



## **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**

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# ***Pneumocystis* Pneumonia** (Last updated March 28, 2019; last reviewed June 26, 2019)

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## **Epidemiology**

*Pneumocystis* pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a ubiquitous fungus. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the *Pneumocystis* that infects rats, and *P. jirovecii* refers to the distinct species that infects humans. However, the abbreviation PCP is still used to designate *Pneumocystis* pneumonia. Initial infection with *P. jirovecii* usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* by age 2 years to 4 years.<sup>1</sup>

Rodent studies and case clusters in immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by new acquisition of infection and by reactivation of latent infection.<sup>2-11</sup> Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of patients with AIDS;<sup>12</sup> the course of treated PCP was associated with a 20% to 40% mortality rate in individuals with profound immunosuppression. Approximately 90% of PCP cases occurred in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm<sup>3</sup>. Other factors associated with a higher risk of PCP in the pre-ART era included CD4 cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA levels.<sup>13,14</sup>

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is <1 case per 100 person-years.<sup>15-17</sup> Most cases of PCP now occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV,<sup>18</sup> and in those with advanced immunosuppression (i.e., CD4 counts <100 cells/mm<sup>3</sup>).<sup>19</sup>

## **Clinical Manifestations**

In patients with HIV, the most common manifestations of PCP are subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed in patients who do not have HIV is less common among patients with HIV.<sup>20,21</sup>

In mild cases, pulmonary examination while the patient is at rest usually is normal. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.<sup>21</sup> Oral thrush is a common co infection. Fever is apparent in most cases and may be the predominant symptom in some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.<sup>22</sup>

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen [PO<sub>2</sub>] ≥70 mm Hg or alveolar-arterial PO<sub>2</sub> gradient [A-a] DO<sub>2</sub> <35 mm Hg) to moderate ([A-a] DO<sub>2</sub> ≥35 to <45 mm Hg) to severe ([A-a] DO<sub>2</sub> ≥45 mm Hg). Oxygen desaturation with exercise is often abnormal but is non-specific.<sup>23</sup> Elevation of lactate dehydrogenase levels to >500 mg/dL is common but also non-specific.<sup>24</sup> The chest radiograph typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern;<sup>21</sup> however, in patients with early disease, a chest radiograph may be normal.<sup>25</sup> Atypical radiographic presentations, such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, intrathoracic adenopathy, and pneumothorax, also occur. Spontaneous pneumothorax in a patient with HIV infection should raise the suspicion of PCP.<sup>26,27</sup> Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis or an additional pathology. In fact, approximately 13% to 18% of patients with documented PCP have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma, or bacterial pneumonia.<sup>28,29</sup>

Thin-section computed tomography (CT) is a useful adjunctive study, since even in patients with mild-

to-moderate symptoms and a normal chest radiograph, a CT scan will be abnormal, demonstrating “ground-glass” attenuation that may be patchy, while a normal CT has a high negative predictive value.<sup>30,31</sup>

## Diagnosis

Because clinical presentation, blood tests, and chest radiographs are not pathognomonic for PCP (and because the organism cannot be cultivated routinely), histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples<sup>20,28,29,32</sup> is required for a definitive diagnosis of PCP. Spontaneously expectorated sputum has low sensitivity for the diagnosis of PCP and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both the cystic and trophic forms of *P. jirovecii* but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Some laboratories prefer direct immunofluorescent staining. The sensitivity and specificity of respiratory samples for PCP depend on the stain being used, the experience of the microbiologist or pathologist, the pathogen load, and specimen quality. Previous studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: <50% to >90% for induced sputum, 90% to 99% for bronchoscopy with BAL, 95% to 100% for transbronchial biopsy, and 95% to 100% for open lung biopsy.

Polymerase chain reaction (PCR) is an alternative method for diagnosing PCP. PCR is highly sensitive and specific for detecting *Pneumocystis*; however, PCR cannot reliably distinguish colonization from active disease, although higher organism loads as determined by quantitative PCR (Q-PCR) assays are likely to represent clinically significant disease.<sup>33-35</sup> 1,3  $\beta$ -D-glucan ( $\beta$ -glucan), which is a component of the cell wall of *Pneumocystis* cysts, is often elevated in patients with PCP. The sensitivity of the  $\beta$ -glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in patients with a low level of  $\beta$ -glucan (e.g., <80 pg/mL using the Fungitell assay). However, the specificity of  $\beta$ -glucan testing for establishing a PCP diagnosis is low,<sup>36-38</sup> since many other fungal diseases, cellulose membranes used for hemodialysis, and some drugs can elevate  $\beta$ -glucan levels.

