Update on Opportunistic Infections (OIs) 2023

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Disclosures

- No conflicts to disclose
- Many of the drugs described are being used in off-label fashion, as they were not studied for these indications

Challenges in a 60 Minute OI Talk

- The topic is vast
- The incidence of OIs in the US has decreased, so most clinicians see fewer
  - A general framework for epidemiology, prevention, diagnosis and treatment is needed
- But ID clinicians see complex OIs
  - Relevant detail and nuance are needed
- Practice differs in low- and medium- income countries (LMIC)
  - LMIC are the source of many recent high quality randomized controlled trials (RTCs)
  - How do we integrate these approaches in the US and other high income countries?

Learning Objectives

Using a contextual framework and patient presentations:

1. Understand key principles in the prevention, diagnosis and treatment of OIs
2. Recognize the presentation of OIs in the combination ART era, including immune reconstitution inflammatory syndrome or “IRIS”
    - Unmasking IRIS
    - Paradoxical IRIS
3. Review the management of OIs in the ART era, highlighting
    - Timing of ART
    - Role of steroids

Key Principles

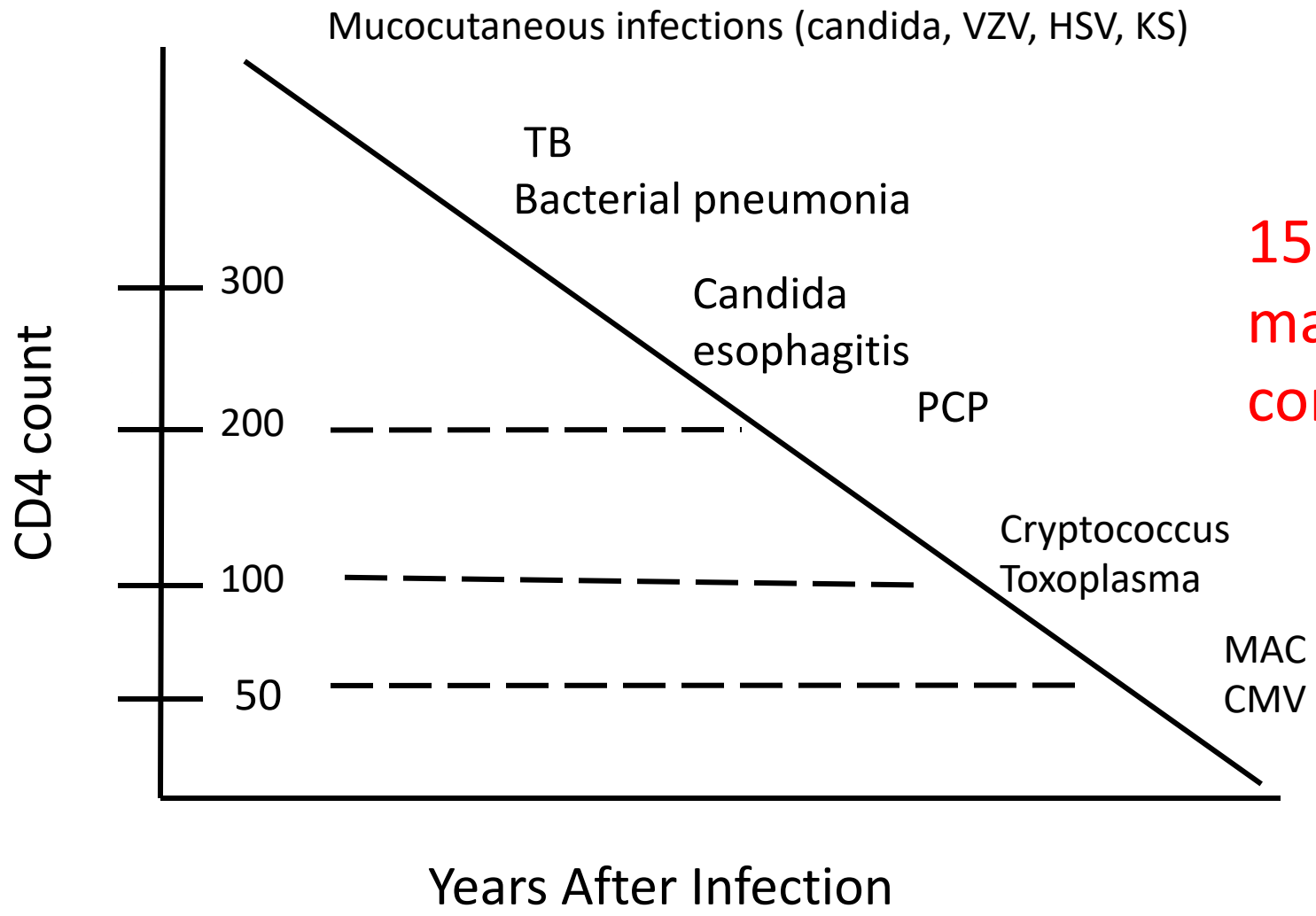
IDSA/DHHS Guidelines

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines

- Regularly updated information with rationales and references
- Improved alignment with ACIP, CDC and other guidelines
- Updated DDI
- ~500,000 page downloads and 20,000 PDF downloads in 2023
- 2023 updates: Mpox, Chagas Disease

Opportunistic Infections Increase as CD4 Declines

“normal” CD4 350-1500, US median 1000



15-30% have >1 major OI concurrently

As CD4 declines, Infections Disseminate, Become Higher Titer and Become More Lethal (example here is TB)

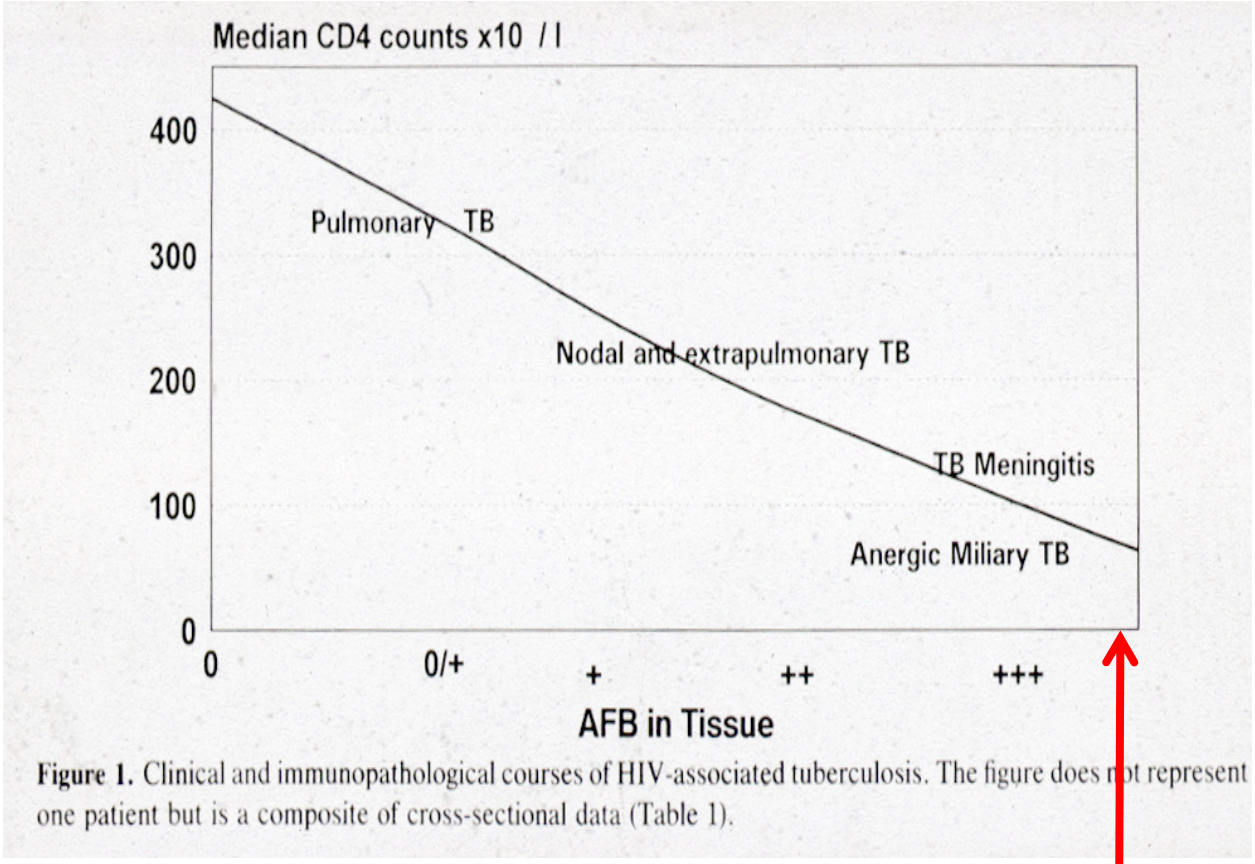


Figure 1. Clinical and immunopathological courses of HIV-associated tuberculosis. The figure does not represent one patient but is a composite of cross-sectional data (Table 1).

Highest mortality

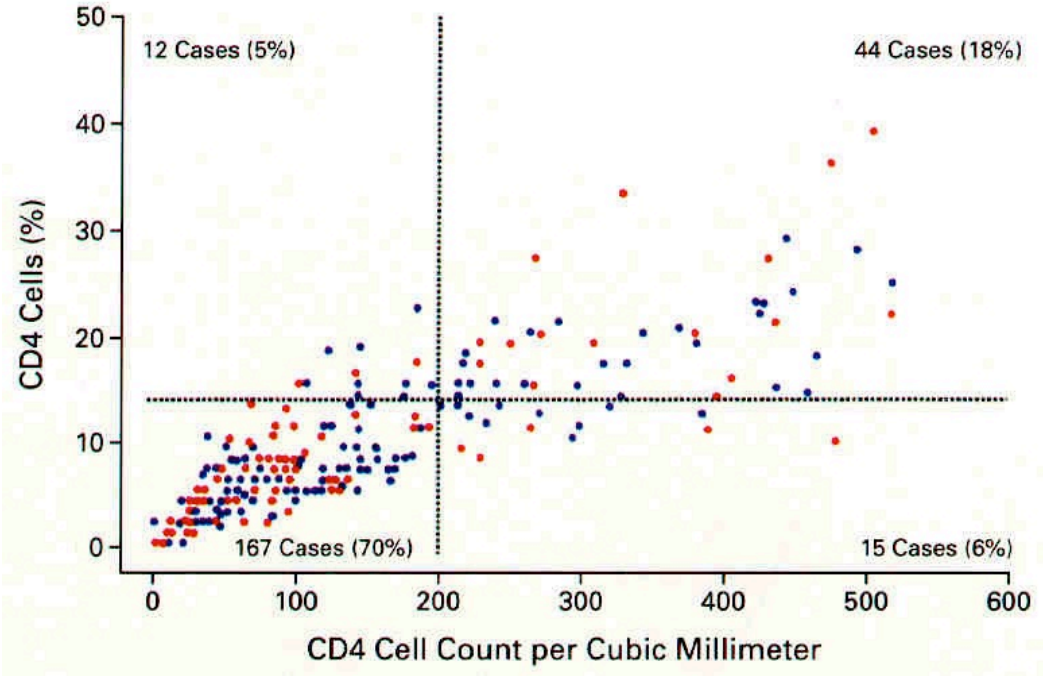
Clinical Corollary eg TB

- If CD4<100, especially <50, evaluate all sites of potential involvement *rapidly*
  - Perform rapid and extended testing (eg Gene Xpert)
- Begin empiric therapy for TB *(and possibly other disseminated infections*) while awaiting results

Jones et al. Am Rev Respir Dis 1993; 148:1292, Perlman et al CID 1997: 25:242

CD4 Best But Not Only Predictor of OI Risk

CD4 at PCP Diagnosis



CD4 <200, CD4% <14%, Thrush all risk factors

CD4 at CNS OI Diagnosis

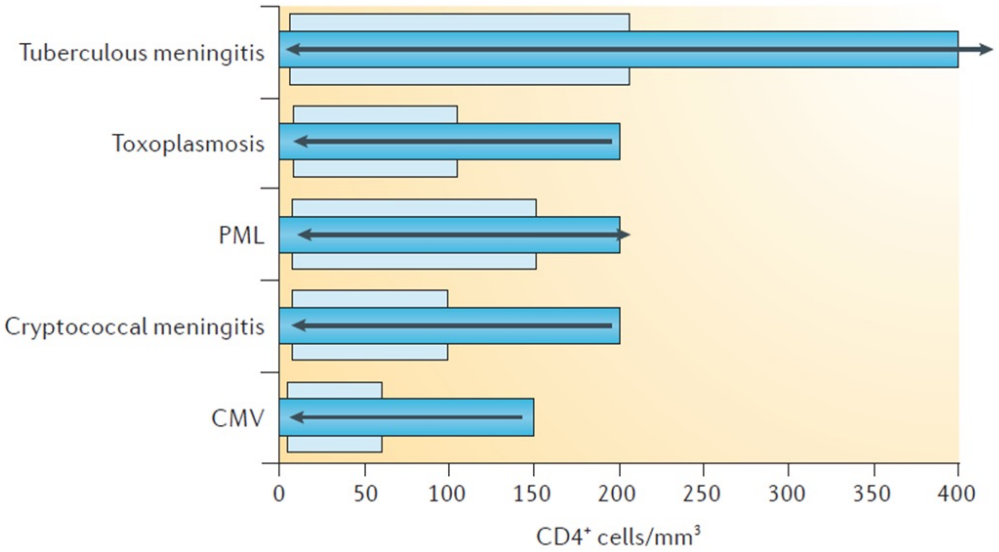


Figure 1 | **Level of immunosuppression and risk of opportunistic infections.** This figure depicts the concentration of $CD4^+$ cells in which a given HIV-associated CNS opportunistic infection can develop (dark blue bars). Rare cases of infections reported past these limits are indicated by arrows. The light blue overlay grossly depicts the most common $CD4^+$ cell counts for each respective opportunistic infection[14,34,106,113–115]. CMV, cytomegalovirus infection, PML, progressive multifocal leukoencephalopathy.

