS disease may be difficult as fungal stains, culture and even serological tests may all be negative.

Treatment

Treating Mild to Moderate Pulmonary Infection

Preferred Therapy: Fluconazole 400 mg PO once daily ***or***

Itraconazole 200 mg PO three times daily - for 3 days then twice daily

Treating Severe Pulmonary or Extrapulmonary Infection (except meningitis)

Preferred Therapy: Lipid formulation Amphotericin B 3–5 mg/kg IV daily

Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily

Treatment For Meningeal Infections

Preferred Therapy: Fluconazole 400–800 mg IV or PO once daily

Alternative Therapy: Itraconazole 200 mg PO two to three times daily ***or***

Voriconazole 200–400 mg PO twice daily

Discontinuing of therapy

Focal Coccidioidal Pneumonia:

Therapy can be stopped if,

- There is a clinical response for ≥3 months of antifungal therapy and
- CD4 count ≥250 cells/mm^3 and
- Virologic suppression on ARVs

Continued monitoring for recurrences using serial chest radiographs and coccidioidal serology is necessary.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

Relapse can occur in 25% to 33% of patients without HIV and can occur in patients with HIV who have CD4 counts >250 cells/ mm^3.

Duration is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts.

Coccidioidal Meningitis:

Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong.

Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus Histoplasma capsulatum. CD4 count of less than 150 cells/μL is associated with an increased risk of symptomatic illness in people with HIV. Histoplasmosis is acquired by inhalation of microconidia that form in the mycelial phase of the fungus in the environment. Asymptomatic dissemination of infection beyond the lungs is common.

Clinical Manifestations

In patients with HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnoea occur in approximately 50% of patients. Central nervous system (CNS), gastrointestinal (GI), and cutaneous manifestations occur in a smaller percentage of patients. CNS histoplasmosis typically experiences fever and headache, and if brain involvement is present, seizures, focal neurological deficits, and changes in mental status. CNS histoplasmosis typically experience fever and headache, and if brain involvement is present, seizures, focal neurological deficits, and changes in mental status.

In patients with CD4 counts >300 cells/μL, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

Diagnosis

H. capsulatum can can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or samples from other involved sites. Histoplasma antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated and acute pulmonary histoplasmosis. Histopathological examination of biopsy material from involved tissues often demonstrates the characteristic 2 to 4 μm in diameter budding yeast cells.

Treatment

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy - for ≥2 weeks or until clinically improved

Preferred Therapy: Liposomal amphotericin B at 3 mg/kg IV daily

Alternative Therapy: Amphotericin B lipid complex at 5 mg/kg IV daily

Maintenance Therapy

Preferred Therapy: itraconazole 200 mg PO three times a day for 3 days, then two times a day for ≥12 months

Talaromycosis

Talaromycosis is an invasive fungal infection caused by the dimorphic fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*), which is endemic in Southeast Asia (in northern Thailand, Vietnam, and Myanmar), East Asia (in southern China, Hong Kong, and Taiwan), and South Asia (in north-eastern India). This disease was previously called Penicilliosis and is now called Talaromycosis. HIV is a major risk factor for Talaromycosis in highly endemic regions and also a major cause of HIV-associated opportunistic infections in these regions, making up to 16% of hospital admissions due to AIDS. Infection occurs predominantly in individuals who have a very advanced HIV disease with a CD4 T lymphocyte (CD4) cell count of less than 100cells/µl. Talaromycosis related mortality despite antifungal therapy in patients both with and without HIV is up to 30%.

Clinical Manifestations

Disseminated infection involving multiple organ systems is the most common manifestation of Talaromycosis in patients with advanced HIV disease. The infection frequently begins as a subacute illness characterized by fever, weight loss, hepatosplenomegaly, lymphadenopathy, and respiratory and gastrointestinal abnormalities. These clinical features are non-specific and indistinguishable from disseminated tuberculosis, other systemic mycoses, or infections.

Skin lesions are the most specific but late manifestations of Talaromycosis, with central-necrotic papules appearing on the face, trunk, and extremities. Pulmonary involvement is manifested as cough or shortness of breath and gastrointestinal involvement present as diarrhoea or abdominal

pain, significant hepatosplenomegaly with intra-abdominal lymphadenopathy causing abdominal distention and pain. Concurrent infections with other opportunistic pathogens occur like oropharyngeal candidiasis and tuberculosis.

Common laboratory findings associated with Talaromycosis include anaemia and thrombocytopenia due to bone marrow infiltration.

Diagnosis

Diagnosis of Talaromycosis should be considered in all patients with HIV with CD4 less than 100 cells/µl and who have travelled to or have lived in Talaromycosis-endemic areas and present with a systemic infection involving the reticuloendothelial system.

The current diagnostic methods for Talaromycosis are still based on conventional microscopy, histology, and culture. A definitive diagnosis of Talaromycosis can be made by the histopathologic demonstration of the organism in biopsy specimens.

Indication for Primary Prophylaxis

Primary prophylaxis is only recommended for patients with HIV with CD4 counts less than 100 cells/µL who reside in highly endemic regions. The drug choices for prophylaxis are oral itraconazole 200 mg once daily or oral fluconazole 400 mg once weekly. Primary prophylaxis is not recommended in patients who are on or about to start effective ART.

Discontinuation of Primary Prophylaxis

Primary prophylaxis for Talaromycosis can reasonably be discontinued in patients who are ART adherent and have a sustained CD4 count >100 cells/µL for over 6 months.

Treatment

Disseminated Talaromycosis is fatal if untreated. The case fatality rates with antifungal therapy range from 10% to 30%. Antifungal therapy for Talaromycosis is divided into induction, consolidation, and maintenance phases.

Induction therapy

Deoxycholate amphotericin B for 2 weeks

Consolidation therapy

Itraconazole for 10 weeks was shown to be highly effective.

The treatment success rate (defined by negative blood culture and resolution of fever and skin lesions at the end of a 12-week treatment course) was 97%.

Voriconazole has been used for induction therapy in patients who could not tolerate Amphotericin B and was shown to have favourable clinical and microbiological outcomes. Induction therapy should be followed by consolidation therapy with oral Itraconazole, 200 mg every 12 hours for a subsequent duration of 10 weeks.

Maintenance therapy (or secondary prophylaxis)

Oral Itraconazole 200 mg/day is recommended to prevent recurrence until the CD4 count rises above 100 cells/μL for ≥6 months.

For patients unable to tolerate any form of Amphotericin, induction therapy with IV Voriconazole 6 mg/kg every 12 hours on day 1 (loading dose), then 4 mg/kg every 12 hours or with oral Voriconazole 600 mg every 12 hours on day 1 (loading dose), then 400 mg every 12 hours for 2 weeks is recommended. Thereafter, either oral Voriconazole or oral Itraconazole 200 mg every 12 hours can be used for consolidation therapy for 10 weeks, followed by Itraconazole 200 mg/day for secondary prophylaxis. The optimal dose of Voriconazole for secondary prophylaxis beyond 12 weeks has not been studied. Itraconazole is not recommended as induction therapy for Talaromycosis, regardless of disease severity.

Chagas disease

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi,* and transmitted to humans by infected triatomine bugs, and less commonly by transfusion, organ transplant, from mother to infant, and in rare instances, by ingestion of contaminated food or drink.

The parasite enters the human body through the bite wound, or through the intact conjunctiva or another mucous membrane. Vector-borne transmission occurs only in America, where an estimated 8 to 10 million people have Chagas disease where the transmission occurred largely in rural areas in Latin America where it is endemic.

Clinical Manifestations

The acute phase of *T. cruzi* infection typically goes unrecognized. The other symptoms of acute infection are usually limited to a non-specific febrile illness. However, acute, life-threatening myocarditis or meningoencephalitis may occur in a small proportion of patients. Most patients with chronic *T. cruzi* infection have no signs or symptoms and are said to have the indeterminate

form of the disease. Over the course of their lives, 20% to 30% of them will progress to clinically evident Chagas disease, most commonly cardiomyopathy.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized in HIV-infected patients. Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts less than 200 cells/µl. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas). The presentation may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of AIDS patients with CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in HIV-infected patients is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease. Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation, or rapid progression of existing chronic cardiomyopathy. Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach, or intestine.

Diagnosis

Diagnosis of Chagas disease requires a combination of imaging, serology, PCR, and if available histological confirmation. Asymptomatic individuals with HIV infection from an endemic area should be screened with serology and, if positive, be further evaluated for disease.

Diagnosis of chronic infection relies on serological methods to detect IgG antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA).

A definitive re-activation diagnosis is established by identifying the parasite or its products in tissue, such as on brain biopsy, CSF, or blood.

In HIV-infected patients with epidemiologic risk factors for Chagas disease, co-infection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias, or heart failure. The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than Toxoplasma lesions. Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter.

Treatment

Benznidazole is the treatment of choice for acute primary infection or reactivation of Chagas disease.

Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days

Alternative therapy

Nifurtimox 8–10 mg/kg/day PO for 90–120 days

Following treatment, secondary prophylaxis with benznidazole 5 mg/kg three times weekly is recommended: there is no evidence to guide the optimum duration, but the duration is likely to be governed by the same factors as other opportunistic infections and be influenced by the immunological and virological response to HAART.

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Cardiovascular Disease

Dr. Lasanthi Siriwardena

Introduction

Atherosclerotic Cardiovascular disease (ASCVD) is a significant contributor to the non-AIDS death in People Living with HIV (PLWH) on ART (Boettiger et al., 2020). PLWH are twice at risk of developing CVD than people without HIV and the global burden of HIV associated CVD has almost tripled over the last two decades with the greatest impact in Sub Saharan Africa and Asia Pacific region (Shah et al., 2018). The high prevalence of traditional risk factors for ASCVD in PLWH and the persistent inflammation associated with long term ART and HIV infection itself is contributory for this (Boettiger et al., 2020).

ASCVD risk factors in PLWH

In addition to the standard risk factors such as age, genetics, physical inactivity, obesity, diabetes, hypertension and smoking, coinfections like hepatitis C and CMV, HIV related inflammation and immune activation and certain ART can increase the risk of ASCVD in PLWH.

Some classes of ARV drugs e.g., PIs and abacavir can increase the risk of premature CVD (Friis-Møller et al., 2007, Costagliola et al., 2020). However, **the overall beneficial role of ART on HIV morbidity and mortality has been demonstrated to outweigh potential CVD risks in people with HIV.**

Cardiovascular disease risk calculators

The future risk of CVD can be estimated using algorithms such as Framingham risk score and the Atherosclerotic Cardiovascular Disease Risk Score. However, these algorithms are not specific to PLWH and are developed predominantly using data from the Western, Caucasian populations.

The D.A.D Risk score is more specific for PLWH but has not been validated for Asian populations. Another risk score in use is the QRISK3 which is developed for the UK populations which has its attributes by considering different ethnicities and various comorbidities that are common in PLWH (Choi et al., 2022)

Management of CVD

- **Screening** – CVD risk should be screened using an appropriate risk calculator (D.A.D. risk score or QRISK3 may be considered)
- **Lifestyle Management:**
  Diet – reduce saturated fatty acids, refined carbohydrates and red meat and increase poly and monounsaturated fatty acids, vegetables, fruits and whole grain products.
  Exercise – Promote an active lifestyle
  Maintenance of Body Weight – In Asia overweight is defined as 23-25kg/m2 and obesity as >25 kg/m2 and central obesity is >90cm waist circumference for men and >80cm waist circumference for women.
  Smoking cessation
- **Management of key modifiable risk factors**

  Lipids – Lipid profile should be done at baseline and 3-6 months after ART and annually thereafter. The target level of LDL for primary prevention of CVD is <2.0 mmols/L (77.34 mg/dl) and secondary prevention is <1.4 mmols/L (54.14 mg/dl). If LDL remains elevated despite lifestyle modifications, lipid lowering agents should be initiated with ART modification if necessary. (e.g., switching to TDF or NRTI sparing regime for those with >10% CVD risk)

  Type 2 Diabetes – Fasting blood sugars should be assessed at baseline and annually thereafter.

  Hypertension – Blood pressure should be assessed at least every 6 months. If systolic >140mmHg and diastolic >90mmHg treatment should be considered particularly if the CVD risk is >10%. For those >65 years the systolic blood pressure should be 130-139 mmHg.

- **Antiretroviral therapy**
  Early initiation
  Choice of ART regime in initiation and switching
  - Lopinavir/r and Abacavir should be avoided when suitable alternatives are available.
  - First-line ARV therapy with tenofovir plus emtricitabine or lamivudine is preferred
  - Adverse effects of lipid parameters should be considered when selecting a regimen.

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Diabetes Mellitus (Type 2)

Dr. Buddhika Perera

Introduction

People with HIV are more likely to have type 2 diabetes than people without HIV. Antiretroviral medications such as AZT, LPV/r and other boosted protease inhibitors also can make them more susceptible to develop type 2 diabetes. Furthermore, there are drug-drug interactions between ARTs and anti-hypoglycemic medications. Therefore, it is important to screen and diagnose the patients with HIV for type 2 diabetes and also to monitor them once diagnosed. There is no evidence to suggest that patients with HIV need specific protocols for the management of type 2 diabetes.

Screening

All adults with HIV infection are recommended to be screened for diabetes prior to ARV commencement and annually thereafter with fasting plasma glucose (FPG).

Diagnosis

Test	Pre-diabetes	Diabetes Mellitus
Fasting Plasma Glucose (FPG)	100-125 mg/dl (5.6-6.9 mmol/L)	> 126 mg/dl (7.0 mmol/L)
Two-hour plasma glucose in 75 gm oral glucose tolerance test (OGTT)	140-199 mg/dl (7.8-11.0 mmol/l)	> 200 mg/dl (11.1 mmol/L)
HbA1c	5.6-6.4%	> 6.5%
Other		A random plasma glucose >200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis

Confirming diagnosis

Unless a clear clinical diagnosis (patient in a hyperglycaemic crisis or with classic symptoms of hyperglycaemia) is available, diagnosis should be confirmed by repeating the same test with a new blood sample or by another test. If the patient is having discordant results from two different tests, then the test result that is above the diagnostic cut off should be repeated.

Management and Monitoring

Management, monitoring and risk-reduction strategies need to be employed in partnership with general practitioners and other healthcare providers to avoid duplication. Therefore, it is advisable to liaise with physicians and endocrinologists to optimize management and monitoring.

Management goals

- Lifestyle modification and patient education
  - Medical nutrition therapy
  - Physical activity
  - Quit smoking
  - Control alcohol intake
- Maintenance of good glycaemic control
  - Pharmacotherapy
- Multiple risk factor management
  - Hypertension
  - Dyslipidaemia
  - Cerebro- vascular disease
  - Chronic Kidney disease
- Prevention of complications

Monitoring

Glycaemic targets

Plasma glucose monitoring can be performed every 3 monthly till the glycaemic control is achieved and 6 monthly thereafter.

Liaise with the other healthcare providers to avoid duplication of testing.

Test	Target
FPG (8 to 12 hours fasting)	80–130mg/dL (4.4–7.2mmol/L)
Post prandial plasma glucose/ Peak postprandial* capillary plasma glucose *(1-2 hrs after the beginning of a meal)	<180 mg/dL (<10.0 mmol/L)
HbA1c	6.5% if no drug induced hypoglycaemic episodes. 7.0% if associated with drug induced hypoglycaemic episodes.

Commonly used oral hypoglycaemics

Class	Medication
Biguanides	Metformin
Sulfonylureas	Tolbutamide, Gliclazide, Gliclazide MR*, Glipizide, Glibenclamide, Glimepiride
α-Glucosidase inhibitors	Acarbose
DPP-4 inhibitors	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin
GLP1 receptor agonists	Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide, Semaglutid
TZD	Pioglitazone
SGLT2 Inhibitor	Dapagliflozin, Canagliflozin, Empagliflozin

* Gliclazide Modified Release tablets

Common interactions between ART and oral hypoglycaemics

DTG and Metformin: Co-administration of metformin and DTG increases metformin concentration significantly. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin in order to maintain glycaemic control. It is recommended to limit the total daily dose of metformin to 1000 mg when co-administering with DTG.

DRV/cobi and Metformin: Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with darunavir/cobicistat. Careful patient monitoring and dosage adjustment of metformin is recommended.

DRV/R and Sulfonylureas: Darunavir/ritonavir could potentially increase sulfonylurea concentrations except for tolbutamide. Monitor clinical effect and reduce sulfonylurea dosage if needed. But tolbutamide concentrations may be reduced and may need dose increase to get the desired effect.

Screening for end organ damage

Screening for microvascular complications in Type 2 DM should be started at diagnosis and repeated at least annually. End organ damage in diabetes and the screening methods include;

- **Diabetic neuropathy**
    - Distal symmetrical polyneuropathy
        - A careful history and 10-g monofilament testing with at least one of the following tests:

          Pinprick sensation, ankle reflex or vibration perception using 128 Hz tuning fork, vibration perception threshold
    - Autonomic neuropathy – symptom screening
- **Peripheral arterial disease**
    - Examine the extremity for pulse, non-healing wounds and gangrene
    - Ankle- Brachial index (ABI) is indicated in the following circumstances
        - Clinical PAD
        - Age> 50 years or < 50 years with other PAD risk factors (e.g., smoking, hypertension, hyperlipidaemia)
- **Diabetic nephropathy** - Spot urinary albumin to creatinine ratio -preferably in the first void sample and serum creatinine with estimated glomerular filtration rate (eGFR)
- **Diabetic retinopathy** – ophthalmoscopy/ slit lamp and fundus lens/ mydriatic or non-mydriatic fundus photography

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Hypertension

Dr. Buddhika Perera

Introduction

Hypertension is defined as, systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg in all adults under the age of 60 years and SBP of ≥150 mmHg and/or a DBP of ≥90 mmHg in those aged 60 years or more. Hypertension is considered as a major risk factor for cardiovascular disease even among the general population. Although there is no evidence to suggest the need for more intense protocols, monitoring and control of blood pressure remains important among people living with HIV, being identified as a group with increased risk of CVD.

Screening

- It is recommended that blood pressure should be measured at each visit in all patients with HIV.
- Mercury sphygmomanometer using an auscultatory technique is the method of choice for measurement of blood pressure in the clinic.
- Take two measurements; wait one minute before repeating the measurement in the same arm.
- If there is a substantial difference between the two readings (SBP 10 mmHg or DBP 6mmHg) have the patient rest for 5 minutes and then take several readings until consecutive readings do not vary by greater than above values. Record the lower of the last two measurements as the clinic blood pressure.

Diagnosis

- If the final SBP is ≥180 mmHg and/or DBP is ≥110 mm Hg, the diagnosis of hypertension can be made at the first visit itself.

- If the final clinic SBP is <180 and DBP is < 110 mmHg but SBP is > 140 and DBP is >90 mmHg at the first visit the diagnosis should be confirmed at an additional patient visit, usually 1 to 4 weeks after the first visit. Diagnosis of hypertension is confirmed if SBP is ≥140 mmHg and/or DBP is ≥90 mmHg at both visits.

Evaluation of a patient with hypertension

The initial evaluation of a patient with hypertension is aimed to,

- Exclude or identify secondary causes of hypertension
  - Acromegaly, chronic kidney disease, coarctation of aorta, Cushing syndrome, drug-induced hypertension, hyperthyroidism, obstructive sleep apnoea, pheochromocytoma, polycystic kidney disease, primary hyperaldosteronism, renovascular hypertension
- Determine target organ damage
  - Retina: hypertensive retinopathy
  - Heart: heaving apex, cardiomegaly, heart failure, arrhythmias
  - Peripheral arteries: peripheral vascular disease
  - Kidney: proteinuria, renal impairment
  - Brain: stroke, TIA, dementia
- Assess total cardiovascular risk of the individual – refer the section on CVD

Further evaluation and management

It is advisable to liaise with physicians and cardiologists in further evaluation and management of the patients diagnosed with hypertension.

Treatment

Treatment approach to hypertension

- Step 1 - Decide the treatment category (lifestyle modifications alone or lifestyle modifications + antihypertensive medication)
- Step 2 – Decide on lifestyle modifications
- Step 3 – Decide on optimum antihypertensive medication (if indicated) based on compelling indications and contraindications
- Step 4 – Set targets for control of blood pressure
- Step 5 – Follow up

Decide the treatment category

A. Start anti-hypertensive medications in addition to lifestyle modifications immediately after diagnosis, if the SBP ≥160 and/or DBP ≥100 mmHg.
B. In those with SBP 140-159 mmHg and/or DBP 90-99 mmHg, start anti-hypertensive medications in addition to lifestyle modifications, immediately after diagnosis, if they have any of the following.
    - Established cardiovascular disease (CHD, stroke, TIA, PVD)
    - Albuminuria / CKD
    - Target organ damage
    - Diabetes mellitus
    - A 10-year cardiovascular risk equivalent to 20% or greater.
C. In those with SBP 140-159 mmHg and/or DBP 90-99 mmHg without any of the conditions listed under treatment category B above start,
    - lifestyle modifications
    - regular BP monitoring
    - anti-hypertensive medications only if,
        - SBP becomes ≥160 and/or DBP becomes ≥100 mmHg at any stage.
        - SBP remains ≥140 and/or DBP remains ≥90 mmHg over 6-12 months

Lifestyle modification

- Cessation of smoking
- Moderation of alcohol consumption
- Diet and salt consumption
    - A diet plan with local and cultural acceptance should be formulated with a dietician where necessary. Hypertensive patients should be advised to eat vegetables, low-fat dairy products, soluble fibre, whole grains and protein from plant sources, reduced in saturated fat and cholesterol.
    - Studies have shown that salt reduction had a 3 mm Hg greater reduction in systolic blood pressure than the control group. A daily intake of salt should not exceed 5– 6 g. (1 teaspoon salt = 5 grams)
- BMI
    - A reduction of approximately 9 kg may produce a reduction in systolic blood pressure of 5 to 20 mm Hg. Maintenance of a healthy body weight (BMI of about 23 kg/m^2) and waist circumference (<80 cm in females and <90 cm in males) is recommended.
- Physical exercise

Choice of antihypertensive drug based on Target Organ Damage (TOD) and associated clinical conditions

Condition	Beneficial Anti-hypertensive
Diabetes mellitus	ACEI, ARB
Asymptomatic TOD	
LVH	ACEI, ARB
Microalbuminuria/albuminuria	ACEI, ARB
CKD stage 1-3	ACEI, ARB
Symptomatic TOD	
Stroke	Thiazides, CCB
CKD stage 4-5	CCB, ACEI/ ARB (with caution due to hyperkalaemia) BB,
CHD	ACEI, ARB, CCB
Heart failure	ACEI, ARB, Diuretics
PVD	ACEI, CCB

ACEI - Angiotensin Converting Enzyme Inhibitors, ARB - Angiotensin Receptor Blockers, CCB – Calcium Channel Blockers, BB- Beta blockers, LVH – Left Ventricular Hypertrophy, CKD – Chronic Kidney Disease, CHD – Coronary heart Disease, PVD – Peripheral vascular Disease

Treatment targets for hypertension

- Age < 60 years - SBP <140 mmHg and DBP <90mmHg
- Age ≥ 60 years – SBP <150 mmHg and DBP <90mmHg
- Patients with DM or CKD (irrespective of the age) - SBP <140 mmHg and DBP<90 mmHg

Follow up

- Blood pressure monitoring
  - BP monitoring should be done every 2 to 4weeks at initiation of treatment or after adjusting medication till target BP is achieved.
  - Thereafter BP should be monitored at least every 3 months.
  - More frequent monitoring is required in patients with target organ damage and vascular risk factors.
- Laboratory monitoring
  - Annual monitoring of serum electrolytes, serum creatinine, blood glucose, lipid profile (total cholesterol if lipid profile is not available) is recommended.

- In renal impairment more frequent monitoring of serum creatinine and serum electrolytes should be done as guided by clinical assessment
- When ACEI, ARB, diuretics and aldosterone antagonist are used, serum creatinine and serum electrolytes should be done at baseline and 2 weeks after initiation of treatment; thereafter when clinically indicated.

- Emphasis on lifestyle changes Blood pressure monitoring

ARV – Antihypertensive interactions

AVT and CCB: Both classes are known to increase the PR and QR intervals and may need ECG monitoring.

No other major interactions between the commonly used agents

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Dyslipidaemia in HIV

Dr. Umedha Jayasinghe

Introduction

HIV dyslipidaemia is a common problem, and it is associated with an increase in incidence of cardiovascular disease. Dyslipidaemia in patients with HIV needs consideration from the normal population, since HIV increases insulin resistance and HIV treatment may induce dyslipidaemia and it may interact with lipid-lowering medication.

Reasons for Dyslipidaemia in HIV

- HIV disease itself is associated with dyslipidaemia and insulin resistance (1).
- Administration of combined antiretroviral therapy
  - ART is associated with an increase in the incidence of metabolic risk factors (insulin resistance, lipoatrophy, dyslipidaemia, and abnormalities of fat distribution in HIV patients) (1,2).

Common Lipid Abnormalities seen in HIV-Infected

- Untreated, advanced HIV disease-
  - Patients typically have low total cholesterol, low low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, and High triglycerides (TG).
  - The possible mechanisms for HIV-induced dyslipidaemia are (1)
    - increased cytokine levels (TNF and IL-6),
    - decreased lipid clearance
    - increased hepatic synthesis of very low-density lipoprotein (VLDL)

- Patients on ART-
  - With initiation of antiretroviral therapy, total and LDL cholesterol levels tend to increase if low at baseline, regardless of the type of antiretroviral regimen.
  - HDL cholesterol generally increases.
  - Changes in triglycerides are variable and dependent on the specific ART used. (Ritonavir-boosted PIs and Efavirenz often cause some degree of triglyceride elevations. A minority of patients are sensitive to low doses of ritonavir used to boost protease inhibitors and may develop significant hypertriglyceridemia)

Investigations to Assess Dyslipidaemia

- Lipid profile (fasting 8–12 hours) - done at base line and annually if otherwise stable.
- Patients initiating antiretroviral therapy who have baseline hypertriglyceridemia
  - should have lipids checked within 1 month of starting therapy.
- Patients initiating antiretroviral therapy without baseline hypertriglyceridemia
  - should have a lipid panel sent within 3 months. LDL cholesterol is a calculated value in a standard lipid panel, and the calculation is not accurate when triglycerides exceed 400mg/dL (4.6mmol/L). In the setting of hypertriglyceridemia, it is helpful to calculate the non-HDL cholesterol value (total cholesterol—HDL cholesterol) to estimate the quantity of circulating atherogenic lipoproteins.

Management of Dyslipidaemia

- Assessment of the 10-year CHD risk using Framingham score

  (According to EACS guidelines)

- The management algorithm depends on the fasting triglyceride level.
  - Triglyceride levels greater than 500mg/dL (6mmol/L), (ISDA Guidelines) Triglyceride lowering agent - Fibrate
  - For all others, LDL-cholesterol is the initial primary target. Triglyceride levels between 200 and 500 mg/dl with elevated non-HDL-C (AHA Guideline, NCEP guidelines) - Statin first

    (The non-HDL target is simply the LDL target plus 30mg/dL (0.8mmol/L)

- Lifestyle modification - exercise diet, and smoking cessation
  - At least 30 minutes of aerobic activity on most (if not all) days of the week.
  - Dietary interventions. referral to a dietician to encourage weight loss in the overweight or obese patient.

- Do a fasting lipid profile after 6 weeks of lifestyle intervention.
- If the individual is unable to reach lipid targets with lifestyle modification interventions, lipid-lowering drugs should be started, or alteration of ART should be considered.

- Modifying antiretroviral therapy to manage dyslipidaemia?
  - PIs;
    - Atazanavir and Darunavir often do not affect lipids dramatically, lopinavir/ritonavir often causes triglyceride elevations.
    - Switching a PI to nevirapine, rilpivirine, etravirine, raltegravir, or within PIs to atazanavir.
  - NRTIs;
    - zidovudine improves lipids by switching to tenofovir or abacavir.
- Consider drug-drug interactions between some statins and ART
  - For patients on PIs, lovastatin, and simvastatin are contraindicated
    - The levels of these statins may increase dramatically with inhibition of cytochrome P450 isoenzymes by the protease inhibitor
    - Cases of rhabdomyolysis and death have been reported that were attributed to these interactions.
  - Atorvastatin and rosuvastatin levels increase modestly when co-administered with PIs, and these statins appear to be safe at low doses.
  - Pravastatin levels decrease modestly when co-administered with some PIs but increase when co-administered with darunavir.
  - Coadministration of darunavir and pravastatin is not recommended.
  - Data on fluvastatin are limited, but it is not likely to interact significantly with PIs.
  - Efavirenz lowers levels of atorvastatin, pravastatin, and simvastatin by about 40 to 60%, which may necessitate higher doses of the statin.

Significant interaction Concurrent use contraindicated	Moderate interaction initiate at low dose	Low potential for interaction
Lovastatin	Atorvastatin	Fluvastatin
Simvastatin	Rosuvastatin	Pravastatin*

*Pravastatin should be used at the lowest possible dose when combined with darunavir/ritonavir because of increased pravastatin exposure.
(Adapted from Glesby MJ. HIV and cardiovascular risk. New York: Oxford University Press. 2011.)

Dosage of Statins

For patients on PIs (or NNRTI, delavirdine)

Atorvastatin 10mg daily

Fluvastatin 20 to 40mg daily

Pravastatin 20 to 40mg daily (should be used at the lowest possible dose (e.g., 10–20mg daily) when combined with darunavir/ritonavir)

Rosuvastatin 5mg daily

- Statin doses can be titrated upward at 4 to 6-week intervals if LDL reduction is insufficient and the drug is tolerated (including stable liver enzymes).
- The maximum dose of each statin in the setting of PI therapy is not established but should probably not exceed 40mg daily for Atorvastatin, 80mg for Fluvastatin and Pravastatin (except if on darunavir), and 10mg for Rosuvastatin.

If desired LDL Cholesterol level is not achieved despite a Statin

- Patients on Efavirenz who are not also taking a PI may need higher doses of statins. Simvastatin and lovastatin may be used in patients who are not taking PIs.
- Switching within the statin class to a more potent statin (e.g., rosuvastatin, atorvastatin) may be an option for patients who are on a less potent statin (e.g., pravastatin).
- Consider drug-drug interactions. Efavirenz and possibly other NNRTIs may have reduced statin exposure due to induction of cytochrome P450 and may require higher doses of statins.

Management of Hypertriglyceridemia

- Lifestyle modification - should be attempted first
- This consists of dietary counselling (ideally by a dietician) and exercise.
- Reduce/stop excessive alcohol use
- Optimizing glycaemic control in diabetic patients
- Triglyceride levels exceed 1,000mg/dL (11mmol/L),
    - Pharmacologic intervention should be introduced concurrently with lifestyle modification. (Since there is a risk of pancreatitis)
- Triglycerides less than 500mg/dL (5.6mmol/L)
    - LDL-cholesterol and non-HDL-cholesterol lowering with a statin if indicated.
- Triglyceride levels greater than or equal to 500mg/dL (5.6mmol/L
    - Fibrate drugs (gemfibrozil, fenofibrate, bezafibrate)

    - Fish oil (2–4g daily)
    - Extended-release niacin (starting at 500mg at bedtime with escalation every 4 weeks to 2,000mg as tolerated)
    - Switching antiretroviral regimens
- As triglyceride lowering is achieved, LDL cholesterol will generally increase. If LDL cholesterol is not a goal, consideration can be given to adding a statin to fenofibrate (the fibrate of choice with regard to risk of myositis if combining with a statin), fish oil, or niacin.

