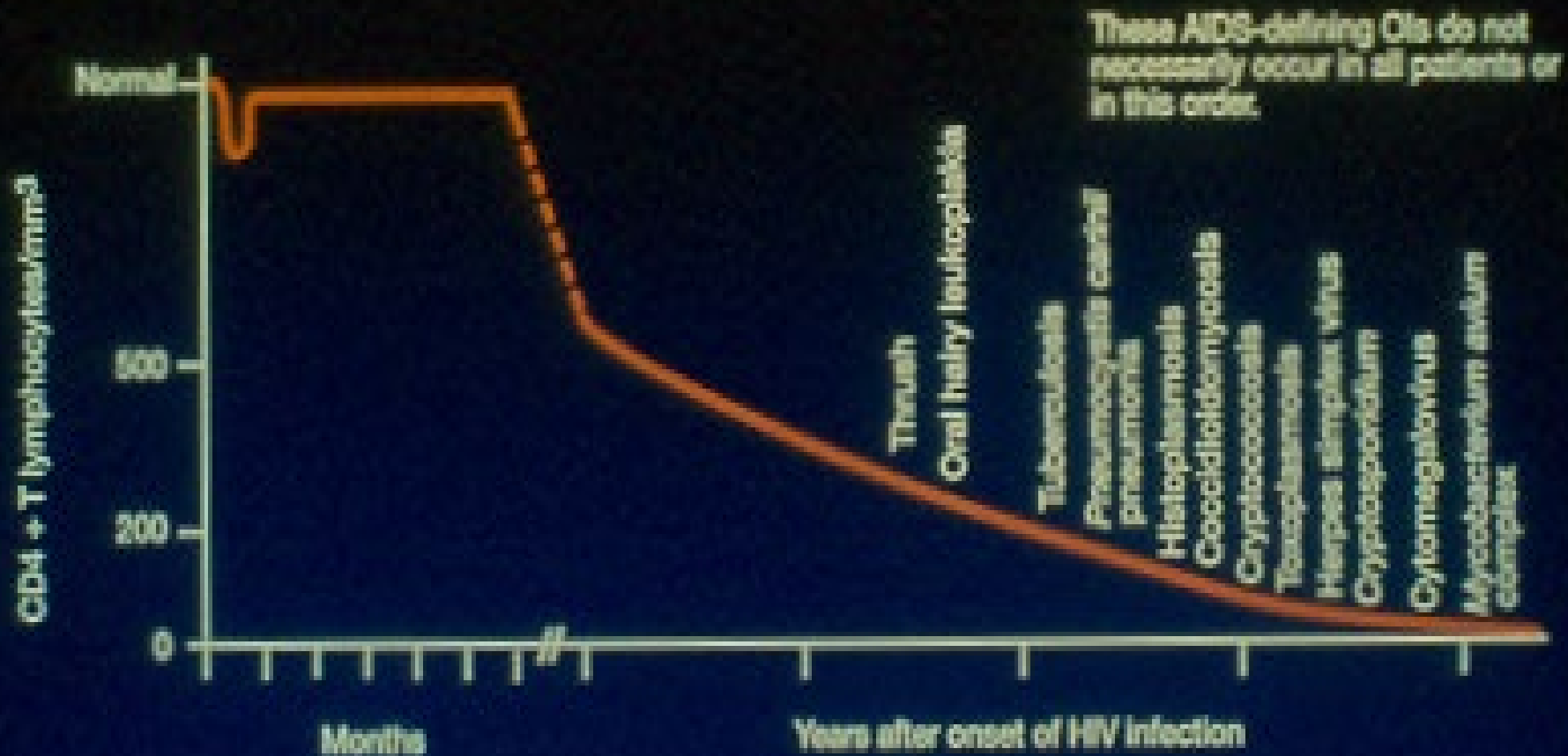




Opportunistic Infections: Brief Overview

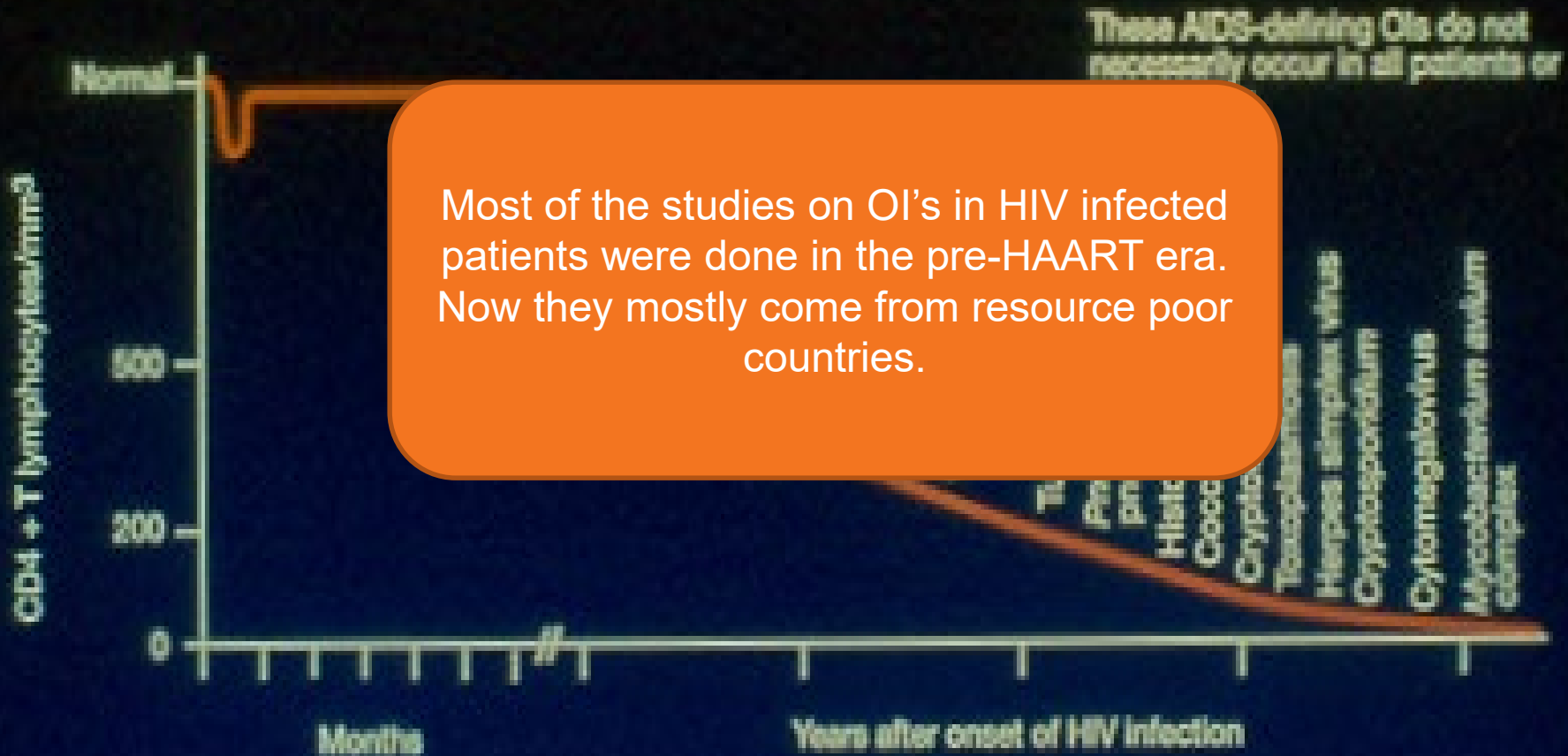
Stephen Raffanti MD MPH

Opportunistic Infections in HIV Disease



This graph is idealized. Specific OIs can occur earlier/later and at higher/lower CD4 cell counts.

Opportunistic Infections in HIV Disease



This graph is idealized. Specific OIs can occur earlier/later and at higher/lower CD4 cell counts.

Opportunistic Infections 1997

n=23,527

Opportunistic Infection	%
Candidiasis (esoph, trach, lung)	16
Cervical cancer	0.6
Coccidiomycosis, extrapulmonary	0.3
Cryptococcosis, extrapulmonary	5
CMV	7
HSV	5
Histoplasmosis	0.9
Dementia	5
Wasting	18
Isosporiasis	0.1
Kaposi's Sarcoma	7
lymphoma	0.7
MAC	5
MTB	9
PCP	38
Recurrent Pneumonia	5
PML	1
Salmonella	0.3
Toxoplasmosis	4

