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PREVENTING and TREATING
*Pneumocystis Jirovecii* Pneumonia (PCP) and *Mycobacterium Avium* Complex (MAC):

A Continuing Challenge in HIV/AIDS Care

Cindy Meng Hou, DO, MBA, and Sindy Paul, MD, MPH, FACPM

Sponsor: UMDNJ-Center for Continuing & Outreach Education-Division of AIDS Education.

Funding: This activity is supported by an educational grant from NJDHSS Division of HIV/AIDS Services through an MOA titled “Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS. Pharmaceutical review was provided in-kind through the New York/ New Jersey AETC.

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Preventing and Treating Pneumocystis jirovecii Pneumonia (PCP) and Mycobacterium Avium Complex (MAC): A Continuing Challenge in HIV/AIDS Care

Release Date: December 12, 2009  Expiration Date: November 30, 2011  Course Code: 11HC08-DE01  Nursing Credit for this activity will be provided through November 30, 2011.

Sponsor
Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), Center for Continuing & Outreach Education, Division of AIDS Education.

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Target Audience
This activity is designed for physicians, nurses, pharmacists, and other health care professionals in New Jersey who are involved in the care of persons with HIV/AIDS.

Statement of Need
The CDC, with the Infectious Disease Society of America, released updated Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents on April 10, 2009. These Guidelines emphasize the critical role of ART in preventing and treating OIs, and thus significantly reducing mortality from HIV/AIDS.

Learning Objectives
Upon the completion of this activity, participants should be able to:
1) Identify gaps between the recommended levels of prophylaxis and actual practice in the United States.
2) Identify gaps between the recommended levels of prophylaxis and actual practice in the United States.
3) Incorporate CDC/JISA guidelines for when to start, to stop, and to restart chemoprophylaxis for HIV/AIDS patients into their practices.
4) Identify and address the adverse effects and drug interactions associated with medications for PCP and MAC prophylaxis and treatment.

Faculty
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Method of Participation
Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a letter of credit and the test answer key four (4) weeks after receipt of the self-assessment test, registration, and evaluation materials; or may complete the activity on the internet at www.umdnj.edu/ccoe. Estimated time to complete this activity as designed is 0.75 hour for physicians and 1.0 hour for nurses and other health professionals.

Accreditation
Physicians: UMDNJ-Center for Continuing and Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
UMDNJ-Center for Continuing and Outreach Education is an approved provider of continuing nursing education by the New Jersey State Nurses Association, an approved accreditor by the American Nurses Credentialing Center’s Commission on Accreditation. Provider Number P173-11/09-12. Provider Approval is valid through November 30, 2012.
This activity is awarded 1.0 contact hours. (60 minute CH)
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Review: This activity was peer reviewed for relevance, accuracy of content, and balance of presentation by Patricia Kloser, MD, MPH; Debbie Mohammed, MS, MPH, APRN-BC, AACRN; John J. Faragon, PharmD, BCPS, AAHIVE; and Brenda Christian, MD, PA-C; Director of UMDNJ-CCOE-Division of AIDS Education; and pilot tested for relevance and time required for participation by Kinshasa Morton, MD, Clinical Instructor of Family Medicine, UMDNJ-Robert Wood Johnson School of Medicine, ; Bonnie Abedini, MSN, RN; Director; Quality & Compliance, Rutgers Health Services; Mary C. Krug, MSN, APN; Associate Director Health Services, Hurtado Health Center, Rutgers University; Kara Winslow, BSN, RN; Clinical Care Coordinator, UMDNJ-University Hospital; and George Rusuoloj, PharmD, Pharmacist, Bell Pharmacy.

Disclosure Declarations
There were no relevant financial relationships to disclose reported by the activity director, faculty, planning committee members, editor, content reviewers or field testers.

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PREVENTING and TREATING

Pneumocystis Jirovecii Pneumonia (PCP) and Mycobacterium Avium Complex (MAC):

A Continuing Challenge in HIV/AIDS Care

Cindy Meng Hou, DO, MBA, and Sindy Paul, MD, MPH, FACPm

Upon completion of this activity, participants should be able to:

1. Describe the CDC and Infectious Disease Society of America guidelines for identifying HIV/AIDS patients at highest risk of the opportunistic infections Pneumocystis jirovecii pneumonia (PCP) and Mycobacterium avium complex (MAC), and providing effective prophylaxis.

2. Identify gaps between the recommended levels of prophylaxis and actual practice in the United States.

3. Incorporate CDC/IDSA guidelines for when to start, to stop, and to restart chemoprophylaxis for HIV/AIDS patients into their practices.

4. Identify and address the adverse effects and drug interactions associated with medications for PCP and MAC prophylaxis and treatment.