Because the clinical manifestations of several disease processes are similar, it is important to seek a definitive diagnosis of PCP disease rather than rely on a presumptive diagnosis, especially in patients with moderate-to-severe disease. However, PCP treatment can be initiated before a definitive diagnosis is established because *P. jirovecii* persist in clinical specimens for days or weeks after effective therapy is initiated.<sup>32</sup>

## Preventing Exposure

*Pneumocystis* can be quantified in the air near patients with PCP,<sup>39</sup> and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients.<sup>5-11,40</sup> Although these findings strongly suggest that isolating patients with known PCP from patients at high risk for PCP may be beneficial, there are insufficient data to support isolation as standard practice to prevent PCP (**III**).

## Preventing Disease

### *Indication for Primary Prophylaxis*

Adults and adolescents with HIV, including pregnant women and those on ART, with CD4 counts <200 cells/mm<sup>3</sup> should receive chemoprophylaxis against PCP (**AI**).<sup>12,13,41</sup> Persons who have a CD4 cell percentage <14% should also be considered for PCP prophylaxis (**BII**).<sup>12,13,41</sup> If ART initiation must be delayed and frequent monitoring of CD4 counts (e.g., every 3 months) is impossible, some experts recommend starting PCP chemoprophylaxis at CD4 counts  $\geq$ 200 cells/mm<sup>3</sup> to  $\leq$ 250 cells/mm<sup>3</sup> (**BII**).<sup>13</sup> Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (**AII**).<sup>42</sup>

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP (**AI**).<sup>41,43-45</sup> One double-strength TMP-SMX tablet daily is the preferred regimen (**AI**), but one single-strength tablet

daily<sup>45</sup> is also effective and may be better tolerated than the double-strength tablet (**AI**). One double-strength TMP-SMX tablet three times weekly also is effective (**BI**).<sup>46</sup> TMP-SMX at a dose of one double-strength tablet daily confers cross protection against toxoplasmosis<sup>47</sup> and many respiratory bacterial infections.<sup>43,48</sup> Lower doses of TMP-SMX may also confer such protection, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non life threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution of the drug should be considered after the reaction has resolved (**AII**). Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis (**AIII**). Patients who have experienced adverse events, including fever and rash, may better tolerate re-introduction of TMP-SMX if the dose is gradually increased according to published regimens (**BI**)<sup>49,50</sup> or if the drug is given at a reduced dose or frequency (**CIII**). As many as 70% of patients can tolerate such re-institution of TMP-SMX therapy.<sup>48</sup>

For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone (**BI**),<sup>43</sup> dapsone plus pyrimethamine plus leucovorin (**BI**),<sup>51-53</sup> aerosolized pentamidine administered with the Respigard II nebulizer (manufactured by Marquest; Englewood, Colorado) (**BI**),<sup>44</sup> and atovaquone (**BI**).<sup>54,55</sup> Atovaquone is as effective as aerosolized pentamidine<sup>54</sup> or dapsone<sup>55</sup> but substantially more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin (**BI**),<sup>51-53</sup> or atovaquone, with or without pyrimethamine, plus leucovorin (**CIII**).

The following regimens cannot be recommended as alternatives to TMP-SMX because data regarding their efficacy for PCP prophylaxis are insufficient:

- Aerosolized pentamidine administered by nebulization devices other than the Respigard II nebulizer
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine

Clinicians can consider using these agents, however, in situations in which TMP-SMX or the recommended alternative prophylactic regimens cannot be administered or are not tolerated (**CIII**).

### ***Discontinuing Primary Prophylaxis***

Primary *Pneumocystis* prophylaxis should be discontinued in adult and adolescent patients who have responded to ART with an increase in CD4 counts from <200 cells/mm<sup>3</sup> to >200 cells/mm<sup>3</sup> for >3 months (**AI**). In observational and randomized studies whose findings support this recommendation, most patients had CD4 counts >200 cells/mm<sup>3</sup> for >3 months before discontinuing PCP prophylaxis.<sup>56-65</sup> At discontinuation of prophylaxis, the median CD4 count was >300 cells/mm<sup>3</sup>, most participants had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 months to 19 months.

