Natural History of HIV Infection

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Module Objectives

- Pathogenesis (how HIV infects immune cells)
- Natural history
- Acute HIV infection (presentation, diagnosis and treatment)
- Chronic HIV infection (manifestations and management)
Course of HIV Infection

- Primary Infection
- Seeding of Lymphoid Organs
- Virus Dissemination

Clinical Latency

CD4 cells/µl

Virus RNA copies/ml

CD4 Count

Opportunistic Infections

Death

Weeks

Years
Pathogenesis of Acute HIV Infection

HIV makes contact with cells located within the genital mucosa

Virus is carried to regional lymph nodes (1-2 days)

Exponential viral replication

There is widespread systemic dissemination to the brain, spleen, distant lymph nodes, etc (5-11 days)
Pathogenesis Continued…

- Following widespread dissemination…
  - Development of virus specific T cell responses (CD8 cells)
  - Symptoms of acute infection occur
  - Decrease in plasma viral load
  - Symptoms of acute infection resolve
From Antigen-Presenting Cell to CD4 Cell Destruction
How Does HIV Work?

1. Attachment to host cell
2. The virus changes from RNA to DNA
3. Integration into host cell’s nucleus
4. Reproduction of viral components
5. Assembly of new HIV viruses
Course of HIV Infection

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Clinical Latency

Virus RNA

Opportunistic Infections

Death

CD4 cells/µl

HIV RNA copies/ml

Weeks

Years

0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11
Primary HIV: Definition

- Refers to new HIV infection
- Encompasses ‘acute’ and ‘early’ HIV
- **Acute infection**: days-weeks after infection, during which there are high levels of replicating virus and an attempt by the host immune system to control virus
- **Early infection**: variably defined as within 3-12 months of infection
Epidemiology of Primary HIV Infection

Estimated that 14,000 new infections occur each day in the world, predominantly through sexual contact.

How Often Do People With Primary HIV Infection Seek Health Care?

- Swiss cohort
  - 87% of seroconverters (20/23) in cohort study had symptoms
  - 95% of these patients had medical evaluation
  - Primary HIV Infection considered in only 5 of 19 patients

- Primary HIV Infection often leads to medical evaluation, but is under-diagnosed
MACULAR PAPULAR RASH
Case One

- Ms J.G- 29 years old domestic worker
- 1 week history of fever, rash, myalgia and a sore throat. Previously healthy patient.
- Systemic Enquiry: not on contraception.
  
  LNMP: 1/3/04 Has one child- 1 year old (breastfeeding). Had an HIV test 1 year ago during her pregnancy → negative
- Unmarried with one partner for the last 4 years. Not using condoms. Unsure if her partner has other casual sexual partners as they do not live together.
Clinical Examination

- Temp- 39°C, 0.5-1cm posterior and anterior cervical and suboccipital lymph nodes. No evidence of wt loss. Mild pharyngitis. No thrush. Rest of the systems- normal

- Differential diagnosis includes:
  - viral infections - EBV, rubella
  - secondary syphilis
  - acute hepatitis

Is there anything else that you would consider in DD?

Acute retroviral syndrome
The HIV-1 Elisa test done is NEGATIVE

Need to either:

- Repeat the test in one month.
- P24 antigen test or
- Quantitative or qualitative viral assays – useful for early diagnosis, but not widely available in KZN.

You decide to repeat the HIV-1 Elisa test in 1 month:

- Result is now POSITIVE
Testing for HIV Infection

<table>
<thead>
<tr>
<th>TIME</th>
<th>Amount of Virus in the Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Level at which antibody can be detected</td>
</tr>
<tr>
<td>4-6wks</td>
<td>Viral Load</td>
</tr>
<tr>
<td></td>
<td>HIV antibody</td>
</tr>
<tr>
<td>8-10yrs</td>
<td>No Symptoms</td>
</tr>
<tr>
<td></td>
<td>HIV Related Symptoms</td>
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- **Viral Load**
- **HIV antibody**

- **Time when person becomes infected**
- **Window Period**
- **No Symptoms**
- **HIV Related Symptoms**
Symptoms and Signs of ARS

- Fever: 90%
- Fatigue: 80%
- Rash: 60%
- Headache: 50%
- Lymph nodes: 60%
- Pharyng: 70%
- Diarrhoea: 40%

Patients reporting symptoms.
Treatment of ARS

- Area of much research interest and therapeutic options are not resolved.
- 2 options:
  
  Use of antiretroviral therapy may lower viral set-point and alter the natural history of HIV infection.
  
  Early treatment may necessitate the patient being on ARV therapy for an unnecessarily long time.