(Continued on next page)
PROPHYLAXIS against opportunistic infections reduces the rate of HIV progression, delays or reduces the occurrence of subsequent OIs, and improves survival.

ALL PROVIDERS MUST UNDERSTAND WHO IS ELIGIBLE for prophylaxis, to prescribe first-line medications to these patients, and to counsel on adherence to ART and chemoprophylaxis agents.

PREVENTING AND TREATING PCP AND MAC
A Continuing Challenge in HIV/AIDS Care

Introduction
Remarkable progress has been made in treating patients with HIV/AIDS. Opportunistic infections (OIs) were a leading cause of morbidity and mortality for HIV/AIDS patients until the widespread use of combination antiretroviral therapy (ART) in the mid-1990s.

CHEMOPROPHYLAXIS was also developed to prevent first-time episodes (primary prophylaxis) and subsequent bouts (secondary prophylaxis) of these OIs. Prophylaxis against opportunistic infections reduces the rate of HIV progression, delays or reduces the occurrence of subsequent OIs, and improves survival.1

The U.S. Department of Health and Human Services-Health Resources and Services Administration (HRSA) has established a series of core HIV/AIDS measures, which include ensuring compliance with PCP and MAC prophylaxis. The HRSA performance measure for PCP is the percentage of clients with HIV infection and a CD4+ count below 200 cells/µL who were prescribed PCP prophylaxis.2 The HRSA performance measure for MAC is the percentage of clients with HIV infection with CD4+ count <50 cells/µL who were prescribed MAC prophylaxis within the measurement year.3

This article focuses on the 2009 recommendations for prophylaxis, diagnosis and treatment of two important OIs, Pneumocystis jirovecii pneumonia (PCP) and Mycobacterium avium complex (MAC). All providers must understand who is eligible for prophylaxis, to prescribe first-line medications to these patients, and to counsel on adherence to ART and chemoprophylaxis agents.
Preventing and Treating PCP and MAC:
A Continuing Challenge in HIV/AIDS Care

Providers Still Miss Opportunities To Prevent Opportunistic Infections

Even in this era of ART and chemoprophylaxis, OIs continue to cause significant morbidity and mortality. Patients knowledgeable of their HIV status may either decline ART or fail to comply with their prescribed ART regimen. Pharmacokinetics and unexplained biologic factors may result in inadequate virologic or immunologic responses to ART. Many patients are diagnosed late in the disease process with AIDS and have OIs at diagnosis.1

- HIV care providers must become aware of the decline in rates of MAC and PCP prophylaxis in eligible patients, as well as the need for continued vigilance to return to close monitoring, prophylaxis, and treatment of PCP and MAC.
- The Healthy People 2010 objectives outlined by the Centers for Disease Control and Prevention, as well as HRSA, set the target adherence for both PCP pneumonia and MAC prophylaxis at 95% of eligible patients.
- HRSA collects data on care provided to HIV medical clinics funded through the Ryan White CARE Act, which serve 531,000 low-income HIV-infected patients.
  > In 2005, HRSA gathered data for a midcourse review of progress toward the Healthy People 2010 goals, including PCP prophylaxis in HIV patients with CD4+ counts < 200 cells/µL. They found that the rate of prophylaxis for this group decreased from 80% in 1997 to 70% in 2002, reversing course from earlier progress toward the goal of 95%.
  > For MAC prophylaxis, clinics reported only a 29% improvement toward the targeted goal, moving from 44% of targeted patients in 1997 to 59% in 2002, toward a goal of 95% by 2010.4

Pneumocystis jirovecii Pneumonia (PCP)

BACKGROUND

Pneumocystis jirovecii Pneumonia (PCP) is an acute to sub-acute, often fatal pulmonary disease. It occurs in high-risk patients including those who are chronically ill, malnourished, and immunosuppressed.1

- The etiologic agent of PCP is Pneumocystis jirovecii. It was previously known as Pneumocystis carinii. However, it is still commonly referred to as PCP.5
- The DNA structure analysis classifies PCP as a fungus but the organism retains several morphologic and biologic similarities to a protozoan.1
- This pathogen is a major opportunistic infection and an indicator disease for AIDS.5
- The mode of transmission is thought to be airborne invasion of the respiratory pathway. However, the incubation period has not been defined.1

Prior to the advent of primary PCP prophylaxis and ART, 70-80% of patients with AIDS developed PCP, with a PCP-associated mortality of 20-40% in those who were diagnosed with this infection. The current incidence of PCP among person with AIDS in Western Europe and the United States is 2-3 cases per 100 person-years, or a 2-3% annual incidence rate. PCP occurs predominantly among persons previously undiagnosed with HIV disease or not receiving ongoing HIV care.1
Individuals at high risk for PCP include the chronically ill, malnourished, and immunosuppressed.

