

# *Pneumocystis* Pneumonia

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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 the preferred acronym to designate the clinical syndrome of *Pneumocystis pneumonia*,<sup>1</sup> although PJP is commonly used. 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>2</sup>

Rodent studies and case clusters in immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by both new acquisition of infection and by reactivation of latent infection.<sup>3-12</sup> Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of people with advanced HIV,<sup>13</sup> with a 20% to 40% mortality rate in individuals despite anti-*Pneumocystis* therapy. Approximately 90% of PCP cases occur in people with HIV with CD4 T lymphocyte (CD4) cell counts <200 cells/mm<sup>3</sup>.

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; incidence among people with HIV in Western Europe and the United States is <1 case per 100 person-years.<sup>14-16</sup> Most cases of PCP now occur in people with HIV who are unaware of their HIV status or are not receiving ongoing care for HIV,<sup>17</sup> and in those with advanced immunosuppression (i.e., CD4 counts <100 cells/mm<sup>3</sup>).<sup>18</sup>

## Clinical Manifestations

In people 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 people who do not have HIV is less common among people with HIV. A more fulminant course can occur particularly after initiation of therapy.<sup>19-21</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>20</sup> Fever is present in most cases and may be the predominant symptom in some people. Pneumonia limited to the apices and extrapulmonary disease, which can occur in any organ, are rare and have 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 partial pressure [PaO<sub>2</sub>] ≥70 mmHg or alveolar-arterial gradient [A-a gradient] <35 mmHg) to moderate (A-a gradient ≥35 to <45 mmHg) to severe (A-a gradient ≥45 mmHg). Oxygen desaturation with exercise is often abnormal but is nonspecific.<sup>23</sup> Elevation of lactate dehydrogenase levels to >500 mg/dL is common but also nonspecific.<sup>24</sup> The chest radiograph typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern<sup>20</sup>; however, in people with HIV 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 person with HIV should raise the suspicion of PCP.<sup>26,27</sup> Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancies, and their presence may indicate an alternative diagnosis or an additional pathology. People with HIV who have documented PCP may have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma, toxoplasmosis, or fungal or bacterial pneumonia.<sup>28,29</sup>

Thin-section computed tomography (CT) without contrast 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. A normal CT has a high negative predictive value, and alternate diagnoses should be excluded.<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>19,28,29,32</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 main life forms of *P. jirovecii*—cysts and trophic forms—but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain only the cyst wall. Some laboratories prefer direct immunofluorescent staining, which has higher sensitivity than the colorimetric stains.<sup>33</sup> 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. 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.<sup>34-40</sup>

Polymerase chain reaction (PCR) is an increasingly utilized method for diagnosing PCP and has replaced staining methods in many laboratories. PCR is highly sensitive and specific for detecting *Pneumocystis*. While PCR cannot reliably distinguish colonization from active disease, quantitative PCR (qPCR) is favored over qualitative assays, as a higher organism load by qPCR is likely to represent clinically significant disease.<sup>41-43</sup> However, the broad range of organism loads in patients with PCP and the lack of commercially available U.S. Food and Drug Administration (FDA)–approved qPCR kits for diagnosis make establishment of cutoffs for colonization versus disease difficult to standardize.

1,3  $\beta$ -D-glucan ( $\beta$ -glucan), which is a component of the cell wall of *Pneumocystis* cysts, is often elevated in people with HIV who also have PCP. The sensitivity of the  $\beta$ -glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in people with HIV 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>44-48</sup> since many other fungal diseases, cellulose membranes used for hemodialysis, and some drugs can elevate  $\beta$ -glucan levels.<sup>47,48</sup>

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 should be initiated before a definitive

diagnosis is established if clinical suspicion is high. *P. jirovecii* persist in clinical specimens for days or weeks after effective therapy is initiated, allowing definitive diagnosis to be established even after initiating therapy.<sup>32</sup>

## Preventing Exposure

There are insufficient data to support isolation as standard practice to prevent PCP (**CIII**). *Pneumocystis* can be quantified in the air near people with PCP,<sup>49</sup> and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients as well as other immunosuppressed populations.<sup>6-12,50</sup> Although these findings strongly suggest that isolating people with known PCP from people at high risk for PCP may be beneficial, no study to date has documented the benefit of such an approach.