Validated OI's 1998-2005

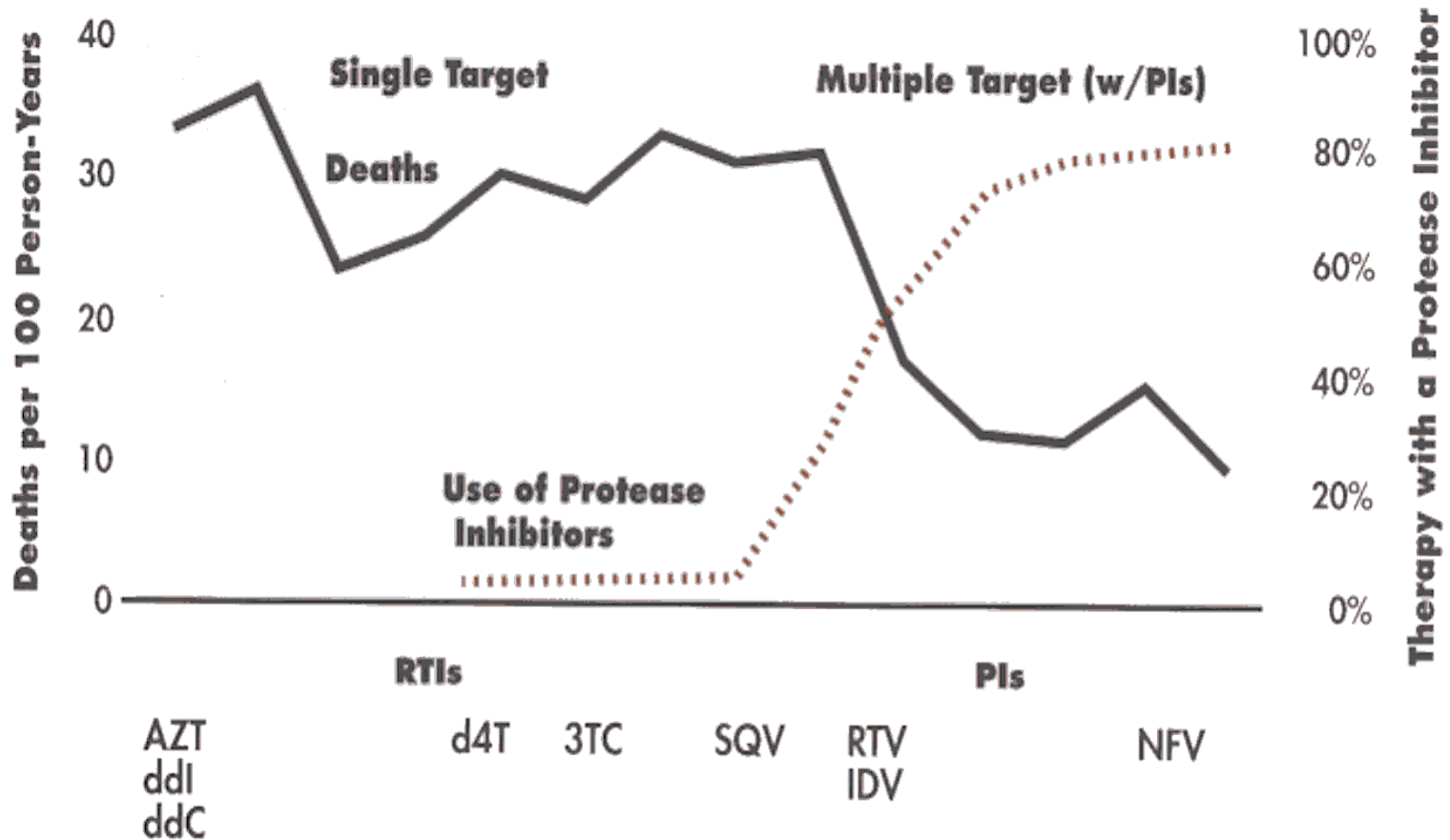
Category	Category Total	Category %
Burkitt's Lymphoma	4	0.4
Candidal Esophagitis	83	8.4
Candidiasis	4	0.4
Carcinoma	4	0.4
CMV	37	3.8
Coccidioidomycosis	1	0.1
Cryptococcal Infection	48	4.9
Cryptosporidiosis	9	0.9
Dementia	48	4.9
Herpes Simplex	3	0.3
Histoplasmosis	30	3.0
Kaposi's Sarcoma	37	3.8
MAC	51	5.2
Malignant Lymphoma	18	1.8
Microsporidiosis	1	0.1
Non-Hodgkin's Lymphoma	4	0.4
PCP	172	17.5
PML	9	0.9
Pneumococcal Meningitis	1	0.1
Pneumococcal Septicemia	2	0.2
Pneumonia	41	4.2
Salmonella	1	0.1
Toxoplasmosis	34	3.5
Tuberculosis	62	6.4
Wasting/Weight Loss	278	28.3
Zoster	1	0.1

Swiss Cohort Study

Hasse B et al. Clin Infect Dis. 2011;53:1130-1139

Endpoint	Total (%)	Rate (95% CI)/1000PY
Bacterial Pneumonia	201 (20)	9.03 (7.87-10.4)
Fracture	123 (12.4)	5.48 (4.60-6.54)
Non-AIDS malignancy	115 (12.0)	5.12 (4.27-6.15)
CDC Stage B event	100 (8)	4.52 (3.72-5.51)
CDC Stage C event	95 (8)	4.32 (3.53-5.28)
Coronary Angioplasty	76 (7)	3.38 (2.70-4.23)
Diabetes	70 (7)	3.12 (2.46-3.94)
Osteoporosis	61 (6)	2.71 (2.11-3.48)
Myocardial Infarction	55 (5.5)	2.44 (1.88-3.18)
Kidney events	31 (3)	1.37 (0.96-1.95)

Relationship of Potent Therapy to Mortality



From a cohort of 1,255 patients with CD4 count <100 cells/mm³.
 Palella FJ Jr, et al. *N Engl J Med.* 1998;338:853-860.

So What's New in OI's?

- They still occur in the undiagnosed and the untreated.
- They should never occur in a patient followed in a clinic.
- Many can be prevented-HAART is the ultimate prophylaxis.
- IRIS is real.