Discontinuation of primary prophylaxis in patients with CD4 count increase to >200 cells/mm<sup>3</sup> as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited;<sup>58,64</sup> stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens. Prophylaxis should be reintroduced if the patient's CD4 count decreases to <200 cells/mm<sup>3</sup> (**AIII**).

A combined analysis of European cohorts,<sup>16,66</sup> a small randomized trial,<sup>67</sup> and a case series<sup>68</sup> found a low incidence of PCP in patients with CD4 counts between 100 cells/mm<sup>3</sup> and 200 cells/mm<sup>3</sup>, who were receiving ART and had HIV plasma viral loads <50 to 400 copies/mL, and who had stopped or never received PCP prophylaxis, suggesting that primary and secondary PCP prophylaxis can be safely discontinued in patients with CD4 counts between 100 cells/mm<sup>3</sup> to 200 cells/mm<sup>3</sup> and HIV plasma RNA levels below limits of

detection of commercial assays. Data on which to base specific recommendations are inadequate, but one approach would be to stop primary prophylaxis in patients with CD4 counts of 100 cells/mm<sup>3</sup> to 200 cells/mm<sup>3</sup> if HIV plasma RNA levels remain below limits of detection for ≥3 months to 6 months (**BII**). Similar observations have been made with regard to stopping primary prophylaxis for *Toxoplasma* encephalitis.<sup>69</sup>

## Treating Disease

TMP-SMX is the treatment of choice for PCP (**AI**).<sup>70,71</sup> Standard doses are summarized in the table; lower doses may also be effective, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens for PCP treatment. Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because efficacy in preventing this toxicity is questionable and some evidence exists for a higher failure rate in preventing PCP (**AII**).<sup>72</sup> Outpatient therapy with oral TMP-SMX is highly effective in patients with mild-to-moderate disease (**AI**).<sup>71</sup>

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.<sup>73-76</sup> Patients who have PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (**BIII**).

Patients with documented or suspected PCP and moderate-to-severe disease, defined by room air PO<sub>2</sub> <70 mm Hg or PAO<sub>2</sub>-PaO<sub>2</sub> ≥35 mm Hg, should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting specific PCP therapy (**AI**).<sup>77-82</sup> The benefits of starting steroids later are unclear, but most clinicians would administer them even after 72 hours for patients with moderate-to-severe disease (**BIII**). Intravenous (IV) methylprednisolone at 75% of the corresponding oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone and TMP (**BI**),<sup>71,83</sup> which may have efficacy similar to TMP-SMX with fewer side effects, but is less convenient given the number of pills; clindamycin plus primaquine (**BI**)<sup>84-86</sup> (clindamycin can be administered IV for more severe cases, but primaquine is only available in an oral formulation); and atovaquone suspension (**BI**),<sup>70,87</sup> which is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects. Whenever possible, patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before primaquine or dapsone is administered.

Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or IV pentamidine (**AI**).<sup>86,88,89</sup> Some clinicians prefer clindamycin plus primaquine because this combination is more effective and less toxic than pentamidine.<sup>86,90-92</sup>

Aerosolized pentamidine **should not be used** to treat PCP because it has limited efficacy and is associated with more frequent relapse (**AI**).<sup>88,93,94</sup>

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days (**AII**).<sup>20</sup> The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of pulmonary illness, degree of immunodeficiency, timing of initiation of therapy, and comorbidities.

Although overall the prognosis for patients with respiratory failure due to PCP is poor, over the past decades, survival for patients who require ICU care has improved as management of respiratory failure and HIV comorbidities has improved.<sup>95-98</sup> Special attention is necessary regarding the use of ART in such critically ill patients.<sup>99</sup>

### *Special Consideration with Regards to Starting ART (Including IRIS)*

If not already started, ART should be initiated in patients, when possible, within 2 weeks of diagnosis of PCP (**AI**). In a randomized controlled trial of 282 patients with opportunistic infections (OIs) other than TB,

63% of whom had definite or presumptive PCP, the incidence of AIDS progression or death (a secondary study endpoint) was significantly lower among participants who initiated ART early than among those who delayed ART (median 12 days and 45 days after OI therapy initiation, respectively).<sup>100</sup> Of note, none of the participants with PCP enrolled in the study had respiratory failure requiring intubation;<sup>100</sup> initiating ART in such patients is problematic given the lack of parenteral preparations and unpredictable absorption of oral medications, as well as potential drug interactions with agents commonly used in the ICU.<sup>101</sup>