## Preventing Disease

| Recommendations for Preventing First Episode of <i>Pneumocystis</i> Pneumonia (Primary Prophylaxis)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <p>Indications for Initiating Primary Prophylaxis for Patients Not on ART and Patients Starting ART</p> <ul style="list-style-type: none"> <li>• CD4 count &lt;200 cells/mm<sup>3</sup> (AI)</li> <li>• For people with HIV currently on ART, see <i>Indication for Restarting Primary Prophylaxis</i> below.</li> <li>• <b>Note:</b> Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).</li> </ul> <p>Preferred Therapy</p> <ul style="list-style-type: none"> <li>• TMP-SMX 1 DS tablet PO daily (AI), <i>or</i></li> <li>• TMP-SMX 1 SS tablet PO daily (AI)</li> <li>• <b>Note:</b> TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections.</li> </ul> <p>Alternative Therapy</p> <ul style="list-style-type: none"> <li>• The following regimens can be used for people who are seropositive or seronegative for <i>Toxoplasma gondii</i>: <ul style="list-style-type: none"> <li>◦ TMP-SMX 1 DS tablet PO three times weekly (BI), <i>or</i></li> <li>◦ Dapsone<sup>a</sup> 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), <i>or</i></li> <li>◦ Dapsone<sup>a</sup> 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), <i>or</i></li> <li>◦ Atovaquone 1,500 mg PO daily with food (BI)</li> </ul> </li> <li>• The following regimens should only be used in people who are seronegative for <i>Toxoplasma gondii</i>: <ul style="list-style-type: none"> <li>◦ Dapsone<sup>a</sup> 100 mg PO daily or dapsone 50 mg PO twice a day (BI), <i>or</i></li> <li>◦ Aerosolized pentamidine 300 mg via Respigard II nebulizer every month (BI), <i>or</i></li> <li>◦ Intravenous pentamidine 300 mg every 28 days (CIII)</li> </ul> </li> </ul> <p>Indication for Discontinuing Primary Prophylaxis</p> <ul style="list-style-type: none"> <li>• CD4 count increased from &lt;200 cells/mm<sup>3</sup> to ≥200 cells/mm<sup>3</sup> for ≥3 months in response to ART (AI)</li> </ul> |

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| <ul style="list-style-type: none"> <li>• 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)</li> </ul> <p>Indication for Restarting Primary Prophylaxis</p> <ul style="list-style-type: none"> <li>• CD4 count &lt;100 cells/mm<sup>3</sup> regardless of HIV RNA (AIII)</li> <li>• CD4 count 100–200 cells/mm<sup>3</sup> and HIV RNA consistently above detection limit of the assay used (AIII)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Prepregnancy and Pregnancy Considerations</b></p> <ul style="list-style-type: none"> <li>• Clinicians who are providing prepregnancy care for women with HIV receiving PCP prophylaxis can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued with their patients (BIII).</li> <li>• During pregnancy, chemoprophylaxis for PCP should be administered as it would be for other persons with HIV (AIII). TMP-SMX is the recommended prophylactic agent (AIII). For women who are receiving TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day if they are capable of becoming pregnant or as soon as possible in their first trimester (BIII).</li> <li>• Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, clinicians may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during the first trimester (CIII) rather than withholding chemoprophylaxis.</li> </ul> |
| <p><b>Other Considerations/Comments</b></p> <ul style="list-style-type: none"> <li>• For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.</li> <li>• If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution 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).</li> <li>• TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for primary PCP prophylaxis.</li> </ul>                                                                                                                                                                                                           |

<sup>a</sup> G6PD levels should be checked before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; PCP = *Pneumocystis pneumonia*; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

## Indication for Primary Prophylaxis

Chemoprophylaxis against PCP should be given to adults and adolescents with HIV (including during pregnancy) and CD4 counts <200 cells/mm<sup>3</sup> who either are not on ART or are initiating ART (AI).<sup>13,51</sup> For people with HIV currently on ART, PCP chemoprophylaxis should be initiated if either (1) CD4 count decreases to 100 to 200 cells/mm<sup>3</sup> in the setting of sustained increases in plasma HIV RNA levels (AIII), or (2) CD4 count drops to <100 cells/mm<sup>3</sup>, regardless of plasma HIV RNA levels (AIII). Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).<sup>52</sup>