Opportunistic Infections: Generalities

- Original criteria still hold: CD4 < 200 cells/mm³ or CD4 %<14 or thrush;
- Nadir CD4 count is not significant in terms of current risk;
- Updated resource: **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**
 - <http://aidsinfo.nih.gov/guidelines>

Diagnosing the Opportunistic Infection

- Although there are many potential OI's, most will present as one of a few clinical scenarios:
 - Respiratory distress;
 - Headache or CNS signs/symptoms;
 - Dysphagia/odynophagia
 - Fever, failure to thrive;
 - Diarrhea;

Respiratory Syndromes

- PCP, bacterial pneumonia, less likely MAI, MTB, Histoplasmosis, Cryptococcosis.
 - In the patient at risk:
 - Fever +/- dyspnea, cough, productive or not;
 - Onset may help (PCP can be indolent depending on activity level).
 - CXR can be wnl, should desaturate on exertion (A-a gradient should be elevated)
 - *You must prove that a patient at risk does not have PCP.*

Respiratory Syndromes

- PCP, bacterial pneumonia, less likely MAI, MTB, Histoplasmosis, Cryptococcosis
 - In the patient
 - Fever +/-
 - Onset may be insidious (low on activity level).
 - CXR can be normal or show a gradient
 - should be considered
 - *You must prove that a patient at risk does not have PCP.*

Non AIDS defining illnesses include:
CHF, PE, COPD.

PCP

Organism: *P. jiroveci*; ubiquitous, 2/3 children seropositive by age 4;

Transmission: probable airborne, reactivation > new acquisition;

Incidence: 70-80% of AIDS pts. prior to prophylaxis, now most common new ADE OI in untreated patients.

Prognosis: lethal if untreated; advanced HIV and severe PCP carry 20-40% mortality.

Risk factors: CD4 < 200 cells/mm³ (90%), CD4 < 14%, thrush, wasting, recurrent pneumonia, elevated HIV-1 RNA

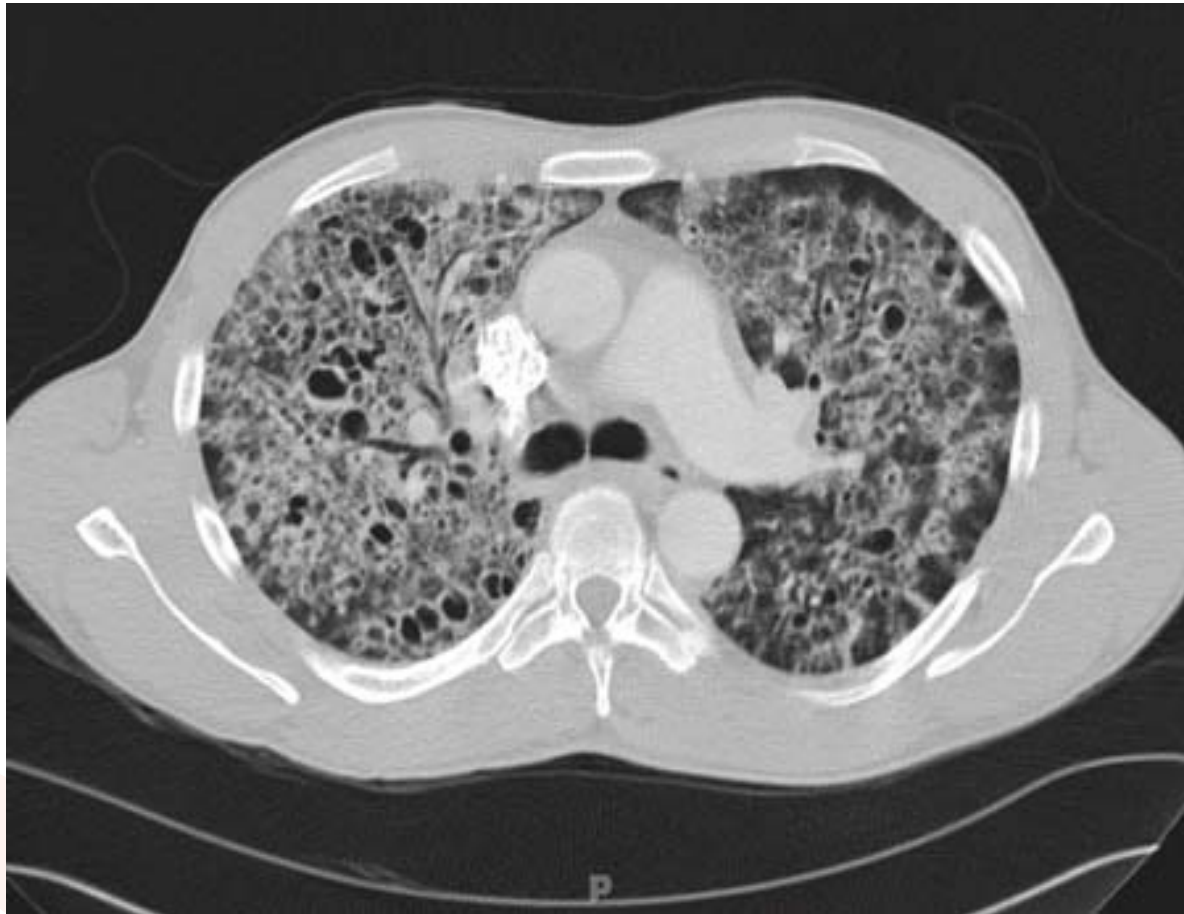
PCP

- Clinical presentation depends on duration of illness, concurrent morbidities and patient's activity level.
- Early disease: fever, dry cough, some dyspnea on exertion, normal CXR and pO₂; O₂ % sat is not ideal marker; *(RA ABG is critical!)*
- Moderate to severe disease: fever, non-productive cough, progressive dyspnea, chest discomfort, headache; associated advanced HIV disease symptoms;
- Pneumothorax in a patient at risk should be considered PCP until proven otherwise.
- Imaging: early disease may have normal CXR; “classic” findings are butterfly-interstitial pattern, all radiologic patterns have been reported. High resolution CT can help determine appropriate course.

