

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

A decorative wavy line in a light peach color spans the width of the slide, positioned below the text. At the bottom of the slide, there is a solid dark blue horizontal bar, with a small red rectangular section on the far right.

■ 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.

Assessment

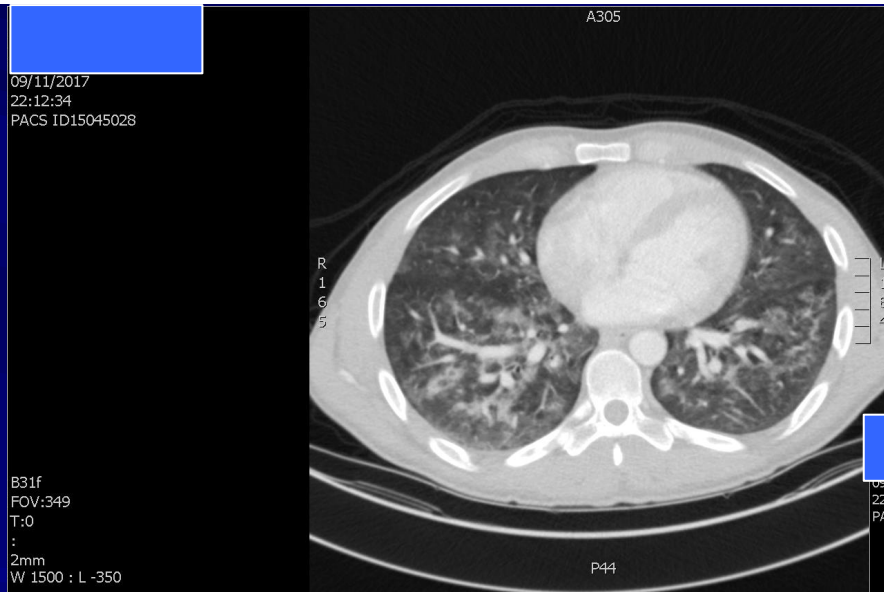
Orchitis, epididymitis, hydrocele

Disposition

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



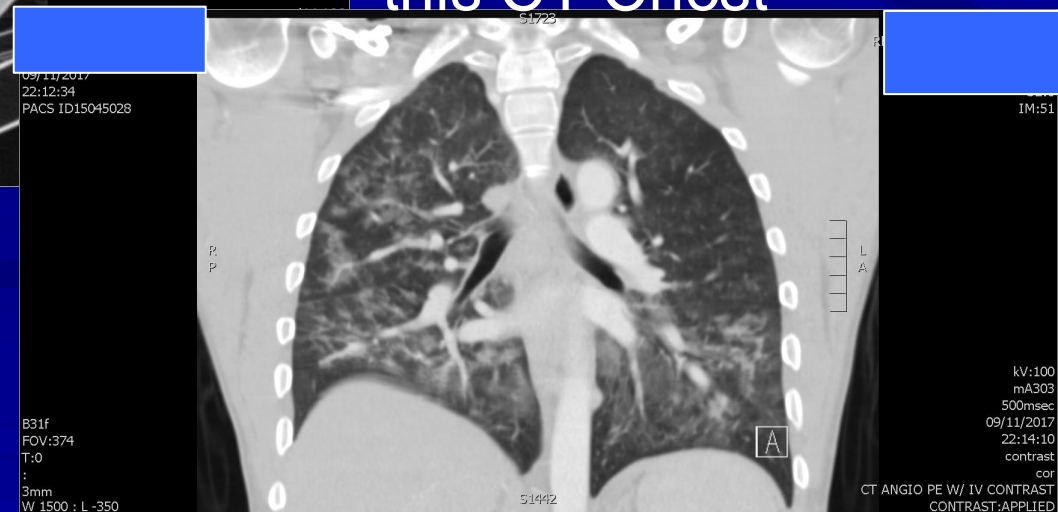
Treated for GC and Chlamydia



Treated for STDs

Not tested for HIV

7 months later presents with dyspnea, hypoxia and this CT Chest



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

- US population- 350 million
- HIV -estimated 1.1 million aged 13 and older
- Thus HIV prevalence $>1/350$ Americans
 - Males- 0.7% (1/150 male Americans)
 - Females-0.2%

United States Preventive Services Task Force recommendations

GRADE A for HIV

Recommendation Summary

Population	Recommendation	Grade
Pregnant persons	The USPSTF recommends that clinicians screen for HIV infection in all pregnant persons, including those who present in labor or at delivery whose HIV status is unknown.	A
Adolescents and adults aged 15 to 65 years	The USPSTF recommends that clinicians screen for HIV infection in adolescents and adults aged 15 to 65 years. Younger adolescents and older adults who are at increased risk of infection should also be screened. See the Clinical Considerations section for more information about assessment of risk, screening intervals, and rescreening in pregnancy.	A

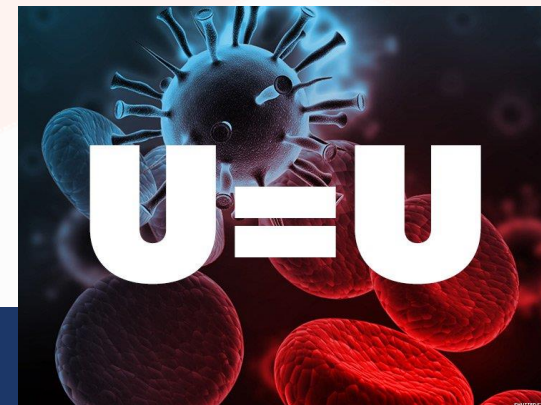
GRADE B for BREAST CANCER SCREEING

Recommendation Summary

Population	Recommendation	Grade
Women aged 50 to 74 years	The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.	B
Women aged 40 to 49 years	The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years.	C

Recommendations for Initiating ART for an HIV infected person

- ART (Antiretroviral therapy or HIV medications) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
- Effective ART reduces transmission to almost “0”
- HIV is easier to treat than Diabetes, COPD, CHF
- Undetectable= Untransmissible



IAS-USA Guidelines- 2004

Wait before starting ART

Table 1. Recommendations for Initiating Therapy in Treatment-Naive Individuals*

Disease Stage	Recommendation	Evidence Rating†
Symptomatic HIV disease	Antiretroviral treatment	IA
Asymptomatic HIV disease		
≤200 CD4 cells/μL	Antiretroviral treatment	II
>200 CD4 cells/μL but ≤350 CD4 cells/μL	Antiretroviral treatment should be considered‡	II
>350 CD4 cells/μL but ≤500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention§	II
>500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention	II

Abbreviation: HIV, human immunodeficiency virus.

