Divya Ahuja, MD, MRCP (London) Prisma-University of South Carolina School of Medicine

Patient seen in the Emergency Department

Diagnostic Results

Testicular ultrasound: Evidence of epididymitis, orchitis with a complex hydrocele

Emergency Department Course

The patient was evaluated by myself in the emergency department. He has remained hemodynamically stable however he was tachycardic upon initial evaluation. I went ahead and treated him with Rocephin and azithromycin. For orchitis and epididymitis the 250 mg of intramuscular Rocephin and 2 g of azithromycin is indicated. Rest ice and NSAIDs and scrotal support also recommended. I gave him information for Columbia urological Associates for further follow-up.

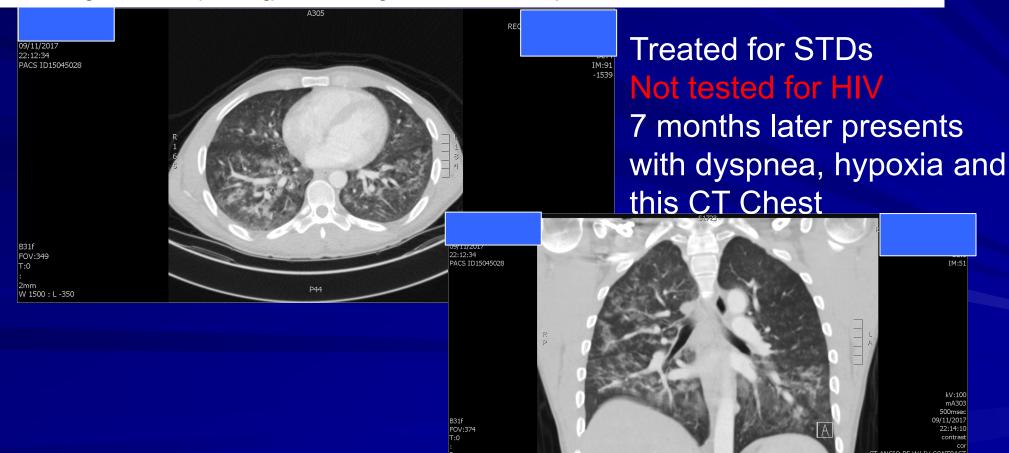
Treated for GC and

Assessment

Orchitis, epididymitis, hydrocele

Disposition

The patient was discharged home to follow up with Urology. Instructions were given to return to the ER with any concerns.



Chlamydia



Volume 25, Number 1

Estimated HIV Incidence and Prevalence in the United States 2014–2018

- US population- 330 million
- HIV -estimated 1.2 million aged 13 and older
- Thus HIV prevalence > 1/330 Americans
 - Males- 0.7% (1/150 male Americans)
 - Females-0.2%



Recommendations for Initiating ART

- In 2016, estimated 39,782 new diagnoses of HIV
 - 81% (32,131) of these new diagnoses in males
 - 19% (7,529) were among females.
- ART (Antiretroviral therapy)
 - Recommended for all HIV-infected individuals to reduce the risk of disease progression.
- Easier to treat than COPD, Heart Disease, CHF or Diabetes







US DHHS & IAS-USA Guidelines: Recommended Regimens for First-Line ART in People Living With HIV

Class	DHHS ^[1]	IAS-USA ^[2]
INSTI	 BIC/TAF/FTC (AI)* DTG/ABC/3TC (AI)* DTG + TAF or TDF/FTC or 3TC (AI) RAL + TAF or TDF/FTC or 3TC (BI; BII) DTG/3TC (AI) 	 BIC/FTC/TAF* DTG/ABC/3TC* DTG + FTC/TAF

^{*}Single-tablet regimens.

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status or intent
- No currently recommended first-line regimens contain a pharmacologic-boosting agent
- With FDA approval of 1200-mg RAL,^[3] all options now available QD (except in pregnancy)^[4]

^{1.} DHHS ART. Guidelines. December 2019; 2. Saag. JAMA. 2018;320:379 (in revision 2020). 3. Raltegravir Pl. 4. DHHS Perinatal Guidelines. October 2018.

HIV: Single Tablet Regimens







Complera



Dovato



Genvoya

Juluca



Triumeq







Odefsey

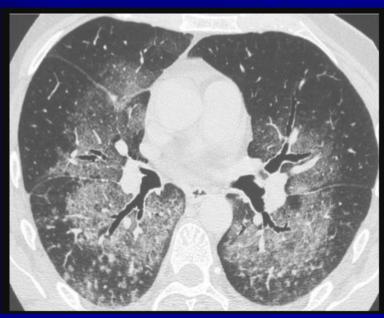


Biktarvy

Case

- 20 year male, newly diagnosed HIV, CD4< 100,
- Presented with a pneumonia, dry cough
- Oral thrush, Hb-11.3, other labs normal, LDH-260





