Viral Co-infections in HIV/AIDS

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Learning Objectives

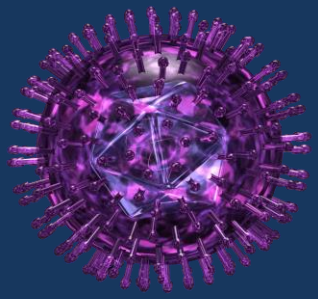
- Understand impact of viral co-infections on HIV disease
- Recognize common viral syndromes
- Describe basic diagnostic and therapeutic approaches to viral infections

Case #1

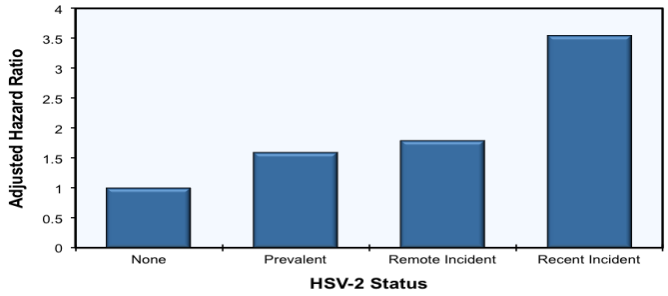
32 M CD4 230 presents with a painful ulcer on the penile shaft with tender lymphadenopathy. Which microorganism is the most likely cause of this syndrome?

A. Chlamydia trachomatis serovars L1-3 (Lymphogranuloma venereum)
B. Treponema pallidum (Syphilitic Chancre)
C. Haemophilus ducreyi (Chancroid)
D. Herpes Simplex virus
E. Not sure

Herpes Simplex Virus



Proposed Mechanisms for the Effects of STDs on HIV Transmission	
Altered HIV Susceptibility	**Altered HIV Infectiousness**
⬇ Mechanical barrier to infection	⬆ Bleeding during intercourse
⬆ Quantity of activated CD4 cells in genital tract	⬆ Serum viral load
⬆ Ease of HIV entry into cells	⬆ HIV viral replication in genital tract
	⬆ HIV-infected cells in genital tract



- DS DNA virus, type 1 and type 2
- South Africa HIV+: 90% (type 1), 79% (type 2)
- HIV patients have more severe manifestations, higher HSV viral loads, slower to resolve, refractory to treatment, more chronic disease
- Increase risk of HIV transmission[1] and progression[2]
  - Increase risk of transmission: genital lesions, higher VL
  - Hasten HIV progression via higher VL or immune activation
- Treating with HSV can decrease HIV VL[3]

1. Corey *JAIDS* 2004
2. Sheth *JID* 2008
3. Zuckerman *JID* 2007, Baetan *JID* 2008, Delaney *AIDS* 2009

Herpes Simplex Virus

- Clinical Manifestations
  - Primary – headache, fever, prodrome, neuropathy
  - Recurrence – more frequent, severe, prolonged, difficult to treat; chronic ulcers
  - Encephalitis, meningitis, keratitis, retinitis, esophagitis, hepatitis, pancreatitis, acute and transverse myelitis, sacral radiculitis, disseminated
  - Acute Demyelinating Encephalomyelitis (ADEM) and hemorrhagic ADEM
- Diagnosis
  - Culture
  - Direct Fluorescent Antibodies or PCR
  - Tzanck prep (60-80% sensitive)
- Acyclovir (ACV) resistance more frequent requiring foscarnet (FSC) 80-120 mg/kg/daily or cidofovir (CDF) 5 mg/kg weekly

<u>Orolabial Lesions (Duration: 5–10 days)</u>
- Valacyclovir (VCV) 1 g PO BID (AIII), or
- Famciclovir 500 mg PO BID (AIII), or
- Acyclovir (ACV) 400 mg PO TID (AIII)

<u>Initial or Recurrent Genital Lesions (Duration: 5–10 Days)</u>
- Valacyclovir 1 g PO BID (AI), or
- Famciclovir 500 mg PO BID (AI), or
- Acyclovir 400 mg PO TID (AI)

Case #2

55 M CD4 120 presents with bilateral lower extremity paresis, decreased sensation and hyper-reflexia 2 weeks after a painful rash. What is this syndrome?

