Chemotherapy for Common Infections among People Living with AIDS

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Scope

1. Prevention of OI
2. Chronic diarrhoea
   1. Cryptosporiodosis
3. Invasive non typhoidal Salmonella
4. PJP
5. MAC
6. VZV
7. Toxoplasmosis
8. Cryptococcal meningitis
9. Viral encephalitis
   1. HSV
10. CMV
Complications of HIV disease are related to lymphocyte count
Opportunistic Infections

- Disease caused by an organism which does not usually cause infections in persons with normal immune systems

- Consequence of:
  - Re-activation of previous infections, as memory response to recall antigens are lost
  - Failure to mount a neoantigen response

Opportunistic infection are frequently the presenting feature of HIV in our population

- Opportunistic infections accelerate HIV progression
Strategies to decrease OI’s

- Antibiotic Prophylaxis e.g. cotrimoxazole
- Decrease exposure to pathogens – infection control, patient education
  - TB isolation
  - Safe food and water, sanitation to combat enteric pathogens
- Vaccinations
  - Pneumococcal, Influenza, Hepatitis B/A
  - Live vaccines: unsafe (Yellow fever safe CD>200, zoster vaccine, MMR)
  - CD4 < 200 - AB response poor and short-lived
  - Transient increase - viral load
Q1: Which statement is true regarding Immunisations in patients with AIDS

A. The 23 valent polysaccharide pneumococcal vaccine induces life long immunity
B. Yellow fever vaccination is mandatory for travellers to Brazil
C. The standard 3 dose schedule for hepatitis B vaccination results in complete protection
D. Varicella vaccination in childhood will prevent varicella zoster infection
E. Measles causes severe disease and all patients born before 1994 must be vaccinated
A. The 23 valent polysaccharide pneumococcal vaccine induces lifelong immunity.

B. Yellow fever vaccination is mandatory for travellers to Brazil.

C. The 3-dose schedule for hepatitis B vaccination results in complete protection.

D. Varicella vaccination in childhood will prevent varicella zoster infection.

E. Measles causes severe disease and all patients must be vaccinated if born before 1994.
S. pneumoniae vaccine - Controversial

- Studies have shown variable results.
  - **Pneumovax (23 valent) Polysaccharide**
    - A CDC report showed a 49% efficacy in immunosuppressed hosts (NEJM 1986;315:1318; JAMA 1993;270:1826)
    - A study in Uganda showed increased rates of pneumococcal disease in vaccine recipients (Lancet 2000;355:2106).

- **Prevanar (13 valent) Conjugate vaccine**
  - Recently evaluated and FDA approved for use in adults >60yrs, non HIV

- **Pneumococcal Conjugate Vaccine (7 valent)**
  - 496 HIV-Infected Adults (N French et al, 2010, Malawi)
    - 5 pneumococcal episodes occurred in the vaccine group and 19 in the placebo group
    - Worked well in px with CD<200
    - Good protection against the 7 vaccine serotypes
    - Cost $40
Immunisation

**Hepatitis B**
- Indication: All patients that are negative for anti HBsAB screening
- Schedule - 3 IM injections given at 0, 1 and 6mths
- In immunocompromised - measure HBsAB levels 1-2 mths after last dose. May require additional doses.

**Hepatitis A**
- **Risk group:**
  - MSM
  - Drug users (injection and non–injection)
  - Persons with chronic liver diseases, chronic HBV and HCV
  - Susceptibility defined by negative anti HAV
- Schedule: HAV vaccine 0.5 ml x 2 separated by 6 months.

**Influenza**
- Indicated for all patients annually
  - Influenza vaccine 0.5 ml IMI each year
  - Use subunit formulation only not LAV
  - **Alternative:** Chemotherapeutic agent
Chronic or recurrent Diarrhoea

- **Definition:** > 3 loose stools/24hrs for >4 weeks ( >250mls stool/day)

- **Diagnostic approach** if 3 stool MCCS over 10 days neg
  - Sigmoidoscopy/colonoscopy with multiple biopsy of normal and abn areas
  - Duodenal biopsy if small bowel diarrhoea suspected

- **Infective diarrhoea:** manage as HIV uninfected

- **Non-infective diarrhoea:**
  - Consider: Drugs, alcohol, pancreatic insufficiency, lactose intolerance
  - **Treatment**
    - Attention to hydration, diet (low fat, avoid milk, sufficient calories, supplementation)
Causes Chronic or recurrent diarrhoea

