Opportunistic Infections
(Excluding TB – discussed separately)

Marsh Gelbart 2010
What about TB?

• Please note. HIV/TB co-infection – by far the most lethal combination - will be discussed separately
Opportunistic infections in people living with HIV

An opportunistic infection (OI) can be defined as –

- One caused by a pathogen, common or atypical which is not normally a problem in people with fully functioning immune systems e.g. Mycobacterium avium intracellular
- A common pathogen found in people with intact immune systems, but experienced in a more virulent form e.g. Herpes Zoster
- Some major OIs are definitive for an AIDS diagnosis
- Many can be prevented by prophylactic medication
A mixed picture for OIs

• The spectrum of OIs differs according to geographical position, e.g. Pneumocystis pneumonia (PCP) is common in the developed world but not in Africa where Tuberculosis (TB) is rife.
• For those who have access to HAART, the profile of OIs have changed. People are less susceptible to previously commonplace OIs, and are more likely to survive if they do develop them.
• However, OIs that occur after advanced immunosuppression, are becoming more common as people survive for longer.
A triple approach to avoiding OIs

• In the developed world, HAART regimes mean that the CD4 count of people living with AIDS can be kept sufficiently high for prolonged avoidance of OIs
• Where necessary, prophylaxis can help prevent OIs developing even when CD4 counts drop
• If an OI does develop, then usually treatment is available, backed up by further prophylaxis after the patient recovers from the acute infection
Prophylaxis can now prevent some of the major OIs

• In the developed world, efforts have concentrated on preventing pneumocystis pneumonia (PCP), tuberculosis and toxoplasmosis
• In recent times, effective prophylaxis for Mycobacterium avium and cytomegalovirus have become available
• Most parts of the world do not have access to adequate treatment, therefore efforts concentrate on avoiding HIV infection
In the developing world, a different picture…

Fig. 2. Presenting diagnoses in 200 patients with HIV disease, Clinique Bon Sauveur, Haiti, 1993–95

- Partner of patient with known HIV or sexually transmitted disease: 10%
- Strongyloidiasis or Loefler’s syndrome: 5%
- Pneumocystis carinii pneumonia: 4%
- Herpes zoster: 2%
- Chronic enteropathies: 8%
- Enteric fever: 5%
- Bacterial pneumonia: 6%
- Weight loss without localizing signs or symptoms (“slim disease”): 8%
- Extrapulmonary TB (excluding TB gastroenteritis): 6%

Source: ref. 39.
<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Initiating Primary Prophylaxis</th>
<th>Discontinuing Prophylaxis</th>
<th>Restarting Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>&lt;200 cells/μL or</td>
<td>&gt;200 cells/μL for</td>
<td>&lt;200 cells/μL</td>
</tr>
<tr>
<td></td>
<td>oropharyngeal</td>
<td>≥3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Candida</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Disseminated Mycobacterium avium</em> complex</td>
<td>&lt;50 cells/μL</td>
<td>Primary:</td>
<td>Primary:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;100 cells/μL for</td>
<td>&lt;50–100 cells/μL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3 months</td>
<td>Secondary:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;100 cells/μL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary: sustained,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. ≥6 months</td>
<td></td>
</tr>
<tr>
<td><em>Cytomegalovirus retinitis</em></td>
<td>≥100–150 cells/μL</td>
<td>CD4 count of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sustained, e.g.</td>
<td>&lt;100–150 cells/μL</td>
<td></td>
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<td></td>
<td>≥6 months</td>
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</table>

*Secondary prophylaxis.*
Classifying HIV and opportunistic infections

• The 1993 Centre for Disease Control classification system for HIV-infected adolescents and adults categorises persons on the basis of clinical conditions associated with HIV infection and CD4 counts.
• The system is based on three ranges of CD4 counts and three clinical stages, and is represented by a matrix of nine mutually exclusive categories.
The three ranges of CD4 counts

- The three CD4 count categories are:
  Category 1: 500 cells/mm³ or more.
  Category 2: 200 - 499 cells/mm³.
  Category 3: Less than 200 cells/mm³.
- Categorisation should be based on the lowest accurate CD4 count, not necessarily the most recent one.
• The pale blue shaded areas denote AIDS-defining conditions.

