

# Management of AIDS-Related Opportunistic Infections

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## Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Masur has no relevant financial relationships with ineligible companies to disclose. (Updated 09/28/22)

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## Learning Objectives

After attending this presentation, learners will be able to:

- Identify reasons for continued morbidity due to HIV-related opportunistic infections
- Describe the role of molecular diagnostics for selected HIV-related infectious diseases
- Assess new options for treatment of HIV-related cryptococcal meningitis

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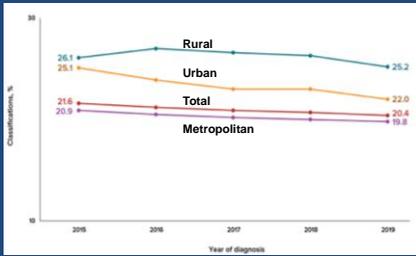
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**AIDS at Time of Diagnosis 2015-2019, United States**  
 20-25% PWH Continue to Present Late in Disease



<https://www.cdc.gov/hiv/data-reports/surveillance/vol25-no2/index.html> Slide 4

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**Primary Cause of Death among People Diagnosed with HIV by Year of Death, District of Columbia, 2015-2019**

Cause of Death	2015		2016		2017		2018		2019	
	%	N	%	N	%	N	%	N	%	N
HIV-related causes	18.3		28.9		28.2		31.3		25.0	
Non-AIDS Defining Illnesses	9.8		15.1		16.4		13.3		9.5	
Cardiovascular	14.4		14.5		19		24.5		18.0	
Substance Use	1.3		1		0.7		1.1		0.5	
Accidental Death	7.2		12.2		12.5		10.1		11.5	
Other**	10.8	47	47		15.4		15.8		11.0	
Unknown	38.2		9.3		7.9		4		24.5	
<b>Total</b>	<b>100</b>		<b>100</b>		<b>100</b>		<b>100</b>		<b>100</b>	

Annual Epidemiology & Surveillance Report, <https://dchealth.dc.gov/service/hiv-reports-and-publications> Slide 5

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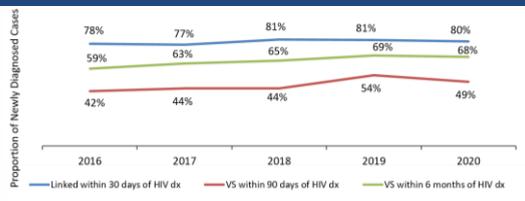
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**Linkage to Care and Viral Suppression among New Cases, District of Columbia, 2016-2020 (N=1,547)**



Annual Epidemiology & Surveillance Report, <https://dchealth.dc.gov/service/hiv-reports-and-publications> Slide 6

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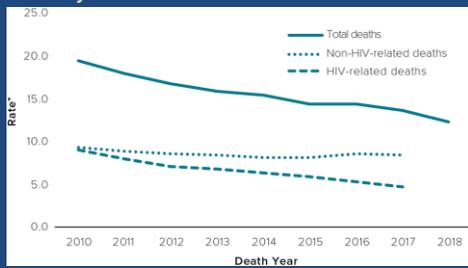
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**Among People with HIV, Deaths from All Causes Decreased  
Mainly Because of Declines in HIV-related Deaths**



<https://www.cdc.gov/hiv/statistics/deaths/index.html> Slide 7

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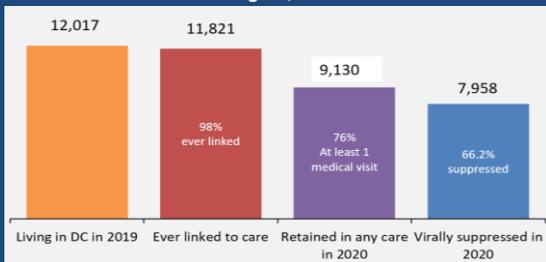
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**HIV Care Continuum among People Living with HIV  
Washington, DC 2020**



Annual Epidemiology & Surveillance Report, <https://dchealth.dc.gov/service/hiv-reports-and-publications> Slide 8

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**At What CD4 Counts Do  
Opportunistic Infections Occur?**

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**Unchanged Since  
Beginning of Epidemic**

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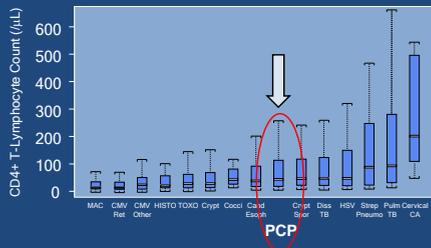
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**CD4+ T-Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS**



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## Answer

A 52-year-old woman without known HIV is diagnosed with PCP

- HIV Ab test positive
- CD4 103, HIV RNA 135,000 copies/ml
- She is still intubated on day 4 of IV trimethoprim-sulfa and corticosteroids

When should she start ART?