**Risk Factors**

In HIV patients, ninety percent of cases occurred with CD4+ counts of < 200 cells/µL. Other risk factors are CD4+ cell percentage <14%, history of prior PCP, oral candidiasis, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA.

**CLINICAL SIGNS AND SYMPTOMS**

Optimal care for patients with PCP depends on prompt diagnosis. Clinical signs and symptoms may occur one or two months after becoming immunosuppressed. The classic symptoms include fever, dyspnea, substernal chest pain, and a non-productive cough. On physical exam, a patient may also have tachypnea, tachycardia, and dry rales with exertion but may otherwise sound clear at rest. Overall, the signs and symptoms of PCP are nonspecific. **Extrapulmonary Pneumocystosis** is rare, but may occur in the central nervous system, liver, spleen, lymph nodes, thyroid gland, kidneys, bone marrow, adrenal glands, and eyes. Previously, most extrapulmonary PCP cases were associated with use of aerosolized pentamidine, which does not have systemic penetration.

**LABORATORY DATA AND STUDIES**

A lactate dehydrogenase level (LDH) will often be higher than 500 mg/dL, but this is not a specific test. The classic chest x-ray shows bilateral interstitial infiltrates, but this is not always seen and is actually normal 10% of the time. If a pneumothorax occurs in a HIV patient, then PCP is in the differential diagnosis. If the x-ray is unremarkable, a computed tomography (CT) scan may show diffuse ground glass attenuations. Definitive diagnosis requires isolation of the organism from bronchoalveolar lavage fluid or lung tissue.

**PCP Prophylaxis**

PCP prophylaxis is recommended for patients with a CD4+ count <200 cells/µL or when the history or symptoms suggest oral-pharyngeal candidiasis. Persons with a history of an AIDS defining illness are potential candidates for prophylaxis. Guidelines for PCP prophylaxis are displayed in Table 1. In 10-15% of cases, PCP develops in patients with CD4+ counts above 200 cells/µL.  

- Trimethoprim-sulfamethoxazole (TMP-SMZ, trade names Bactrim or Septra) is the **drug of choice** for prophylaxis of all forms of pneumocystosis. The preferred regimen is one double strength tablet daily, but one single strength tablet daily or one double-strength three times weekly is acceptable.

- Dapsone 100 mg/day or atovaquone (trade name Mepron) 1500 mg daily with food are equally effective.

- Less commonly used regimens include dapsone 50 mg/day plus pyrimethamine 50 mg/week plus leucovorin 25 mg/week or atovaquone 1500 mg/day orally plus pyrimethamine 25 mg orally plus leucovorin 10 mg orally daily.

- Aerosolized pentamidine at 300 mg/month is now rarely used.

Table 1 summarizes the 2009 CDC/IDSA recommendations for PCP prophylaxis and treatment.

**PCP Prophylaxis During Pregnancy**

PCP prophylaxis is still required during pregnancy. For lower-risk women, the provider may consider withholding prophylaxis in the first trimester secondary to possible teratogenic effects. **The drug of choice is TMP-SMZ, and dapsone may also be given.**

**Discontinuing/Restarting PRIMARY Prophylaxis**

If a patient has been on ART and PCP prophylaxis, and is able to achieve and maintain a CD4+ count >200 cells/µL for three months or more, then primary prophylaxis may be discontinued. With immune reconstitution, the CD4+ count rises above a pathogen-specific threshold level of 200 cells/µL. Immune reconstitution is often so successful on ART that PCP prophylaxis can be stopped. Discontinuing chemoprophylaxis at the appropriate time reduces pill burdens, potential for drug toxicity and interactions and may prevent the emergence of resistant pathogens. If CD4+ counts eventually fall to less than 200 cells/µL, PCP prophylaxis should be restarted.

**Discontinuing/Restarting SECONDARY Prophylaxis**

If a patient successfully completed treatment for PCP but the CD4+ count is <200 cells/µL, then secondary prophylaxis should be initiated. If the patient has achieved immune reconstitution with a CD4+ count >200 cells/µL for three months or more on ART, then secondary prophylaxis may be discontinued. Restarting of secondary prophylaxis should occur when the CD4+ count decreases to <200 cells/µL or if PCP recurs at a CD4+ count >200 cells/µL. If PCP occurred even though a patient’s CD4+ count was >200 cells/µL at the time of the illness, secondary prophylaxis must be employed for life regardless of how high ART increases the patient’s CD4+ count.
**Treatment of PCP Pneumonia**

**EMPIRIC TREATMENT** for PCP pneumonia should be considered in patients with clinical suggestions of disease including abnormal chest radiographs, low CD4+ counts, abnormal oxygenation requirements, especially in the context of elevated LDH levels as well as the lack of PCP prophylactic medications. It is important to initiate early and potentially lifesaving treatment when PCP is suspected and not to withhold treatment until bronchoscopy-proven disease is found. While PCP has some classic associations, this disease can also occur even when the patient has a CD4+ count >200 cells/µL, is on PCP prophylaxis, or has a normal chest x-ray. Such cases are usually diagnosed based on the patient’s history and clinical symptoms.