Management of Patient with Isolated Low HDL-C

- Low levels of HDL cholesterol are often associated with elevated triglyceride levels as part of the metabolic syndrome but can be seen in isolation.
- Patients with untreated advanced HIV infection typically have improvements in HDL cholesterol levels with control of HIV replication. Those already on antiretroviral therapy pose a greater challenge.
- ask about anabolic steroid use (prescribed or purchased at the gym or elsewhere), as these agents can lower HDL cholesterol levels, dramatically in some cases.
- Encouraging physical activity, weight loss if appropriate, and smoking cessation are all important.
- Dietary measures may also help. Saturated fats should be minimized and foods rich in n-3 (omega-3) polyunsaturated fatty acids encouraged. Sources of the latter include certain cold-water fish (e.g., herring, mackerel, salmon, sardines), nuts (e.g., almonds, peanuts, pecans, walnuts), and oils (e.g., canola, flaxseed, olive oil). Mild to moderate alcohol consumption (up to two drinks daily) may raise HDL cholesterol levels,
    - But the risks may outweigh the benefits in patients with underlying liver disease, such as hepatitis C virus infection, or those prone to addiction.
- The role of pharmacologic therapy is uncertain, but options include extended-release niacin, fibrates, or potentially rosuvastatin in patients at high risk of CHD.
- Switching the antiretroviral regimen to a nevirapine-based regimen, if treatment history and resistance profile permit, could result in increases in HDL cholesterol levels, although the clinical significance of such increases is uncertain.

Referral to a Specialist?

A patient has not responded adequately to lifestyle intervention and therapy with two lipid-lowering agents, refer preventive, endocrinologist cardiologist.

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HIV and Renal Disease

Dr. Geethani Samaraweera

Introduction

HIV infected individuals are at a higher risk of developing acute and chronic kidney disease and it is one of the most important comorbidities associated with HIV infection. This is even more important in Sri Lankan context as chronic kidney disease is more common among Sri Lankans specially in some districts (15-23% in Anuradhapura and Kurunegala districts)[1]. Hence when managing patients with HIV infection it is crucial to carry out an initial assessment of the patient for presence of already established renal impairment and risk factors, which predict development of renal disease in future. In addition, new onset kidney diseases can occur at any time due to antiretroviral therapy (ART), other comorbidities and opportunistic infections. Therefore, it is important to do regular monitoring of renal function.

Initial evaluation of HIV infected patient for kidney disease

All HIV infected patients should be evaluated for kidney disease at the time of entry into the HIV care[2].

- Detail history on present or past acute/chronic renal disease, risk factors for renal disease and clinical symptoms and signs should be taken at the initial evaluation.
- Following categories are at higher risk of developing renal disease.
  - Patients with diabetes mellitus
  - Patients with hypertension.
  - Patients with family history of renal disease
  - Elderly patients
  - HIV infected patients with low baseline CD4 count (<200 cells/μL)
  - Patients having AIDS defining illnesses

- HIV infected patients with high viral load >4000 copies/mL
- Patients with Hepatitis B and C infection
- Patients from areas with high prevalence of kidney disease
- Patients who are already on nephrotoxic drugs (eg. Aminoglycoside antibiotics, pentamidine, acyclovir, foscarnet, amphotericin, tenofovir, adefovir, and cidofovir)
- Patients with obesity, dyslipidaemia and smoking

- Following investigations to detect renal problems are recommended routinely for all patients at the entry into HIV care[1,2]
  - Urine analysis
  - Serum electrolytes
  - Serum creatinine
  - BUN
  - Estimated GFR
  - FBS /HBA1c
  - Lipid profile
- If screening shows following abnormalities at baseline or follow up visits the patient should be referred to a Nephrologist[1]
  - creatinine clearance (CrCl) or estimated GFR (eGFR) <60 mL/min/1.73 m2
  - eGFR decline by 25% from baseline
  - Persistent proteinuria ≥1+ or albumin >300mg per day, haematuria in urinalysis (urine dipstick analysis or UFR)
  - However, Dipstick urinalysis is insensitive for microalbuminuria
  - Urine protein to creatinine ration/ Urine albumin to Creatine ration
  - Increasing blood pressure.
  - For management of CKD eGFR<39ml/min/1.73m^2
  - Anatomical abnormality in the USS-abdomen

In patients with high risk of developing kidney disease, following tests need to be done to detect microalbuminuria as that may be the first indication of renal dysfunction.

- **Random urinary albumin-to-Creatine ratio: AlbuminUrine [mg/dL]/ CrUrine [mg/dL].** Highly sensitive for microalbuminuria; normal is <0.03. Should be used at initial screening and for follow-up if microalbuminuria is diagnosed.
- **Random urinary protein-to-Creatinine ratio: ProteinUrine [mg/dL] / CrUrine [mg/dL].** Highly sensitive for proteinuria, but not for microalbuminuria; normal is <0.15.

If there is no evidence of proteinuria at initial evaluation, high risk patients preferably should undergo annual screening.

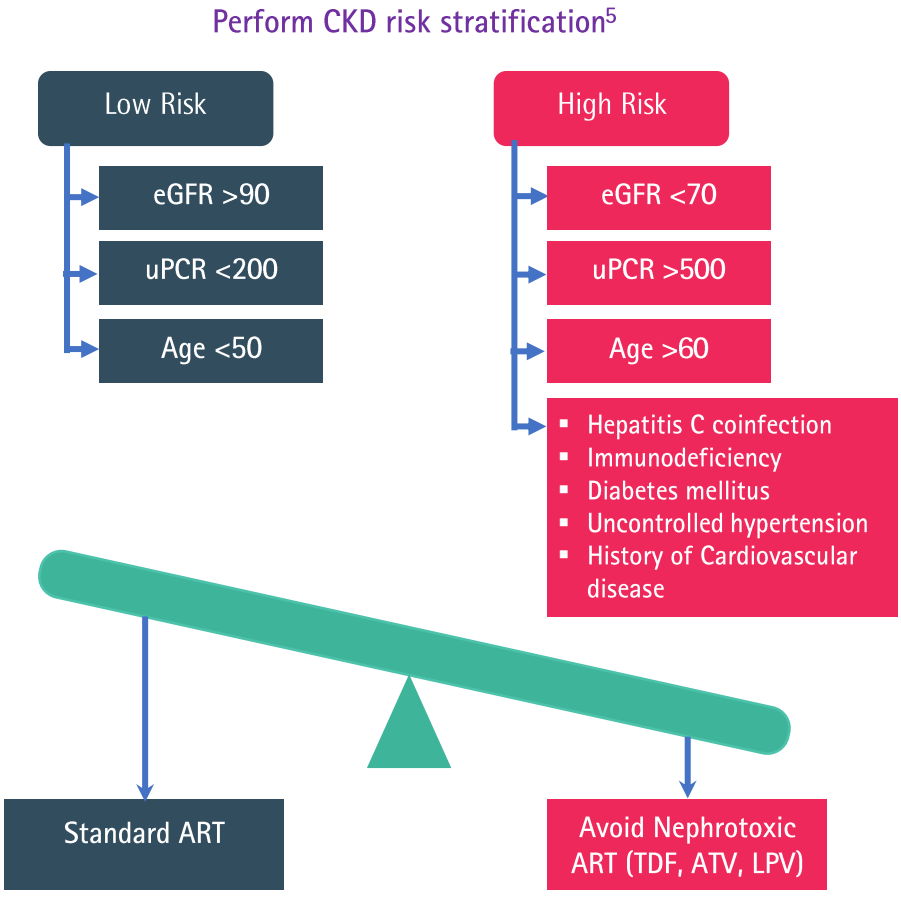
Patients suspected to have HIV induced kidney disease, renal biopsy is indicated.

Routine monitoring of HIV infected patients for detection of kidney damage

1. Serum Creatinine with eGFR- at baseline and every six months in stable patients. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors
2. Urinalysis/ Albuminuria/Proteinuria- at baseline and at least annually. More frequent monitoring may be appropriate for patients with additional kidney disease risk factors

Use of ART in HIV infected patients with kidney disease

ART should be initiated immediately to patients with renal disease. Immunological and virological control is important to reduce incident of acute kidney injury and HIV related kidney disease[3]. Most NRTIs must be dosed according to renal function and some ARVs should be avoided.



- If patient is diagnosed as having a chronic kidney disease (eGFR<60) it is always better to avoid nephrotoxic drugs such as tenofovir disoproxil fumarate (TDF), atazanavir (ATV) or Lopinavir as they may further increase the risk of kidney disease[3,4].

- In Tenofovir treated patients who confirm eGFR decline >25% of baseline or below 60ml/min/1.73m2 it is recommended to substitute tenofovir with alternative ART specially when there is evidence of renal tubular dysfunction such as
  - Euglycemic glycosuria
  - Increase urinary phosphorus excretion
  - Hypophosphatemia
  - New onset worsening proteinuria (Urine albumin to protein ratio <0.4)
- Rilpivirine, Dolutegravir, Cobicistat and Ritonavir and possibly Raltegravir although not intrinsically nephrotoxic, affect the clinically useful relationship between serum creatinine and eGFR and result in difficulty in interpreting the results. If using these medication, renal function is assessed after 4 weeks of starting of these drugs to establish the new 'eGFR setpoint' as a reference to compare subsequent measurements. Furthermore, eGFR declines of 10–20% can be anticipated with these drugs and should not immediately raise concern if non-progressive and seen in isolation. Patients with substantial eGFR reduction at 4 weeks should have this rechecked a month later to ensure that no further decline has occurred[3]. In such instances alternative estimations of eGFR (Based on cystine C) should be obtained instead of S. Creatine[4]

Table 14.1 Renal adverse effects of commonly used ART[3,6]

Drug	Disorder/ Pathology	Findings	Comments/ Suggestions
TDF	TDF-associated renal insufficiency	↑ Cr, usually small; slight decrease in eGFR over time	▪ Of unclear clinical significance, but warrants monitoring of renal function ▪ May be associated with duration of HIV infection, concomitant RTV-boosted PIs (which boost TDF levels), pre-existing renal dysfunction, or diabetes ▪ Check serum electrolytes and eGFR every 3-6 months on TDF; check UA every 6 months. Consider more frequent monitoring in patients with eGFR ≤90 mL/min/1.73 m2, renally secreted drugs, RTV-boosted PIs, diabetes, or hypertension ▪ Adjust TDF dosage based on steady-state CrCl ▪ Usually resolves with discontinuation of TDF, but can lead to permanent damage, ESRD
	Proximal tubular injury (ATN)	Fanconi syndrome (Metabolic acidosis, ↑ Cr, ↓ serum K^+ and phosphate, ↑ urine bicarbonate, phosphate, and glucose)	
ATV	Nephrolithiasis	Renal colic, dysuria, urgency; mild ↑ Cr; ATV-containing stones	Treat with hydration; if symptoms do not resolve, or if symptoms recur, may need to discontinue drug

Preferred regimens in patients with kidney disease

1. ABC+ 3TC/FTC+ DTG/EFV
2. AZT +3TC/FTC+ DTG/EFV
3. TAF+ 3TC/FTC+ DTG/EFV

- If PI is needed Darunavir is preferred[4]
- Nucleoside-sparing regimens- Higher risk of virologic failure in CKD patients especially among those who had a baseline VL>100 000 copies/mL or a baseline CD4 <200 cells/uL, and a higher risk of drug resistance.
- If tenofovir is necessary (Hepatitis B coinfected patients) TAF is preferred if eGFR is between 30-60ml/min/1.73m^2 [(4)]
- Avoid TDF, Lopinavir/ritonavir and Atazanavir/ritonavir if eGFR is less than 60[4]

Several NRTIs (including TDF, lamivudine and emtricitabine) may need to be dose adjusted if used when no alternatives are available in patients with renal impairment. When there is renal insufficiency, NRTI dose adjustments are indicated as mentioned below.

Table 14.2 NRTI Dosing for Patients with Decreased Renal Function (based on CrCl)[3,4]

Drug	Standard Dosage	Adjusted Dosage/Notes	
ABC	300 mg PO BID	Dosage adjustment for renal insufficiency does not appear necessary	
		CrCl (mL/min)	
FTC	200 mg PO QD	≥50	No adjustment
		30-49	200 mg Q48H
		15-29	200 mg Q72H
		<15	200 mg Q96H
		Haemodialysis	200 mg Q96H, give after dialysis
3TC	150 mg PO BID or 300 mg PO QD	≥50	No adjustment
		30-49	150 mg QD
		15-29	150 mg first dose, then 100 mg QD
		5-14	150 mg first dose, then 50 mg QD
		<5	50 mg first dose, then 25 mg QD

TDF	300 mg PO QD		Experience in patients with CrCl <60 mL/min is limited. Preliminary data suggest:
		≥50	300 mg QD
		30-49	300 mg Q48H
		10-29	300 mg twice weekly (72-96h)
		Haemodialysis	300 mg weekly (an additional dose may be needed if >12 h HD per week)
TAF+ FTC	TAF 25 mg PO daily in FDC tablets	>30	No adjustment
		<30 not on HD	Not recommended
		<30 on HD	One tablet once daily
AZT	300 mg PO BID	>15	No adjustment
		<15	100 mg Q6-8H or 300mg QD
		Haemodialysis	100 TID
TDF + FTC	300mg/200mg daily	>50	No dose adjustment
		30-49	1tab 48hly
		<30	Should not use combination pill

Adapted from McNicholl IR, Rodriguez RA. Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis. San Francisco: University of California San Francisco, Center for HIV Information; 2010. Accessed April 1, 2011

- **For NNRTI and PI, no dose adjustment is necessary in patients with CKD**
- Integrase inhibitors

  Raltegravir: No dose adjustment needed with CKD or ESRD

  Dolutegravir: CrCL >30: No dose adjustment

  CrCL <30: Use with close monitoring of viral load – Risk of virologic failure

Follow up

In patients with high risk of developing renal disease, renal function should be monitored every 6 months. In patients who have established renal disease after starting non nephrotoxic ART

regimen, the renal function should be monitored as requested by the nephrologist. If having CKD,

- Blood pressure control:

  In patients with CKD normal to mild proteinuria (<30mg/day) the desired blood pressure should be <140/90mmHg.

  In patients with CKD and moderate to severe proteinuria (30-300mg/day) target BP should be < 130/80mmHg

- Initiate ACEIs or ARBs for patients with confirmed or suspected HIVAN, clinically significant albuminuria (>30mg/day in diabetic patients, >300mg/day in nondiabetic patients) or hypertension
- Use of statins in patients with ESRD or CKD to prevent cardiovascular disease in patients with higher cardiovascular risk (e.g., >7.5% 10-year risk of cardiovascular disease)
- Use of Aspirin (75-100md/day) to prevent cardiovascular disease in HIV infected patients with CKD (after balancing the risk of bleeding)
- Screen for and/or maximize treatment for diabetes and dyslipidaemia
- Screen for and treat hematologic abnormalities
- Advise on protein- and salt-restricted diet; refer to renal dietician.
- Refer for substance abuse counselling, when appropriate, to decrease risk of nephropathy associated with use of heroin or other illicit substances.

Dialysis and the placement of arterio-venous fistula should not be withheld for patients solely because of HIV infection. Renal transplant should be considered for patients with end stage renal disease. ART should not be withheld from patients simply because of the severity of their renal dysfunction.

Addition of ACE inhibitors/angiotensin receptor blockers and prednisolone should be considered in patients with HIVAN if ART alone does not result in improvement of renal functions.

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HIV and Bones

Dr. Malathi Pathiraja

Introduction

HIV causes a chronic inflammatory condition which leads to immune dysregulation. The low bone marrow density [BMD] in HIV patients leads osteopenia and osteoporosis and to fractures. HAART is effective in controlling the disease but regimens which include Tenofovir Disoproxil Fumarate (TDF) can cause reduced BMD.

In HIV-infected patients, bone loss is primarily enhanced by two pivotal factors: HIV infection and its direct consequences, and HAART, mainly during the first years of treatment (1-6). Among HIV-infected individuals on HAART, the presence of osteoporosis appears to be about three times higher than those uninfected (1-6).

Some reports indicate that low BMD is not completely attributable to HIV infection alone or HIV infection plus treatments with HAART (7-15).

HIV factors associated with low BMD:

- Gender - females have low BMD than males
- Duration of infection
- HIV viral burden
- More advanced HIV disease (16-18): (higher viral RNA and lower CD4+ T cell counts at baseline were associated with more pronounced reductions in BMD). Low CD4 count is an independent risk factor in low BMD. However, the bone loss continues for 2 years after initiation of HAART, and it is not reversible after immune reconstitution. (18)
- Influenced by the specific type of treatment: Low BMD has been associated with regimens such as nucleoside analogue reverse-transcriptase inhibitors (NRTIs) (19-20). Individuals exposed to tenofovir disoproxil fumarate (TDF)-based treatment in particular exhibited a

more accentuated BMD loss compared to individuals on other regimens. However, others have reported contradictory findings regarding TDF-therapy duration and BMD loss, even after long-term exposure to the drug (21)

Pathophysiology

The infection can lead to osteoclast infection and thereby increase activity of the osteoclastogenesis and osteolytic activity. The infection produces deleterious effects on the osteoblastic activity and the precursor cells of mesenchymal stem cells and bone loss.

Regarding the NRTI associated bone loss, it was found that increased lactic acid concentration leads to loss of calcium hydroxyapatite from the trabecular bones due to the labile of the calcium storage (21). Regarding the TDF associated with low BMD: mitochondrial toxicity, hyperphosphaturia due to tubular dysfunction and renal osteodystrophy are considered as reasons (23,24-26).

Besides the BMD reduction related to NRTIs, available data regarding protease inhibitors (PIs) remain contradictory (27). Lastly, in vivo and in vitro studies demonstrate that PIs atazanavir (ATV) and lopinavir (LPV) also decrease BMD by impairing the mesenchymal stem cells (MSCs) differentiation to osteoblasts (28,29,30).

Finally, in addition to immune cells, the HIV-coreceptor CCR5 has been involved in the regulation of the function of bone cells by directly modulating osteoclastogenesis and the communication between osteoclasts and osteoblasts (31-33). In this regard, epidemiological evidence suggests that the functional loss of CCR5 is correlated with a lower incidence of bone-destructive diseases as well as of HIV transmission.

These data suggest that important roles are played directly by HIV and/or indirectly by the immune response in BMD loss.

BHIVA Recommendations

TDF is not recommended for people with osteoporosis and a history of fragility fracture or FRAX score >10%. (Major osteoporotic fracture).

In the studies comparing the effects of TAF and TDF on bones; most showed low BMD, renal tubular dysfunction and reduced estimated glomerular filtration (eGFR) with TDF. A meta-analysis showed that these changes are not very significant for the majority of PLHIV and the

differences among TDF and TAF was due to the use of pharmacological boosters like cobicistat and ritonavir in the 3rd drug in a regimen.

BHIVA concluded that these differences among TAF and TDF should be considered for people with established bone or renal diseases and any other condition which can worse bone or renal diseases.

When considering the effect of PI on the BMD it was found in the randomized clinical trials that boosted PI reduce BMD by 0.8%. Some other studies combining the boosted PI with TDF showed greater reduction of BMD and it is thought due to the high concentration of the TDF as a result of co administration of TDF with boosted PI.

Transgender people (TG)

Sex hormones are very important in bone health. It was found that gonadectomy can increase the risk of osteoporosis both in TG men and TG females. Early DEXA scan is recommended.

When using the FRAX Score their gender should be put as the gender at birth.

Switching Antiretroviral Drugs Due to Adverse Effects in CDC (Last updated June 3, 2021; last reviewed June 3, 2021)

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious.

If there are Bone Density Effects, TDF can be switched to TAF or ABC.

Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.

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HIV Associated Neurological Conditions

Dr. Piyumi Perera

Introduction

HIV associated neurological conditions are a vast spectrum of diseases, where all the levels of neuraxis can be involved. Neurological disease is the first manifestation of symptomatic HIV infection in roughly 10-20% of persons. About 60% with advanced HIV disease will have clinically evident neurologic dysfunction during the course of their illness. These conditions can be related to opportunistic infections or not.

Even though the incidence of severe forms of HIV associated neurological diseases has gone down with the widespread use of effective combination ART, subtle forms of neurological manifestations, specially related to the brain, known as HIV-associated neurocognitive disorders are still prevalent. Therefore, it is important to be aware of these conditions and detect them at the initial stages so that appropriate interventions can be done.

Pathophysiology

HIV is a neurovirulent virus. However, it does not directly infect central or peripheral neurons, astrocytes or oligodendroglial cells. During the initial systemic infection, HIV crosses the blood brain barrier and enters the nervous system. This will lead to latent infection in the CNS.

Latent or low-level HIV infection in the CNS is maintained by virus infected cells of the monocyte/ macrophage lineage. Macrophages are activated and will result in dysregulation of cytokines and chemokines, free radical (oxidative stress) injury and secretion of soluble factors that are potently neurotoxic. All these have been implicated as effectors of nervous system injury in HIV.

Common symptoms and signs

These depends on the level of the neuraxis involved. Symptoms and signs can be classified according to the following criteria.

1. The neuro-anatomical location: Brain and meninges, spinal cord, neuromuscular.
2. Presenting symptoms/clinical syndrome: Focal or diffuse
3. Timing of onset: Acute, sub-acute, chronic

Table 16-1: Classification of symptoms/signs according to anatomical location

Anatomical location	Clinical condition	Type of symptoms/ signs
Brain and brain stem	Encephalitis Dementia/ encephalopathy	Non focal, parenchymal symptoms and signs
	Space occupying lesion Stroke like syndromes	Focal neurological symptoms and signs
Meninges	Meningitis	Meningeal symptoms and signs
Spinal cord	Myelopathy Radiculopathy	Focal neurological symptoms and signs
Neuro muscular	Neuropathy 1. Distal symmetric polyneuropathy (DSPN) 2. Mononeuropathy multiplex 3. Chronic inflammatory demyelinating polyneuropathy 4. Progressive lumbosacral polyradiculopathy Myopathy	Focal neurological symptoms and signs

Table 16-2: Classification of symptoms and signs according to the clinical syndrome

Focal	Non focal	Meningeal
Movement changes in a specific area Paralysis Weakness Increased/ loss of muscle tone Involuntary movements - tremor	Unconsciousness or decreased consciousness Amnesia Personality changes Unsteadiness Dizziness Generalised seizures, tremors	Headache Photophobia Neck stiffness Nausea/ vomiting
Sensory changes in a specific area Paraesthesia Numbness Decreased sensation		
Horner's syndrome		
Loss of coordination		
Speech or language difficulties		
Visual defects		

Approaching a PLHIV with a neurological condition

- The most important factor in determining the differential diagnosis is the **degree of immunosuppression** in the host. CNS mass lesions are most common in severely immunosuppressed patients with CD4 cell counts <200/µL.
- The leading diagnostic considerations in a patient with advanced immunosuppression are toxoplasma encephalitis (TE), primary CNS lymphoma, progressive multifocal leukoencephalopathy, TB, HIV encephalopathy, and CMV encephalitis.
- CT or MRI must be performed **before and after injection of contrast material** to determine whether a lesion enhances on neuroimaging. Enhancement usually signifies the **presence of inflammation.** An MRI is more sensitive than a CT brain in determining if a lesion is truly solitary.
- CNS mass lesions are characterized by the presence of swelling, oedema, and mass effect on surrounding structures. (TE, PCNSL, TB)
- **Lesions without mass effect usually do not enhance** after the injection of contrast material and are not associated with a risk of herniation. The vast majority of these lesions are due to progressive multifocal leukoencephalopathy or HIV-associated encephalopathy.
- **Lumbar puncture is contraindicated** in patients with focal signs or with lesions producing a mass effect, especially in the posterior fossa, due to the risk of transtentorial herniation.
- A trial of empiric therapy for possible TE may be considered as an alternative to brain biopsy in certain toxoplasma-seropositive patients with characteristic radiographic findings.
- Corticosteroid therapy should be considered in the presence of mass effect since these patients are at increased risk of herniation.

- Stereotactic brain biopsy is the gold standard for the diagnosis of focal CNS lesions in AIDS.

Differential diagnoses

The discussion of the full spectrum of differential diagnoses is beyond the capacity of this chapter. The commonest differential diagnoses among PLHIV are shown in the table below.

Table 16-3: Differential diagnoses of HIV related opportunistic infections and malignancies of the CNS

Presentation	Main causes
Space occupying lesion(s)	Toxoplasmosis, primary CNS lymphoma, PML*, TB, cryptococcus, metastatic non-Hodgkin lymphoma (NHL), syphilitic gummae, bacterial abscess
Encephalitis	HIV, VZV, HSV, syphilis
Meningitis	HIV seroconversion, Cryptococcus, TB, syphilis, bacterial meningitis e.g., Streptococcus pneumoniae
Spastic paraparesis	HIV- vacuolar myelopathy, transverse myelitis from VZV, HSV, HTLV-1, toxoplasmosis or syphilis
Polyradiculitis	CMV, NHL

*May be present with focal non space occupying lesions

Table 16-4: Investigations to be considered in a patient presenting with a neurological condition

Neuroanatomical site	Investigations
Brain and meninges	Contrast enhanced CT/ MRI brain CSF cell analysis, Viral/ Bacterial PCR from CSF, pyogenic cultures, VDRL/TPPA Stereotactic brain biopsy
Spinal cord	Imaging – X ray, CT, MRI spine
Neuromuscular	Nerve conduction studies Electromyography Biopsy of peripheral nerves, muscles
Serology for common diseases	Toxoplasma antibody, cryptococcal antigen, syphilis serology, HTLV ½ antibody, CMV antibody

Table 16-5: CSF analysis in various types of meningitis

CSF analysis	Bacterial	Tuberculosis	Viral	Fungal	Aseptic
Pressure	Increased	Increased	Normal to elevated	Normal to mild increase	Increased
Colour	Turbid	Turbid	Clear	Clear	Clear to turbid
Glucose	< 40 mg%	Low	Normal to mildless	Low to normal	Low
Proteins	Elevated	Greatly elevated	Normal to mild elevation	Normal to mild increase	Elevated
Lactate	Elevated (> 6 mmol/L)	Elevated	0–6 mmol/L	Normal	Normal
RBCs	Elevated	Elevated	Normal	Normal	Elevated
WBCs	10-2000/µL	Elevated but < 500	>100/µL	10–50/µL	Mildly elevated
WBC types	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes	Neutrophils
Gram stain	Positive	Acid fast bacilli	Negative	Negative India ink for spores/fungi	Negative
Microbial Culture	Positive	Positive (yield is high in early stages)	Negative	Positive	Negative
Biomarkers	Elevated C-reactive proteins	Antibodies in CSF (detection of anti-M37Ra, anti-antigen 5, and anti-M37Rv) Elevated CSF procalcitonin, Adenosine deaminase	Low CRP and adenosine deaminase		Seen following neurosurgery or antibiotic use
PCR test		Help in identification of organisms even after antibiotics are started	Helps in identification of the organisms		

Table 16-6: CSF changes in acute demyelinating/inflammatory diseases

Condition	Clinical features	CSF findings
Transverse myelitis	▪ Bilateral (not necessarily symmetric) sensorimotor and autonomic spinal cord dysfunction ▪ Clearly defined sensory level ▪ Hyperreflexia, Babinski positive	▪ Signs of inflammation (pleocytosis, elevated protein concentration, oligoclonal bands, or elevated IgG index) ▪ Elevated CSF IL-6 ▪ PCR negative of infections. ▪ CSF sugar, pressure usually normal
Multiple sclerosis (different types)	▪ Loss of sensation ▪ Muscle weakness ▪ Visual loss ▪ Incoordination, cognitive impairment ▪ Fatigue, pain ▪ Bladder and bowel disturbance	▪ Pleocytosis (5–50 cells/µL; lymphocytes) ▪ Elevated protein ▪ Oligoclonal bands may be present (highly diagnostic) ▪ Ig G index (increase CSF IgG compared to serum IgG levels)
Neuromyelitis Optica	▪ A severe transverse myelitis. ▪ An acute unilateral or bilateral optic neuropathy. ▪ No other clinical involvement	▪ Nonspecific ▪ Pleocytosis (5–50 cells/µL; lymphocytes) ▪ Elevated protein ▪ Oligoclonal bands may be present (Most cases) ▪ Normal glucose levels
Acute Disseminated Encephalomyelitis	▪ Fever, meningeal signs, and acute encephalopathy ▪ The level of consciousness ranges from lethargy to frank coma. ▪ Maximum progression 4–7 days ▪ Common in children ▪ MRI diagnostic	▪ Pleocytosis (5–50 cells/µL) and/or increased protein concentration ▪ May be normal ▪ CSF non diagnostic. ▪ Presence of oligoclonal band favours diagnosis of MS
Guillain Barrie syndrome	▪ Acute progressive weakness, areflexia, symmetrical ▪ Post infection ▪ Autonomic dysfunction ▪ Cranial nerve involvement ▪ Mild sensory signs	▪ Normal CSF cell count ▪ Elevated CSF protein level ▪ Cyto-albuminergic disassociation

Table 16-7: The CSF criteria supporting a diagnosis of neurosyphilis

CSF parameters	In HIV-negative individuals	In HIV-positive individuals
WBC	>5 µL	>20 µL *OR* 6–20 µL (on ART/ plasma HIV VL undetectable, or blood CD4 <200)
Protein	>0.45 g/L	>0.45 g/L
RPR/VDRL	+	+
TPPA	>1:320	>1:320

HIV associated neurocognitive impairment

This may present with a wide spectrum of clinical symptoms and typically includes patterns involving ineffective learning and difficulties in decision making or executive function. The cognitive impairment classically described in HIV infection is a subcortical dementia, more similar to the cognitive deficits seen in Parkinson or Huntington's disease than the cortical dementia of Alzheimer disease.

Classification of this condition is done using neuropsychiatric assessment and measuring of activities of daily living (ADL) scales. Three categories have been identified according to this classification.

- HIV associated asymptomatic neurocognitive impairment (ANI) – Patients with abnormal neuropsychiatric testing results, who are otherwise asymptomatic. (Neuropsychiatric assessment is abnormal but no change in ADL)
- HIV-associated mild neurocognitive disorder (MND) – Patients who are mildly symptomatic. (Neuropsychiatric assessment is abnormal with mild changes in ADL)
- HIV-associated dementia (HAD) - Patients who are severely symptomatic. (Neuropsychiatric assessment is abnormal with severe changes in ADL)

Several screening tools are used to conduct the neuropsychiatric assessment. The commonest screening tools used are International HIV Dementia Scale and Montreal Cognitive Assessment. (Annexure 12 and 13)

Risk factors for the development of neurocognitive disorders are poorly understood and are likely to be multifactorial including both HIV disease factors and concomitant diseases. Low CD4+ T-cell nadir continues to be a significant risk factor for the development of HIV-associated neurocognitive disorder in the era of antiretroviral therapy.

Recommendations

- Individuals with symptomatic HIV-associated neurocognitive disorders should start ART immediately, irrespective of CD4 cell count.
- Individuals with HIV-associated neurocognitive disorders should start standard combination ART regimens.
- Avoid efavirenz-containing regimens in individuals with HIV-associated neurocognitive disorders.
- The CPE (Clinical Penetration Effectiveness) score of ART should not influence therapeutic decisions in patients with neurocognitive impairment commencing antiretroviral therapy as the evidence in this regard is conflicting.

In patients with continuing or worsening neurocognitive impairment despite ART, the following factors should be considered.

- Reassessment for confounding conditions.
- Assessment of CSF HIV RNA and genotyping of CSF HIV RNA.
- In patients with detectable CSF HIV RNA, modifications to antiretroviral therapy should be based on paired plasma and CSF genotypic results

HIV-associated neurocognitive disorders are diagnoses of exclusion. Therefore, re-evaluation of patients with ongoing neurocognitive impairment despite antiretroviral therapy for confounding conditions, with expert input from other clinical specialties such as psychiatry, neurology and neuropsychology are recommended. Non-infectious comorbidities, which are risk factors for neurocognitive impairment should also be managed optimally.

Management should also involve consideration of any potential antiretroviral toxicities and side effects. For instance, a trial of switching from an efavirenz-containing regimen to an alternative may be considered.

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Psychiatric Aspects of HIV Infection and AIDS

DR. S.N Weerawardene

Introduction

Modern highly effective antiretroviral therapy made HIV a chronic disease in the majority and with the massive effort at education resulted in a decrease in the spread of HIV in the people who were able to modify their risk behaviours but certain vulnerable groups like homosexual men, intravenous drug users and their partners, and those trade sex for money and drugs have made HIV still a major public health problem.