Paradoxical immune reconstitution inflammatory syndrome (IRIS) following an episode of PCP is rare but has been reported.<sup>102,103</sup> Most cases occurred within weeks of the episode of PCP; symptoms included fever and recurrence or exacerbation of pulmonary symptoms including cough and shortness of breath, as well as worsening of a previously improving chest radiograph. Although IRIS in the setting of PCP has only rarely been life-threatening,<sup>104</sup> patients should be closely followed for recurrence of symptoms after initiation of ART. Management of PCP-associated IRIS is not well defined; some experts recommend use of corticosteroids in patients with respiratory deterioration if other causes are ruled out.

### ***Monitoring of Response to *Pneumocystis Pneumonia* Therapy and Adverse Events***

Careful monitoring during PCP therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially if therapy has been with an agent other than TMP-SMX or was shortened because of toxicity.

In patients with HIV, rates of adverse reaction to TMP-SMX are high (20% to 85% of patients).<sup>70,71,83,85,89,105-109</sup> Common adverse effects are rash (30% to 55% of patients) (including Stevens-Johnson syndrome), fever (30% to 40% of patients), leukopenia (30% to 40% of patients), thrombocytopenia (15% of patients), azotemia (1% to 5% of patients), hepatitis (20% of patients), and hyperkalemia. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued (**AIII**). Rashes often can be “treated through” with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone;<sup>71,83</sup> azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine;<sup>87-89,108</sup> anemia, rash, fever, and diarrhea with primaquine and clindamycin;<sup>71,84,85</sup> and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.<sup>70,107</sup>

### ***Managing Treatment Failure***

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after  $\geq 4$  days to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of patients with mild-to-moderate PCP disease. However, there are not any convincing clinical trial data on which to base recommendations for the management of PCP treatment failure due lack of drug efficacy.

Clinicians should wait  $\geq 4$  days to 8 days before switching therapy for lack of clinical improvement (**BIII**). In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 days to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause of clinical failure;<sup>28,29</sup> bronchoscopy with BAL should be strongly considered to evaluate for this possibility, even if the procedure was conducted before initiating therapy.

Treatment failure attributed to treatment-limiting toxicities occurs in up to one-third of patients.<sup>71</sup> Switching to another regimen is the appropriate management for treatment-related toxicity (**BII**). When TMP-SMX is not effective or cannot be used for moderate-to-severe disease because of toxicity, the common practice is to use parenteral pentamidine or oral primaquine combined with IV clindamycin (**BII**).<sup>85,86,89</sup> For mild disease, atovaquone is a reasonable alternative (**BII**). Although a meta-analysis, systematic review, and cohort study

concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy,<sup>86,91,92</sup> no prospective clinical trials have evaluated the optimal approach for patients who experience a therapy failure with TMP-SMX.

## Preventing Recurrence

### *When to Start Secondary Prophylaxis*

Secondary PCP prophylaxis with TMP-SMX should be initiated immediately upon successful completion of PCP therapy and maintained until immune reconstitution occurs as a result of ART (see below) **(AI)**.<sup>110</sup> For patients who are intolerant of TMP-SMX, the alternatives are dapsone, dapsone plus pyrimethamine plus leucovorin, atovaquone, and aerosolized pentamidine.

### *When to Stop Secondary Prophylaxis*

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from  $<200$  cells/mm<sup>3</sup> to  $>200$  cells/mm<sup>3</sup> for  $>3$  months as a result of ART **(AII)**. Reports from observational studies<sup>57,63,111,112</sup> and from two randomized trials<sup>64,113</sup> and a combined analysis of European cohorts being followed prospectively<sup>66,114</sup> support this recommendation. In these studies, patients responded to ART with an increase in CD4 counts to  $\geq 200$  cells/mm<sup>3</sup> for  $>3$  months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was  $>300$  cells/mm<sup>3</sup> and most patients had a CD4 cell percentage  $>14\%$ . Most patients had sustained suppression of plasma HIV RNA levels below the limits of detection for the assay employed; the longest follow-up was 40 months. Based on results from the COHERE study, secondary prophylaxis in patients with CD4 counts of 100 cells/mm<sup>3</sup> to 200 cells/mm<sup>3</sup> can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for  $\geq 3$  months to 6 months **(BII)**.<sup>66</sup>