- Immediately
- In the next 2 weeks
- After completing 21 days of trimethoprim-sulfa
- At her first outpatient clinic visit

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### When to Start ART Following Opportunistic Infection

- **Most OIs**
  - **Within 2 weeks** of diagnosis

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### ART Initiation Following HIV Related Opportunistic Infections Early Favors Survival

Survival Without Additional OI

The graph shows survival without additional opportunistic infections (OI) over a 48-week period. The y-axis represents survival probability from 0.0 to 1.0. The x-axis represents time to death from AIDS-defining illness in weeks, from 0 to 48. Two curves are shown: 'Early Initiation' (solid line) and 'Later Initiation' (dotted line). The early initiation group shows a higher survival rate, starting at 1.0 and ending at approximately 0.95 at 48 weeks. The later initiation group starts at 1.0 but drops to approximately 0.85 by 48 weeks. The number of patients at risk is shown at the bottom of the x-axis: 121 for early initiation and 119 for later initiation.

Zolopa PLoS One 2009;4:e5575  
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### When to Start ART Following Opportunistic Infection

- **Tuberculosis: 2-8 weeks after initiation RX**
  - CD4<50 or Pregnant-within 2 weeks of diagnosis
  - CD4>50-within 8 weeks of diagnosis
- **Cryptococcal Meningitis: 4-6 weeks after initiation of RX**
  - Sooner if mild and if CD4<50
  - Later if severe
- **“Untreatable” OIs, i.e., PML, Cryptosporidiosis**
  - Start immediately

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**When to Start ART Following Opportunistic Infection**  
 Tuberculosis 2-8 weeks after initiation ART

**Is This Still True?**

- This is what current guidelines recommend
- Data are from decades ago or more currently from resource limited sites
- More tools now to manage IRIS
- How should patients be managed in 2022

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***Pneumocystis Jirovecii***  
 (Formerly *P. carinii*)

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**Diagnosis of Pneumocystis Pneumonia**

<p><u>Specimen Acquisition</u></p> <ul style="list-style-type: none"> <li>Open lung biopsy</li> <li>Transbronchial biopsy</li> <li>Bronchoalveolar lavage</li> <li>Induced sputum</li> </ul>	<p><b>1957</b></p>  <p><b>2022</b></p>	<p><u>Organism Detection</u></p> <ul style="list-style-type: none"> <li>Methenamine silver</li> <li>Immunofluorescence</li> <li>Giemsa / Diff Quik</li> <li><b>PCR</b></li> </ul>
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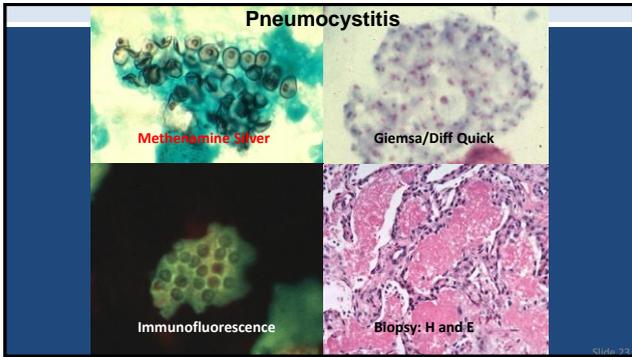
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**PCR**  
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **Highly sensitive in BAL**
  - Not useful in blood/serum/plasma
- **High biologic specificity**
  - Positive result might be infection or disease
  - Cycle number (copy number) helpful but not definitive

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**PCR**  
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- High
  - Not
- High
  - Po
  - Cy

**Negative BAL PCR rules out PCP**

**Positive BAL PCR *might* be PCP**

- Colonization vs Disease

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## Central Nervous System Infections

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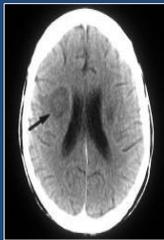
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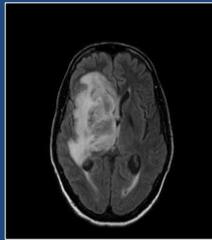
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## CNS Mass Lesions



Non Contrast CT



Flair MRI

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## Evaluation of CNS Mass Lesions in Patients with HIV/AIDS

- Toxoplasmosis
- Lymphoma
- Tuberculosis
- Fungus
- Nocardia
- Bacterial
- Syphilis
- Kaposi
- Chagoma
- Glioblastoma

**Radiologic Results**  
Non-specific

**Laboratory Studies to Perform**  
Serology: Toxo IgG, Toxo PCR  
Serum Crypt Ag and Histo ag  
Blood culture - AFB, fungus  
CSF - Crypt Ag  
PCR (EBV, CMV, Toxo)  
Urine - Histo Ag

**Response to Empiric Therapy**

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## Therapy for Cerebral Toxoplasmosis