Sex and substance use behaviours are driven by the brain's reward system and those behaviours are commonly seen in patients with untreated mental disorders and are more likely to be practiced both unsafely at a higher frequency.

These patients are not only vulnerable to non-adherence to treatment but also less likely to take medications correctly and end up with immune suppression and high viral load.

Internationally psychiatric disorders have been identified in both developed and developing countries as an important comorbidity in the risk of infection, poor likelihood of successful treatment with high morbidity and mortality. Single most important factor in successful treatment is the ability to take prescribed medications accurately and completely ["treatment adherence"]. This treatment adherence is poor in mentally ill and IV drug users.

Psychiatric disorders compromise the ability to take medication correctly, adhere to the treatment, practice safe sex, and stop using iv drugs.

When considering all these factors one may think that HIV infection is a psychiatric epidemic. Therefore, the ability to provide adequate psychiatric care is critical for the prevention of HIV spread.

Psychiatric conditions in the HIV clinics

1. Delirium
2. HIV associated dementia.
3. Major depressive disorder [MDD].
4. Bipolar affective disorder [BAD].
5. Schizophrenia
6. Post-traumatic stress disorder and other anxiety disorders.
7. Substance use disorders.

Aim is to recognize common psychiatric conditions, associated risks and to lean interventions at primary care level.

Recommend referring to a psychiatry textbook for more comprehensive knowledge in particular conditions. Some important topics are discussed below.

Delirium

A state of global derangement of cerebral functions due to a medical aetiology. The incidence is between 40-60% and if untreated risk of mortality is 20%.

The clinical features are of an acute or subacute onset, fluctuating, disorientation, disorganised thinking or confusion, impaired consciousness, emotional lability and illusions, hallucinations, and delusions.

The general risk factors are older age, multiple medical problems, multiple medications, previous episodes of delirium, and HIV associated dementia [HAD].

The differential diagnosis includes HAD, AIDS mania, MDD, BAD and schizophrenia but rapid onset fluctuating symptoms and underlying medical aetiology could help to differentiate.

A comprehensive medical, toxicological, metabolic causes need to be excluded in the assessment.

In the treatment consider,

- To identify and remove underline causes
- To reorientate the patient by maintaining a normal diurnal variation of light cycle
- To manage behaviour with antipsychotics [Haloperidol, Quetiapine, Olanzapine]
- To use Benzodiazepine cautiously and avoid anticholinergic.

Major Depressive Disorder

Evidence suggests that HIV is a causal factor in depression and that depression is a causal factor in HIV transmission and its morbidity.

So, depression is a treatable vector in the HIV epidemic and suggests the importance of mental health care in the HIV treatment.

The major depressive disorder is a disease state, and it is different from depressive symptoms seen in chronic medical illness like HIV/AIDS. Sometimes differentiating these two may be difficult.

Although the direct evidence is limited to say that HIV is a causal factor, a two-fold increase in the prevalence of major depression seen in patients with HIV suggest a role of the stress axis and immune axis in the causation of depression.

This is also supported by the two and half fold increase in the rate of depression in the patient with CD4 cell count below 200 cells/µl.

The direct injury to subcortical areas of the brain by the HIV virus and chronic stress also may play a role.

Initial psychological distress and social isolation may trigger episodes of major depression in the vulnerable.

Major depression is a risk factor for HIV infection and its treatment outcome due to its negative impact on the quality of life [self-destructive behaviour, poor partner choice in relationships, substance abuse] and treatment adherence. Also, there is a high prevalence of HIV infection, and major depression is seen among homosexuals and substance abusers.

Considering all, the treatment of major depression could improve the HIV treatment outcome. But despite everything depression remains underrecognized, underdiagnosed and undertreated.

The differential diagnoses

The diagnosis of major depression in the HIV clinics is complicated by the high prevalence of depressive symptoms that are associated with chronic medical illnesses, neurological conditions, complex medical treatment, substance abuse related conditions and ongoing unresolved social issues.

Studies show that the worsening of fatigue and insomnia are highly correlated with depression than the progression of HIV infection [CD4 count]. Nonspecific somatic symptoms [aches and

pains, headaches, dizziness and vertigo, fatigue, etc.] are often the result of depression rather than HIV infection and warrant a full psychiatric assessment.

Common conditions that need to be excluded at the time of diagnosis are grief, demoralisation, substance withdrawal and intoxication, dysthymia, delirium, and dementia.

Uncommon conditions like CNS infections and injuries, reappearance of the great imitator: CNS syphilis also needs to be considered to complete the diagnosis.

Depressive symptoms are also associated among male patients with low testosterone levels and often treatment resistance.

Furthermore, certain antiretroviral agents [Efavirenz, Raltegravir], interferon and steroids treatment can give depressive symptoms.

Recommend referring to a psychiatry textbook for comprehensive knowledge but presence of following symptoms almost every day for more than two weeks may suggest depressive disorder.

Pervasive low, sad, miserable mood is a common presentation, but anxious, angry, apathetic moods are also not uncommon. Usually, these moods are worse in the mornings and get better towards evening.

Lack of interest and enjoyment in usually pleasurable activities together with reduced energy are the cardinal features of moderate to severe depression.

Other features that help to measure the severity are,

- Biological symptoms – sleep, appetite disturbances, loss of libido and weight, somatic complaints and constipation.
- Depressive cognitions- worthlessness and helplessness, feeling of guilt, suicidal thoughts.

There are numerous atypical presentations which may hinder the diagnosis.

Treatment

Pharmacotherapy is the mainstay of treatment but combined with suitable psychotherapy may give a better outcome.

All antidepressants are equally effective in the treatment, but patient adherence is the most important factor when it comes to selecting an agent.

The general rule is to start at a low dose and increase slowly to an effective tolerable dose while monitoring adverse effects. The therapeutic effects come in two to four weeks following the onset.

Drug interactions are common with ART medication. Most of the time HIV medications may increase the serum levels of antidepressants.

Fluoxetine [SSRI] may increase the serum level of HIV medications while Venlafaxine [SNRI] may decrease Indinavir but the clinical significance is minimal and dose adjustments are not necessary for both categories.

Major depression is associated with a reduction in the adherence to ART. Untreated depression may be equally and more detrimental to HIV disease progression than any medication interactions.

Recommended safe medications which can be used in the initial treatment are,

- Escitalopram 10-20 mg, Sertraline 50-150 mg in the morning.
- Promethazine 25-100 mg or Trazodone 25-150 mg for sedation.

Non responders may need combinations of antidepressants and other medications with different side effects profile.

Combining psychoeducation, interpersonal psychotherapy, and CBT especially group CBT may help to combat stigma and improve social circumstances.

Timely recognition of suicidal risks and necessary interventions are mandatory.

Schizophrenia

A chronic mental illness characterized by having positive and negative symptoms, disordered thinking, and disorganized behaviour.

There is no direct evidence that HIV infection is a causative factor. Their behaviours like unprotected sex, with multiple partners or, exchange sex for money and use of addictive substances make them more vulnerable to the transmission of HIV infection. Simple psychoeducation does not prevent the HIV spread in this group but needs more comprehensive treatment that includes medications, psychosocial support and rehabilitation.

Recommend avoiding Efavirenz containing regimes due to the risk of neuropsychiatric side effects.

Bipolar affective disorder

A chronic mental illness with episodic alteration of mood with an increased rate of substance use and impulsive behaviour makes them more vulnerable for HIV infection.

The symptoms of bipolar spectrum range from more retarded depressive symptoms to hypomanic and manic symptoms. These hypomanic and manic symptoms may range from euphoria, improved self-attitudes and elevated vital sense, increased energy, decreased need for sleep, expansive self-attitudes, disordered thinking, pressure of speech and disorganized behaviour complicated by hallucination and paranoid delusion leading to a more agitated and violent behaviour making it more difficult to separate it from schizophrenia.

This clinical variety of bipolar disorder can occur anytime in the course of HIV infection among the individuals with pre-existing bipolar disorder and genetic predisposition.

AIDS mania syndrome

A type of mania that appears to be associated with the late stage of HIV infection together with cognitive impairment. There is usually a progressive cognitive decline prior to the onset of mania. The mood is more irritable than euphoric and psychomotor retardation is more prominent than hyperactivity. It shows more chronic malignant course with more relapses usually with the cessation of treatment.

The treatment of mania in the early stages of HIV infection is similar to standard treatment of bipolar disorder with mood stabilizing agents like Lithium carbonate, Sodium Valproate, Carbamazepine, Lamotrigine, and atypical antipsychotic agents.

AIDS mania in advanced HIV disease with low CD4 cell count is more a medical illness and is difficult to treat with traditional anti-manic agents as it is more prone to get extrapyramidal side effects and delirium. Atypical anti-psychotics started in low doses with gradual titration are recommended for the treatment.

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HIV and GI Manifestations

Dr. Manjula Rajapakshe

Introduction

Diarrhoea is common among people living with HIV, even in the era of ART. If the diarrhoea is watery and large volume, it is more likely to be due to small bowel pathology while if it is of small volume, with cramping lower abdominal pain, mucous, blood, fever or rectal symptoms, it is more suggestive of a large intestinal pathology.

Diarrhoea persisting for more than 4 weeks duration is defined as chronic diarrhoea. Chronic diarrhoea is more likely to be associated with opportunistic infections in people living with HIV than in the general population, particularly those with lower CD4 counts.

Causes

Infectious causes

- **Bacteria:** *Salmonella* spp, *Shigella, Campylobacter, Clostridium difficile, Escherichia coli* (pathotypes), *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare* complex, *Mycobacterium kansaii*, *Chlamydia trachomatis* | Lymphogranuloma verereum(LGV)
- **Parasite and Fungi** *Giardia lamblia*, *Entamoeba histolitica*, *Strongyloides stercoralis,* Cystoisospora belli, Cyclospora, Cryptosporidia spp Microsporidia
- **Virus** CMV, HSV, Adenovirus, Rotavirus, Norovirus, Coronavirus, Astrovirus

Non-infectious causes

- Pancreatic exocrine insufficiency
- HIV enteropathy
- ART and other medications
- Inflammatory bowel disease
- Systemic disease –Thyrotoxicosis
- Kaposi Sarcoma
- Lymphoma

Diagnosis

- Faecal microscopy, examination for ova, cysts and parasites including Cryptosporidia, Cyclospora and Cystoisospora within 10 days (at least 3 samples should be tested).
- Stool culture - Bacterial culture including Clostridium difficile culture.
- Bacterial blood cultures (especially diarrhoea with fever), including blood cultures specific for MAC.
- Stool sample for C. difficile toxin or polymerase chain reaction (PCR) assay should be done from following patients,
    - who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy
    - those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized)
    - those who reside in a long-term care facility
    - those with CD4 counts <200,
    - who are on acid suppressive medication
- Endoscopy and biopsy (Gastroscopy/Duodenoscopy/ Sigmoidoscopy/Colonoscopy) should generally be reserved for patients in whom stool culture, microscopy, C. difficile toxin assay, and blood culture fail to reveal an aetiology or in whom treatment for an established diagnosis fails.
- Biopsy specimens should be examined with special stains such as Giemsa and modified Ziehl- Neelsen, and immunohistochemistry, viral and mycobacterial cultures, LGV PCR.
- If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, diagnostic evaluation for STDs with anoscopy, culture, and biopsy should be considered.

Treatment

General Considerations

- Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhoea.
- Consuming a bland diet and avoiding fat, dairy, and complex carbohydrates are useful since diarrheal disease can produce temporary malabsorption or lactose intolerance.
- Antimotility agents should be avoided if there is concern about inflammatory infectious diarrhoea, including Clostridium difficile infection.
- Diagnostic faecal specimens should be obtained prior to initiation of empiric antimicrobial therapy.
- If stool sample is obtained, antibiotic susceptibilities should be performed.
- Risk of a bacterial enteric infection and bacteraemia increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/µL.
- If no clinical response after 3 to 4 days, consider follow up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug-drug interactions.
- Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Symptomatic treatment

- Loperamide 4-32 mg daily by mouth in divided doses if inflammatory causes excluded.

Empiric Treatment of Bacterial Enteric Infections (Pending Diagnostic Studies)

For patients with advanced HIV (CD4 count <200 cells/µL or concomitant AIDS-defining illnesses) and clinically severe diarrhoea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills).

Preferred Therapy	Alternative Therapy
▪ Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h	▪ Ceftriaxone IV 1 g q24h or ▪ Cefotaxime IV 1gq 8h

Table 18-1 - Specific treatment for selected bacterial organisms

Organism	Diagnosis	Treatment
Salmonella	Stool culture Blood culture Urine culture	Preferred therapy ▪ Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h Alternative Therapy ▪ Levofloxacin 750 mg (PO or IV) q24hor ▪ Moxifloxacin 400 mg (PO or IV) q24hor If susceptible, alternatives to fluroquinolone may include one of the following: ▪ Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) q12h, or ▪ Ceftriaxone IV 1g q24hor ▪ Cefotaxime IV 1gq8h Duration of Therapy for Gastroenteritis without Bacteraemia o If CD4 count >200 cells/µL: 7–14days o If CD4 count <200 cells/µL particularly if primary illness was severe: 2–6weeks Duration of Therapy for Gastroenteritis with Bacteraemia o If CD4 count >200 cells/µL: 14days; longer duration if bacteraemia persists or if the infection is complicated (e.g., metastatic foci of infection are present) Secondary Prophylaxis may be recommended for: ▪ Patients with recurrent bacteraemia, or ▪ Patients with recurrent gastroenteritis (with or without bacteraemia) with CD4 count <200 cells/µL When to Stop Secondary Prophylaxis: ▪ After resolution of Salmonella infection and response to ART with sustained viral suppression and CD4 count >200 cells/µL

Shigella	Stool culture	Preferred Therapy ▪ Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h Alternative Therapy (Depending on Susceptibility Results) ▪ Levofloxacin 750 mg (PO or IV) q24hor ▪ Moxifloxacin (PO or IV) 400 mgq24h ▪ Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV q12h ▪ Azithromycin 500 mg PO daily for 5days (Note: Azithromycin is not recommended for Shigella bacteraemia) Duration of Therapy ▪ Gastroenteritis: 7–10 days (except Azithromycin, treat for 5 days) ▪ Bacteraemia: ≥14days ▪ Recurrent infections: up to 6weeks Chronic Maintenance or Suppressive Therapy ▪ Not recommended for first-time Shigella infections
Clostridium difficile infection (CDI)	Clostridium difficile toxin and culture	Preferred Therapy ▪ Vancomycin 125 mg (po) four times per day X 10-14 days Alternative Therapy ▪ For mild, outpatient disease: Metronidazole 500 mg (po) three times per day
Campylobacter	Stool culture	Mild to Moderate Disease Preferred Therapy ▪ Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h—if susceptible, or ▪ Azithromycin 500 mg PO daily for 5 days (Not recommended for bacteraemia) Alternative Therapy (Depending on Susceptibility Results) ▪ Levofloxacin 750mg PO or IV q24h or ▪ Moxifloxacin 400 mg PO or IV q24h

		Bacteraemia ▪ Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h + an aminoglycoside to limit the emergence of antibiotic resistance <u>Duration of Therapy</u> ○ Gastroenteritis: 7–10 days [5 days if Azithromycin is used] ○ Bacteraemia: ≥14days ○ Recurrent bacteraemic disease: 2–6weeks <u>Chronic Maintenance or Suppressive Therapy</u> ▪ Not recommended for first-time Campylobacter infections
Mycobacterium tuberculosis	▪ Colonoscopy + biopsy for histology (AFB smear) + mycobacterium culture (preferred to molecular test for intestinal tuberculosis) ▪ Intestinal tissue molecular test ▪ CT preferred mode of imaging	See the separate chapter on TB
Mycobacterium avium complex	Definitive diagnosis requires culture in ▪ blood ▪ from bone marrow aspirate ▪ fluid from a normally sterile site ▪ biopsy specimen	See the separate chapter on treatment of Mycobacterium avium complex
Chlamydia trachomatis/ LGV	Rectal swab molecular test, if *C. trachomatis* positive then test DNA for LGV-specific serovars	As per national STI guidelines ▪ Oral Doxycycline 100 mg bd for 21 days

Table 7 - Specific treatment for selected parasitic organisms

Organism	Diagnosis	Treatment
Cryptosporidia	Microscopic identification of the oocysts in stool or tissue with ▪ modified acid-fast staining or ▪ direct immunofluorescence ▪ PCR	<u>Preventing Chronic Cryptosporidiosis</u> ▪ Initiation of ART before the patient becomes severely immunosuppressed should prevent the disease <u>Preferred Management Strategies</u> ▪ Aggressive oral and/or IV rehydration and replacement of electrolyte loss, and symptomatic treatment of diarrhoea with antimotility agent. ▪ Initiate or optimize ART for immune restoration to CD4 count >100cells/µL Consider: ▪ Nitazoxanide 500–1000 mg PO BID with food for 14 days + optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, or ▪ Paromomycin 500 mg PO QID for 14 to 21 days + optimized ART, symptomatic treatment and rehydration and electrolyte replacement <u>Other Considerations:</u> ▪ Because diarrhoea can cause lactase deficiency, patients should avoid milk products
Microsporidia	Stool culture	<u>Preventing Chronic Microsporidiosis</u> ▪ Initiation of ART before the patient becomes severely immunosuppressed should prevent the disease ▪ Severe dehydration, malnutrition, and wasting should be managed by fluid support and nutritional supplements ▪ Anti-motility agents can be used for diarrhoea control, if required h

		For Gastrointestinal Infections Caused by *Enterocytozoon bieneusi* ▪ The best treatment option is ART and fluid support. ▪ No specific therapeutic agent is available for this infection. ▪ Fumagillin 60mg PO daily and TNP-470 are two agents that have some effectiveness ▪ Nitazoxanide may have some effect, but the efficacy is minimal in patients with low CD4 cell count For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than *E. bieneusi* and *Vittaforma corneae* ▪ Albendazole 400 mg PO BID, continue until CD4count>200 cells/µL for >6 months after initiation of ART For Disseminated Disease Caused by *Trachipleistophora or Anncaliia* ▪ Itraconazole 400 mg PO daily plus Albendazole 400 mg PO two times a day
Cyclospora	ZN or auramine staining of faeces. Oocysts can also be seen using phase contrast microscopy, and PCR-based diagnostic methods have been developed	Preferred Therapy ▪ Trimethoprim 160 mg/Sulfamethoxazole 800 mg PO bd for 7days followed by 3 times weekly as prophylaxis
Entamoeba histolytica	▪ Faecal microscopy with or without faecal antigen/PCR or colonic biopsy. ▪ Serology and imaging for extraintestinal disease	▪ Metronidazole 800mg tid for 10 days; or Tinidazole2g once a day for 3days ▪ Followed by either Diloxanide furoate 500mg tid PO for 10 days or Paromomycin 30mg/kg/day in three divided doses po for 10days

Giardia lamblia	Faecal microscopy or faecal antigen detection ELISA	See the separate chapter on TB
Mycobacterium avium complex	Definitive diagnosis requires culture in ▪ blood ▪ from bone marrow aspirate ▪ fluid from a normally sterile site ▪ biopsy specimen	Preferred Therapy ▪ Metronidazole 400mg tid for 7 days or 1g daily po for 3days Alternative Therapy ▪ Tinidazole 2g po once only or 500mg bd for 7days
Cystoisospora belli	Direct microscopy of iodine-stained faecal smears or fluorescence microscopy	Preferred Therapy ▪ Trimethoprim 160 mg/Sulfamethoxazole 800 mg bd po for 7 days Alternative Therapy ▪ Trimethoprim 160 mg/Sulfamethoxazole 800 mg qds for 10 days or ciprofloxacin 500 mg bd followed by the same antibiotic as prophylaxis *Remarks: Antibiotic prophylaxis required until effective response to ART*
Strongyloides stercoralis	▪ Stool culture to detect larvae in faeces. ▪ Serology (may have cross-reaction with other parasitic nematode infection)	Preferred Therapy ▪ Oral Ivermectin (200 µg/kg once or twice only) Alternative Therapy ▪ Albendazole 400 mg bd for 3days

Table 8 - Specific treatment for selected viral organisms

Virus	Diagnosis	Treatment
CMV	Biopsies + histology (if GI symptoms) from upper or lower GI endoscopy; CMV molecular test	Ganciclovir (5 mg/kg bd iv) 2–4 weeks/until symptom resolution. For non-severe infection, oral valganciclovir (900 mg bd) may be used. Second line: Foscarnet (90 mg/kg bd iv) for 2 weeks

HSV	Rectal swab molecular test for HSV	As per National guidelines: ▪ Acyclovir 400 mg tds or valaciclovir 500 mg bd
Cyclospora	ZN or auramine staining of faeces. Oocysts can also be seen using phase contrast microscopy, and PCR-based diagnostic methods have been developed	Preferred Therapy ▪ Trimethoprim 160 mg/Sulfamethoxazole 800 mg PO bd for 7days followed by 3 times weekly as prophylaxis
Rotavirus	ELISA, latex agglutination or molecular test (preferred method)	Supportive measures
Norovirus	Molecular test (preferred method), ELISA	Supportive measures
Adenovirus	Molecular test, EIA, histology	Cidofovir IV if clinically significant infection (rare) Induction ▪ 5 mg/kg weekly for 2 weeks Maintenance ▪ 5 mg/kg fortnightly
Coronavirus	Molecular test (preferred), EIA	Supportive measures

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HIV and Liver Disease

Dr. Thilani Rathnayaka

Introduction

Pathology related to liver in HIV infection are due to multiple aetiologies and associated with high levels of morbidity and mortality. Between 13% and 18% of all-cause mortality in HIV-infected patients involves liver-related damage. Liver damage is one of the main causes of death not related to acquired immunodeficiency syndrome (AIDS) . Even when HIV infected patients are on correct ART and viral load is under control, they have a higher chance of developing liver pathologies due to various causes not related to HIV or ART which include alcohol liver disease, non-alcoholic fatty liver, viral hepatitis and age-related liver damage than in HIV negative individuals. Furthermore, treatment used in HIV including ART can cause liver damage which sometimes can end up with severe hepatic failure.

Infectious causes for Liver disease in HIV	Non-infectious causes for liver disease
HIV infection	Alcohol related
Co infections Hepatitis A, B, C, D and E	Non-alcoholic fatty liver
Opportunistic infections and malignancies TB, CMV, EB virus, Herpes virus KS, NHL	Treatment related (ART and other)

Hepatitis B virus (HBV)

Globally 10 % of HIV infected patients have chronic Hepatitis B infection. Sexual transmission, peri natal transmission and transmission through sharing needles among IDU are the main modes of transmission of HBV and the average incubation period is 90 days (60 -150 days) from

exposure to onset of jaundice. Usually in HIV negative population 70% of acute infection is asymptomatic and 80% recover without going to chronic infection but among HIV infected patients' higher percentage can go to chronic hepatitis B infection. Most patients with chronic hepatitis B could be asymptomatic or have non-specific symptoms and fatigue as a prominent symptom.

Compared with individuals with HBV mono infection, those with HIV/HBV coinfection have higher levels of HBV viremia. The likelihood of sero clearance is low in HIV infected patients, a high chance of having detectable HBeAg, lower rate of seroconversion to anti HBs and increased risk of cirrhosis and development of Hepato Cellular Carcinoma (HCC).

All HIV infected patients should be tested for hepatitis B before starting ART.

Recommended initial screening tests,

1. For hepatitis B infection
    - Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc total)
2. For immunity status
    - Hepatitis B surface antibody (anti-HBs)

Persistence of HBsAg for more than 6 months indicates chronic hepatitis B infection. which can be further classified into 4 categories (HBeAg-positive chronic HBV infection, chronic active hepatitis, HBeAg negative chronic infection and HBeAg negative chronic active hepatitis) depending on the presence of HBeAg and antibodies antiHBe, HBV DNA and active involvement of the liver. (Refer STD guideline - Hepatitis section)

If chronic infection is confirmed patients should have the following investigations

- HBV e-antigen (HBeAg)
- Antibody to HBeAg (anti-HBe)
- HBV DNA
- Serum ALT AST
- Screening for HAV - anti Hep A
- Screening for HCV - anti Hep C
- HDV antibody (with HDV RNA if positive) should be performed on all HBsAg-positive
- In addition, patients should have a complete blood count, albumin, total bilirubin, alkaline phosphatase, international normalized ratio (INR),
- Abdominal ultrasound
- Liver fibrosis assessment at initial visit, and every 6 to 12 months. Liver fibrosis can be assessed using both non-invasive methods (serum markers and elastography) and liver biopsy which is rarely indicated.
- HCC surveillance every 6 months
    - For patients with cirrhosis
    - Asian male >40 years

- Asian females > 5o years
- HIV-co infection

Occult Hepatitis B infection

Is defined as chronic active hepatitis B in which patients does not express Hep BeAg but active liver damage has happened with elevated levels of transaminases and HBV DNA. Therefore, it is important to suspect having occult hepatitis infection and perform an HBV DNA in,

- Patients with isolated anti-HBc (negative HBsAg and anti-HBs) and unexplained elevated transaminases
- Patients whose transaminases are persistently raised and all other tests (including HBsAg, HCV RNA and anti-HEV) are negative

Treatment Hepatitis B co infection

Treatment should be aimed to minimize liver damage and prevent hepatitis B related morbidity and mortality. All patients should be referred to a hepatologist and managed under MDT.

Recommendations

- All HIV/HBV co infected patients should receive TDF or TAF based ART regimen unless there are contra indications. (CrCl <30ml)
- Preferred first choice of NRTI back bone should include TDF or TAF and 3TC or FTC regardless of CD4 count and HBV DNA level.
- Both TDF and FTC have an action against Hepatitis B.
- TDF and TAF act against both wild type and lamivudine resistance type of HBV and both have a higher barrier for development of HBV resistance.
- Best ART option for co infection –Elvitegravir/cobicistat/TAF/FTC
- ART regimens in which 3TC or FTC is the only active drug against HBV should be avoided as there is a risk of resistance development.
- If TDF and 3TC cannot be recommended can use Entecavir in addition to an ART regimen with fully suppressed HIV viral load
- Tenofovir (TDF and TAF), entecavir, lamivudine, emtricitabine, and telbivudine should not be used alone in co infection.
- Entecavir with 3TC or FTC is better than entecavir alone. Entecavir alone is not recommended when 3TC resistance mutation is detected (M184)
- If 3TC resistance is suspected need to increase entecavir dose from 0.5 mg to 1 mg

- Adefovir and Telbivudine are other alternative drugs but with side effects and higher rates of treatment failure. Renal disease with adefovir and myopathy and neuropathy with telbivudine are seen.
- Adefovir alone is not recommended for coinfected patients. Should be used with 3TC or FTC or telbivudine in addition to fully suppressed ART regimen.
- When there is a need to switch ART to another which does not have anti hep B action the risk of a flare up needs to be considered and it is recommended to monitor transaminase levels every 6 weeks, 3 months and then 6 months.

Other treatment options

Pegylated interferon-alfa-2a monotherapy has activity only against HBV and may be considered for patients with HIV/HBV coinfection who are not receiving ART.

Prevention of HBV infection

All HIV infected patients should be educated and given information on hepatitis infection, transmissions and avoidance of risky behaviours for acquiring the infection related to sexual risk and sharing needles and syringes, tattooing etc

- All household contacts and sexual contacts of HBAg s positive patients should be vaccinated
- All HIV patients (at risk of hepatitis B) should be vaccinated against hep B using following options (refer the vaccination schedule for hepatitis B)
- All hep B positive patients should be vaccinated against hepatitis A

IRIS and hepatitis B

Reactivation of hepatitis B induced liver damage as a result of immune reconstitution after initiation of ART is well recognized condition. This should be suspected when serum transaminases rise rapidly with an increase of CD4 count in the first 6 to 12 weeks of ART initiation. IRIS could be difficult to distinguish from drug/ART induced hepatotoxicity and other infective causes of hepatitis (acute Hepatitis A C, D and E, CMV, EB virus etc). It is essential to monitor ALT levels and clinical signs of hepatitis after starting ART for early detection of IRIS.

Hepatitis C co-infection

Both HCV and HIV can be transmitted through blood specially among IDUs who shared needles and syringes, unprotected sex and from infected mother to child. HCV is approximately 10 times

more infectious than HIV through percutaneous blood exposures and transmission via injection drug use remains the most common mode of transmission. Heterosexual transmission is uncommon but more likely in HIV co infected patients. Out breaks of HCV has been reported among HIV infected MSMs as sexual transmission is an important mode of transmission among this high-risk group with multiple sexual contacts. Unprotected receptive anal intercourse. use of sex toys, chem sex and presence of other STDs are risk factors for HCV transmission. Mother to child transmission of HCV varies from 4-7% with detectable HCV RNA levels and this incidence can be high as 10- 20 % in HIV co infected mothers.

Most of the acute HCV infections are asymptomatic and majority of acutely infected patients can develop chronic HCV infection. Symptomatic patients may have low-grade fever, mild right upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum ALT or AST levels may be the only serological evidence in acute and chronic infections. HIV infection can accelerate the course of progression to cirrhosis and then end stage liver damage and HCC particularly if CD4 count is less than 200. Vasculitis, renal disease and cutaneous porphyria tarda are also associated with HCV.

Diagnosis

- All HIV infected patients should be tested for HCV infection as a baseline investigation with hepatitis C antibody test.
- If positive, confirmation is by quantitative HCV RNA. Genotyping is important for management.

False negative anti-HCV can result when the patient is in the initial window period which can vary from 2 weeks to 12 weeks. It's advisable to do an HCV RNA level when clinical suspicion is high in a patient whose initial antibody test is negative.

Management

Treatment options for HCV is rapidly evolving and treatment options depends on many factors including genotype of HCV. Current evidence is to treat acute HCV infection to prevent chronic infection within the first 6-12 months. But some clinicians prefer not to treat during the first 6 months but observe because certain percentage of acute infection can spontaneously cure specially in patients positive for C/C IL28B genotype.

In general, the goals of therapy, treatment regimen, and monitoring parameters for HIV/HCV coinfected patients are similar to those recommended for HCV mono infected patients. All HCV/HIV infected patients should be referred to hepatologists and managed under an MDTm

To prevent further liver damage patients should be advised to,

- Avoid alcohol consumption

- Limit hepatotoxic medication
- Avoid iron supplements if no evidence of iron deficiency

All HCV infected patients should be tested for HBV and HAV infection and immunity and vaccinate against HBV and HAV. Patients should have regular liver function tests (ALT, AST, Albumin, INR), imaging studies for liver fibrosis and alpha fetoprotein levels for HCC.

Treatment

Current evidence is for combination therapy with pegylated interferon with directly acting antivirals (ribavirin, boceprevir, telaprevir,) for 24 weeks or 48 weeks. PEG-IFN monotherapy is not an option for HCV. Careful monitoring for interaction with ART is important.

(Refer to HCV, STD Guideline or specific guidelines for treatment options)

Prevention

As there is no effective vaccine or post exposure prophylaxis for HCV, patients should be educated and counselled to avoid risky behaviours associated with contracting HCV.

Hepatitis E

HEV should be considered and excluded in patients with HIV infection and elevated liver transaminases and/or liver cirrhosis when other common causes of elevated transaminases have been excluded.

Drug related Liver toxicity

ART as well as other medications used to treat OIs in HIV infection can affect the liver in different intensities. NNRTIs particularly Nevirapine is replaced by less liver toxic drugs in most settings. Most new ART has fewer toxic effects and recent evidence is that effective ART treatment is associated with reduced progression of liver disease.

ART-associated hepatotoxicity may be dose-dependent or idiosyncratic. The risk of ART-associated hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases (ALT, AST) and the presence of HBV or HCV coinfection. Therefore, its

recommended to have baseline AST and ALT levels and monitor AST and ALT levels in 6 weeks and 12 weeks and at least at 6-month intervals. ART should be stopped and switched to non-hepatotoxic drugs when AST and ALT levels are > 5 times the normal.