- USA guidelines suggest that patients with ARS should be offered treatment.
Primary HIV Infection: Conclusions

- Primary HIV Infection is under-diagnosed
- May represent a critical opportunity to intervene
- High index of suspicion, recognition of key signs & symptoms, and lab testing required for the diagnosis
- HAART may provide opportunity for improved long-term virologic control of HIV
- Ongoing studies should clarify the role of treatment during PHI
Is Diagnosing Acute HIV Feasible?

- Costly!!!
- No official guidelines regarding treatment

So, what can you do if you suspect Acute HIV Infection?
Feasible Interventions

- Assess risk factors for HIV infection
- Encourage alterations in sexual behavior (positive prevention)
- Encourage follow up for antibody testing
Chronic HIV Infection

Natural History

Clinical Manifestations
Course of HIV Infection

- Primary Infection
- Seeding of Lymphoid Organs
- Virus Dissemination

Clinical Latency

CD4 cells/µl

Virus RNA

Opportunistic Infections

CD4 Count

Death

Weeks

HIV RNA copies/ml

Years
Diagnosis of Chronic HIV Infection

- Rapid HIV-1 Testing
  - Pretest counselling
  - Blood obtained via fingerstick
  - Results in approximately 20 minutes
  - Must be confirmed with a second rapid test
Diagnosis
Real Time testing at a HIV Clinic
Diagnosis

- HIV-1 antibody ELISA (Enzyme Linked Immunosorbent Assay) test:
  - Requires blood draw
  - Takes approximately 2 weeks for results
  - Must be confirmed with second ELISA test or a Western Blot Test
Laboratory Monitoring of Chronic HIV Infection
CD4 count and HIV RNA

- CD4 count decline is a function of HIV RNA level – The higher the HIV RNA, the faster the decline in CD4 cells
- Typically, CD4 cells decline by approximately 50 cells/year
- HIV RNA remains stable during intermediate stage of HIV then typically increases dramatically during later stages of disease
CD4 Count and OIs

- Tuberculosis, Herpes zoster (shingles)
- Oral candida, Herpes simplex, Bacterial pneumonias
- Pneumocystis carinii (PCP)
- Toxoplasmosis, Cryptococcus, Esophageal candida, Histo, Kaposi’s
- Cytomegalovirus (CMV), Mycobacteria avium complex
Common Clinical Manifestations of Chronic HIV Infection

- Constitutional Symptoms
  - fever
  - weight loss/wasting
  - fatigue

- Organ/System Specific
  - virtually all organ systems can be affected

- Consider HIV testing for unexplained syndromes
Wasting

By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging
Skin Manifestations of HIV Infection
- Staphylococcus skin infections
- Seborrheic dermatitis
- Genital herpes simplex virus (HSV) – Severe chronic, non-healing perianal ulcerative HSV seen in late stage AIDS
- Human papilloma virus (HPV) infection (warts)
- Varicella Zoster Virus (VZV) (shingles)
Kaposi’s Sarcoma

By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging
Anal warts (Human Papilloma Virus)
Molluscum contagiosum
Case 2

- Mr John Dube, 42 yr old truck driver, presents to MOPD with a productive cough, pleuritic chest pain and fever for 3 days. Previously well with no past history of alcohol use or TB.
- Married, but admits to occasional casual sexual partners (if away from home for a long time). Inconsistent condom usage
- O/E: no weight loss, no lymphadenopathy, no thrush
- chest x-ray: lobar pneumonia
RML Lobar Pneumonia
Pneumococci with pus cells on sputum
Case 2

A 36 year old HIV positive man presents to OPD with:

- Increasing shortness of breath
- dry cough for 2 week.
- He doesn’t know his CD4 count, but he had shingles in 1999.
Case 2 Continued

- Vital signs
  - Cyanosed
  - Respiratory rate – 30 b/min
  - Pulse – 120/min
  - Temperature – 39°C
  - Oxygen saturation – 85% on room air
  - Oral thrush
  - Cervical adenopathy
  - Chest: clear
Case 2 Continued

Normal Chest X-ray

Diffuse ground glass opacification

PCP
Case 2 Continued

- What should be included in your differential?
  - Pneumocystis carini pneumonia?
  - TB?
  - Bacterial pneumonia?
  - Cryptococcus neoformans pneumonia?
  - Pulmonary Kaposi’s sarcoma?
Diagnosing PCP

- Difficult to do at most centers
- Gold standard: bronchoalveolar lavage
- Alternative: induced sputum
- Often diagnosis is presumptive based on xray and symptoms
  - Fever
  - Progressive exertional dyspnea
  - Cough – oftentimes non-productive
Evaluation of a hospitalised HIV + patient with CAP