*Excludes pregnant women with specific regard to prevention of HIV transmission to the infant.

†See Box for explanation of evidence ratings.

‡The closer to 200 CD4 cells/μL, the stronger the recommendation for treatment, particularly if the plasma viral load is high (>50 000-100 000 copies/mL) or if the CD4 cell count is declining rapidly (>100/μL per year).

§Consider treatment for patients with high plasma viral load or with rapid decline of CD4 cell count.

2021- Initiate ART immediately (or as soon as possible)

DHHS^[1]

- Initiate ART immediately (or as soon as possible) after HIV diagnosis

WHO^[2]

- Recommended where feasible

IAS-USA^[3]

- Start ART as soon as possible, **including immediately after diagnosis**, if patient is ready

The START Trial

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

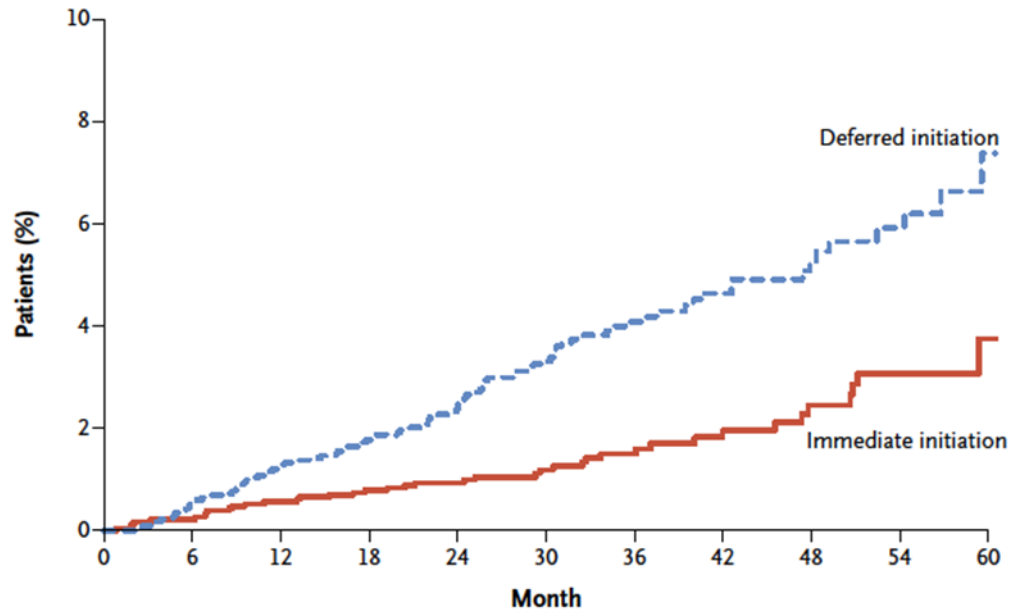
AUGUST 27, 2015

VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic
HIV Infection

The INSIGHT START Study Group*

A Time to First Primary Event



The START Trial

57% reduction in primary end point
of AIDS, non-AIDS cancer, non-
AIDS event or death

HPTN 052- reduction in transmission with ART

ORIGINAL ARTICLE

Antiretroviral Therapy for the Prevention of HIV-1 Transmission

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Suwat Chariyalertsak, M.D., *et al.*, for the HPTN 052 Study Team*

Article Figures/Media

Metrics

September 1, 2016

- Multicentre randomized controlled trial
 - Early versus delayed ART
 - HIV infected adults with CD4 counts of 350-550 cells/mm³
- 93% reduction in HIV transmission to sexual partner
- Delayed time to AIDS events with early treatment

- **U=U: Undetectable virus equals untransmissible**

DHHS Guidelines: Recommended Regimens for First-line ART

Class	Regimen
INSTI	▪ BIC/TAF/FTC (Biktarvy®)
	▪ DTG/ABC/3TC (Triumeq®)
	▪ DTG + (TAF or TDF)/FTC (Tivicay® + Descovy® or Truvada®)
	▪ RAL + (TAF or TDF)/FTC (Isentress® + Descovy® or Truvada®)
	▪ DTG + 3TC (Dovato®)

Except for individuals with:

- HIV RNA >500,000 copies/mL
 - HBV coinfection
- Initiation prior to HIV genotypic resistance testing for reverse transcriptase or HBV testing results

