# Natural History of HIV Infection

Dr Farida Amod

KZN Provincial ARV Training

NRM School of Medicine

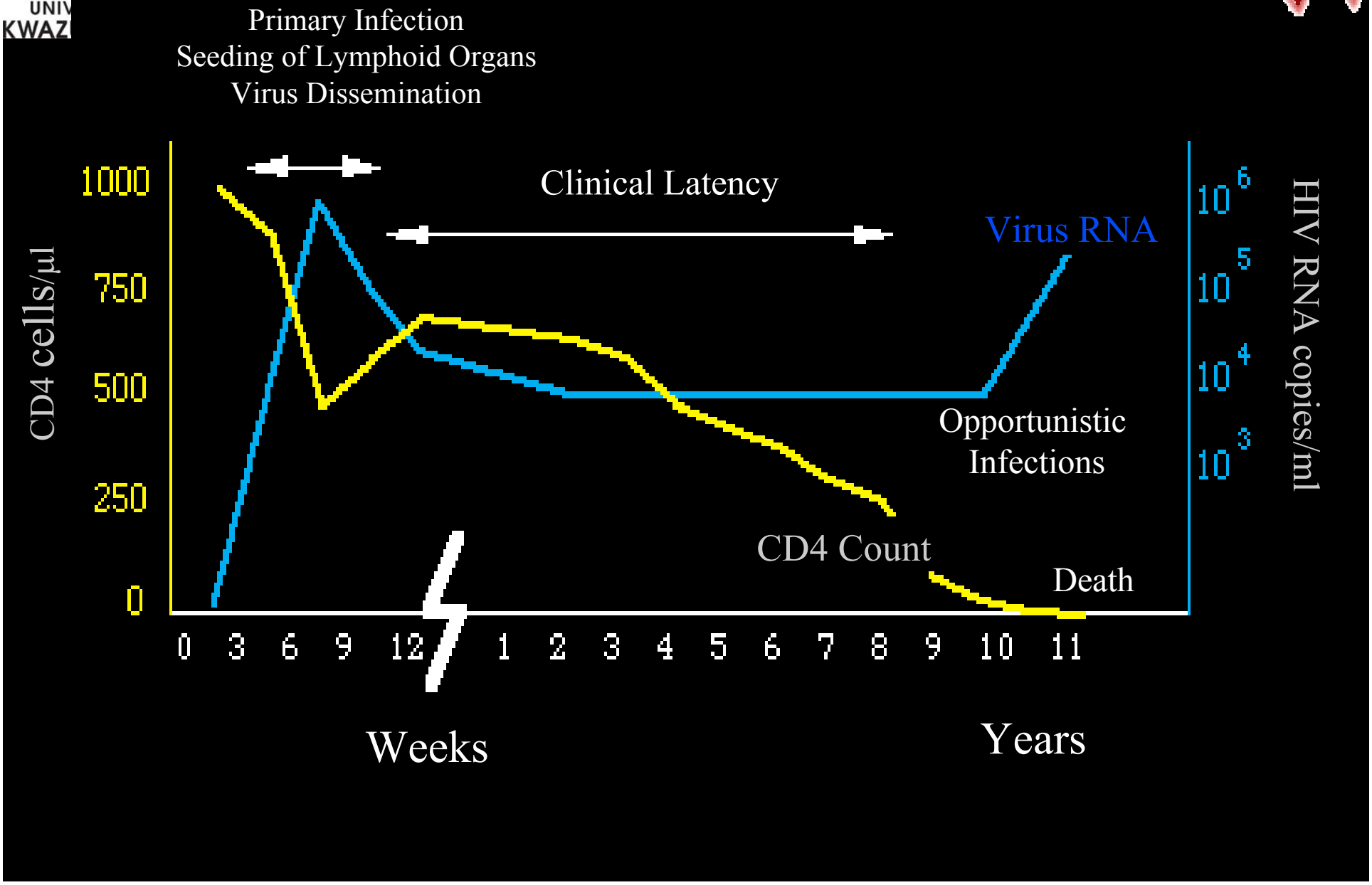
University of Kwa-Zulu Natal

UNIVERSITY OF KWAZULU-NATAL

# 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



UNIVERSITY OF KWAZULU-NATAL

# 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

↓

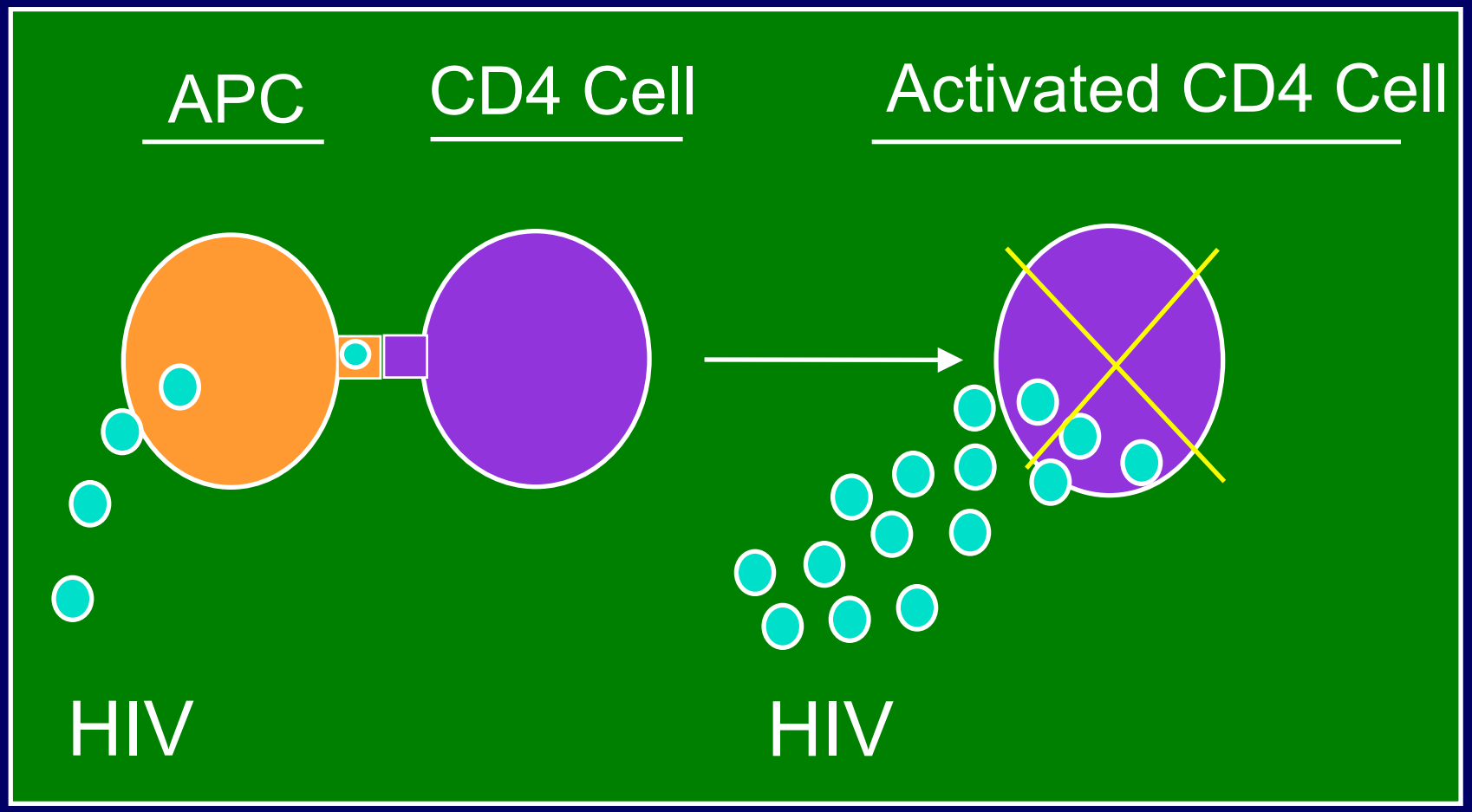
There is widespread systemic dissemination to the brain, spleen, distant lymph nodes, etc ( 5-11 days )

UNIVERSITY OF KWAZULU-NATAL

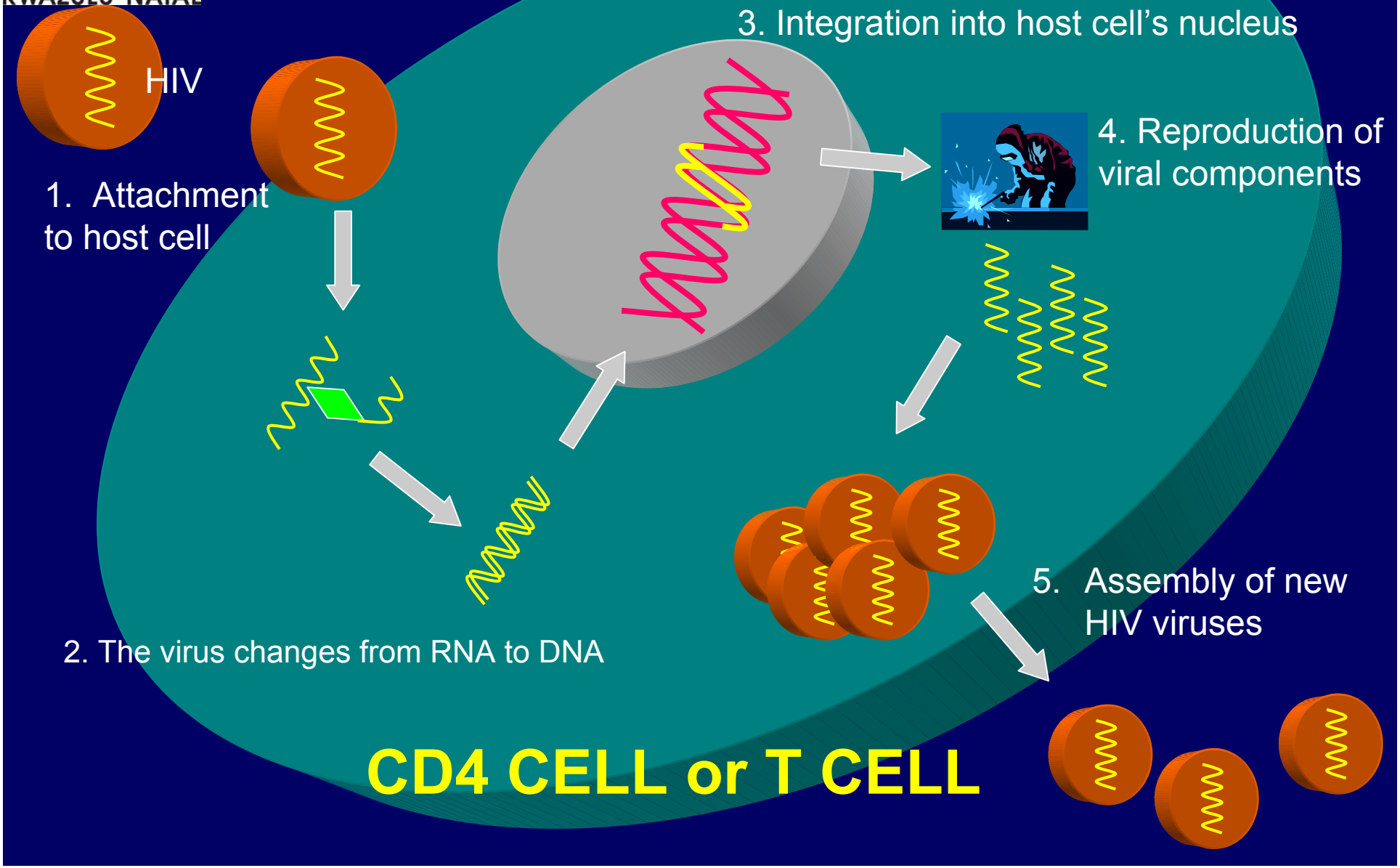
# Pathogenesis Continued…

- 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

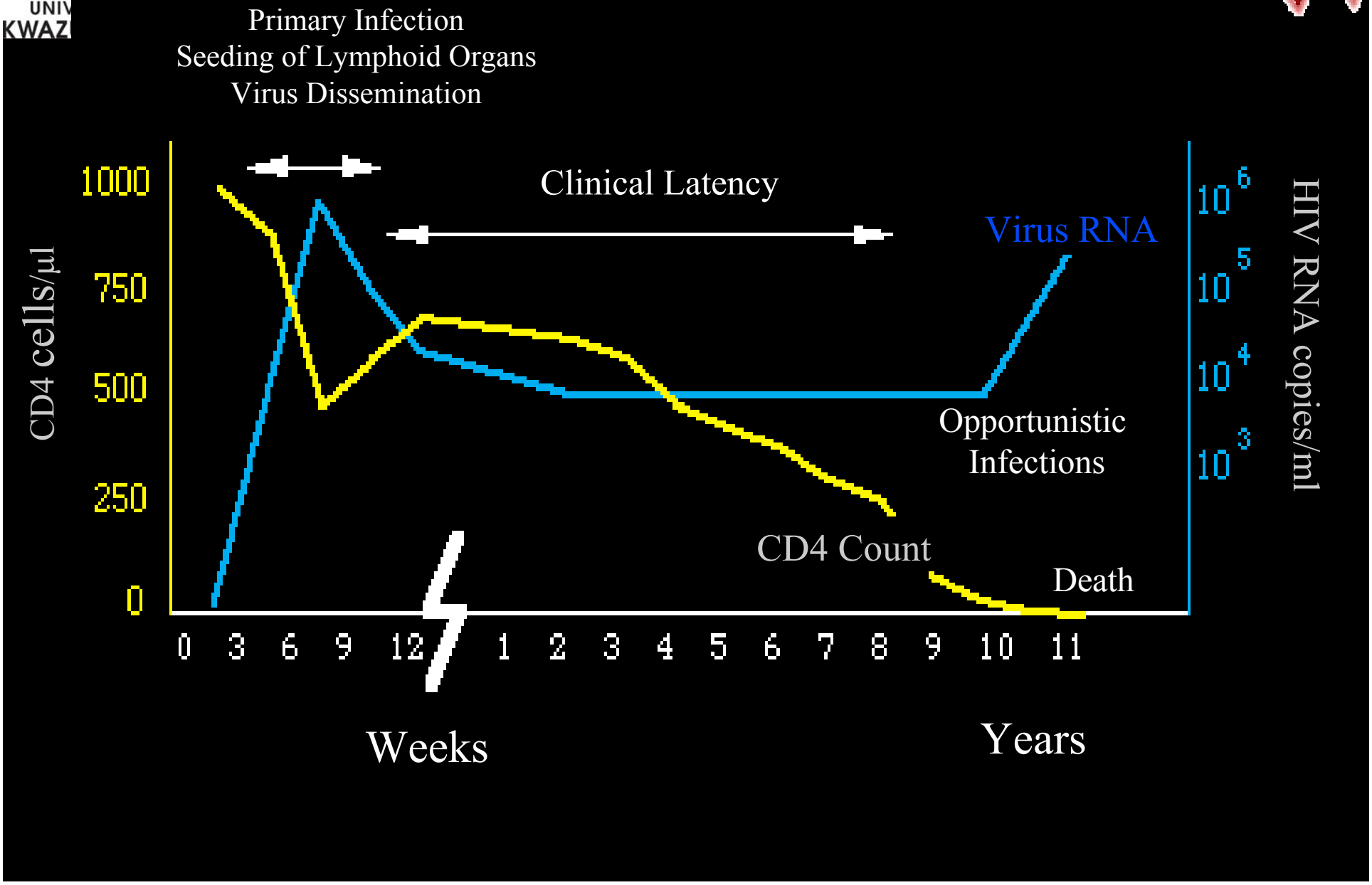
# From Antigen-Presenting Cell to CD4 Cell Destruction