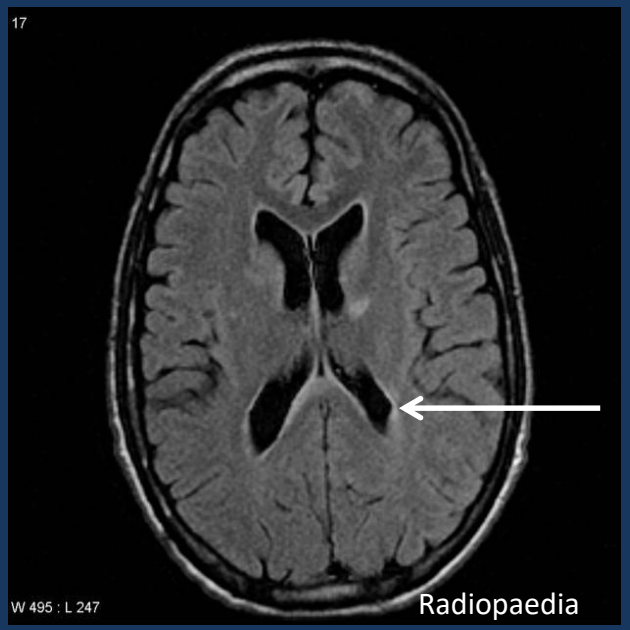
A. Tabes dorsalis
B. Transverse myelitis
C. Acute myelitis
D. Guillain-Barre (GBS)
E. Not sure
F. Monday Morning

Cytomegalovirus

- DS DNA virus
- 100% of HIV+ South Africans
- Immune activation
- Diagnosis requires observing pathology in tissue of interest; CMV blood Ag/PCR; formal eye exam
- Retinitis
  - Floaters, field defects, decreased visual acuity, yellow-white infiltrate +/- hemorrhage
  - CD4 <50 (30% if no ART); vitreous fluid PCR
  - Intravitreal gancivlorvir (GCV) for 7-10 d + valganciclovir (VGC) 900 mg bid (14-21 days) for severe disease
  - >6 months relapse associated with resistance and poor CD4 recovery
  - High level resistance also with FSC/CDF
  - IRIS with reconstitution
  - Maintenance (VGC 900 mg) until CD4>100 x 3-6 months

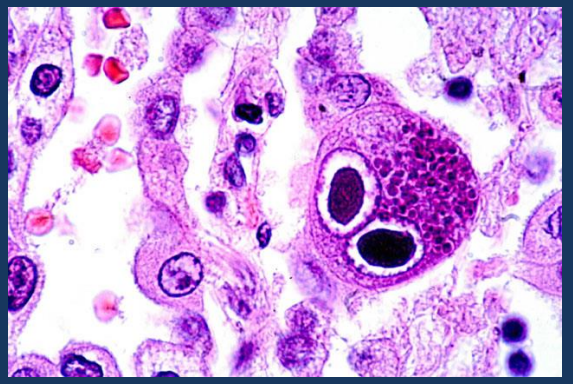
CMV Neurologic Complications

- Dementia/encephalitis
  - Lethargy, confusion, fever, slower onset
  - CSF: lymphocytes, high protein
- Ventriculoencephalitis
  - Delirium, cranial nerves, ataxia, nystagmus
  - CSF: mononuclear cells, high protein
  - MRI: periventricular enhancement
- Acute and Transverse myelitis
  - Weak, hyperreflexive, spastic
  - MRI: cord enhancement
- Ascending polyradiculomyelitis
  - Legs to bowel/bladder, GBS-like, flaccid
  - CSF: neutrophils, high protein, low glucose
- Mononeuritis multiplex – multiple peripheral or cranial nerves (especially laryngeal)
- GCV 5 mg/kg bid + FSC 60 mg/kg to stabilize, then switch to VGV 900 bid for 14-21 days



CMV Other Complications

- Gastrointestinal
  - Esophagitis
    - Fever, odynophagia, nausea, retrosternal pain, shallow distal ulcers
    - CD4 <50, GCV 5 mg/kg IV q12h, then VGC 900 bid
  - Colitis
    - Fever, weight loss, diarrhea, abdominal pain, ulcers, hemorrhage, perforation
    - CD4 <50, VGC 900 bid for 21-42 days
  - Gastritis: higher CD4, uncertain treatment benefit
  - Hepatitis, Cholangitis, Pancreatitis: pathology, uncertain treatment benefit
- Pneumonitis
  - Fever, cough, dyspnea, infiltrates
  - Path, absence of other organism or response to other treatment
  - Same treatment as peripheral retinitis