ART with potential toxicity to liver

NRTIs	Stavudine, Didanosine, Zidovudine
NNRT	Nevirapine, Efavirenz
PIs	Ritonavir, Indinavir, Saquinavir, Tipranavir

Mechanisms involved in ART liver toxicity

1. Mitochondrial damage.
   Most NRTIs induce mitochondrial damage and have a potential for the development of direct liver injury that may evolve to acute liver failure. The main feature is accumulation of microvesicular steatosis in liver cells and mitochondrial depletion. Clinically patients develop lactic acidosis and the cumulative exposure to NRTI is an important factor. Lactic acidosis appears after prolonged exposure to NRTIs usually years and correlates with the number of concomitant NRTI.

2. Hypersensitivity reaction
   Is an idiosyncratic reaction of the host, not related to the dose of the drug. Commonly seen with Sulphas inducing these immune-mediated reactions involving the liver. Reaction is apparent within the first 4-6 weeks of treatment. Commonly seen in patients taking NVP, on some occasions with fatal outcome, linked to women with CD4 counts >250cells/mm within 6 weeks after initiation of treatment. Pathology involves the generation of neoantigens formed by the reaction of liver proteins with reactive drug metabolites. In addition to NVP, hypersensitivity reactions have been reported with abacavir (ABC) (HLA B57) and zalcitabine (ddC).

3. Direct toxicity
   Some ART can induce direct liver toxicity. ARTs metabolised in the liver through the cytochrome pathways may cause liver toxicity when there are polymorphisms in the enzymes which leads to the development of hepatotoxicity in certain individuals. Some drugs may potentiate the activation of death receptors and/or intracellular stress pathways resulting in an increase in transaminases

4. Metabolic toxicity
   Some ARTs induce lipodystrophy syndrome, with marked abnormalities in the metabolism of both lipids and glucose, including insulin resistance. As a result, mild-to-moderate degrees of steatosis have been found in the liver leading to hepatotoxicity or NASH.

Non-alcoholic fatty liver Disease (NAFLD)

Is the inflammation arising from the accumulation of fat in the liver. NAFLD and its more severe form is called non-alcoholic steatohepatitis (NASH). Both conditions are responsible for a growing proportion of advanced liver disease worldwide. As a result of inflammation, NAFLD can lead to fibrosis, cirrhosis and even liver cancer.

Fatty liver disease is also recognized as a metabolic syndrome and often accompanied by abdominal obesity, hypertension and abnormal blood sugar and fat levels. With no effective approved medical therapies, NAFLD management is dependent on lifestyle changes such as weight loss and exercise.

In HIV infection more NAFLD is commonly reported among young patients who acquired HIV perinatally and associated with overweight and high BMI. According to the researchers' viral load and CD4 cell count, generally did not differ significantly in people with and without fatty liver disease, except the lower CD4/CD8 T-cell ratio.

Ultrasound assessment should be considered for the screening of NAFLD among people with perinatally acquired HIV in routine clinical practice.

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HIV Associated Haematological Conditions

Dr. Visaka Ratnamalala

Introduction

Haematological abnormalities associated with human immunodeficiency virus (HIV) infection were the commonest clinical problems in the early years of the acquired immune deficiency syndrome (AIDS).

Those are encountered far less frequently in the current era of combination anti-retroviral therapy (ART).

For those who are not on combination antiretroviral therapy, either because of lack of access to medical care or because of delay in diagnosis, the natural history of untreated HIV remains linked to a high prevalence of anaemia, neutropenia and thrombocytopaenia and other haematological conditions. Incidence of cytopenias correlate directly with the degree of HIV-induced immunosuppression. In addition, isolated cytopenias, particularly thrombocytopaenia, can manifest as the initial signal of HIV infection.

Direct suppression of bone marrow progenitor cells by HIV infection or indirectly through excessive secretion of inflammatory cytokines induced by HIV, suppress haematopoiesis. In addition, HIV infects multipotent haematopoietic progenitor cells and establish latent cellular reservoirs, disturbs the bone marrow microenvironment and also causes immune dysregulation. Nutritional deficiencies, infiltrative bone marrow disease of infectious or neoplastic origin, and adverse drug effects also affect bone marrow function.

HIV is also a prothrombotic state with an increased incidence of thromboembolic disease. These are less frequently encountered in the current era of ART.

Haematological emergencies occurring in this setting includes high-grade lymphomas, particularly Burkitt lymphoma, and thrombotic thrombocytopenic purpura (TTP), immune thrombocytopenic purpura (ITP), opportunistic infections and severe drug side-effects.

Common Haematological manifestations

- Anaemia
- Neutropaenia
- Thrombocytopaenia
- Thrombotic thrombocytopaenic purpura (TTP)
- Thrombosis
- Other coagulation disorders
- Malignancy – Myeloma, Lymphomas
- Haemophagocytic lymphohisteocytosis (HLH)
- Paraprotinaemia Bone marrow abnormalities - Necrosis, Pure red cell aplasia, Eosinophilia

Anaemia

Anaemia is the commonest haematological disorder that frequently occurs in HIV patients. More than 70% of people living with HIV got anaemia.

Incidence of anaemia

- 3% in patients with asymptomatic HIV infection,
- 12% in patients with CD4+ counts <0·2 × 10^9 cells/L
- 37% among those with AIDS-defining illness.
- 35% of ART treated patients may be anaemic at any given time.
- HIV-infected women have a higher incidence of anaemia than men.

Haemoglobin concentration for the diagnosis anaemia

Age group	No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
Children 6-59 months	>11	10-10.9	7-9.9	<7
Children 5-11 years	>11.5	11-11.4	8-10.9	<8
Children 12-14 years	>12	11-11.9	8-10.9	<8
Non pregnant women (>15 years of age and above)	>12	11-11.9	8-10.9	<8
Pregnant women	>11	10-10.9	7-9.9	<7
Men	>13	11-12.9	8-10.9	<8

Source: Haemoglobin concentration for the diagnosis of anaemia and assessment of severity. WHO

Mainly normocytic normochromic anaemia is observed in HIV. However, all the other below mentioned causes to be excluded at the diagnosis as patients may present with anaemia due to HIV unrelated causes.

Symptoms and sings of anaemia

Shortness of breath on exertion, hair loss, lethargy, tiredness, sleepiness and loss of appetite. Pallor is the main sign. In extreme cases, other organ related sign may appear.

Morphological types of anaemia in general

Hypochromic microcytic anaemia

- Iron deficiency,
- Thalassaemia syndrome,
- Sideroblastic anaemia
- Anaemia of chronic disease.

Macrocytic anaemia

- B12 / folate deficiency,
- Drugs induced,
- Liver pathology
- Haemolytic anaemia

Normocytic normochromic anaemia

- Acute blood loss
- Mixed deficiency
- Anaemia of chronic disease (renal failure, chronic arthritis, chronic autoimmune disease etc)
- Chronic infection
- Malignancy

Investigations of anaemia

- Full blood count - Provide the details to find the type of anaemia.
- Blood Picture - Informative. Gives a closest diagnosis.
- Iron studies - Serum iron, Total iron binding capacity.
- Serum ferritin level – Estimate the iron stores when patient is clinically normal.

- Retic count – Helpful in haemolysis, assess red cell production after treatment for anaemia
- Serum B12 level
- Serum or red cell folate levels
- Stools for occult blood or endoscopies – may be helpful.
- Retic count – Helpful in haemolysis, assess red cell production after treatment for anaemia
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Diagnosis	Investigations	Treatment
HIV related anaemia	Low/normal MCV in FBC Normal bone marrow iron Low erythropoietin level, ferritin >225 µg/l	ART, Erythropoietin Blood transfusions
Iron deficiency	Serum Fe < 11 µmol/l Transferrin < 3 g/l Ferritin < 45 µg/l MCV < 80 fl	Elemental iron 60 mg 2–3 times daily; Consider intravenous iron in intolerance to oral iron.
Folic acid deficiency	Serum folic acid < 2–4 µg/l MCV > 100 fl Reticulocytes < 2·0%	Folic acid 1 mg/d for 3 months.
Vitamin B12 deficiency	Serum B_{12} (cyanocobalamin) <125–200 ng/l MCV > 100 fl Reticulocytes < 2·0%	Vitamin B_{12} 1 mg/d intramuscular injection for 7 d, then once weekly ×4, then monthly until malabsorption resolved. (Optional: oral or sublingual vitamin B_{12} 1 mg/d)
Parvovirus B19	Severe anaemia (haemoglobin < 10 g/dl), typically with normal neutrophil and platelet counts PCR or DNA dot-blot hybridization for parvovirus B19	IVIG 400 mg/kg/d for 4–5 d or 1000 mg/kg for 2 days. If relapse in <6 months, consider 2 g/kg over 2 days. Consider maintenance dosing of 0·4 g/kg every 4 weeks for relapse. ART may be effective

Marrow infiltration by tumour or infection	MCV 80–100 fL Reticulocytes < 2·0% Pancytopenia Bone marrow biopsy abnormal	Treat the specific cause
Drug-induced anaemia	MCV > 100 fL	Discontinue the drug or use Erythropoietin
G-6PD deficiency, and other haemolytic anaemias	MCV 80–100 fL Reticulocytes > 2·0% Indirect bilirubin > 20·5 µmol/L LDH > normal Haptoglobin < 250 mg/L	Severe methemoglobinemia can be treated with 1 mg/kg intravenous methylene blue

Haemolytic anaemia

Haemolysis may also play an important role in HIV-associated anaemia. Several mechanisms are involved.

- Antibody-mediated haemolysis
- Microangiopathic haemolytic anaemia
- Drug-induced haemolytic anaemia in patients with G-6PD deficiency (rare)

Related investigations

- Direct coomb's test, (positive)
- LDH, ANA
- Reticulocyte count
- Demonstration of splenomegaly by ultrasound scan abdomen

If the diagnosis cannot be established, a referral to haematologist is recommended.

Treatment

Treatment of anaemia should be according to the causative factor. It's essential to establish the underlying pathology before commencement of treatment unless urgent.

Neutropoenia

Ten to thirty percent of patients with early symptomatic HIV infection will be neutropenic, and this may progress to ≥ 50% in those with AIDS. Moderate neutropenia is most often identified

in the course of routine laboratory assessment during the standard care of patients receiving ART.

Neutropenia also common with zidovudine-containing regimens, and in those with low CD4+ cell counts.

Absolute Neutrophil count (ANC)	Severity of neutropenia
>1.5 x 109/L (1500/µl)	Normal
1.5 – 1x 109/L (1500- 1000/ µl)	Mild neutropenia
1 – 0.5 x 109 /L (1000 – 500/ µl)	Moderate neutropenia
< 0.5 x 109/L (<500 /µl)	Severe neutropenia

The risk of infection begins to increase at an absolute neutrophil count of (ANC) 1·0 × 109/L and becomes increasingly more severe when the ANC is <0·5 × 10^9/L.

Treatment of neutropenia

- The correction of potentially reversible causes of neutropenia.
- Commencing ART early in the course of HIV infection is now recommended in treatment of neutropenia.
- When possible, medications associated with neutropenia should be discontinued,
- Infections should be treated aggressively.
- Treatment with Granulocyte colony-stimulating factor (G-CSF) should be considered. ANC <0·25 × 109/L, and possibly <0·5 × 109/L are reasonable thresholds below which G-CSF can be considered.
- G-CSF, a conventional starting dose is 1–5 µg/kg/d (Usual adult dose 300 micrograms) administered subcutaneously until the ANC reaches 1·0–2·0 × 109/L.
- Adverse effects of G-CSF may include bone pain, dysuria and elevated levels of lactate dehydrogenase, serum aminotransferases and uric acid.
- The use of G-CSF is generally contraindicated in patients with sickle cell disease.

Thrombocytopaenia

Thrombocytopaenia may occur at any time during the course of HIV infection. Its incidence generally correlates with the degree of immunosuppression and is more frequent in those with AIDS. Incidence has decreased significantly with the introduction of ART.

Normal platelet count:150,000 – 400,000 /µL

Thrombocytopaenia: < 150,000 /µL

Risk of bleeding: < 20,000/μL

Aetiology

- Auto immune
- Direct infection of megakaryocytes by HIV
- Elevated C-reactive protein (CRP) enhances IgG-mediated platelet destruction by binding to phagocytes
- Drugs
- Alcohol
- Infections
- Neoplasm

Symptoms and sings

Minor cutaneous and sub-mucosal bleeding, characterized by petechiae, ecchymosis and occasional epistaxis.

Investigations

- **FBC:** Isolated thrombocytopaenia
- **Blood picture:** Confirms thrombocytopaenia, excludes other causes including leukaemia etc.
- **ANA:** Confirms autoimmune origin or relation to SLE.
- **Bone marrow biopsy:** Increased or normal number of megakaryocytes. Exclude malignancies.

Bone marrow aspiration or biopsy will show an increase in megakaryocytes in response to peripheral platelet phagocytosis in ITP, whereas megakaryocytes may be decreased in HIV-induced thrombocytopaenia.

Bone marrow biopsy is not necessary to make a clinical diagnosis of ITP unless atypical laboratory or clinical features are present.

Treatment for HIV-associated thrombocytopenia

- ART
- Prednisone 30–60 mg/d and taper with response
- IVIG infusion 1 g/kg, 2 days
- Eltrombopag 50 mg/day or Romiflostim

- Rituximab 375 mg/m2 weekly for 4 doses if patients are refractory to front line treatment
- Splenectomy

Thrombotic disorders: Venous Thrombo-Embolism (VTE)

Incidence of VTE in HIV-infected patients was 2·6/1000 person-year.

Aetiological factors of thrombosis

Patient-specific factors
- HIV infection
- Highly active antiretroviral therapy
- Opportunistic infections
- Malignancies
- Venous damage caused by intravenous drug use
- Sedentary lifestyle
- Hyperlipidaemia
- Age over 45 years old

Other risk factors
- Central venous catheters
- Tissue fibrosis
- Free protein S deficiency
- Antiphospholipid antibodies
- Increased factor VIII
- Increased fibrinogen concentration
- Autoimmune haemolytic anaemia
- Protein C, protein S & antithrombin III deficiency (congenital causes)

Thrombosis – Management

- Thrombus should be confirmed by a Doppler scan or other relevant imaging.
- Before commencement of anticoagulants, baseline investigations to be performed- Renal functions, Liver functions, Prothrombin time (PT), Activated partial thromboplastin time (APTT), FBC.
- Commencement of a suitable anticoagulant. (Low molecular weight heparin/ High molecular weight heparin)
- Warfarin sodium or new oral anticoagulant to be considered according to the patient's condition.

- Graduated stockings. limb elevation are some local measures.
- Anticoagulation should be continued for minimum of three months.
- Thrombophilia screening to be planned three months after the acute event- especially coagulation-based tests to be done one week after stopping warfarin sodium, 24hrs after enoxaparin and 48 hrs after stopping new oral anticoagulants.
- Genetic tests can be performed at any time while on warfarin sodium or other anticoagulant.
- When the thrombophilia tests are positive, prolong warferinization/anticoagulation is recommended.

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura is a very serious but, fortunately, rare complication of HIV infection. Its prevalence is 0·09 per 1000 person-years in the ART era, and often associated with AIDS rather than asymptomatic HIV infection.

It is characterized by,

- Microangiopathic haemolytic anaemia
- Fever
- Thrombocytopenia
- Fluctuating neurological findings
- Renal dysfunction

Aetiological factors of TTP

- Malignancy
- Pregnancy
- Drugs most strongly associated with TTP include quinine, ciclosporin, ticlopidine and tacrolimus.
- Chemotherapy drugs - vincristine, sunitinib, mitomycin, gemcitabine and docetaxel.

Treatment of TTP

- Plasma exchange
- Steroids
- Supportive care

Coagulation disorders

Acquired haemophilia or development of antibodies to factor viii or factor ix can be seen in HIV. This antibody development is seen in HCV co-infection, pre-existing haemophilia, or in the context of ART and immune reconstitution inflammatory syndrome.

Signs and symptoms

- Muscle and joint bleeding
- Unusual bleeding following a minor injury
- Haematuria

Treatment

- Corticosteroids
- Cyclophosphamide
- Rituximab

Malignancies

HIV infection increases non-Hodgkin lymphoma incidence by 60 - 200-fold. The postulated mechanisms include chronic antigen stimulation, cytokine deregulation and Epstein Barr virus (EBV) and Human Herpes virus 8 (HHV8) co-infection.

EBV has been identified in up to 40% of HIV-related lymphomas.

Malignancies in HIV

- Non-Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Plasmablastic lymphoma
- Burkitt lymphoma/ leukaemia, lymphoma arising in HHV8-associated multicentric Castleman disease
- Hodgkin lymphoma
- Myeloma
- Kaposi sarcoma

Investigations

- FBC
- Blood picture
- Imaging- X ray, Ultrasound scan, CT scan or PET scan
- Bone marrow biopsy
- Flowcytometry
- Fluorescent in situ Hybridization (FISH)

Paraproteinemia and myeloma

Introduction

Monoclonal proteins are detected frequently in HIV infected individuals. Monoclonal protein is an antibody found in unusually large amounts in the blood or urine of people with plasma cell tumours. It's also called M protein or paraproteins.

Transient paraproteinemia's, while others have persistent paraproteins, which may or may not be associated with true plasma cell malignancies.

Investigations

- FBC
- Blood picture
- Serum protein electrophoresis
- ESR
- Serum calcium
- Serum creatinine
- LDH
- Bone marrow biopsy

Bone marrow biopsies in HIV

The diagnostic value of bone marrow aspiration is low as 16%, But it is considerably better when combined with trephine biopsy (30%).

It's a useful tool in the isolation and diagnosis of infections such as Mycobacterium sp. infection and Histoplasma capsulatum infections. Bone marrow biopsy is essential in the diagnosis and staging of lymphomas. It's also useful in paraproteinemia and multiple myeloma etc.

However, it should be the last diagnostic tool due to the pain and invasiveness of the procedure.

Bone marrow changes in HIV

- Trilineage dysplasia
- Necrosis of bone marrow
- Fibrosis
- Haemophagocytosis leading to HLH
- Pure red cell aplasia
- Granulomas in tuberculosis
- Eosinophilia

Preparation

A written request should be sent to the Haematologist and book a date and time with the written consent of the patient.

Special preparations are not required as it's done under local anaesthesia.

Procedure will be explained to the patient and samples will be taken using a bone marrow biopsy needle under sterile conditions. Staff who are involved in the examination should wear protective cloths and equipment's.

Cultures and all other samples should be sent to the laboratory for processing immediately or within two hours.

No special concerns except bleeding in some rare occasions.

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Dermatological Manifestations in HIV Infection

Dr. Janaka Akarawita

Spectrum of dermatological manifestation in HIV infection

Morphology of lesions	Differential diagnosis
Follicular pustules/ papules	Bacterial folliculitis, eosinophilic folliculitis, pityrosporum folliculitis, follicular eczema
Eczematous	Seborrhoeic dermatitis, dermatitis, drug eruptions
Papular (non-follicular)	Molluscum contagiosum, HPV, Scabies, Cryptococcosis, Histoplasmosis, Kaposi's sarcoma, Pruritic papular eruption
Macular/Maculopapular/ Papulo-squemous	Secondary syphilis, Parvo virus B19, HBV, Disseminated candidiasis, widespread scabies and drug reactions. Consider OI with skin manifestations such as cryptococcosis, histoplasmosis, penicilliosis and coccidiomycosis
Vesicular	Herpes zoster, Varicella zoster infection, herpes simplex and drug reactions
Petechial and pustular (non-follicular)	Bacterial causes such as disseminated gonococcal infection, pseudomonal, staphylococcal sepsis, infective endocarditis, listeriosis, Viral causes such as Parvo virus B19, cutaneous vasculitis and drug reactions
Nodular	Prurigo nodules from persistent scratching, basal and squamous cell carcinoma, Kaposi's sarcoma, mycobacteria (Lupus vulgaris, warty TB), bartonella, histoplasmosis, coccidiomycosis
Psoriasiform lesions	Psoriasis, Reiter's syndrome

Non infectious diseases

Condition	Clinical features	Diagnosis	Treatment
Eosinophilic folliculitis	Erythematous, pruritic, follicular papules / pustules (centred around follicles) on face, upper trunk, upper arms, Intense itching; This can lead to excoriation with secondary bacterial infections, prurigonodularis, lichen simplex chronicus and post-inflammatory hyperpigmentation.	Clinical, Biopsy	Treat mild disease with topical steroids and oral antihistamines. Moderate to severe disease: combine above with oral Itraconazole, isotretinoin, or phototherapy
Pruritic papular eruptions (PPE)	Hyperpigmented, hyperkeratotic pruritic papules and nodules which are usually symmetrically distributed on the arms, legs, lower back, buttocks	Clinical, Biopsy	Topical steroids, systemic antihistamines, topical keratolitics. If secondary impetigo occurs topical or systemic antibiotic. Phototherapy is also recommended. The condition improves with immune recovery on ART but scarring from old lesions may be permanent
Seborrhoeic dermatitis	Mildly itchy erythematous/skin-coloured papules/ thin plaques with greasy scaling on the scalp, face, postauricular area, chest, upper back and pubic area Treatment resistant/ Frequently relapsing in HIV patients.	Clinical	*In mild cases:* ketoconazole shampoo for scalp, topical antifungal + 1% hydrocortisone for body and face. *In moderate/severe cases:* combine betamethasone lotion for scalp, betamethasone cream + topical antifungals for the body. *In refractory cases:* oral itraconazole/ fluconazole for 2-4 weeks.

Xerosis	Dry and rough skin, sometimes with fine cracks. Can be associated with diffuse hyperpigmentation.	Clinical	Antihistamines, (sedative antihistamines may be helpful). Emollients including urea, lactic acid or salicylic acid. The condition improves with ART
Psoriasis	This can present for the first time at the progression to AIDS. Well defined salmon pink plaques bearing large, adherent silvery white scales. There are different types- Plaque psoriasis, scalp, guttate, flexural, palmar, plantar and pustular. There can be nail changes such as thimble pitting, onycholysis and sub- ungual hyperkeratosis. In addition, can have psoriatic arthropathy.	Clinical	Topical applications- coal tar, steroids, calcipotriol, salicylic acid, dithranol, In flexural psoriasis topical steroids + antifungals are used When extensive systemic treatment can be given. (PUVA/UVB, retinoids, Methotrexate, Cyclosporin, biological agents)
Drug reaction	HIV infected people have a higher incidence of drug reactions. These may have different morphologies. Generalized erythematous maculo-papular, pruritic rash with or without fever & signs of hepatotoxicity. Severe drug reactions (Stevens-Johnson syndrome & Toxic epidermal necrolysis) result in necrosis with blistering & peeling of skin with mucous membrane involvement, typically in the first days to weeks of commencing the new drug. Drug reaction with eosinophilia and systemic symptoms (DRESS) can occur 3 to 6 weeks after use of the drug. *Use of ART can cause lichenoid eruptions, morbilliform eruptions, genital and oral ulceration	Clinical, Biopsy	Stop the causative drug. Give antihistamines and topical emollients/steroids. Hospitalization is needed for patients with SJS and TEN. Once suspected dermatological referral is needed. Short course of systemic steroids, Immunoglobulins, cyclosporin or other measures with specialized skin care in cases of severe cutaneous adverse reactions. In DRESS systemic steroids need to be used for longer period with close monitoring of liver functions.

Primary HIV infection	Generalized erythematous maculopapular rash usually with fever and systemic symptoms	Clinical suspicion is important Serology for HIV RNA/ DNA or P24 Ag (may be negative in very early primary Infection)	No specific treatment is indicated for the rash or for primary infection. Patient counselling, education and behaviour modification are necessary
Kaposi's Sarcoma	Brown, purple, or red patches/ plaques/ nodules on the skin. The lesions can affect organs, too, including the lungs, liver, and parts of the digestive tract, where they can cause potentially life-threatening symptoms and breathing problems.	Biopsy and relevant investigations to assess internal involvement	Highly active antiretroviral drugs have greatly reduced the incidence of Kaposi sarcoma and can help treat it if it develops. Kaposi Sarcoma generally responds to radiation, surgery, and chemotherapy.

Viral infections

Infection	Clinical features	Diagnosis	Treatment
Varicella zoster or chickenpox	Crops of mildly pruritic vesicles that becomes generalized (centripetal). Malaise, headache, fever, myalgia. Greater incidence of complications as encephalitis, pneumonitis and hepatitis	Clinical, Tzanck smear, Culture, PCR	Acyclovir 800mg 5 times daily for 7 days Valacycovir / Famcyclovir 500mg tds - 5-7 days Prevention with vaccination.

Herpes zoster	Typically, painful blisters in clusters along dermatomes. Can involve the eye. HIV infection should be suspected if lesions are multi dermatomal or episodes are recurrent. Prodromal symptoms include paraesthesia and or pain in the dermatome a few days before the rash appear. Fever, malaise and headache may precede the outbreak of blisters.	Clinical, Tzanck smear	Acyclovir 800mg 5 times daily for 7 days should be started within 72 hours of onset of the blisters. Famciclovir and Valacyclovir are alternatives. For ophthalmic zoster, acyclovir ointment can be applied in the eye every 4 hours Pain is managed with paracetamol 1g 6 hourly; stronger analgesics can be used if necessary. Amitriptyline 25-50mg before bedtime or gabapentin is useful for the control of the neuropathic pain and for post herpetic neuralgia, which may persist for months after the episode.
Herpes simplex	Typical grouped blisters, with pain and tingling, usually genital area or face. Chronic HSV infection presents as progressive, shallow, clean based ulcers on genitalia, perianal, perioral areas. May not self-heal.	Clinical, Tzanck smear, Isolation in cell Culture, Serology	Saline wash-2-4 times a day Keep the area clean and dry Analgesics Acyclovir 400mg 3 times daily – 5 - 7 days Valacyclovir 500mg bd - 7d Famciclovir 250 tds-7d In immunosuppressed, HSV can be chronic and invasive (Esophagitis and encephalitis) Recurrence: suppressive therapy - refer STI management guidelines
Molluscum contagiosum	Raised dome shaped, yellowish/ skin-coloured papules with central umbilication usually on face, neck, genital area, axilla and groins Giant lesions and numerous lesions occur in HIV infection	Clinical (Biopsy of lesions molluscum bodies on Giemsa staining)	Cryotherapy, curettage, TCA, Imiquimod under occlusion, topical cidofovir in recalcitrant disease, often improves with ART

Extensive Viral Warts	Greyish papular lesions with rough surface and tiny dark spots in some. Widespread flat lesions may occur. In genitalia, can become condyloma accuminata (papules, nodules or plaques with appearance of cauliflower, pink or meat, usually soft to the touch and prone to bleeding.)	Clinical	Cryotherapy Cauterization 5% 5-fluorouracil in cream (application 1-3 times per week) 0.5% podophyllotoxin in solution or gel, applied every 12 hours for three consecutive days weekly Imiquimod 5% cream, daily night application three times a week for 16 weeks Podophyllin in 10-25% suspension - wash and remove at 3-4 h. Surgical excision CO2 laser

Fungal infections-superficial

Infection	Clinical features	Diagnosis	Treatment
Dermatophyte infections	Tinea cruris, corporis, onychomycosis Proximal nail white onychomycosis is also a marker of HIV infection Can present as deep dermal morphologies as multiple fluctuant erythematous nodules on extremities	Clinical, Microscopy of scrapings with (KOH) Preparations, Culture	Superficial disease with topical applications Widespread disease with systemic antifungals Griseofulvin, Terbinafine or Itraconazole Onychomycosis can be treated with oral Terbinafine/ Itraconazole in addition to topical therapy.
Malassezia furfur (Pityriasis versicolor)	Minimally pruritic macules with fine scales on rubbing. On the face, chest, back and shoulders Can cause pruritic folliculitis.	Clinical, Microscopy of scrapings with KOH	Topical Antifungals, if fails systemic Fluconazole, itraconazole

Fungal infections-Systemic

Infection	Clinical features	Diagnosis	Treatment
Systemic fungal infections	Can spread to the skin with a wide range of morphologies (Pustules, Crusted papules, Papulonodules, verrucous plaques, Mucocutaneous ulcerations)	Skin Biopsy (histology/ culture), Blood culture	Systemic antifungals

Parasitic infestations and infections

Infection	Clinical features	Diagnosis	Treatment
Scabies	Very itchy rash leading to excoriations in finger webs spreading to proximal areas and trunk. burrows in web spaces, and wrist; genital papules/ nodules, (face Spared)	Clinical Microscopy of skin scrapings, KOH or mineral oil preparation	Permethrin cream 5%: Apply from chin to toes and take a shower 12-14 hours later; repeat after 1 week Or 25% benzyl benzoate solution/ 5-10% Sulphur ointment: Apply below head. The application is left to dry on the skin and then repeated for 3 consecutive days. Itching can be relieved by taking Antihistamines and applying crotomitone cream locally. Clothes and bedding should be washed/boiled and kept separately for 3 days to prevent re-infestation. Household contacts should be treated. After treatment, all the clothes and bed linen should be washed/boiled or iron and dried. Clothes which cannot be washed has to be tied up in bags for 2-3 weeks Household and other close contacts require the same treatment. Oral ivermectin dose of 200 µg / kg, 2-3 doses separated at intervals for 1-2 weeks.
Norwegian scabies	Extensive crusting (psoriasis like lesions) with thick hyperkeratotic scales on elbows, knees, palms and soles		

Leishmaniasis	Skin lesions present as asymptomatic or mildly itchy papules nodules or plaques which may ulcerate later, mainly on the exposed areas. Muco- cutaneous disease affect the nasal, buccal and pharyngeal areas with disfiguring. Bone marrow, liver, spleen, lymph nodes, GI and respiratory involvement occur in visceral disease. Visceral disease has been reported but very rare in Sri Lanka	Demonstration of parasite in smear, tissue, scrapings, skin biopsy, Culture, PCR	Sodium Stiboglucoate Cryotherapy, Miltesofine Sodium Stiboglucoate (Intralesional/ IM/ IV). Cryotherapy, Oral Miltesofine. Thermotherapy. Pentavalent antimonial salts.

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Oral and Oesophageal Manifestations of HIV

Dr. Darshani Wijewickrama

Oral Candidiasis

There are four types.

1. Pseudomembranous
   - The most common manifestation
   - Characterized by painless, creamy white, plaque-like lesions on the buccal surface, hard or soft palate, oropharyngeal mucosa, or tongue surface.
   - Lesions can be easily scraped off with a tongue depressor or other instrument.
2. Erythematous
   - Erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue
3. Angular cheilitis
   - Erythematous flaking lesions at the corners of the mouth
4. Hyperplastic
   - Least common type
   - Thick white plaques over the mucosa

Treatment

1. Oral therapy

Drug of choice -	Fluconazole 100mg/d for 7-14d (except during pregnancy)
Alternative drugs-	Itraconazole oral solution 200mg for 7 to 14 days
	As effective as oral fluconazole but less well tolerated

Posaconazole oral suspension 400mg bd for day 1 followed by 400mg daily/ delayed release tablet

As effective as fluconazole, generally better tolerated than itraconazole solution but both posaconazole and itraconazole have more drug-drug interactions than fluconazole

2. Topical therapy
    - Miconazole 50 mg mucoadhesive buccal tablet once daily
    - Clotrimazole 10 mg troches five times daily
    - Nystatin suspension 4-6 ml four times daily or 1-2 lozenges four to five times daily
    - Low concentration Gentian violet (0.00165%) applied twice daily

Oesophageal Candidiasis

Empirical diagnosis is based on the presence of oral candidiasis (80%) with odynophagia and response to therapy. The definitive diagnosis of oesophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic candida yeast forms in tissue and confirmation by fungal culture and speciation.

Treatment

A diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. Signs and symptoms improve within 48 to 72 hours. Currently there is no evidence that ART needs to be delayed until treatment for candidiasis is completed.