AIDS and Pulmonary complications

- Bacterial pneumonia
- COPD
- PCP (Pneumocystis jirovecii)
- Tuberculosis
- Other opportunistic infections
 - Cryptococcus
 - endemic mycoses (Histoplasma, Coccidiodes, and Blastomyces)
 - Rhodococcus
 - Penicillium (Talaromyces) marnafeii
- Lymphocytic Interstitial Pneumonitis
- Malignancies

Pneumonia in HIV

- When in doubt, Respiratory isolation for Tb
 - Streptococcus. pneumoniae is increased > 100 fold
 - PCP
 - Tuberculosis
 - Other atypical pathogens
 - Cryptococcus
 - Histoplasma

Bacterial pneumonia

- The most frequent cause of lower respiratory tract infection in patients with HIV
- In Strategic Timing of AntiRetroviral Treatment (START) study
 - 40% of serious bacterial infections were due to bacterial pneumonia
- S. pneumoniae, Haemophilus, Pseudomonas, Staphylococcus aureus, Klebsiella
- Risk factors
 - Low CD4 cell count
 - Absence of ART
 - Tobacco smoking
 - IVDU
 - Infectious hepatitis
- Influenza vaccination rates 26–57% in cohort studies- vaccinate

Seasonal influenza vaccination rates US 1999-2013; Clin Infect Dis. 2015 Mar 15;



Community acquired pneumonia

- CAP
- Acute onset (3–5 days) of symptoms, fevers, chills, rigors, chest pain, cough productive of purulent sputum, and dyspnea.
- Incidence of invasive pneumococcal disease (including bacteremia)
 - Significantly higher in individuals with HIV
 - 173 cases / 100,000 in those with HIV infection
 - General population
 - **3.8 / 100,000 in adults aged 18–34 years**
 - 36.4 / 100,000 among those aged ≥65 years
- (Vaccinate PCV13 and PPSV23)



CAP guidelines

- Blood Cultures- only in severe CAP
 - Yield of blood cultures in most series of adults with nonsevere CAP is low
 - 2% (outpatients) 9% (inpatients)
- Influenza
 - recommend testing for influenza with a rapid influenza molecular assay (i.e., influenza nucleic acid amplification test

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia					
	Standard Regimen				
No comorbidities or risk factors for MRSA or <i>Pseudomonas</i>	Amoxicillin or				
aeruginosa <u>*</u>	doxycycline or				
	macrolide (if local pneumococcal resistance is <25%) [±]				
With comorbidities [‡]	Combination therapy with				
	amoxicillin/clavulanate or cephalosporin				
	AND				
	macrolide or doxycycline [§]				
	OR				
	monotherapy with respiratory fluoroquinolone.				

 $Definition \ of \ abbreviations: \ \mathsf{ER} = \mathsf{extended} \ \mathsf{release}; \ \mathsf{MRSA} = \mathsf{methicillin-resistant} \ \mathit{Staphylococcus} \ \mathit{aureus}.$

*Risk factors include prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics (in the last 90 d).

[†]Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily.

‡Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.

SAmoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2,000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily; AND azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, clarithromycin ER 1,000 mg daily, or doxycycline 100 mg twice daily.

Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily.



PCP

- Pneumocystis pneumonia remains a leading cause of opportunistic infection
 - Pneumocystis spreads by the airborne route.
 - Disease probably occurs by new acquisition of infection and by reactivation of latent infection
- Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART)
 - PCP occurred in 70% to 80% of patients with AIDS
 - 90% of PCP cases occurred in patients with CD4 <200 cells/mm³

Risk Factors for PCP

- CD4 < 200 or CD4 cell percentage <14%
- Previous episodes of PCP
- Oral thrush
- Recurrent bacterial pneumonia
- Not on Prophylaxis
- Unintentional weight loss, and higher plasma HIV RNA levels

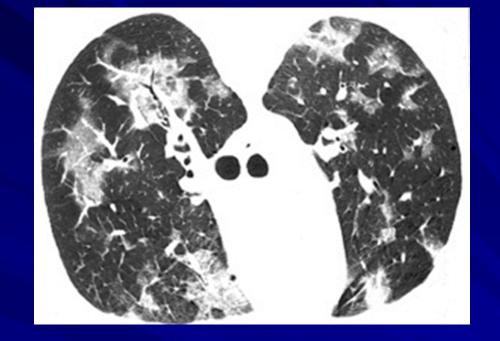
Gingo PLoS One. 2013; 8(3):e58812.