**THE DRUG OF CHOICE FOR PCP PNEUMONIA IS TMP-SMX, AND THE TREATMENT COURSE IS FOR 21 DAYS.**

- As displayed in Table 1, in mild disease, the regimen may be given orally, as with TMP-SMX DS 2 tabs PO q 8 x 21 days.
- With moderate-to-severe disease, with a room air arterial oxygen (paO₂) of <70 mm Hg, steroids, e.g. prednisone, should be initiated.
- Furthermore, in inpatient settings, intravenous TMP-SMX should be employed, with the dosing as 15 mg-20 mg/kg per day divided every 6 to 8 hours for 21 days, based on the trimethoprim component.¹

**THERE ARE MANY ALTERNATIVE AGENTS THAT CAN BE USED FOR TREATMENT OF PCP PNEUMONIA.**

- If there is a sulfa allergy, mild-to-moderate disease may be treated with 1) dapsone plus trimethoprim (TMP), 2) primaquine plus clindamycin, and 3) atovaquone suspension. Prior to starting primaquine, one should evaluate for glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- The drug of second choice for severe PCP pneumonia is intravenous pentamidine, and an alternative combination is clindamycin plus primaquine.¹

### PCP Prophylaxis¹,¹¹

**TABLE 1**

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>CD4+ COUNT</th>
<th>DRUG OF CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Primary Prophylaxis</td>
<td>&lt; 200 or oral candidasis</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Stopping Primary Prophylaxis</td>
<td>&gt; 200 for three months on ART</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Restarting Primary Prophylaxis</td>
<td>&lt; 200</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Post-PCP Treatment: Starting Secondary Prophylaxis</td>
<td>&lt; 200</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Stopping Secondary Prophylaxis</td>
<td>&gt; 200 for three months on ART</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Restarting Secondary Prophylaxis</td>
<td>&lt; 200 or PCP occurred at &gt;200</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
<tr>
<td>Secondary Prophylaxis for Life</td>
<td>PCP occurred while the patient had a CD4+ &gt;200 and regardless of how high ART increases the CD4+ count</td>
<td>TMP-SMX 1 DS PO daily or DS PO 3x/week</td>
</tr>
</tbody>
</table>

### PCP Treatment

**SCENARIO**

<table>
<thead>
<tr>
<th>DRUG OF CHOICE</th>
<th>ADJUNCT TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Disease</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX DS 2 tabs PO q 8 x 21 days</td>
<td>Prednisone 40 mg PO BID on days 1-5, Prednisone 40 mg PO daily on days 6-10, Prednisone 20 mg PO daily on days 11-21</td>
</tr>
<tr>
<td>Inpatient</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX IV at 15-20 mg/kg per day of the Trimethoprim component, divided q6-q8 for 21 days</td>
<td>Prednisone 40 mg PO BID on days 1-5, Prednisone 40 mg PO daily on days 6-10, Prednisone 20 mg PO daily on days 11-21</td>
</tr>
</tbody>
</table>
**Monitoring and Treatment Failure**

While on therapy, the patient should be evaluated to ensure adequate treatment response, to ensure medication adherence, and to monitor for adverse effects.

- After a CD4+ count is >200 cells/µL for three months or more, it is important that CD4+ counts be continually checked to detect early relapse.1
- Signs of worsening respiratory failure include lack of improvement after 4 to 8 days of anti-PCP treatment and worsening oxygenation.
- Lack of a treatment response may occur if patients are not immediately placed on corticosteroids within three days of starting anti-PCP therapy.
- The differential diagnosis should also include hospital-acquired infections as well as other causes of dyspnea.1

**Side-Effect Profile of PCP Medications**1

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim or Septra)</td>
<td>Rash, Stevens-Johnson Syndrome, bone marrow suppression, hepatotoxicity, increase in serum creatinine, nausea, vomiting, crystalluria, hyperkalemia</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Methemoglobinemia, rash, fever, hemolytic anemia</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Hemolysis especially with h/o G6PD deficiency, rash, fever, diarrhea</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Azotemia, pancreatitis, hypoglycemia/hyperglycemia, leukopenia, electrolyte abnormalities, cardiac dysrhythmias</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Anemia, rash, fever, diarrhea</td>
</tr>
<tr>
<td>Atovaquone (Mepron)</td>
<td>Headache, nausea, diarrhea, rash, transaminitis</td>
</tr>
</tbody>
</table>