Chest Radiograph

- Diffuse Infiltrate
  - Suspect PCP and consider TB
  - Investigate and treat for PCP
  - Response and resolution

- Focal Consolidation
  - Suspect usual bacterial pathogens
  - Investigate and treat for CAP
  - No response
  - Refer for special investigations
Pneumocystis pneumonia

Severe Infection
DUAL INFECTIONS (N = 11)

- TB = 9
- PCP = 4
- S. aureus = 2
- C. albicans = 1
- CMV = 1
- H. influenzae = 1

- Other pairs
  - PCP + CMV
  - S. aureus + HSV 1

- Triple Infections (n=3)
Treating PCP

- Start treatment empirically
- Preferred Treatment
  - Bactrim 15/75 mg/kg/day i.v. or p.o. for 21 days
  - Prednisone: If pO2 <70 mmHg or A-a gradient >35 mm Hg
  - Oxygen to maintain O₂ saturation
Preventing PCP

- Cotrimoxazole SS  2 tablets per day

- Prevention
  - **Indication**:  $\text{CD}_4 < 200$ or WHO clinical 2/3/4
  - **When to stop**:  $\text{CD}_4 > 200$ for $\geq 3$ mo
  - **When to restart**:  $\text{CD}_4$ falls to $< 200$
A 55 y.o. woman presents to the emergency department in a post ictal state. Her daughter says that she witnessed her mother have what she described as a generalized seizure.

- Vitals – arousable but not alert
  - BP 150/90
  - Respiratory Rate 12
  - Temperature 34°C
Case 2 Continued

You admit her and obtain a CT scan the next day
Case 2 Continued

- What would you include your differential?
  - Tuberculoma?
  - Toxoplasmosis?
  - Primary central nervous system lymphoma?
  - Cryptococcoma?
Toxoplasmosis

- Usually limited to patients with CD4 counts <100
- Symptoms
  - Focal neurological deficits
  - Seizure
  - Fever
  - Headache
  - Altered mental status
- Typical radiological findings
  - Multiple ring enhancing lesions
Toxoplasmosis

- **Treatment**
  - Bactrim: 10/50 mg/kg/d orally for 30 days
  - **Primary Prophylaxis** (No previous episode of toxoplasmosis)
    - Cotrimoxazole 2 SS per day when CD4 < 100
    - Can discontinue when CD4 > 200 for ≥ 3 months
  - **Secondary Prophylaxis** (previous episode of toxoplasmosis)
    - CD4 count > 200 for > 6 months and completed initial toxoplasmosis therapy and is asymptomatic
Other CNS Lesions

Primary CNS lymphoma with enhanced lesion and slight mass effect
Other CNS Lesions

Tuberculomas visualized as small, ring enhancing lesions
Patient Presentation

- 26 year old male with Class C3 AIDS (history of cryptococcal meningitis and CD4+ T-cell count 40 presents with non-healing anal ulcer

- On examination:
Non-healing anal ulcer in a patient with AIDS

- What is the differential?
- How would you assess the patient?
Patient Presentation

- Ulcer is swabbed for HSV culture and DFA.
- Patient is treated empirically for anal herpes with acyclovir 400 mg three times daily.
- Results return positive for HSV-2 by DFA and culture.
- Ulcer resolves after 4 weeks.
Case 3

A 20 year old man presents to your HIV clinic.

He was diagnosed positive 3 years ago and his CD4 count at that time was 450.

He has been lost to follow-up. Now he presents to resume his care.
By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging
Case 3

On exam you discover the following:

What is this?
Is this the same infection?

No, it’s oral hairy leukoplakia
Treating Candidiasis

- Oral thrush – clotrimazole troches 5 times per day for 14 days
- Oesophageal thrush – fluconazole 200 mg/day for 10-14 days
- Vaginal: Miconazole 200mg vaginal suppositories or oral fluconazole 150 mg (one dose only)
Case 4

- A 37 year old man presents with intense, burning pain on his shoulder. The pain began two days prior.

- Clinical examination reveals:
On exam you find:

Case 4
Case 4

- What is it? Herpes Zoster
- Should you treat it? Maybe
- Why? Helps healing and helps post herpetic neuralgia
- How? Acyclovir
Complications of HZ Infection

- Post-herpetic neuralgia
- Aseptic Meningitis
- Encephalitis
- Bacterial skin infections
- Herpes zoster ophthalmicus
- Retinal necrosis
- Herpes zoster oticus
Case 5

A 26 year old woman presents to OPD with headache and “just not feeling well” for 1 week. When her mother leaves the room she tells you that she is HIV positive.