PCP

- Subacute pneumonia caused by Pneumocystis jirovecii
- Ubiquitous organism
 - Upto 83% of infants had Pneumocystis antibody titers> 1:16 by 7 months
- S/S
 - Dyspnea, dry cough, chest discomfort, fever
 - CXR normal in 10-20%, CD4 > 200 in 10-20%
 - Cavitation and pleural effusion are uncommon
- A normal CT chest has a high negative predictive value

PCP







Diagnosis of PCP

- Pneumocystis cannot be cultured
- Direct visualization of cysts in sputum by silver stain
 - poor sensitivity (50%)
- Direct Fluorescent Antibody
 - Sputum or BAL: highest sensitivity and specificity for antigen
- 1,3B-D-glucan: component of fungal cell walls
 - β-glucan > 80pg/ml Sensitivity 92%, specificity was 65% Sax PE, CID. Jul 15 2011;53.; E. Karageorgopoulo, 2012, Clinical Microbiology and infection
- LDH: > 300 has 85% sensitivity; poor specificity
- PCR is highly sensitive and specific
 - PCR cannot distinguish colonization from disease; (Li-Chao Fan, PLOS one 2013)
 - Reduced serum S-adenosylmethionine

Treatment

- Trimethoprim/Sulfamethoxazole
 - 5 mg/kg Q6-8 hours IV or 2 DS PO TID
 - Adjust for creatinine clearance
- Corticosteroids if PO2 < 70
 - Reduces the inflammatory response from destruction of the fungus within alveoli
- Clindamycin and primaquine
- Other alternatives
 - Pentamidine IV
 - Atovaquone

Pregnancy: TMP-SMX

Clinical failure: lack of improvement or worsening

after at least 4 - 8 days of Rx

Summary of Five Controlled Trials Evaluating Adjunctive Corticosteroid Therapy for PJP

Table 1. Summary of Five Controlled Trials Evaluating Adjunctive Corticosteroid Therapy for AIDS-Related Pneumocystis Pneumonia.*

VARIABLE	STUDY				
	A	3	c	D	£
Site No. of patients evaluated	Vancouver 38	California 251	Miami 23	Europe 53	San Francisco 41
Randomized	Yes	Yes	Yes	Yes	Yes
Placebo controlled	Yes	No	Yes	No	Yes
Oxygenation entry criteria	Saturation 85-90% on room air†	Hypoxemia ratio >75	Arterial pressure <75 mm Hg at 35% inspired fraction	Arterial pressure <67.5 mm Hg on room air	Arterial pressure <51 mm Hg on room air
Maximal interval between initiation of antipneumocystis drug and corticosteroid (hr)	48	36	72	24	Unlimited
Corticosteroid therapy Drug (route) Initial dose Duration (days)	Prednisone (oral) 60 mg daily 21	Prednisone (oral) 40 mg every 12 hr 21	Methylprednisolone (IV) 40 mg every 6 hr 7-10	Methylprednisolone (IV) 0.5 mg/kg every 6 hr 10	Methylprednisolone (IV 60 mg every 6 hr 8
Outcome — % corticosteroid/% r	no initial				
Death Mechanical ventilation Substantial deterioration in oxygenation	6/0 NA NA	14/29‡ (0.01) 15/33 (0.003) 17/37 (0.002)	25/82 (0.008) 25/82 (0.008) NA	7/32 (0.02) 11/44 (0.007) NA	31/37 (0.75) NA NA

^{*}IV denotes intravenous, and NA not available. †At rest, or a 5 percent decrease with exercise on pulse oximetry. ‡For patients whose hypoxemia ratio at entry was between 75 and 350.



- Primary Pneumocystis prophylaxis
 - Discontinued for patients with an increase in CD4 counts from <200 cells/mm³ to >200 cells/mm³ for >3 months
- Primary and secondary PCP prophylaxis can be safely discontinued
 - In patients with CD4 counts between 100 200 and undetectable HIV RNA

Indications	First Choice	Alternative
CD4 count < 200 cells/mm³ (AI) or Oropharyngeal candidiasis (AII) CD4 < 14% cells/mm³ or history of AIDS-defining illness (BII) CD4 count > 200 but < 250 cells/mm³ if monitoring CD4 count every 1-3 months is not possible (BII)	TMP-SMX 1 DS qd (AI); or TMP-SMX 1 SS qd (AI)	 TMP-SMX 1 DS 3x/wk (BI); or Dapsone 100 mg qd (BI) or Dapsone 50 mg bid (BI); or Dapsone 50 mg qd + Pyrimethamine 50 mg qwk + Leucovorin 25 mg qwk (BI); or Aerosolized pentamidine 300 mg via Respigard II nebulizer qmonth (BI); or Atovaquone 1500 mg qd (BI); or Atovaquone 1500 mg qd + Pyrimethamine 25 mg qd + Leucovorin 10 mg qd (CIII)

Mocroft A, Clin Infect Dis. Sep 1 2010;51(5):611-619

 Fungi — The three most important causes of fungal pulmonary infection are Pneumocystis jirovecii, Aspergillus species (especially A. fumigatus), and C. neoformans



Cryptococcal pulmonary disease

- Indolent or subacute pulmonary disease
 - Diffuse pulmonary infiltrates or nodules
- Disseminated disease and cryptococcal meningoencephalitis
- Check Serum Cryptococcal Antigen in PLWH with CD4 < 100 and unexplained fever, infiltrates, weight loss etc.
- Fluconazole 6mg/kg PO daily times 6-12 months