**TABLE 2.**

**BECAUSE OF TOXICITIES RELATED TO DRUGS, as many as 33% of patients need to discontinue treatment.**

In these cases, alternative agents should be prescribed, such as atovaquone for mild disease and parenteral pentamidine or primaquine plus clindamycin for moderate-to-severe disease.1
Mortality

- The mortality rate of PCP in immunocompromised patients approaches 100% if untreated.\(^1\)
- Prognosis is related to the degree of hypoxemia when the patient presents.
- A room air arterial oxygen pressure (pO\(_2\)) of ≤70 mm Hg or more on room air indicates more serious PCP infection.\(^5\)
- Other risk factors for mortality are a low-serum albumin and the requirement for early ICU admission.\(^14\)

**CASE #1: PCP Diagnosis**

**A 65 year-old Asian female** presented to the emergency room with fever and dyspnea. She had tried over the counter Tylenol to no avail. Her daughter visited and brought her to the hospital.

**ON REVIEW OF SYSTEMS,** the patient had lost approximately 30 pounds unintentionally over the past few months.

- The patient was febrile and hypoxic with an arterial oxygen saturation of only 55% on room air. The white cell count was 2.3.
- Her chest radiograph showed bilateral interstitial infiltrates, and she was diagnosed with a community-acquired pneumonia.
- Despite being placed on antibiotics, her respiratory status worsened.

She received a bronchoscopy and Pneumocystis organisms were reported on Giemsa stains.

- The patient was started on oral prednisone and intravenous trimethoprim-sulfamethoxazole.
- Because PCP is an AIDS defining illness, the patient was tested for HIV after consent was obtained from the patient’s daughter.
- Ultimately, the patient’s HIV ELISA was positive, and a Western blot proved confirmatory.

**This case illustrates the importance of considering the diagnosis of HIV regardless of a patient’s age. If there is a suspicion for HIV, steroids and empiric treatment for PCP should be initiated and not withheld until bronchoscopic proof is provided.**
**MAC** is a combination of *Mycobacterium avium* and *Mycobacterium intracellulare*. They cause a pulmonary disease of indolent cavitation and disseminated multi-organ disease in patients with immunosuppression.\(^1\) *Mycobacterium avium* is the organism responsible for over 95% of disseminated MAC in AIDS patients. Prior to the availability of chemoprophylaxis or ART, disseminated MAC was the most common bacterial complication of AIDS. It occurred in 20-40% of AIDS patients.\(^1\)

- Although MAC is found in water, soil, dust, animals, and certain food products, there is no known evidence of person-to-person transmission.\(^1\)
- Neither close contacts nor household contacts appear to be at increased risk for MAC.
- No environmental exposure or behavior has been consistently linked to MAC.
- The mode of transmission may be through inhalation, ingestion, or inoculation from the respiratory or gastrointestinal tracts.\(^1\)

**Patients with HIV/AIDS are most susceptible to MAC when the CD4\(^+\) count is <50 cells/µL. Other risk factors include HIV RNA loads of >100,000 copies/mL, history of OI's, colonization in the sputum or gastrointestinal tract with MAC, and defective T cells.**\(^1\)

### DIAGNOSIS

#### Clinical Signs and Symptoms

**EARLY SYMPTOMS MAY BE MINIMAL AND MAY OCCUR SEVERAL WEEKS PRIOR TO DETECTABLE MYCOBACTEREMIA.**

- Patients with disseminated mycobacterial disease can have clinical signs and symptoms such as fever, night sweats, weight loss, and fatigue.\(^1\)
- On physical exam, hepatomegaly, splenomegaly, or lymphadenopathy may be found.\(^1\)

#### Laboratory Data and Studies

**THERE ARE SEVERAL HELPFUL LABORATORY STUDIES.**

- Five percent of patients with disseminated MAC have increased serum alkaline phosphatase.\(^1\)
- Anemia can occur and is often severe.\(^1\)
- MAC can be isolated from cultures from blood, lymph node, bone marrow, and other body fluids.
- Additional studies include an acid fast bacillus (AFB) smear, stool culture, and tissue biopsy.\(^1\)
Preventing and Treating PCP and MAC: A Continuing Challenge in HIV/AIDS Care

MAC Prophylaxis

INITIATING PRIMARY CHEMOPROPHYLAXIS against MAC should occur when the CD4+ count is <50 cells/µL. **Azithromycin** (1200 mg by mouth, as one dose/week or 600 mg by mouth as two doses per week) is the usual regimen. Another acceptable regimen is **clarithromycin** (500 mg by mouth/twice each day). **Rifabutin** (300 mg orally once each day) is an alternative prophylactic agent for MAC disease.1 Table 3 on page 12 summarizes the 2009 CDC/IDSA recommendations for MAC prophylaxis and treatment.