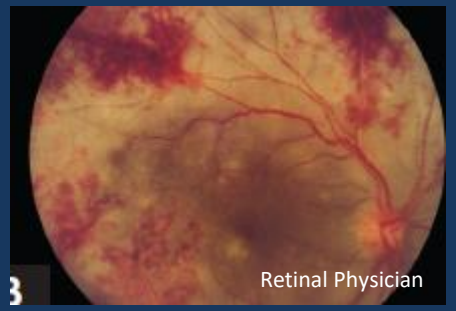
CMV inclusions in lung tissue

Varicella Zoster Virus

- 88% seropositive in HIV+ South Africans
- Reactivation in dermatomal pattern ("shingles") 15x more common in HIV+
- Can present several months after ART
- Seen in all CD4 counts (more if <200)
- Post-herpetic neuralgia
  - ≥55 years old at greater risk
  - Gabapentin, tricyclics, carbamazepine
  - Opioids, corticosteroids?
- Rare chronic verrucous lesions
- Disseminated
  - Abdominal pain, respiratory distress
  - Meningoencephalitis
  - Elevated liver enzymes, lipase
- Clinical diagnosis, DFA, PCR, Tzanck (60%)

VZV Ocular and Neurologic Findings

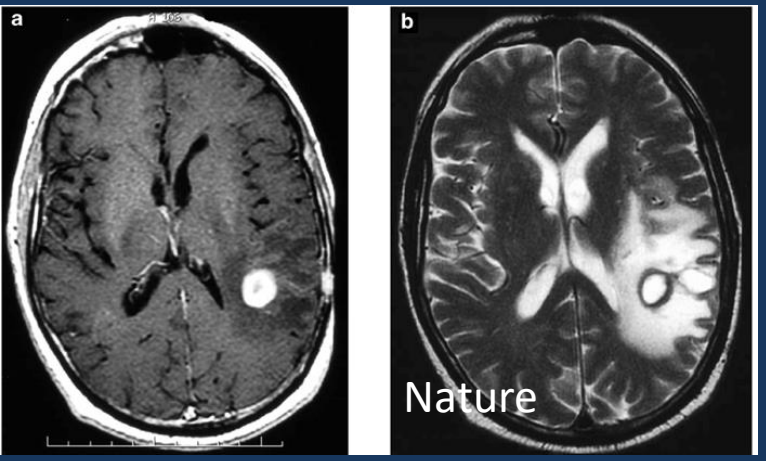
- Progressive Outer Retinal Necrosis (PORN)
  - Rapid vision loss with CD4 < 50
  - Multifocal retinal opacification
  - GCV and/or FSC AND intravitreal GCV and/or FSC
- Acute retinal necrosis (ARN)
  - Peripheral necrotizing retinitis, pain, photophobia
  - Retinal detachment, higher CD4
  - Vitritis and aqueous humor inflammation
- Neurologic complications
  - Acute and transverse myelitis
  - Facial (Bell's) palsy
  - Mononeuritis multiplex
  - Radiculitis
- Treatment/Prevention
  - ACV 10-15 mg/kg q8h for severe, then VCV 1g tid (or ACV 800 5x/day) for 10-14 days
  - VariZIg post-exposure for non-immune
  - Vaccines only if CD4 ≥200/15%



PORN

ARN

Epstein-Barr Virus



- 99.5% HIV+ South Africans
- Oral hairy leukoplakia
  - Treat for pain or cosmetic request
  - Podophyllin, Cryotherapy, surgery, VCV 1g q8h
- Lymphoma
  - Primary CNS
    - 2-6% (1000x HIV-), CD4 < 50, 4 months survival pre-ART
    - Confusion, headache, focal signs, aphasia, seizures
    - Single or multiple isodense, ring-enhancing lesions, > 4 cm, mass-effect, Thalium-SPECT+
    - CSF EBV PCR > 94% specificity, 50-80% sensitivity
    - XRT + steroids or MTX; chemo for higher CD4
  - Primary Effusion (Body Cavity) Lymphoma
    - 0.004-0.14%, no masses, 2-6 months survival
    - ART + CHOP; treatment can reduce effusion size
- Meningitis: CSF mononuclear cells, high protein
- Acute and Transverse myelitis
- Hepatitis: mild ↑ liver enzyme, VCA IgM, EBNA