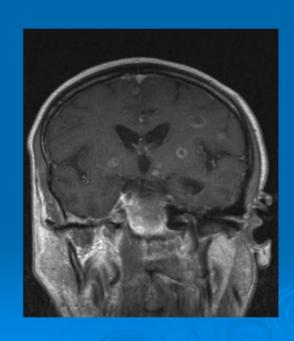
Example of cryptococcal pneumonia





Cryptococcal Meningo-encephalitis

- C. neoformans
 - encapsulated yeast, acquired by inhalation
- Clinical manifestations are Subacute
 - Headache, fever, malaise,
 - Average duration of symptoms is 30 days
- Tests
 - Serum cryptococcal antigen
 - Cerebrospinal fluid (CSF)- crypto Ag- 99%
- Treatment:
 - IV Amphotericin and PO Flucytosine
 - Maintenance therapy with PO Fluconazole





37 year Chinese male now has AIDS

- Penicillium (Talaromyces) marneffei
- Disseminated and progressive infection
- 3rd most common opportunistic infection in PLWH in certain parts of Southeast Asia.
 - Common clinical features include fever, weight loss, and anemia.
 - The organism has been isolated most commonly from skin, blood, and bone marrow

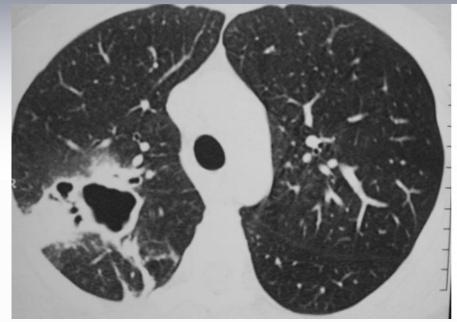


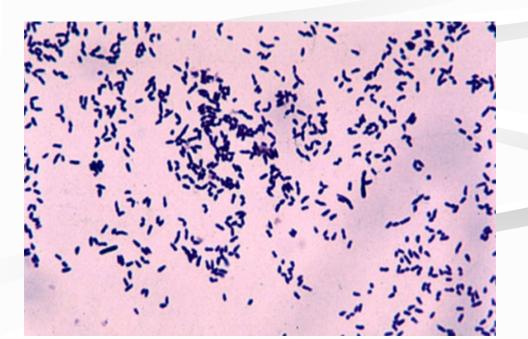






42 year male with AIDS





Rhodococcus

- Rhodococcus
 - Gram positive coccobacillus
 - Also weakly acid fast
 - Nodular infiltrate, 50% cavitate
 - Subacute to chronic illness, but high fever, hemoptysis common
 - CNS including meningitis, skin involved
 - Bacteremia in > 50%
- Rx macrolides, quinolone with/without rifampin for oral; Vancomycin or Carbapenem IV

Viral pneumonias

- CMV
 - Culture from BAL or cells showing cytopathic change do NOT need treatment
 - Treatment when concomitant pathogens are present is NOT recommended
 - Treat with Valganciclovir or Ganciclovir if other causes excluded
- HSV can be found in respiratory secretions but rarely needs treatment



HIV and COVID outcomes

- New York
 - In a retrospective matched cohort of PLWH and people without HIV
 - In hospitalized patients- outcomes were similar.

 Savannah K-T Journal of acquired immune deficiency syndromes.
- New York
 - Outcomes of people with and without HIV hospitalized for COVID-19 were similar
 - Traditional markers of HIV such as
 - HIV Viral Load
 - CD4
 - Have not been strongly associated with COVID-19 morbidity among PLWH
 Sigel K, Clinical Infectious Diseases 2020.
- South Africa
 - PLWH were 2.3 times as likely to die from COVID-19 as people without HIV, after age and sex standardization



Is Anti-retroviral therapy protective in COVID-19? Don't know!

- Protease Inhibitors
 - Initial excitement about Kaletra and Darunavir has faded
- NRTIs
 - Small cohort (n=88) of PLWH hospitalized with COVID-19 in New York City
 - Being on a nucleoside reverse transcriptase inhibitor was protective against death Sigel K, Clinical Infectious Diseases 2020.

Cohort of over 77,000 PLWH receiving ART in Spain

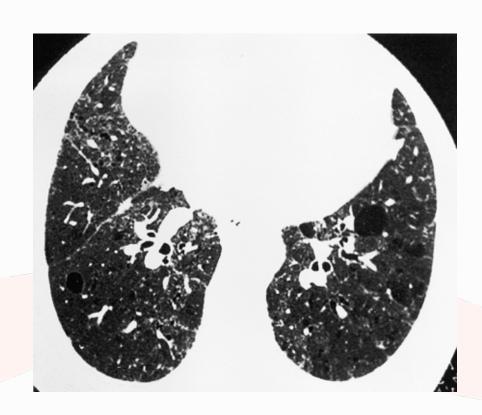
Tenofovir/emtricitabine was protective against COVID-19 & hospitalization

del Amo J, Annals of Internal Medicine 2020.