### TABLE 3: EVALUATION OF DIARRHEA BASED ON CD4 COUNT

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Common Pathogens</th>
<th>Method of Identification</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 cells/mm³</td>
<td>Cryptosporidium</td>
<td>Antigen assay or modified Kinyoun stain</td>
<td>Moderate to severe ARV-related diarrhea; should only be used after bacterial or amoebic etiology has been excluded</td>
</tr>
<tr>
<td></td>
<td>Microsporidia</td>
<td>Trichrome stain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterocytozoon bieneusi</td>
<td>Biopsy with Giemsa stain or electron microscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Septata intestinalis</td>
<td>Biopsy with Giemsa stain or electron microscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclospora</td>
<td>No fecal leukocytes, AFB smear of stool for oocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isospora</td>
<td>No fecal leukocytes, AFB smear of stool for oocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>Biopsy demonstrating intranuclear inclusion bodies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAC</td>
<td>Blood culture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histoplasma capsulatum</td>
<td>Blood culture and urine antigen assay</td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Giardia</td>
<td>Antigen assay and/or stool examination for ova and parasites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common bacterial pathogens:</td>
<td>Fecal leukocytes, and stool and blood cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
<td>Fecal leukocytes, stool cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigella species</td>
<td>Fecal leukocytes, stool cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Campylobacter jejuni</td>
<td>Fecal leukocytes, stool cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Giardia</td>
<td>Antigen assay and/or stool examination for ova and parasites</td>
<td></td>
</tr>
<tr>
<td>Any CD4</td>
<td>Clostridium difficile</td>
<td>Fecal leukocytes, antigen assay for toxin a and b</td>
<td></td>
</tr>
</tbody>
</table>
Cryptosporidiosis

- Protozoan implicated in chronic diarrhoea in CD4 < 100
- Disseminated infection – sclerosing cholangitis and pancreatitis following papillary necrosis, pneumonia
- Prophylaxis – feco- oral – animal, food, water contact
- Treatment
  - Nitazoxanide – 500mg BD for 3 days improved parasite clearance in HIV uninfected.
  - Initiate or optimize ART (PI) for immune restoration
  - Aggressive oral and/or IV rehydration and replacement of electrolyte loss
  - Symptomatic - anti-motility agent
- Other regimens
  - Nitazoxanide 500–1000 mg PO BID with food for 14 days
  - Paromomycin 500 mg PO QID for 14 to 21 days
Cryptosporidiosis
Q2 Which is TRUE for Salmonella sp (non typhoid) in AIDS

1. Is the commonest cause of Gram negative bacteraemia
   A. A and C
   B. B and D
   C. A and D
   D. All statements

2. Has a predilection for endovascular disease and can cause endocarditis

3. Is a cause of acute and recurrent gastroenteritis

4. Chronic carriage status <1%
Q2 Which is TRUE for Salmonella sp (non typhoid) in AIDS

1. Is the commonest cause of Gram negative bacteraemia
   A. A and C
   B. B and D
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   D. All statements

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4. Chronic carriage status <1%
NTS: CLINICAL ENTITIES

**Bacteraemia**
1-4% in I competent

**Gastroenteritis**
IP 6-48hrs
Resolves in 1/52
+/- systemic symptoms
Carrera 4-5/52

**Vascular infection**
10-25%, > 50yrs
Aorta
Endocarditis, arteritis
Mortality 14-60%
Sx + ABIO

**Chronic carrier status**
<1%
>1 year in stool/urine
Biliary or UT abn

**Localised infection**
assoc abnormality
Sites-bone, soft tx,
CNS, lung, UT, joints

**Enteric Fever**
++ systemic signs
// typhoid
## BACTERIAEMIA

<table>
<thead>
<tr>
<th>International Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunocompetent</strong></td>
</tr>
<tr>
<td>• Severe NTS: empiric FQ + ESC – de-escalate when sensitivity available</td>
</tr>
<tr>
<td>• 10-14d IVI</td>
</tr>
<tr>
<td>• For high grade bacteraemia (&gt;50% of &gt;3b/c +) Rx: 4-6wks IVI ESC or 2wks IVI FQ then 4wks PO FQ</td>
</tr>
<tr>
<td>• Search for an endovascular focus</td>
</tr>
<tr>
<td><strong>HIV+</strong></td>
</tr>
<tr>
<td>• FIRST EPISODE: attempt to eradicate organism 14d IVI FQ or ESC followed by 4wks PO FQ</td>
</tr>
<tr>
<td>• RELAPSES: Long term suppressive therapy needed with FQ (some say TMX adequate)</td>
</tr>
<tr>
<td>• Indication to commence HAART with AZT containing regimen</td>
</tr>
</tbody>
</table>
Pneumocystis jiroveci Pneumonia (PJP)