HIV: Single Tablet Regimens



Atripla



Genvoya



Complera



Dovato



Juluca



Triumeq



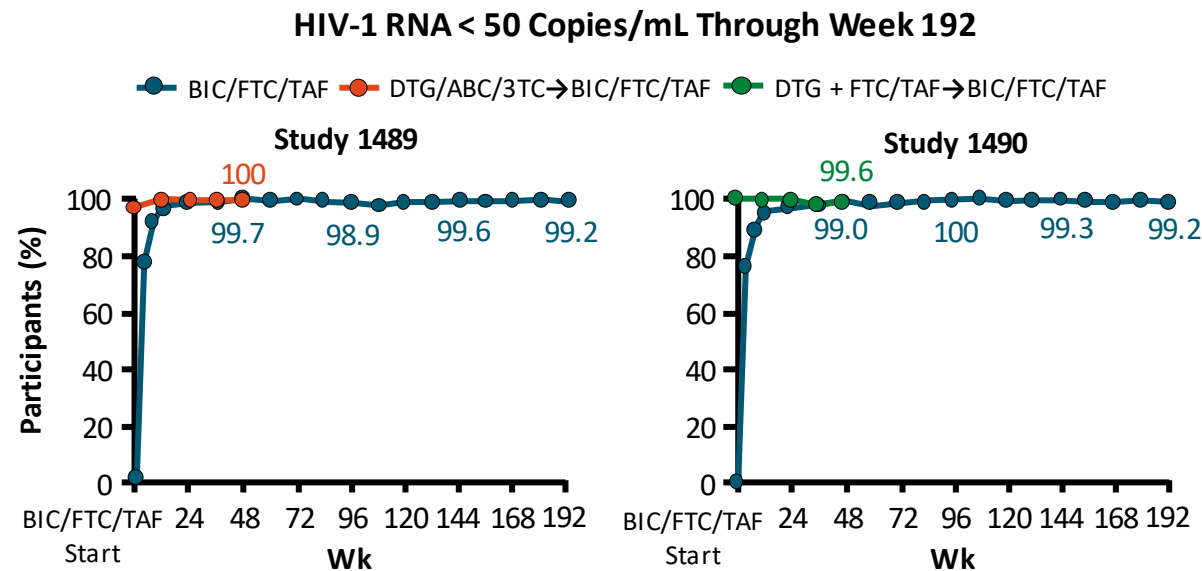
Odefsey

Stribild



Biktarvy

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE: Week 192 Virologic Outcomes and Resistance



- No emergent resistance detected to any BIC/FTC/TAF component in any group
- One participant developed NRTI resistance (M184V) with DTG/ABC/3TC; switched to BIC/FTC/TAF and achieved and maintained HIV-1 RNA < 50 copies/mL
- Efficacy maintained in participants who switched from DTG-containing regimens to BIC/FTC/TAF at Wk 144 or later

TWO DRUG REGIMENS

Dovato[®]

- Dolutegravir + Lamivudine (DTG + 3TC)
- April 2019
- For treatment naïve patients (GEMINI 1 & 2)
- For simplification/switch therapy in virologically suppressed patients (TANGO, SALSA)

Juluca[®]

- Dolutegravir + Rilpivirine (DTG + RPV)
- November 2017
- Approved for simplification/switch therapy in virologically suppressed patients
- SWORD 1 & 2

Cabenuva

- Cabotegravir + Rilpivirine (DTG + RPV)

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*, *Coccidioides*, and *Blastomyces*)
 - Rhodococcus
 - Penicillium (*Talaromyces*) *marnafeii*
- Lymphocytic Interstitial Pneumonitis
- Malignancies

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 aeruginosa</i> [*]	Amoxicillin or
	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: ER = extended release; MRSA = methicillin-resistant *Staphylococcus 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.

[§]Amoxicillin/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)
 - 90% of PCP cases occurred in patients with CD4 <200 cells/mm³

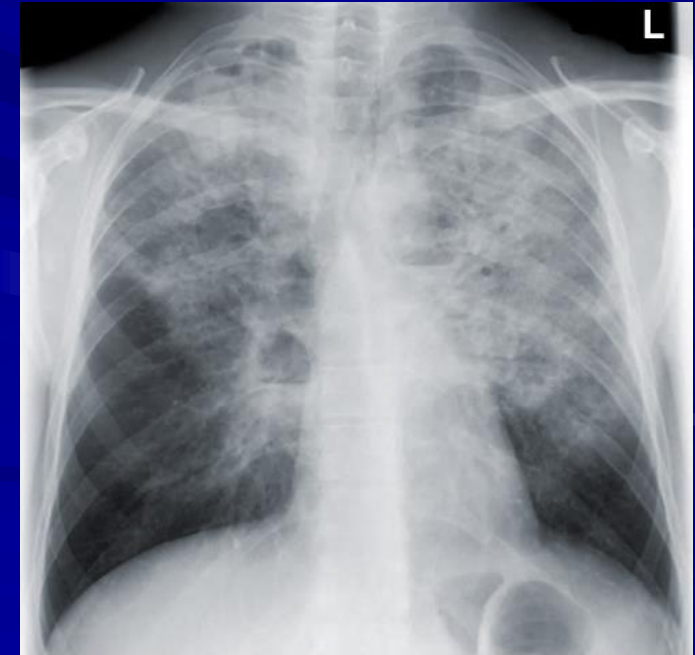
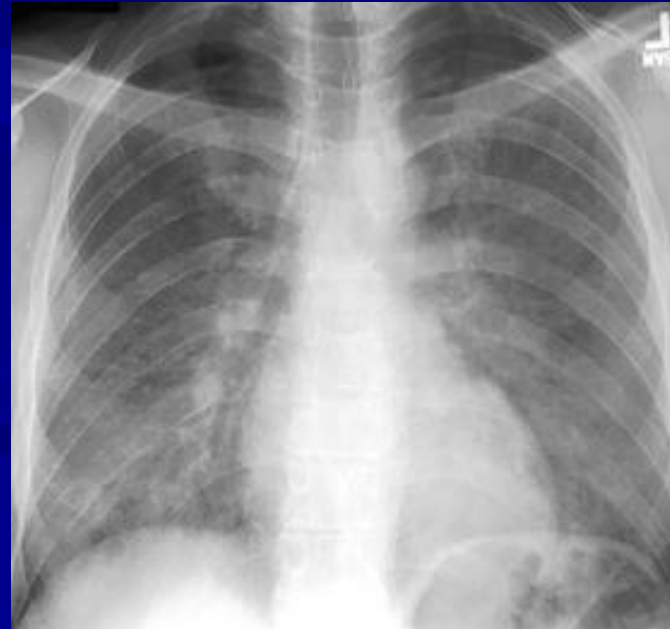
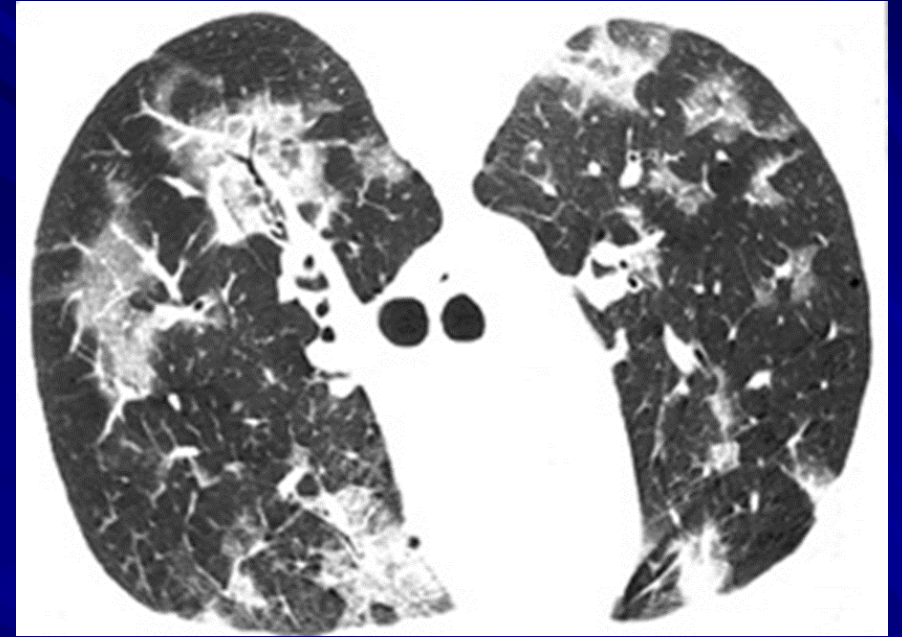
Risk Factors for PCP