Bowen, L. *et al. Nat Rev Neurol 2016.*

OIs at Higher CD4

May Have "Atypical" Features

- Course may be more indolent
- Ag based tests may initially be negative
- Path may show more inflammation including granulomas, with rare or absent organisms

May Be Associated With Other Risk Factors

- Higher HIV RNA
- Malnutrition
- Steroids
- Pregnancy
- Recent/concurrent OI
- Advanced medical illness
- Epidemiology (recently acquired or primary infection as opposed to reactivation)
- Lack of immunization
- Host genetic factors
- Other –syndrome of Ois during primary infection

Daley CL, et al. N Engl J Med 1992.

Bidirectional Interaction Between HIV and OIs

- HIV causes the immunosuppression that allows OIs to cause disease BUT ALSO
- OIs have adverse effects on the viral load and CD4
  - Having a major OI such as TB is associated with
    - A significant rise in viral load (eg $\geq$ 1 log)
    - A significant decline in CD4 count
  - These may improve just with treatment of the OI

Who Gets OIs in the US 2023?

- New diagnoses with late HIV
  - ≥ 20% of HIV still diagnosed with CD4 < 200
- Perinatally-infected patients, particularly around transition from pediatric to adult care
- Persons who are not linked to care and/or not taking treatment

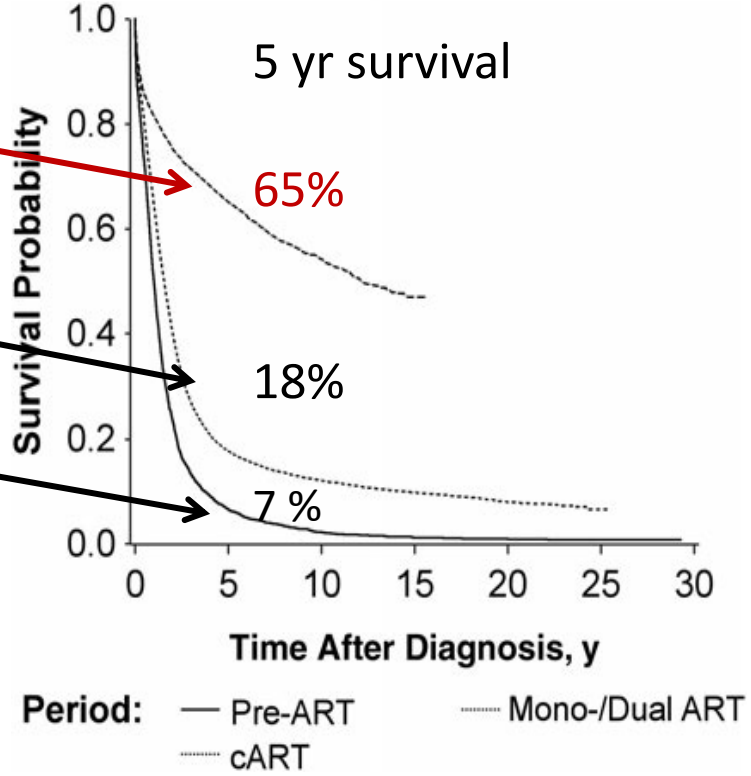
- Persons living with:
  - Substance use disorder
  - Socioeconomic disadvantage (concentrated poverty and associated stresses)
  - Stigma
  - Racism

I Use the Same Rubric for OIs as for all of ID

- Prevention
  - Universal HIV testing and linkage to care
- Diagnosis
- Treatment
- Prevention, again

Even in the cART era, Major OIs Adversely Impact Survival

- 1997-2012 (cART)
- 1987-1996 (Mono/Dual ART)
- 1981-86 (pre ART)



Survival remains very poor with CNS lymphoma and JC virus encephalitis (PML)

Djawe et al, J Infect Dis 2015

Most Common Major OIs in the US

Lung	GI	CNS	Disseminated
PCP	Candida esophagitis	Cryptococcus	Mycobacterium avium complex (MAC)
Bacterial	Bacterial gastroenteritis eg Shigella, Salmonella, Campy	Toxoplasmosis	Cytomegalovirus (CMV)
TB	Protozoal parasites eg giardia, cryptosporidium, microsporidium	TB	TB
Fungi, eg crypto, endemic fungi		JC virus (PML)	Fungi eg crypto, endemic fungi

"Most Likely"- PCP

"Most Lethal" – Crypto and TB

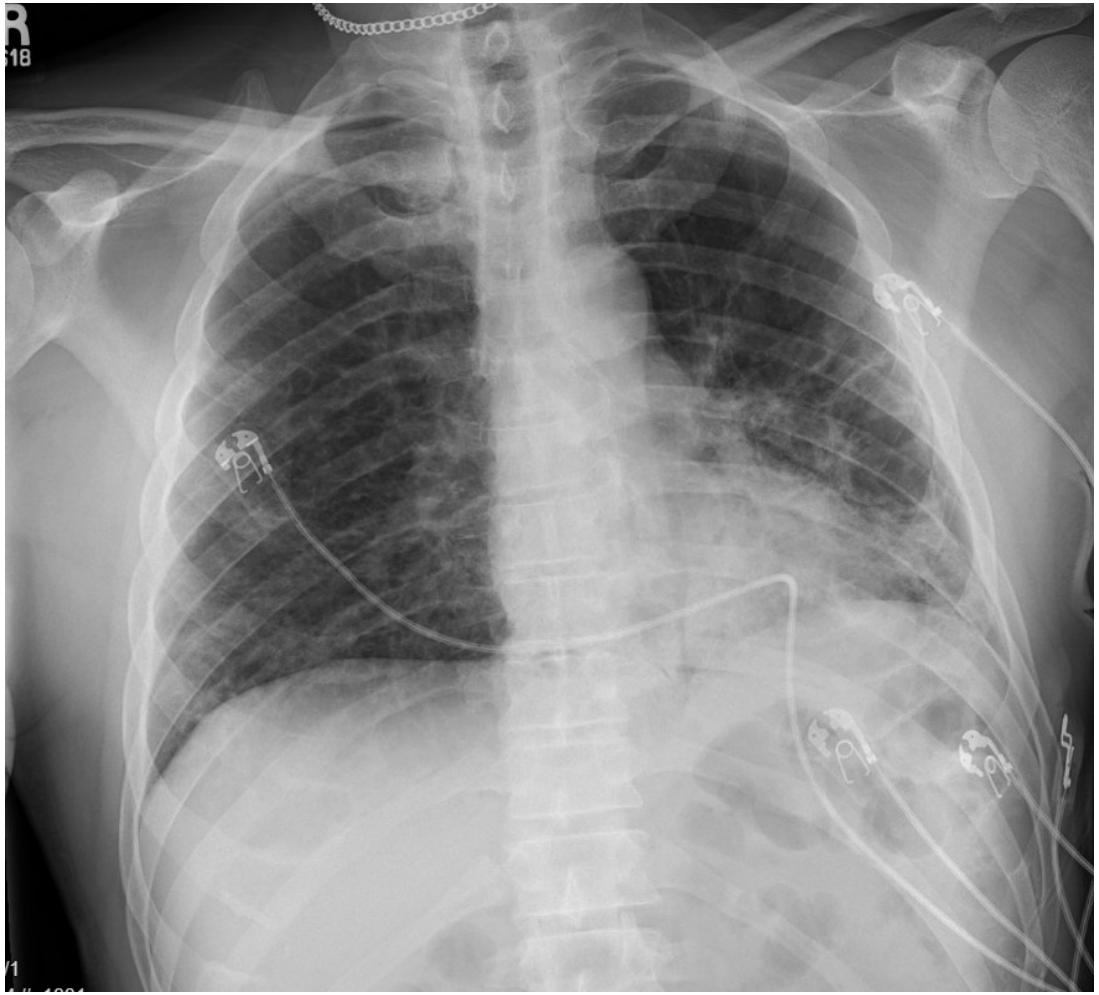
Patient 1

- 55 year old male with HTN, DM2, anxiety
- OSH ED visits for sciatica and DM 2016-2021
- Epi: b in the DR, travel in Central America and southeastern US
- June 1, 2023: MWH ED
  - 10 days cough, SOB, chills, sweats, anorexia and weight loss
  - VSS including normal 02 sat RA
  - Labs with hyperglycemia, WBC 4.8 with ALC 590, CXR read as LLL pneumonia, Rx amox-clav and doxy
- June 22, 2023: found down at home, minimally responsive and SOB. Admitted to NSMC with shock, hypoxemia, worsening chest imaging (“?septic emboli”) and worsening multifocal CNS disease (“? CNS emboli”)
- Tox screen + cocaine

NSMC Evaluation and Treatment

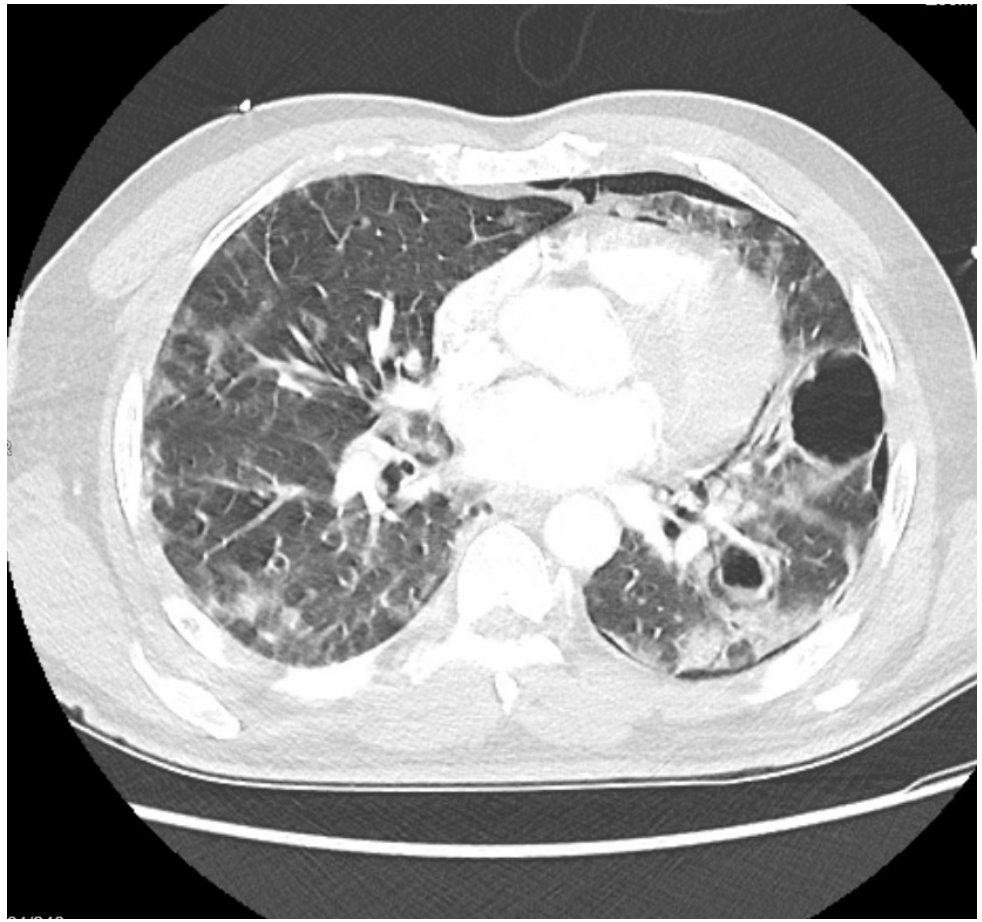
- Intubated for airway protection
- Begun on vanco/ceftriaxone/metronidazole and voriconazole
- Labs with AKI and mildly elevated transaminases and alk phos

Chest X ray



- “Multifocal lower lobe predominant ill-defined airspace opacities in both lungs along with bilateral cavitary pulmonary lesions. Small left pneumothorax.”