# How Does HIV Work?



# Course of HIV Infection



UNIVERSITY OF KWAZULU-NATAL


# 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

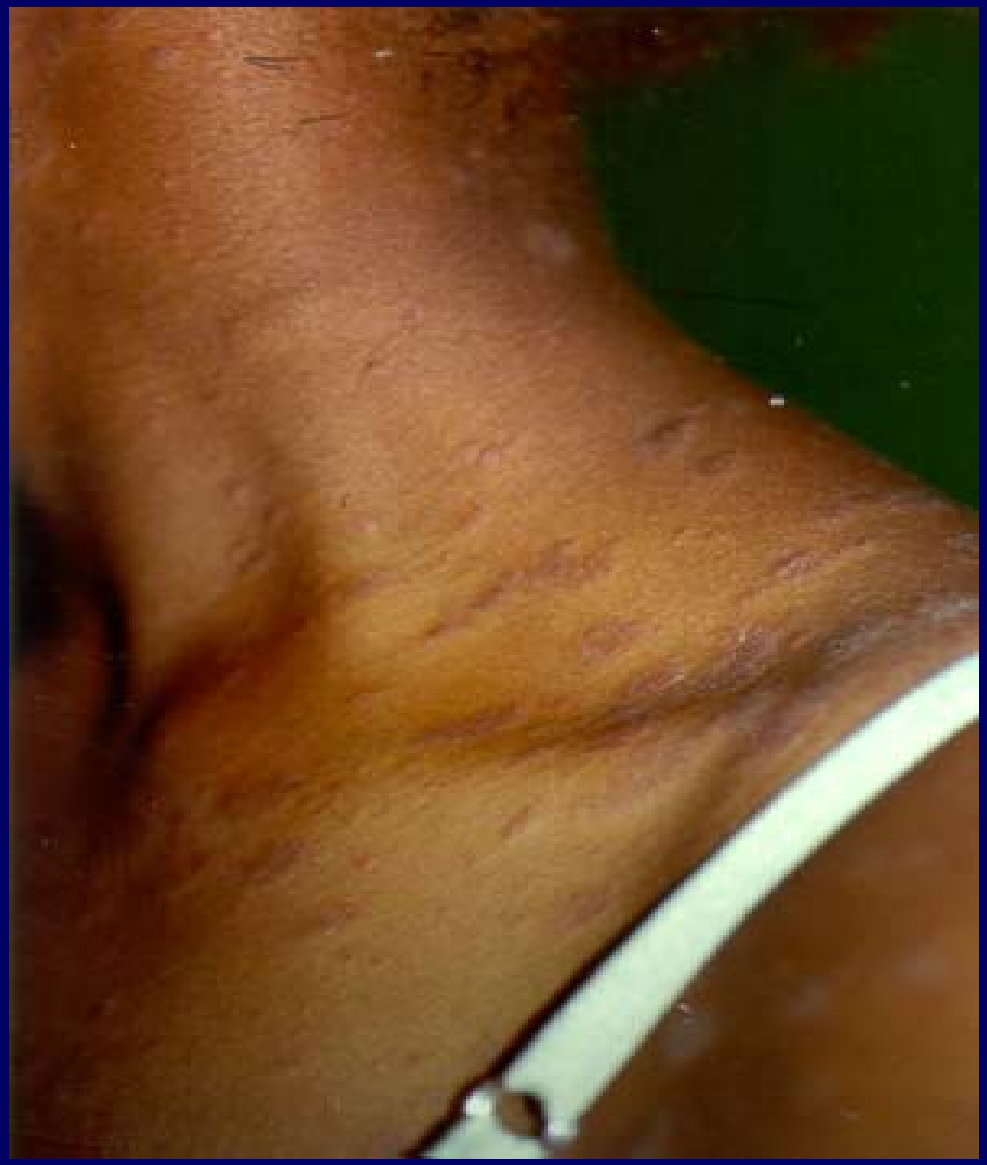
# Epidemiology of Primary HIV Infection

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

Joint United Nations Programme on AIDS. AIDS epidemic update: December, 2001. Geneva: UNAIDS;2001:1-36.

# 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- 1year 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$^0$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

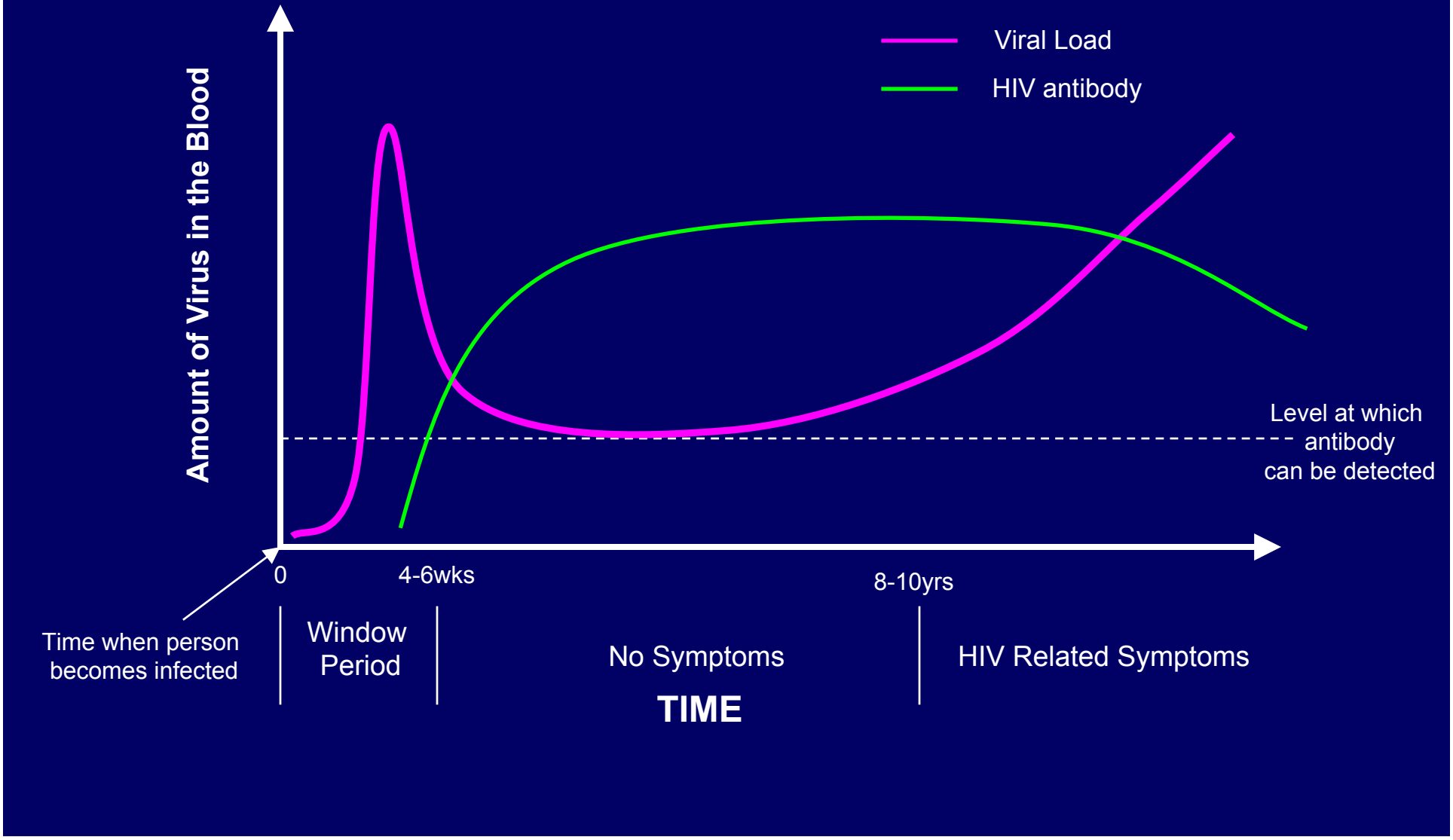
Is there anything else that you would consider in DD?

**Acute retroviral syndrome**

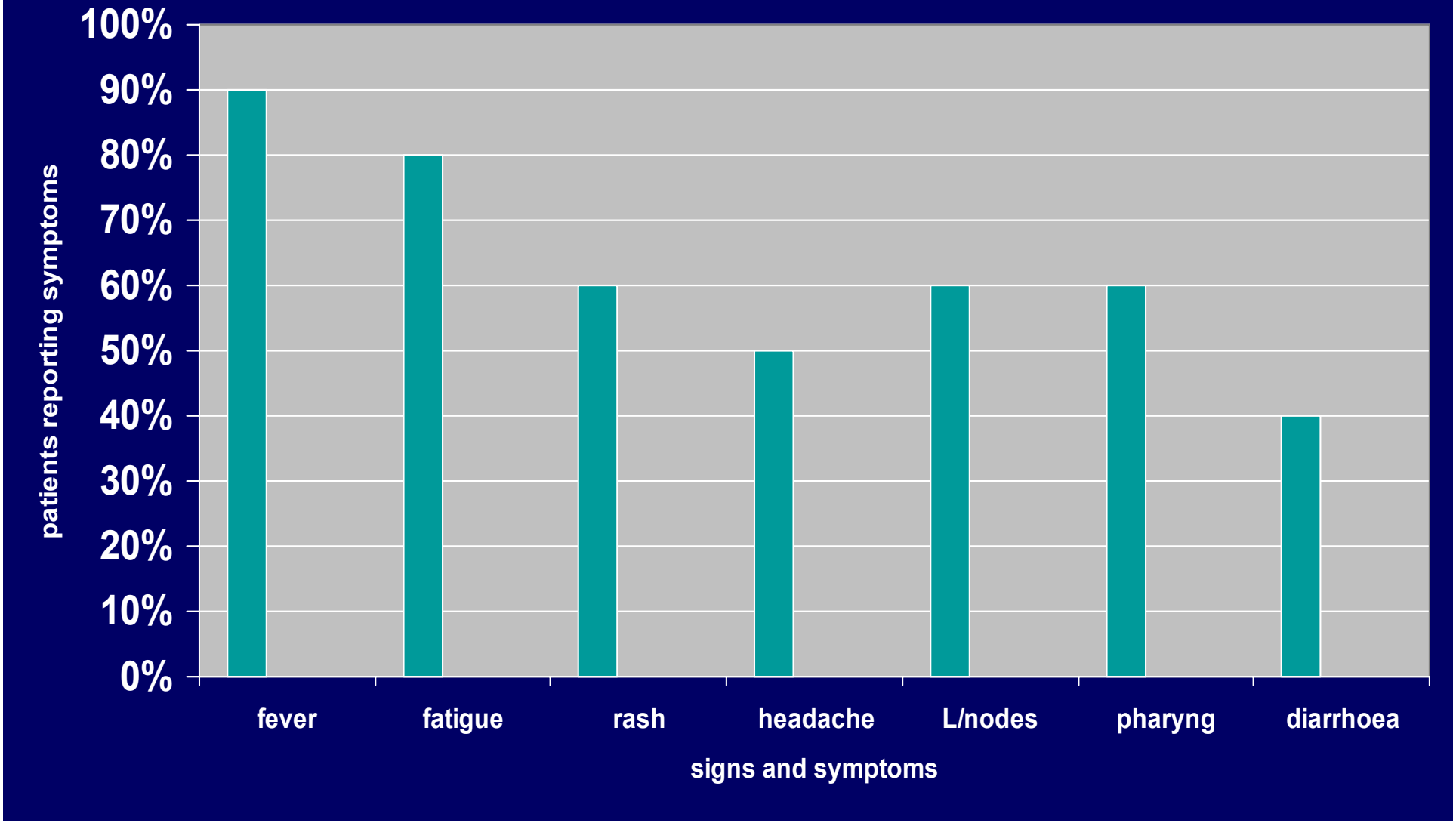
- The HIV-1 Elisa test done is NEGATIVE
- Need to either:
  - Repeat the test in one month.
  - P24 antigen test or
  - Quantitative or qualitative viral assays –useful for early diagnosis, but not widely available in KZN.
- You decide to repeat the HIV-1 Elisa test in 1 month:
- Result is now POSITIVE