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP (AI).<sup>51,53-55</sup> One double-strength TMP-SMX tablet daily or one single-strength tablet daily<sup>55</sup> are the preferred regimens (AI); there is greater experience with the double-strength tablet, but the single-strength tablet may be better tolerated. One double-strength TMP-SMX tablet three times weekly is also effective (BI).<sup>56</sup> TMP-SMX confers cross-protection against toxoplasmosis<sup>57</sup> and many

respiratory bacterial infections.<sup>53,58</sup> TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in people with HIV who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction (e.g., rash without vesicles, bullae, or ulcerations), reinstitution of the drug should be considered after the reaction has resolved **(AII)**.<sup>59</sup> Therapy should be permanently discontinued (with no rechallenge) in people with HIV 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 reinstitution of TMP-SMX if the dose is gradually increased according to published regimens **(BI)**<sup>60,61</sup> or if the drug is given at a reduced dose or frequency **(CIII)**. As many as 70% of people with HIV can tolerate such reinstitution of TMP-SMX therapy.<sup>58</sup>

For people with HIV in whom TMP-SMX use may need to be avoided (e.g., intolerance, severe renal dysfunction, early pregnancy, significant myelosuppression), alternative prophylactic regimens include dapsone **(BI)**,<sup>53</sup> dapsone plus pyrimethamine plus leucovorin **(BI)**,<sup>62-64</sup> aerosolized pentamidine administered with the Respigard II nebulizer (manufactured by Marquest; Englewood, Colorado) **(BI)**,<sup>54</sup> intravenous (IV) pentamidine **(CIII)**,<sup>65-67</sup> and atovaquone **(BI)**.<sup>68,69</sup> For people with HIV who are seropositive for *Toxoplasma gondii* and cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin **(BI)**<sup>62-64</sup> or atovaquone **(CIII)**. Dapsone alone and pentamidine (aerosol or IV) have not been shown to have activity against toxoplasmosis, and should only be used in people who are seronegative for anti-*Toxoplasma* antibodies.<sup>57,70,71</sup> Glucose-6-phosphate dehydrogenase (G6PD) levels should be checked prior to starting dapsone, and an alternative regimen should be used if G6PD deficiency is present, given the risks of hemolysis and methemoglobinemia in patients with G6PD deficiency.<sup>72</sup>

The utility of IV pentamidine as PCP prophylaxis has been evaluated primarily in retrospective/observational studies in immunosuppressed patients without HIV, especially in pediatric populations; experience in people with HIV is limited. Aerosolized pentamidine should be administered in an appropriately configured negative pressure room.<sup>73</sup> Pyrimethamine has become extremely expensive and can be difficult to obtain in the United States, and atovaquone has variable and unpredictable bioavailability. Atovaquone is as effective as aerosolized pentamidine<sup>68</sup> or dapsone<sup>69</sup> but substantially more expensive than the other regimens, and less preferred by patients due to the taste of the suspension.

The following regimens **are NOT recommended** as alternatives to TMP-SMX for PCP prophylaxis **(AIII)**:

- Aerosolized pentamidine administered by nebulization devices other than the Respigard II nebulizer<sup>74</sup>
- Oral clindamycin plus primaquine, because this regimen has not been studied for PCP prophylaxis, and clindamycin alone was poorly tolerated as a potential prophylactic regimen for toxoplasmosis.<sup>75</sup>

## ***Discontinuing Primary Prophylaxis***

Primary *Pneumocystis* prophylaxis should be discontinued in adult and adolescent people with HIV 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 people with HIV had CD4 counts  $>200$  cells/mm<sup>3</sup> for  $>3$  months before discontinuing PCP prophylaxis.<sup>76-85</sup> At discontinuation of prophylaxis, the median CD4 count was  $>300$  cells/mm<sup>3</sup>, most participants had a CD4 cell percentage  $\geq 14\%$ , and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 to 19 months.