- 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.

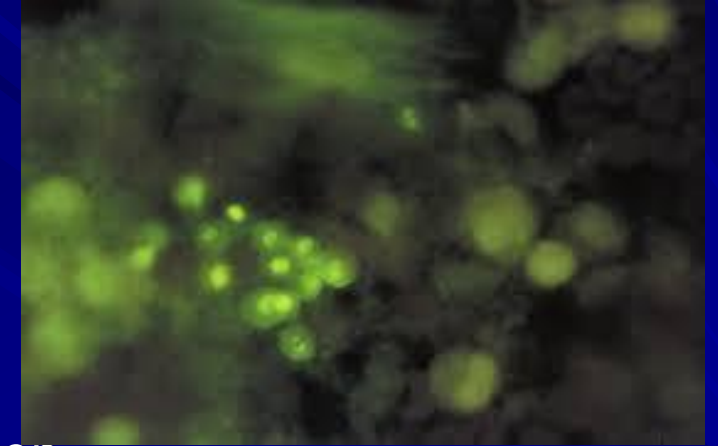
PCP

- 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%, Cavitation and pleural effusion are uncommon
- A normal CT chest makes PCP unlikely



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
 - But PCR cannot distinguish colonization from disease; (*Li-Chao Fan, PLOS one 2013*)



Treatment

- Trimethoprim/Sulfamethoxazole
 - 5 mg/kg Q6-8 hours IV or 2 DS PO TID
 - Adjust for creatinine clearance
- Corticosteroids if $PO_2 < 70$
 - Reduces the inflammatory response from destruction of the fungus
- Alternatives:
 - 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

Prophylaxis of PCP

- Primary and secondary PCP prophylaxis can be safely discontinued
 - In patients with CD4 counts between 100 - 200 and undetectable HIV RNA

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

Indications	First Choice	Alternative
CD4 count < 200 cells/mm ³ (AI) or Oropharyngeal candidiasis (AII)	TMP-SMX 1 DS qd (AI) ; or TMP-SMX 1 SS qd (AI)	<ul style="list-style-type: none"> • 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)
CD4 < 14% cells/mm ³ or history of AIDS-defining illness (BII)		
CD4 count > 200 but < 250 cells/mm ³ if monitoring CD4 count every 1-3 months is not possible (BII)		

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

Cryptococcal Meningo-encephalitis

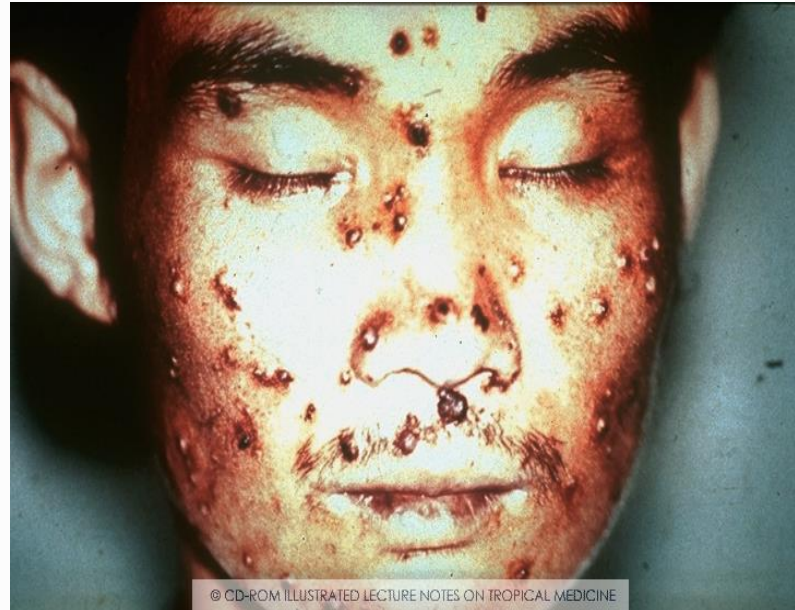
- *C. neoformans*
 - encapsulated yeast, acquired by inhalation
- Clinical manifestations are Subacute
 - Headache, fever, malaise,
 - Average duration of symptoms is 30 days
- Tests
 - Serum cryptococcal antigen
 - Cerebrospinal fluid (CSF)- crypto Ag- 99%
- Treatment:
 - Intra-venous Amphotericin and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