UNIVERSITY OF KWAZULU-NATAL

# Testing for HIV Infection



# Symptoms and Signs of ARS



# 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?***

UNIVERSITY OF KWAZULU-NATAL

# Feasible Interventions

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

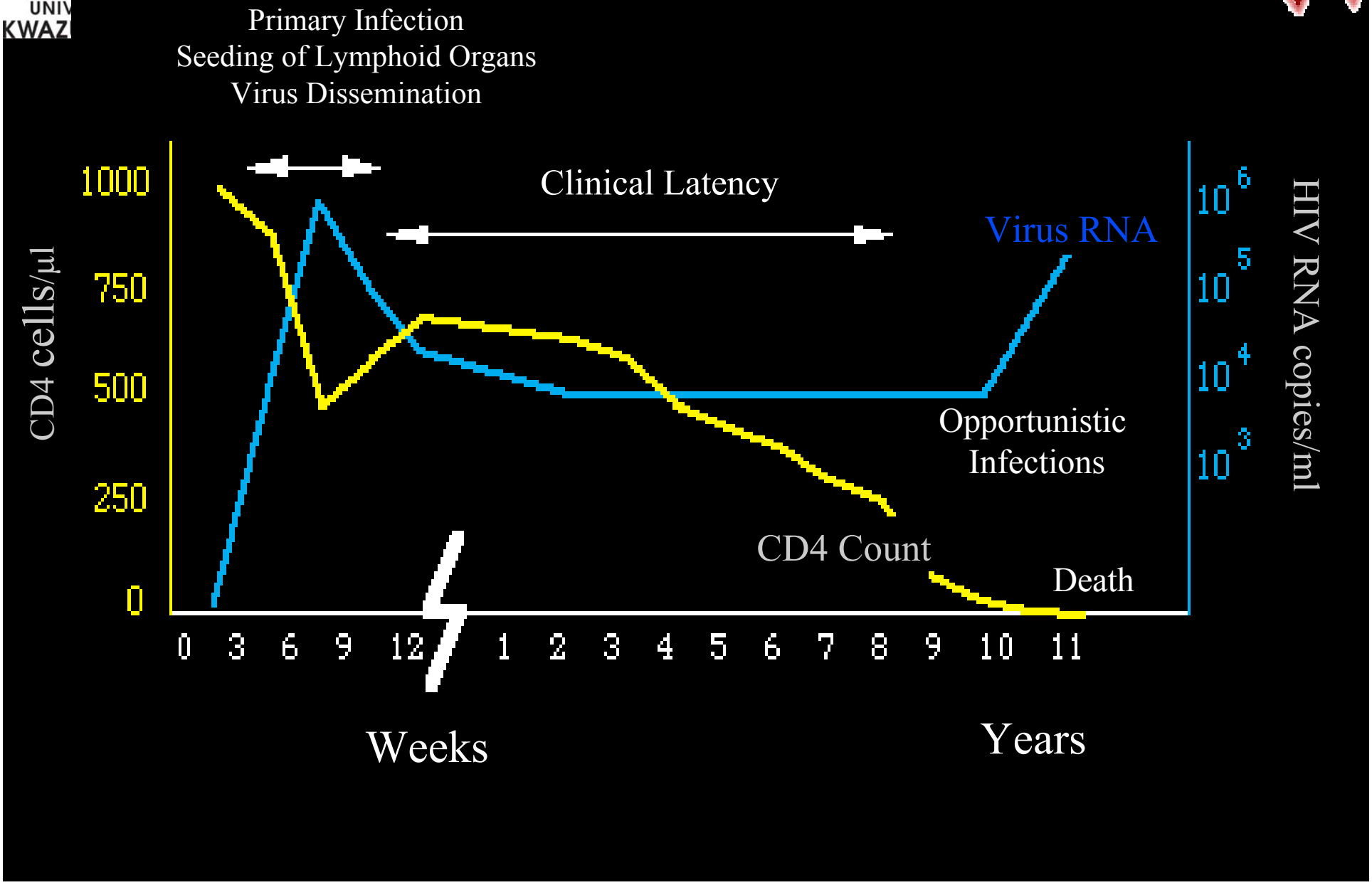
UNIVERSITY OF KWAZULU-NATAL


# Chronic HIV Infection

Natural History

Clinical Manifestations

# Course of HIV Infection

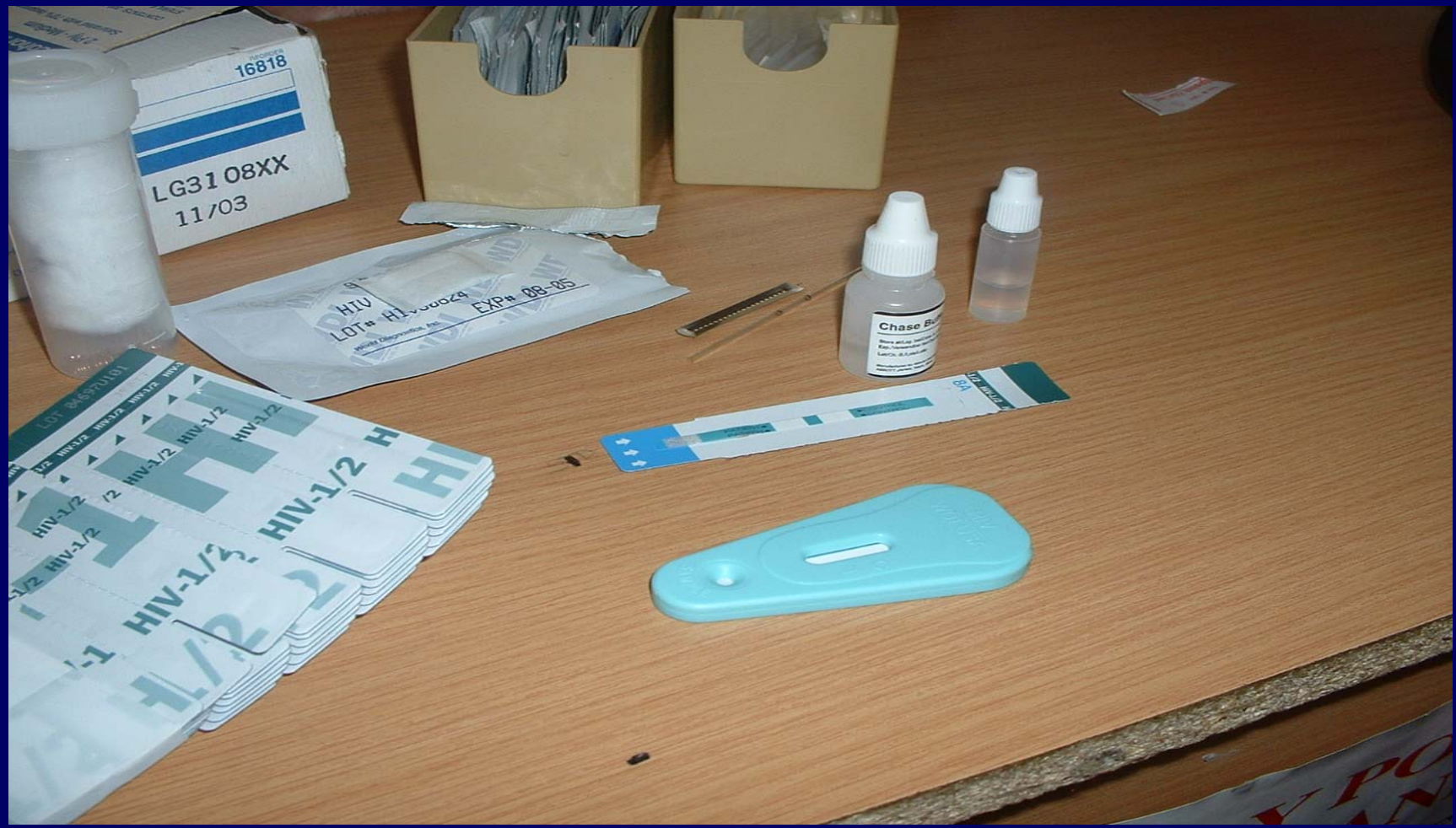


# Diagnosis of Chronic HIV Infection

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

UNIVERSITY OF KWAZULU-NATAL

# Diagnosis



UNIVERSITY OF KWAZULU-NATAL

# Real Time testing at a HIV Clinic

UNIVERSITY OF KWAZULU-NATAL

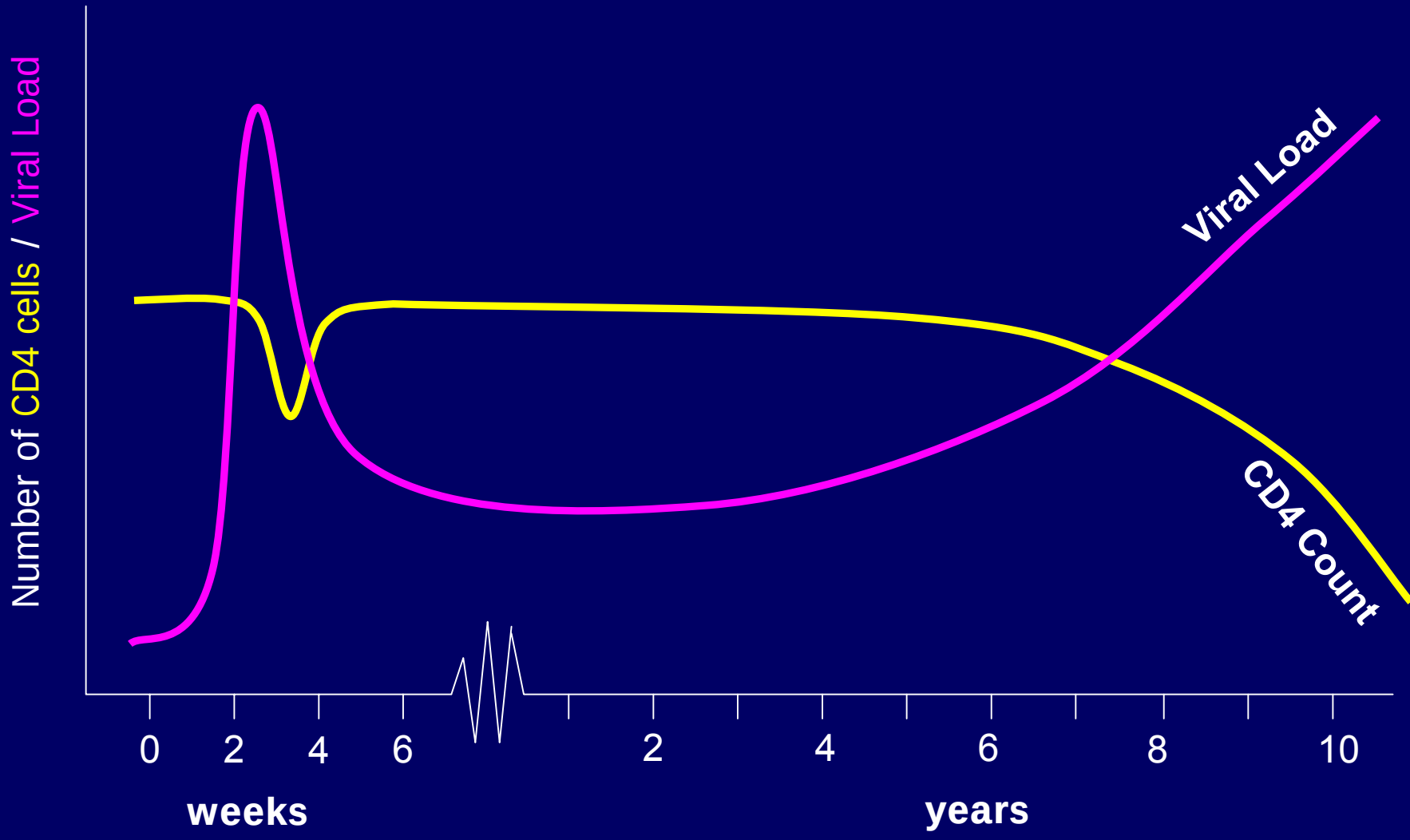

# Diagnosis

- 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

UNIVERSITY OF KWAZULU-NATAL


# Laboratory Monitoring of Chronic HIV Infection

# Natural History of HIV Infection

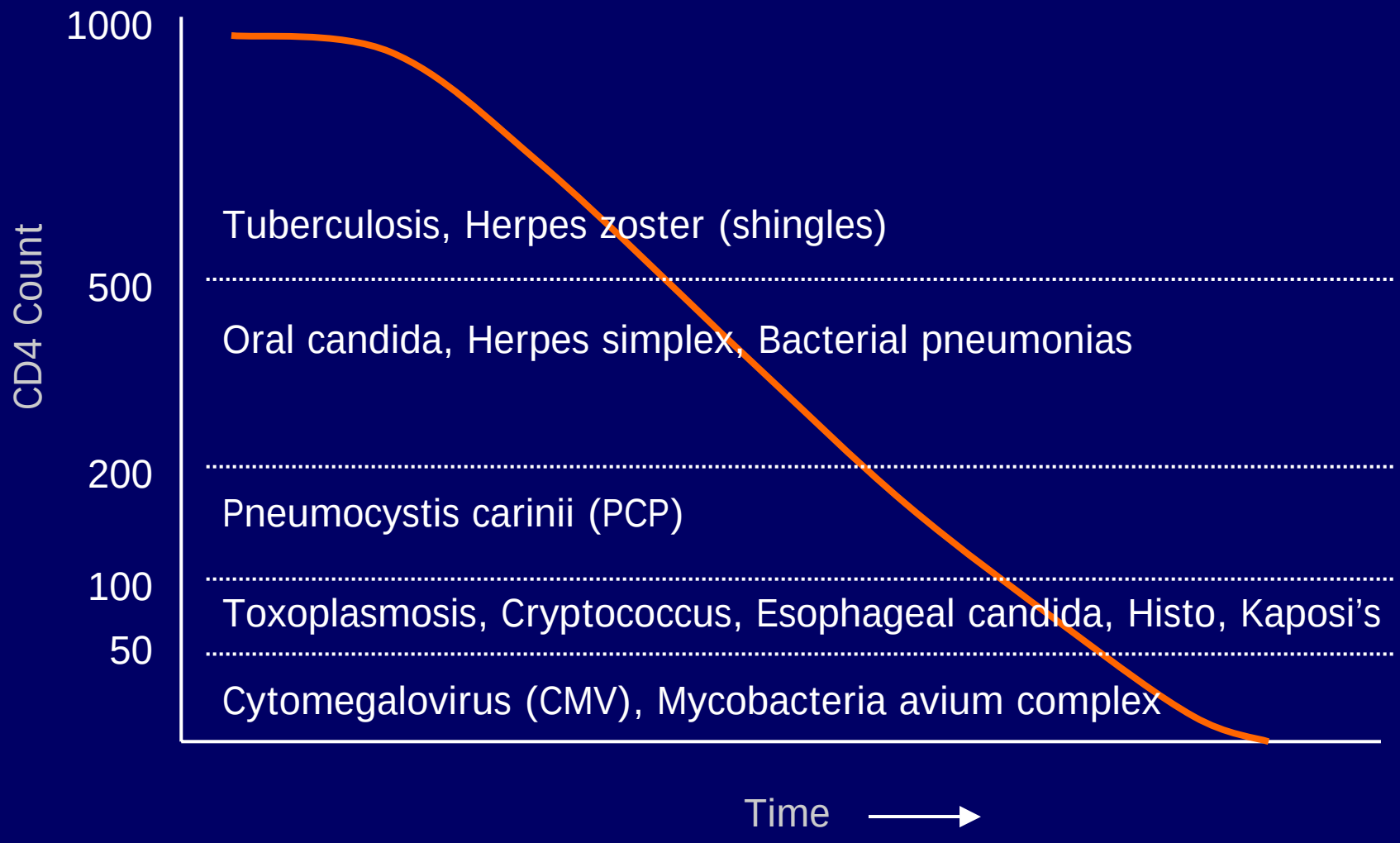