Chest CT



1. No pulmonary embolism.
2. Multifocal ill-defined predominantly peripheral groundglass and consolidative opacities in both lungs most likely infective pneumonia/aspiration.
3. Small left pneumothorax.
4. Multiple thick-walled parenchymal cysts in both lungs; largest in the lingula measuring 5.3 x 2.5 cm; suggesting underlying cystic lung disease. Differential would include septic emboli/cavitary infection (such as tuberculosis or fungal infection) versus cavitary metastases.

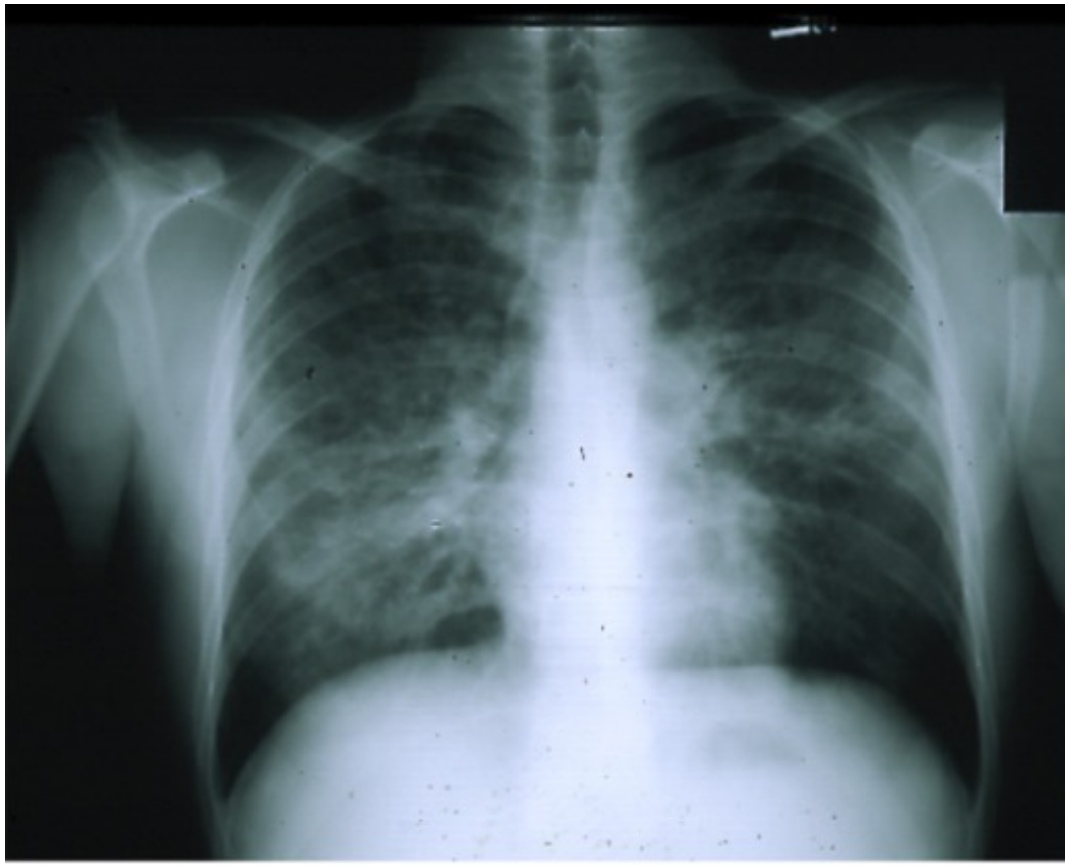
HIV Ag/Ab positive, CD4 28, HIV RNA PCR 673,000

CSF bland, initial smears and cultures neg, CSF crypto Ag neg

Patient 1: Pulmonary Presentation is Most Likely

1. Pneumocystis jiroveci pneumonia (PCP) alone*
2. PCP + bacterial infection (pneumonia or septic pulmonary emboli)
3. PCP + another fungal infection eg histoplasma
4. PCP + Mycobacterium tuberculosis
5. Other

“Classic” Pulmonary PCP



Pulmonary agent	Epidemiology	Clinical	CD4	Lab Evaluation	Imaging
PCP (PJP)		Subacute Dry cough Difficulty with deep inspiration O2 desat with activity	Median <50	LDH 1,3 ß-D-glucan Induced/ETT sputum stain; PCR (+ may be colonization)	Interstitial and alveolar (GGOs and later consolidation) blebs, pneumothorax
Bacterial: Pneumococcus, H. flu Klebs/other gnr S. aureus Legionella	Smoking; Seasonal variability	Acute Early toxicity Productive cough	Any	BCx x 2 Strep pneumo and legionella urinary Ags	Focal (lobar or peribronchial) Effusion Cavitation
Other fungal (crypto, histoplasma, cocci; aspergillus uncommon without neutropenia or steroids)	Histo: hyperendemic Midwest US. Cocci: endemic in the southwest US and Mexico; Both occur worldwide	Typically subacute to chronic Dry cough	Depends on extent of disease	Serum crypto Ag+ Urine histo Ag+ Depends on extent of disease.	Nodules Focal infiltrates LAD Effusions

TB has its own lecture (Dr. Rocio Hurtado) Noninfectious: KS, lymphoma, immunologic, pulmonary HTN

Clinical, Radiographic and Path Features Vary in Early and Late PCP

Earlier

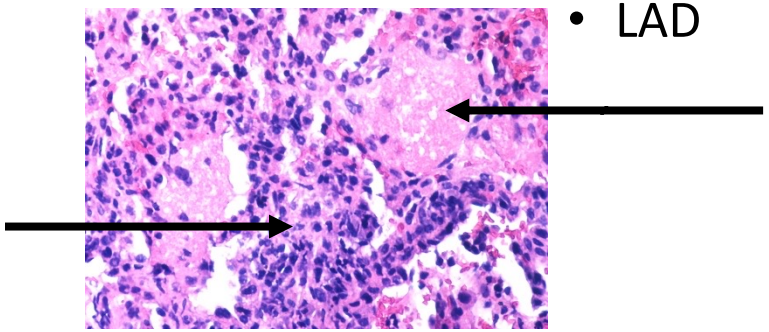
- Subacute (3-6 weeks, mean 28 days)
- Dyspnea on exertion
- 02 sat at rest normal
  - Desaturation with walking
- Shallow inspiration “can’t take a deep breath in”
- “Doorstop cough “When I try to take a deep breath, I cough”
- Interstitial and ground glass opacities

Later

- Shortness of breath and hypoxia at rest
- Focal opacities with consolidation
- blebs, pneumothorax
- Fibrosis, architectural distortion

Rarely or Never

- Nodules (may see granulomatous inflammation)
- Effusions
- True cavitation
- LAD



Diagnosis of PCP

Lab	Sensitivity and Specificity	Comments
Lactic dehydrogenase (LDH)*	95% sensitive 50% specific	Marker of tissue inflammation Present in many tissues
Beta-d- glucan	90-95% sensitive 75-90% specific	Marker of organism burden Present in some other fungi, some "contaminants"
Organism stain	Induced sputum 70-90% sensitive** BAL 90-99% sensitive Lung biopsy 90-100% sensitive	Direct fluorescent antibody (DFA) stain more sensitive than Giemsa and GMS BAL more sensitive than induced sputum (ensure deep specimen!)
PCR	95-100% sensitive 85-95% specific	+ PCR may reflect colonization or treated infection

Randomized Controlled Trials (RCTs)

Antimicrobials

- *Severe* PCP
  - TMP/SMX Oral or IV
  - Pentamidine IV: equivalent or slightly inferior to TMP/SMX
- *Mild to moderate* PCP
  - Clinda IV or oral and primaquine oral*
  - Trimethoprim and dapsone
  - Atovaquone
    - Tablets had poor oral bioavailability (those who absorbed them well did well)
    - Suspension better

Corticosteroids

Consensus protocol

- pO_2 < 70 or A-a gradient > 35
- 02 saturation <90% RA proxy
- Preferably before/with 1st dose
- Prednisone or IV equivalent:
  - 40 mg twice daily x 5d
  - 40 mg once daily x 5d
  - 20 mg once daily x 10d
- Some small series suggest ↑ risk of other OIs
  - Try to shorten dose/duration based on course

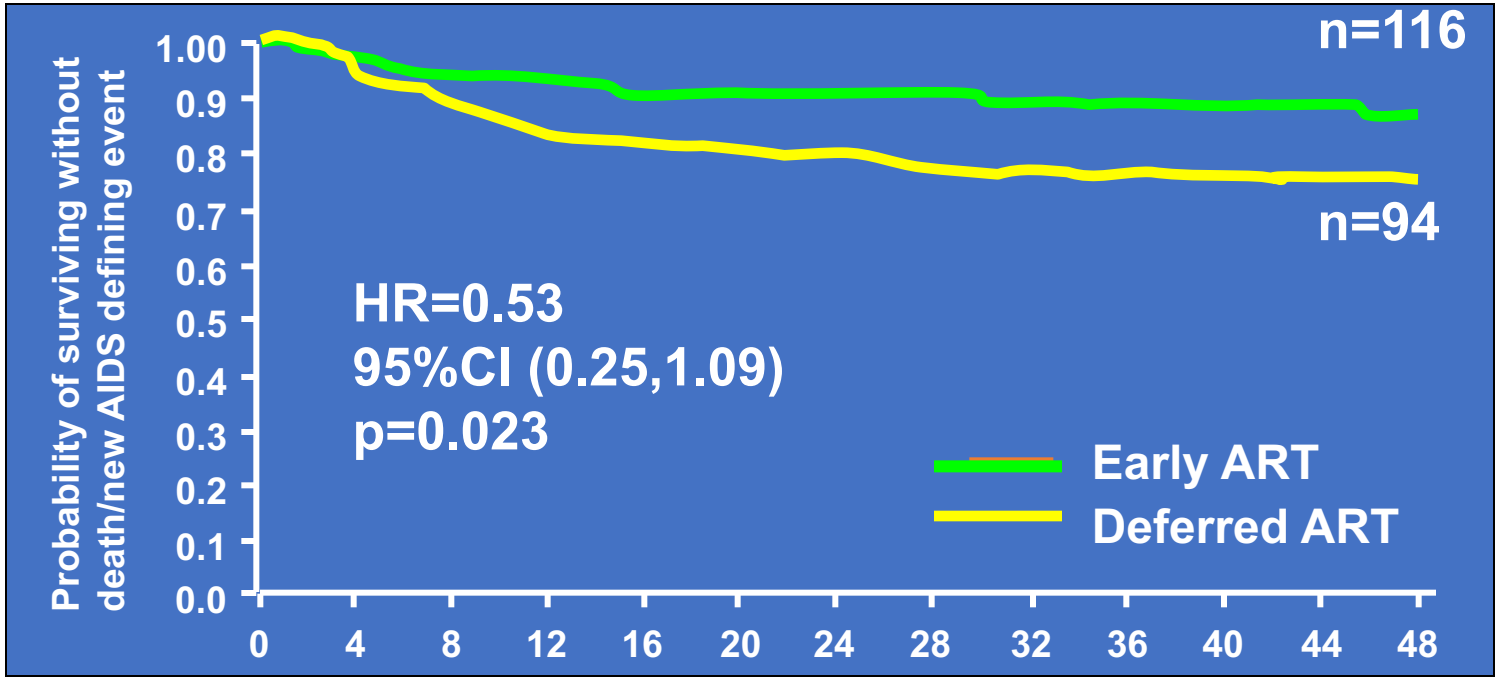
*Clinda/primaquine: non-randomized studies, extensive experience support use in moderate to severe PCP