Example of cryptococcal pneumonia



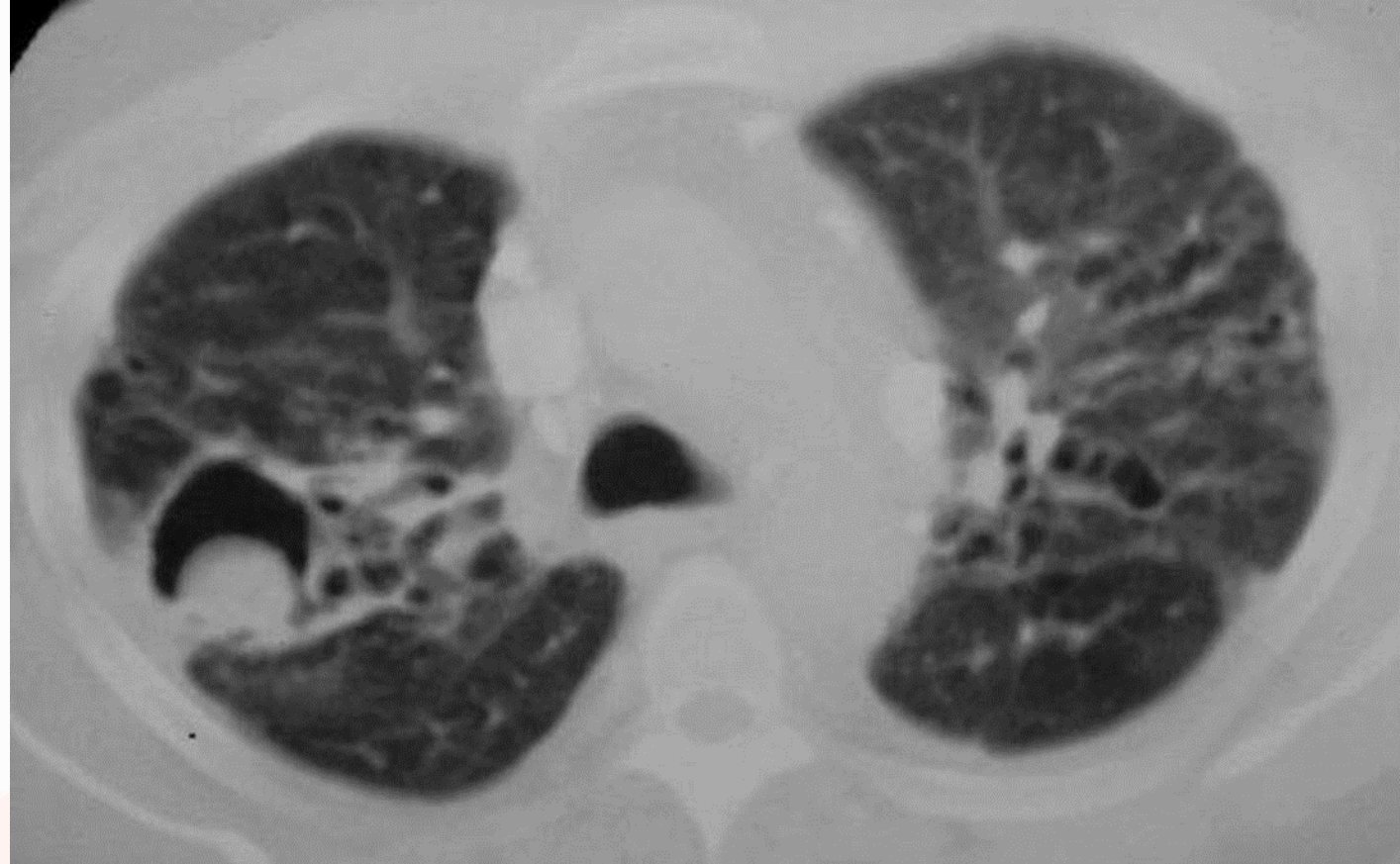
37 year Chinese male now has AIDS

- *Penicillium (Talaromyces) marneffe*
- Disseminated and progressive infection
- Third 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



Pulmonary Aspergillosis

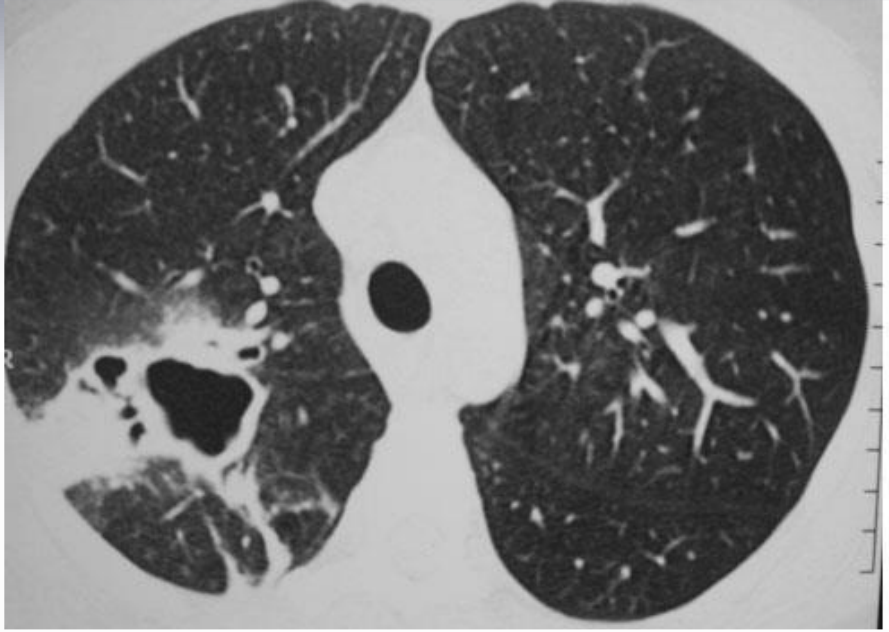
- Uncommon in PLWH
- Acute invasive (IPA)
- Chronic invasive
- Chronic noninvasive
 - aspergilloma
 - allergic bronchopulmonary