# CD4 count and HIV RNA

- 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

UNIVERSITY OF KWAZULU-NATAL

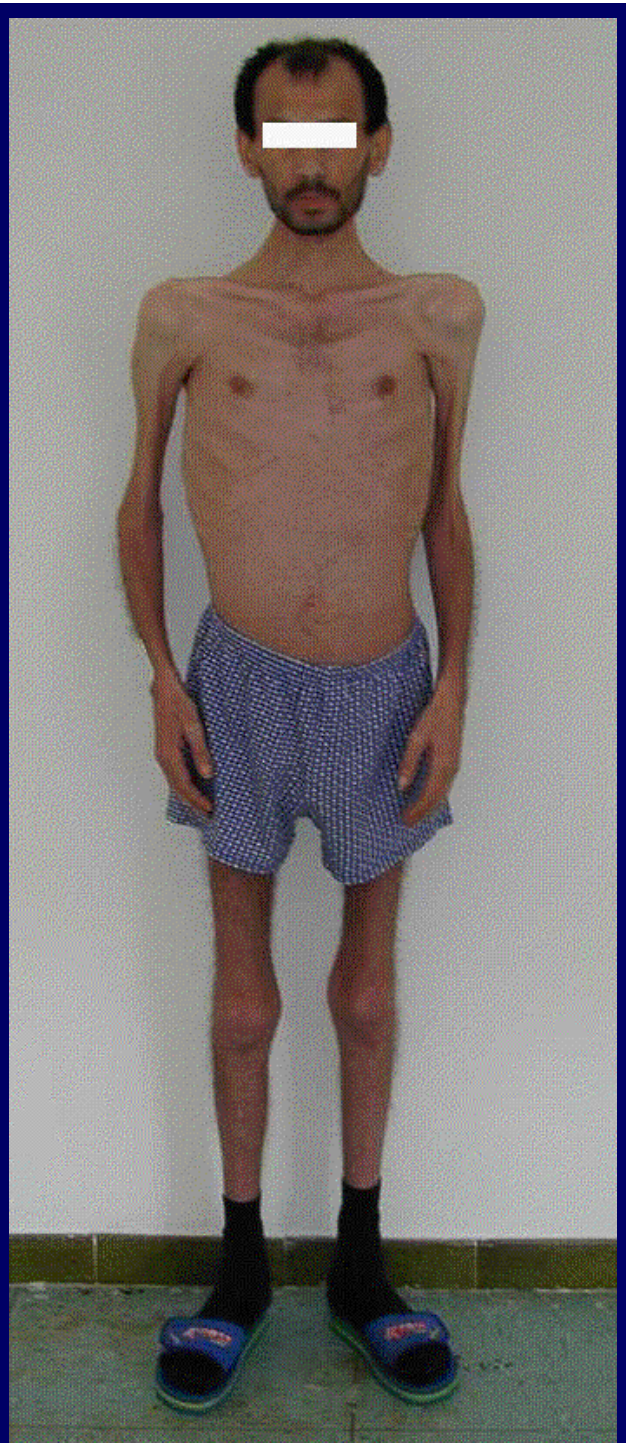
# CD4 Count and OIs



# 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

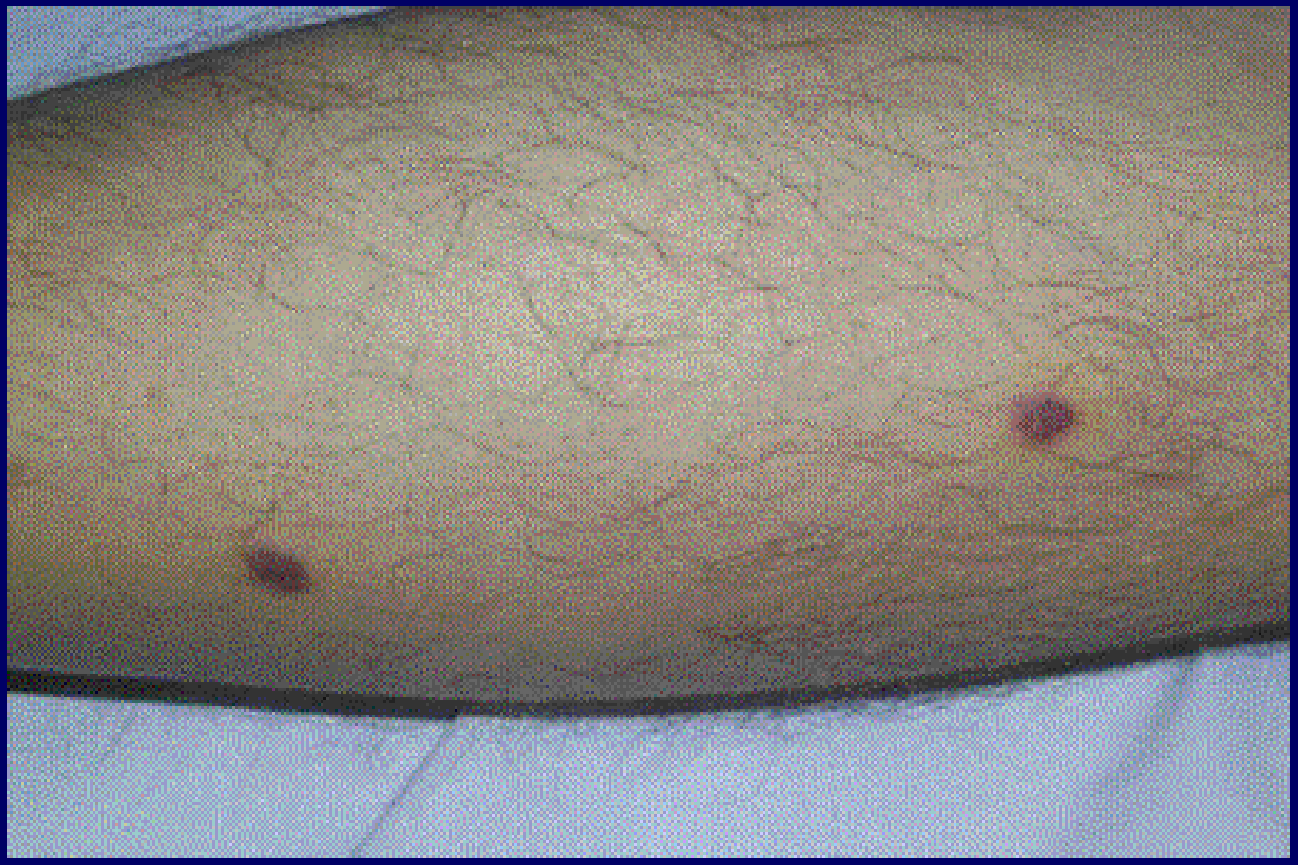
UNIVERSITY OF KWAZULU-NATAL


# Skin Manifestations of HIV Infection

UNIVERSITY OF KWAZULU-NATAL

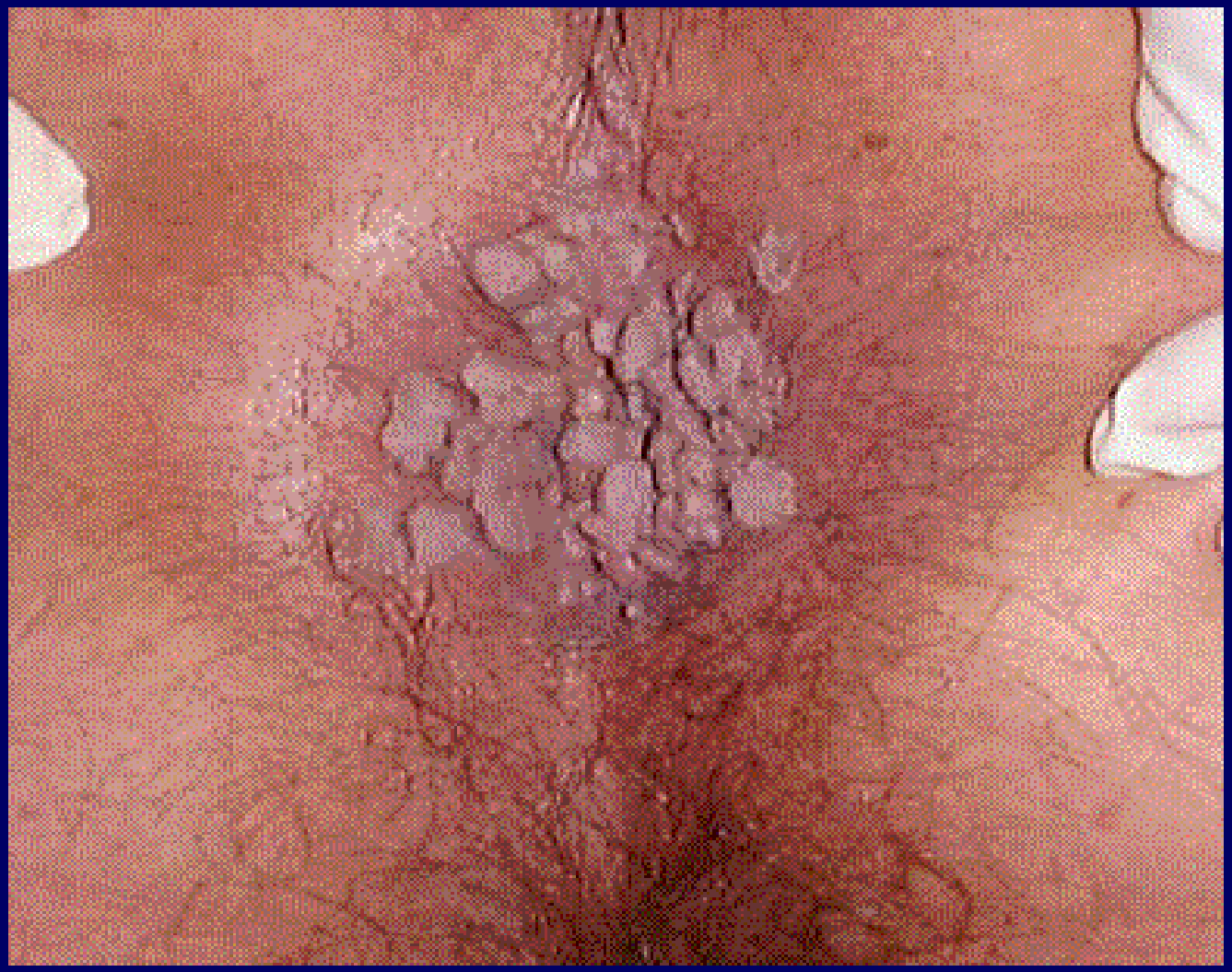
- Staphylococcus skin infections
- Seborrheic dermatitis
- Genital herpes simplex virus (HSV) – Severe chronic, non-healing perianal ulcerative HSV seen in late stage AIDS
- Human papilloma virus (HPV) infection (warts)
- Varicella Zoster Virus (VZV) (shingles)

# Kaposi's Sarcoma



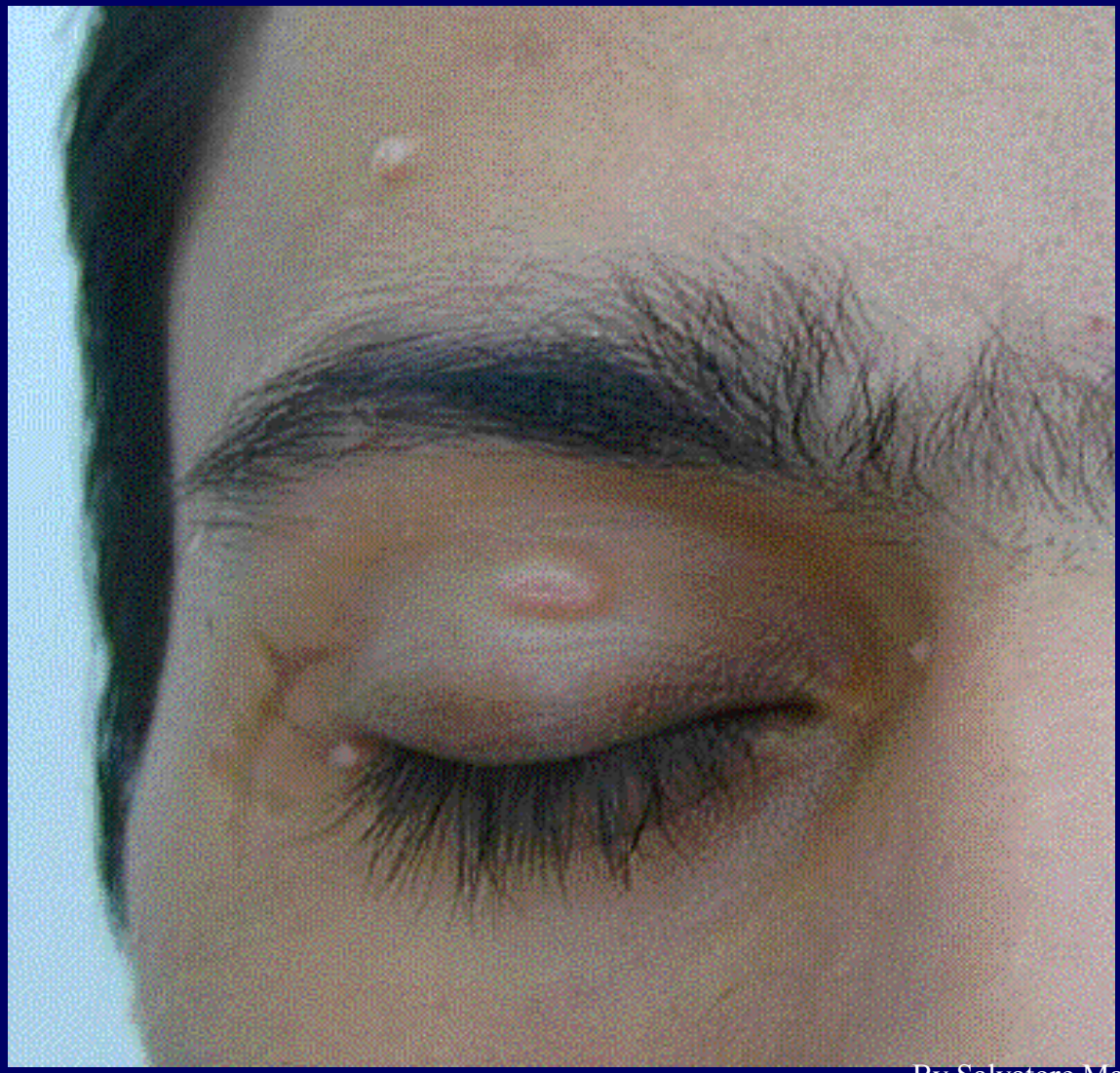
By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging

# Anal warts (Human Papilloma Virus)



By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging

# Molluscum contagiosum



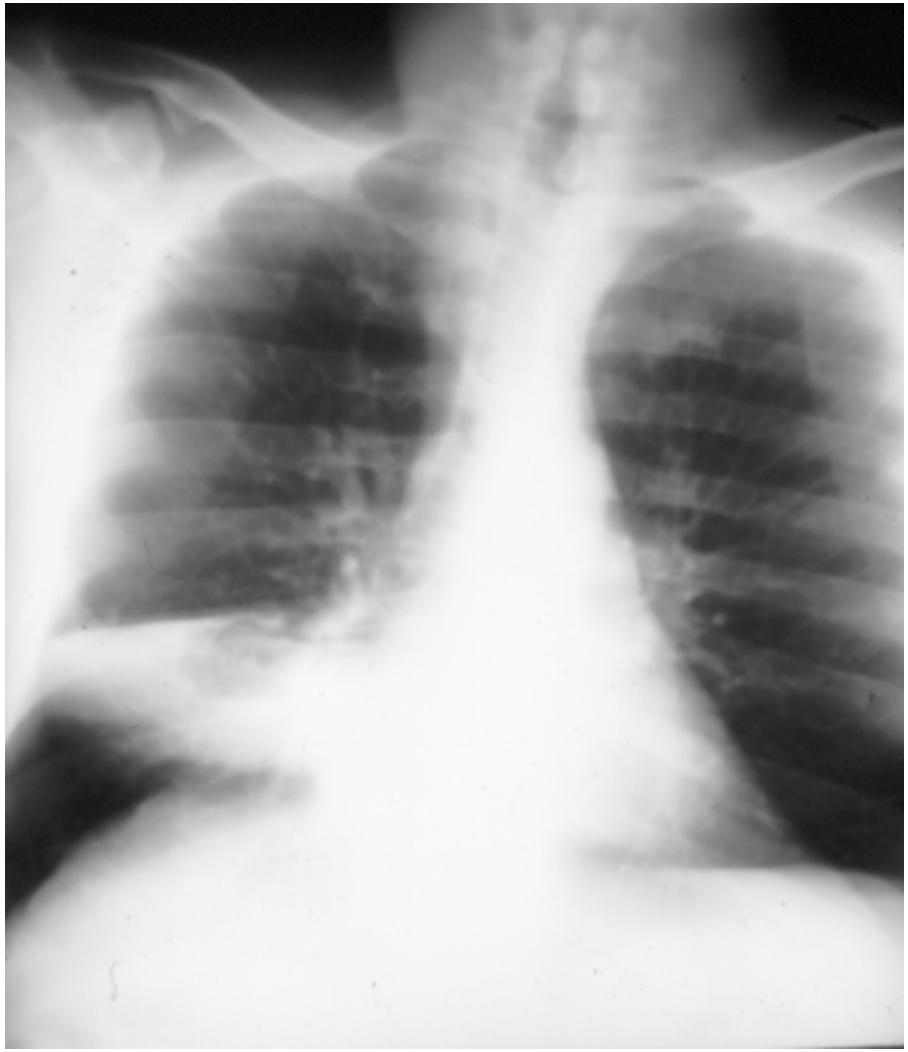
By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging

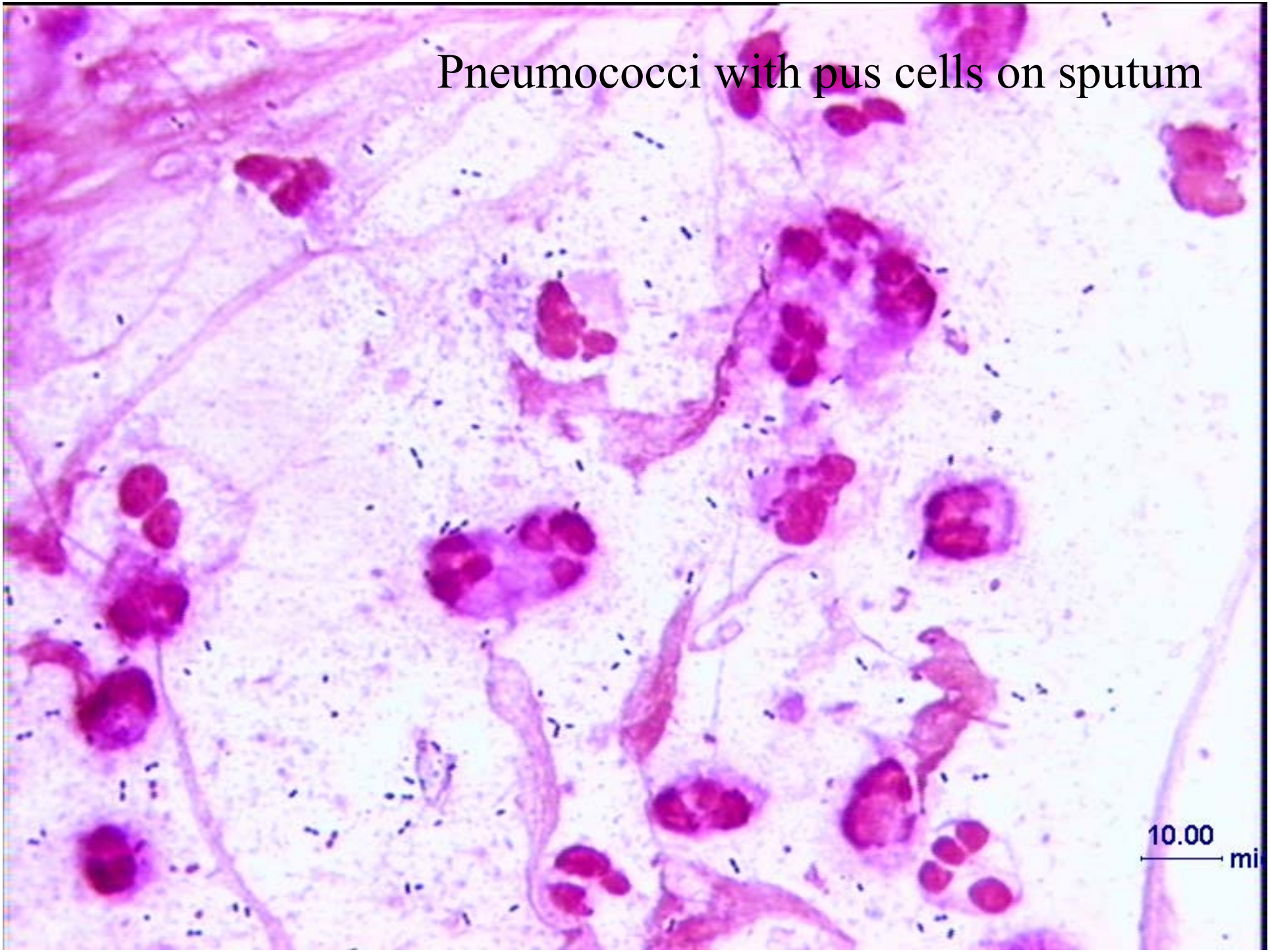
# Case 2

- 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
10.00

# Case 2

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

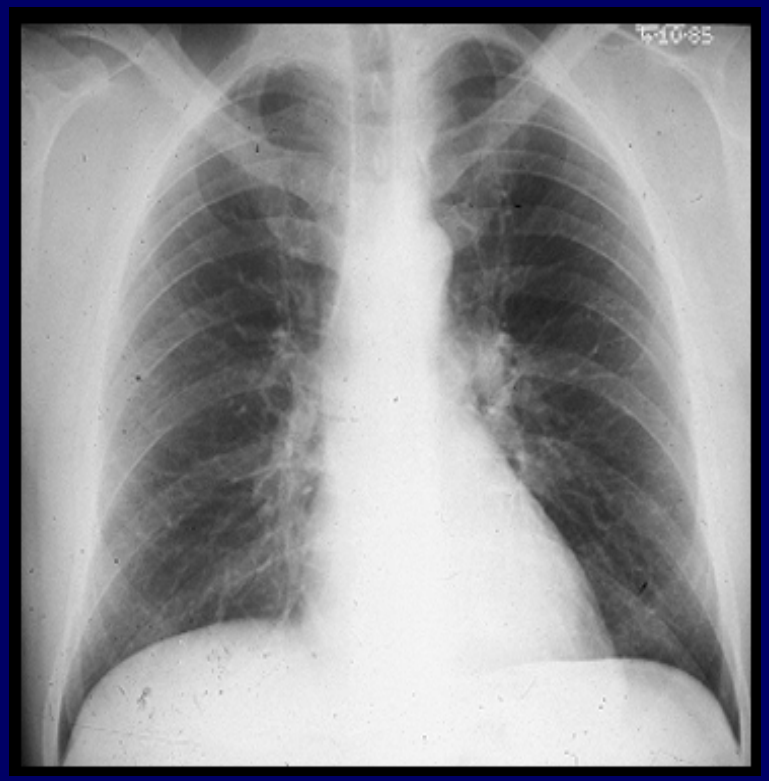
- Increasing shortness of breath
- dry cough for 2 week.
- He doesn't know his CD4 count, but he had shingles in 1999.

# Case 2 Continued

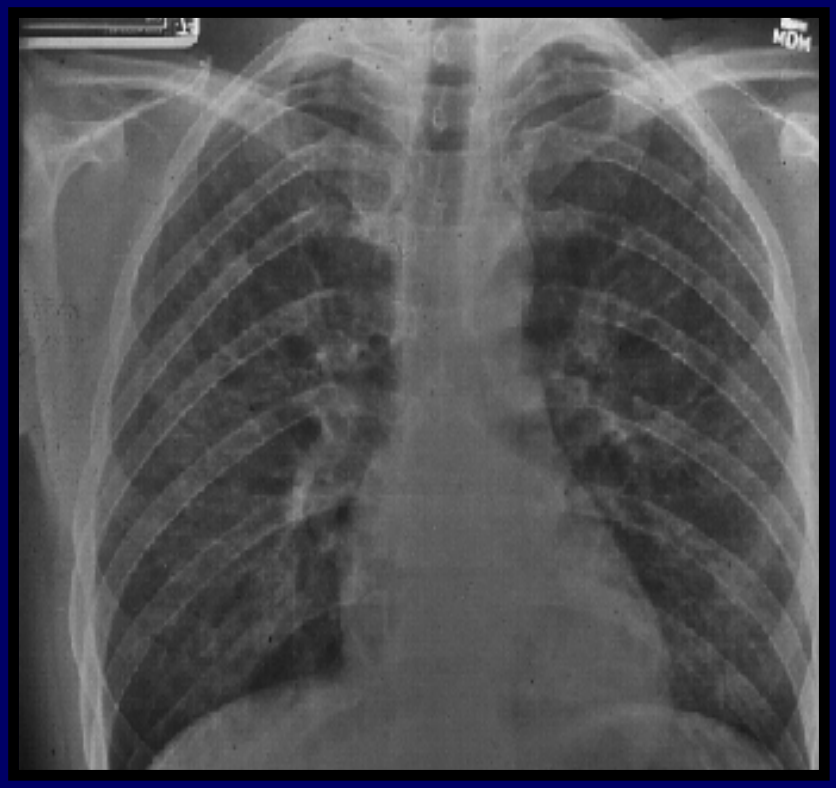
- Vital signs
  - Cyanosed
  - Respiratory rate – 30 b/min
  - Pulse – 120/min
  - Temperature – 39C
  - Oxygen saturation – 85% on room air
  - Oral thrush
  - Cervical adenopathy
  - Chest: clear

# Case 2 Continued

PCP



Normal Chest X-ray



**Diffuse ground glass opacification**

UNIVERSITY OF KWAZULU-NATAL

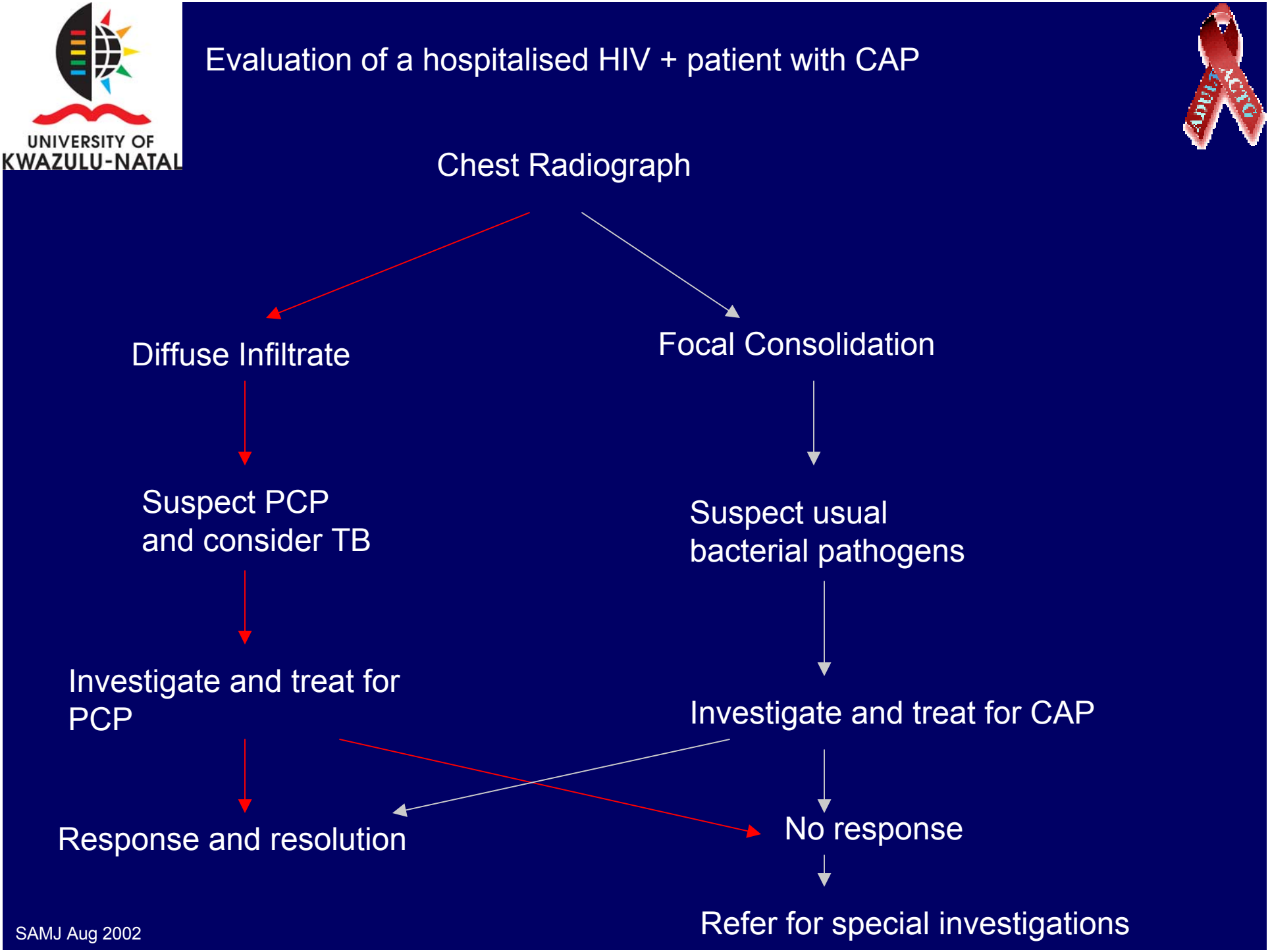
# Case 2 Continued

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

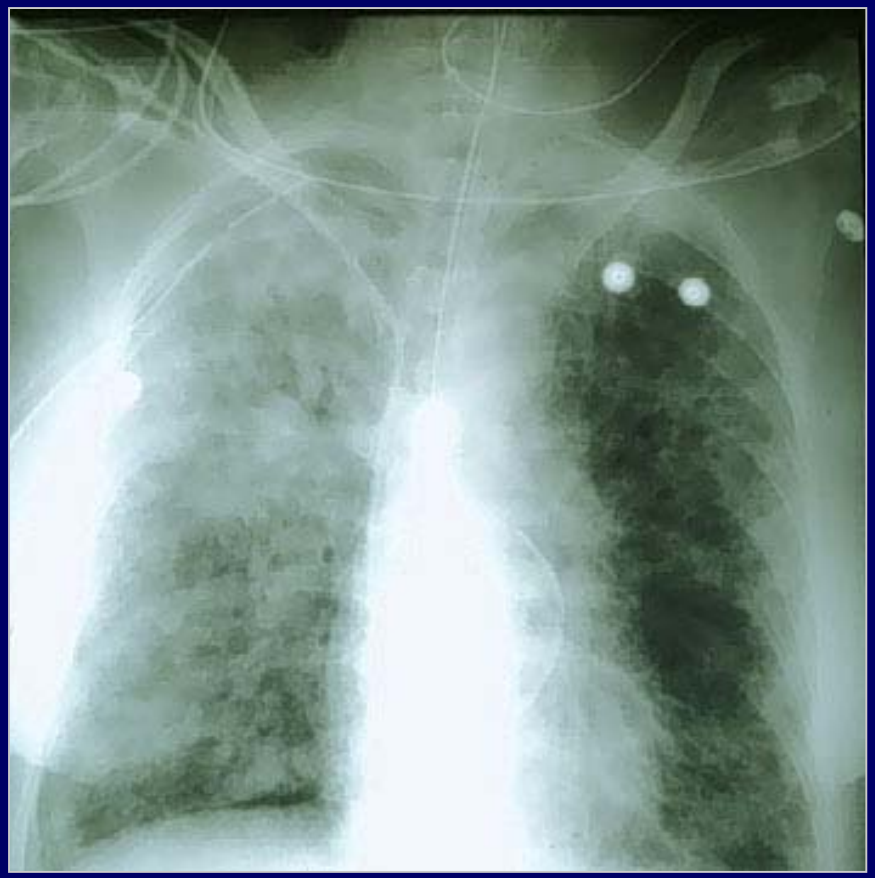
UNIVERSITY OF KWAZULU-NATAL

# 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

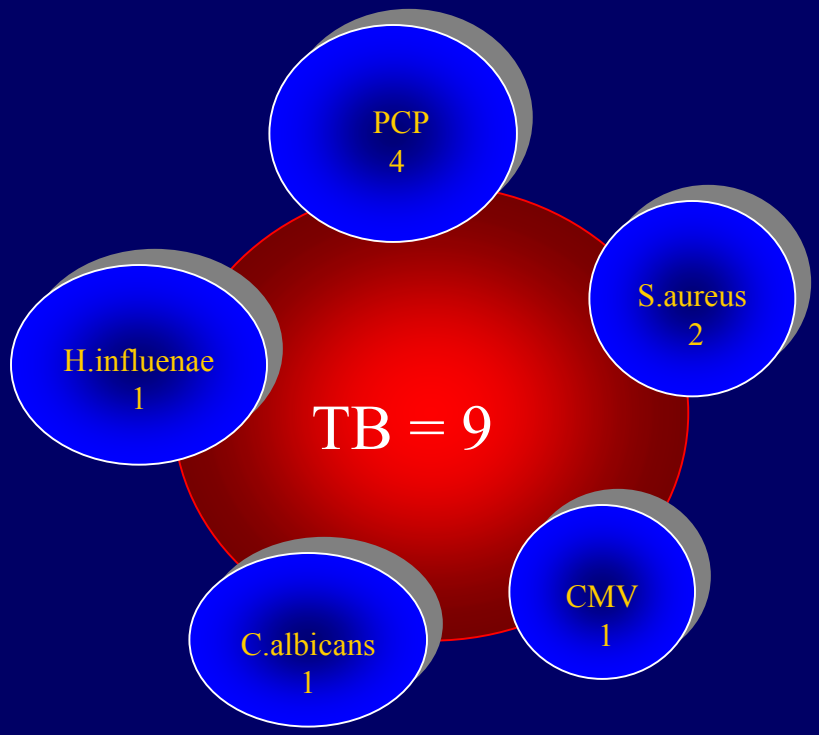

Evaluation of a hospitalised HIV + patient with CAP
Chest Radiograph
Diffuse Infiltrate
Focal Consolidation
Suspect PCP
and consider TB
Suspect usual
bacterial pathogens
Investigate and treat for
PCP
Investigate and treat for CAP
Response and resolution
No response
Refer for special investigations
SAMJ Aug 2002