Patient 1: You Would Start ART

1. Day of PCP diagnosis
2. 1 week after PCP diagnosis*
3. 2 weeks after PCP diagnosis
4. The classic ID answer “it depends”

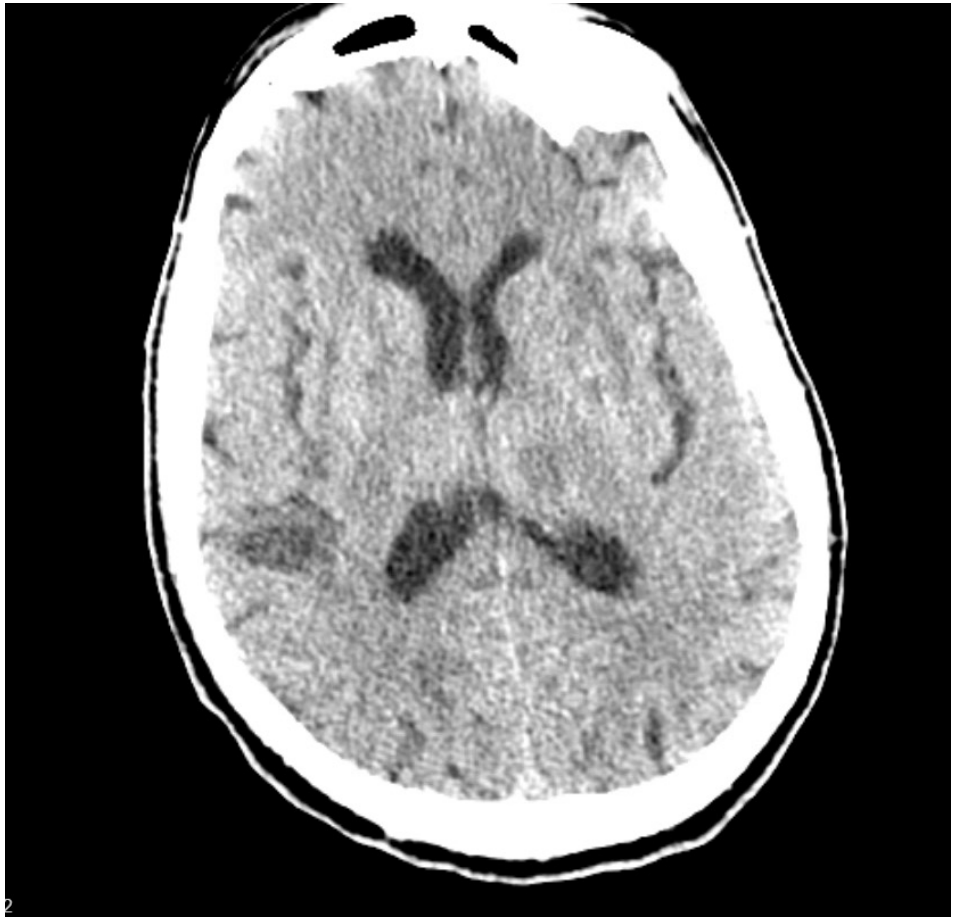
ACTG 5164: Early ART Reduces Risk of AIDS/Death

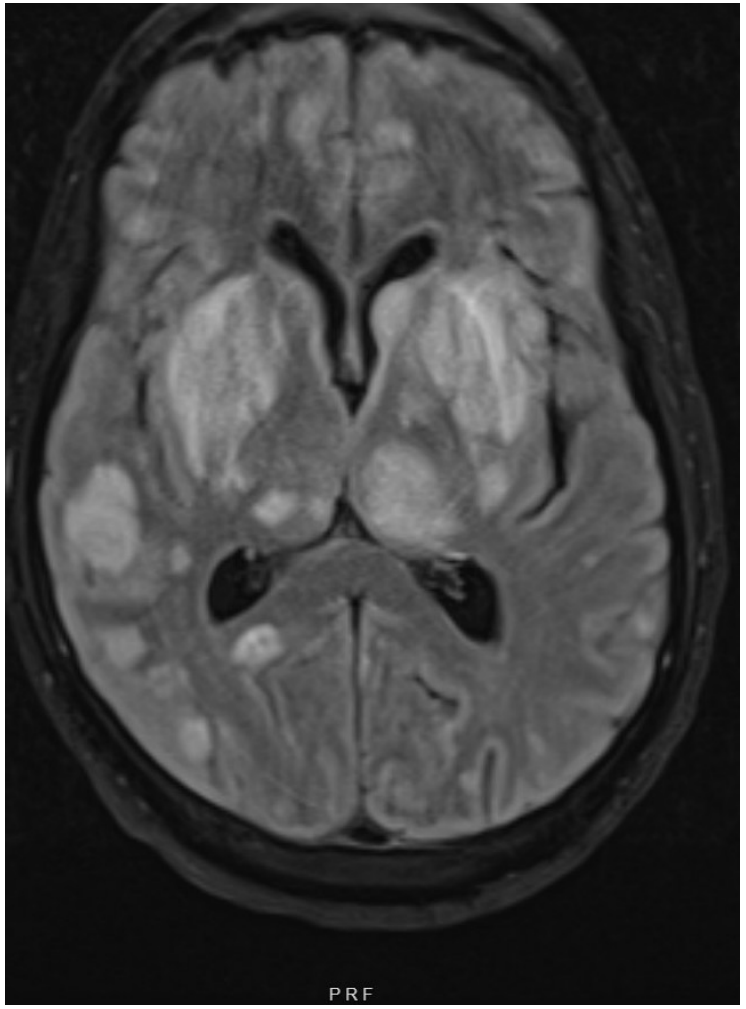
(RCT 282 Participants, Median CD4 29)



- Early (< 2 wks—median 12 d) vs deferred (> 4 wks ART)
- Extrapolate carefully to other OIs, as US study PCP 63% (most received steroids), crypto meningitis 13%, bacterial pneumonia 10%; TB excluded

Patient 1: Brain Imaging on Admission





CNS OIs	Epi	Clinical	CD4	Lab	Imaging	Comment
Toxoplasma	US: 5-10% seroprevalence; worldwide 30-80%	Subacute; HA, focal neuro symptoms including CN	<100	Toxoplasma IgG+; IgM not useful. Toxo PCR from CSF 50-90% sensitive	Multiple enhancing. mass effect, basal ganglia, cerebellum and other; also spine	>90% probability if IgG positive, typical symptoms and imaging; IRIS ≤5%
Cryptococcus	↑Sub-Saharan Africa and Asia	Usually subacute; symptoms of basilar meningitis, CN, elevated ICP	<100			IRIS common
CNS lymphoma		Depends on site, + mass effect	CD4 <50	CSF EBV + in 80-90% who have CNS lymphoma.	Often single, enhancing, mass effect, may cross corpus callosum	
PML		Subacute MS, motor, visual, ataxia		CSF bland,90% JCV PCR+	Patchy demyelination, no edema	IRIS may occur

Treatment of Toxoplasmosis

- Steroids for mass effect or midline shift, not just edema
- Pyrimethamine + sulfadiazine + leucovorin (A1)
- Pyrimethamine + clindamycin + leucovorin (A1)
- TMP/SMX (B1) 10 mg/kg/day divided bid
  - 77 patient RCT
  - Extensive European and now US experience
  - Preferred regimen now, given first price gouging and now limited supply of pyrimethamine
- Pyrimethamine + atovaquone, pyrimethamine + azithromycin (CIII)
- Atovaquone or azithromycin alone (no rating low enough to use here)

Torre et al, AAC 1998


DETOUR

Timing of ART in Pulmonary TB
2 of 4 of the RCTs

- SAPIT Trial: Pulmonary TB in South Africa
  - HIV, smear + TB, open label RCT
  - 2 arms: ART in beginning or after 4 wks or after completing TB therapy
  - DSMB stopped study when mortality was 56% lower in early treatment
  - Survival benefit in all CD4 strata
- STRIDE Trial: Pulmonary TB in South Africa, Asia and US
  - Confirmed or suspected TB, median CD4 77; open label RCT
  - Immediate (2 weeks) vs early (8-12 weeks)
  - Early treatment conferred mortality benefit in CD4 <50
  - More TB IRIS in immediate vs early arm (11% vs 5%), but no ↑ mortality
- Conclusion: early ART critical if CD4 <50, but if no CNS disease, start early
  - IRIS and drug interactions are manageable

Abdool Karim et al NEJM 2010, Havlir et al NEJM 2011

Timing of ART in CNS TB

- Randomized trial of 253 patients with HIV and TB in Vietname
- Early (within 7 days) or late (8 weeks) after TB treatment
  - 35% survival in immediate arm, 40% in delayed arm
  - AEs (including IRIS) 86% early group vs 75% late group
- This and other studies are the basis of guidelines recommendation to wait 8 weeks in TB meningitis
- However, these were late stage patients with high mortality in both arms—not generalizable
- We experts recommend you initiate earlier where close monitoring for IRIS and toxicity are feasible

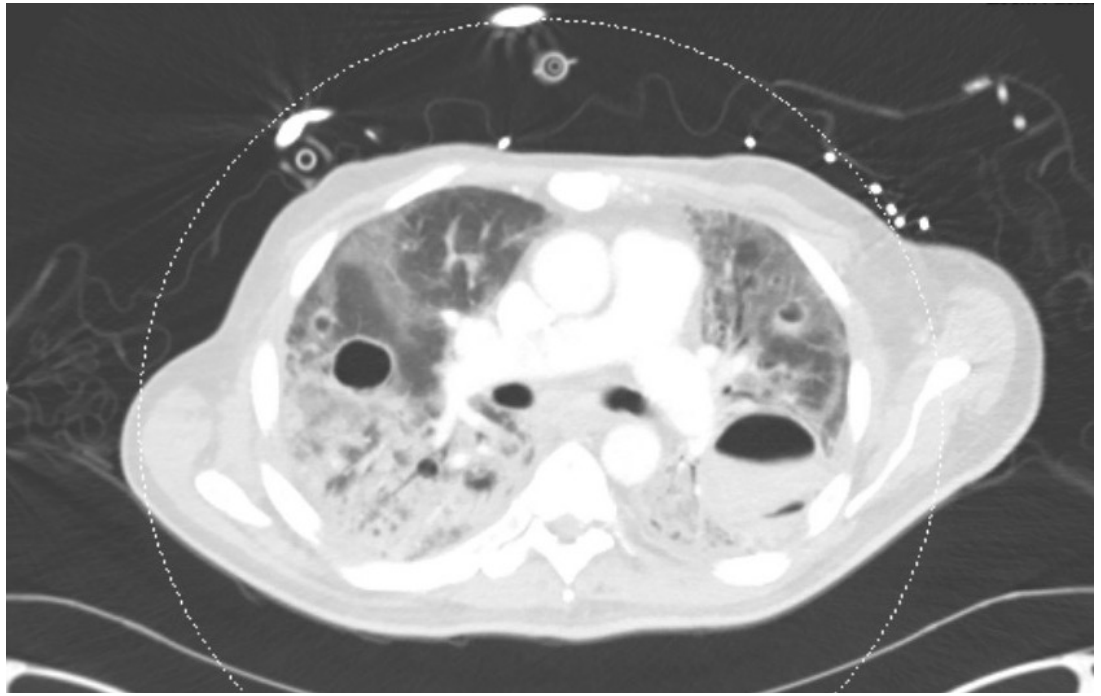
Torok et al, CID 2011

Treatment of Toxoplasmosis

- Acute full dose therapy at least 6 weeks, then chronic maintenance 5 mg/kg/d until asymptomatic and CD4 >200 >6 mos, then secondary prophylaxis 1 DS qd
- Clinical response
  - May be seen as early as day 3
  - 70 % by day 7
  - 90-95% by day 14
- Radiographic response slower
  - Early reimaging only if worse or suspicion for multiple processes
  - Reimage > 2-4 weeks

Patient 1

- Oxygenation worsens
- LDH rises to 428
- Treated for Klebsiella VAP without significant improvement
- What is this?