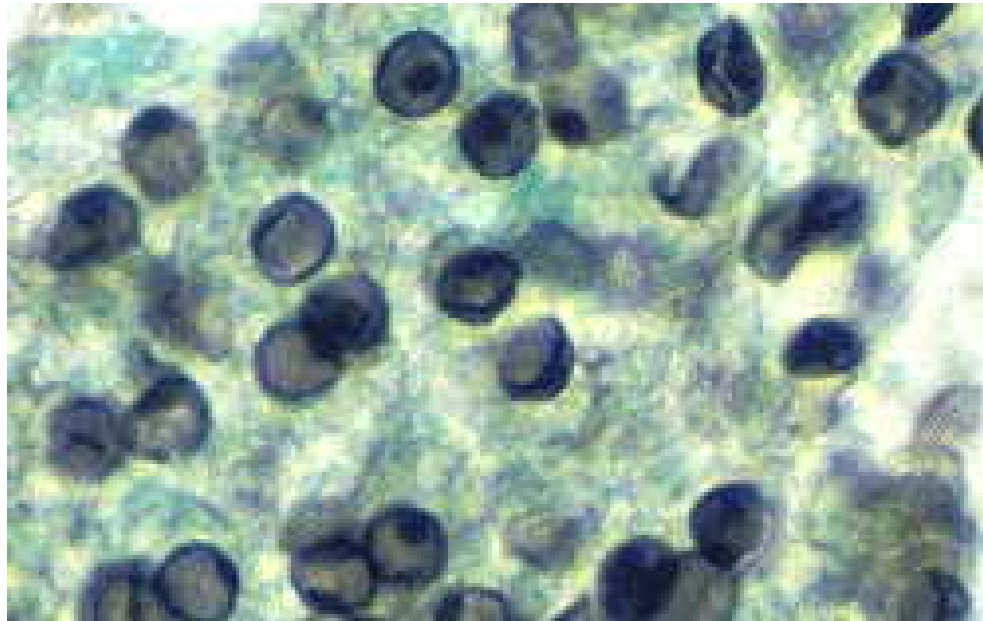
PCP

- Diagnosis:
 - Diagnosis considered in setting of appropriate clinical presentation; (*prove the patient doesn't have PCP*)
 - Organism cannot be cultured, serology is not helpful. Demonstration of organism in tissue required for definitive diagnosis:
 - GMS in BAL (90-99%), Bronch BX (95-99%), spontaneous sputum (50%)
 - Immunofluorescence similar to GMS stains, nucleic acid stains less specific
 - Cysts remain present after treatment;
 - Presumptive diagnosis of PCP may be considered in certain cases.

PCP



PCP



Headache

- In at risk patients headache must be evaluated:
 - Cryptococcus, toxoplasmic encephalitis, CNS lymphoma.
 - Work up should include emergent imaging of brain, cryptococcal and toxoplasma serology. LP can come later.

Headache

- IN at risk patients headache must be evaluated:
 - Cryptococcus, toxoplasmic encephalitis, CNS lymphoma.
 - Work up should include emergent imaging of brain, cryptococcus, and other organisms that can come later.

Bacterial meningitis is not significantly more frequent in HIV. Thrombotic events are more frequent, so stroke is a concern.

Cryptococcal Meningitis

- *C. neoformans* is an encapsulated yeast, inhaled into the small airways where it usually causes sub-clinical disease; dissemination to the CNS is not related to pulmonary response.
- *C. neoformans* produces no toxins and evokes little inflammatory response. The main virulence factor is the capsule.

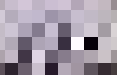
Cryptococcal Meningitis

- Clinical manifestations:
 - headache (70-90%), fever (60-80%), malaise (76%), stiff neck (20-30%), photophobia (6-18%), seizures (5-10%) nausea. (*true meningismus is rare*)
- Average duration of symptoms is 30 days.
- Predictors of poor outcomes are altered mental status, increased opening pressure, WBC<20 cells/mm³.
- Diagnosis made by CSF examination with india ink (74-88%), Crypto Ag serum/CSF (99%), CSF culture.
- Level of Crypto Ag is not indicative of severity of disease nor a marker of response to therapy. Serum Crypto Ag can rule out clinical disease in HIV positive but not negative patients.

Cryptococcal Meningitis

- Increased ICP is closely linked to mortality;
 - Patients with elevated pressures must have serial LP's until pressures are normal;
 - Patients who either do not tolerate daily LP's or deteriorate neurologically despite serial LP's should undergo CSF shunting;
 - Steroids, mannitol and acetazolamide are not effective in treating increased ICP;
- Up to 30% of patients with cryptococcal meningitis have shown signs of IRIS on initiation of HAART;
- No environmental recommendations or primary prophylaxis are recommended.