# Pneumocystis pneumonia



Severe Infection

# DUAL INFECTIONS (N = 11 )




- Other pairs
  - PCP + CMV
  - *S. aureus* + HSV 1
- Triple Infections (n=3)

UNIVERSITY OF KWAZULU-NATAL

# 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 $O_2$ saturation

# Preventing PCP

- Cotrimoxazole SS  2 tablets per day
- Prevention
  - Indication:  $CD_4$ < 200 or WHO clinical 2/3/4
  - When to stop:  $CD_4$ > 200 for ≥  3 mo
  - When to restart: $CD_4$  falls to < 200

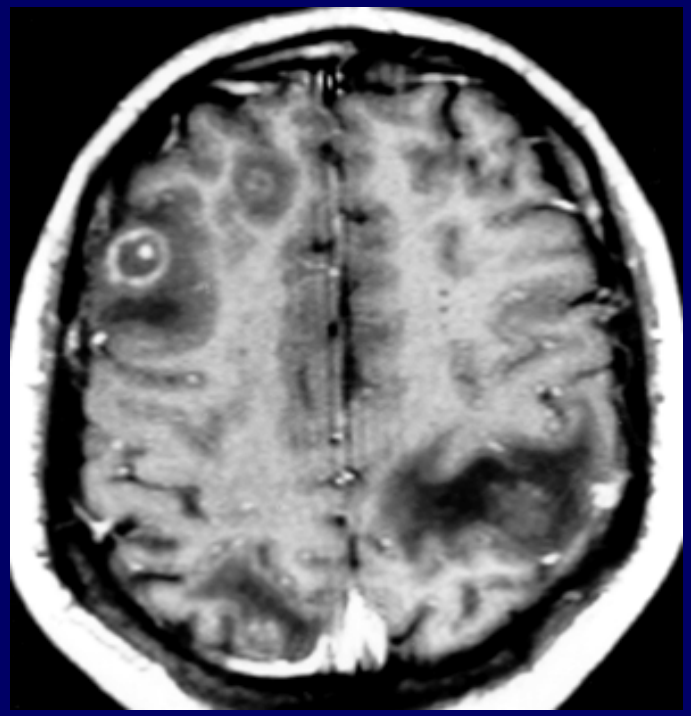
# Case 3

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 $34^0C$

# 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?

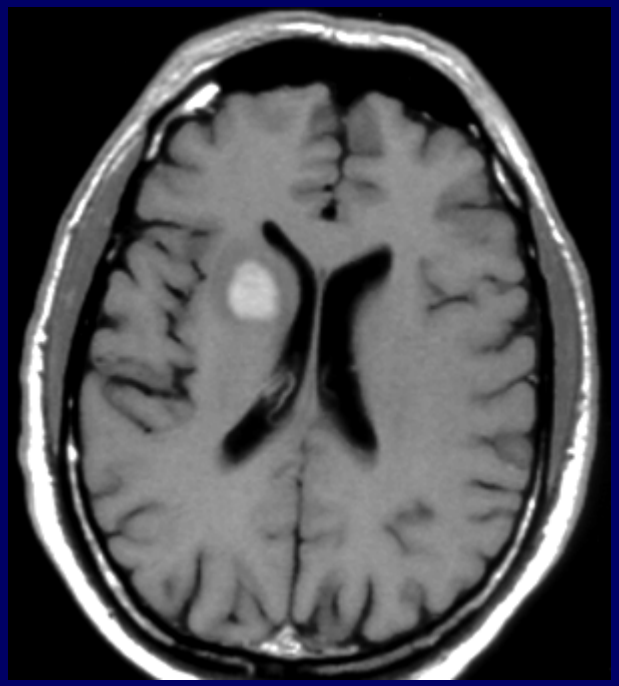
# Toxoplamosis

- 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

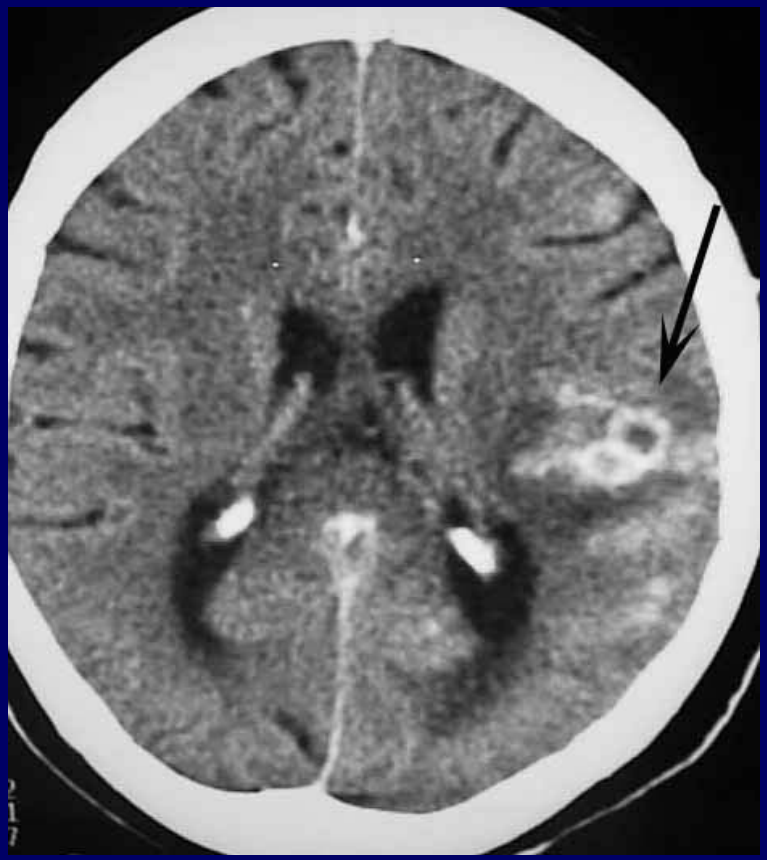
- Treatment
  - Bactrim: 10/50 mg/kg/d orally for 30 days
- Primary Prophylaxis (No previous episode of toxoplasmosis)
  - Cotrimoxazole 2 SS per day when CD4 <100
  - Can discontinue when CD4 > 200 for $\geq$ 3 months
- Secondary Prophylaxis (previous episode of toxoplasmosis)
  - CD4 count >200 for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

# Other CNS Lesions



Primary CNS lymphoma with enhanced lesion and slight mass effect

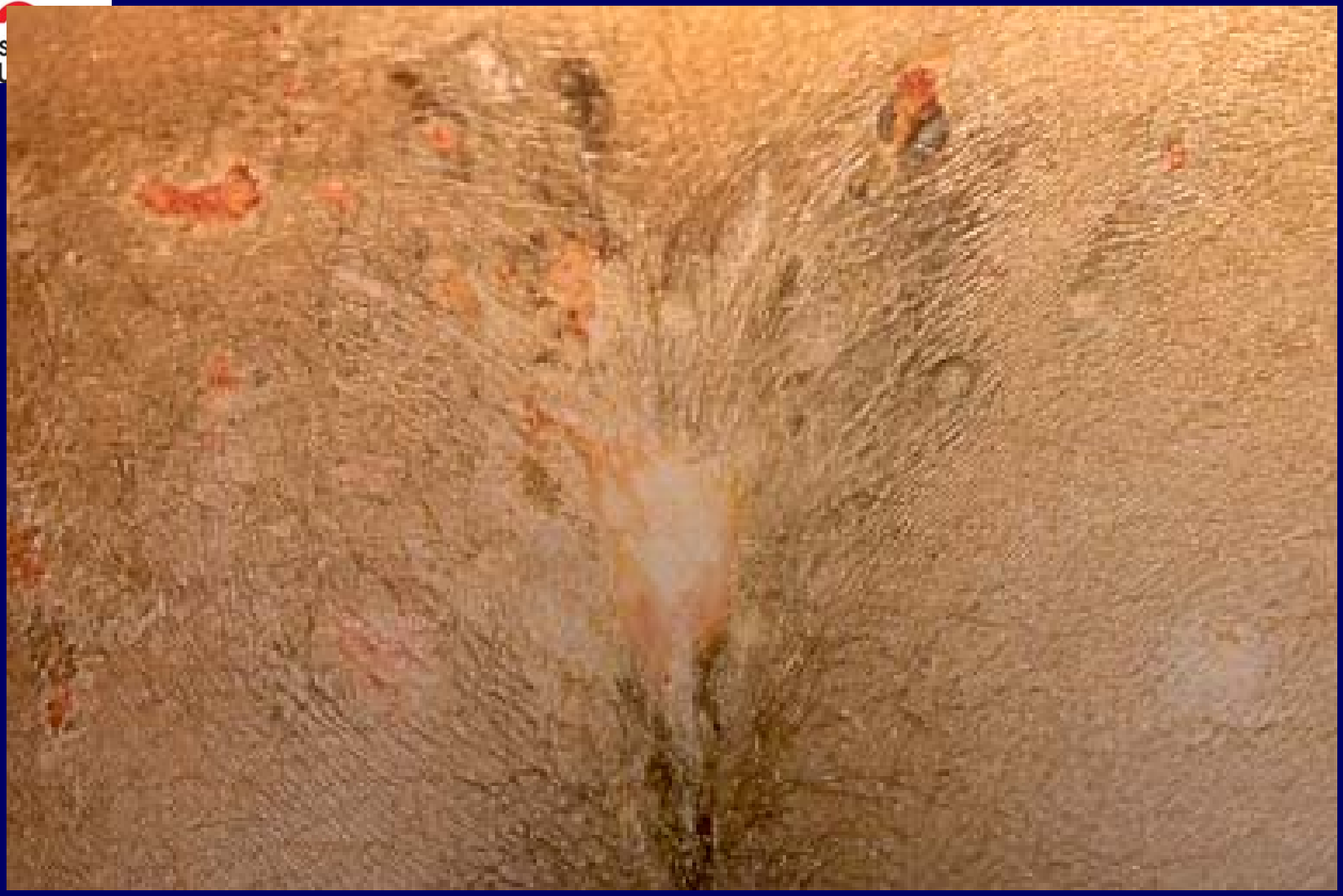
# Other CNS Lesions



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:



UNIVERSITY OF KWAZULU-NATAL

# 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.

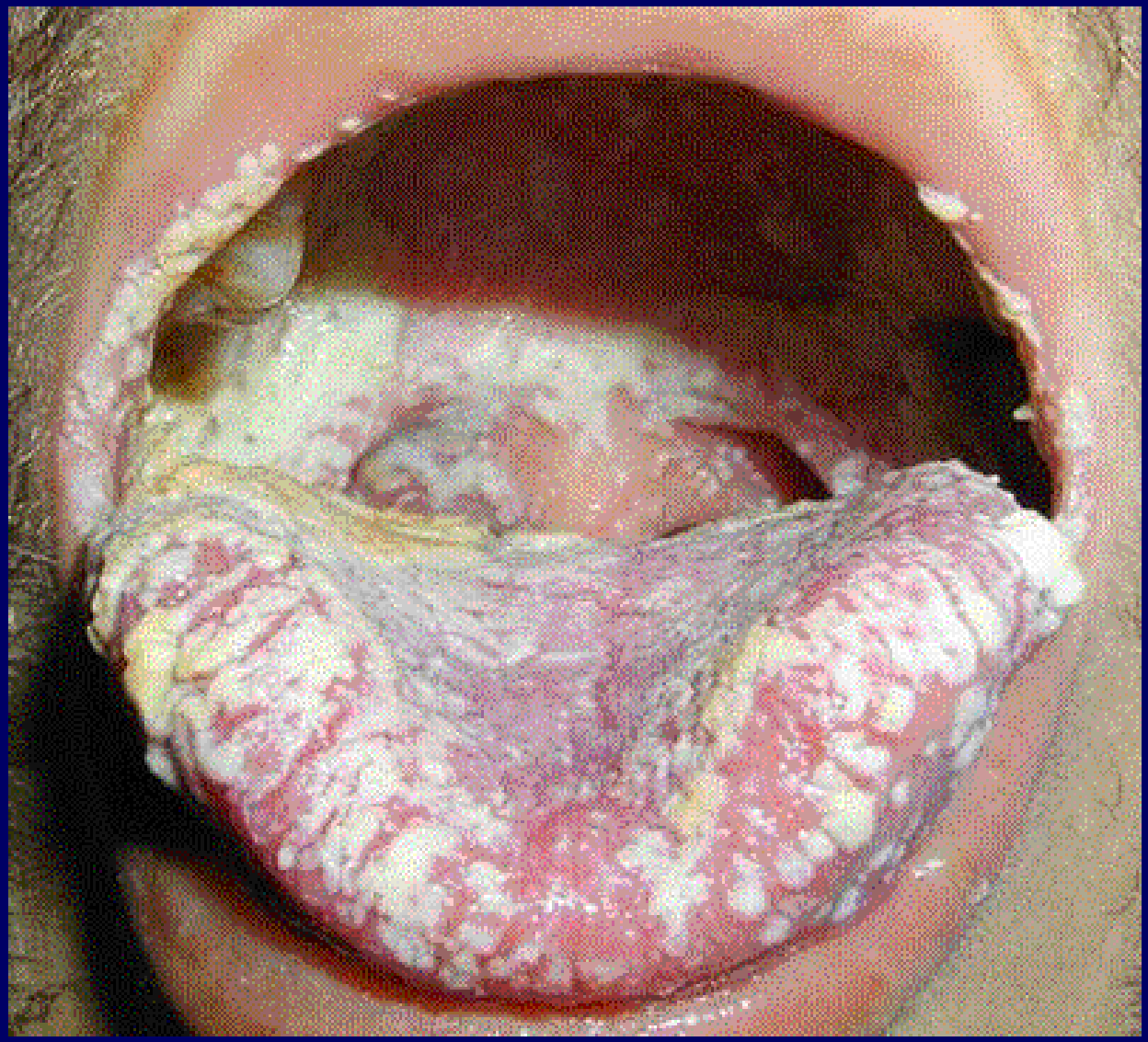
UNIVERSITY OF KWAZULU-NATAL


# Case 3

A 20year old man presents to your HIV clinic.