HHV-8

- Kaposi's Sarcoma
  - 20,000x higher general population
  - Firm brown to purple nontender/pruritic nodules on extremities, genitalia, trunk; lymphedema
  - GI tract, lung lesions with hemorrhage
  - Good prognosis if skin only, CD4 > 150, no "B" symptoms
  - Anthracyclines, paclitaxel, IFNα, vinca alkaloids , bleomycin
    - > 25 lesions
    - Refractory to local treatment
    - Visceral lesions with symptoms
    - "B" symptoms
    - Extensive edema
  - Unclear benefit with antivirals, ART ↓ tumor burden
- Primary Effusion Lymphoma (BCL)
- Multicentric Castleman's Disease (MCD)
- Kaposi's Inflammatory Cytokine Syndrome (KICS)

Herpesvirus Antiviral Response

	HSV	VZV	EBV	CMV	HHV 6-8
Acyclovir	++	+	+	-	-
Famciclovir	++	+	+	-	-
Valacyclovir	++	+	+	-	-
Ganciclovir	++	+	++	++	+
Foscarnet	+	+	++	+	+
Cidofovir	+	+	++	+	++

Case #3

48 F started TB treatment and 3 weeks later EFV/FTC/TDF. She presents with jaundice at 6 months. What would you recommend?

A. Stop all medications
B. Stop ART only
C. Stop TB meds
D. Assess adherence, check HBV DNA, HBeAg, HIV VL and CD4 count
E. Not sure
F. Call Prof Moosa

Hepatitis A Virus

Epidemiology

- High incidence in MSM, fecal-oral, food transmission
- About 50% symptomatic
- Less than 1% fatal, no chronic form

Clinical

- HIV prolongs HAV viremia*
- HIV patients at risk for liver failure and death because of frequently having underlying liver disease

Prevention

- Recommend vaccination in MSM, IDU or chronic liver disease if not immune (40-90% seropositive in South Africa)
- Appears to be safe but seroresponse can vary by†
  - CD4 count: 68% for >200 cells, 9% for <200 cells
  - HIV Viral Load
  - Can wane more rapidly over time; three doses more effective (check IgG 1 month after completing series)

*Wallace 1998, Laurence 2005
†Kemper 2003, Weismman 2006, Overton 2007

Hepatitis C Virus

Epidemiology

- Transmitted by IDU/blood products, sex or vertical
- South Africa 0.1-3.5% in population, 13.4% HIV*, genotype 5

Clinical

- Fever, mild RUQ pain, N/V, anorexia, dark urine, and jaundice (<20%), usually elevated LFTs; spontaneous clearance 15%
- Cirrhosis risk 5-25% in 20 yrs; liver failure 1-2%/yr; HCC 1-7%/yr
- HCV VL higher and risk of cirrhosis/liver failure/HCC 3x higher with HIV (especially with low CD4)
- Cryoglobulinemia, arthritis, myelitis, mononeuritis multiplex, vasculitis, renal disease, erythema nodosum, porphyria cutanea

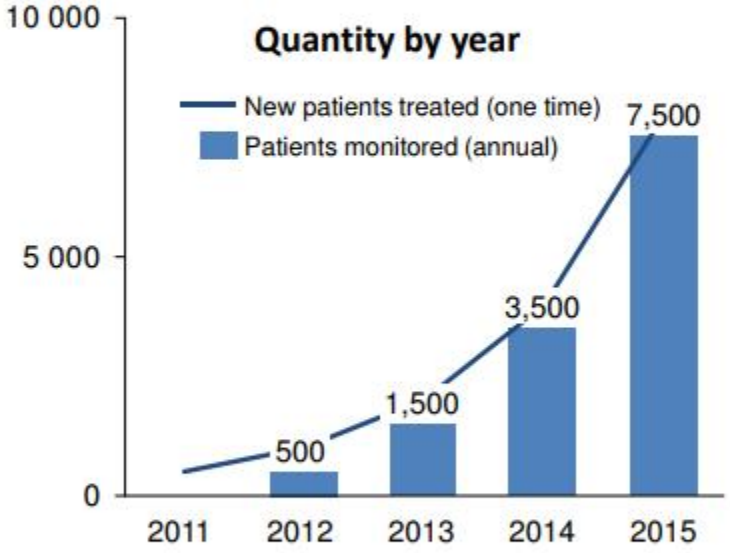
Prevention

- Avoid alcohol, paracetamol, hepatotoxic agents
- HAV/HBV vaccines, follow LFTs, FBC, INR, and ultrasound if cirrhotic for HCC