- **Prophylaxis**
- Rate of PJP with primary or secondary prophylaxis 0-4%/yr
- **Indications:**
  - Symptomatic HIV
  - WHO clinical stage 3,4
  - CD4 <200
  - Prior PJP
  - TB
Prophylaxis - Primary and Secondary

TMP – SMX 2 ss(400/80) or 1 ds(800/160) per day

Alternative Regimens

- TMP – SMX 1 DS 3x/wk
- Dapsone 100 mg/ d or 50 mg PO bid Doesn’t prevent other opportunistic infection: toxoplasmosis, isosporiasis, bacterial infections
- Aerosolized pentaminididine 300 mg/month by Respirgard II NEBILIZER
- Atovaquone 1500 mg PO OD with meals, expensive, not used with RIF
PJP Treatment

Co-trimoxazole: 3-4 ss tabs qid po (15-20/75-100 mg/kg/day) in 4 doses IV/PO
- Duration is 21 days
- Toxicity – hypersensitivity rash, low platelets and WBC, hepatitis, azotemia, hyperkalaemia

- Adding leucovorin to prevent myelosuppression is not recommended
- Adjustment for renal impairment

- Alternative: dapsone 100mg daily plus trimethoprim 300mg tds or Clindamycin 450mg tds + primaquine 15 mg daily

- Monitor respiratory rate and oxygenation
- Secondary prophylaxis mandatory
- Poor response in 10%
- Sulpha drug resistance uncertain clinical outcome
Diagnosis:

- Polymerase chain reaction (PCR) is an emerging method
  - The sensitivity of PCR for bronchoalveolar lavage appears to be high; the ability of PCR to distinguish colonization from disease is less clear.

- 1,3β-D-glucan may be elevated in patients with PCP, but the assay’s sensitivity and specificity for establishing a PCP diagnosis are problematic.

- Commence HAART within 2 weeks

- Steroids

<table>
<thead>
<tr>
<th>Adjunctive Corticosteroids: For Moderate to Severe PCP Based on the Following Criteria (All):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PaO₂ &lt; 70 mmHg at room air or</td>
</tr>
<tr>
<td>- Alveolar-arterial O₂ gradient ≥ 35 mmHg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Schedule: Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-5</td>
</tr>
<tr>
<td>Days 6-10</td>
</tr>
<tr>
<td>Days 11-21</td>
</tr>
</tbody>
</table>
- Treatment duration at least 1 year
- Add third agent (rifabutin) in severe disease
- Possible 4th agent aminoglycoside
- Do susceptibility testing for clarithro and azithro
- Secondary prophylaxis until CD4>100 for 6 months
- Rifampicin, NNRTI’s not used with clarithro

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevention</th>
<th>Treatment</th>
<th>Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated Clarithromycin 500 mg bid + Ethambutol 15 mg/kg qd + Rifabutin 300 mg qd (Rifabutin 300 mg qd)*</td>
<td>Disseminated Clarithromycin 500 mg bid + Ethambutol 15 mg/kg qd + Rifabutin 300 mg qd (Rifabutin 300 mg qd)*</td>
<td>Clarithromycin 250 mg qd + Ethambutol 15 mg/kg qd + Rifabutin 300 mg qd (Aminoglycoside)</td>
<td>Preferred Alternative</td>
</tr>
</tbody>
</table>

**TABLE 250-3 Regimens for the Treatment and Prevention of Mycobacterium avium Complex**

- **Preferred**
- **Alternative**

**Principles and Practice of Infectious Diseases**
Mandell, Douglas and Bennett
Sixth Ed
Q3 Which statement is true Regarding Varicella Zoster

A. The commonest clinical presentation is rash in a lumbar dermatomal distribution
B. Since the virus involves the dorsal roots, motor symptoms do not occur
C. Acyclovir is used only if the patient presents within 72hrs of rash appearance
D. Zosteriform herpes simplex is associated with more frequent recurrences
E. Acyclovir is inferior to the newer agents i.e. valacyclovir
Q3 Regarding Varicella Zoster