Lymphocytic Interstitial Pneumonia

- Rare form of Interstitial lung disease
 - Seen more in children with AIDS
- Associated with RA, Sjogren's, HIV
- Form of pseudolymphoma
 - Dysproteinemia
 - Weight loss
 - Fevers
 - Arthralgias
- Poor prognosis





HIV Infection and Cancer Risk

- In one study, HIV infection was independently associated with a hazard ratio of 3.6 for lung cancer
 - Kirk GD, Clin Infect Dis 2007;45:103–110.
- 4194 HIV-infected patients in a French cohort study.
- Total of 251 new cases of cancer were diagnosed in > 4000 patients
 - 107 were AIDS-defining and 144 were not.
- Most common AIDS-defining cancer
 - Non-Hodgkin lymphoma
 - The most non-AIDS defining cancer: lung cancer
 - Bruyand M et al. Clin Infect Dis 2009 Oct 1; 49:1109.



Kaposi's Sarcoma

- Usually cutaneous or oral but visceral involvement also occurs
- Causative organism human herpes virus 8 (HHV-8)
- Seroprevalence in United States = 1-5%
 - Higher in MSM regardless of HIV serostatus

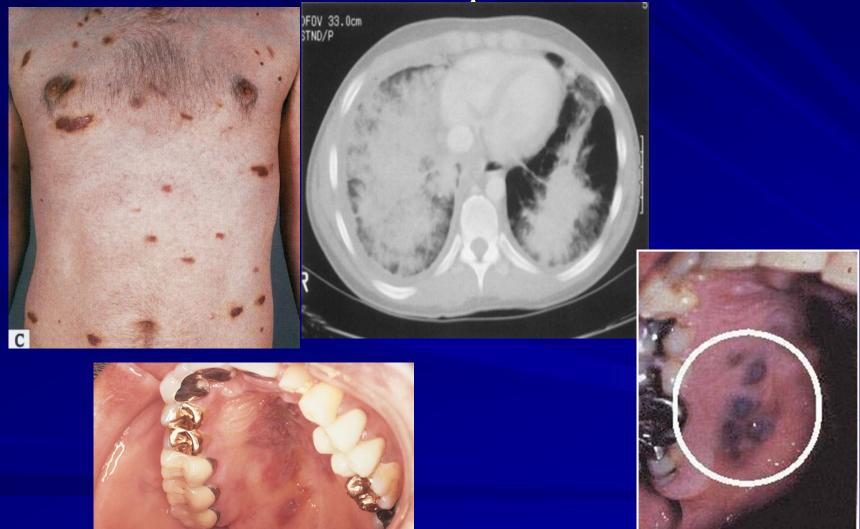
Presentations:

GI, respiratory tract

Primary Effusion Lymphoma

- lymphomatous growth in body cavities :pleural, pericardial, peritonium
- Multicentric Castleman's disease
- Treatment
 - ART
 - Chemotherapy

Presentation of Kaposi's sarcoma



Ptoto Credit: Boston University

COPD

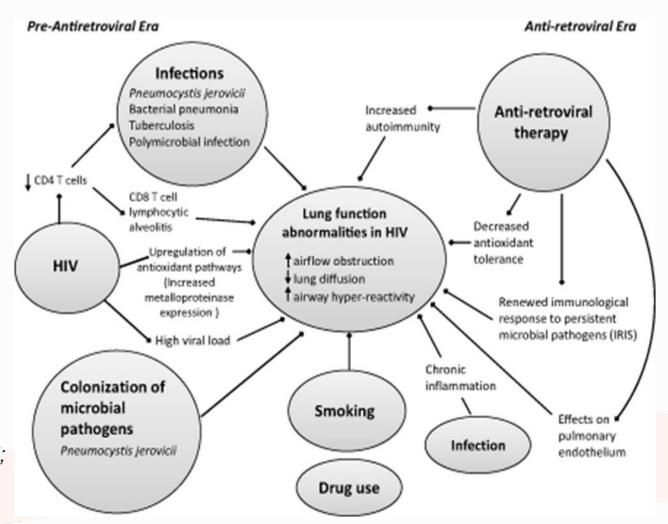
- In one study 23% of HIV infected smokers had emphysema compared to matched controls
- Predisposing factors include
 - Risk behaviors(smoking, IVDU)
 - Repeat infections
 - HIV induced lymphocytic alveolitis
 - Increased oxidative stress
 - Increased apoptosis due to HIV proteins Tat and Nef



COPD

- PLWH infrequently get diagnostic pulmonary function testing
- Six-minute walk distance
 - Validated measure of functional capacity
- PFTs
 - Spirometry
 - HIV independent risk factor for DL_{CO} impairment