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 in the absence of other treatable pulmonary infections
- *HSV RARELY causes pneumonia*

42 year male with AIDS

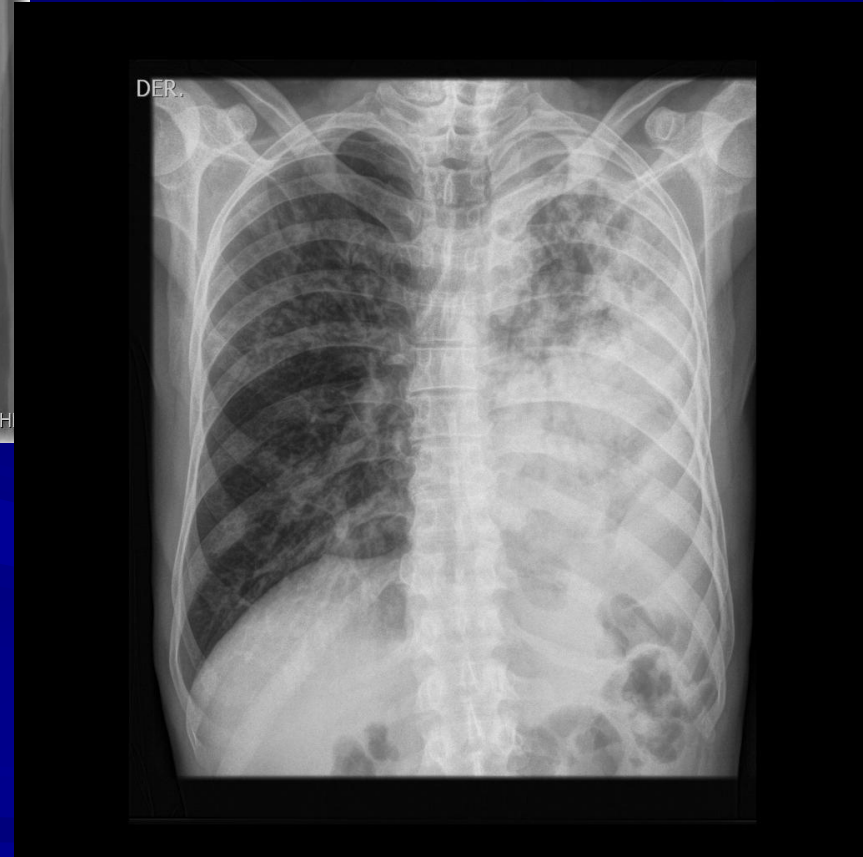


Cavitary pneumonia

- Tuberculosis
Actinomyces
Nocardia
Klebsiella
Staphylococcus aureus
Anaerobic organisms
- **Fungal infection** Histoplasmosis
Coccidiomycosis, aspergillus

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



Centers for Disease Control and Prevention

MMWR

Recommendations and Reports / Vol. 69 / No. 1

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 ($P = 0.09$).

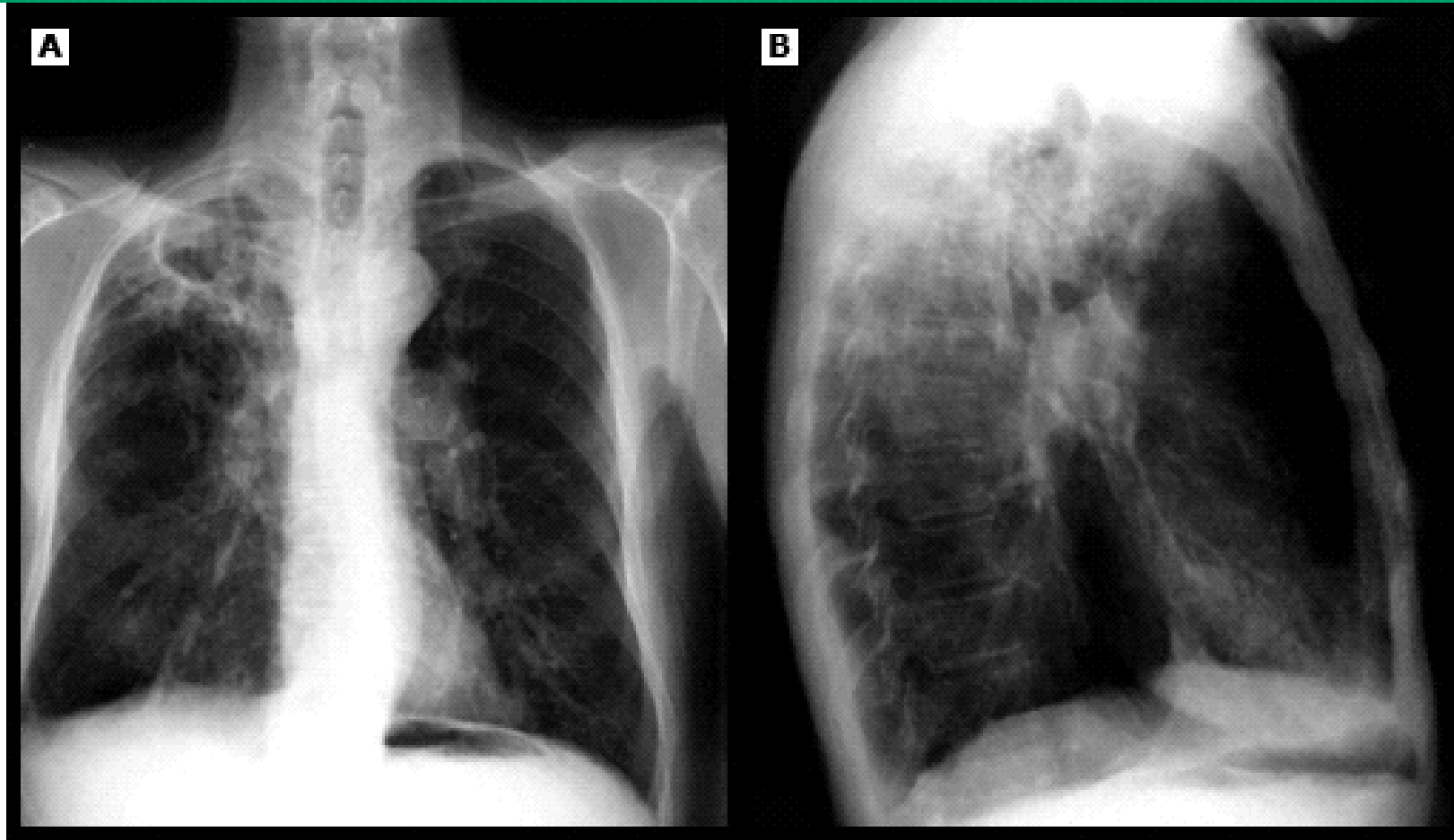
Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons

Sterling, Timothy R.^a; Scott, Nigel A.^b; Miro, Jose M.^c; Calvet, Guilherme^d; La Rosa, Alberto^e; Infante, Rosa^e; Chen, Michael P.^b; Benator, Debra A.^{f,g}; Gordin, Fred^{f,g}; Benson, Constance A.^h; Chaisson, Richard E.ⁱ; Villarino, M. Elsa^b 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.0000000000001098

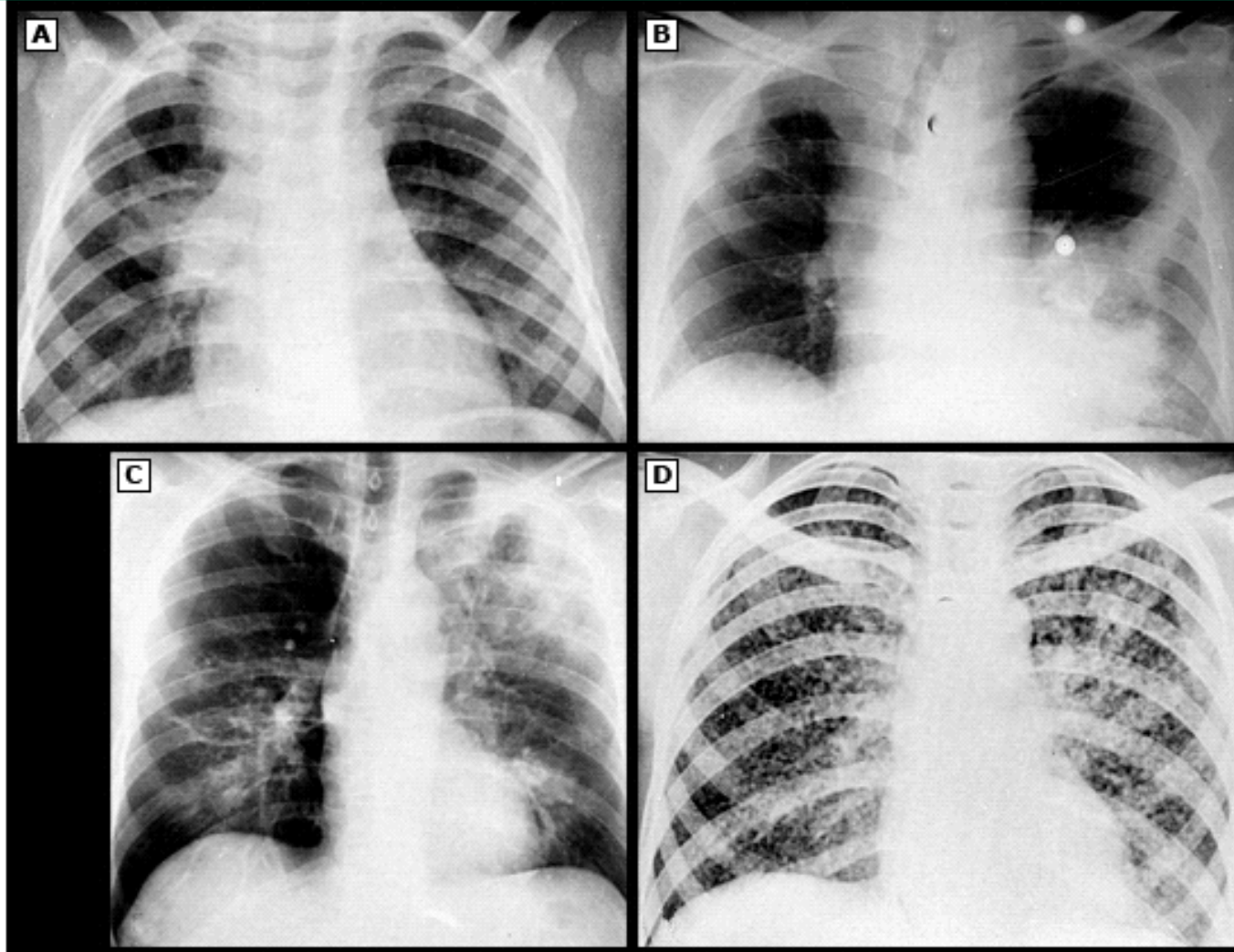
Chest radiographs of tuberculosis



Chest radiographs (posteroanterior and lateral views) demonstrating cavitary reactivation of latent tuberculosis infection in the posterior apical segment of the right upper lobe.

Reproduced with permission from: Crano JD, Glassroth J, Karlinsky JB, King TE

Chest radiographs of different presentations of tuberculosis



(A) Primary tuberculosis in a child (note the right-sided hilar adenopathy, right-sided lower lobe infiltrates, and volume loss).