A. Lumbar dermatomal distribution is the commonest clinical manifestation

B. Since the virus involves the dorsal roots, motor symptoms do not occur

C. Acyclovir is used only if the patient presents within 72hrs of rash appearance

D. **Zosteriform herpes simplex** is associated with more frequent recurrences

E. Acyclovir is inferior to the newer agents ie valacyclovir
Varicella Zoster

- Lifetime risk is 15% to 20%
- Highest incidence- elderly and immunocompromised
- The incidence is >15-fold higher for HIV-infected adults than for age-matched controls.
- Can occur in HIV adults at any CD4 count, but frequency of disease is highest with CD4 counts of <200 cells/μL.
- ART has not been shown to reduce the incidence
- Neurologic syndromes in HIV- CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, aseptic meningitis,
- Eye - ARN and PORN
- 10-20% develop post herpetic neuralgia
Preferred Therapy
• Valacyclovir 1000 mg PO tds
• Famiciclovir 500 mg PO tds

Alternative Therapy
• Acyclovir 800 mg PO 5 times daily

Duration
• 7–10 days, longer if resolve slowly

Extensive cutaneous lesion or visceral involvement
• Acyclovir 10–15 mg/kg IV q8h until clinical improvement

Modify dose in renal impairment

Analgesia – paracetamol, NSAID, opioids

Adjunctive corticosteroids
  – Reduces acute pain, inflammation, healing time.
  – Eye preservation in ophthalmic branch of trigeminal nerve involvement
  – No effect of post herpetic neuralgia
Varicella Post Exposure Prophylaxis

Chickenpox is more infectious than shingles to a seronegative individual who has no history of varicella infection.

- VZIG 5 vials (6.25 ml) IM within 10 days
- Acyclovir as prophylaxis/pre-emptive treatment
  - Acyclovir 800 mg PO 5 times/day for 5–7 days
  - Valacyclovir 1 g PO TID for 5–7 days
- Varicella vaccine (Varivax) is a live attenuated vaccine contraindicated in HIV CD4<200
- VZV vaccine (Zostervax) to prevent shingles after chicken pox is available as single subcut injection for >50 yrs but is also live formulation
Toxoplasmosis

- Seroprevalence 50-80% in Europe, Asia

- Presents focal encephalitis with fever, headache, motor weakness and confusion. CNS mass lesion in 75% of cases

- Chorioretinitis, pneumonia and multisystem disease is less common

- Most disease due to reactivation when CD4 < 100 cells/ul

Diagnosis

- Serum Toxoplasma Ig G is positive >90%. 2 year risk among AIDS pts with + Ig G Toxo 26%

- PCR in CSF has high specificity (96%–100%), but low sensitivity (50%), especially once specific anti-toxoplasma therapy has been started

- Most important differential diagnosis is tuberculoma, lymphoma, brain abscess, PML
Necrotising retinitis with granulomatous inflammation

Multiple ring enhancing lesions with surrounding oedema
Toxoplasmosis Prophylaxis

- All HIV+ patients should be tested for IgG
- Advise patients not to eat raw or undercooked meat (pork, lamb, venison, shell fish) cook to 66°C or until no longer pink (> 72°C).
- Wash hands after contact with raw meat, soil, vegetables, cat care
- Drug prophylaxis - CD4 < 100: Cotrimoxazole 2ss tabs daily
- Vaccine – Live attenuated S48 sheep in Europe and N Zealand
Toxoplasmosis Treatment

- Treat empirically - use clinical response in 10-14 days and or radiological improvement as diagnostic parameter.
- Initiate HAART with 2-3 weeks
- DOC sulphadoxime + pyrimethamine
- Treatment options in SA
  - Suphadoxine Trimethoprim 10mg/kg/day in 2 divided doses x 3-6/52 (cotrimoxazole 2ds bd)
  - Alt - Clindamycin 600mg qid IVI + Pyrimethamine 200mg stat followed by 50-75mg/d po
  - Add steroid in CNS, retinitis.
Cryptococcal Meningitis

- About 5-10% of patients with AIDS
- Incidence is high among African AIDS patients (26% Malawi)
- In 50-60% of patients CM is the first AIDS defining condition
- 75% CM have a CD4 count < 50.