Preferred regimen

- Oral or IV Fluconazole 200mg daily up to 400mg daily for 14-21 days

Alternative regimen

- O. Itraconazole solution 200mg for 14-21days
- O. Isavuconazole - initial loading dose of 200 mg, followed by 50 mg once daily;
  or
  a loading dose of 400 mg followed by 100 mg once daily;
  or
  400 mg once weekly for two weeks

- Voriconazole 200mg orally or IV bd daily

Managing treatment failure in oropharyngeal or oesophageal candidiasis

- Treatment failure is defined as the persistence of signs/ symptoms of oropharyngeal or oesophageal candidiasis after 7 to 14 days of appropriate antifungal therapy.
- Refractory disease occurs nearly in 4%- 5% of patients with HIV infection specially with CD4 counts <50 cells/µL and who have received multiple courses of azole antifungals.
- In oesophageal candidiasis, endoscopy is necessary to confirm treatment failure is due to azole resistance or other causes of esophagitis.

Options of therapy in treatment failure

- Posaconazole immediate-release oral suspension 400 mg twice daily for 28 days is effective in 75% of patients with azole-refractory oropharyngeal or oesophageal candidiasis.
- Oral itraconazole solution is effective in approximately two-thirds of patients with fluconazole-refractory mucosal candidiasis
- IV Amphotericin B 0.3-0.7 mg/kg/day for 14-21 days

Secondary prophylaxis

Only with frequent or severe disease

- Oral Fluconazole 100-200mg/day in oropharyngeal or oesophageal candidiasis
- Oral Posaconazole twice daily for oesophageal candidiasis

(Discontinue when CD4 >200 cells/µl.)

Oral hairy leucoplakia

Caused by Epstein bar virus

- Usually, asymptomatic
- White, hyperkeratotic, corrugations over the lateral border of the tongue
- No co-relation with the stage of the disease

Diagnosis

Clinically - does not rub off as in pseudo-membranous candidiasis. Can be confirmed by histology.

Treatment

No treatment is needed usually as the lesions are asymptomatic. Responds to ART.

Gingivitis

1. **Gingival erythema** - (Characterized by 1-3mm erythematous band along gingival margin) Usually asymptomatic.

   May bleed and cause pain

   Management

   - Dental referral
   - Dental scaling, chlorhexidine rinses

2. **Necrotizing ulcerative gingivitis**

   Characterized by ulceration of interdental papilla, pain, halitosis. Usually occurs in late HIV infection, more severe with ulceration extending to alveolar bone, rapid loss of bone and loss of teeth can occur)

   Management

   - Dental referral
   - Topical anaesthetics
   - 0.2% chlorhexidine mouth rinses bd
   - Metronidazole 400mg three times daily, Co-amoxiclav 375mg or 625 mg tablet three times daily, or Clindamycin (one 300-mg tablet three times daily) should be added to the treatment regimen

Oral ulceration

Aphthous ulceration

Multiple, oval, shallow ulcers on non-keratinized oral mucosa Major aphthous ulcers-associated with severe immune deficiency. Can be very painful.

Treatment

Topical regimens may include the following:

- Topical corticosteroids, including dexamethasone, triamcinolone, fluocinonide, and clobetasol
- Immunomodulatory agents, including retinoids, cyclosporine.
- Antimicrobials, including tetracycline, chlorhexidine gluconate, and dilute hydrogen peroxide
- Anaesthetics such as topical lidocaine or benzocaine

Systemic agents may include the following:

- Systemic steroids such as prednisone and dexamethasone
- Immunomodulatory agents such as colchicine, azathioprine, montelukast and Thalidomide.
- Close follow-up, including nerve conduction studies and electromyography every 6 months, is recommended in patients using thalidomide

To be included a dental referral

Other oral ulcers

Herpes simplex type 1 (uncommonly type 2)

- Usually involves peri-oral skin sometimes with oral mucosa
- Can be Primary, or recurrent

Treatment

- Acyclovir 400mg 8h orally 7-10 days

Herpes zoster

Oral herpes zoster generally causes skin lesions. Following a prodrome of pain, multiple vesicles appear on the facial skin, lips, and oral mucosa. Skin and oral lesions are frequently unilateral and follow the distribution of the maxillary and/or mandibular branches of the trigeminal nerve. The skin lesions form crusts and the oral lesions coalesce to form large ulcers. The ulcers frequently affect the gingiva, so tooth pain may be an early complaint.

Management

- Acyclovir 800mg 5 times/d 7-10 days

Cytomegalovirus infection

- Clinically similar to herpes simplex and herpes zoster ulcers but lacks a prodrome.
- Refer management of CMV infection in this guideline

Primary and secondary syphilis

Can present as a chancre, mucous patch or a snail track ulcer. Diagnosed with VDRL and TPPA/TPHA.

Treatment

- Benzathine penicillin 2.4mu IM stat dose

Kaposi sarcoma

Occur in approximately one-third of patients and are predictors of pulmonary involvement and less favourable treatment outcomes.

KS can appear as a red, blue, or purplish lesion. It may be flat or raised, solitary or multiple. The most common oral site is the hard palate, but lesions may occur on any part of the oral mucosa, including the gingiva, soft palate, and buccal mucosa and in the oropharynx. Occasionally, yellowish mucosa surrounds the KS lesion. Oral KS lesions may enlarge, ulcerate, and become infected. Good oral hygiene is essential to minimize these complications.

Local treatment

Appropriate for large oral KS lesions that interfere with eating and talking. Oral KS can be treated surgically or with localized intralesional chemotherapy.

Surgical removal

Suitable for small, well-circumscribed lesions such as gingival or tongue lesions.

Intralesional chemotherapy

Intralesional vinblastine is useful for treating small lesions, particularly on the palate and gingiva.

Radiation therapy

Indicated for large, multiple lesions.

Lymphoma

Diffuse, undifferentiated non-Hodgkin's lymphoma (NHL) is a frequent HIV-associated malignancy. Most are of B cell origin, and Epstein-Barr virus occurs in cells from several cases. Lymphoma can occur anywhere in the oral cavity and there may be soft tissue involvement with or without involvement of underlying bone. The lesion may present as firm, painless swelling that may be ulcerated. Some oral lesions may appear as shallow ulcerations. Oral NHL may appear as solitary lesions with no evidence of disseminated disease.

Treatment

Oncology referral

Oral warts

HPV lesions in the oral cavity may appear as solitary or multiple nodules. They may be sessile or pedunculated and appear as multiple, smooth-surfaced raised masses resembling focal epithelial

hyperplasia or as multiple, small papilliferous or cauliflower-like projections. The lesions will improve with ART. For treatment of warts, refer STI management guidelines by Sri Lanka College of Venereologists.

References

1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV 2021
2. Medscape – management of aphthous ulcerations -2016
3. HIV insite – Oral manifestations of HIV

HIV and Malignancies

Dr. Priyantha Weerasinghe

Introduction

HIV infection is associated with three AIDS-defining malignancies (Kaposi sarcoma, high grade B-cell non-Hodgkin lymphoma and invasive cervical cancer) as well as an increased risk of many other malignancies such as Hodgkin lymphoma, anal cancer and others. Management of PLHIV with malignancies requires multi-disciplinary team approach with many other specialties.

AIDS related Non-Hodgkin Lymphoma

This is the second most common cancer among PLHIV and can be divided into three types based on area of involvement. Median survival in the post-ART era is beginning to approach that of HIV-negative population and depends critically on histological subtype and stage of disease.

Systemic NHL

Commonly diffuse large B cell lymphoma (DLBCL) accounts for more than 80% cases, and usually with late HIV infection, and to a lesser degree Burkitt's lymphoma (BL) which may develop with sustained CD4 levels.

Primary central nervous system lymphoma (PCNSL)

This is an NHL confined to cranio-spinal axis without systemic involvement and tends to develop at CD4 count less than 50 cells/μL.

Primary effusion lymphomas ("body cavity lymphoma")

This is an unusual, rare form of HIV-associated non- Hodgkin lymphoma. Growth in a liquid phase is observed in serous body cavities such as the pleura, peritoneum and pericardial cavities without identifiable tumour masses or lymphadenopathy.

Clinical features

Systemic NHL commonly present with "B" symptoms which include fever, weight loss greater than 10%, and night sweats and enlarged lymph nodes, Further, it may present with extra-nodal involvement, including bone marrow.

PCNSL typically presents with a focal mass lesion in more than 50% of cases and systemic B symptoms are rare. Patients may present with headache, blurred vision, muscular weakness, sensory deficits, personality changes, depression, apathy, confusion, memory impairment, and cranial neuropathies. Some may be present with sub-acute focal neurological signs.

Diagnosis

The diagnosis of NHL should be based on a tissue biopsy and excisional lymph node biopsy in the case of systemic NHL. Apart from basic investigations serum LDH, CT whole body and bone marrow aspiration with trephine biopsy are recommended to stage the disease.

CT Scan of PCNSL may show typical mass with ring enhancement in as many as half the cases. Stereotactic Biopsy is the only confirmatory test. Most commonly, PCNSL presents as diffuse and multifocal supratentorial brain masses.

The presence of Epstein-Barr virus (EBV) in tumour cells is a universal feature of HIV associated PCNSL.

Careful physical examination, bone marrow biopsy, CT scan of chest and abdomen, testicular ultrasound are recommended in patient suspected with PCNSL as occult systemic lymphoma may be detected in few percentages of patient presenting with brain lymphoma.

In some cases, PCNSL could not be reliably separated from toxoplasma encephalitis by imaging. However, lesions that are single, with a periventricular location or demonstrate sub-ependymal spread are suggestive of PCNSL. Hence, the diagnostic algorithm for the management of cerebral mass lesions in HIV-seropositive patients includes a 2-week trial of anti-toxoplasmosis therapy (sulfadiazine 1 g four times a day, pyrimethamine 75 mg once daily).

Magnetic resonance imaging is the most sensitive radiological procedure, and characteristic features are, densely cellular tumour appears as single (65%) or multiple lesions on nonenhanced T1-weighted images, hyperintense tumour and oedema on T2 or FLAIR images and densely enhancing masses after administration of gadolinium.

Treatment

DLBCL - There is no optimal ‘gold-standard therapy’ as limited published data in the era of ART.

First-line treatment includes chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), or infusional therapies such as EPOCH. (Etoposide, prednisone, vincristine, cyclophosphamide and hydroxydaunorubicin)

Chemotherapy regimens should be combined with ART therapy.

Concomitant administration of rituximab in patients with CD4 cell counts <50 cells/µL require additional monitoring.

Prophylaxis for PCP, MAC, fungal infection is generally recommended while on treatment.

PCNSL - Patient should be started on ART. Anti-retrovirals with minimum drug-drug interactions are recommended as it facilitates administration of standard or intensive chemotherapy. High dose methotrexate-containing chemotherapy regimen is recommended for patients with an adequate performance status. Whole brain radiotherapy is a useful palliative treatment modality for control of symptoms when other agents are considered unacceptable.

The prognosis of HIV-associated primary cerebral lymphoma is poor with median survival rarely reported at greater than 9 months.

Kaposi sarcoma (KS)

Kaposi sarcoma is the most common tumour in PLHIV, and HHV-8 is associated with all forms of KS (i.e., classic, endemic, transplant-related, and AIDS-related). KS is described most frequently among PLHIV with more advanced immunosuppression (CD4+ counts of <200 cells/µL), although they can occur at any CD4+ count.

Clinical presentation

Clinical presentations of KS can be varied. Most common clinical presentation is non tender, hyperpigmented, macular or nodular skin lesions. The lesions can vary in colour (brown, pink, red, violaceous) and in size (millimetres to several centimetres). Oral lesions can be seen in nearly one-third of patients. Lymphatic involvement can occur in some patient and may result in lower extremity oedema. Involvement of internal viscera can be seen in up to 50% of cases and diagnosis may be difficult. Patients with visceral involvement may be completely asymptomatic, or present with pulmonary and gastrointestinal symptoms such as shortness of breath, painless rectal bleeding or melena depending on the system involved or other non-specific pulmonary and gastrointestinal symptoms.

Diagnosis

Diagnosis is by histology. CT scans, bronchoscopy and endoscopy are not generally indicated in the absence of symptoms.

Treatment

The introduction of ART is associated with a considerable decline of the incidence of KS. ART should be started in all patients with KS. Initiation of ART alone could result in regression of the lesions and combination with other options can be considered depending on the site of involvement. ART might result in paradoxical KS.

Treatment of KS depends on the severity of the disease and visceral organ involvement.

Chemotherapy, in combination with ART, should be commenced in case of visceral involvement and it could be a useful adjunctive therapy in individuals with disseminated cutaneous KS. Liposomal doxorubicin is considered as the preferred first-line therapy. Paclitaxel has proven effective with relapse following treatment failure with liposomal doxorubicin.

Localized disease may be treated with Local radiotherapy or intralesional chemotherapy (intralesional vinblastine), topical therapy or surgical excision.

Antiviral agents with activity against HHV-8 are currently not recommended for treatment of KS as available data indicate that antivirals have limited efficacy (ganciclovir, cidofovir and foscarnet)

KS-IRIS can present as either first presentation of KS ("unmasking"), or paradoxical worsening of pre-existing KS following ART initiation. Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Adding steroids are strongly discouraged for management of KS-IRIS, as corticosteroid therapy has been associated with exacerbation of pre-existing KS in persons with HIV.

Hodgkin's Lymphoma (HL)

Hodgkin lymphoma (HL) is one of the commonest tumours with a 10- to 20-fold increased incidence among PLHIV and is EBV driven. HL occurs most commonly at CD4 cell counts below 200 cells/µL. However, there is an ongoing risk of developing HL while on ART despite CD4 count.

Clinical features

HL in HIV patients tends to present more frequently in the advanced stage at diagnosis, with extra-nodal involvement, especially bone marrow infiltration, commonly with B symptoms and poor performance status. This makes bone marrow a mandatory investigation among PLHIV with HL.

Treatment

Patients should receive ART during chemotherapy and recommend avoiding PI/ritonavir-boosted regimens due to the additive vinblastine mediated neurotoxicity and neutropenia.

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) remains as the standard therapy for HL in most parts of the world. Number of chemotherapy cycles and the addition of radiotherapy depend on the stage and the risk factors of the disease.

Prophylaxis for PCP, MAC, fungal infection is generally recommended while on treatment.

Anal Cancer

The incidence of anal cancer in PLHIV is up to 40 times higher compared to general population and generally occurs at a much younger age, and highest risk is among HIV infected MSMs.

Clinical Presentation

Presentation can vary from rectal bleeding and anal pain to features of incontinence depending on the extension. Importantly some can be asymptomatic.

Diagnosis

Diagnosis is by examination under anaesthetic (EUA) of the anal canal and rectum with biopsy. Staging for anal cancer needs CT of the chest, abdomen and pelvis and MRI of the pelvis in order to assess regional lymph nodes and tumour extension.

Treatment

First line treatment is concurrent chemoradiotherapy (CRT)

Recommendation is chemoradiotherapy (CRT) with 5-fluorouracil and mitomycin C and ART should be started with opportunistic infection prophylaxis. Salvage surgery may be considered for patients with loco-regional disease persistence or relapse following CRT.

Prevention

Anal cytology screening of HIV-seropositive MSM and of women might be a useful preventive strategy but needs further evaluation on management of abnormal results. At present no internationally agreed recommendations exist for routine screening for anal cancer. Some specialists recommend anal cytologic screening or high resolution anoscopy for HIV positive patients. An annual digital rectal examination may be useful in detecting masses that could be anal cancer. All such palpable, or visible lesions should be biopsied to determine the degree of histological changes.

Multi-Centric Castlemen's disease (MCD)

This is a rare lymphoproliferative disorder associated with HHV-8, most commonly diagnosed among PLHIV, clinically manifest with systemic symptoms including fever, night sweats and examination findings including lymphadenopathy, anaemia and hepatosplenomegaly. MSD may mimic other inflammatory conditions.

Cervical cancer

Almost all cases of invasive cervical cancer are associated with infection with oncogenic types of human papilloma virus (HPV). Women with HIV infection are more likely to have infection with HPV 16 or 18 than women who are HIV negative. Women with HIV infection also have a higher prevalence and incidence of CIN than HIV-negative women.

Incidence of cervical cancer has not changed significantly even after ART, many cases can be prevented by regular cervical screening tests. All women diagnosed with HIV should have cervical surveillance with annual cytology and abnormal cytology should be managed according to the national guidelines.

The presentation of invasive cervical cancer may be suggested by the finding of an abnormal cervix on internal examination, and if any doubt urgent referral to a Gynaecologist is recommended.

The prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. Patients may present with symptoms and signs pointing to involvement of local or distant organs: dissemination and invasion of carcinoma in pelvis could result in different manifestations and could be the first presentation in late disease. Dissemination of carcinoma of the cervix is by invasion of the connective tissue stroma and to the adjacent parametrial tissue and beyond with involvement of the regional lymph nodes. Involvement of the ureters may result in hydronephrosis and renal failure. Invasion of the sciatic nerve roots may cause back pain, and pelvic pain and lymph node involvement may result in oedema of the lower limbs. Distant metastases occur late, with involvement of the para-aortic lymph nodes, lungs, liver and bone.

Diagnosis is based on histopathological examination of cervical biopsies. Radiological assessment is required for staging process.

Women with HIV having invasive cervical cancer should be managed in the same way as HIV-negative women.

In general, invasive cervical cancer is usually treated by radical hysterectomy with lymph node dissection or by radiation therapy for advanced disease. If cone biopsy or loop excision reveals microinvasive cervical cancer with clear margins, a simple hysterectomy can be done. An alternative for women with microinvasive lesions who want to preserve their fertility may be managed with local surgical procedure such as LEEP or cone biopsy with careful follow-up.

Reference

1. British HIV Association Guidelines for HIV associated malignancies 2014
2. Medscape emedicine.medscape.com/article/1389907-overview (accessed July 2017)
3. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centers for Disease Control and Prevention, The National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2022.http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf..

Cervical Cancer Screening

Dr. Himali Perera

Introduction

Cervical cancer is the fourth commonest cancer globally and third commonest cancer in Sri Lanka, ninety six percent of cervical cancer cases are above the age of 40 years and 50% of patients were diagnosed at the stage of III or IV.

The screening carried out in the clinics is conventional pap tests, However, FDA approved HPV DNA PCR can be used if the test is available.

Screening for cervical cancer is of particular importance for women with human immunodeficiency virus (HIV). The incidence of CIN, as confirmed by colposcopy, is four to five times higher in HIV-positive women and adolescents compared to HIV-negative women with high-risk sexual behaviours. CIN is common in HIV-infected women because:

- Both HIV and HPV are sexually transmitted
- HIV-infected women are more likely to have persistent HPV infection
- Persistent infection with one or more oncogenic HPV subtypes is a major factor in the pathogenesis of premalignant and malignant cervical disease

All women who are diagnosed as HIV should undergo PAP smear at baseline and annually thereafter if baseline PAP smear is normal.

For management of abnormal PAP smears please follow national guidelines for cervical cancer screening.

Table - Management of cervical lesions classified according to Modified Bethesda Classification System

Category Classification	Histological Classification	Recommendation
Negative (NILM)	Normal	Routine annual re-screening
LSIL	CIN I	▪ Repeat the smear in 6 months ▪ If second smear also LSIL refer to gynaecologist for colposcopy ▪ If DNA PCR positive + LSIL ▪ refer for colposcopy
HSIL	CIN II or III	Refer for Colposcopy
ASCUS-low grade	Atypia	Repeat the smear in 6 months
ASCUS-high grade		Refer for Colposcopy. If Colposcopy biopsy is positive treat as HSIL
Glandular cell atypia		Refer for Colposcopy
Invasive carcinoma	Squamous or glandular malignancy	Urgent referral to tertiary cancer centre for gynaecological opinion
Inadequate sample		If two repeat pap smears are inadequate refer to a gynaecologist

HPV DNA-based screening methods

- New screening procedures are based on the detection of high-risk HPV DNA in vaginal or cervical smears.
- Detection of high-risk HPV does not necessarily mean that a precancerous lesion or cancer is present; it indicates simply that there is HPV infection.
- HPV test has a greater sensitivity for CIN 2 and above lesions.

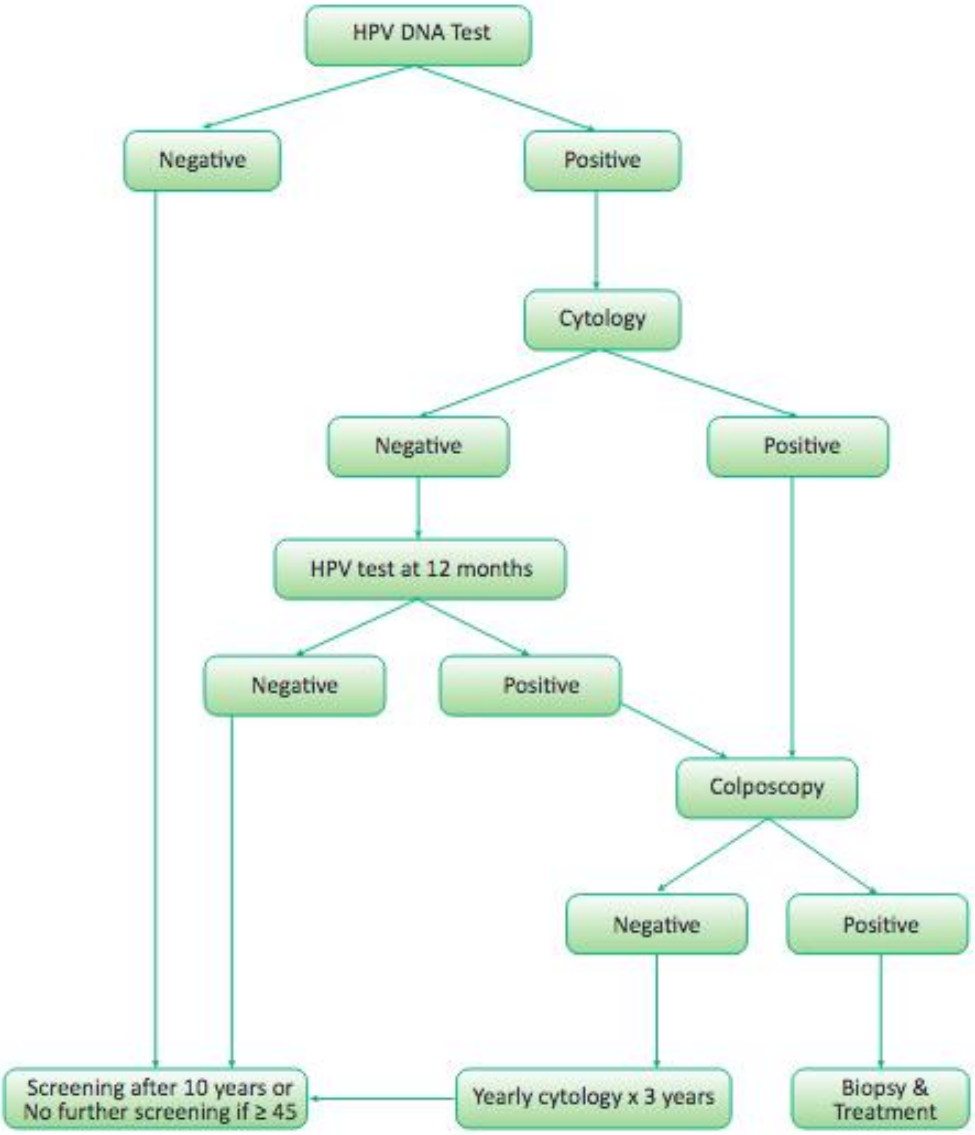

Figure 1.7 Screening for cervical cancer – Algorithm for HPV DNA Test
Source: National Strategic Plan 2019-2023, Well Woman Programme, Family Health Bureau

Treatment

Patients with Pap smear reports of dysplasia or intraepithelial neoplasia require colposcopy and may require, loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) Adjuvant therapy (chemotherapy/radiotherapy) may be required in some patients. Therefore, refer to a gynaecologist.

Management of screening positive women based on colposcopy and histopathology diagnosis.

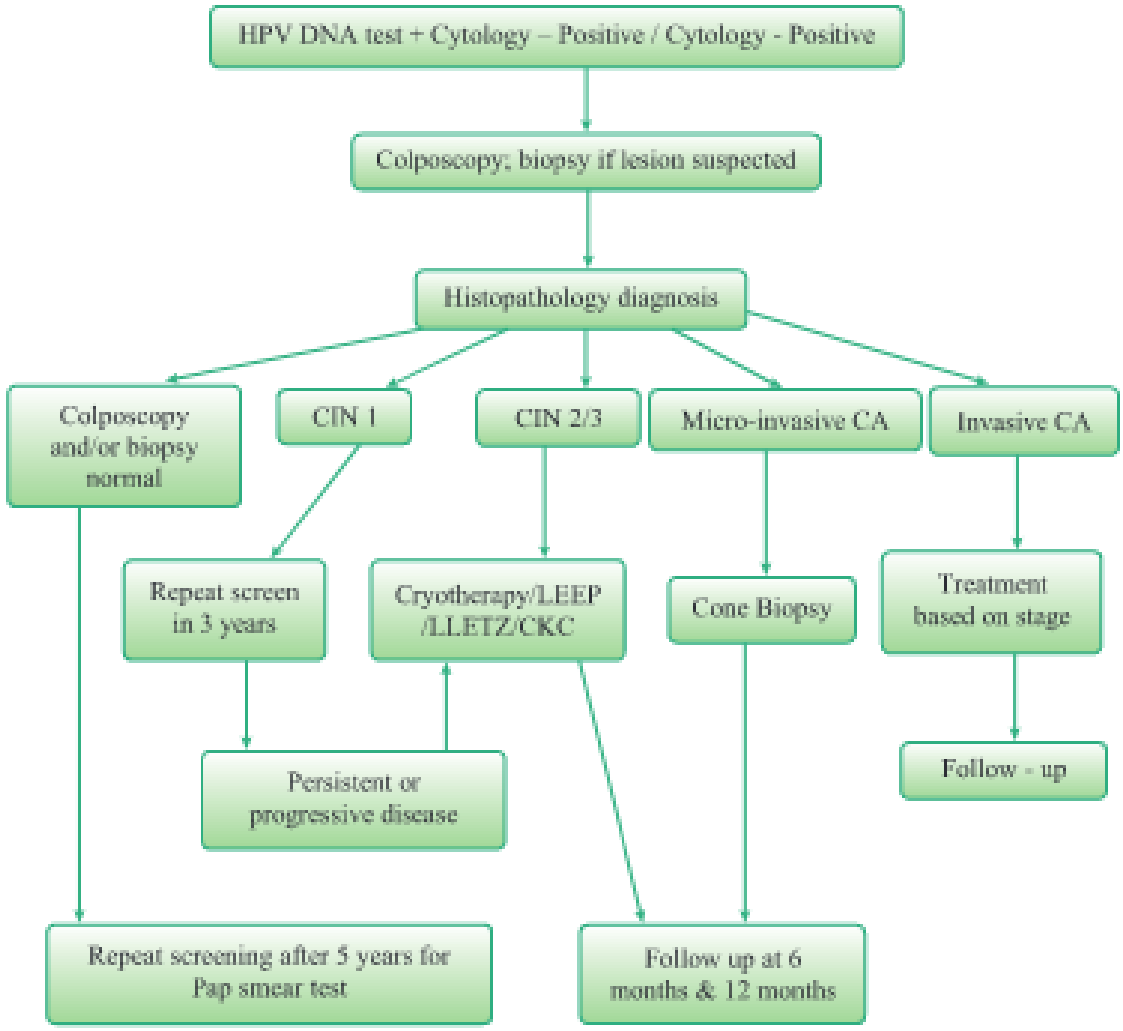

Figure A3.1 Management of screen positive women based on colposcopy and histopathology diagnosis
Source: Training of health staff in colposcopy, LEEP and CKC - Trainees' handbook, World Health Organization,2017

Prevention

- HPV vaccination

References

1. National guidelines for the management of cervical cancer in Sri Lanka, National Cancer Control Programme Ministry of Health, Sri Lanka. 2021

Herpes Group of Viruses

Dr. Gayani Nanayakkara

Introduction

The herpesviruses are a large family of DNA viruses that cause disease in humans. In herpes virus infection, three phases of infection can be observed: primary infection, latency and reactivation. Immunocompromised individuals are at increased risk of more severe and atypical primary infection and reactivation of latent virus.

Herpesviruses are classified into three groups

1. Alpha herpesviruses - Herpes simplex virus 1 and 2 (HHV-1 &2), Varicella zoster virus (HHV- 3). The primary target cell is muco-epithelial with latency developing in nerve cells.
2. Beta herpesviruses - Cytomegalovirus (HHV -5), Human herpes viruses 6 and 7
3. Gamma herpesviruses - Epstein–Barr virus (HHV -4) and Kaposi's sarcoma herpes virus (HHV-8)

This chapter describes infection associated with alpha herpes viruses in detail. Disease related to CMV, Epstein–Barr virus and Kaposi's sarcoma herpes virus associated with neoplastic disease are described in separate chapters.

Herpes simplex virus infection

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Approximately 70% of people with HIV are HSV-2 seropositive, and 95% are seropositive for either HSV-1 or HSV-2.

There is an interaction between HSV and HIV infection. HSV-2 infection increases the risk of HIV acquisition two to three folds and in co-infected patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions, hence increasing the transmission of HIV.

Individuals with lower CD4 counts or higher HIV viral loads with advanced HIV disease are more likely to have severe clinical episodes of primary infection, severe recurrence of disease and to shed virus asymptomatically.

Clinical manifestations

HSV type 1

Causes orolabial herpes (cold sores), the most common clinical manifestation of HSV type 1. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer, and crust. The course of illness in an untreated patient is 5 days to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

HSV type 2

Causes genital herpes, the most common manifestation of HSV-2 infection. Infection occurs from contact with infectious secretions on oral, genital, or anal mucosa or abraded skin. Following primary infection, HSV establishes viral latency in the cells of local sensory ganglia. Increasingly first-episode genital herpes can be caused by HSV-1 also and is clinically indistinguishable from HSV-2 infection although recurrences and viral shedding occur less often with genital HSV-1 infection.

- Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces.
- Vesicles are commonly seen on skin on or around the genitals (e.g., the penile shaft, mons pubis, thighs).
- Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge.
- Local symptoms - sensory prodrome with pain and pruritus. Inguinal lymphadenopathies are common particularly in primary infection.
- HSV infection of the CNS can cause aseptic meningitis, encephalitis, myelitis and radiculopathy. Aseptic meningitis is usually a consequence of primary HSV-2 infection and may be recurrent. t.

Primary genital herpes:

Defined as the first infection with either HSV-1 or HSV-2 in an individual with no pre-existing antibodies to either HSV type.

Non-primary genital herpes:

Defined as the first infection with either HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other HSV type.

Recurrent episode:

Recurrence of clinical symptoms due to reactivation of pre-existingHSV-1 or HSV-2 infection after a period of latency. The frequency of recurrences is greater for HSV-2 than for HSV-1

Genital herpes in people with HIV,

- Primary HSV may not resolve spontaneously but persist with the development of progressive, eruptive and coalescing mucocutaneous anogenital lesions.
- Atypical presentations of genital herpes including chronic erosive and chronic hypertrophic lesions which mimics neoplasia and requires biopsy for diagnosis.
- In severe immune depletion extensive, deep, non-healing ulcerations can occur and those may be associated with acyclovir resistant HSV.
- Non mucosal or systemic HSV infection is more common and may be more severe in immuno- compromised patient, but the clinical presentation may be similar to immune-competent individuals.
- Healing of uncomplicated lesions may be delayed beyond 2–3 weeks and is often associated with systemic symptoms such as fever and myalgia.
- Severe systemic life-threatening complications, such as hepatitis, pneumonia, aseptic meningitis and urinary retention may develop, but rare.
- HSV encephalitis has been reported in HIV seropositive patients with fever, headache, decreased or fluctuating level of consciousness and seizures.
- In recurrent genital herpes, the frequency and severity of recurrent disease is significantly greater in HIV infected persons with low CD4 cell counts.
- HSV is a significant cause of proctitis in men who have sex men with HIV infection and may not be associated with external anal ulcers.
- HSV eye disease includes keratoconjunctivitis and acute retinal necrosis.