COPD in HIV-Infected Patients: Risso K, PLoS One. 2017;





HIV related pulmonary Hypertension

- Prevalence is estimated at approximately 1/ 200 (0.5%) among HIV-infected persons, compared with 1-o 2 cases/ million in the non–HIV-infected population
- Cohort studies in the ART era suggest in 8-35% of PLWH
 - Elevated pulmonary arterial pressures assessed via echocardiogram
 - Clinically significant elevations in the tricuspid regurgitant velocity (TRV)
 - OR Pulmonary artery systolic pressure (PASP)

Sitbon O, Am J Respir Crit Care Med. 2008 Jan 1; 177(1):108-13.

Mondy KE, SUN Study Investigators.Clin Infect Dis. 2011 Feb 1; 52(3):378-86.



Pulmonary Aspergillosis

- Uncommon in PLWH
- Acute invasive (IPA)
- Chronic invasive
- Chronic noninvasive
 - aspergilloma
 - allergic bronchopulmonary

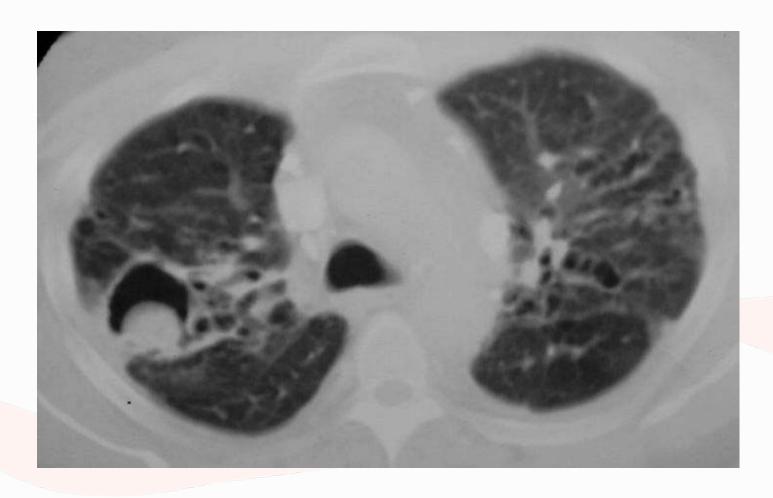


ABPA





Aspergilloma





Immune Reconstitution Inflammatory Syndrome

- Characterized by fever, worsening clinical signs of the OI
 - Or symptoms of new OI
- Associated with a rise in CD4 and/or a fall in viral load
- Usually occurs within first few weeks of ART but may occur up to several months later

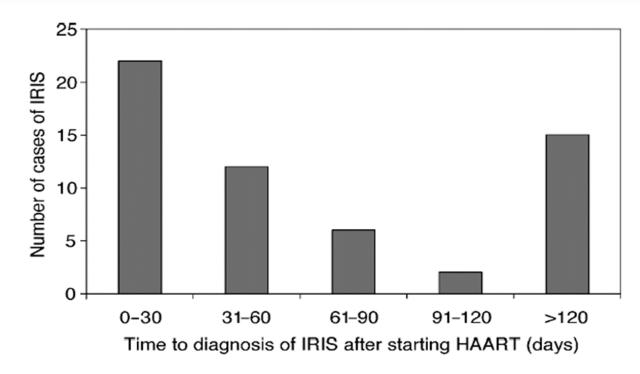


Fig. 1. Time to diagnosis of IRIS after starting HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Parasitic Pneumonia

- Toxoplasmosis
 - Rare but can mimic atypicals
 - Diagnosis is by identification of tachyzoites on Giemsa stain
- Strongyloides stercoralis
- Cryptosporidium
- Microsporidia