*Parboosing KZN 2008

HCV Treatment

Priority3:Hepatitis C Treatment with DAAs



Currently, less than 300 patients are treated for Hep C each year in South Africa

Over 300,000 persons in South Africa with Chronic Hep C infection, of which at least 30% will need treatment.

Non-monetary challenges to scale up:

- *MCC & NEMLC approval and procurement of at least one combination DAA (e.g. "Harvoni" SOF/L) by beginning of 2019 to avoid large volume of Section 21 requests.*
- *Need ~ 1 full-time clinician with specialty training in hepatology per 1000 patients*
- *Training programs at UCT will need to be approved and funded to train the number of clinicians needed to meet these scale up numbers*
- *Need to do enough additional screening in high-risk populations to find Hep C patients in 2019 and beyond*

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Dr Kgomotso Vilakazi Nhlapo
8th RSA AIDS Conference

Case #4

33 F CD4 121 on LPV/r+3TC/ZDV developed an flu-like illness. In a follow up visit 4 months later she complained of persistent dyspnea and this FBC. What is the likely pathogen?

A. Parainfluenza
B. Parvovirus B19
C. Adenovirus
D. Influenza
E. Not sure

Parvovirus B19

- Presentation depends upon age, hematologic and immunologic status
- 50% influenza like illness in week 1
- 25% arthralgia, edema, lacy reticular rash on the trunk and extremities (± malar) in week 2
- Severe, acute or chronic Pure Red Cell Aplasia (PRCA) may occur due to impaired humoral responses with low CD4
- Also role for cell-mediated immunity suggested by improvement in chronic anemia after CD4 recovery
- Serology (IgM and IgG), PCR
- IVIg used to treat PRCA; can require retreatment for relapses

Influenza

Epidemiology

- Greater severity and higher mortality in HIV pre-ART, reduced with ART
- Incidence equivalent (except Boschini 2006), but symptoms may be prolonged and complications increased pre-ART*
- Underreported, decreased severity or confounded by co-infections, comorbid illnesses, or tobacco use in ART era

Treatment

- Unknown risk:benefit with antivirals (beneficial in HSCT)
- Resistance if prolonged shedding

Prevention

- Annual vaccination (inactivated virus) is recommended by WHO; able to produce most effective HA titer on ART, double-dose better†
- No evidence of decreased T cell function, increased IA, progression or death
- Mixed results showing transient ↑VL
- Ab response best for high CD4 and low VL, but clinical response good

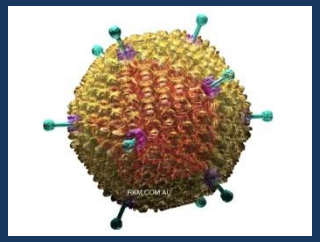
	Data source	Population	Data available	Outcome	Number of outcomes per 1000 person-years in disease-positive population (95% CI)	Number of outcomes per 1000 person-years in control (95% CI)
Thompson[2]	National Center for Health Statistics database	General population	..	Influenza-associated deaths*	NA	All ages: 0·03; 65 years or older: 0·22
Thompson[3]	National hospital discharge survey	General population	..	Influenza-associated hospital admissions†	NA	All ages: 0·52; 65 years or older: 2·81
Neuzil[35]	Tennessee Medicaid database (women 15–64 years for HIV and for controls)	HIV, pre-HAART	1725712 person-years of data	Combined, excess hospital admissions and deaths	1973–93: 33·4	0·4
Lin[36]	National Center for Health Statistics database (13 years or older for AIDS, 25–54 years for controls)	AIDS, pre-HAART	149 256 person-years of data	Excess deaths from pneumonia or influenza during influenza seasons‡	1991–92: 1·26 (1·07–1·45); 1992–93: 1·47 (1·28–1·65); 1993–94: 0·94 (0·80–1·08)	0·01 (0·009–0·01); 0·009 (0·009–0·01); 0·009 (0·008–0·009)
Neuzil[37]	Tennessee Medicaid database (HIV positive, 15–50 years)	HIV, post-HAART	7368 person-years of data	Excess hospital admissions Excess deaths	1995–96, pre-HAART: 48 (16–81); 1996–99, post-HAART: 5 (-0·5–11); 0·5 (-4·8–5·7)	NA
Vilchez[62]	University of Pittsburgh transplant programme database	Organ transplant	3569 organ transplants over 10 years	Hospital admissions	Lung transplant: 4·18–41·8§ Liver transplant: 0·28–2·8§ Kidney transplant: 0·43–4·3§	NA