(B) Lower lung field tuberculosis infiltration and cavity with air-fluid level in lingula.

(C) Reactivated tuberculosis, far-advanced disease with bronchogenic spread.

(D) Miliary tuberculosis

Immune Reconstitution Inflammatory Syndrome

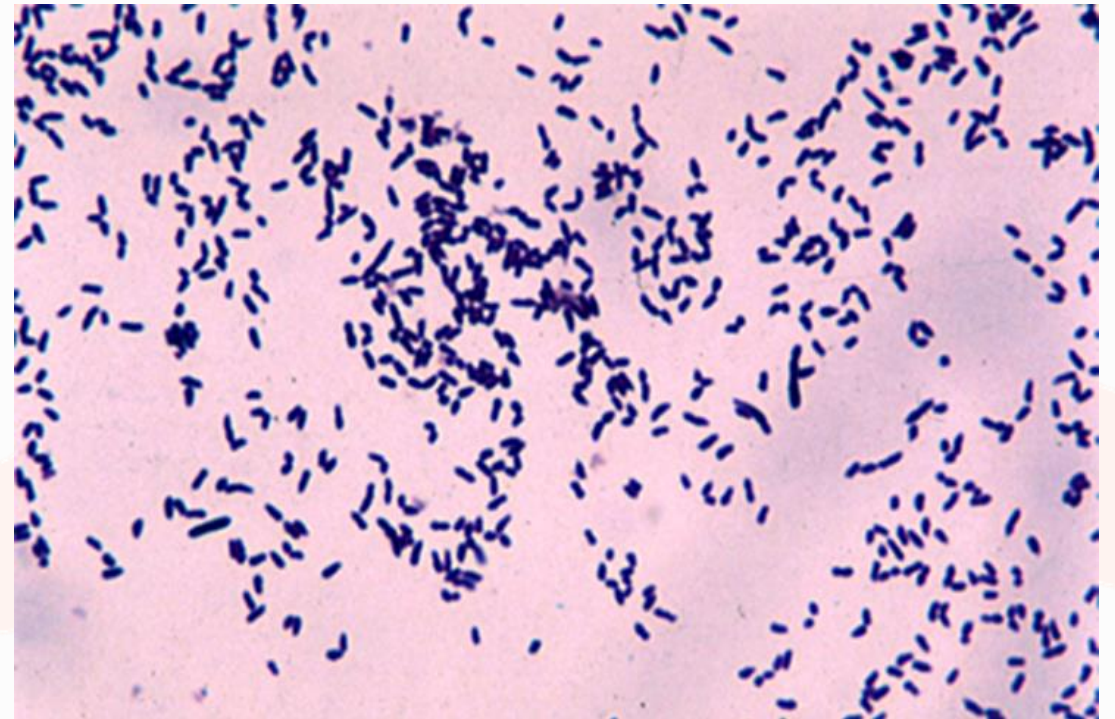
- Characterized by fever, worsening clinical signs of the OI; symptoms of new OI
- Associated with a rise in CD4 and/or a fall in viral load
- Usually occurs within first few weeks of ART but may occur up to several months later

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

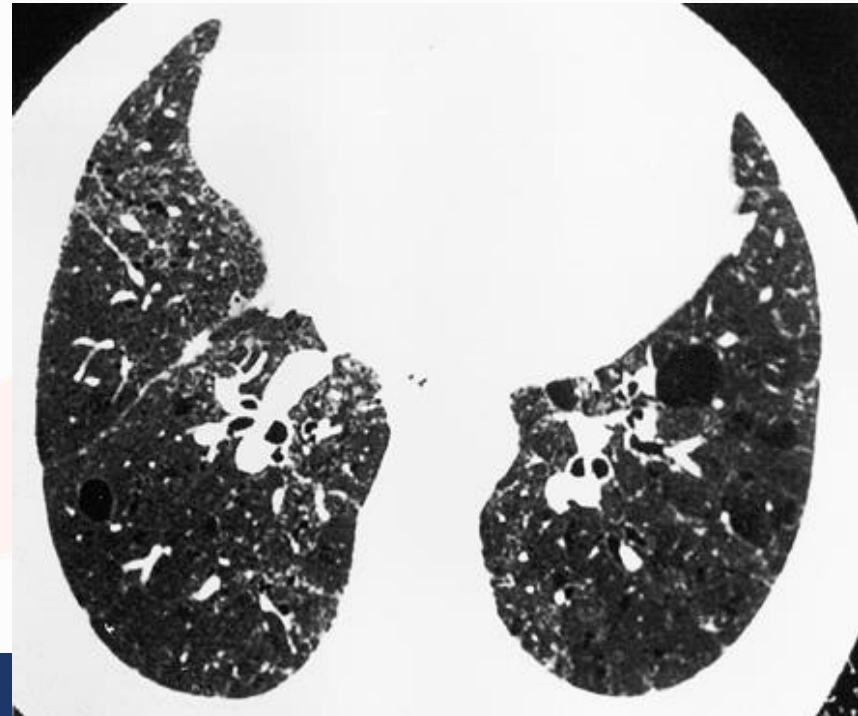
Rhodococcus

- 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



Lymphocytic Interstitial Pneumonia

- Rare form of ILD but 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



Photo Credit: Boston University

COPD

- Strong association with smoking
- However, studies have identified HIV infection as an independent risk factor
- Contributors to COPD
- Oxidative stress, systemic inflammation, cellular senescence, immune activation, and endothelial dysfunction.
- Six-minute walk distance is a validated measure of functional capacity
- Pulmonary function testing is indicated
- PLWH infrequently get diagnostic pulmonary testing-Spirometry
- HIV - independent risk factor for DL_{CO} impairment

COPD in HIV-Infected Patients: Risso K, PLoS One. 2017; 12(1):e0169359.

HIV related pulmonary Hypertension

- Prevalence is estimated at approximately 1/ 200 (0.5%) among HIV-infected persons, compared with 1-0 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.