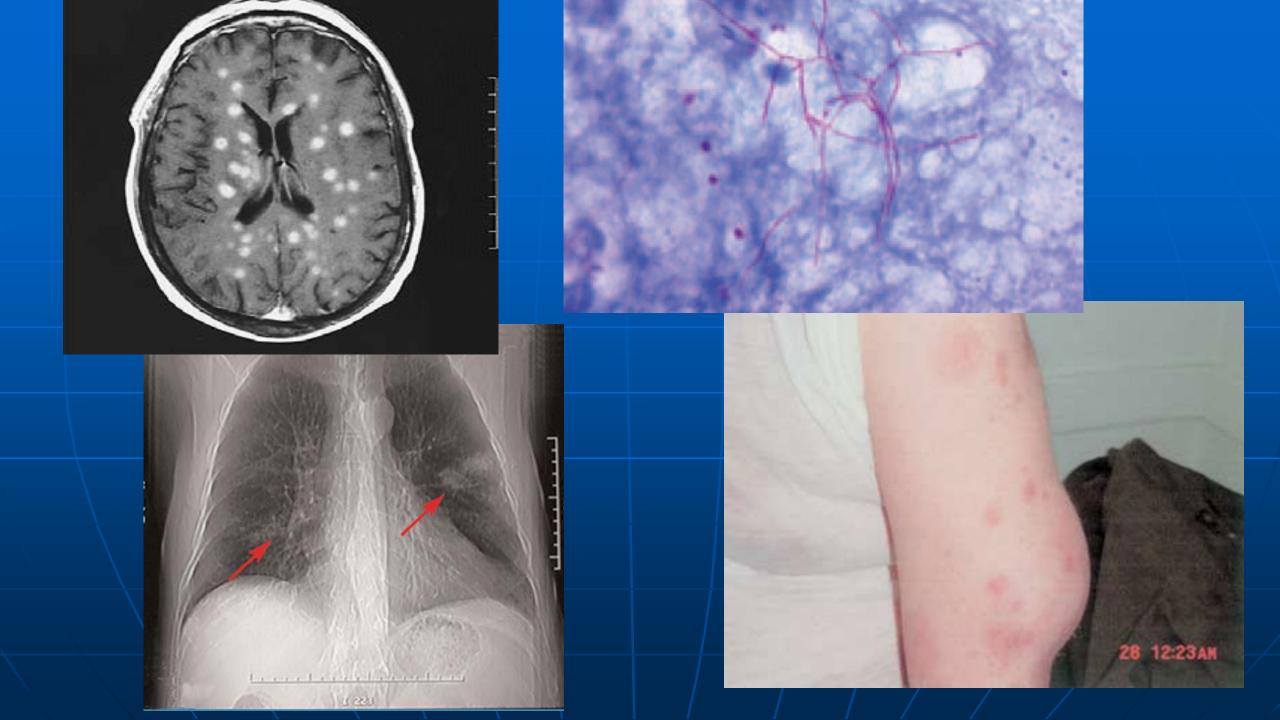


Prophylaxis in PLWH

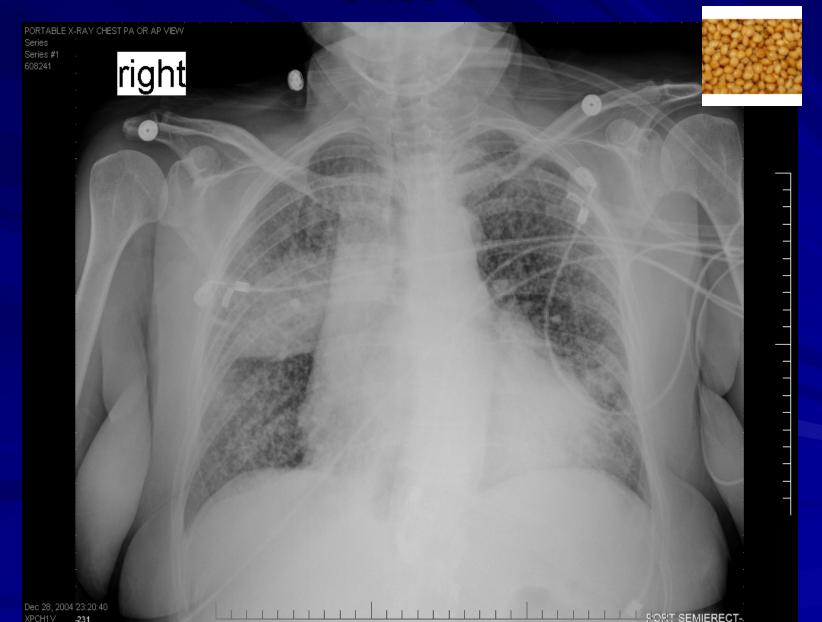
- Pneumocystis jiroveci pneumonia (PCP)- TMP/SMX
- Tuberculosis- IGRA
- Toxoplasmosis- TMP/SMX
- *Mycobacterium avium* complex (MAC)- Azithromycin
- Vaccinations:
 - S pneumoniae
 - Hepatitis A and B
 - Zoster
 - Influenza
 - TDaP
 - Meningococcal
 - HPV
 - COVID-19??

Nocardiosis

- Filamentous, aerobic members of Actinomycetes
- Speciation in evolution; currently N. asteroides complex, nova, brasilensis and farcinica common in USA
- Aerosols, trauma usual entry
- 20% disseminated infection esp. CNS, skin, bone
- 2/3 assoc. with cell-mediated immune dysfunction, also CGD, PAP, anti-TNF agents