-=not reported or data not collected. NA=not applicable. *Data reported are for underlying pneumonia and influenza deaths. Data for all-cause deaths showed rates of 0·20 for all ages, and 1·32 for patients 65 years and over. †Data reported are for influenza or pneumonia listed under any diagnosis. Data for influenza as primary diagnosis showed 0·37 endpoints per 1000 person-years for all ages. ‡Excess deaths calculated as difference between deaths during influenza season and before influenza season. §Ranges provided because complete person-years data not reported.

Kunisaki *Lancet* 2009

* Maldarelli 1988, Cohen 1989, Fine 2001, Boschini 2006, Oliveira 2009, Giseldorf 2009, Jain 2009/Peters 2010, Louie 2009, Kumar 2009

† Nelson 1988, Oliveira CROI 2011, Bickel CROI 2011



Adenovirus

Epidemiology

- Reports of severe pneumonia in AIDS patients*
- Spanish study of 67 cases of CAP in HIV patients over 3 years (only two required ventilation) found respiratory viruses in 14 (8 had only a virus); 5 were adenovirus, 6 coronovirus, 3 influenza†
- Disseminated with hepatic necrosis and liver failure¥

Treatment

- Cidofovir or ribavirin in children post HSCT

Prevention

- Difficulty in using adeno as a vector in HIV vaccine development (STEP trial)

*de Blic *Arch Dis Child* 1989, Koopman *Infection* 2000, Adeyemi *AIDS Reader* 2008
†Perello *EIMC* 2008
¥Krilov *Rev ID* 1990, Dombrowski *Virchows Arch* 1997

Other Respiratory Viruses

- Garbino *AIDS* 2008 – Examined 59 BAL of 55 patients 2003-2006 in Swiss HIV Cohort Study
  - 11.7% hospitalized
  - 18.6% positive for at least one respiratory virus
    - Coronavirus 27.3%
    - PIV 2, 3, 4, bocavirus, rhinovirus A, hMPV (each 9%)
    - 63.6% only viruses found
    - 63.6% cases occurred in the winter
- Madhi *J Ped* 2000 – Compared severe LRTI for HIV + and HIV – children < 2 yrs old in Johannesburg, South Africa
  - HIV+ more viral burden (RSV, Influenza A/B, PIV 1-3, Adeno)
  - More bacterial than viral for HIV+ c/w HIV-
  - No seasonal variation for RSV
  - Higher mortality for children with virus and HIV

HTLV I/II

- Sexual contact, vertical transmission and transfusion of contaminated blood or blood products (same risk factors for HIV)
- Endemic in South Africa, co-infection common (van der Ryst *SA Med J* 1992)
- Tropical Spastic Paraparesis (or HTLV associated myelopathy)
  - 1-3.7% of carriers
  - Insidious onset of slowly progressive weakness and spasticity lower extremities, hyperreflexia, ankle clonus, extensor plantar responses, lumbar pain, detrusor instability (nocturia, urinary frequency, incontinence)
  - MRI: atrophy of spinal cord and/or WM lesions in subcortical and periventricular regions
  - CSF: Serum antibody ratio, culture and proviral DNA PCR
  - EMG with posterior column and peripheral nerve dysfunction
  - No proven therapy: corticosteroids, ZDV +/- 3TC, IFN β1a, danazol
  - Can lead to chronic myelitis
- Adult T cell Leukemia/Lymphoma – acute, lymphomatous, chronic and smoldering; skin, pulmonary and bone lesions, hypercalcemia, ↑alk phos and LDH; tx ZDV + IFN α
- Other diseases implicated: isolated mild cognitive deficits, peripheral neuropathy, neurogenic bladder dysfunction, amyotrophic lateral sclerosis , dermatitis, gastric cancer, uveitis, polymyositis, inflammatory arthropathy, ITP, Sjogrens