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CNS syndromes

- In patients with advanced disease, focal neurologic findings must be emergently evaluated.
 - CNS intracranial lesions (toxoplasmosis, lymphoma, cryptococcosis) as well as spinal lesions (toxoplasmosis, lymphoma, Mycobacterium tuberculosis, HIV myelopathy) must be considered.
 - Lower extremity motor loss can be due to central, spinal or demyelination processes.
 - CMV can cause central or ocular lesions.

CNS syndromes

- In patients with advanced disease, focal neurologic findings must be emergently evaluated.
 - CNS intracranial lesions (toxoplasmosis, lymphoma, cryptococcoma) as well as spinal lesions (HIV myelopathy) must be considered.
 - Lower extremity weakness, sensory deficits, and spastic paraparesis are common in HIV myelopathy. Acute findings must be worked up emergently. Chronic neurologic complaints are common in HIV infected individuals.
 - CMV can cause periventricular lesions.

Peripheral Neuropathy

- Two most frequent types: **DSPN** and **toxic neuropathy**. Clinical manifestations are similar. Both present as sensory symptomatology with little sensory dysfunction. Both usually involve the lower extremities, show absent achilles DTR's and axonal degeneration on NCS. Patients can have negative NCS/EMG and abnormal findings on skin biopsy and examination of epidermal nerve fibers. Differentiating between the two syndromes is based on history and concurrent meds.

Peripheral Neuropathy

- DSPN is a frequent (30%) complication of advanced HIV. Course is gradually progressive and may be severe enough to disable patient. Factors associated with DSPN include low CD4 count, high viral load, concurrent ADC.
- Toxic neuropathy is associated with antiretrovirals and other medications. Factors associated with toxic neuropathy include length of time on neurotoxic medications, pre-existing neuropathic syndrome, concurrent administration of multiple neurotoxic agents.

Progressive Motor Syndromes in HIV

- IDP can present very early in disease as AIDP, with rapid progressive involvement of muscles of two or more limbs. Sensory involvement may precede motor. Course may resemble GBS.
- CIDP is a slower progressive, principally motor, syndrome of the lower extremities which may have relapsing course over several months.
- NCS shows slow nerve conduction velocities and findings c/w primary demyelination. Some axonal degeneration may be present. AIDP findings may be less pronounced. Sural nerve bx results show perineural edema, perivascular infiltrates and macrophage mediated segmental demyelination. CMV inclusion in Schwann cells have been identified in late stage CIDP.
- Treatment options include plasmapheresis, IV Ig, prednisone which have all shown efficacy but are often of temporary benefit. Up to 15% of patients will resolve without specific therapy.

Progressive Motor Syndromes in HIV

- Other causes of motor weakness include:
 - CMV disease and HIV-1 Myelopathy
 - Cord lesions caused by infectious/neoplastic processes are usually more fulminant, have discrete sensory levels, include back pain, may involve thoracic or cervical spine and should have imaging or CSF findings c/w diagnosis.
 - Patients from endemic areas should be tested for HTLV-I co-infection.
 - Rarely, mononeuritis multiplex may present as motor weakness.

Dysphagia/Odynophagia

- Very common manifestation of AIDS, one of the most frequent ADE's in large studies.
 - Coated tongue is often misdiagnosed as thrush with significant consequences.
 - Thrush is usually not painful, often absent in the setting of esophageal candidiasis.
 - Dysphagia or Odynophagia can be easily handled in the outpatient setting following a fairly simple protocol.

Dysphagia/Odynophagia

- Very common manifestation of AIDS, one of the most frequent
- Coated tongue is a significant sign of HIV infection.
 - The presence of oral thrush is a sign of advanced immune suppression and is at risk for CMV.
 - Dysphagia/odynophagia can be examined then if no HSV lesions, 48 hour trial of oral fluconazole. If no response move to EGD and consider empirically treating HSV. Patients with advanced immune suppression are at risk for CMV.
- Dysphagia/odynophagia can be managed in the outpatient setting following a fairly simple protocol.

Oral Candidiasis



Atrophic Oral Candidiasis



Oral Hairy Leukoplachia



Angular Cheilitis



Coated Tongue



Mucocutaneous Candidiasis

- Oropharyngeal, esophageal and vulvovaginitis are common complications;
 - Oropharyngeal candidiasis:
 - painless white exudate on buccal, oropharyngeal or tongue surface;
 - Diagnosed visually, scraping with KOH will identify yeast forms;
 - Culture may be indicated if resistance is considered;
 - Isolated coated tongue is not usually candidiasis;
 - Angular cheilitis may be present;

Mucocutaneous Candidiasis

- Esophageal candidiasis:
 - Usually presents with dysphagia (“food sticking”), less frequently odynophagia (retrosternal burning);
 - May be aggravated by reflux disease;
 - Diagnosis is made either by response to empiric therapy or by endoscopic evaluation;
 - Common presenting symptoms in the ED;
 - Treatment choice may be based on multiple factors: history of recurrence, history of clinical or microbiological resistance (c. glabrata or kruzeii), prior toxicities and insurance/availability status;

Fever, Failure to Thrive

- Broad category of syndromes that present with few localizing signs. Findings may be due to untreated AIDS.
- Most presentations are non-emergent and can be worked up in the outpatients setting.
- Reasons for quick ED evaluation include significant headache, inability to keep fluids down, refractory diarrhea, blurred vision.