### *When to Restart Primary or Secondary Prophylaxis*

Primary or secondary PCP prophylaxis should be reintroduced if the patient's CD4 count decreases to  $<100$  cells/mm<sup>3</sup> **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for patients with CD4 counts of 100 cells/mm<sup>3</sup> to 200 cells/mm<sup>3</sup> with HIV plasma viral load above detection limits of the assay used **(AIII)**. Based on results from the COHERE study, primary or secondary PCP prophylaxis may not need to be restarted in patients with CD4 counts of 100 cells/mm<sup>3</sup> to 200 cells/mm<sup>3</sup> who have had HIV plasma RNA levels below limits of detection for  $\geq 3$  to 6 months **(BII)**.<sup>16,66</sup>

If an episode of PCP occurs at a CD4 count  $>200$  cells/mm<sup>3</sup> while a patient is on ART, it would be prudent for the patient to continue PCP prophylaxis for life, regardless of how high their CD4 cell count rises as a consequence of ART **(BIII)**. For patients in whom PCP occurs at a CD4 count  $>200$  cells/mm<sup>3</sup> while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for  $\geq 3$  to 6 months, although there are no data to support recommendations in this setting **(CIII)**.

## Special Considerations During Pregnancy

PCP diagnostic considerations for pregnant women are the same as for women who are not pregnant.

Indications for PCP therapy are the same for pregnant women as for non-pregnant women. Some data suggest an increased risk of PCP-associated mortality in pregnancy, although there are no large, well-controlled studies evaluating the impact of pregnancy on PCP outcomes.<sup>115</sup>

The preferred initial therapy for PCP during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX **(AI)**.<sup>116</sup> In case-control studies, trimethoprim has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after first-trimester exposure.<sup>117-119</sup> One small study reported an increased risk of birth defects in infants born to women receiving antiretrovirals and folate antagonists, primarily

trimethoprim; by contrast, no such increase was observed among infants exposed to either an antiretroviral or a folate antagonist alone.<sup>120</sup> Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP still should be treated with TMP-SMX because of its considerable benefit **(AIII)**.

Although folic acid supplementation at 0.4 mg/day is routinely recommended for all pregnant women,<sup>121</sup> there are no trials evaluating whether supplementation at higher levels (e.g., 4 mg/day as recommended for pregnant women who previously had an infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use in women with HIV. Epidemiologic data suggest that folic acid supplementation may reduce the risk of congenital anomalies.<sup>118,119</sup> In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received folic acid 6 mg/day (odds ratio [OR] 1.24; 95% CI, 0.94–1.62).<sup>117</sup> Although the risk of multiple congenital abnormalities associated with TMP-SMX use persisted despite supplemental folic acid, the OR decreased from 6.4 for TMP-SMX without folic acid to 1.9 for TMP-SMX plus folic acid. On the basis of these findings, clinicians can consider giving supplemental folic acid (>0.4 mg/day routinely recommended) to women in their first trimester who are on TMP-SMX **(BIII)**. On the other hand, a randomized, controlled trial demonstrated that adding folic acid to TMP-SMX treatment for PCP was associated with an increased risk of therapeutic failure and death.<sup>72</sup> In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent folic acid use.<sup>122</sup> Therefore, if supplemental folic acid (>0.4 mg/day routinely recommended) is given, its use should be limited to the first trimester during the teratogenic window **(AIII)**. Whether a woman receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy **(BIII)**.

A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality, specifically kernicterus, than infants who received oxytetracycline.<sup>123</sup> Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, although no published studies to date link late third-trimester exposure to either drug with neonatal death or kernicterus.

Adjunctive corticosteroid therapy should be used to improve the mother's treatment outcome as indicated in non-pregnant adults **(AIII)**.<sup>124-127</sup> Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air PO<sub>2</sub> <70 mm Hg or PAO<sub>2</sub> - PaO<sub>2</sub> >35 mm Hg, should receive adjunctive corticosteroids as early as possible. A systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4 increased odds of delivering a baby with a cleft palate.<sup>128</sup> On the other hand, other large population-based studies have not found an association between maternal use of corticosteroids and congenital anomalies.<sup>129,130</sup> Corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, glucose intolerance or gestational diabetes, and infection.<sup>131</sup> Maternal glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk of glucose intolerance is increased **(AIII)**. Moreover, women receiving 20 mg/day of prednisone (or its dosing equivalent for other exogenous corticosteroids) for >3 weeks may have hypothalamic-pituitary-adrenal (HPA) axis suppression and use of stress-dose corticosteroids during delivery should be considered **(BIII)**. HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Alternative therapeutic regimens for mild-to-moderate PCP disease include dapsone and TMP, primaquine plus clindamycin, atovaquone suspension, and IV pentamidine.