Enteric viruses

--35% Sx & 12% Asx had astrovirus, calcivirus, picobirnavirus, adenovirus (Grohmann *NEJM* 1993)

--23% in Kenya (Kiulia *J Trop Ped* 2009) and 22% in Burkina Faso (Djeneba *Pak J Biol Sci* 2007) HIV+ children with diarrhea had rotavirus

--Enterovirus-71 epidemic in HIV + children in Nairobi, Kenya (Chakraborty *AIDS* 2004)

Acute viral myelitis, encephalitis, meningitis: coxsackie (Berger *J Neurovirol* 2009), echovirus-6 (Dyer *J Neurovirol* 1998), poliovirus/enterovirus-71

Myocarditis: coxsackie (Buhler Schweiz *Med Woch* 1994)

Rhabdomyolysis: coxsackie (Beressi *Ann Clin Lab Sci* 1994)

Pretoria, SA: HIV patients given OPV can eventually excrete pathogenic virus after chronic infection (Pavlov Diag *Micro ID* 2006)

Case #5

52 M presents with acute delirium and fever in the setting of 2 months of progressive dementia. What pathogen caused this?

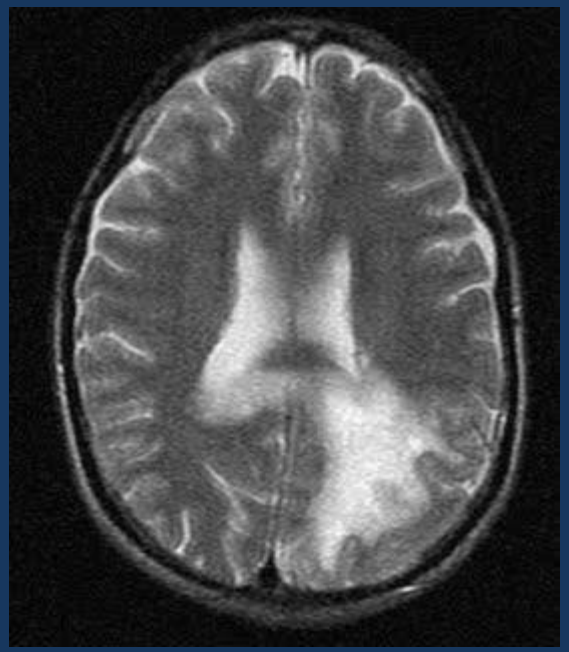
A. HSV
B. VZV
C. WNV
D. JCV
E. A and D
F. None of the above
G. JZ + MNM

Encephalitides

- Encephalitis deaths remain higher than general population (Khetsuriani *Epid Inf* 2007)
- West Nile
  - One case report of acute flaccid paralysis in LA (Torno *Neurology* 2007) CD4 324, VL 25K no AIDS/ART
  - 30% seropositive in Ghana blood-donor study (33% HIV-infected), no symptomatic disease or viremia but appear to have robust immunity
  - Concern for use of CCR5 antagonists
- Japanese E
  - Case series (3/16) of concomitant HIV/JEV infection during an outbreak in India (Neogi *J Commun Dis* 1998)
  - Low vaccine response rate