Fever, Failure to Thrive

- Broad category of syndromes that present with few localizing signs. Seen in untreated AIDS.
- Most present with fever. Can be worked up in the outpatient setting.
- Reasonable workup includes:
 - Antigen
 - Plasma CMV PCR
 - T-Spot
 - Blood culture for AFB
 - Consider CXR
 - Baseline labs
- Reasonable workup includes:
 - Headache
 - Diarrhea
 - Significant laboratory

Diarrhea in HIV + Patients

- Differential can be broad and influenced by:
 - CD4 count;
 - Antibiotic exposure;
 - Recent food history;
 - Sexual practices;
 - Travel or country of origin.

Cryptosporidiosis

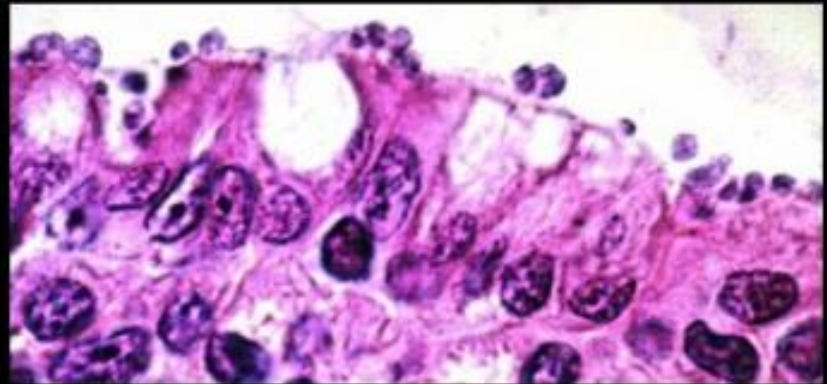
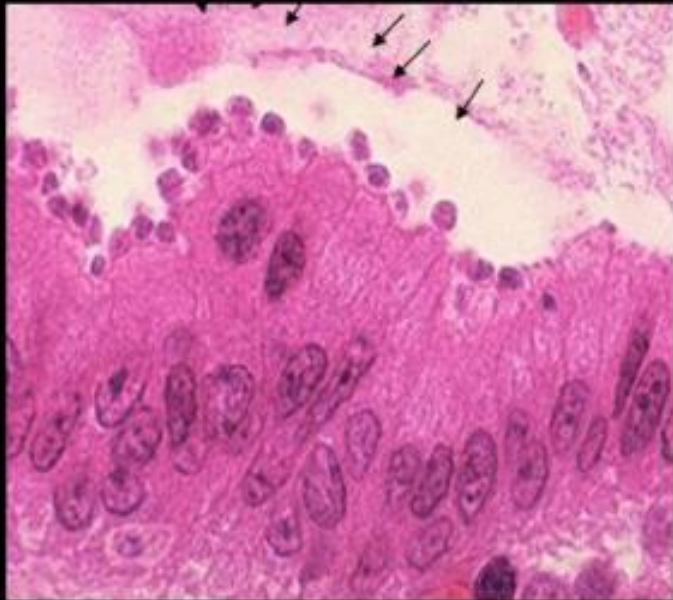
- Cryptosporidiosis is a protozoan infection of the upper and lower bowel caused by three organisms: *C. hominis*, *C. parvum*, *C. meleagridis*;
- Infection occurs through ingestion of oocytes;
- Exposure can occur with infected feces from humans, animals, contaminated water and standard water supplies;
- Person to person transmission is common with MSM;

Cryptosporidiosis

- Clinical presentation:
 - In advanced disease, insidious onset of watery, foul-smelling diarrhea, cramping, flatulence, weight loss, fever (30%);
 - Nausea and vomiting may occur as patient becomes more dehydrated;
 - Severe malabsorption may occur;
 - Biliary tract involvement can occur in a small percentage of patients
 - Self-limiting enteritis can occur in HIV patients with adequate CD4 cell counts;

Cryptosporidiosis

- Diagnosis:
 - Stool examination with modified acid fast staining is very sensitive in high volume diarrheal illness;
 - Direct immunofluorescence of stool sample most sensitive;
 - Colonoscopy may add sensitivity, upper GI endoscopy with biopsy increases sensitivity for patients with enteritis;
 - Evaluation for diarrheal syndrome should always include studies for cryptosporidia in patients with advanced disease;



Intestinal (duodenal) biopsies: Cryptosporidia are seen adhering to the epithelial cells (arrows)

www.aids-images.ch



Intestinal (duodenal) biopsies: Cryptosporidia are seen adhering to the epithelial cells in these images obtained by the scanning electron microscope

Picture credits: (left) www.stanford.edu/class/humbio103/ParaSites2005/Cryptosporidiosis
(right) McDonald V, at <http://www.icms.qmul.ac.uk/centres/gastroenterology/staff-research.htm>

www.aids-images.ch

Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS occurs in patients who are responding to HAART and experiencing a recovery of their immune system.
- It is more likely to occur in the first 6-12 weeks, in patients who have a robust response from a low baseline CD4 count.
- The most worrisome pathogens involved include cryptococcus, MAI, MTB, CMV and KS.