### • Preferred Regimen

- Sulfadiazine plus pyrimethamine plus leucovorin (PO only)
  - *Note: these drugs each may be unavailable or cosmetically expensive*

- **Trimethoprim-sulfamethoxazole (PO or IV)**

### • Alternative Regimens

- Clindamycin plus pyrimethamine
- **Atovaquone +/- Pyrimethamine**

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## Cryptococcal Meningitis

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## Asymptomatic Cryptococcal Antigenemia

### • Recommendation:

- Screen patients with CD4 < 100
  - Frequency: 2.9% if CD4 < 100, 4.3% if CD4 < 50
- Positive serum ag predicts development of active disease

### • If Positive Serum Crypt Ag

- Perform LP and Blood Cultures to determine Rx
- If CSF positive or serum LFA is  $\geq 640$ 
  - Treat like crypt meningitis/disseminated (Ampho/5FC)
- If CSF negative and low Crag titer or LFA  $\leq 1:320$ 
  - Treat with fluconazole 400mg or 800mg x6 months

IDSA OI Guidelines for Crypt 2022

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### BioFire FilmArray for CSF

Viruses	Bacteria	Fungi
Cytomegalovirus	<i>Escherichia coli</i> K1	<i>Cryptococcus neoformans/gattii</i>
Enterovirus	<i>Haemophilus influenzae</i>	
Herpes simplex virus 1	<i>Listeria monocytogenes</i>	
Herpes simplex virus 2	<i>Neisseria meningitidis</i>	
Human herpes virus 6	<i>Streptococcus agalactiae</i>	
Human parechovirus	<i>Streptococcus pneumoniae</i>	
Varicella zoster virus		

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### BioFire FilmArray for CSF

Viruses	Bacteria	Fungi
Cytomeg		
Enterovir		
Herpes s		
Herpes s		
Human h		
Human parechovirus	<i>Streptococcus pneumoniae</i>	
Varicella zoster virus		

Cryptococcal antigen more sensitive than PCR

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### Therapy of Cryptococcal Meningitis and Extrapulmonary Disease

Liposomal Ampho B 3-4 mg/kg qd plus Flucytosine* 25 mg/kg QID	→ 2 weeks – Induction
Fluconazole <del>200</del> 800 mg po qd	→ 8 weeks – Consolidation
Fluconazole 200 mg po qd	→ ≥ 52 weeks – Maintenance

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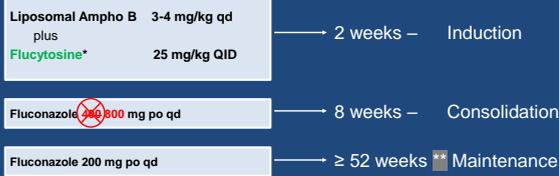
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## Therapy of Cryptococcal Meningitis



\*5FC Associated with Earlier sterilization CSF  
Fewer relapses  
Improved survival

Flucon 800mg Consolidation  
\*Fewer relapses 800 vs 400

\*\* Stop after 12 m total therapy if CD4 >100, 150 x >3m  
Asymptomatic  
VL <50 copies

© 2016, 2018

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## Induction Therapy – New Options

- Liposomal ampho B, **single dose 10mg/kg IV** on day 1 only plus 5FC 25 mg/kg PO four times a day x 14 d plus Fluconazole 1200 mg/d x 14 d (A)
- Amphotericin B deoxycholate 1 mg/kg/d IV x 1 week plus 5FC 25 mg/kg PO q6h x 1 week plus Fluconazole 1,200 mg/d PO x 1 week (B)

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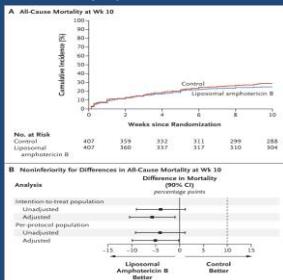
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## Cumulative All-Cause Mortality Up to Week 10 and Noninferiority Analyses



Jarvis JN et al. N Engl J Med 2022;386:1109-1120

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**Conclusions**

- Similar to the regimen used in the US

**Does anyone in the US use this regimen**

**Patients are recommended to be hospitalized for 14 days**

Jarvis JN et al. N Engl J Med 2022;386:1109-1120

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**Elevated CSF Pressure**

- **75% of patients have Opening Pressure >20 cm CSF**
  - Abnormal = >25 cm CSF
- **Symptoms**
  - Blurred vision, confusion, obtundation
- **Management: IF symptomatic and >25cm**
  - Remove volume to reduce pressure by half or <20cm H2O or remove 20-25 ml
  - Continue LPs daily for symptomatic patients until stable for at least 2 days
  - Shunt if regular LPs required for “many” days
- **Not routinely recommended**
  - Corticosteroids, Mannitol, Acetazolamide

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**Q and A Session**



2022 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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