US Center for Disease Control and Prevention. 1993 revised classification system for HIV infection

<table>
<thead>
<tr>
<th>CD4 Categories</th>
<th>Asymptomatic</th>
<th>Symptomatic, Not A or C Conditions</th>
<th>AIDS—Indicator Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) ≥500 cells/mm³</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>(2) 200–499 cells/mm³</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>(3) &lt;200 cells/mm³ or CD4% &lt;14</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>

HIV Web Study (www.HIVwebstudy.org)
Defining the syndrome - Stage A. (Asymptomatic HIV Disease)

• In Stage A
  • You may have had acute (primary) HIV infection with accompanying illness (sometimes known as seroconversion illness)
  • You are now asymptomatic, other than possible persistent generalised lymphadenopathy (PGL).
  • If you have had any of the AIDS-defining diseases listed for stages B or C, then you are not in this category.
Stage B

You have never had any stage C diseases (see next slide) but have had at least one of the following defining illnesses --

- Bacillary angiomatosis
- Candidiasis, oropharyngeal or vulvovaginal thrush; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhoea for longer than 1 month
- Oral hairy leukoplakia
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy
- Remember, your CD4 count will further determine your classification
Stage C (AIDS)

If -- your T-cells have dropped below 200 or you have had at least one of the following defining illnesses --

- Candidiasis of the oesophagus, bronchi, trachea, or lungs
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers) (greater than 1 month's duration);
- Kaposi's sarcoma
- Lymphoma,
- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Toxoplasmosis of brain
- Wasting syndrome due to HIV
The major AIDS defining illness

- **Opportunistic infections**
  - *Protozoal*: Cryptosporidiosis, Toxoplasmosis
  - *Fungal*: Pneumocystis pneumonia (PCP) oesophageal candidiasis, cryptococcal meningitis
  - *Bacterial*: TB, Mycobacterium avium intracellulare (MAI), recurrent bacterial pneumonias
  - *Viral*: herpes simplex, cytomegalovirus, Progressive multifocal leukoencephalopathy (PML)

- **Opportunistic tumors**
  - Kaposi’s sarcoma, Lymphoma, cervical carcinoma

- **Neurological**
  - HIV neuropathy, HIV dementia

- **Other**
  - wasting syndrome
Cryptosporidiosis

- Caused by the parasite *Cryptosporidium parvum*,
- *Cryptosporidium* lives on the lining of the gastro-intestinal tract, especially the small bowel
- It causes voluminous watery diarrhoea, cramping abdominal pain, loss of appetite, weight loss, nausea, vomiting
- Cryptosporidiosis may result from being exposed to the organism for the first time, or from the activation of latent infection
Toxoplasmosis

- Caused by a protozoan called *Toxoplasma gondii*
- Can lead to brain lesions/abscesses
- Found in undercooked meat and in cat faeces. Pregnant women vulnerable, even if their immune system intact.
- Toxoplasmosis is much less common in the HAART era due to use of antiretroviral therapy,
Pneumocystis pneumonia (PCP)

- A lung disease initially thought to be caused by a protozoal organism *Pneumocystis carinii*, but now known to be caused by a fungus named *Pneumocystis jiroveci*.
- Greatest risk if CD4 cell count falls below 200 cells/mm³.
- The most common early symptoms of PCP are shortness of breath, particularly after exercise, or fever. Often accompanied by a persistent dry cough.
Preventing and treating PCP

• Initially a lethal opportunistic infection, treatment and prophylaxis for PCP have improved dramatically
• Commence Co-trimoxazole tablets 960mgs a day for prophylaxis when the CD4 count falls below 200 to 250 cells/mm³, or if they develop other AIDS-defining illnesses. Nebulised Pentamadine now considered a second line treatment, less efficacious, plus danger of side effects.
• Co-trimoxazole is also the standard first-line treatment for an episode of PCP, but given IV and in greater concentrations
Oesophageal Candida