Immune Reconstitution Inflammatory Syndrome (IRIS)

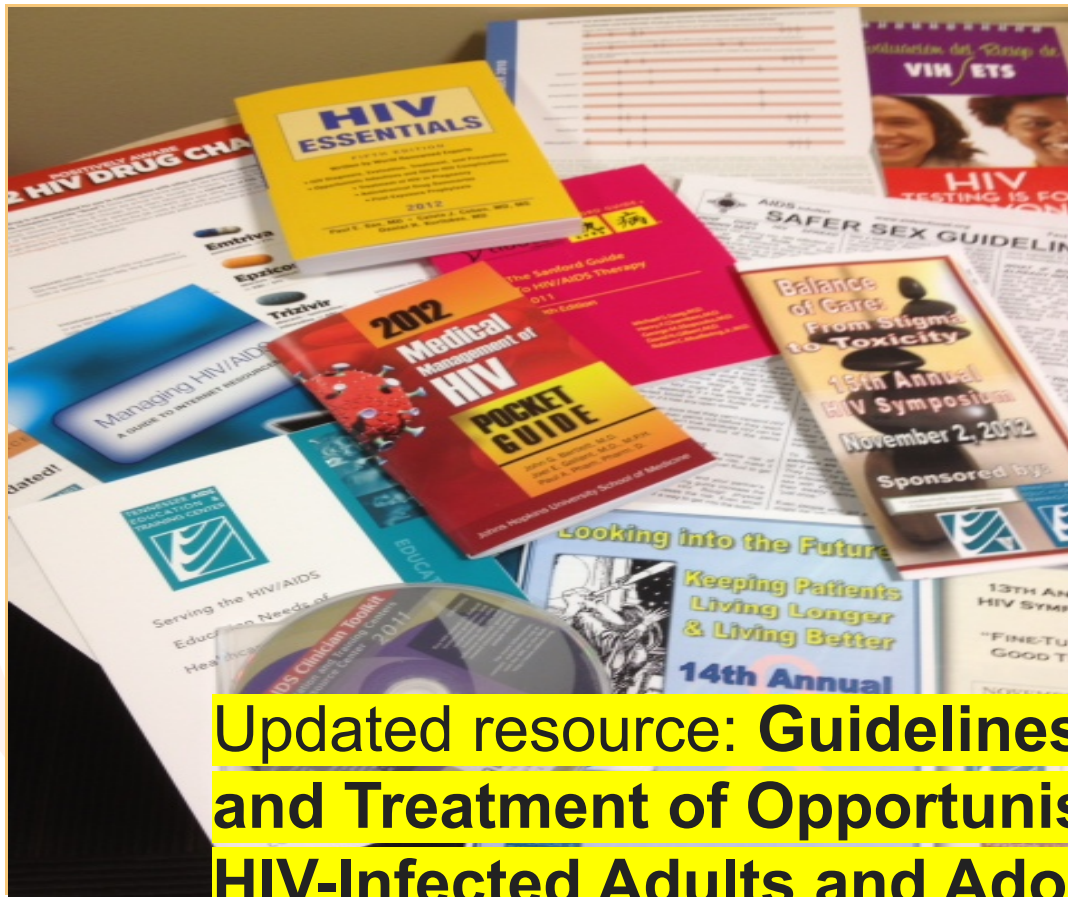
- IRIS occurs in patients who are responding to HAART and experiencing a recovery of their immune system.
- It is more likely to occur within 2-6 weeks, in patients who have a low baseline CD4 count.
- The most common pathogens that cause IRIS include cryptococcus, MAI, and CMV.

IRIS usually presents as a febrile illness with symptoms related to pathogen involved.

Summary

- Opportunistic Infections still occur in HIV infected patients at risk.
- The most frequent can be evaluated quickly following well-established protocols.
- Triaging HIV infected patients is based on recent evaluation of immune status (risk).
- IRIS should be considered in patients recently started on HAART.

Resources



Updated resource: **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

<http://aidsinfo.nih.gov/guidelines>

Useful HIV Websites

WWW.SEAETC.com

www.vanderbilthealth.com/vccc

www.aidsinfonyet.org

www.aidsetc.org

www.hivatis.org (DHHS, USPHS/IDSA Guidelines)

www.cdc.gov/nchstp/hiv_aids.htm

www.hiv-web.lanl.gov (Resistance mutations)

www.niaid.nih.gov

www.AIDS.medscape.com

www.hopkins-aids.edu

www.iapac.org

www.igm.gov

www.centerwatch.com

www.ucsf.edu/medical

www.virology.net