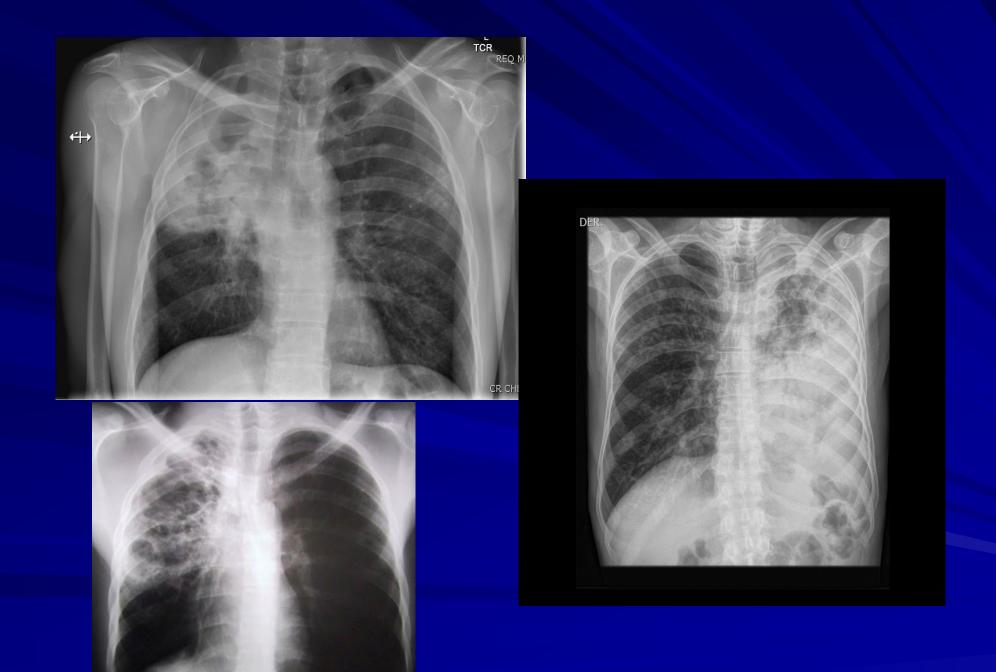


Case?



TB/HIV Co-Infection

- Reactivation of latent TB
 - More likely in HIV-infected patients
 - 7-10% annual risk in HIV-infected patients with positive tuberculin skin test (TST)
 - In HIV uninfected, 5-10% lifetime risk
- The treatment of TB in patients with HIV infection should follow similar principles as for non HIV
- Directly observed therapy is strongly recommended



Tuberculosis treatment

- RIP form the mainstay of treatment and Ethambutol is added protection till susceptibility to first 3 drugs is confirmed
- A 5-8% relapse rate with standard treatment
- When relapse occurs it is usually in the 12 months following treatment
- Shortening the duration to 4 months with a quinolone based regimen lead to an increased relapse rate of 13-20%



TB: Paradoxical Reactions

- Transient worsening of TB symptoms and lesions in response to ATT
- More common in HIV+ pts
 - When associated with ART, designated as IRIS
 - Assoc. with earlier initiation of ART and CD4<50
- Stride/ SaPIT Studies
 - 7.6- 12 % with TB IRIS
 - 69% mild or moderate in severity
 - 31% hospitalized and more than half received corticosteroids





Morbidity and Mortality Weekly Report

February 14, 2020

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020



LTBI

- Guidelines favor rifamycin-based regimens over Isoniazid monotherapy
- Isoniazid and rifapentine weekly for three months (3HP)- recommended.
 - Higher cost
 - But Higher treatment completion rates
 - Drug interactions with weekly rifapentine are fewer than with rifampin
 - Need to take 10 pills once weekly compared with 2-3 daily
 - Relatively low hepatotoxicity rates Rifampin daily for four months (4R)
 - A/E- drug interactions, including warfarin, oral contraceptives, azole antifungals, and HIV antiretroviral therapy
- Isoniazid and rifampin daily for three months (3HR)
- Alternative- INH monotherapy



3HP in HIV infected patients

Median baseline CD4⁺ cell counts were 495 (IQR 389–675) and 538 (IQR 418–729) cells/µl in the 3HP and 9H arms, respectively (P = 0.09).

Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium* tuberculosis infection in HIV-coinfected persons

Sterling, Timothy R.a; Scott, Nigel A.b; Miro, Jose M.c; Calvet, Guilhermed; La Rosa, Albertoe; Infante, Rosae; Chen, Michael P.b; Benator, Debra A.f,g; Gordin, Fredf,g; Benson, Constance A.h; Chaisson, Richard E.i; Villarino, M. Elsab the Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26/ACTG 5259)* * The investigators of the TB Trials Consortium and the AIDS Clinical Trials Group for the PREVENT TB Trial are listed in the Supplement, item 17.

Author Information ⊗

AIDS: June 19, 2016 - Volume 30 - Issue 10 - p 1607-1615 doi: 10.1097/QAD.000000000001098





Monthy 1st and 3rd Wednesday and

12:00pm-1:00pm EST

11:00am-12:00pm CST 09:00am-10:00am PST

4th Wednesday

12:00pm-1:00pm CST 01:00pmpm-2:00pm EST

10:00am-11:00am PST

South East Viral Hepatitis Interactive Case Conference