- Caused by *Candida albicans*, it is an AIDS-defining condition.
- Systemic therapy is required. Fluconazole or Itraconazole tablets or solution may be prescribed.
- Recent research has linked oesophageal candidiasis in HIV-infected people to high viral load, regardless of CD4 count.
Cryptococcal meningitis

- Cryptococcal meningitis is a serious infection of the brain and spinal column that can occur in people living with HIV, particularly those with a CD4 count below 100. About 5 to 10% of people with HIV develop it.
- Caused by *Cryptococcus neoformans*, a yeast-like fungus which is found worldwide, often in soil which has been contaminated by bird excrement.
- It usually gets into the body through the lungs, and is not spread from person to person.
- Treated by IV anti-fungals such as amphotericin, fluconazole and itraconazole.
DIAGNOSIS AND TREATMENT OF CRYPTOCOCCAL MENINGITIS

- HIV-positive patient, CD4+ lymphocyte count <200,000/ml

History suggestive of cryptococcal meningitis (CM)

(and/or)

- Headaches, fever, with/without mental status changes
- Positive serum cryptococcal antigen

Lumbar puncture

No evidence of CM
Continue diagnostic evaluation

Evidence of CM
Positive culture for Cryptococcus neoformans, positive CSF cryptococcal antigen, positive India ink stain

Amphotericin B (0.7mg/kg/day) iv plus flucytosine (25mg/kg) q6h for 2 weeks, then fluconazole 400mg po for 8 weeks, then fluconazole 200mg po for life

No evidence of CM
Fluconazole 200mg orally indefinitely
Mycobacterium avium intracellulare (MAI)

• *Mycobacterium avium* and *M. intracellulare* are very similar bacteria which are usually grouped together.
• MAI organisms are found in the soil and tap water throughout the world. They are generally thought to enter the body in food, water or inhaled dust.
• In people with HIV who have CD4 counts less than 100 cells/mm³, and often below 20 cells/mm³, MAI can spread widely or 'disseminate' throughout the body, affecting almost any organ, but especially the liver, spleen and bone marrow.
Preventing and Treating MAI

• Since the introduction of HAART, the incidence of MAI has fallen significantly among HIV-infected people.
• Current United States guidelines recommend that HIV-positive people whose CD4 cell count is below 50 cells/mm3 should start to take clarithromycin or azithromycin as MAI prophylaxis.
• MAI treatment should generally consist of a combination of two or more drugs, one of which should be clarithromycin or azithromycin. Ethambutol is commonly the second drug prescribed in addition to azithromycin or clarithromycin.
Kaposi's sarcoma

- Caused by human herpes virus 8 (HHV 8)
- HHV is found in the saliva and in peripheral mononuclear blood cells of infected individuals
- If the CD4 count falls below 250, KS can affect internal organs such as the lungs and become life threatening
Preventing and treating Kaposi’s sarcoma

• The best way to avoid KS, is to boost the immune system with HAART
• In particular, protease inhibitor-based combinations have proved effective
• Chemotherapy is an option, either systemic or topical for skin lesions
• Radiotherapy can shrink tumours, alleviating blockages of the lymph system.
Lymphomas in HIV

- Lymphomas are tumours affecting lymphoid tissue.
- Non-Hodgkin’s lymphoma (NHL) is the commonest lymphoma seen in people with HIV, and involves the unregulated production of B-cells.
- NHL may occur in the lymph nodes, spleen, digestive system, liver, kidney or – in a particular form seen in immuno-suppressed people – in the brain, where it often occurs without any further spread and is called primary CNS (central nervous system) lymphoma.
Preventing and treating lymphomas

- Lymphomas are associated with low CD4 count, HAART to boost immune system and prevent their development
- Systemic lymphoma is usually treated with combination chemotherapy
- Standard treatment for primary CNS lymphoma, is radiotherapy of the brain accompanied by a short course of steroids, e.g. dexamethasone. Intrathecal or intraventricular chemotherapy are also options
- Some limited NHL in lymph nodes and skin may also respond to radiotherapy
Recurrent pneumonias