Secondary prophylaxis:
- Fluconazole 200 mg po daily for life or until CD4 > 200 cells/μl for more than 6 months, stable on HAART, received at least 12 months fluconazole in total, falling AG titre.
- Primary prophylaxis NOT recommended – selection of resistance in candida and no effect on mortality
Treatment Cryptococcal Meningitis

Antifungal

- Amphotericin B + FC are the drugs of choice
- Fluconazole is alternative? Dose of choice (itraconazole, posaconazole)
- No role for echinocandins, steroids

Pain relief – paracetamol, mild opiate

Avoid NSAID (nephrotoxicity)

Control of ICP – remove 20-30ml (20-50% of initial LP). May need daily CSF taps
### Table 1: Summary of treatment recommendations and dosage for HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal)

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Drugs available</th>
<th>Pre-hydration + electrolyte replacement + toxicity monitoring/management</th>
<th>Induction phase options $^{14}$</th>
<th>Consolidation phase options</th>
<th>Maintenance/secondary prophylaxis options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Amphotericin B $^{15}$ ± flucytosine</td>
<td>Available</td>
<td>a. Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day &lt;br&gt;b. Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day</td>
<td>Fluconazole 400-800 mg/day</td>
<td>Fluconazole 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B $^{15}$</td>
<td>Not available for full 2 week induction period</td>
<td>Amphotericin 0.7-1 mg/kg/day &lt;br&gt;short course (5-7 days) + fluconazole 800 mg/day (2 weeks)</td>
<td>Fluconazole 800 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B not available</td>
<td>Not available</td>
<td>a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day &lt;br&gt;b. Fluconazole 1200 mg/day alone</td>
<td>Fluconazole 800 mg/day</td>
<td></td>
</tr>
</tbody>
</table>
Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis


RESULTS
The 26-week mortality with earlier ART initiation was significantly higher than with deferred ART initiation (45% [40 of 88 patients] vs. 30% [27 of 89 patients]; hazard ratio for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; P = 0.03). The excess deaths associated with earlier ART initiation occurred 2 to 5 weeks after diagnosis (P = 0.007 for the comparison between groups); mortality was similar in the two groups thereafter. Among patients with few white cells in their cerebrospinal fluid (<5 per cubic millimeter) at randomization, mortality was particularly elevated with earlier ART as compared with deferred ART (hazard ratio, 3.87; 95% CI, 1.41 to 10.58; P = 0.008). The incidence of recognized cryptococcal immune reconstitution inflammatory syndrome did not differ significantly between the earlier-ART group and the deferred-ART group (20% and 13%, respectively; P = 0.32). All other clinical, immunologic, virologic, and microbiologic outcomes, as well as adverse events, were similar between the groups.

CONCLUSIONS
Deferring ART for 5 weeks after the diagnosis of cryptococcal meningitis was associated with significantly improved survival, as compared with initiating ART at 1 to 2 weeks, especially among patients with a paucity of white cells in cerebrospinal fluid. (Funded by the National Institute of Allergy and Infectious Diseases and others; COAT ClinicalTrials.gov number, NCT01075152.)
Appendix A: Clinical decision-making algorithm

Reflex cryptococcal antigen screening CD4 < 100 specimens

- **POSITIVE**
  - Contact patient for urgent follow-up
  - Screen for meningitis symptoms *
  - Check for other clinical conditions †

  - **Symptomatic**
    - Start Fluconazole 400 mg daily and refer immediately for lumbar puncture

    - Lumbar puncture (+)
      - In hospital treatment with Amphotericin B alone for 2 weeks
      - Start ART after 2 weeks of cryptococcal therapy

    - Lumbar puncture (-)
      - Outpatient treatment with Fluconazole 400 mg daily ‡

      - Start ART after 2 weeks of cryptococcal therapy

- **NEGATIVE**
  - Initiate ART
    - No fluconazole

* Patient is symptomatic if they have any of the following:
  1. Headache greater than 24 hours
  2. Fever
  3. Confusion or coma
  4. Blurry vision
  5. Neck stiffness

† Other clinical conditions include:
  - Patients on tuberculosis medications
  - Patients on nevirapine
  - Patients with previous history of cryptococcal meningitis
  - Pregnancy or breastfeeding mothers
  - Liver disease
  - Children

‡ A lumbar puncture may be considered if available.

§ A lumbar puncture may be considered if available.