Diagnosis

Laboratory diagnosis of all suspected HSV mucosal infections, should be done

1. Detection of HSV in clinical lesions

   Preferred methods for diagnosis of mucocutaneous lesions are, HSV DNA polymerase chain reaction (PCR)and viral cultures. PCR is the most sensitive method of diagnosis. HSV detected in genital lesions should be typed as HSV-1 or HSV-2 which is important in-patient counselling.

2. Detection of Type specific Antibodies (serology)

   Type-specific serologic assays are commercially available and can be used for diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions but there are some important limitations of currently available serologic tests, as false positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.5). In such situations, confirmatory testing with a second serologic test is recommended.

3. Presence of multinucleated giant cells in a scraping from lesions stained with Giemsa stain

A diagnosis of HSV-2 should be accompanied by counselling. (Ref. STD Management Guideline-2019)

Management

Management includes general advice, specific antiviral treatment, management of complications, supportive therapy and follow up

(Ref the section on STD management Guideline 2019 – chapter 3)

Treatment of Herpes in HIV infected patients

For patients with HSV infection, episodic antiviral therapy can be used when symptomatic lesions occur. To prevent recurrences, daily suppressive therapy can be started. Acyclovir, valacyclovir, and famciclovir are effective for suppressive and episodic therapy. Valacyclovir has improved oral bioavailability, and it is the prodrug of acyclovir with decreased dosing frequency, compared to acyclovir.

In persons with HIV and HSV-2 coinfection, following factors should be considered when initiating suppressive therapy for HSV 2 infection.

- Frequency and severity of the HSV recurrence.
- Risk for genital ulcer disease (GUD) when initiating ART

Episodic treatment for individual recurrences of GUD does not influence the natural history of genital HSV-2 infection.

Treatment for orolabial herpes

First episode or severe recurrent orolabial herpes infection should be treated with antiviral therapy such as oral acyclovir, valacyclovir, or famciclovir for 5 days to 10 days. For severe oral mucocutaneous disease, treatment should be initiated with acyclovir intravenously.

Treatment for first episodes of genital HSV

In patients who are not on ART, the primary genital herpes may be severe with prolonged, multifocal, progressive coalescing ano-genital lesions with potentially life-threatening complications or disseminated infection.

First episode of genital HSV should be treated with oral acyclovir, valacyclovir, or famciclovir for 7 days to 10 days. Severe mucocutaneous HSV lesions or systemic complications respond best to initial treatment with intravenous (IV) acyclovir. Patients can be switched to oral antiviral therapy once the lesions begin to regress. Therapy should be continued until the lesions have completely healed.

Rarely HSV necrotizing retinitis can be seen in patients with HIV, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus. Patients with HSV eye complications should be seen urgently by an ophthalmologist and managed jointly.

Special Considerations with Regard to Starting Antiretroviral

The decision on when to start ART in persons co-infected with HSV should not be interfered with the presence of clinical orolabial or genital HSV. In HIV/HSV-2 coinfected persons transient increases in HSV-2–associated genital ulcers have been observed during the first 6 months after initiation of ART. Suppressive anti-HSV therapy can be considered in those patients to minimize the clinical disease. With the immune reconstitution by using ART the frequency and severity of clinical episodes of genital herpes is often reduced. However, the frequency of genital HSV shedding does not reduce by the immune reconstitution.

Monitoring of Response to Therapy and Adverse Events (IRIS)

Laboratory monitoring is not needed for patients receiving episodic or suppressive HSV therapy except who have advanced renal impairment. However, for patients receiving high-dose IV acyclovir, monitoring of renal function, is recommended and dose adjustment might be necessary.

During the first 6 months after initiation of ART, HSV-2 shedding and GUD can increase particularly in those with low CD4 counts. Atypical mucocutaneous lesions and occasionally resistance to therapy have been reported in individuals initiating ART and have been attributed to immune reconstitution inflammatory syndrome (IRIS).

Management of Treatment Failure

If herpes-related lesions do not begin to resolve within 7 days to 10 days after initiation of anti-HSV therapy, treatment failure due to acyclovir resistance should be suspected. If new lesions are forming after 5 days, despite increasing the doses of antiviral drugs then therapy should be reviewed and changed. In persons with suspected acyclovir resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing should be done to confirm drug resistance. Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is not yet available.

The treatment of choice for acyclovir resistant HSV is IV foscarnet. IV cidofovir is a potential alternative. A novel agent, the helicase-primase inhibitor pritelivir, is currently being tested in clinical trials for treatment of acyclovir-resistant herpes in immunocompromised persons (Clinical Trials. gov Identifier: NCT03073967). There is an Expanded Access Program available for oral pritelivir for these populations; for more information see AiCuris Pritelivir Early Access website.

Topical trifluridine, foscarnet, cidofovir, and imiquimod also have been used successfully to treat external lesions, but prolonged application for 21 days to 28 days or longer may be needed.

Recurrent genital herpes in HIV-seropositive patients

These may be prolonged and more severe; however, most episodes are mild and self-limiting and can be managed with supportive and general measures only or with antiviral treatment for 5-10 days. The severity of recurrent episodes is reduced with immune reconstitution with ART, although rates of genital HSV shedding are unchanged.

Efficacy of suppressive therapy in HIV-infected individuals appears to be less than that in HIV-negative individuals with one meta-analysis showing a 66% reduction in recurrences.

Prevention of recurrent disease

- Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences of HSV lesions and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences.

- Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed on an annual basis, particularly if immune reconstitution has occurred.
- Persons starting ART with CD4 counts <250 cells/µL have an increased risk of HSV-2 shedding and GUD in the first 6 months on ART.
- Suppressive acyclovir decreases the risk of GUD nearly 60%, and may be recommended for persons with CD4 counts <250 cells/µL starting ART.
- In **persons who are taking ART**, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation and are not useful for these ends.
- Antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners and should not be used in place of ART to delay HIV progression.
- Although there is no data specific to persons with HIV, in hematopoietic stem cell recipients, the risk of developing acyclovir resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.

Special consideration during pregnancy

Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for caesarean delivery for recurrent HSV in HIV-seronegative women and is likely to have similar efficacy in women with HIV infection. Maternal genital herpes was a risk factor for perinatal HIV transmission in the era preceding availability of ART. Whether HSV facilitates HIV transmission in pregnant women on ART is unknown.

HSV and pregnancy (Ref STD treatment Guideline- 2019)

Recommendations for Treating Herpes Simplex Virus Infections

Note: Compared to acyclovir, valacyclovir has improved bioavailability and requires less frequent dosing.

Treating Orolabial Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day (AIII), or
- Famciclovir 500 mg PO twice a day (AIII), or
- Acyclovir 400 mg PO three times a day (AIII)

Treating Initial Genital Lesions (Duration: 7–10 Days) or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day (AI), or
- Famciclovir 500 mg PO twice a day (AI), or
- Acyclovir 400 mg PO three times a day (AI)

Treating Severe Mucocutaneous HSV Infections (AIII)

- For initial therapy, acyclovir 5 mg/kg IV every 8 hours
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Chronic Suppressive Therapy

Indications:

- For patients with severe recurrences (AI), or
- Patients who want to minimize the frequency of recurrences (AI), including pregnant women, or
- To reduce the risk of genital ulcer disease in patients with CD4 counts <250 cells/μL who are starting ART (BI)

Treatment:

- Valacyclovir 500 mg PO twice a day (AI), or
- Famciclovir 500 mg PO twice a day (AI), or
- Acyclovir 400 mg PO twice a day (AI)
- Evaluate ongoing need for suppressive therapy annually.

For Acyclovir-Resistant Mucocutaneous HSV Infections

Preferred Therapy:

- IV Foscarnet 80–120 mg/kg/day in 2–3 divided doses until clinical response (AI)

Alternative Therapy (Duration: ≥21–28 Days, Based on Clinical Response) (CIII):

- IV cidofovir 5 mg/kg once weekly, or
- Topical trifluridine 1% three times a day, or
- Topical cidofovir 1% gel once daily, or
- Topical imiquimod 5% cream three times a week, or
- Topical foscarnet 1% five times a day

Notes:

- Topical formulations of trifluridine, cidofovir, and foscarnet are not commercially available.
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet.
- An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir resistant HSV infection; for more information see AiCuris Pritelivir Early Access website.

Varicella zoster virus Infection

Varicella zoster virus (VZV) is a human neurotropic alpha herpes DNA virus that is usually transmitted by the respiratory route. It is the causative agent of both varicella (chickenpox) and zoster (shingles).

VZV establishes lifelong latency in the cells of the dorsal root ganglia following primary infection with reactivation resulting in herpes zoster disease. In HIV-seropositive patients' reactivation is more common, and in those with severe immune deficiency, it may result in severe and disseminated clinical disease.

Clinical presentation

Varicella

As result of prior exposure and infection in childhood, primary varicella infection is uncommon in the HIV-seropositive adult population but if it occurs, can result in severe disease with visceral dissemination, particularly pneumonitis.

Herpes zoster (HZ)

HZ may occur at any stage of HIV infection and may be the first clinical evidence of the undiagnosed HIV infection.

Presentations

Cutaneous disease

Herpes zoster usually appears as a localized, erythematous, maculopapular eruption along a single dermatome, but may be multi-dermatomal evolving over 1–2 days to form vesicles, pustules, and crusts. In HIV-seropositive patients, zoster may be particularly bullous, haemorrhagic, necrotic, and painful. Recurrent episodes are increased among HIV sero positive patients, which may be more severe with increasing immune deficiency.

In patients with advanced HIV disease,

- Prolonged lesion formation can be seen,
- Dissemination of virus can occur with widespread cutaneous dissemination making it indistinguishable from primary varicella infection.

In patients who have been started ART, HZ can be developed as IRIS. Majority of HIV-seropositive patients do not develop life-threatening complications, and most have an uncomplicated clinical course.

Eye disease

Herpes zoster ophthalmicus (HZO) involves the ophthalmic division of the trigeminal nerve. In addition to skin lesions, involvement of the conjunctiva, cornea and other eye structures can occur resulting in visual loss, keratitis, anterior uveitis, severe post herpetic neuralgia and necrotizing retinopathy.

CNS disease

Herpes zoster dissemination can occur in HIV seropositive patients causing severe disease in the CNS.

Following multiple clinical presentations have been reported.

- Multi-focal leukoencephalitis
- Vasculitis with cerebral infarction
- Myelitis
- Ventriculitis
- Myeloradiculitis
- Optic neuritis
- Meningitis and focal brainstem lesions

Herpes zoster CNS disease should always be considered in the differential diagnosis of HIV-seropositive patients presenting with neurological disease, even if they are without dermatomal lesions especially with advanced Immune suppression.

Diagnosis

Dermatomal herpes zoster and chickenpox are generally diagnosed empirically depending on the clinical appearance of characteristic lesions.

For confirmation of atypical cutaneous presentation, laboratory studies may be required.

- PCR to detect VZV in skin lesions – rapid and most sensitive.
- DFA and Viral cultures – not recommended generally as less sensitive, viral cultures may be useful in identifying resistance cases.

- CSF examination in suspected CNS disease

  Pleocytosis, mildly raised protein and positive PCR for VZV DNA are supportive of the diagnosis of herpes zoster CNS disease although the absence of a positive PCR for VZV DNA in the CSF does not exclude a diagnosis of zoster CNS disease.

Treatment

Treatment for Varicella in HIV seropositive patients

Treatment of primary varicella in HIV-seropositive patients should begin as early as possible.

- Intravenous acyclovir (5–10 mg/kg every 8 h) for 7–10 days

More prolonged treatment may be required until all lesions have healed. It is possible to switch to oral therapy (800 mg five times per day) when the patient becomes afebrile and there is no evidence of visceral involvement.

Oral acyclovir may be considered if initiated within 24 h of onset of the varicella rash in patients with higher CD4 cell counts and uncomplicated disease.

- Alternative oral agents include famciclovir and valaciclovir.

Treatment of zoster in HIV-seropositive patients

Treatment should begin as soon as possible (preferably within 72 h of onset of the skin rash) and be continued for at least 7 days or until all lesions have dried and crusted.

- For localised dermatomal herpes zoster- oral acyclovir 800 mg five times per day for 7days
- Famciclovir and valaciclovir can be used as alternative agents.

For severe cutaneous disease or disseminated herpes zoster infection with evidence of visceral involvement, including CNS disease,

- Admission to hospital
- Intravenous acyclovir (10 mg/kg every 8 h) for10–14 days

Acyclovir resistance

Persistent disseminated VZV infection that fails to respond to intravenous or oral acyclovir has been described in patients with advanced HIV disease. intravenous foscarnet is the agent of choice for acyclovir resistant VZV infection.

Prophylaxis against varicella

Post exposure prophylaxis following significant exposure of an HIV-seropositive patient to VZV, is indicated and Varicella Zoster Immunoglobulin provides maximum benefits when administered as soon as possible after exposure but may be effective if administered at late as 10 days after exposure.

References

1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centers for Disease Control and Prevention: 2022 update.
2. British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive Individuals 2011

Substance Misuse and HIV

Dr. Thilani Rathnayaka

Introduction

People misuse both pharmacological and non-pharmacological substances in various forms. Substance misuse is a common problem among PLHIV and it's important to identify the problem from the beginning of patient management. Substance misuse is not only a main mode of transmission for HIV among people who inject drugs but also have other harmful effects on health of already HIV infected patients. Following are some of the negative outcomes.

1. Weaken the immune system
2. Damage to the liver
3. Interaction with ART
4. Poor adherence to ART

Some use more than one substance which is called polysubstance use and could be due to multiple reasons. Some consume two types to improve the euphoria associated with two substances (e.g., use of cocaine and heroin mixtures as "speedballs") while others to reduce the adverse effects of a particular substance (e.g., the use of alcohol or benzodiazepines to reduce the anxiety caused by cocaine use).

Most common substances known to cause problems among HIV patients are alcohol, cannabis, cocaine and heroin, benzodiazepines, opioids, methamphetamine and tobacco.

Chem sex

Chem sex means using drugs as part of sex life. This is commonly seen among men who have sex with men, but it is also becoming more common among people having heterosexual sex and people identifying as LGBT+. The risk for acquiring HIV and STIs is high for chem sex users

because it involves house parties where many casual sex happens with unknown partners, unprotected sex and sex for long period with possible trauma. High incidents of HIV, Gonorrhoea and HCV has been reported among MSM groups who involve in chem sex.

There are three specific drugs usually involved:

- Methamphetamine is a stimulant. It's also known as crystal meth, crystal, meth, tina and crank.
- Mephedrone is a stimulant. It's known as meph, drone or meow meow.
- GHB and GBL are sedatives - gamma-hydroxybutyrate and gamma-butyrolactone, also known as G, gina, geebs and liquid ecstasy

Screening question/s on drug and alcohol misuse should be asked and look for signs of substance abuse in the initial consultation and documented. HIV care providers should have non-judgmental attitudes towards substance misuse disorders among PLHIV and a comprehensive care package should include drug and alcohol rehabilitation and other treatment for cessation and replacement.

Substance misuse and risky behaviours

Substance use may increase the likelihood of risk-taking behaviours (e.g., risky sexual behaviours, injecting and needle sharing) which put a person at risk of acquiring HIV and STIs. Under the influence of drugs and alcohol, safe sex behaviours are less likely but more likely to have unprotected sex, exchange of sex for drugs and sex with many casual contacts.

Ongoing substance use delays patient coming for HIV testing, therefore more likely to have late diagnosis and increased mortality.

Substance misuse and ART

Substance misuse can affect ART in two ways.

1. Drug and alcohol use can make it hard to focus and stick to daily ART regimen, therefore low ART adherence which directly have negative effect on undetectable viral load. Taking ART in irregular manner can damage the immune system.
2. Interaction with ART reported for some illicit drugs. Overdoses of club drugs such as ecstasy (MDMA) or GHB with ARTs which suppress cytochrome 450 metabolic pathway has been observed. Similar interactions are reported for benzodiazepines when used with ritonavir or cobicistat boosted ART because some benzodiazepines are cytochrome P (CYP) 3A4 substrates. The blood concentrations of such drugs can increase significantly, leading to enhanced and prolonged sedating effects.

Liver toxicity

Alcohol and substance use can be an over burden to the liver when patient is on ART because most substances including alcohol and ART are metabolized through liver. Prescribing ART for a patient with alcoholic liver disease could be a challenge. Monitoring for liver toxicity with regular measurement of transaminases and imaging is important in HIV infected patient on ART and known to use alcohol and other substances.

Tobacco smoking

Smoking tobacco has many negative effects on HIV patients even if they have well controlled viral load while on ART. Smoking is associated with increased risk for many health conditions, including lung cancer, cervical cancer, cardiovascular disease, and pulmonary disease.

Important facts to consider when managing a HIV infected patient with a history of substance misuse

1. Alcohol and substance misuse is common among HIV infected patients and should be assessed in detail during the first consultation with non-judgmental attitude towards substance misuse. Standard screening question/s about alcohol, smoking and illicit drug use should be asked, and should look for signs of chronic substance abuse during examination. May ask about use of Chem drugs or involvement of chem sex, from MSMs.
2. Record ART adherence in each visit in patients known to misuse alcohol and drugs. Vice versa, detailed assessment of substance misuse is important in patients with adherence issues.
3. Drug and alcohol rehabilitation should be considered as an important part of comprehensive care in HIV and such patients should be referred to psychiatry and other relevant services for treatment of substance dependency.
4. HIV patients are likely to overuse or misuse pharmacological substances as a way out of depression and anxiety. Detailed history on all medication other than ART is important during each clinic visit.
5. Liver toxicity and acute liver failure could be an adverse outcome when starting ART on a patient who got alcoholic liver disease or cirrhosis. Regular monitoring of liver function is important.
6. Closely monitor for interaction between illicit drugs and ART particularly for overdose of substances such an ecstasy, benzodiazepines, ketamine etc. which are substrates for cytochrome P450 when prescribing ritonavir or cobicistat.

7. Taking ART daily could be difficult with substance abuse. Emerging evidence is that long-acting injectable ARTs may have a place for HIV infected patients known to have adherence issues related to substance misuse.

References

1. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health,2022.

HIV and Vaccination

Dr. Darshanie Mallikarachchi

Introduction

Immunization is an important measure to protect people living with HIV/AIDS (PLHIV) against certain vaccine-preventable diseases. PLHIV often have an increased risk of infection and they could experience more severe diseases compared to uninfected persons. However, as HIV infection alters immune function, vaccination of PLHIV may not confer the same degree of protection gained by immunocompetent persons. The antibody response is frequently impaired in PLHIV, as the virus attacks the CD4 T cell, which is important in antibody formation. However, many of these vaccines still afford protection but the immunity may remain lower and decline more rapidly compared to HIV-negative individuals. To overcome this issue, some vaccines could be administered with a modified schedule such as more frequent doses and a higher antigen content which improves the immunogenicity[1]. Certain vaccines enhance HIV virus replication and transiently increase HIV viral load, but this does not preclude vaccination[2].

Ideally for PLHIV, the vaccine should be given before the immune status of the patient is suppressed. Persons with severe immunodeficiency* may have impaired humoral response and may not respond to vaccines or they may require supplemental doses to develop serological evidence of protection. If possible, vaccines should be administered before the CD4 count decreases to <200 cells/µL.

In general, all inactivated vaccines could be administered safely to persons with altered immunocompetence[3]. However, live vaccines may pose a risk to PLHIV. Nevertheless, antiretroviral therapy (ART) induced immune restoration reduces the possibility of having adverse effects and shifts the risk-benefit ratio in favour of vaccination. Therefore, live vaccines such as varicella (VZV), yellow fever and MMR could be considered for individuals whose immunity is not severely compromised or is restored with ART (children <5 years with CD4 T lymphocyte cell

percentage >15% and those aged >5 years with CD4 counts ≥ 200 cells/μL)[3]. Before administering live vaccines, consultation with an immunologist or a vaccinologist is advised.

* HIV-infected persons >5 years of age with CD4 counts <200 cells/μL. Children ≤5 years of age with CD4 percentage <15% are considered to have severe immunosuppression

General principles of immunization in HIV-infected children

Vaccines may be less effective in HIV-infected children. However, these children also have an increased risk of infectious diseases and may have more severe illnesses. Therefore, HIV-infected children should be protected from vaccine-preventable diseases. Hence completing immunization is important, but consideration should be given to the most appropriate time for immunization. It is important to immunize the HIV-infected children prior to the impairment of their immune system or after immune reconstitution occurs with ART.

Table 27-1: Immunization schedule for HIV infected children**

Age	Standard schedule	Child with HIV	Remarks
0-4 weeks	BCG	If vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. Therefore, BCG vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4 >25%)[4]	Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks[4] Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART4 However, if the mother is having a detectable viral load at the time of delivery it is better to postpone BCG till HIV is excluded in the infant. Exclusion of HIV in infants will take 4-6 months

On completion of			
2 months	Pentavalent (DTP-Hep B-Hib) & OPV (1st dose) fIPV (fractional IPV) (1st dose)	Pentavalent (DTP-Hep B-Hib) + inactivated polio vaccine*** - (1st dose) Pneumococcal conjugate vaccine (PCV) -1st dose	OPV and fIPV are not recommended in infants with HIV infection
4 months	Pentavalent (DTP-Hep B-Hib) & OPV (2nd dose) fIPV (fractional IPV) (2nd dose)	Pentavalent (DTP-Hep B-Hib) + inactivated polio vaccine*** - (2nd dose) PCV - 2nd dose	OPV and fIPV are not recommended in infants with HIV infection
6 months	Pentavalent (DTP-Hep B-Hib) & OPV (3rd dose)	Pentavalent (DTP-Hep B-Hib) + inactivated polio vaccine*** - (3rd dose) PCV -3rd dose	OPV is not recommended in infants with HIV infection
9 months	MMR	MMR	MMR- should be postponed in severe immunodeficiency
12 months	Live JE	Hep A 1st dose (2nd dose 6-12 months later)	Live JE is not recommended for HIV-infected children Children with severe immunosuppression may have a suboptimal response to Hep A vaccine
13-15 months		Varicella - 2 doses 3 months apart[3] PCV booster dose	Patients who are severely immunosuppressed should not receive the vaccine
18 months	DTP& OPV (4th dose)	DTP + Inactivated Polio vaccine***	OPV is not recommended for children with HIV infection
3 years	MMR 2nd dose	MMR 2nd dose	Patients who are severely immunosuppressed should not receive the vaccine

5 years	DT+OPV	DT + Inactivated polio*** Pneumococcal polysaccharide vaccine[3]	OPV is not recommended for children with HIV infection
10-15 years	HPV (quadrivalent) 2 doses (females) (0, 6 months)	HPV (quadrivalent) 3 doses (both females and males) (0, 2, 6 months)	
10-15 years	ATd	aTd	

** Adopted from national immunization schedule

*** IPV dose and route - 0.5ml Intramuscular

COVID 19 vaccination for children and young people with HIV infection[5]

Young people aged 16 -17 years

Young people aged 16 to 17 years with HIV infection should receive two doses of the COVID 19 vaccine at an interval of at least eight weeks. Those who have severe immunosuppression with a CD4 count of <200 cells/µl should receive a third primary dose of the COVID 19 vaccine. The third dose should be given ideally at least 8 weeks after the second dose. A booster dose should then be given at least three months later.

Children and young people aged 12-15 years

Children and young people aged 12 to 15 years with HIV infection should receive two doses of Pfizer BioNTech vaccine at an interval of at least eight weeks. Children aged 12 years and over with immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/µL should receive a third primary dose of COVID 19 vaccine at least 8 weeks after the second dose. A booster dose should then be given at least three months later.

Children aged 5-11 years

Children and young people aged 5 to 11 years with HIV should receive two doses of the paediatric dose (10 micrograms) of the Pfizer BioNTech vaccine at an interval of at least eight weeks. The third dose should be given ideally at least 8 weeks after the second dose.

General principles of immunization in HIV infected adults

Live vaccines

- Persons with symptomatic HIV infection or CD4 counts <200 cells/µL should not be given live vaccines. Vaccination may be reconsidered when immune restoration occurs with ART[1].
- HIV infected adults with a CD4 count of 200-300 cells/µL have a moderate immunodeficiency[1]. When administering live vaccines for them it is important to weigh the risk and benefits before vaccination.
- Co-administration of multiple live vaccines to HIV-infected individuals is not recommended due to issues related to safety, immunogenicity, and efficacy. It is recommended to have at least an interval of four weeks between vaccinations[1].

Inactivated vaccines

In persons with CD4 counts <200 cells/µL, the response to inactivated vaccines is reduced[1]. Delaying vaccination till immune restoration could be considered in these patients. However, if the risk of exposure is high, vaccination could be done. If indicated, vaccination could be repeated following immune restoration on ART.

Table 27-2: Vaccination of adults with HIV

Vaccine	Indication	Primary course	Boosting	Remarks
COVID -19 vaccines	All people living with HIV should be prioritized for early vaccination regardless of their CD4 count	All COVID vaccine doses recommended for people without HIV are recommended for PLHIV with a current CD4 count >200 cells/µL. For the people with a CD4 count of <200 cells/µL an additional vaccine dose should be administered as part of the extended primary series and should be given 1–3 months after the second dose	A booster dose can be taken 4 to 6 months after the completion of the primary vaccination series	Completion of the vaccine series is recommended to improve the response

Haemophilus influenzae type b (Hib)	At risk	Single dose	None	Could be given regardless of the CD4 cell count
Hepatitis A	At risk	Two or three doses	Every ten years if at risk	Three doses at 0,1, and 6 months if the CD4 cell count is <350 cells/μL and two doses at 0 and 6 months if the CD4 cell count is >350 cells/μL
Hepatitis B	All non-immune	Four doses**** (At 0, 1, 2, 6 months)	If HBsAb ≥ 10 - <100 IU/L –need one booster dose and retesting If HBsAb ≤ 10 IU/L need three further vaccine doses one month apart and retesting	Could be given at all CD4 cell counts. Screen HBsAb levels according to initial response
Human papillomavirus	Age and gender related	Three doses of quadrivalent vaccine 0, 2 and 6 months apart	None	Could be given regardless of the CD4 cell count
Inactivated polio	To all non-immune	Five doses (At 0,1,2 months, 5 years and 10 years)	Every ten years if at risk	Could be given regardless of the CD4 cell count
Influenza	For all	Single dose	Annually	Could be given regardless of the CD4 cell count
Japanese Encephalitis Inactivated Vero cell derived	At risk	Two doses 1 month apart	One booster dose 1 to 2 years later for those at continued risk with a further boost after 10 years	Could be given regardless of the CD4 cell count

Meningococcal (conjugated)	At risk	Two doses 2 months apart	Every five years if at risk	Could be given regardless of the CD4 cell count
MMR	To all non-immune	Two doses at least 1 month apart	None	Could be given when the CD4 cell count is >200 cells/µL
Pneumococcal (polysaccharide) PPSV23 and pneumococcal (conjugate) - PCV13/10 is preferred	For all	One dose of PCV13/10 followed by one dose of PPSV23 at least 8 weeks later. Second dose of PPSV23 at least 5 years after the previous dose. One final PPSV23 at 65 years or older[6]	None	Could be given regardless of the CD4 cell count
Rabies vaccine	For exposed non-immune	Rabies immunoglobulin + five doses of the vaccine IM at 0, 3, 7, 14 and 30 days	None	Could be given regardless of the CD4 cell count
Tetanus - diphtheria (aTd)	To all non-immune	Five doses at 0, 1, 2 months, 5 years and 10 years	Every ten years	Could be given regardless of the CD4 count
Tetanus toxoid	To all non-immune	Five doses at 0, 1, 2 months, 5 years and 10 years	Every ten years	Could be given regardless of the CD4 count
Typhoid Vi capsular polysaccharide	At risk	Single dose	Every three years if at risk	Could be given regardless of the CD4 count
Varicella	All non-immune	Two doses 3 months apart	None	Could be given when the CD4 cells count is >200 cells/µL

***Yeast based vaccine 40 µg/dose

Recommendation for pre-exposure vaccination in HIV-infected adults[1]

Haemophilus influenzae type b vaccine (Hib)

The vaccine has been shown to produce protective antibodies in HIV-infected individuals, but the response can vary with the CD4 cell count. It is recommended that HIV-positive individuals with the following conditions who are at risk of having an infection and should receive one dose of a Hib-containing vaccine whether or not they were immunized previously and regardless of CD4 count, ART use and viral load[1].

- Asplenia
- Splenic dysfunction
- Complement deficiency

Hepatitis A vaccine

It is recommended to perform pre-vaccination screening for hepatitis A immunity in HIV-positive adults who are at risk of hepatitis A. The following categories could be considered as at risk for hepatitis A infection.

- Close contacts with Hepatitis A
- Men who have sex with men
- Injecting and non-injecting drug users
- Persons who have chronic liver disease or conditions that can lead to chronic liver disease
- Those with occupational exposure to Hepatitis A
- Persons who require frequent blood /blood product transfusions
- Persons with special needs living in residential institutions and their carers
- Persons who travel to countries with high or intermediate endemicity of infection

If serologically negative for hepatitis A, they should be offered a monovalent hepatitis A vaccine. The immune response to the hepatitis A vaccine is generally reduced in HIV-positive individuals compared to HIV-negative individuals. But the response improves with increasing CD4 cell counts and viral load suppression on ART. If the CD4 count is less than 200 cells/μL, or when the patient is having symptomatic HIV infection, it is preferable to differ vaccination until several months after initiation of ART and an improvement of the CD4 count. However, it should not be deferred in patients who are clinically unlikely to achieve increased CD4 cell count.

HAV IgG should be performed at least 1 month after the last dose of vaccination to identify the non-responders6. Non-responders should be revaccinated. The vaccine is safe and well-tolerated in HIV-positive individuals including those who receive three doses over 6 months.

Hepatitis B vaccine

HIV infection affects the response to the Hepatitis B vaccine and the HBsAb seroconversion strongly correlates with CD4 cell count and viral load. Revaccination of non-responders once the CD4 count is >350 cells/μL, suppression of viral load with ART, and the use of higher and more frequent vaccine doses are some of the strategies available to improve the vaccine response among HIV infected individuals. Duration of vaccine-induced protection is unknown in HIV-positive individuals and in general, post-vaccination antibody levels are lower and disappear more quickly than in HIV uninfected individuals.

When using recombinant vaccines, a high dose (40 μg i.e., 2 doses of 20 μg/mL vaccine) vaccination should be offered. Four vaccine doses should be given at 0, 1, 2 and 6 months1. It is recommended to measure the HBsAb levels 4-8 weeks after the last dose of vaccine.

Antibody level >100 IU/L is regarded as ideal, whereas a level <10 IU/L is classified as non-responsive. It is recommended that individuals with HBsAb levels ≥10 but <100 IU/L should receive one booster dose1. If retesting of HBsAb shows that it is between 10 - 100 IU/L regular annual HBsAb testing is needed to guide subsequent boosting requirements.

Individuals who have HBsAb levels <10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is better to delay the revaccination until the viral load is suppressed on ART and the CD4 count has increased > 350 cells/μL.

Screening of HBsAb levels with longer intervals (2-4 yearly) is indicated for individuals with initial HBsAb levels >100 IU/L, CD4 count >350 cells/μL, and viral load suppression on ART. Other individuals should undergo yearly HBsAb screening.

Human papillomavirus vaccine

HIV-infected individuals are at higher risk of HPV acquisition, persistence and at increased risk of HPV-related malignancies. The response to the vaccine is highest in those receiving ART and showing high CD4 cell count and suppressed viral load. Studies are still ongoing to demonstrate the duration of vaccine-induced protection. Even though younger individuals are more likely to benefit from the vaccine, older men and women may continue to have at least a partial benefit from vaccination.