PAPOVA

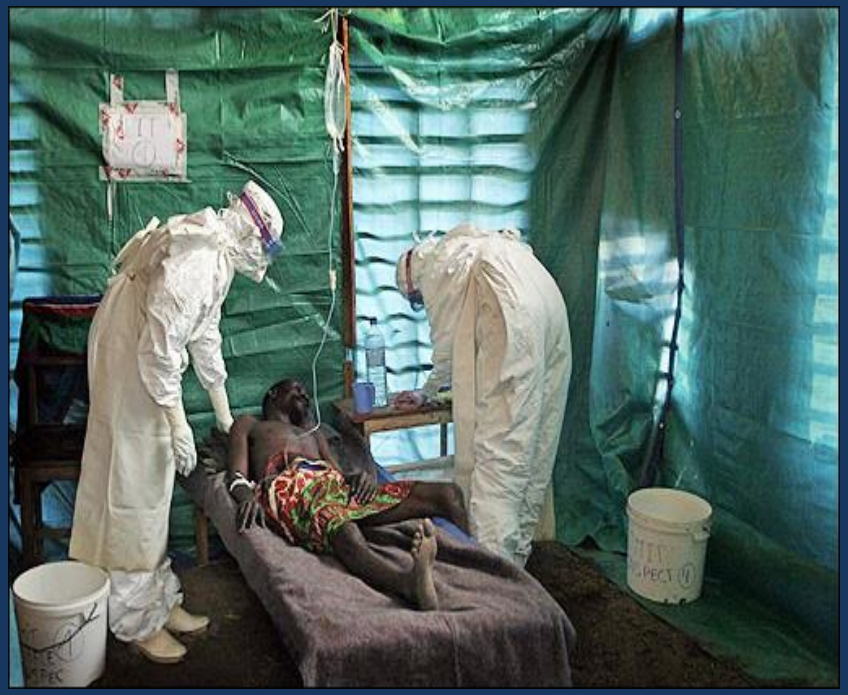
- Papilloma: HPV, increased risk of cervical, anal and head/neck cancer; 6-12 months screening
  - 33-45% vs 7-14% SIL
  - 0-9 fold increase in cervical cancer (CD4 dependent)
  - HIV VL correlates with HPV VL
  - 80-fold increase in anal cancer
- Polyoma – increased shedding and isolation in HIV patients
  - JC: 1-25%, CD4 35-100, but 7-25% > 200; confusion, motor/speech, VF, coordination, no fever; CD4 best predictor, some improvement on ART, no clear benefit CDF, 1-6 months prognosis
  - BK: nephropathy (Sukov *Am J Kid Dis* 2008); hem cystitis (Barouch *CID* 2002), no BK found in blood 68 hosp pts (Sachithanandham *IJMM* 2009)
- Vacuolating: SV-40
  - Seroprevalence ~ HIV neg (Jafar *J Med Virol* 1998)
  - Isolated in AIDS dementia (Comar *Curr HIV Res* 2007)
  - AIDS-related NHL (Vilchez *Virology* 2005 and *JAIDS* 2002)



Hypodense, WM lesions w/o enhancement

Hemorrhagic Fever Viruses

- Dengue
  - India: rate not increased[1]
  - Singapore: 5 infections:, no hemorrhagic fever, mild disease[2]
  - Thai: HIV VL decrease[3]
- Ebola Virus
  - Excess death rates in Guinea 16.2% (713), Liberia 13% (155) and Sierra Leone 9.1% (223)[4]
  - Biological and systematic synergy



1 Goyal *Indian J Med Micro* 2007
2 Siong *SEA JTMPH* 2008
3 Watt *CID* 2003
4 Hira *AIDS* 2016

Live Vaccine Viruses

- MMR
  - No serious adverse events in HIV+ children (*MMWR* 1988)
  - Measles Pneumonitis after vaccine (*MMWR* 1996)
  - Vaccine with reduction in HIV VL?, safe and effective if higher CD4 count (Moss *PIDJ* 2009, Aurpibul *CID* 2007, Ho *AIDS Pt Care STD* 2008)
- Yellow Fever
  - Fatal myeloencephalitis in Thailand (Kengsakul *J Med Assoc Thai* 2002)
  - Higher CD4 safe but weaker response (Veit Swiss HIV Cohort *CID*)
- Smallpox
  - Disseminated vaccinia in military recruit (Redfield *NEJM* 1987)
  - Additional 10 recruits with no significant symptoms (Tasker *CID* 2004)
- Also Varicella, Oral Polio, bCG and Intranasal Influenza
- All contraindicated for low CD4; may be safe and more effective if higher CD4 count and/or ART
  - Severe adverse reactions
  - Potential for increased immune activation
  - Less robust response that wanes more quickly as compared to HIV negative

Summary

- Immune activation and systemic inflammation is higher with herpesvirus co-infection
- Interruption of HBV treatment can be life-threatening
- HCV is curable but cost is high and unclear mortality benefit in some settings
- Severity and mortality higher with respiratory viruses if low CD4/no ART
- Avoid live vaccines if low CD4/no ART

Questions?