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

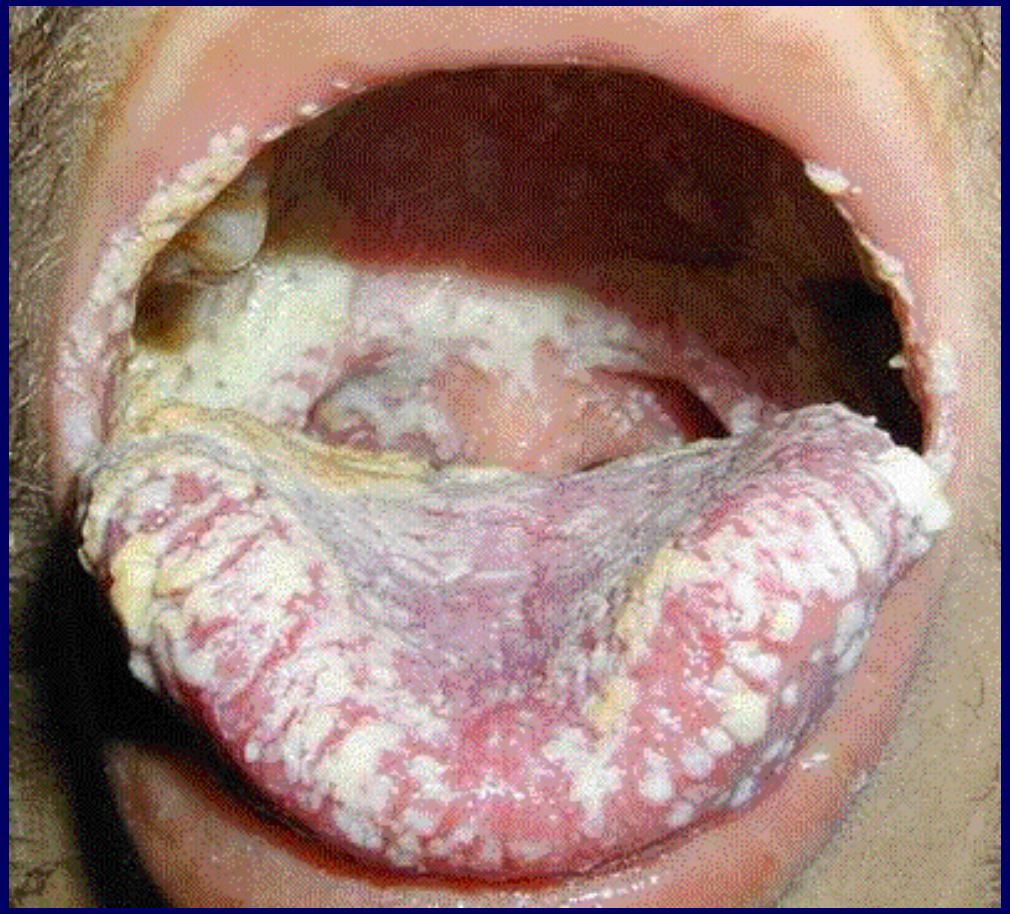
He has been lost to follow-up. Now he presents to resume his care.



By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging

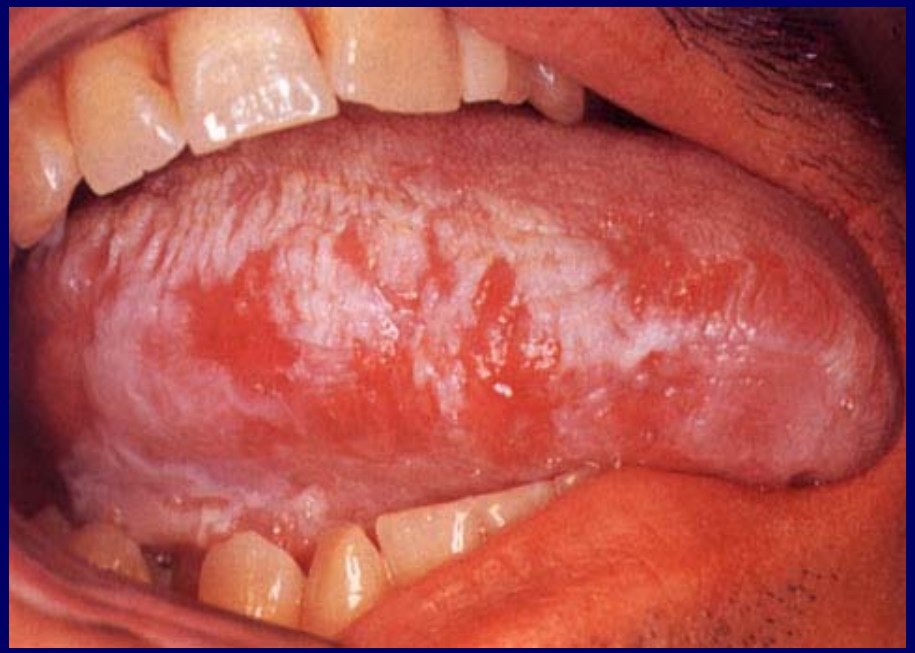
# Case 3

On exam you discover the following:



**What is this?**

# Is this the same infection?



**No, it's oral hairy leukoplakia**

UNIVERSITY OF KWAZULU-NATAL

# Treating Candidiasis

- Oral thrush – clotrimazole troches 5 times per day for 14 day
- Oesophageal thrush – fluconazole 200 mg/day for10-14 days
- Vaginal: Miconazole 200mg vaginal suppositories or oral fluconazole 150 mg (one dose only)

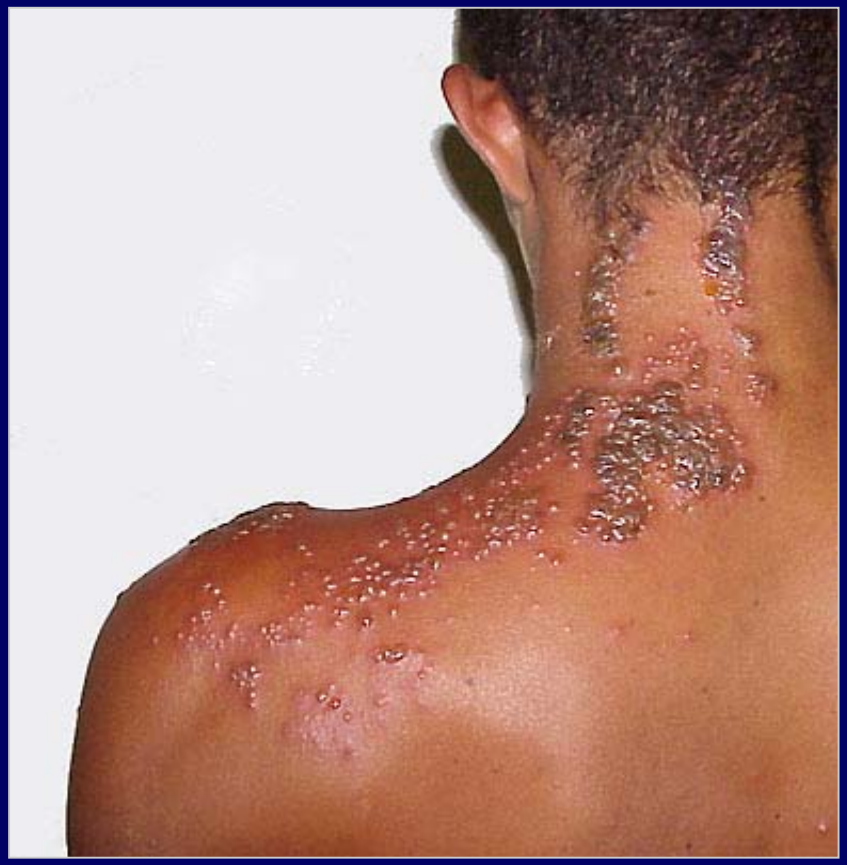
# Case 4

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

- Clinical examination reveals:

# Case 4

On exam you find:



UNIVERSITY OF KWAZULU-NATAL

# 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

UNIVERSITY OF KWAZULU-NATAL

# Diagnosis

- Lumbar puncture
  - Obtaining an opening pressure is key!!!
    - Usually markedly elevated
    - >20 $cmH_20$ 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)*

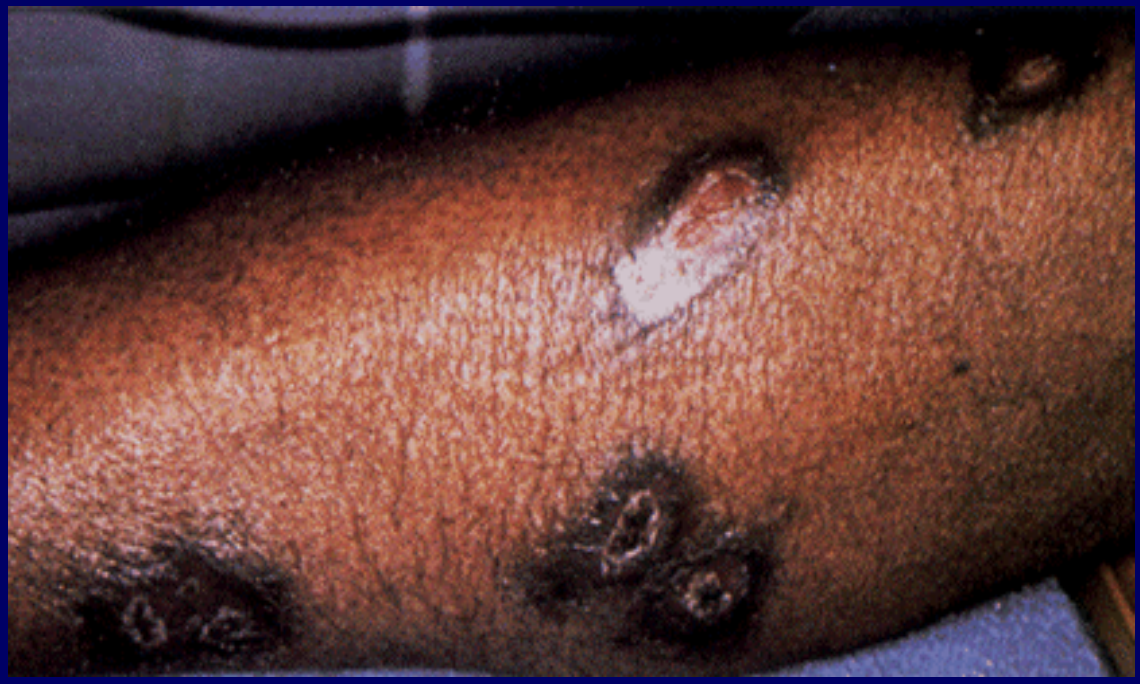
# Management of Intracranial Hypertension

- 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)