### Discontinuing/Restarting Primary Prophylaxis

PATIENTS WHO HAVE RESPONDED TO ART with an increased CD4+ count to >100 cells/µL for greater than or equal to three months may discontinue therapy.

- Appropriately stopping primary MAC prophylaxis reduces pill burden, drug toxicity and interaction potential, drug resistant pathogens, and costs.
- If the CD4+ count decreases to <50 cells/µL, primary prophylaxis should be restarted.1

### Discontinuing/Restarting Secondary Prophylaxis

SECONDARY PROPHYLAXIS begins after treatment for MAC.

- If patients have received 12 or more months of MAC treatment, are asymptomatic, and have CD4+ >100 cells/µL while on ART for six months, then secondary prophylaxis can be stopped.
- If the CD4+ count decreases to <100 cells/µL, secondary prophylaxis should be restarted.
- If patients are unable to achieve immune reconstitution on ART and have disseminated MAC disease, then they need to have chronic maintenance therapy or secondary prophylaxis for their entire lives.1

### MAC Treatment

Patients should be treated for disseminated disease as confirmed by bone marrow, blood culture, tissue biopsy, or node biopsy. Patients do not need treatment based on colonization of stool or sputum.

- The **preferred drug combination** for MAC treatment is **clarithromycin** 500 mg PO BID plus ethambutol 15 mg/kg PO daily for a period of one year.

- **Azithromycin** may also be used, susceptibility testing should include clarithromycin and azithromycin.

- A third drug, **rifabutin can be added** to MAC therapy. Standard dosing is 300 mg PO daily, however dosage adjustments are required when patients are receiving ARV therapy. Rifabutin can be added in the settings of a CD4+ count <50 cells/µL, high mycobacterial loads (>2 log10 colony forming units/mL of blood), or if available ART options are not producing therapeutic effects.

- **Alternative third and fourth drug agents** include:1
  - Streptomycin 1gm IV or IM daily; or
  - Ciprofloxacin 500-750mg PO BID; or
  - Levofloxacin 500mg PO daily; or
  - Moxifloxacin 400mg PO daily.1

MAC Prophylaxis During Pregnancy

IN PREGNANCY, MAC prophylaxis may still be provided.

- Azithromycin is the favored drug and **not clarithromycin** due to the risk of spontaneous abortions.

- For secondary prophylaxis (chronic maintenance therapy), the drug regimen of choice is azithromycin plus ethambutol (EMB).1
Drug-drug interactions

DRUG-DRUG INTERACTIONS CAN ALSO OCCUR WITH MAC PREVENTION AND TREATMENT. Protease inhibitors (PIs) increase the concentration of clarithromycin in the body, often requiring dosage reductions in clarithromycin. Efavirenz, an NNRTI (non-nucleoside reverse transcriptase inhibitor), decreases the level of clarithromycin in the bloodstream, use azithromycin as an alternative. When using rifabutin with PI and NNRTI based HAART, rifabutin dosage adjustments are likely, or may need to be avoided. Tables 4 and 5 (pages 13 and 14) describe the multitude of drug-drug interactions of antimycobacterial agents with protease inhibitors and NNRTIs.
### TABLE 4: Drug Interactions Between Protease Inhibitors (PIs) and Antimycobacterials