It is recommended that previously unvaccinated HIV-infected men and women aged up to 26 years should be offered HPV vaccination regardless of CD4 count, ART use, and viral load. Previously unvaccinated HIV-positive men having sex with men aged up to 40 years should be offered HPV vaccination regardless of CD4 count, ART use, and viral load[1].

It may be useful to offer HPV vaccination for previously unvaccinated HIV-positive women aged up to 40 years regardless of CD4 count, ART use, and viral load1. In ART naïve patients with

CD4 cell count <200 cells/μL, vaccination may be postponed until the patient is established on ART.

It is recommended that three doses of the quadrivalent vaccine need to be administered at 0, 2 and 6 months to HIV-infected individuals1. If the schedule is interrupted, vaccine series need to be completed rather than restarted. Nonavalent (9vHPV) can replace quadrivalent vaccine for both men and women once available[1].

Inactivated polio vaccine

Inactivated polio vaccine could produce neutralizing antibodies in HIV positive adults and children and in patients with CD4 count <300 cell/μL. It is safe and well tolerated. It is recommended that individuals who are unvaccinated should receive 3 doses of vaccine at monthly intervals followed by 2 reinforcing doses after 5 and 10 years[1]. Fully vaccinated individuals should receive booster doses every 10 years if at risk of exposure. Fractionated intradermal IPV is not recommended.

Inactivated influenza vaccine

HIV infected individuals are at four-to-eight-fold risk of influenza and are 1.5 times more likely to die compared to HIV uninfected individuals7. Vaccination against influenza has been identified as an effective preventive strategy.

Vaccine response is lower compared to HIV negative individuals and correlates with CD4 cell count and viral load. Vaccine may have a low immune response especially when the CD4 count is less than 200 cells/μL. However, as the vaccine is still effective in preventing and reducing complications in patients with HIV infection, it is recommended to offer an annual inactivated influenza vaccine to all HIV infected individuals, especially for HIV infected pregnant women.

Japanese encephalitis vaccine

Live JE vaccine is not recommended in HIV-infected patients. There is insufficient evidence on the safety, immunogenicity, and clinical efficacy of JE vaccination in HIV-positive adults. However, it is recommended that HIV-infected individuals be offered an inactivated Vero cell-derived JE vaccine with two doses given 1 month apart. A booster dose could be given 1-2 years later for those at continued risk with a further booster planned after 10 years[1]. This vaccine is not available in Sri Lanka at present.

Meningococcal vaccine

Patients with HIV infection are at higher risk of invasive meningococcal infection especially those with CD4 cell count <200 cells/µL and viral load >400 copies/mL. However, HIV infection alone is not currently an indication for the meningococcal vaccine. It is recommended that HIV-positive individuals should follow the general indications for meningococcal vaccination and should be offered the vaccination as needed. Individuals who are in close contact with patients with meningococcal disease should be offered antibiotic prophylaxis and appropriate vaccination. Two doses of conjugated vaccine given at an interval of two months are recommended for individuals with HIV infection[1]. The individuals who received MenACWY should be offered a booster dose every five years if there is an ongoing risk[1].

MMR vaccine

The prognosis of rubella and mumps does not show much difference between HIV-infected individuals and the general population. However, measles could be life-threatening in persons with advanced HIV infection. Therefore, it is recommended to offer two doses of MMR vaccine at least 1 month apart to measles seronegative HIV-infected patients with CD4 cell counts > 200 cells/µL. However, based on the likelihood of exposure, vaccination may be postponed in patients with CD4 cell count >200 cells/µL who have not started on ART.

After a significant exposure to measles, HIV-infected individuals should be screened for measles IgG within 3 days regardless of a history of previous vaccination. After a risk assessment about the need and the mode of post-exposure prophylaxis, measles seronegative adults:

- with CD4 count >200 cells/µL preferably on ART with a stable viral load could receive MMR vaccine within 3 days of contact or IM preparation of human immunoglobulin (HNIG) within 6 days of contact[1].
- with CD4 counts <200 cells/µL could be given HNIG within 6 days[1].

However, the protection afforded with HNIG/IVIG will be short-lived.

It is also recommended to give MMR vaccine to rubella seronegative HIV-positive women of childbearing age provided their CD4 count is >200cells/µL and they are not pregnant. Vaccine responses are reduced in HIV-infected individuals, but effective ART can improve the response.

Pneumococcal vaccine

HIV-infected individuals are at higher risk of developing pneumococcal disease and show an increased risk of mortality. Studies conducted on the clinical efficacy of the pneumococcal polysaccharide vaccine (PPSV23) in HIV-positive adults have shown inconsistent findings. However, serological studies conducted on the pneumococcal conjugate (PCV) vaccine have

shown immunogenicity in HIV-infected persons[1]. With both vaccines, the response is low in HIV-positive individuals compared to HIV-negative individuals. However, the PCV vaccine has demonstrated superiority with certain serotypes over PPSV in serological studies[1].

It is recommended to give both the pneumococcal vaccines to HIV-infected individuals irrespective of the CD4 cell count, ART use, and viral load.

One dose of PCV 13/10 should be administered followed by one dose of PPSV23 at least 8 weeks later. The second dose of PPSV23 should be administered at least 5 years after the previous dose. One final dose of PPSV23 should be administered at 65 years or older. This dose should be given at least 5 years after the most recent dose of PPSV23[8].

Rabies vaccine

When giving post exposure prophylaxis, each case should be assessed individually. The following categories should be considered non-immune for rabies and should be given rabies immunoglobulin (RIG) and five doses of cell culture derived vaccine intramuscularly at 0,3,7,14 and 30 days[1]. Intradermal ARV is not recommended for these patients.

- Unvaccinated
- Partially vaccinated (< 3 doses)
- Given a complete course of vaccination (5 doses) but without serological evidence of an adequate antibody response
- Uncertain vaccination history
- CD4 cells<500 cells/μL and not receiving ART

In patients who previously received 5 doses of the vaccine and had adequate antibody response with a CD4 count >500 cells/μL, viral suppression (>6 months) and on ART may be managed with 2 intramuscular doses given at 0 and 3-7 days without RIG[1].

After the full course of vaccination, all patients should undergo serological testing 2 weeks after the last vaccine dose, and non-responders are offered a double dose or more frequent vaccine doses after obtaining specialist advice.

Tetanus-Diphtheria vaccine (aTd)

The HIV-infected adults who require vaccination against tetanus and diphtheria could be given aTd vaccine regardless of CD4 cell count, ART use, and viral load. It is recommended to give three vaccine doses at 1-month intervals, followed by 2 reinforcing doses after 5 and 10 years[1].

Tetanus toxoid

The vaccine has been shown to be immunogenic in HIV-infected individuals even though the response is less compared to HIV non-infected individuals. However, the immunity improves following successful ART.

If the patient is unvaccinated for tetanus, it is recommended to give the adult tetanus vaccine regardless of CD4 count, ART use, and viral load in three vaccine doses given at 1month intervals, followed by two reinforcing doses after 5 and 10 years. Fully vaccinated individuals should receive a booster dose every 10 years.

Following a potential exposure,

- Individuals with uncertain or incomplete vaccination, 3 vaccine doses at monthly intervals should be given regardless of the type of wound and level of risk.
- Individuals who have previously received three vaccine doses with a clean wound and negligible risk should receive one dose if the last dose received was >10 years previously.
- Individuals who received at least three vaccine doses with tetanus prone wounds should receive tetanus immunoglobulin and 1 dose of vaccine if the last dose received was >10 years previously.

Typhoid vaccine

HIV-infected individuals are at higher risk of developing infections with salmonella and are more likely to develop complications. It is recommended to offer Vi capsular polysaccharide vaccine to HIV-infected individuals who are likely to be exposed to poor sanitary conditions. The vaccine should be given at least 2 weeks before the expected exposure. The booster dose could be given every 3 years for those who remain at risk.

Varicella zoster vaccine

HIV-infected individuals who acquire chickenpox are at higher risk of developing severe and fulminant disease. In addition, they are at increased risk of developing VZV reactivation especially with low CD4 count and with a viral load of >400 copies/mL. Even with ART, the disease burden is 3-5 times higher compared to HIV-negative individuals.

The chickenpox vaccine was shown to be safe and immunogenic in children with asymptomatic or mildly symptomatic HIV infection. However, only limited data are available on HIV-positive adults[1].

Two doses of the varicella vaccine 3 months apart are recommended for varicella seronegative patients who have CD4 cell count >200 cells/μL and are on ART[1].

Yellow fever vaccine

It is recommended that HIV-infected individuals aged <60 years and with CD4 cell count >200 cells/μL who are planning to travel to countries in which there is a risk of exposure should be offered the vaccination after counselling on the benefits and risks of vaccination. One vaccine dose at least 2 weeks before travel is recommended[1]. Higher CD4 counts and a suppressed viral load on ART are likely to maximize the safety and efficacy of vaccination.

COVID -19 vaccine

Recent literature suggests that people infected with HIV at any CD4 cell count are at increased risk for severe outcomes and death due to COVID-19 complications compared with people without HIV[9]. Furthermore, many people living with HIV has one or more comorbidities that may put them at increased risk for a more severe COVID-19.

Latest studies have revealed that HIV infection is a significant independent risk factor for severe COVID-19 presentation at hospital admission. These studies have also found that the risk of developing severe or fatal COVID-19 was 30% greater in PLHIV compared to people without HIV infection[9]. Therefore, the individuals infected with HIV should receive all the doses of vaccines recommended for COVID regardless of their treatment status, nadir, current CD4 cell count, and current viral load.

Despite the differences in the efficacy of the vaccines, still, there are not enough data to recommend one vaccine type over another for people with HIV[9]. Therefore, it is recommended to accept the first vaccine that is offered. People with HIV should be informed about the side effects of the vaccine and there is no indication at present for doing antibody testing either pre- or post-vaccination to evaluate the vaccine response. It is recommended that in people with acute illnesses, including COVID-19, vaccination should be deferred until clinical recovery and to around 4 weeks after the first onset of symptoms or first positive RNA test.

PLHIV should be informed that the onset of protection after the first dose requires 2–3 weeks and that completion of the recommended vaccine series is needed to achieve better protection. Even after vaccination, PLHIV should follow the general guidance to reduce the risk of future infection.

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Chapter 28

HIV Transmission, the Law and the Clinical team

Dr. Prageeth Premadasa

Introduction

An underlying principle in the provision of clinical care for people with HIV is the need for a secure and confidential environment in which extremely sensitive matters can be frankly and fully discussed.

Maintaining the rights and dignity of people who have been diagnosed or are at risk of HIV infection creates a conducive environment for successful prevention, treatment and care services.

Confidential information

- (In law, Confidentiality is not absolute.) The public interest in maintaining confidentiality may sometimes be outweighed by another public interest favouring disclosure to third parties. Ultimately the public interest is decided by the courts.
- A healthcare worker must maintain the confidentiality of patient information unless the patient has consented to disclose, disclosure is necessary in the public interest or is required by a court of law.
- A failure to maintain confidentiality may give rise to legal liability.

A healthcare worker should explain to the patient:

- The nature of the disease
- Its medical, social and occupational implications, as appropriate.
- Ways of protecting others from infection

- The **importance of giving the information about the patient's disease or condition to other care givers to facilitate management.**

Make sure the patient understands that practitioners cannot provide adequate clinical management and care without knowledge of their patients' conditions.

Recommendations for Clinical Practice

- Normally, the overall responsibility for the patient rests with the consultant of record, who should in all cases be clearly identified.
- All healthcare professionals working with people with HIV must be familiar with the ways in which data is stored and the confidentiality of medical information is maintained within their service and be able to explain this to patients as required.

The particular roles of health care professionals in this area are:

- To advise PLHIV appropriately about HIV infection and the implications for themselves and others.
- To support patients with HIV appropriately
- To ensure confidentiality of medical information

Advice that should be provided by the clinical team to all patients diagnosed with HIV infection

- All advice given to people with HIV should be fully documented in the clinical record and advice must be up to date.
- Advice given by members of the multidisciplinary team to people living with HIV must be consistent and advice should be provided in both verbal and written forms in appropriate language, ensuring the patient understands. (Taking into account language, cultural sensitivities, educational level, literacy and other factors)
- Clinicians should discuss sexual behaviour regularly with patients and ensure that advice given is appropriate for the current state of affairs.

Clinical documentation

It is important to observe proper practice in documentation of the clinical process and discussions with and about patients as follows:

- Document clearly in the notes the name of the consultant with overall responsibility for a patient's clinical care.
- Maintain full, contemporaneous notes that are dated and signed.
- Document advice given to patients by whatever route – telephone conversations, letters, visits and print and file copies of emails
- Document discussions that are held about the patient with third parties and other professionals keeping copies of all letters in the main clinical file.

The duty to properly advise

Healthcare practitioners must properly advise a patient on ways of protecting their sexual partners from infection. A failure to do this may give rise to legal liability.

Circumstances in which a breach of confidentiality would probably be considered to be in the public interest, and therefore lawful

- When the infected person and the partner both are under the care of the same institution/ care giver, as there is a duty to care for own patients, failure to disclose will be breach of duty.
- If the close contact is not a patient of the health care practitioner, there is no legal duty. However, disclosure would be lawful because of the public interest in protecting the contact from infection. There is power to disclose but no legal obligation to do so. (eg- marital partners)

Disclosure to other healthcare professionals

- A doctor should explain to the patient that other care givers cannot provide adequate clinical management and care without knowledge of their patients' conditions. Where the patient is prepared to consent to third party disclosure, no legal issue should arise.
- If you are in doubt about whether disclosure is appropriate, you should seek advice from an experienced colleague/ legal and ethical committee.
- You should inform patients before disclosing information.
- You must be prepared to justify a decision to disclose information against a patient's wishes.
- These should be documented early.

PLHIV should be advised that that there have been successful prosecutions when transmission of HIV has been proved to have taken place and that the risk of prosecution is likely to be higher if the patient

- has not disclosed the fact of his/her HIV infection to the sexual partner before having intercourse
- has only disclosed his/her HIV infection after having sex
- has given false information to a partner
- has not used condoms.

Support for the process of disclosure to sexual partners after diagnosis.

- Disclosing HIV infection to sexual partners can be very difficult. It is important that individuals are given enough time and appropriate support.
- Disclosure should be seen as a process rather than an event and patients should be given support throughout that process. There should be discussion and agreement about an appropriate time frame for disclosure wherever possible.
- The clinical team should give patients information about, and where necessary direct referral to, additional sources of support, peer groups and other agencies to get help in disclosure.
- In circumstances of non-disclosure, this should be discussed sensitively on an individual basis to establish barriers that exist and provide support in addressing these.
- In complex cases of continued non-disclosure and failure to follow medical advice will require assessment to be made on a case-by-case basis at a higher level (ethical and legal committee).

Disclosing information in court

- Although medical evidence is confidential it is not legally privileged.
- This means that if a health care professional is required to testify in court under oath all information must be disclosed.
- Failure to give such information would be in contempt of court.

Disclosing information to the police

- If an adult patient has become HIV-positive as a result of potentially criminal actions by a third party, it is that patient's choice whether or not to bring it to the attention of the police.

- It is for the patient to decide to take that decision and to initiate it with appropriate legal guidance, NOT the health care provider.
- Health care professionals have no duty to answer questions that the police ask about their patients **unless the request is sanctioned by a court order.**
- Medical records are the property of the individual hospital. Any request for access to health care records by an outside agency, including the police should be directed to the Director/ NSACP or RDHS/PDHS/ hospital director.

Legal and ethical considerations related to PMTCT

- If a pregnant mother defaulting treatment risking the foetus for HIV infection irrespective of all the advises and measures taken by health care professionals, it may lead to legal liability.
- If an HIV infected mother acts against the medical advice pertaining to prevention of HIV in new-born (avoiding prophylaxis ART etc) can be raised as a safeguarding issue and act accordingly.

HIV infected healthcare professionals

All health care workers are under ethical and legal duties to protect the health and safety of their patients. They also have a right to expect that their confidentiality will be respected and protected. Provided appropriate infection control precautions are adhered the majority of procedures in the health care setting pose no risk of transmission of the human immunodeficiency virus (HIV) from an infected health care worker to a patient.

It is recommended that, as far as is practicable, patients should only be notified if they have been at distinct risk of bleed-back from the particular exposure prone procedures (EPP) performed on them by an HIV infected health care worker.

Management of HIV infected HCWs

HIV infected HCWs must

a. be on effective combination antiretroviral therapy (cART), and
b. have a plasma viral load undetectable
c. be subject to plasma viral load monitoring every three months

Exposure Prone Procedures (EPP)

Exposure prone procedures are those invasive procedures where there is a risk that injury to the worker may result in the exposure of the patient's open tissues to the blood of the worker (bleed-back). These include procedures where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (e.g., spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times.

Procedures where the hands and fingertips of the worker are visible and outside the patient's body at all times, and internal examinations or procedures that do not involve possible injury to the worker's gloved hands from sharp instruments and/or tissues, are considered not to be exposure prone provided routine infection control procedures are adhered to at all times. Examples of such procedures include:

- taking blood (venepuncture)
- setting up and maintaining intravenous lines or central lines (provided any skin tunnelling procedure used for the latter is performed in a non-exposure prone manner)
- minor surface suturing
- the incision of external abscesses
- routine vaginal or rectal examinations
- simple endoscopic procedures.

However, the final decision about the type of work that may be undertaken by an HIV infected health care worker should be made on an individual basis. HIV infected health care workers must not rely on their own assessment of the risk they pose to patients.

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Partner Disclosure in HIV

Dr. Darshani Wijewickrama

- Health care professionals should advise and support patients in decision making according to professional guidance and the law.
- Advice must include the routes of HIV transmission and how to prevent transmission, with information about safer sexual practices, the use of condoms and suppression of viral load. Advice must be given in a non-judgmental way.
- In Sri Lanka, it is an offence to knowingly infect another person. (Sri Lankan penal code, marginal notes 262,263)
- When considering breaching confidentiality, it is important to weigh up all potential harms as there may be situations where disclosure of HIV status to protect a sexual partner result in considerable harm to an individual. e.g., domestic violence.
- In situations where a health care professional believes that an HIV positive individual continues to put sexual contacts at risk, their duties and subsequent action depend upon the type of contact.
- No information should be released to the police unless patient's consent has been verified or there is a court order in place.
- It is up to an individual person to make a decision about complaining to the police that they have become infected with HIV, and health care workers should remain impartial during discussions with patients.
- A healthcare worker must maintain the confidentiality of patient information unless the patient has consented to disclosure or disclosure is necessary in the public interest. A failure to maintain confidentiality may give rise to legal liability.
- A healthcare worker must properly advise a patient on ways of protecting their sexual partners from infection. A failure to do this may give rise to legal liability if the patient's sexual partner becomes infected as a result. Liability may also arise where a healthcare worker negligently fails to diagnose the patient as having the infection.
- The health care professional may disclose information to a known sexual contact of a patient with a HIV, if the health care professional has a reason to think that the partner

is at risk of infection and that the patient has not informed the partner and cannot be persuaded to do so. In such circumstances, the patient should be informed before the disclosure, if it is practicable and safe to do so. Health care professional must be prepared to justify a decision to disclose personal information without consent.

- If the sexual contact is also a patient of the healthcare professional, it is considered likely that the courts would recognise a duty by a doctor to disclose the HIV diagnosis to the sexual contact. A failure to disclose might therefore be a breach of the duty owed to the sexual contact, if the contact became HIV-positive as a result.

Reference

1. BHIVA 2013

Partner Notification in HIV

Dr. Darshani Wijewickrama

Introduction

HIV partner notification is a process in which contacts of people with HIV are identified and offered HIV testing.

There are two main contact categories.

- Contacts whose HIV status is known
- Contacts whose HIV status is unknown

Status-known contacts

These include known HIV positive contacts and known HIV negative contacts. (Contacts who have a negative result on a fourth generation HIV test performed 4 weeks or more after the exposure are highly unlikely to have HIV infection).

Status-unknown contacts

These are divided into two groups based on whether or not we know enough details of the partners.

a. Contactable
   - People who have enough information to be identified
   - Eg: working mobile number or email address, and sufficient demographic data like name and address.
   - All information sources should be used with index case agreement in attempting to identify contacts.

a. Uncontactable
   - People for whom the index case (or HCP) has no means of contact.

1. Partner notification process should be initiated by the consultant/doctor.
2. Every newly diagnosed HIV positive patient should be referred to the PHI/PHNS for partner notification interview. Partner notification process should be continued, if the index patient is transferred to another STD clinic also.
3. It is important that the patients are not forced to reveal the names of partners for the purpose of contact tracing. Partner notification should be mentioned in post-test counselling and should be regularly discussed as there may be additional partners identified over time. It is essential the privacy and confidentiality of the index patients ensured at all times. The PHI/PHNS need to support and assist the patient in informing his or her contacts in practical terms. (eg; making a plan on notification) The index patient's identity and sexuality should not be revealed to the contacts being notified unless the index patient requests to do so. Likewise, the outcomes and results of the partner notification should not be revealed to the index patient.
4. The outcomes of the partner notification should be recorded in the patient's notes by the PHI/PHNS. If the patient declines to see the PHI/PHNS, the doctor should raise the issue of partner notification with the patient and record it in the notes.
5. When the patient feels unable to inform his or her contacts, the PHI/PHNS can offer provider referral. This may be carried out by:
   a) The PHI/PHNS offering to inform the contacts in the presence of the index patient, or in the absence of the index patient, when the contact is available in the clinic after being informed to come by the index patient
   b) The PHI/PHNS informing the contacts without divulging the index patient's identity

In provider referral, it is essential to discuss each case on its own merit to decide whether provider referral is appropriate, for example if there may be significant harm to the index patient and/ or their contacts. Any decisions taken should be clearly documented in the index patient's notes.

It is crucial that the contact is given sufficient information to make an informed decision to test or not.

Where there is an ongoing risk of HIV transmission to a contact, and the contact is unaware of the patient's HIV positive status, there may be different legal and ethical considerations. e.g., law on wilful HIV transmission where the risk to an individual may outweigh the confidentiality of the index patient. The consultant has to decide on an appropriate course of action.

[Ref - SSHA Manual for sexual health advisers, UK -2004]

Look back period in HIV

An estimate, based on a risk assessment, of when infection is likely to have occurred should be made and all contacts since, and in the three months prior to this estimate, should be notified. If this is not possible, all previous partners should be contacted and offered HIV testing. The risk assessment should consider sexual history, HIV testing history (including antenatal and blood transfusion service testing history), and history of possible seroconversion illness.

[BASHH statement on partner notification for STIs -2012]

References

1. BASHH and BHIVA statement on HIV partner notification 2015
2. SSHA Manual for sexual health advisers, UK -2004
3. BASHH statement on partner notification for STIs -2012

Defaulter Tracing

Dr. Shyama Somawardana

1. When a patient comes for care, follow- up date is given and follow- up date is entered in the diary.
2. All the files due on the day are selected according to the registration number in the diary.
3. When the patient visits for follow- up the number in the diary is marked in red.
4. Other files which indicate patients who did not attend for the follow- up on the given date are selected as defaulters.
5. The defaulted files are kept for one week to see whether the patients attend for follow-up.
6. At the end of one week period, Consultant/ Senior registrar/Registrar/Medical officer goes through all these files, paying more attention to those on ART.
7. Defaulter tracing action is decided- phone calls, letters, text messages or visit in urgent cases.
8. If they do not attend within 3 months, files are labelled as lost to follow-up (LFU)
9. Before labelling files as LFU every possible effort will be made to trace the patient and to get back them for services.

Defaulter tracing module is included in to the EIMS.

1. The defaulters are traced, and the action plan entered in the defaulter management list by the medical officer daily.
2. PHI/PHNS take the relevant action suggested by the medical officer and enter the response.
3. If it is noticed that the patient hasn't attended according to the action plan within 3 months, files are labelled as LFU.
4. Training module for defaulter tracing is available in the EIMS learning platform.

However, keeping the defaulter calendar system for HIV-positive patients is important as a backup method.

Annexures

Check list for follow up visits of HIV positive patients

Dr. Shyama Somawardana

Please check the following aspects of care at each and every visit. plan investigations at appropriate intervals

01. Ask for symptoms of OIs and Tuberculosis
02. Any other symptom
03. Performance scale
04. Adherence issues
05. ART Side effects
06. Drugs in hand, pill count if possible
07. Any other medication use including herbal and ayurvedic medication
08. Last sexual exposure
09. Condom usage
10. LMP
11. Contraception
12. Partners' sero-status
13. Investigations (CD4, VL, FBC, LFT, RFT, Lipid profile, FBS)
14. Annual STI Screening
15. Annual PAP smear
16. Vaccination status (HPV and HBV vaccine where appropriate)
17. Dietary habits and advice
18. Exercise
19. Advice on smoking and alcohol usage
20. Non -communicable disease and follow-up
21. Other medical conditions
22. Serious non-AIDS conditions (non-AIDS malignancies, cardiovascular disease and end stage kidney failure
23. Safer sex counselling
24. Adherence counselling
25. Condom counselling
26. Any psychosocial issues

Counselling for initial visits and before starting ART

Dr. Udari Gallage

In the initial visit,

01. Explain the natural history of HIV
    a. What HIV/ AIDS is
    b. Natural history and progression (CD4/ Viral load/ OI)
    c. Modes of transmission and myths related
02. Discuss importance of early diagnosis and early initiation of treatment
03. Briefly discuss the availability of ART, other health care facilities and importance of regular follow up.
04. Possibility of Rapid initiation of ART.
05. Advise for healthy lifestyle measures (Diet/Exercise/Stopping alcohol, smoking and other substance abuse)
06. For female patients - pregnancy issues, pap smears, family planning methods
07. Prevention
    a. Sexual exposures - safe sex and condom demonstration
    b. Mother to child transmission
    c. Blood and body fluids - safe handling and first aid, not to donate
    d. Availability of PrEP and PEPSE
08. Prevention of infection – availability of prophylaxis treatment, hygienically prepared food and sanitary hygiene, vector born infection
09. Discuss disclosure related issues and the support available
    a. Need for partner and children screening and PMTCT
    b. Availability of positive support groups

Before starting ART

01. Explain the need to start ART & objectives of treatment (increase immunity, prevent OIs, improve survival & quality of life, reduce AIDS defining and non-AIDS defining complications)
02. Adherence counselling – please refer A Guide to antiretroviral therapy, 2020 by NSACP, section 1.6 (page 14)
03. In addition, discuss-
    a. The importance of informing regarding possible drug interactions, concurrent use of other medications including ayurvedic treatment
    b. The need to attend HIV clinic regularly for monitoring of efficacy and adherence.
    c. Issues of storage and keeping drug stocks for emergency situations. Eg ; travelling for long distances or staying overnight outside home
04. Reassess treatment support, partner screening.
05. If treatment supporter is present, discuss his/ her role in supporting treatment.

Protocol for screening partners of HIV-positive patients

Dr. Gayan Mahakumbura

01. All the HIV positive patients who are registered for HIV services should be advised and counselled on the importance of partner screening. (15% of partners tested by Partner Services were positive for HIV and previously undiagnosed - CDC)
02. HIV partner notification should be a voluntary process where trained healthcare workers, including lay providers, should inquire people diagnosed with HIV about their sexual partners, drug-injecting partners.
03. Partner tracing should be done with the consent of the HIV-positive client and HIV testing should be offered to these partners. Partner notification should be provided using passive or assisted approaches.
04. Mandatory or coercive approaches to partner notification should never be done. People should always be counselled about the benefits and risks so that they can make safe and informed choices.
05. Healthcare providers should always consider possible social harm or other adverse events following voluntary HIV partner notification. Therefore, partner notification services should be offered appropriately and safely. Associated counselling and support services can also be utilized to reduce the potential risk of harm. (Ex - Helplines etc.)
06. When a patient brings the partner, he/ she should be registered at the STD clinic as a new patient and full STI screening and counselling should be done depending on the situation.
07. In instances where the patient is reluctant to bring his/ her partner/s to the STD clinic due to confidentiality issue etc., the doctor should communicate with the public health staff at the STD clinic and take appropriate measures with the consent of the index patient.
08. The necessary screening needs to be carried out by the medical Officer at the STD clinic. Privacy and confidentiality should be maintained at all times.
09. Partner tracing has been included in to the EIMS and the relevant training module is available in the EIMS eLearning platform: https://eims.nsacp.headstartcloud.com/

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Guideline to the TB/ HIV reporting and recording

Dr. Udari Gallage

Diagnosed TB patients

1. Referring TB patients to STD clinic

(Form-TB/ HIV 1, Version: Nov 2021)

All diagnosed TB patients are referred to STD clinic for HIV screening with this form by chest clinic doctors.

Original form is sent to STD clinic with the patient while the copy is compiled at the chest clinic.

2. Back referral of TB patients from STD clinic back to chest clinic

(Form-TB/ HIV 1a, Version: Nov 2021)

The TB patients referred to STD clinic for HIV screening are back referred to chest clinic with this form.

Original form is sent to chest clinic with the patient while the copy is compiled at the STD clinic.

Diagnosed HIV patients

3. Referring HIV patients to the chest clinic

(Form-TB/ HIV 2, Version: Nov 2021)

All diagnosed HIV patients are referred to the chest clinic for TB screening with this form by the STD clinic doctors.

Original form is sent to the chest clinic with the patient while the copy is compiled at the STD clinic.

4. Back referral of HIV patients from chest clinic back to STD clinic

(Form-TB/ HIV 2a, Version: Nov 2021)

The HIV patients referred to the chest clinic for TB screening are back referred to the STD clinic with this form.

Original form is sent to the STD clinic with the patient while the copy is compiled at the chest clinic.

Register of HIV/ TB Co infection

1. TB/ HIV 3 (version: June 2014)

This register has to be maintained at each district chest clinics., All the patients with HIV/ TB Co infection are registered, and the register is kept confidentially.

2. TB/ HIV 4 (version: June 2014)

This register must be maintained in all district STD clinics where all HIV patients screened for TB are registered and the register is kept confidentially.

Version: Sep 2021

TB/HIV 1

(to be sent to STD clinic)

National Programme for Tuberculosis Control and Chest Diseases

Referral form

When a patient is reffered by chest clinic /CRP to STD clinic/ Con virologist, use this format

Name of the chest clinic	
Name of the patient	District TB registration No
Referred by (Name of the Clinic/ Clinician and designation)	
Referred to (Name of the Clinic/ Clinician and designation)	

Reason for referral

For HIV testing		For HIV confirmation		Known HIV infected	
Other					

TB status

	Active TB disease	Chest X ray Insert the picture	HIV screening results
	Bacterial confirmed		
	Clinical diagnosis		
	EPTB		
	Latent TB infection		
	No evidence for TB		

Mantoux: test ……..mm Date	Treatment	New	Previously treated	Preventive Treatment	None
Culture: Date	Date treatment started:				
(Positive/ Negative/ Not done/ Pending results)	Drug regimen and prescribed drugs				
DST results:	Intensive Phase		Continuation Phase		
	R				
	H				
	Z				
	E				

Remarks :……
……
……

Date signature

(for the chest clinic records)

Version: Sep 2021

TB/HIV 1a

(to be sent to Chest clinic)

National STD/AIDS Control Programme

Back referral form

When a patient referred through TB/HIV 1 is back referred to chest clinic, use this format

Clinic registration No:

Name of the patient	District TB registration No
Referred back by (Name of the Clinic/ Clinician and designation)	
Referred back to (Name of the Clinic/ Clinician and designation)	

HIV screening test		Positive		Negative		Not done
Confirmatory test		Positive		Negative		Not done

CD4 count and date of the test . ……..……...……

……..……..