† Some clinicians prefer to use a higher dose.
TESTS

Latex agglutination

Lateral Flow Assay
40 UI of CSF, serum, plasma, urine
Result in 15 min
Validated in Thailand, SA, Uganda
FDA approved
Urine has lower sensitivity (92% vs serum 96%)
Point of care test
2usd/assay
Viral Encephalitis

- Distinguished from viral meningitis and encephalopathy

- Aetiology
  - Common – Herpes family, rabies, JC, enterovirus
  - Exotics- JBE, WNV, VEE
  - Post viral syndrome- measles, polio, influenza

- Pathology – cerebral oedema, perivascular infiltration, haemorrhage, neuronal invasion

Table 1: Causes of viral encephalitis

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus (HSV-1, HSV-2)</td>
</tr>
<tr>
<td>Other herpes viruses: varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6)</td>
</tr>
<tr>
<td>Adenoviruses</td>
</tr>
<tr>
<td>Influenza A</td>
</tr>
<tr>
<td>Enteroviruses, poliovirus</td>
</tr>
<tr>
<td>Measles, mumps and rubella viruses</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Arboviruses— for example, Japanese B encephalitis virus, St Louis encephalitis virus, West Nile encephalitis virus, Eastern, Western, and Venezuelan equine encephalitis virus, tick borne encephalitis viruses</td>
</tr>
<tr>
<td>Bunyaviruses— for example, La Crosse strain of California virus</td>
</tr>
<tr>
<td>Reoviruses— for example, Colorado tick fever virus</td>
</tr>
<tr>
<td>Arenaviruses— for example, lymphocytic choriomeningitis virus</td>
</tr>
</tbody>
</table>

Modified from Chaudhuri and Kennedy, with permission.
Viral Encephalitis

- CNS entry via blood stream, retrograde nerve (rabies, polio, HSV, VZV), olfactory nerve (HSV, amoeba)
- Severe disease – altered consciousness, seizures, infarction, raised ICP, meningism
- Laboratory findings
  - Variable pleocytosis mononuclear cells usually but not exclusively eg CMV
  - Significant RBC- HSV, Naegleria
  - Raised protein, usually normal or mildly decrease sugar
  - PCR is mainstay for aetiological diagnosis
- Imaging – CT usually unhelpful. MRI better for demyelination and oedema
- Treatment – Pleconoril for picornoviruses,
  - acyclovir for HSV
  - gancyclovir for CMV
- HAART
Herpes Simplex Encephalitis

- Commonest cause of encephalitis is US – 95% HSV1
- Biphasic age distribution – 5-30yrs and again at 50 yrs
- No seasonality
- Pathogenesis – olfactory spread, reactivation from trigeminal or ANS nerve roots, skin lesions
- Clinical hallmarks – fever, focal neurologic symptoms (temporal lobe)
- Diagnosis- CT/MRI, PCR
- Treatment – IVI Acyclovir 30mg/kg/day in 3 divided doses for 21 days. Given over 1 hr in adequately hydrated px
- Neurological sequelae in patients >35yr
- Monitor renal function
Cytomegalovirus (CMV)

- High seroprevalence and association with progression of HIV
- Causes: retinitis, eosophagitis, colitis, enteritis, hepatitis.
- CNS – dementia, meningoencephalitis, polyradiculopathy, ventriculoencephalitis - acute course, with focal neurologic signs, often cranial nerve palsies or nystagmus, and rapid progression to death.
  
  Diagnosis – focal necrotising lesions with periventricular enhancement on CT/MRI + PCR

Mounting evidence implicating CMV in cardiovascular disease

- Disease: CD4 <50 cells/mm³
- Diagnostic dilemma – test have poor PPV
- High mortality in AIDS despite gancyclovir. Survival 4-9mths
- Secondary Prophylaxis stopped if CD4>100 and px had 3-6 months of treatment
CMV Treatment

- HAART – IRIS is a concern in CNS and retinitis. CMV replication controlled within 1 to 2 weeks after anti-CMV therapy. Most experts will wait 2 weeks – balance of risks
- Colitis - Ganciclovir 5 mg/kg IV q12h, switch to valganciclovir 900 mg PO q12h once able to absorb and tolerate
- Retinitis - Intravitreous injections, implants, oral or IV
- CNS – initial synergistic therapy ganciclovir IV + foscarnet IV

- Drug toxicity
  Ganciclovir/valganciclovir - anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction.
  Neutropenia reversed G-CSF
  Foscarnet – 90mg/kg/day in 2 divided doses
  nephrotoxicity, Ca/PO4/Mg; seizures

- Monitor FBC, U&E, CPM
twice weekly during induction:
  least once weekly during maintenance
Conclusion: Trends in OIs - 1st 20 years of pandemic

HAART
PRESERVES the immune system → prevents OIs
RESTORES the immune system → reduce/eliminates the risk of OIs

- Can prophylaxis be discontinued?
  - Primary?
  - Secondary

HAART-Partial immune reconstitution