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>Protease Inhibitor (PI)</th>
<th>Effect on PI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-mycobacterials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>ATV + RTV</td>
<td>Clarithromycin (Clar) area under the curve (AUC) ↑ 94%</td>
<td>May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>DRV/r ↑ Clar AUC 57%; IDV ↑ Clar AUC 53%; IDV ↑ Clar AUC 77%; LPV/r ↑ Clar AUC 77%; RTV ↑ Clar 77%; SOV ↑ Clar 45%; Clar ↑ SOV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%</td>
<td>Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl &lt; 30mL/min.</td>
</tr>
<tr>
<td></td>
<td>FPV</td>
<td>↑ APV</td>
<td>No dose adjustment.</td>
</tr>
<tr>
<td></td>
<td>NFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>ATV + RTV</td>
<td>ATV ↑ rifabutin AUC 2.5-fold; FPV/r, DRV/r, IDV/r: no PK data, expect ↑ rifabutin; DRV/r (500mg bid) ↑ rifabutin 4X; IDV/r LPV/r ↑ rifabutin AUC 3-fold, ↑ 25-O-desacetyl metabolite 47.5-fold; LPV/r 47.5-fold; SOV/r Rifabutin ↓ unboosted SQV 40%; TPV/r ↑ rifabutin AUC 2.9-fold</td>
<td>Rifabutin 150 mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly and RTV-boosted PIs. May consider therapeutic drug monitoring and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>FPV</td>
<td>↑ rifabutin</td>
<td>Rifabutin 150 mg daily or 300 mg 3x/week.</td>
</tr>
<tr>
<td></td>
<td>IDV</td>
<td>↑ rifabutin ↓ IDV</td>
<td>Rifabutin 150 mg daily or 300 mg 3x/week + IDV 1,000 mg q8h or consider RTV boosting. Levels: rifabutin ↑ 2X, IDV ↓ 32%</td>
</tr>
<tr>
<td></td>
<td>NFV</td>
<td>↑ rifabutin 2X; ↓ NFV 750 mg Q8H 32%</td>
<td>Rifabutin 150 mg daily or 300 mg 3x/week.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>Approximately &gt;75% ↓ in PI concentrations</td>
<td>Do not co-administer rifampin and PIs.</td>
</tr>
</tbody>
</table>

### TABLE 4 KEY TO ANTIRETROVIRALS

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV</td>
<td>Atazanavir</td>
<td>IDV</td>
<td>Indinavir</td>
<td>RTV or r</td>
<td>Ritonovir</td>
</tr>
<tr>
<td>DRV</td>
<td>Darunavir</td>
<td>LPV</td>
<td>Lopinavir</td>
<td>SOV</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>FPV</td>
<td>Fosamprenavir</td>
<td>NFV</td>
<td>Nelfinavir</td>
<td>TPV</td>
<td>Tipranavir</td>
</tr>
<tr>
<td></td>
<td>Lexiva</td>
<td></td>
<td>Viracept</td>
<td></td>
<td>Aplitivus</td>
</tr>
</tbody>
</table>

Adapted from Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, November 2008, Table 15a. [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf) p. 110
### TABLE 5: Drug Interactions Between NNRTIs and Antimycobacterials

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>NNRTI</th>
<th>Effect on NNRTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-mycobacterials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLV</td>
<td>Clarithromycin</td>
<td>↑ 100% DLV ↑ 44%</td>
<td>Reduce clarithromycin dose by 50% in patients with CrCl 30-60 mL/min and by 75% in patients with CrCl &lt; 30 mL/min.</td>
</tr>
<tr>
<td>EFV</td>
<td>Clarithromycin</td>
<td>↓ 39%</td>
<td>Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.</td>
</tr>
<tr>
<td>ETR</td>
<td>ETR AUC ↑ 42%, clarithromycin AUC ↓ 39% and minimum plasma concentration (Cmin) ↓ 53%, OH-clarithromycin AUC ↑ 21%</td>
<td>Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.</td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>NVP ↑ 26%, clarithromycin ↓ 30%</td>
<td>Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLV</td>
<td>DLV ↓ 80%</td>
<td>Co-administration not recommended.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifabutin ↑ 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>Rifabutin ↓ 35%</td>
<td>Increase rifabutin dose: rifabutin 450-600 mg once daily or 600 mg 3x/week if EFV is not co-administered with a PI</td>
<td></td>
</tr>
</tbody>
</table>
| ETR                         | ATV ↑ rifabutin AUC 2.5-fold; FPV/r, DRV/r, IDV/r: ETR AUC ↓ 37% & Cmin ↓ 35% Rifabutin AUC ↓ 17% & Cmin ↓ 24%, 25-O-desacetylrifabutin AUC ↓ 17% & Cmin ↓ 22% | Dose: rifabutin 300 mg once daily if ETR is not co-administered with a RTV-boosted PI.  
If ETR is co-administered with DRV/r or SQV/r and rifabutin is needed, consider alternative ARV agent to ETR.  
If ETR is co-administered with LPV/r, use rifabutin 150 mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly and RTV-boosted PIs. Consider therapeutic drug monitoring and adjust dose accordingly. |
| NVP                         | ↑ NVP                                         | Rifabutin 150 mg daily or 300 mg 3x/week |
|                             | ↓ Rifabutin                                    |                                             |
| **Rifampin**                |       |                                                   |                                             |
| DLV                         | DLV ↓ 96%                                      | Contraindicated – do not co-administer. |
| EFV                         | ↓ EFV 25%                                      | Maintain efavirenz dose at 600 mg once daily and monitor for viral response. Some clinicians suggest EFV 800 mg dose in patients >60 kg. |
| ETR                         | Potential for significant ↓ ETR levels          | Do not co-administer. |
| NVP                         | ↓ NVP 20%–58%                                  | Do not co-administer rifampin and PIs. |

Adapted from Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, November 2008, Table 15b. [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf) p. 115
Monitoring and Treatment Failure

- With appropriate treatment, providers should expect to see resolution of symptoms and reduced quantity of mycobacteria in blood or tissue within 2-4 weeks although this can be delayed in AIDS patients.