- As with other opportunistic infections, the incidence of bacterial pneumonia has fallen since combination antiretroviral therapy was introduced.
- However, if a person on HAART does get recurrent pneumonia, it is associated with a relatively poor prognosis.
- That is because, in the era of combination therapy, people who develop recurrent bacterial pneumonia, tend to have advanced HIV disease.
CMV retinitis

- **Cytomegalovirus (CMV)** is a member of the herpes family of viruses.
- A common opportunistic infection in HIV, usually seen when CD4 + <50
- CMV retinitis is infection of the back of the eye, causing the retina to become swollen and inflamed. If left untreated, the retina can become scarred, leading to permanent damage to the eyesight or blindness.
- Retinal detachment frequently complicates CMV retinitis

- Prior to highly active anti-retroviral therapy, CMV retinitis was easily recognized as a “pizza pie” retinopathy. Now, patients on HAART may be more difficult to diagnose
Preventing and Treating CMV Retinitis

• Before protease inhibitors became available, CMV retinitis, if left untreated, would usually get worse within three weeks of diagnosis
• Therapy with oral or IV ganciclovir (an anti-CMV drug) usually was able to delay further loss of vision for about eight weeks
• PI-based therapy usually boosts CD4+ cell counts and, since its introduction, has brought about remission for some people with retinitis
• Another approach is to place anti-CMV drugs directly into the eye, a slow-release form of ganciclovir, provides about 6 months of protection
Progressive multifocal leukoencephalopathy (PML)

- A rare disease of the central nervous system which results in the destruction of the sheath that covers the nerves.
- PML is caused either by primary infection or reactivation of a virus called the JC virus which is a type of papovavirus.
- The majority of the population (around 70%) is believed to have been exposed to this virus, but are asymptomatic.

- MRI scan showing frontal and occipital white matter lesions.
Preventing and treating PML

• Prior to the introduction of HAART people with PML survived an average of two to four months after diagnosis
• HAART has extended the average survival time of people with PML
• However, there remains neither a cure nor an effective treatment for PML, treatment is symptomatic and supportive.
• Despite HAART, one third of patients will die within two years of their PML diagnosis
HIV Related Dementia

• Also known as AIDS dementia complex (ADC), a broad spectrum of neurological manifestations
• Patients with ADC usually present with a triad of cognitive, motor function, and behavioural symptoms. Alternatively, patients with ADC can initially present solely with psychiatric symptoms such as depression, mania, or psychosis
• The rate of HIV dementia in patients with late-stage disease ranges from 7-27%. Milder forms of ADC affect an additional 30-40% of patients
Preventing and treating HIV related dementia

• Incidence rates have declined following the introduction of HAART.
• However despite the drop in incidence rates, the actual number of cases of HIV dementia may actually continue to rise as survival rates for individuals with advanced HIV infection lengthen
• Higher plasma viral load and lower CD4 counts appear to be strongly predictive of higher dementia risk
• HAART regimes incorporating stavudine and abacavir appear to have some effect in preventing or slowing down HIV related dementia
HIV related peripheral neuropathy

• More than one third of patients with HIV-AIDS have peripheral neuropathy
• There is an association between increased plasma HIV virus load and intensity of neuropathy
• Nucleoside reverse transcriptase inhibitors may, by causing mitochondrial toxicity, initiate some cases of peripheral neuropathy
Preventing and treating HIV related neuropathy

• It is believed that reduction in viral load will help alleviate peripheral neuropathy
• The anticonvulsant, lamotrigine, resulted in significant pain relief, although only in combination with HAART regimes which included ddI, ddC, and stavudine/d4T
• Unfortunately these nucleoside reverse transcriptase inhibitors may have a direct toxic effect on the peripheral nerves
HIV related wasting syndrome

• HIV related wasting syndrome is defined as - the unexplained loss of 10% or more of normal body weight, including lean muscle mass.

  *plus*

• chronic diarrhoea (for 30 days or more), or chronic weakness with fever (for 30 days or more)

• Causes include poor appetite, poor nutrient absorption and altered metabolism
Resources 1


Resources 2