Hint

Immune Reconstitution Inflammatory Syndrome (IRIS)

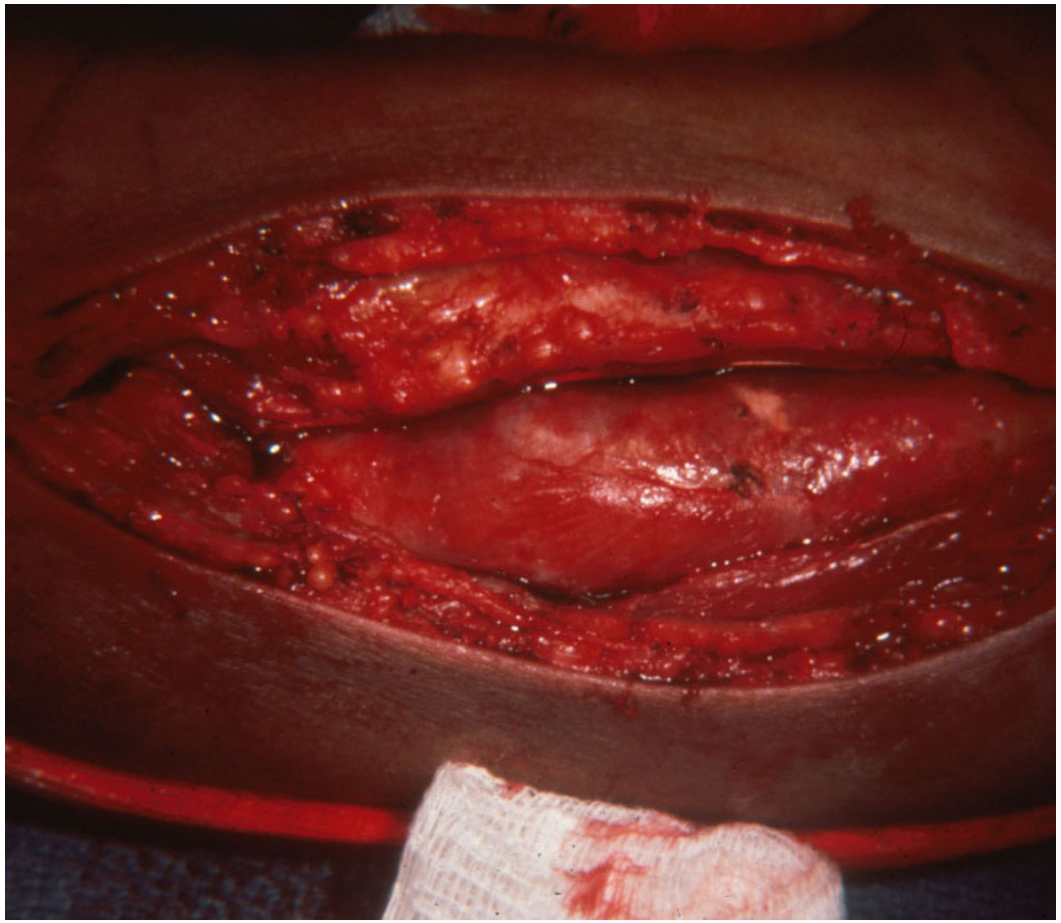
1. Paradoxical IRIS
2. Umasking IRIS

Remember “Paradoxical Worsening” of Infectious Diseases

- Infections gets worse on therapy before they get better, related to immune response to killing of organisms (antigen release)
  - Tuberculosis: CNS tuberculomas, TB meningitis, pulmonary TB, lymphadenitis
  - Leprosy: worsening neuritis
  - HIV: Worsening of moderate or severe PCP
- HIV: Not only antigen release, but concurrent re-arming of the inflammatory response leading to a HYPER inflammatory syndrome
  - TB, MAC, crypto, PCP, KS (particularly visceral), PML
  - Reported in many OIs

Extra Credit Question

Paradoxical worsening: what body part and what infection is this?



Paradoxical IRIS

- Worsening of an OI either diagnosed or suspected before the ART is started
- Antigen release + early rearming of the inflammatory response
- Criteria for diagnosis
  - New, worsening, or recurrent signs or symptoms consistent with an exaggerated or atypical inflammatory reaction to the previously diagnosed OI
  - Localized inflammatory manifestation on exam, imaging or path
  - Exclusion of a new infection, a medication toxicity or other disease process as a possible cause of the worsening
- Beware of hypercalcemia in granulomatous infection, esp TB

Paradoxical IRIS

- Highest incidence in TB, MAC, PCP, Crypto, KS, PML
- May be associated with:
  - Initially or persistently high antigen levels
  - Low CSF WBC count (cryptococcal meningitis)
  - Alterations in cytokine profiles (pro-inflammatory)
  - Differences in host immuno-genetics
- Treatment options:
  - Anti-inflammatories, analgesics
  - Corticosteroids (for prevention as well as treatment
    - Best studied in TB
  - Intensify and extend treatment of underlying OI to decrease organism burden

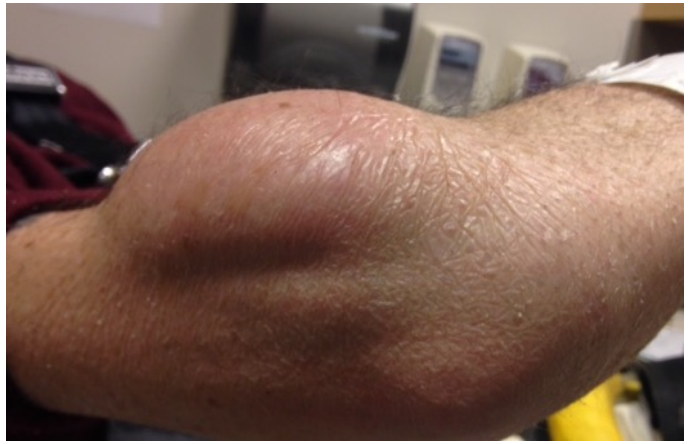
Bahr NC et al *Clin Infect Disease* 2022. Meintjes G et al. *AIDS* 2010.

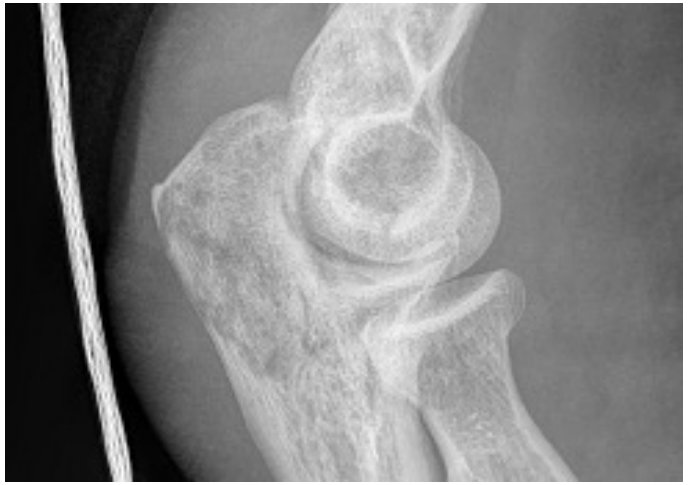
A Different PCP Patient

3 Months After Starting ART

- CD4 up to 208, HIV RNA <20
- R elbow erythema, pain and swelling without drainage
- No trauma
- Imaging with bursitis, arthritis, osteomyelitis
- Gram stain and bacterial culture negative

Aspirate: *Mycobacterium kansasii*
Sputum and blood cultures negative





What is this?

Unmasking IRIS

- Unmasking" IRIS. Inflammatory presentation of a previously unsuspected infection (subclinical site or new site)
- Host anergy allows initially *asymptomatic* replication of organism to high titer, followed by antigen release + early rearming of the inflammatory response
- Most common in TB, DMAC ,crypto, CMV (15-30%), but can occur with other infectious and noninfectious conditions
  - Average 4-12 wks after ART, but as short as 3-7 days and as long as 3-12 mos
- Higher risk if nadir CD4 <50-100
- Early diagnosis is critical
  - Ask patient to report even relatively minor new symptoms and signs early
  - Schedule regular, in person follow up
  - Maintain a high suspicion for another infection and perform or repeat exam, labs and imaging as appropriate

Stopping Secondary OI Prophylaxis: Guidelines

Organism	Primary Prophylaxis	Secondary Prophylaxis	Comments
PCP	CD4 >100, VL undetectable for > 3 months	CD4 >200 and VL undetectable for 3 months "Potentially" if CD4 >100 and RNA < 50 for 3 months*	*BII recommendation based on limited data
Toxoplasma	CD4 > 200 > 6 months		
Mycobacterium avium complex (MAC)	No longer recommended for CD4 <50	CD4 >100 x 6 months AND 12 months treatment AND stable disease	
Cytomegalovirus (CMV)		CD4 > 100 for 3-6 months	
Crypto		CD4 >100, VL undetectable for	CD4 >100, VL undetectable x 3 months AND 12 months azole

D'Egidio et al, AIDS. 2007, Mocroft et al CID 2010

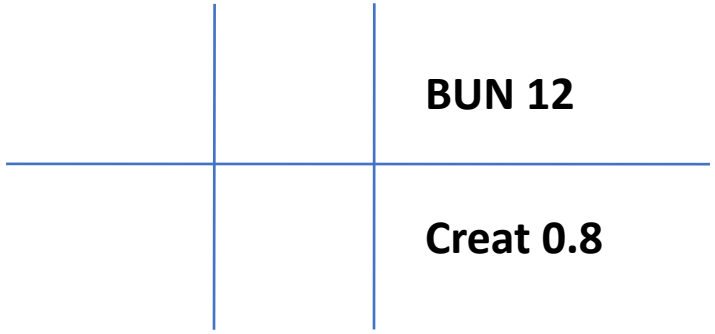
Stopping Secondary Prophylaxis Is About Risk Tolerance

- It stands to reason that if OIs OCCUR at higher CD4, they can RECUR at higher CD4
- Does disease threaten sight, function or life?
- Was disease difficult to control?
- Does clinical assessment and/or imaging suggest active disease?
- Is treatment well tolerated?

Patient 2

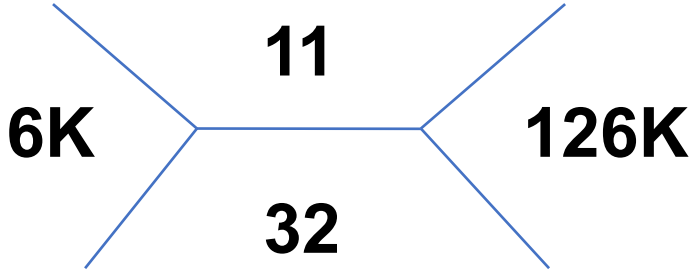
- 46 y/o Zimbabwean woman, in US x 3 years
- Presents with
  - 1 month of alteration in mental status, headache and blurring of vision
  - 2 weeks of bilateral hearing loss
  - 4 days of lethargy
- In ED, well nourished, afebrile, somnolent
- Mild nuchal rigidity, mild L sided weakness

Admission Labs and Imaging



CD4: 19
HIV RNA 18,300 copies

MRI: small infarct in the posterior limb of the right internal capsule and basal ganglia (no edema or mass effect)



83% P % P, 9 % L

LP: Opening pressure 55
Glucose 36
Total protein 34
7 WBC (90% lymphs)

Serum crypto Ag 1:4096
CSF crypto Ag 1:8192

For antifungal therapy, you recommend:

A. Ampho alone
B. Ampho and 5 flucytosine (5FC)
C. Ampho and steroids
D. Ampho, 5 FC and steroids
E. High dose fluconazole and 5 FC

IDSA Guidelines for Crypto Meningitis

“Induction”

- Lipid formulation 3-4 mg/kg/d preferred over Amphotericin B 0.7-1.0 mg/kg/d at *least 2 weeks* + 5FC 100/mg/kg/d x 2 weeks
- 2nd line (BII): Fluconazole 800 -1200 mg/d + 5 FC
- Consider LP to document negative culture prior to switch to fluconazole

- **“Consolidation”**
  - Fluconazole 400 mg/d at least 8 weeks
- “**Maintenance”**
  - Fluconazole 200 mg/d x at least 1 year, until CD4 > 100 and VL undetectable x at least 3 months

LM Improves Slowly

- Daily LPs then lumbar drain then VP shunt
- Improved to her cognitive baseline, remained blind
- MRI with small, evolving subacute infarcts in the R basal ganglia and subcortical white matter
- Tolerated FC x 2 wks
- CSF sterile at 21 days, CSF crypto Ag still 1:1024 with few visible budding yeast
- You recommend ART at