- If patients initially respond to therapy but then encounter a relapse, then susceptibility testing for clarithromycin and azithromycin in cultures is the norm.

- If a new regimen is necessary, two susceptible drugs (which were not initially prescribed) should be given, and the choices are usually: ethambutol, rifabutin, amikacin, or a quinolone (moxifloxacin, ciprofloxacin, or levofloxacin).1

Adverse Effects

Adverse events associated with treatment of MAC include drug-related events related to the antimycobacterial agents, drug-drug interactions, and immune reconstitution inflammatory syndrome (IRIS).

- Clarithromycin and azithromycin cause nausea, vomiting, abdominal pain, dysgeusias, transaminitis, and hypersensitivity reactions.

- Rifabutin doses of ≥450 mg/day are contraindicated with clarithromycin and other drugs that interact by the cytochrome P450 system.1 See Tables 4 and 5 for dosage adjustments with antimycobacterial drugs and antiretrovirals.”

Drug-drug interactions can also occur.

- Rifabutin and clarithromycin will require dosage adjustment with PI and NNRTI-based HAART regimens, since they are metabolized by CYP450. See Tables 4 and 5 for additional details.1

IRIS causes signs and symptoms similar to active MAC such as fever and fatigue.

- When a patient’s immune functioning is recovering during ARV treatment, the underlying opportunistic infection may paradoxically worsen.

- It can occur when patients with MAC are started on ART and who quickly achieve an increase in their CD4+ count to at least 100 cells/µL.

- The symptoms may need to be treated with non-steroidal anti-inflammatory medication or steroids.1

Remarkable progress has been made in treating patients with HIV/AIDS. Opportunistic infections (OIs) were a leading cause of morbidity and mortality for HIV/AIDS patients until the widespread use of combination antiretroviral therapy (ART) in the mid-1990s.
CASE #2: MAC Follow-Up

A 57-year-old heroin user with history of AIDS with an unknown CD4+ count, presented with fever, fatigue, and dyspnea.

- He had a fever of 103°F Fahrenheit and was hypoxic, with 96% oxygen saturation on 4 liters of oxygen.
- His chest radiograph did not have any evidence of cavitation.
- He was intubated and brought to the intensive care unit.
- The patient received a bronchoscopy, and a culture was positive for acid fast bacillus. His PPD was negative.
- The patient was empirically started on azithromycin, ethambutol, and rifabutin.
- An infectious disease specialist started tenofovir/emtricitabine (truvada) and lopinavir/ritonavir (kaletra).
- The patient initially recovered and was able to be extubated, but he acutely decompensated one evening.
- A chest radiograph showed a new right lower lobe consolidation, and he was exceedingly hypoxic with a temperature of 102°F Fahrenheit.
- Upon suctioning the patient to clear his airway for an intubation, there were thick purulent secretions.
- The patient was felt to have a new nosocomial pneumonia.

This case illustrates that when a patient is recovering from MAC, is started on ART, and then worsens, the differential diagnosis includes IRIS and hospital-acquired pneumonia, among other diagnoses. In this case, the patient had a new consolidation, fever, and purulent secretions. He was treated with the appropriate antibiotics, and ultimately, the patient recovered.

Conclusion

OPPORTUNISTIC INFECTIONS can be overwhelming in immunocompromised patients, and particularly in patients with HIV/AIDS, where rapidly progressive infections may be life-threatening. PCP and MAC are two dangerous opportunistic infections that must be managed appropriately by practicing physicians. Early recognition and treatment are imperative, and it is now evident that many opportunities for prevention and early intervention have been missed.

PROPHYLAXIS IN BOTH MAC AND PCP INFECTIONS IS EFFICACIOUS. However, it is vital to understand guidelines for initiation, discontinuation, and re-initiation of prophylaxis. While prevention is obviously preferable to treatment, all providers should also be aware of the drugs of choice for treatment against PCP and MAC. Ultimately, both providers and patients need to work together to prevent further morbidity and mortality from opportunistic infections.
REFERENCES


5. Walzer, PD. Pneumocystis carinii in Mandell, Douglas, and Bennett, Principles and Practice of Infectious Diseases; Fifth edition, Churchill Livingstone, Philadelphia, 2000 Vol. 2; Chapter 260 pg 2781-2795.


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