Co-Trimoxazole started	Yes		No	

ARV treatments prescribed	Other medications currently on (except anti TB drugs

Remarks :……
……
……

Date signature

(for the STD clinic records)

Version: Sep 2021

TB/HIV 2

(to be sent to Chest clinic)

National STD/AIDS Control Programme

Referral form back to Chest clinic

When a patient is referred by STD clinic/ Con Venereologist to chest clinic, use this format

Clinic registration No:

Name of the patient	Registration No
Referred by (Name of the Clinic/ Clinician and designation)	
Referred to (Name of the Clinic/ Clinician and designation)	

Reason for referral

Reason for referral		Previous screening for TB	
	For TB screening		Previously screened for TB in(month & year)
	Previous history of TB		Previously not treated for TB
	Other		

CD4 count and date of the test. ……..……

……..…..

Co-Trimoxazole started	Yes	…… Date	No	

Current medical history	ARV treatment prescribed ……..
	Other medications currently on (except anti TB drugs ……

Remarks :……
……
……

Date signature

(for the STD clinic records)

Version: Sep 2021

TB/HIV 2a

(to be sent to STD clinic)

National Programme for Tuberculosis Control and Chest Diseases

Back-Referral form

When a patient referred through TB/HIV 2 is back referred to STD clinic,use this format

District TB registration No:

Name of the patient	HIV referral registration No
Referred back by (Name of the Clinic/ Clinician and designation)	
Referred back to (Name of the Clinic/ Clinician and designation)	

Past history of TB (site)
Treatment outcome:

Current TB status

	Active TB disease		Chest X ray Insert the picture
		Bacterial confirmed	
		Clinical diagnosis	
		EPTB	
	Latent TB status		
	No evidence of TB		

Mantoux: test ……..mm Date	Treatment	New	Previously treated	Preventive Treatment	None
Culture: Date	Date treatment started:				
(Positive/ Negative/ Not done/ Pending results)	Drug regimen and prescribed drugs				
DST results:	Intensive Phase		Continuation Phase		
	R				
	H				
	Z				
	E				

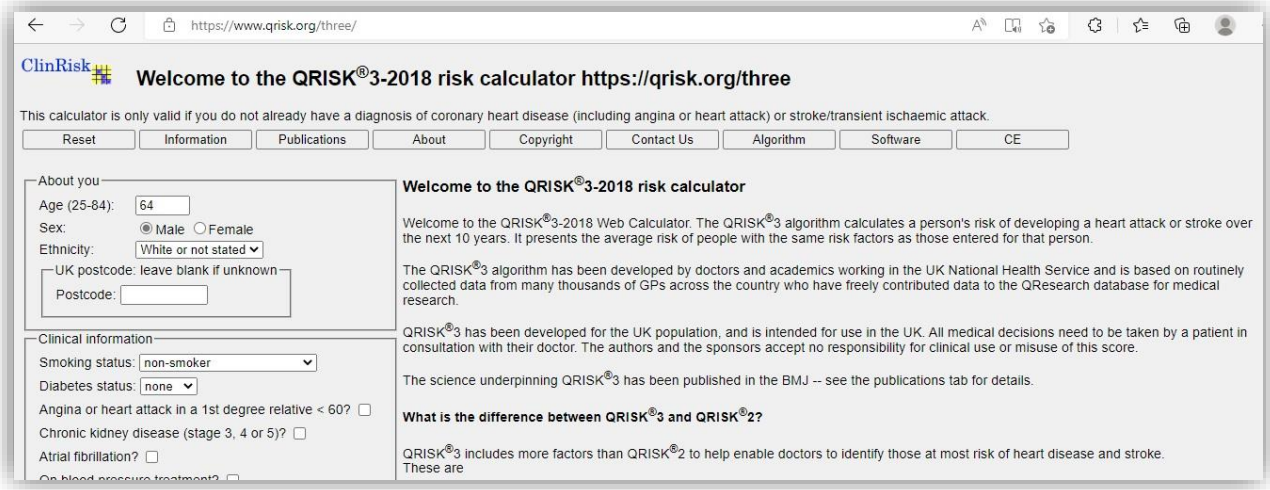
Remarks :……
……
…….

Date signature

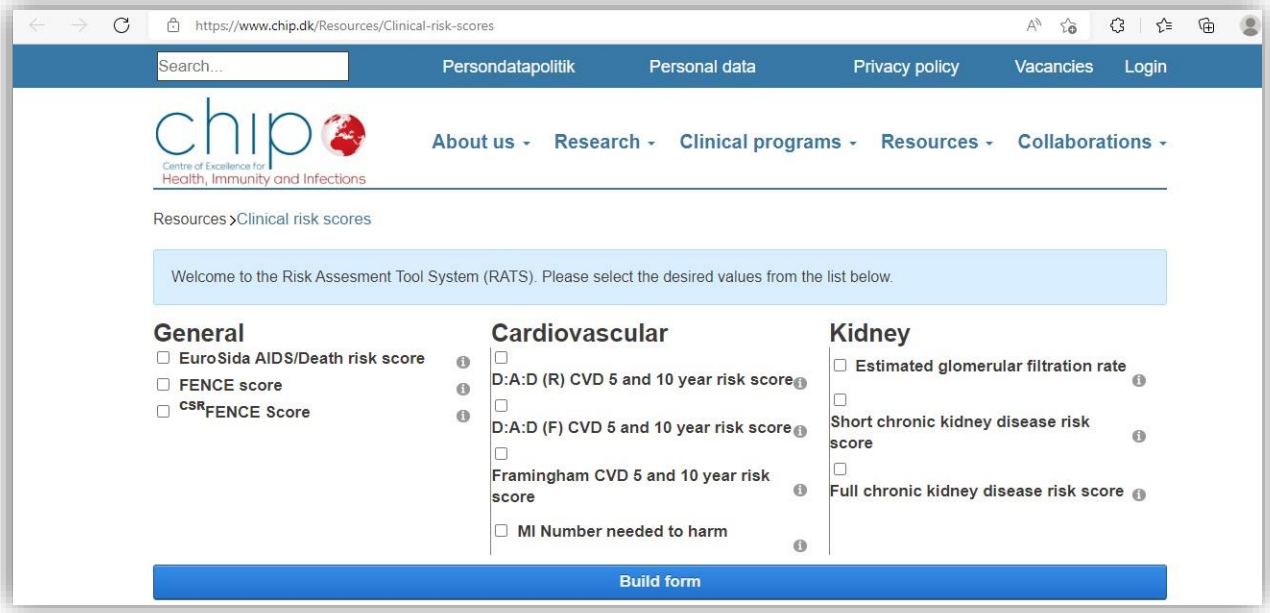
(for the chest clinic records)

Calculator web pages for CVD risk assessment

- https://www.qrisk.org/three/



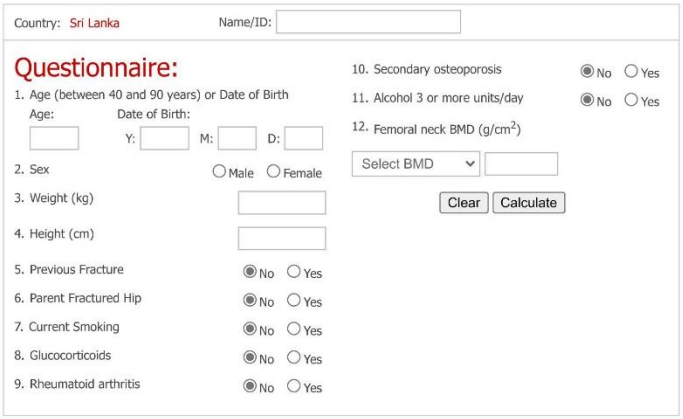
- https://www.chip.dk/Resources/Clinical-risk-scores



FRAX® Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Risk factors

For the clinical risk factors a yes or no response is asked for. If the field is left blank, then a "no" response is assumed. See also notes on risk factors.

The risk factors used are the following:

Age	The model accepts ages between 40 and 90 years. If ages below or above are entered, the programme will compute probabilities at 40 and 90 year, respectively.
Sex	Male or female. Enter as appropriate.
Weight	This should be entered in kg.
Height	This should be entered in cm.
Previous fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors).
Parent fractured hip	This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no.
Current smoking	Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors).
Glucocorticoids	Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).
Rheumatoid arthritis	Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).
Secondary osteoporosis	Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease
Alcohol 3 or more units/day	Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors).
Bone mineral density (BMD)	(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm2). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center).

Drug interactions with Rifampicin

Dr. Kanchana Wirasinghe

- Currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs and these interactions should be taken into consideration before initiating therapy (see Table X).
- Recommend undertaking a complete medicines reconciliation prior to starting treatment for either TB or HIV
- Rifampicin is a known potent inducer of cytochrome P450 enzymes and the drug transporter P-gp, and induction of these proteins in the gut and liver reduces bioavailability and increases systemic clearance of a broad range of co-medications. Rifampicin also increases clearance of drugs through induction of glucuronidation. HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs; efavirenz, nevirapine and etravirine) are also P450 inducers whereas PIs and cobicistat are potent inhibitors of CYP3A; ritonavir is also an inducer of glucuronidation.

Table A-1: Pharmacokinetic drug-drug interactions between Anti-Retroviral Drugs and Rifampicin/Rifabutin

Drug	Interacting with	Mechanism/effects	Recommendations
Rifampicin	Abacavir	Potential mild decrease in abacavir exposure due to increased glucuronidation with rifampicin	Use standard doses of both drugs
	Atazanavir/r	Substantial decrease in Atazanavir AUC even with double dosing or boosting with ritonavir	Avoid this combination
	Darunavir	Substantial decrease in darunavir concentration	Avoid this combination
	Dolutegravir	Dolutegravir AUC decreased 54%	Increase Dolutegravir dose to 50mg bd orally
	Efavirenz	Efavirenz decreased 22%	No dose adjustment needed. Reduced doses of efavirenz 400 mg od is not recommended

	Emtricitabine	No clinically significant interaction (tenofovir exposure reduced by 12%)	Use standard doses
	Etravirine	Significant reduction in etravirine concentration	Avoid this combination
	Indinavir	Indinavir AUC decreased 89%	Avoid this combination
	Boosted Lopinavir	Lopinavir AUC decreased 75%	Avoid this combination Dramatic effects of rifampin on AUC may be overcome by doubling the dose of LPV/r, (e.g., 800/200 mg bd) or 'super boosting' with ritonavir (e.g., 400/400 mg bd) has been used in adults, and additional ritonavir boosting in children. Monitor for liver and gastrointestinal toxicity. Lopinavir/r od is contraindicated with rifampicin
	Maraviroc	Maraviroc AUC decreased 63%	Avoid this combination
	Nevirapine	Nevirapine AUC decreased >50%	Used with caution. Monitor ART response
	Raltegravir	Raltegravir AUC decreased 40%	Increase Raltegravir dose to 800mg bd orally
	Tenofovir alafenamide	Rifampicin may reduce tenofovir alafenamide bioavailability through transporter (P-gp)	Induction is not recommended
	Tenofovir disoproxil fumarate	No clinically significant interaction (tenofovir exposure reduced by 12%)	Use standard doses
	Zidovudine	Zidovudine AUC decreased 47%	Monitor zidovudine efficacy, dose modification not warranted
Rifabutin	Abacavir	No interaction	Use standard doses
	Atazanavir Darunavir	Rifabutin AUC increased to 210% Inhibit metabolism of Rifabutin	Decrease rifabutin dose to150mg three times a week Reduce rifabutin dose to 150 mg od, or 300 mg x3/week; monitor for rifabutin toxicity
	Dolutegravir	No clinically significant effect	Use standard doses of both drugs
	Efavirenz	Rifabutin AUC decreased 38%	Increase rifabutin dose to 450 mg od to compensate for reduced exposure due to efavirenz; monitor for rifabutin toxicity

Etravirine	Rifabutin AUC decreased by 17%	Use standard dose of rifabutin 300mg daily
Boosted Lopinavir	Rifabutin AUC increased 303%	Reduce rifabutin dose to 150 mg od. Dose of rifabutin 300 mg x3/week with lopinavir/r has been associated with subtherapeutic rifabutin exposure and development of rifamycin mono-resistance; monitor for rifabutin toxicity
Tenofovir alafenamide	Expected to reduce tenofovir alafenamide exposure through P-gp induction, it has not been tested in patients to confirm PK and virologic efficacy	Expected to reduce tenofovir alafenamide exposure through P-gp induction; the combination is not recommended
Tenofovir disoproxil fumarate	No clinically significant interaction (not studied)	Use standard doses
Raltegravir	Rifabutin AUC increased 430%	Decrease Rifabutin dose to 150mg three times a week
Zidovudine	No interaction	Use standard doses

Colour coding:
- these drugs should not be co-administered
- potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
- no clinically significant interaction expected

Recommend using prescribing resources (e.g., the Liverpool University HIV drug interactions website: www.hiv-druginteractions.org; or the Toronto General Hospital website: https://hivclinic.ca/druginformation/drug-interaction-tables/) to screen for drug–drug interactions (DDIs) in all individuals with TB/HIV co-infection.

Reference

1. British HIV Association guidelines for the treatment of TB/HIV co-infection. HIV Medicine. British HIV Association Guidelines. United Kingdom. 2022 interim update; 11: 46 - 50
2. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. July 2021; V12, V24

Renal adverse effects of drugs commonly used in HIV infections

Dr. Geethani Samaraweera

Renal adverse effects of drugs commonly use in HIV infection[1]

Drug	Disorder/ Pathology	Finding	Comments
Acyclovir	Crystalluria	May precipitate ARF	Treat with hydration; avoid rapid intravenous bolus; adjust dosage for renal function.
Amphotericin B	Increased tubular permeability and/or renal vasoconstriction	↑Cr, ↓serum K^+ and Mg^{++}, ↓urine bicarbonate; distal renal tubular acidosis; non-anion-gap metabolic acidosis	More severe renal failure likely with concurrent nephrotoxins (aminoglycosides, foscarnet), diuretic use, hypovolemia, chronic renal failure. Hydration with normal saline is somewhat protective. Switch to lipid formulation of amphotericin B for rise in Cr of >2.5 mg/dL while on conventional amphotericin B; continue to monitor electrolytes.
Cidofovir	Proximal tubular injury	(See TDF, above)	Incidence reduced with hydration (normalsaline) and probenecid, which blocks absorption of drug by tubular epithelial cells. Check Cr and urine protein within 48 hours before each dose and reduce dosage for decreased CrCl or eGF. Discontinue drug for either Cr ≥0.5 mg/dL above baseline or proteinuria ≥3+ on dipstick analysis.
Foscarnet	ATN Crystal deposition	↑Cr, ↓serum Ca^{++}, Mg^{++}, phosphorus; *some times* ↑ serum $Ca^{++}$and phosphorus	Cr generally increases after 1-2 weeks of foscarnet therapy. Renal toxicity is reduced with infusion of 0.5-1 liter of normal saline with or before foscarnet.

Dosing of Antimicrobial Agents for HIV-Infected Patients with Chronic Kidney Disease

Dr. Geethani Samaraweera

Drug	Dosing category	Dosage
Acyclovir	Usual dosage (Higher dose for zoster)	200–800 mg po 3–5 times per day 5–10 mg/kg of ideal body weight IV q8h
	Dosage for patients with CKD or ESRD	
	CrCl 25–50 mL/min	200–800 mg po 3–5 times per day; 5–10 mg/kg of ideal body weight IV q12h
	CrCl 10–24 mL/min	200–800 mg po q8h; 5–10 mg/kg of ideal body weight IV q24h
	CrCl <10mL/min	200–800 mg q12h; 2.5–5 mg/kg of ideal body weight IV q24h
	CrCl<10mL/min receiving HD	2.5–5 mg/kg of ideal body weight IV q24h; on days of HD, dose post-HD
Ciprofloxacin	Usual dosage	500–750 mg po q12h OR 400 IV q8h-12h
	Dosage for patients with CKD or ESRD	
	CrCl 30–50 mL/min	500–750 mg q12h OR 400 IV q12h
	CrCl<30mL/ min	250–500 mg q18–24h OR 400 IV q24h
	Receiving HD	250–500 mg q24h OR 200–400 IV q24h (days of HD dose post-HD)
Clarithromycin	Usual dosage	500 mg po q12h
	Dosage for patients with CKD or ESRD	
	CrCl<30 mL/min With PI co-administration	Reduce dose by one-half
	CrCl 30–60 mL/min	dose reduction by 50%
	CrCl<30 mL/min	75% reduction with CrCl< 30mL/min
Ethambutol	Usual dosage	15–25 mg/kg of body weight po q24h
	Dosage for patients with CKD or ESRD	
	CrCl 10–50 mL/min	15–25 mg/kg of body weight po q24–36h
	CrCl<10 mL/min	15–25 mg/kg of body weight po q48h

Fluconazole	Usual dosage	200–1200 mg po q24h
	Dosage for patients with CKD or ESRD	
	CrCl ≤50 mL/min	Half-dose
	Receiving HD	Full dose after dialysis
Ganciclovir	Usual dosage	5 mg/kg q12h (I); 5 mg/kg q24h (M)
	Dosage for patients with CKD or ESRD	
	50–69 mL/min	2.5 mg/kg q12h (I); 2.5 mg/kg q24h (M)
	25–49 mL/min	2.5 mg/kg q24h (I); 1.25 mg/kg q24h (M
	10–24 mL/min	1.25 mg/kg q24h (I); 0.625 mg/kg q24h (M)
	<10 mL/min; HD	1.25 mg/kg TIW (I) post-HD; 0.625 mg/kg TIW (M) post-HD
Isoniazid	Usual dosage	300 mg po q24h
	Dosage for patients with CKD or ESRD	
		300 mg q24h (on days of HD, dose post-HD)
Levofloxacin	Usual dosage	250–750 mg po q24h
	Dosage for patients with CKD or ESRD	
	CrCl 20–49 mL/min	500 mg loading dose, then 250 mg q24h
	CrCl 10–19 mL/min	500 mg loading dose, then 250 mg q48h
	Receiving HD or PD	750–500 mg loading dose, then 250–500 mg q48h (dose post-HD on days of dialysis)
Pyrazinamide	Usual dosage	20–25 mg/kg of body weight q24h
	Dosage for patients with CKD or ESRD	
	CrCl < 10 mL/min	15–20 mg/kg q24h
	Receiving HD	20 mg/kg q24h (dose post-HD on days of dialysis)
Rifampin	Usual dosage	600 mg po q24h
	Dosage for patients with CKD or ESRD	
	CrCl 10–50 mL/min	100% of full dose
	CrCl < 10 mL/min	50%–100% of full dose
	Receiving HD	50%–100% of full dose; no supplement
	Receiving PD	50%–100% of full dose; extra 50%–100% of full dose after receipt of peritoneal dialysis. Therapeutic drug monitoring recommended
Sulfadiazine	Usual dosage	1–1.5 g po q6h (1.5 g for >60 kg)
	10–50 mL/min	1–1.5 g po q12h
	< 10 mL/min; HD	1–1.5 g po q24h

Trimethoprim-sulfamethoxazole	**Dosage for prophylaxis of *Pneumocystis jirovecii* pneumonia**	1 double-strength dose po q24h. 1 double-strength dose po 3 times per week. 1 single-strength dose po q24h.
	Dosage for patients with CKD or ESRD	
	CrCl 15–30 mL/min	Half-dose
	CrCl < 15 mL/min	Half-dose or use alternative agent
	Dosage for treatment of *Pneumocystis jirovecii* pneumonia	
	Usual dosage	5 mg/kg (as trimethoprim component) IV or po q6–8h
	Dosage for patients with CKD or ESRD	
	CrCl 10–30 mL/min	5 mg per kg (as trimethoprim component) q12h
	CrCl < 10 mL/min	5 mg per kg (as trimethoprim component) q24h
Valganciclovir	Usual dosage	900 mg po q12h (I); 900 mg po q24h (M)
	Dosage for patients with CKD or ESRD	
	CrCl 40–59 mL/min	450 mg q12h (I); 450 mg qd (M)
	CrCl 25–39 mL/min	450 mg qd (I); 450 mg qod (M
	CrCl 10–24 mL/min	450 mg qod I); 450 mg twice per wk (M)
	CrCl < 10 mL/min	Not recommended by US manufacturer. Use IV ganciclovir or consider 200 mg suspension tiw (I)/100 mg suspension tiw (M)
	Receiving hemodialysis	Consider 200 mg oral powder formulation tiw (I); 100 mg tiw (M

Abbreviations:
CKD, chronic kidney disease; CMV, Cytomegalovirus; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, haemodialysis; HIV, human immunodeficiency virus; HSV, herpes simplex virus; I, induction; IV, intravenous; M, maintenance; PD, peritoneal dialysis; PI, protease inhibitor; po, by mouth; q, every; qd, every day; qh, every hour; qod, every other day; tiw, three times a week; VZV, varicella zoster virus.

Disclosure of serostatus of children

Dr. C. Hathurusinghe

Disclosure of the HIV status is clearly an emotional and pivotal point in a child's life. There are many health benefits of disclosure such as increased access to care services, informed treatments adherence and linking to social support network. In Sri Lankan settings young people are mostly considered to be dependents under the full responsibility of caregivers. The major challenges for caregivers to disclosure are the fear of stigma and negative consequences for children's emotional and social well-being. HIV disclosure should be a well-organized process, not a one-time event. It will sensitize the infected child, family and the caregiver to anticipate both positive and negative outcomes of disclosure, including financial and emotional support, stigma, discrimination and rejection. Reducing stigma will facilitate the disclosure, improving the uptake of treatment, adherence and coping with symptoms and side effects of drugs (ARV). Process of disclosure is complex and depend on the cultural and social issues, age of child, cognitive levels and emotional maturity and social stigma.

The person who discloses the status should be trained personnel with adequate competencies on the subject. He or she can be parent, caregiver or health care worker who is having a good relationship with the child.

Important points

- Health care worker and care giver should prepare a tailor-made disclosure plan. There should be ongoing counselling process with the child regarding health, emotional and socio-cultural issues
- Counselling process should be age appropriate and need to include detailed discussion on HIV infection and treatment modalities and available physio-social support.
- Explaining the medical facts should be a gradual, age-appropriate process. Information on HIV infection, care and support available, psychosocial and emotional support should be elaborated.
- Explore child's knowledge on their own health and HIV/AIDS, assess their coping skills, family and peer support, school/work progress and interests/ambitions.
- Children who are emotionally unstable or who have poor coping skills may need closer post-disclosure follow-up.

Adherence to antiretroviral therapy (ART) and follow up will be improved post-disclosure but the emotional and psychological effects of disclosure may be variable. Post disclosure plan for assessment of the child's emotional well-being and functioning at each visit (school functioning, interests, mood and behaviour) addressing families' widespread fears about potential HIV-related stigma and discrimination if their child's status is revealed to others, and provision of continuous support is very important.

Bone mineral density (BMD) issues with TDF

Dr. Malathi Pathiraja

Bone mineral density (BMD)	(BMD) Please select the make of DXA scanning equipment used and the enter the actual femoral neck BMD (in g/cm2). Alternatively, enter the T – score based on the NHANES iii female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Centre)

Notes on risk factors

Previous fractures

A special situation pertains to a prior history of vertebral fracture. A fracture detected as a radiographic observation alone (a morphometric vertebral fracture) counts as a previous fracture. A prior clinical vertebral fracture or a hip fracture is an especially strong risk factor. The probability of fracture computed may therefore be underestimated. Fracture probability is also underestimated with multiple fractures.

Smoking, alcohol, glucocorticoids

These risk factors appear to have a dose- dependent effect. i.e., the higher the exposure, the greater the risk. This is not taken into account and the computations assume average exposure. Clinical judgement should be used for low or high exposures.

Rheumatoid arthritis (RA)

RA is a risk factor for fracture. However, osteoarthritis is, if anything, protective. For this reason, reliance should not be placed on a patient's report of 'arthritis' unless there is clinical or laboratory evidence to support the diagnosis.

Bone mineral density (BMD)

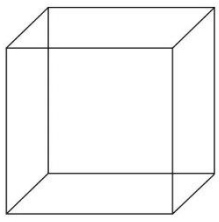
The site and reference technology is DXA at the femoral neck. T – scores are based on the NHANES reference values for women aged 20-29 years. The same absolute values are used in men.

International HIV Dementia Scale

HIV DEMENTIA SCALE

DEPARTMENT OF NEUROLOGY, JOHNS HOPKINS UNIVERSITY

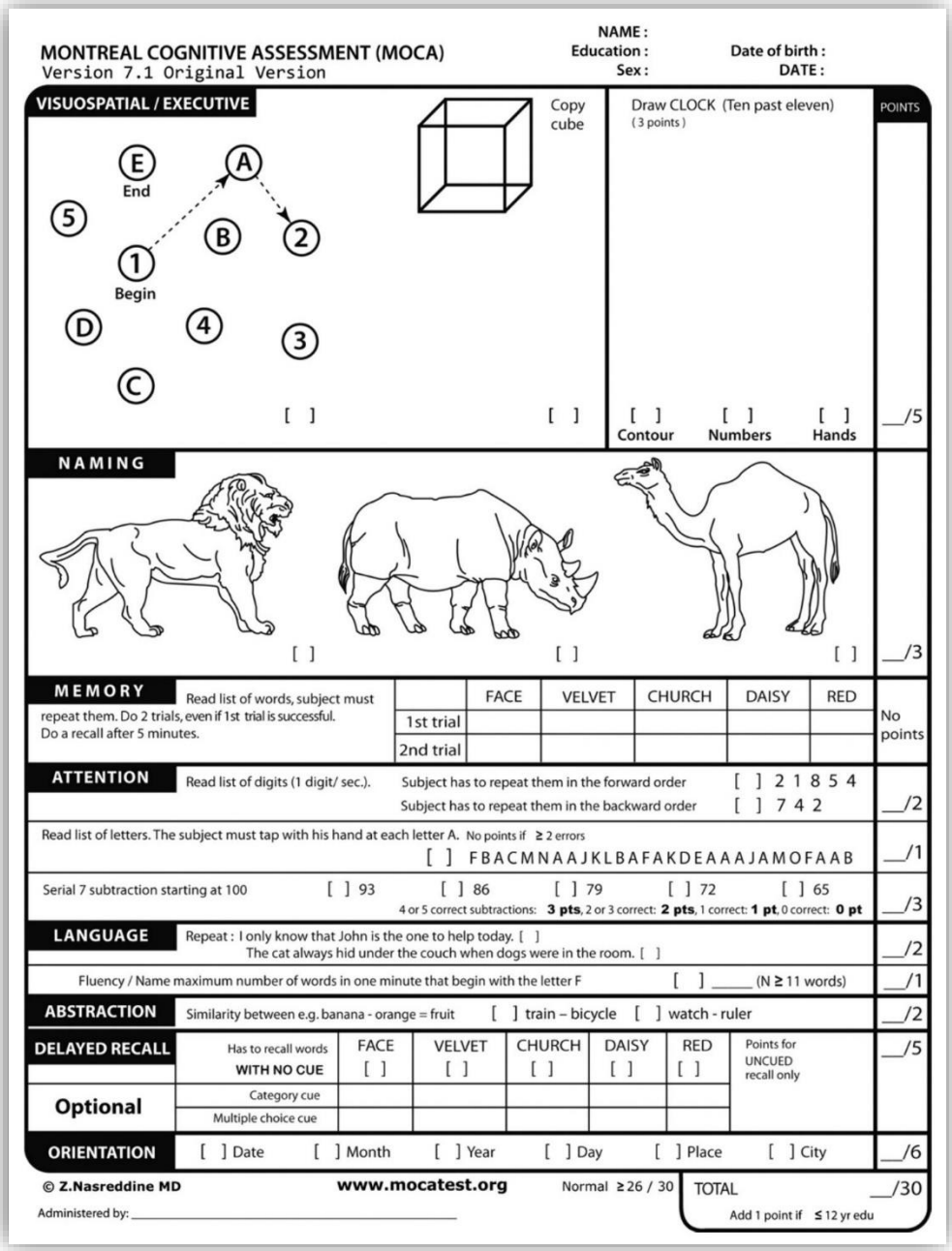
Maximum Score	Score	
		MEMORY - REGISTRATION Give four words to recall (dog, hat, green, peach) – 1 second to say each. Then ask the patient all 4 after you have said them.
4	( )	**ATTENTION** Anti-saccadic eye movements: 20 commands _____errors of 20 trials ≤3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; >6 errors = 0
6	( )	**PSYCHOMOTOR SPEED** Ask patient to write the alphabet in upper case letters horizontally across the page and record time. _____ in seconds. <21 sec = 6; 21.1 to 24 sec = 5; 24.1 to 27 sec = 4; 27.1 to 30 sec = 3; 30.1 to 33 sec = 2; 33.1 to 36 sec = 1; >36 sec = 0
4	( )	**MEMORY/RECALL** Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct word after prompting.
2	( )	**CONSTRUCTION** Copy the cube below; record time: _____ seconds <25 sec = 2; 25 to 35 sec = 1; >35 sec = 0



TOTAL SCORE: _____ /16

- A score of <10 is indicative of HIV associated Dementia

Montreal Cognitive Assessment



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING [ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

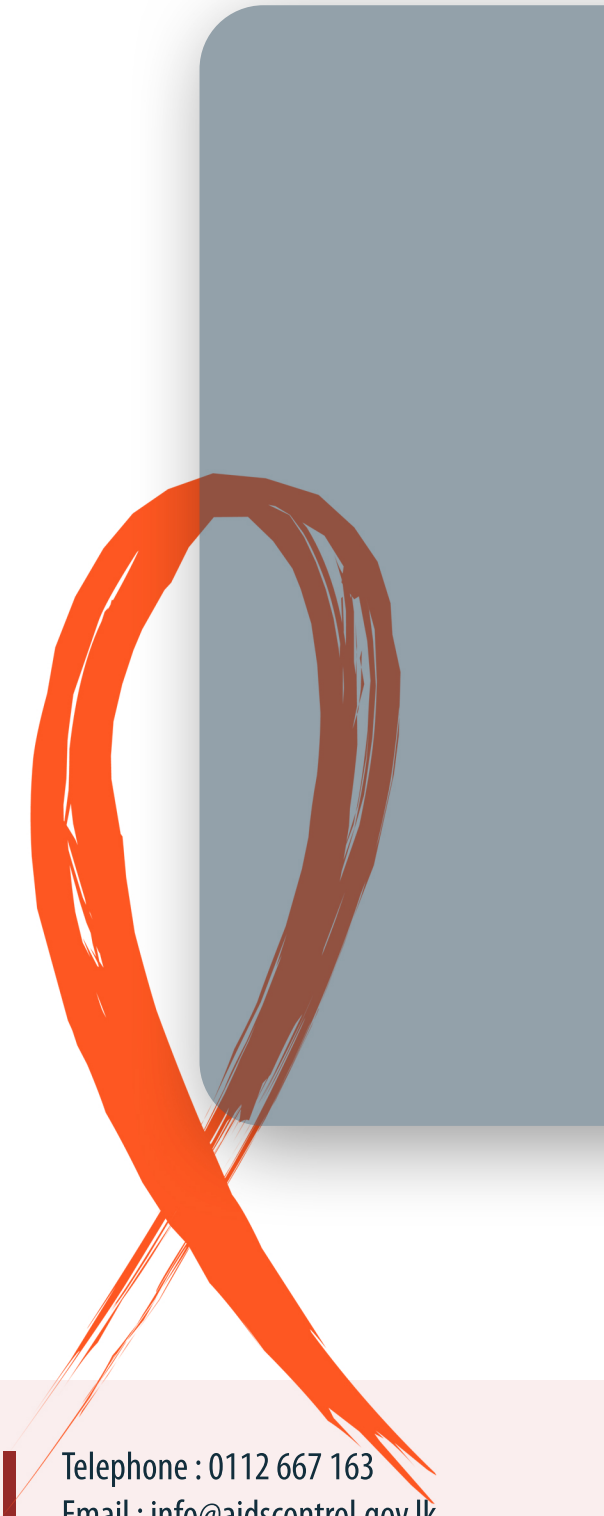
ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

- Sinhala and Tamil translations are validated and are available



NATIONAL STD/AIDS CONTROL PROGRAM

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