A. 2 weeks into treatment (after “induction”)

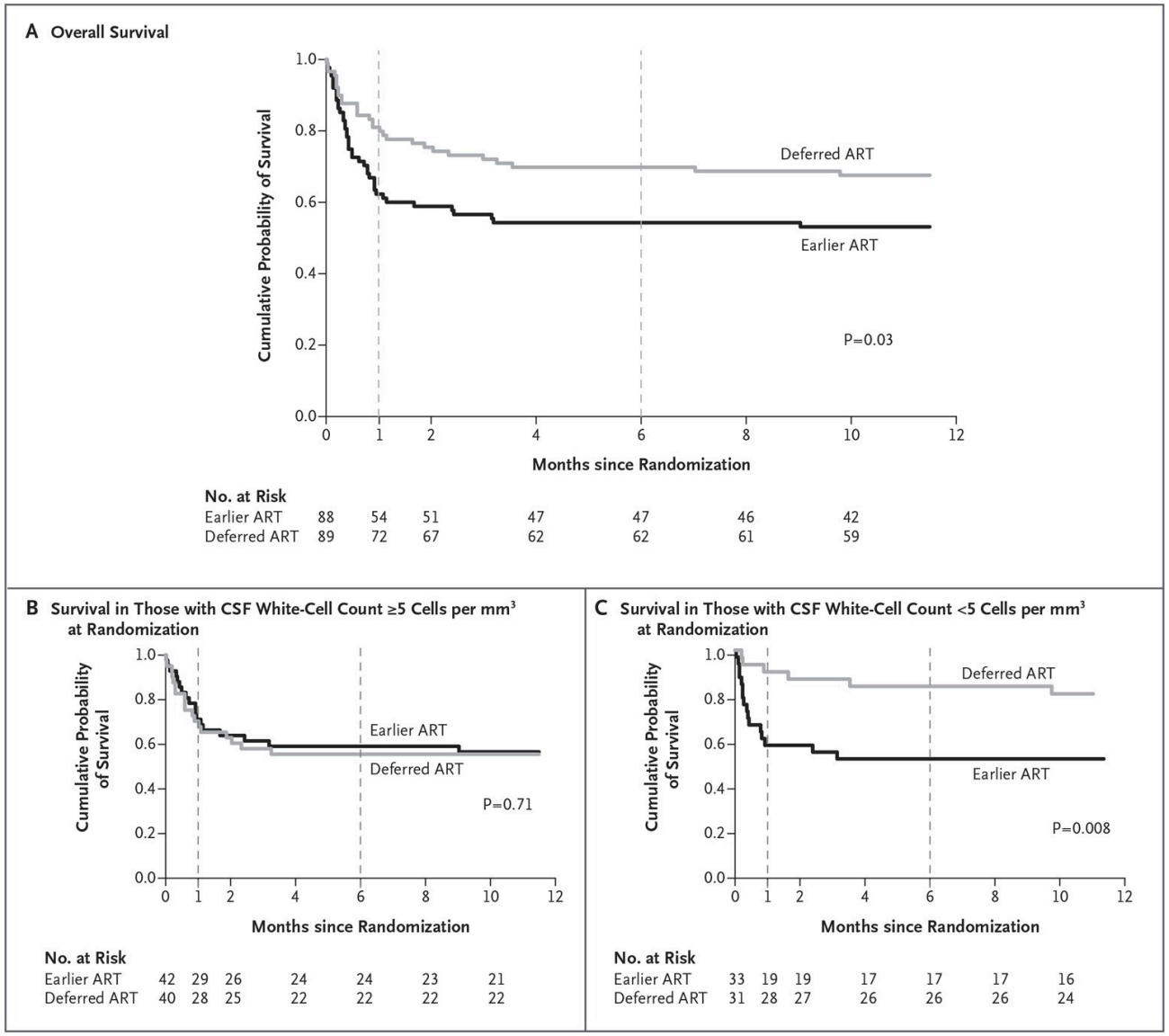
B. 10 weeks or later (after “consolidation”)

ART in Crypto Meningitis is Associated with Paradoxical IRIS

- About 30% will develop IRIS, may be severe or fatal
- Signs and symptoms: ↑ headache, meningeal symptoms, altered mental status, ICP. New CN palsies or stroke
  - 5 days to many months after ART
- Imaging: meningeal enhancement, cryptococcomas, focal or diffuse edema (including shift/herniation), cavitation, stroke,
- Treatment: steroids, treatment of increased ICP, intensification of antifungal treatment
- Many initial studies suggested increased mortality with early ART

Haddow et al, Lancet ID 2010; Rhein et al OFID 2018; 10:1; Meya et al, JID 2015; Zolopa et al, PLoS One 2009; Makadzange et al,CID, 2010;

COAT: Early ART Increases Mortality in CM



- Uganda and South Africa
- Induction with ampho B and fluconazole
- At 26 weeks, mortality 45% for early vs 30% for late ART
- RR death 1.73
- Excess deaths in first 2-5 weeks

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Boulware DR et al. *NEJM,* 2014

Guidelines for ART Initiation in CM

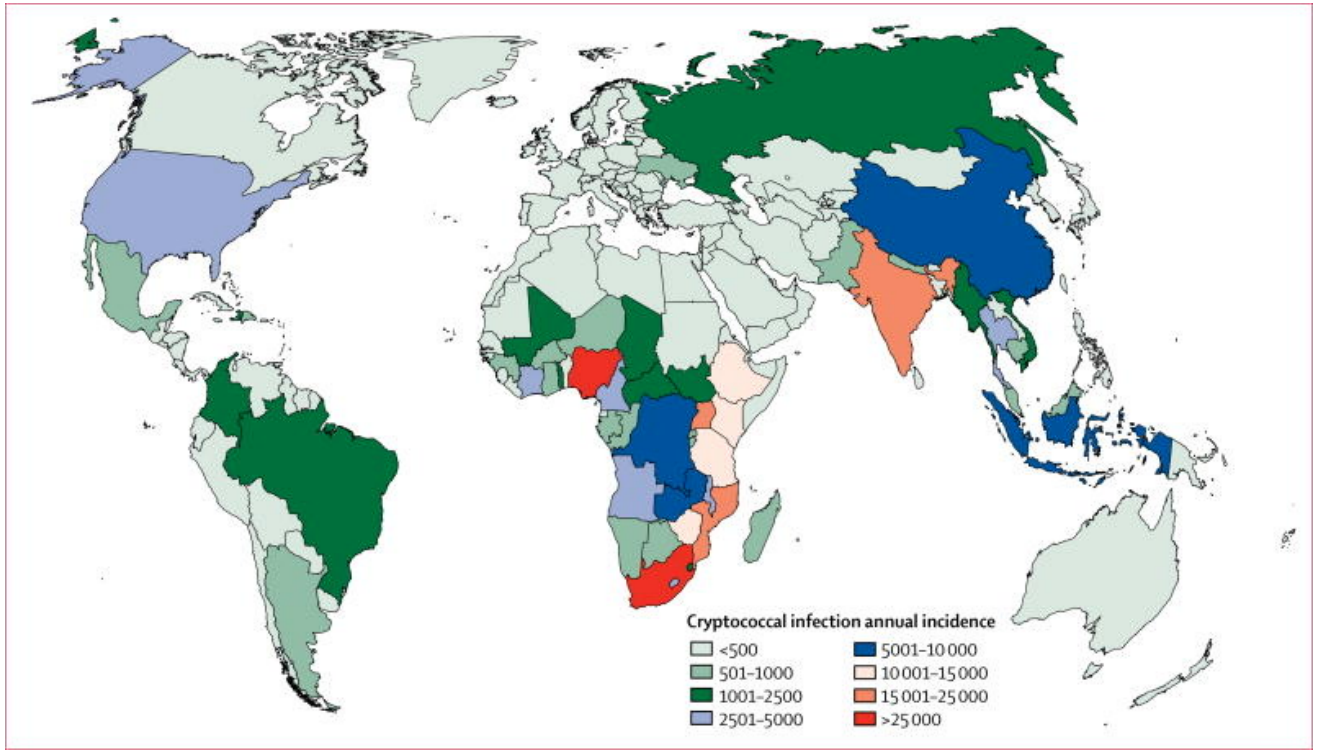
- Delay ART at least until after completion of induction (≥2 wks)
- Delay longer in severe or high risk disease, possibly until induction/consolidation phase (≥10 wks)
  - ↑ CSF OP, ↓ CSF wBC
- Sterile CSF cultures ↓ risk of IRIS
- If ART started prior to 10 wks, “be prepared to aggressively address IRIS
  - Steroids, treatment of ICP, intensification of antifungal treatment

Paradigm Shifts in Crypto Meningitis

"Our Heads Are Round
So Our Thoughts Can
Change Directions"

Francis Picabia 1879-1953

Efforts Must Address the Global Burden

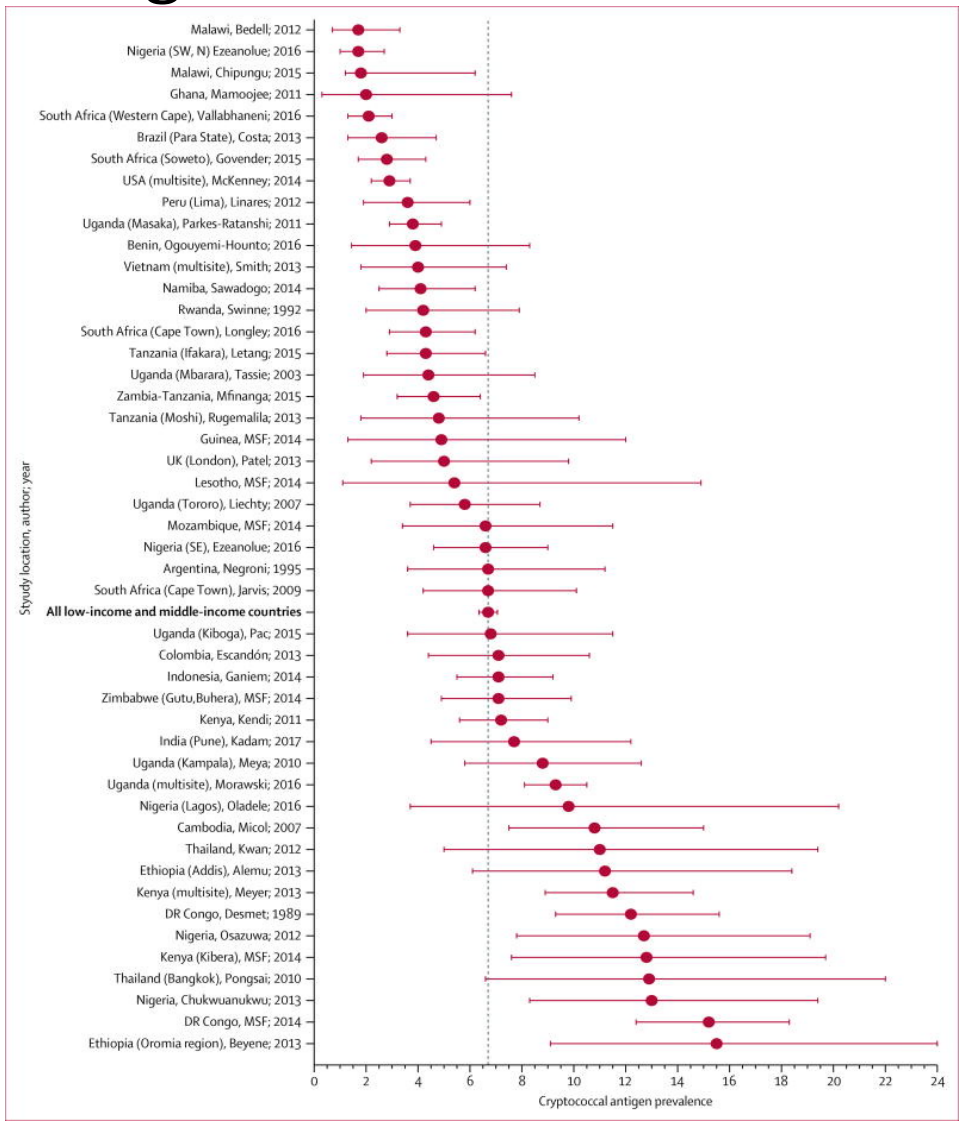


223,100 incident cases meningitis/yr
181,00 deaths/yr (75% in Africa); 15-20% of AIDS mortality
ART roll outs have not improved mortality