Dapsone appears to cross the placenta.<sup>132,133</sup> For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.<sup>133,134</sup> Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of acute hemolytic anemia.<sup>135</sup>

Clindamycin, which appears to cross the placenta, is a Food and Drug Administration (FDA) Pregnancy Category B medication and is considered safe for use throughout pregnancy.



Primaquine generally is not used in pregnancy because of the risk of maternal hemolysis. As with dapsone, there is potential risk of hemolytic anemia in a primaquine-exposed fetus with G6PD deficiency. The degree of intravascular hemolysis appears to be associated with both dose of primaquine and severity of G6PD deficiency.<sup>136</sup>

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated toxicity.<sup>136</sup>

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.<sup>137</sup>

All-cause pneumonia during pregnancy increases rates of preterm labor and delivery. Women at >20 weeks gestation who have with pneumonia should be closely monitored for evidence of contractions **(BIII)**.

Chemoprophylaxis for PCP should be administered to pregnant women as for non-pregnant adults and adolescents **(AIII)**. TMP-SMX is the recommended prophylactic agent. Given theoretical concerns about possible teratogenicity associated with first-trimester drug exposures, health care providers may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during the first-trimester **(CIII)** rather than withholding chemoprophylaxis.

### ***Preconception Care***

Clinicians who are providing pre-conception care for women with HIV receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued (i.e., CD4 cell count >200 cells/mm<sup>3</sup> for 3 months) **(BIII)**.

### **Recommendations for Preventing and Treating *Pneumocystis* Pneumonia**

#### **Preventing First Episode of PCP (Primary Prophylaxis)**

##### Indications for Initiating Primary Prophylaxis:

- CD4 count <200 cells/mm<sup>3</sup> **(AI)** *or*
- CD4 percentage <14% of total lymphocyte count **(BII)** *or*
- CD4 count >200 cells/mm<sup>3</sup>, *but* <250 cells/mm<sup>3</sup> if ART initiation must be delayed and if CD4 count monitoring (e.g., every 3 months) is not possible **(BII)**.

**Note:** Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP **(AII)**.

##### Preferred Therapy:

- TMP-SMX, 1 DS tablet PO daily<sup>a</sup> **(AI)** *or*
- TMP-SMX, 1 SS tablet PO daily<sup>a</sup> **(AI)**

##### Alternative Therapy:

- TMP-SMX 1 DS tablet PO three times weekly **(BI)** *or*
- Dapsone<sup>b,c</sup> 100 mg PO daily *or* dapsone 50 mg PO twice a day **(BI)** *or*
- Dapsone<sup>b</sup> 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly **(BI)** *or*
- (Dapsone<sup>b</sup> 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly **(BI)** *or*
- Aerosolized pentamidine<sup>c</sup> 300 mg via Respigard II™ nebulizer every month **(BI)** *or*
- Atovaquone 1500 mg PO daily with food **(BI)** *or*
- (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily with food **(CIII)**.

##### Indication for Discontinuing Primary Prophylaxis:

- CD4 count increased from <200 cells/mm<sup>3</sup> to ≥200 cells/mm<sup>3</sup> for ≥3 months in response to ART **(AI)**
- Can consider when CD4 count is 100–200 cells/mm<sup>3</sup> and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months **(BII)**

##### Indication for Restarting Primary Prophylaxis:

- CD4 count <100 cells/mm<sup>3</sup> regardless of HIV RNA **(AIII)**
- CD4 count 100–200 cells/mm<sup>3</sup> and HIV RNA above detection limit of the assay used **(AIII)**

## Treating PCP

**Note:** Patients who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (**BIII**).

For Moderate to Severe PCP: Total Duration of Treatment is 21 Days (**AII**)

### *Preferred Therapy:*

- TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given every 6 or 8 hours (**AI**), may switch to PO formulations after clinical improvement (**AI**).