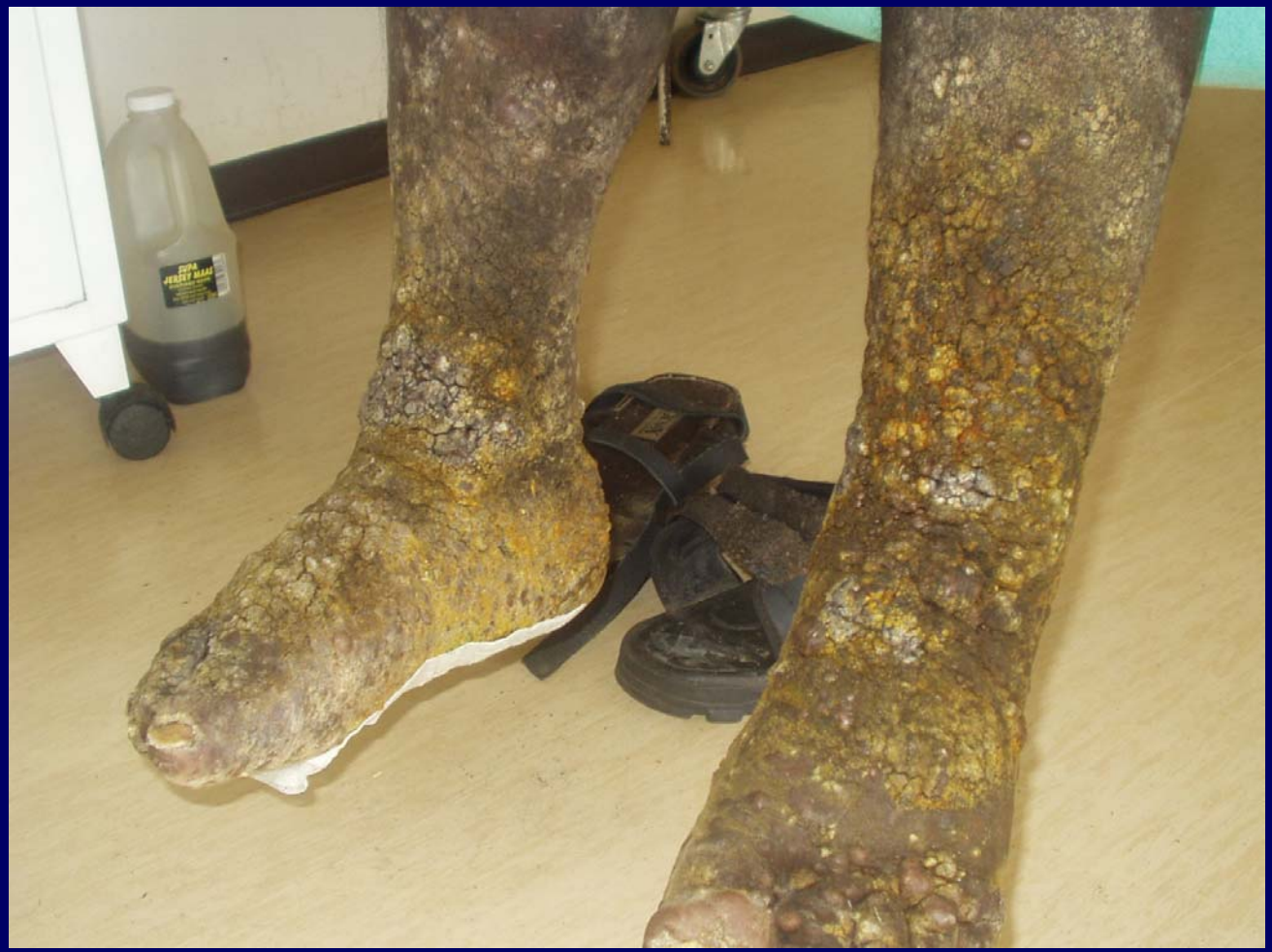
UNIVERSITY OF KWAZULU-NATAL

# What is This?



UNIVERSITY OF KWAZULU-NATAL

# Severe Kaposi's Sarcoma



UNIVERSITY OF KWAZULU-NATAL


# 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.

UNIVERSITY OF KWAZULU-NATAL

# 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)

UNIVERSITY OF KWAZULU-NATAL

# Conclusion

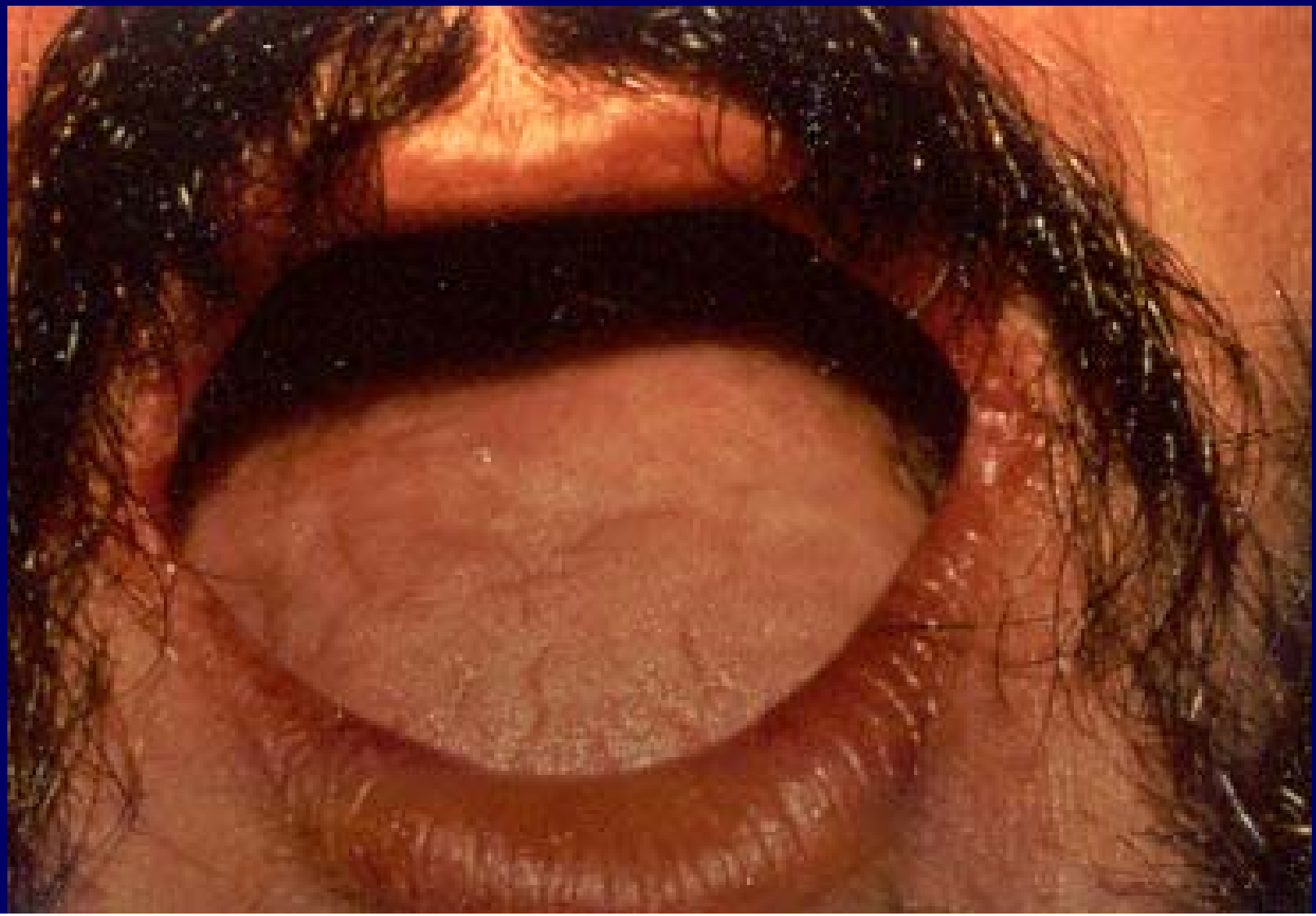
# Acknowledgements


- Contributors:
  - Dr Stephen Tabet
  - Dr. Bisola Ojikutu
  - Dr. Michael Klompas
  - Dr. Janet Giddy

# Oral Manifestations of

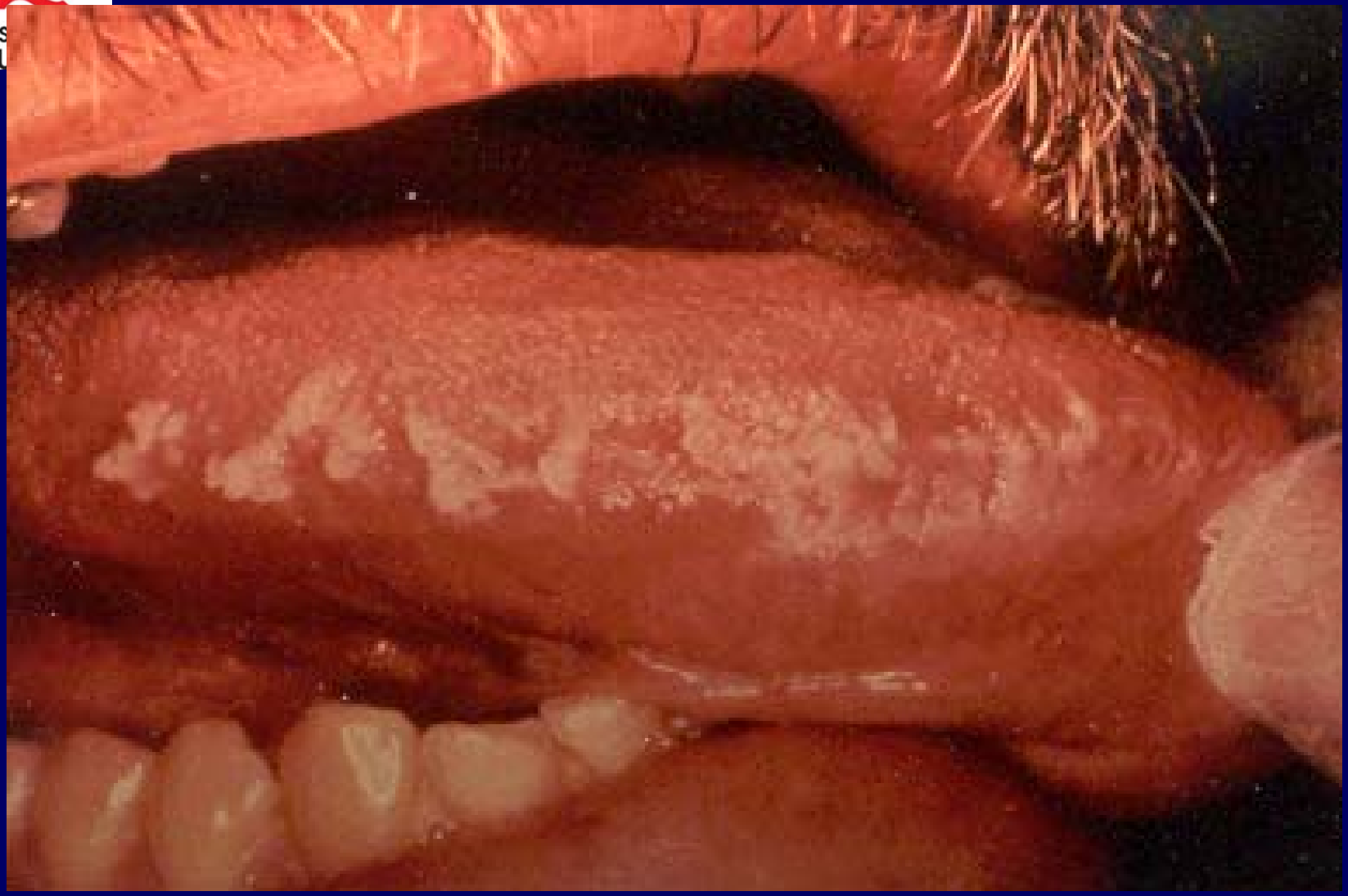
# HIV/AIDS

# Candida angular chelitis

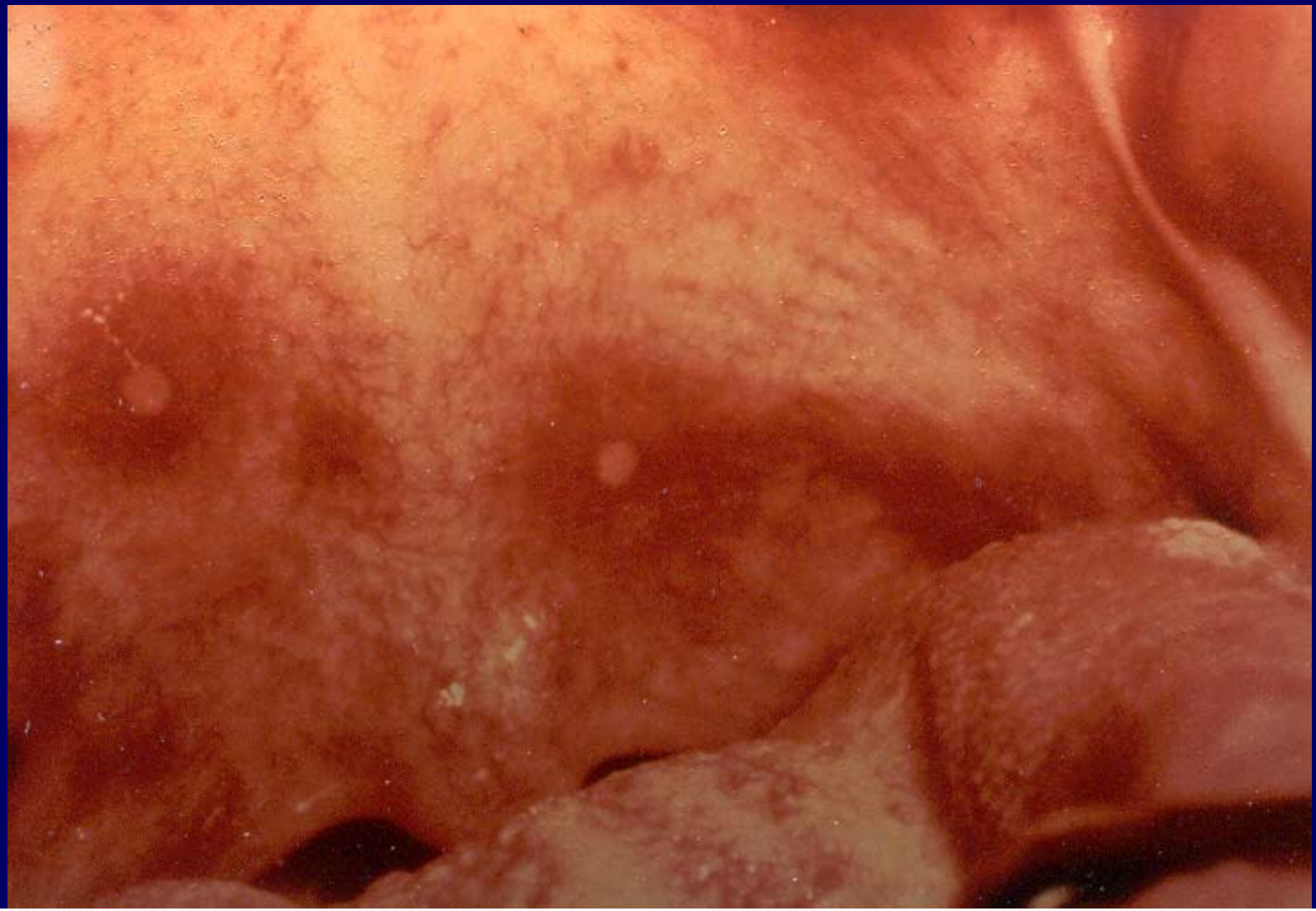


# Oral Hairy Leukoplakia

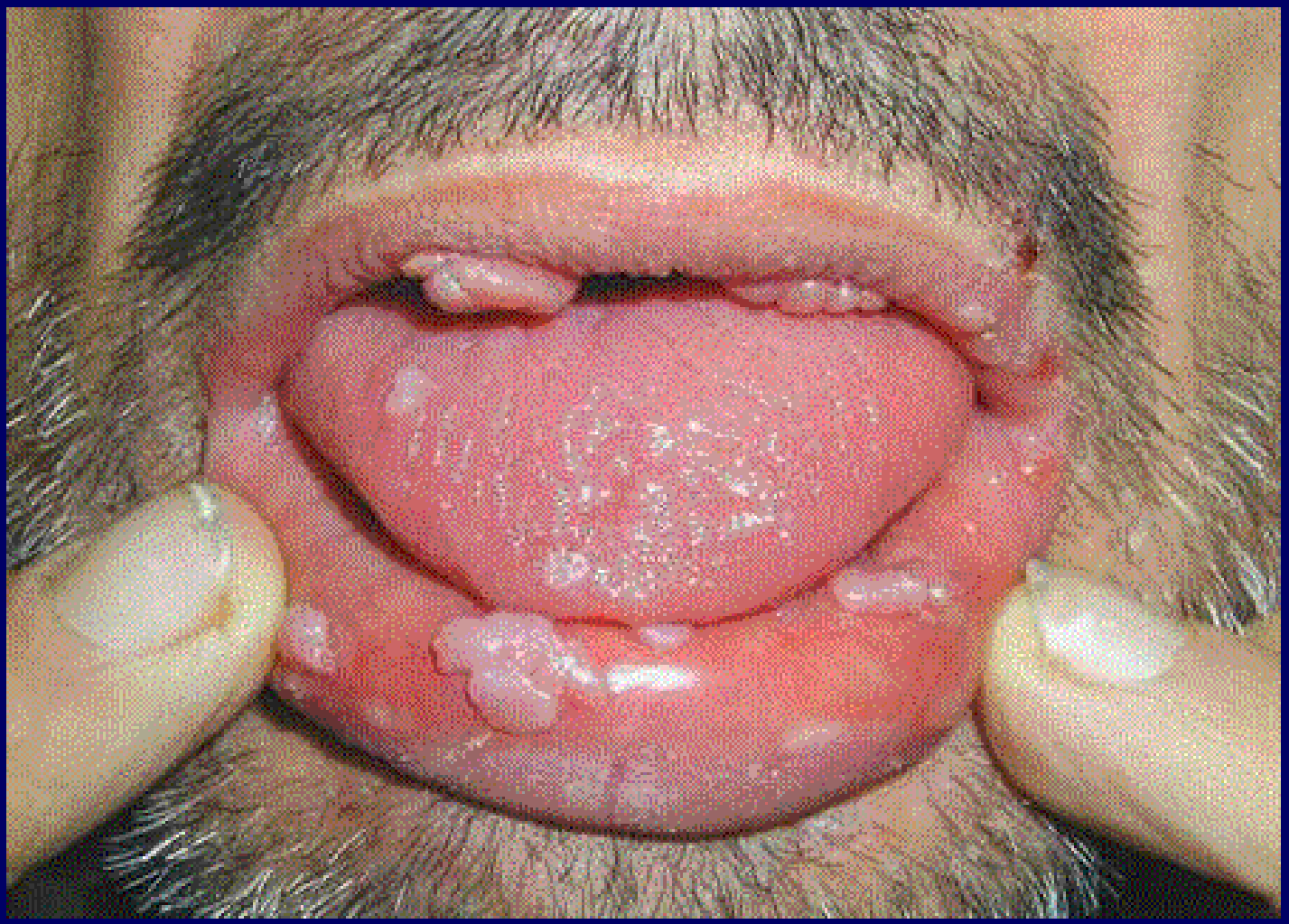
- Epstein-Barr virus (EBV) induced benign epithelial thickening



# Apthous ulcers in HIV-infected patient



# Oral warts (HPV) in patient (CD4 lymphocyte count 120)



By Salvatore Marra, from AIDS imaging
http://members.xoom.it/Aidsimaging

UNIVERSITY OF KWAZULU-NATAL


# 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