Person AK et al, *Clin Infect Dis* 2023, ciad076

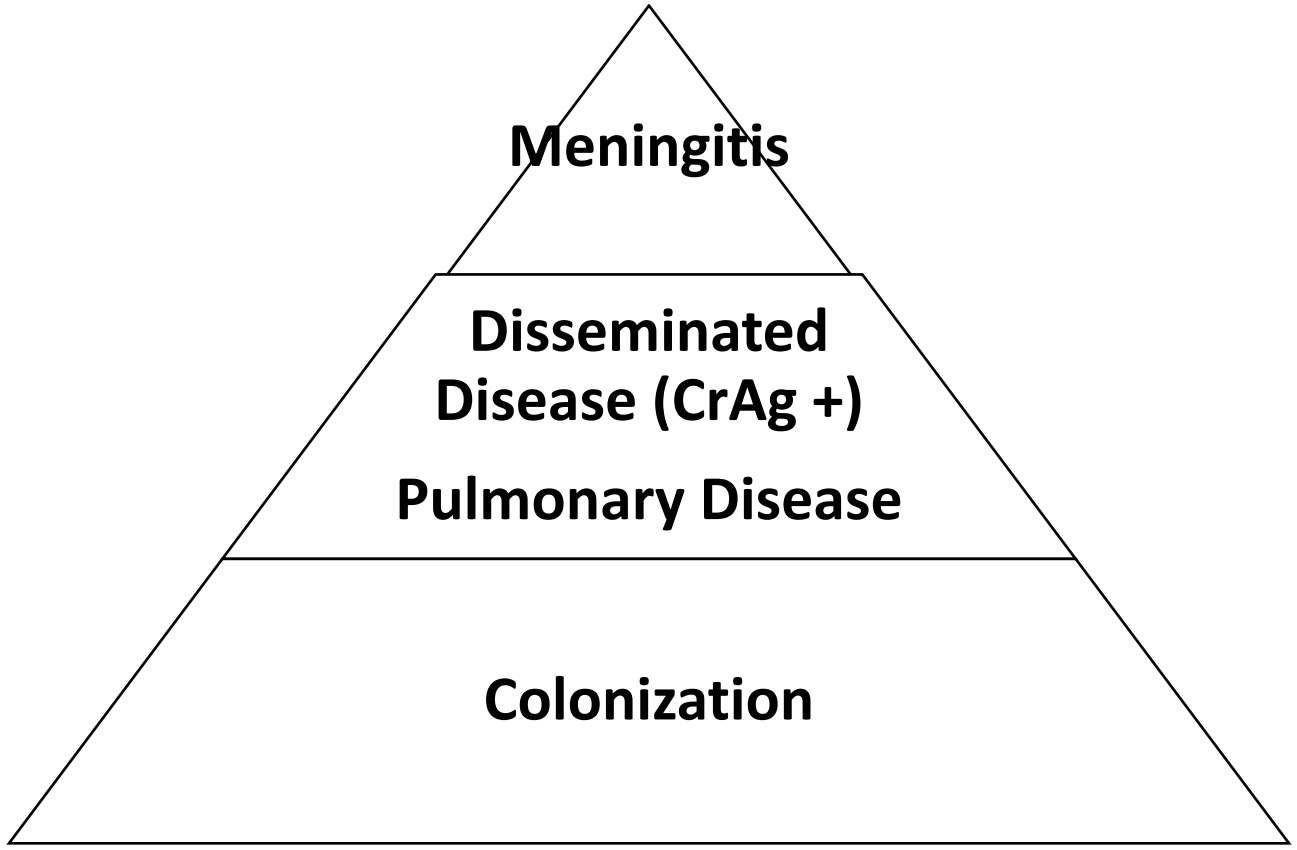
Disseminated Crypto Varies by Region and Precedes Meningitis

- Estimates of disseminated crypto in those with CD4 <100, as indicated by a positive serum crypto Ag
  - Average ≈ 6%
  - As high as 15-25% in some regions of Africa and Asia

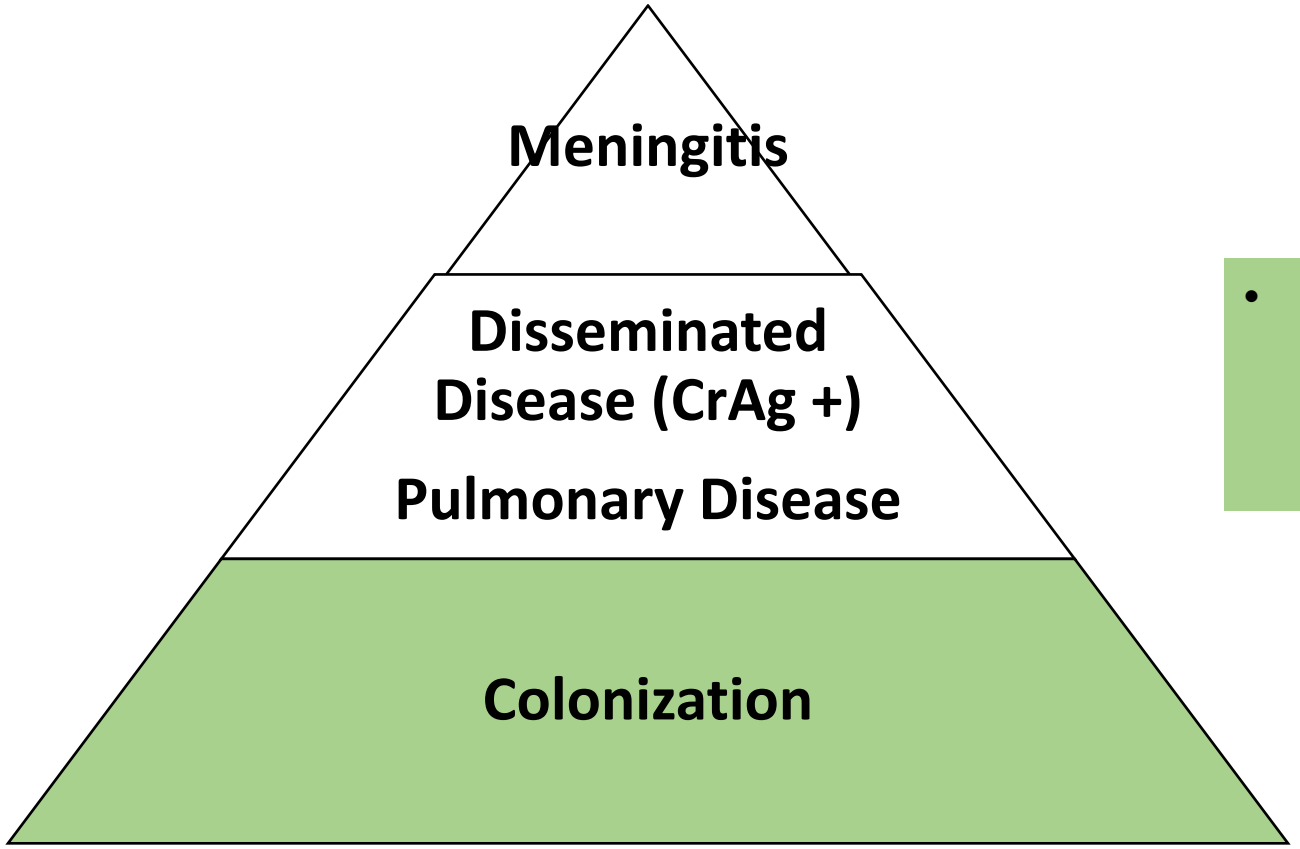


Boulware et al. *Lancet ID* 2017; Kaplan et al. *JAIDS*, 2015

Conceptualizing Crypto Disease as a Pyramid

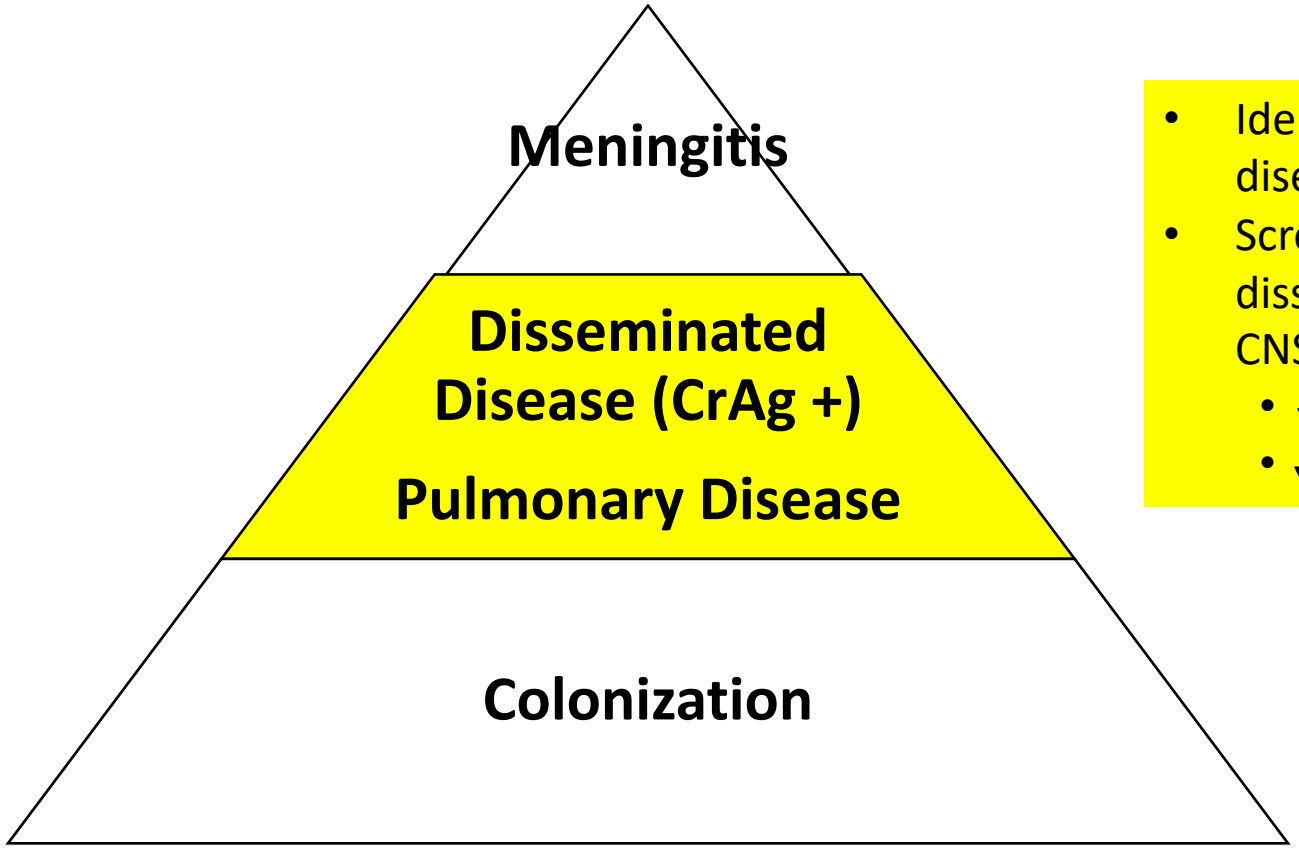


The Pyramid of Cryptococcal Disease



- No behavioral or environmental preventive measures to decrease colonization

The Pyramid of Cryptococcal Disease

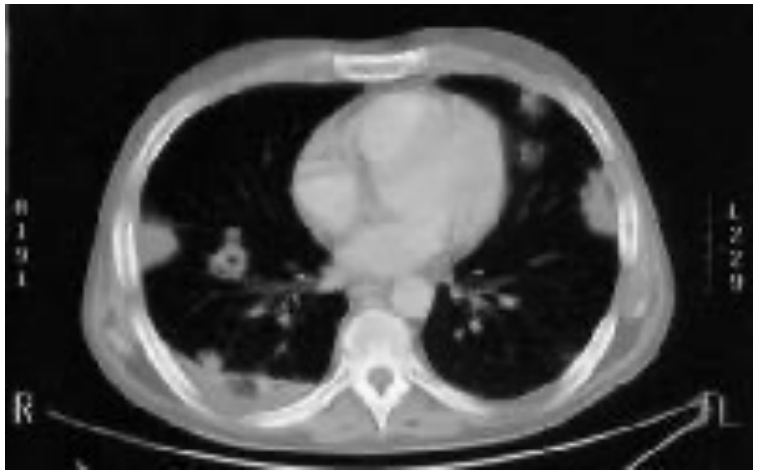


- Identify and treat pulmonary disease before dissemination
- Screen for and treat disseminated disease before CNS disease
  - ↓ incidence of CM
  - ↓ mortality

Temfack E, , et al. Clin *Infect Dis* 2019;68:688.