### *Alternative Therapy:*

- Pentamidine 4 mg/kg IV once daily infused over  $\geq 60$  minutes (**AI**); may reduce the dose to pentamidine 3 mg/kg IV once daily in the event of toxicities (**BI**), *or*
- Primaquine<sup>b</sup> 30 mg (base) PO once daily plus (Clindamycin [IV 600 mg every 6 hours or 900 mg every 8 hours] or [PO 450 mg every 6 hours or 600 mg every 8 hours]) (**AI**).

**Note:** Adjunctive corticosteroids are indicated in moderate to severe cases of PCP (see indications and dosage recommendations below).

For Mild to Moderate PCP: Total Duration of Treatment is 21 Days (**AII**)

### *Preferred Therapy:*

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) PO (3 divided doses) (**AI**), *or*
- TMP-SMX 2 DS tablets PO three times daily (**AI**)

### *Alternative Therapy:*

- Dapsone<sup>b</sup> 100 mg PO daily plus TMP 15 mg/kg/day PO (3 divided doses) (**BI**) *or*
- Primaquine<sup>b</sup> 30 mg (base) PO daily plus Clindamycin PO (450 mg every 6 hours or 600 mg every 8 hours) (**BI**) *or*
- Atovaquone 750 mg PO twice daily with food (**BI**)

## Adjunctive Corticosteroids

For Moderate to Severe PCP Based on the Following Criteria (**AI**):

- PaO<sub>2</sub> <70 mmHg at room air *or*
- Alveolar-arterial DO<sub>2</sub> gradient  $\geq 35$  mmHg

### Dosing Schedule:

- Prednisone doses (beginning as soon as possible and within 72 hours of PCP therapy) (**AI**)
  - Days 1–5: 40 mg PO twice daily
  - Days 6–10: 40 mg PO daily
  - Days 11–21: 20 mg PO daily
- IV methylprednisolone can be given as 75% of prednisone dose.

## Preventing Subsequent Episode of PCP (Secondary Prophylaxis)

Indications for Initiating Secondary Prophylaxis:

- Prior PCP

### Preferred Therapy:

- TMP-SMX, 1 DS tablet PO daily<sup>a</sup> (**AI**) *or*
- TMP-SMX, 1 SS tablet PO daily<sup>a</sup> (**AI**)

### Alternative Therapy:

- TMP-SMX 1 DS tablet PO three times weekly (**BI**) *or*
- Dapsone<sup>b,c</sup> 100 mg PO daily (**BI**) *or*
- Dapsone 50 mg PO twice daily (**BI**) *or*
- Dapsone<sup>b</sup> 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- (Dapsone<sup>b</sup> 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- Aerosolized pentamidine<sup>c</sup> 300 mg via Respigard II™ nebulizer every month (**BI**) *or*
- Atovaquone 1500 mg PO daily with food (**BI**) *or*

- (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily with food (**CIII**)

#### Indications for Discontinuing Secondary Prophylaxis:

- CD4 count increased from <200 cells/mm<sup>3</sup> to >200 cells/mm<sup>3</sup> for >3 months as a result of ART (**BII**) *or*
- Can consider if CD4 count is 100–200 cells/mm<sup>3</sup> and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months (**BII**)
- For patients in whom PCP occurs at a CD4 count >200 cells/mm<sup>3</sup> while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 months to 6 months, although there are no data to support recommendations in this setting (**CIII**).

**Note:** If an episode of PCP occurs at a CD4 count >200 cells/mm<sup>3</sup> while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART (**BIII**).

#### Indications for Restarting Secondary Prophylaxis:

- CD4 count <100 cells/mm<sup>3</sup> regardless of HIV RNA (**AIII**)
- CD4 count 100–200 cells/mm<sup>3</sup> and HIV RNA above detection limit of the assay used (**AIII**).

#### Other Considerations/Comments:

- For patients with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, re-institution of therapy should be considered after the reaction has resolved (**AII**). The dose of TMP-SMX can be increased gradually (desensitization) (**BI**) or the drug can be given at a reduced dose or frequency (**CIII**).
- Therapy should be permanently discontinued, with no rechallenge, in patients with suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (**AIII**).

<sup>a</sup> TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; a lower dose also likely confers protection.

<sup>b</sup> Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. An alternative agent should be used if the patient is found to have G6PD deficiency.

<sup>c</sup> Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in patients who are seropositive for *Toxoplasma gondii*.

**Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = *Pneumocystis pneumonia*; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

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