On exam she has no neurological deficits.
What do you think is wrong?

- Just a headache?
- CNS lesion?
- Meningitis?
- Something else?
Symptoms of Cryptococcal Meningitis

- Most Common
  - Fever
  - Headache
  - Malaise

- Less Common
  - Altered Mental Status
  - Stiff neck
  - Vomiting

- Usually subacute onset
Diagnosis

- Lumbar puncture
  - Obtaining an opening pressure is key!!!
    - Usually markedly elevated
    - >20 cmH\(_2\)O on the initial tap
  - India ink preparation to visualize organisms and/or measurement of cryptococcal antigen
  - Culture is definitive
  - WBC typically low with mononuclear predominance (<50/microliter)
  - Total protein and glucose only slightly abnormal
Recommended Treatment

- **Initial Therapy**
  - Amphotericin B 0.7 mg/kg/day (starting dose) for 14 days
  - Fluconazole 800 mg stat, then 400mg/day for 8-10 weeks

- **Follow-up**
  - Fluconazole 400 mg/day for 8 weeks

- **Maintenance**
  - Fluconazole 200 mg/day lifelong (if not on ARVs)
  - Fluconazole 200 mg/day until immune reconstitution occurs (CD4 >100-200 for >6 months)
Management of Intracranial Hypertension

- Majority of the deaths in studies were associated with increased intracranial pressure, likely reflecting cerebral edema

- Repeat lumbar puncture with any sign of increased pressure
  - Headache
  - Altered mental status (may be slight)
What is This?
Severe Kaposi’s Sarcoma
Kaposi’s Sarcoma

- Most common tumor in HIV infection
- Etiologic factor – human herpes virus 8
- Many manifestations
  - Skin lesions
  - Oral lesions
  - Gastrointestinal tract involvement
  - Pulmonary involvement
Treatment for Kaposi’s Sarcoma

- Cured by antiretroviral therapy in many cases

- Local therapy (i.e. Topical retinoic acid and radiation) for extensive dermatologic disease

- Interferon alpha and chemotherapy for patients with widespread disease
Case 7

A 47 y.o. woman presents to the clinic with fever, night sweats, and overwhelming fatigue.

She is HIV positive with a CD4 count of 45.

Her symptoms have been present for approximately 2 weeks.
Case 7 Continued

- On exam the patient has an enlarged liver
- Lab studies reveal a hemoglobin of 5 and leukopenia
- Thinking that the patient’s constitutional symptoms indicate TB you send sputum for AFB
- They are negative X 2

*What is wrong with this patient?*
Case 7 Continued

- Disseminated Mycobacterium Avium Complex (MAC)
  - Usually limited to patients with CD4 counts less than 50
  - Often presents with non-specific symptoms
  - Enlargement of the liver, spleen and abdominal lymph nodes are common
  - Anemia, neutropenia, and thrombocytopenia are also common with bone marrow involvement
Diagnosis of MAC

- Culture of organism
  - Blood
  - Lymph node
  - Bone marrow
Treatment of MAC Infection

- Formulary limitations may limit intervention
- Preferred therapy
  - Clarithromycin 500 mg po bid and ethambutol 15 mg/kg/day for 12 months
- Alternative
  - Azithromycin 600 mg/day and ethambutol 15 mg/kg/day (may add rifabutin 300 mg per day)
Conclusion
Acknowledgements

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  - Dr Stephen Tabet
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Oral Manifestations of
HIV/AIDS
Candida angular chelitis
Oral Hairy Leukoplakia

- Epstein-Barr virus (EBV) induced benign epithelial thickening
Aphthous ulcers in HIV-infected patient
Oral warts (HPV) in patient (CD4 lymphocyte count 120)
Case 6

- A 17 year old woman presents to clinic for pre-ARV screening
- The medical officer does all of the following:
  - Discusses adherence and disclosure
  - Performs baseline blood tests (i.e. FBC, U&E, screen for syphilis)
  - Screens for TB
  - Discusses antiretroviral therapy in detail

*What did they forget to do?*
Importance of the Pap Smear

- Significantly increased risk for *invasive cervical cancer* in HIV positive women
  - Added to CDC list of AIDS defining conditions in 1993
  - Higher incidence of all stages of cervical intraepithelial neoplasia (CIN)
  - Faster progression to invasive disease
  - Most frequent cause of cancer in women with HIV in many developing countries
Screening

- Recommended screening
  - Perform baseline Pap smear
  - If normal, then repeat yearly
  - If low grade abnormalities, repeat after 6 months
  - If high grade squamous intraepithelial lesion or invasive cancer is reported by pathology, then refer immediately to GYN for colposcopy, biopsy and treatment