Diagnose Pulmonary Disease Before Meningitis

- In clinical series, 10-50% of patients with a crypto diagnosis have evidence of pulmonary disease at some time during their course, often preceding CNS disease
- Cough, chest pain, fever/chills; limited disease often asymptomatic
- If pulmonary or systemic symptoms present, perform CXR and serum CrAg
  - Probability of + CrAg increases with extent of pulmonary disease and lower CD4

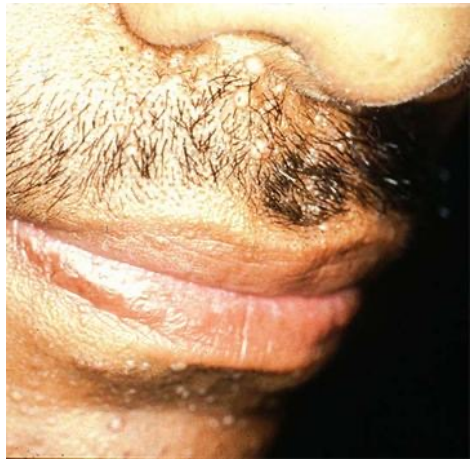


- Imaging findings: nodules, cavitary nodules, infiltrates, enlarged nodes, effusions

Diagnose Disseminated Crypto Before Meningitis

Screen for Symptoms

- Fevers, chills, sweats, weight loss
- Skin lesions

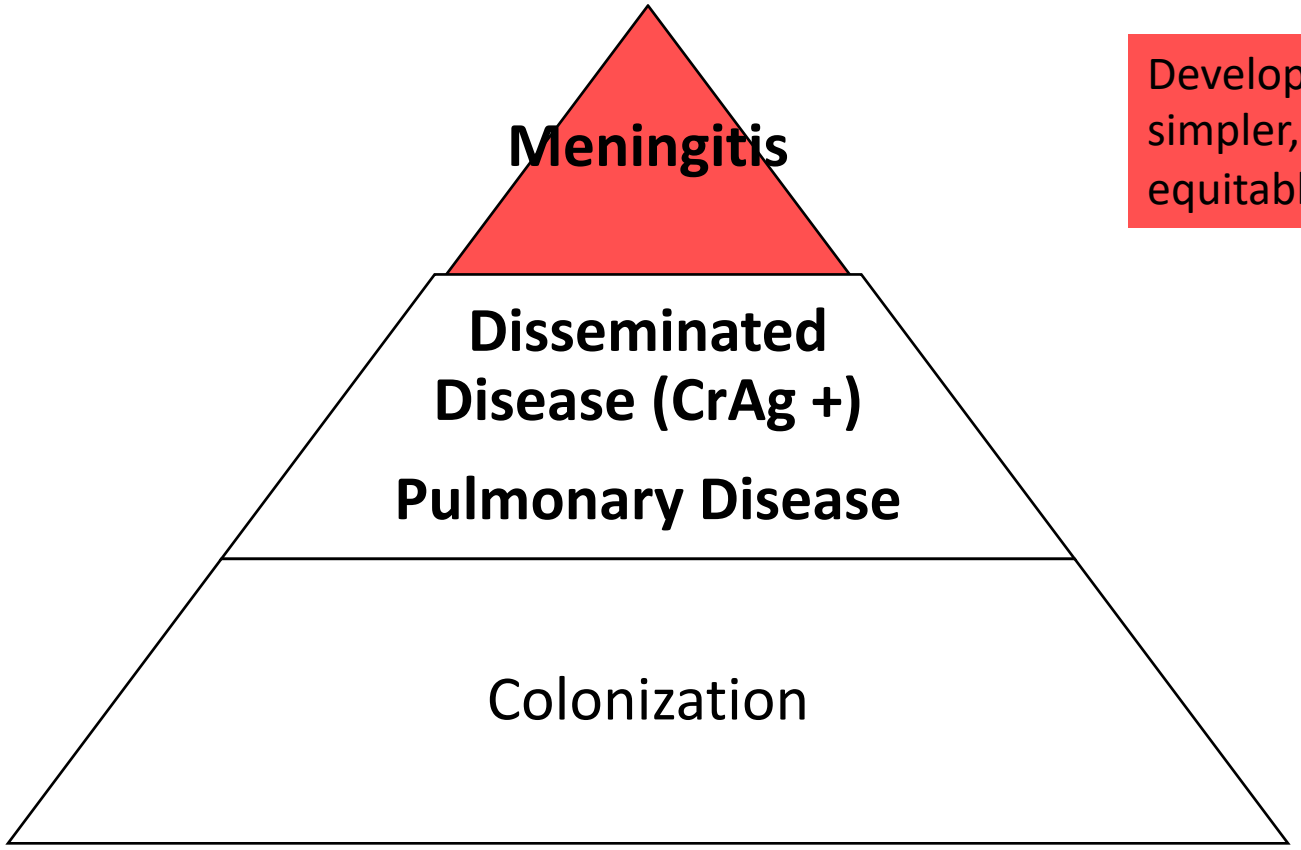


Screen High Prevalence Populations Without Symptoms

- If regional prevalence of +CrAg >4-20% and CD4 <100 or unavailable
  - Screen for + CrAg and treat if positive
  - No LP if no CNS symptoms (or minimal symptoms?)
- In the US, I would *extend screening to immigrants from higher prevalence regions*
- In LMIC, make point of care diagnostic screening (eg lateral flow assays) available

Boulware et al. *Lancet ID* 2017; Kaplan et al *JAIDS,* 2015, Denning et al. *J Fungi* 2017: 3:67

The Pyramid of Cryptococcal Disease



Develop and implement simpler, safer and more equitable treatment of CM

Evolution of CM Treatment

Durban South Africa AIDS Conference

2000

2004

ACTA (Advancing Cryptococcal Treatment in Africa)
1 wk Ampho B combo noninferior to 2 wk

2011

AMBITION-cm (Ambisome Therapy Induction Optimization)

2022

Sub-Saharan Africa consortium with stated goals:

1. Develop/test new antifungal regimens based on current drugs:
   - Safer and more sustainable than Ampho + 5FC
   - More effective than fluconazole monotherapy

Lawrence DS et al. *PLoS Negl Trop Dis* 2021:15. Jarvis JN et al. *N Engl J Med* 2022; 386:1109

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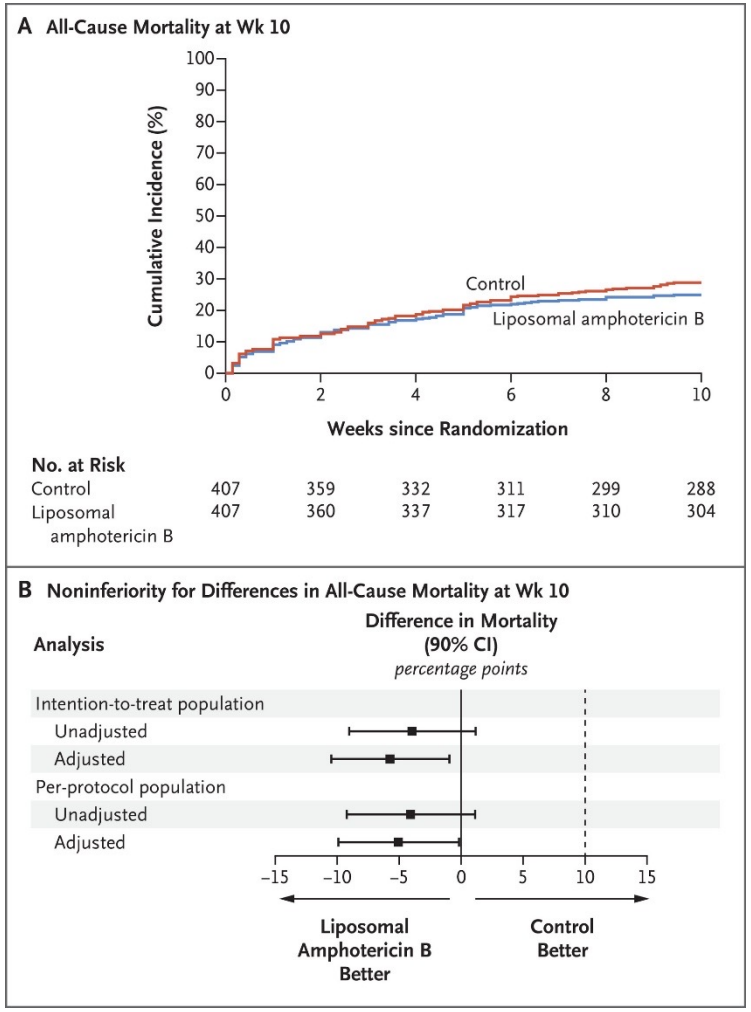
ESTABLISHED IN 1812 MARCH 24, 2022 VOL. 386 NO. 12

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

J.N. Jarvis, D.S. Lawrence, D.B. Meya, E. Kagimu, J. Kasibante, E. Mpoza, M.K. Rutakingirwa, K. Ssebambulidde, L. Tugume, J. Rhein, D.R. Boulware, H.C. Mwandumba, M. Moyo, H. Mzinganjira, C. Kanyama, M.C. Hosseinipour, C. Chawinga, G. Meintjes, C. Schutz, K. Comins, A. Singh, C. Muzoora, S. Jjunju, E. Nuwagira, M. Mosepele, T. Leeme, K. Siamisang, C.E. Ndhlovu, A. Hlupeni, C. Mutata, E. van Widenfelt, T. Chen, D. Wang, W. Hope, T. Boyer-Chammard, A. Loyse, S.F. Molloy, N. Youssouf, O. Lortholary, D.G. Lalloo, S. Jaffar, and T.S. Harrison, for the Ambition Study Group*

AMBITION-CM Trial



- Multicenter Phase 3 noninferiority trial comparing single high dose AmBisome10 mg/kg with 14 days of high dose fluconazole1200 mg mg/day + flucytosine, compared to the WHO standard
- 814 participants, intention to treat analysis
  - Severe disease
  - No patients lost to follow up
  - Median CD4 27, severe disease
- 10 week mortality single dose arm 24%, vs 28% control
- EFA (early fungicidal activity) equal
- Less toxic

Jarvis JN et al, *N Engl J Med* 2022;386:1109

Clinical Infectious Diseases

VIEWPOINTS

How Applicable Is the Single-Dose AMBITION Regimen for Human Immunodeficiency Virus–Associated Cryptococcal Meningitis to High-Income Settings?

Thomas S. Harrison,[1,2,3] David S. Lawrence,[4,5] Henry C. Mwandumba,[6,7,8] David R. Boulware,[9,10] Mina C. Hosseinipour,[11,12] Olivier Lortholary,[13,14] Graeme Meintjes,[15,16] Mosepele Mosepele,[5,17] and Joseph N. Jarvis[4,5,]

Authors Argue Very Applicable

Single-dose AmBisome-based treatment for cryptococcal meningitis in high-income settings

Antifungal activity	Side effects	Acceptability	Cost
Single, high-dose AmBisome-based treatment is at least as fungicidal as 14 days of standard-dose AmBisome Antifungal activity should not differ between settings	The single-dose AmBisome regimen has fewer side effects than 14 days of standard dosing The improved toxicity profile will be beneficial in all settings	Patient and provider preference for the single-dose AmBisome combination regimen is likely to apply in high-income settings	In settings with high hospitalization and medication costs, the single, high-dose AmBisome regimen will likely be cost-saving




Fair to Ask Me? When Would I Consider the One Dose AmBisome Regimen?

Mild to Moderate Disease

- Headache, fever, photophobia, neck stiffness
- No altered mental status or cranial neuropathy
- Mild to moderate elevation of intracranial pressure
- Can be followed in the hospital initially
- Subsequent home monitoring and close outpatient follow up feasible

Unwilling or Unable to Remain in the Hospital

- Ideally with close follow up

Future Directions

- Oral lipid nanocrystal formulation of Ampho B appears safe and effective in Phase 1-2 trials

Abstract 00137, ECCMID, 15-18 April 2023

Take Home Points

- The updated OI guidelines provide a framework for prevention, diagnosis and treatment based on best available US evidence
- Prevention and early detection are key
- To do this, clinicians must
  - Follow high risk patients (nadir CD4 in past year <100) closely
  - Recognize “typical” and “atypical” presentations
  - Appreciate the assessment and treatment of IRIS

Take Home Points

- Basic, clinical and implementation science in international settings are advancing the effectiveness, cost effectiveness and equity of our approach to prevention and treatment of cryptococcal meningitis
- We should work to make this a fully bidirectional interaction