A combined analysis of European cohorts,<sup>86,87</sup> a small randomized trial,<sup>88</sup> and a case series<sup>89</sup> found a low incidence of PCP in people with HIV with CD4 counts between 100 and 200 cells/mm<sup>3</sup>, who were receiving ART and had HIV plasma viral loads of  $<50$  to  $<400$  copies/mL, and who had stopped or never received PCP prophylaxis; this observation suggests that primary and secondary PCP prophylaxis can be safely discontinued in people with HIV with CD4 counts between 100 and 200 cells/mm<sup>3</sup> and HIV plasma RNA levels below the limits of detection of commercial assays. Some clinicians would stop primary prophylaxis in people with HIV with CD4 counts of 100 to 200 cells/mm<sup>3</sup> if HIV plasma RNA levels remain below limits of detection for  $\geq 3$  months to 6 months; definitive data for a more precise recommendation are lacking **(BII)**. Similar observations have been made with regard to stopping primary prophylaxis for *Toxoplasma* encephalitis.<sup>90</sup>

Prophylaxis should be reintroduced if the patient's CD4 count decreases to 100 to 200 cells/mm<sup>3</sup> in the setting of sustained increases in plasma HIV RNA levels **(AIII)** and in any people with HIV whose CD4 count drops to  $<100$  cells/mm<sup>3</sup> **(AIII)**.

## Treating Disease

| Recommendations for Treating <i>Pneumocystis</i> Pneumonia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <p>People with HIV who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX <b>(BIII)</b>.</p> <p>If not already started, ART should be initiated in patients within 2 weeks of diagnosis of PCP, if possible <b>(AI)</b>.</p> <p><b>For Moderate-to-Severe PCP</b></p> <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> <li>• TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) IV given in divided doses every 6 or 8 hours <b>(AI)</b>; may switch to PO formulation after clinical improvement <b>(AI)</b></li> </ul> <p><i>Alternative Therapy</i></p> <ul style="list-style-type: none"> <li>• Primaquine<sup>a</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]) <b>(AI)</b>, or</li> <li>• Pentamidine 4 mg/kg IV once daily infused over <math>\geq 60</math> minutes <b>(AI)</b>; may reduce the dose to pentamidine 3 mg/kg IV once daily in the event of toxicities <b>(BI)</b></li> <li>• <b>Note:</b> Some clinicians prefer primaquine plus clindamycin because it is more effective and less toxic than pentamidine.</li> </ul> <p><i>Adjunctive Corticosteroids for Moderate-to-Severe PCP Based on the Following Criteria <b>(AI)</b></i></p> <ul style="list-style-type: none"> <li>• PaO<sub>2</sub> <math>&lt;70</math> mmHg at room air, or</li> <li>• A-a gradient <math>\geq 35</math> mmHg</li> </ul> <p><i>Corticosteroid Dosing Schedule</i></p> <ul style="list-style-type: none"> <li>• Prednisone doses (beginning as soon as possible and ideally within 72 hours of initiating PCP therapy) <b>(AI)</b></li> </ul> |

- o Days 1–5: 40 mg PO twice daily
- o Days 6–10: 40 mg PO daily
- o Days 11–21: 20 mg PO daily
- IV methylprednisolone can be given as 80% of prednisone dose.
- Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP (BIII).

#### For Mild-to-Moderate PCP

##### *Preferred Therapy*

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

##### *Alternative Therapy*

- Dapsone<sup>a</sup> 100 mg PO daily plus TMP 15 mg/kg/day PO given in three divided doses (BI), *or*
- Primaquine<sup>a</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)

#### Duration of Therapy

- The recommended duration of therapy (irrespective of regimen) is 21 days (AII).
- Secondary prophylaxis should be initiated immediately after completion of treatment (see Recurrence table below).

### Pregnancy Considerations

#### For Moderate-to-Severe PCP

##### *Preferred Therapy*

- TMP-SMX, regardless of disease (AIII)
- Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs potential risk (AIII).
- For women who are on TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day if they are capable of becoming pregnant or as soon as possible in their first trimester (BIII). Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4–6 weeks postpartum or discontinuation of breastfeeding (AIII).
- Whether or not supplemental folic acid is administered during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for follow-up scans subsequently (BIII).

##### *Alternative Therapy*

- IV pentamidine (BIII)
- If other alternatives are not available or tolerated, primaquine plus clindamycin (BIII)
  - o Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient (which cannot be diagnosed antenatally), primaquine (plus clindamycin) should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

#### For Mild-to-Moderate PCP

##### *Preferred Therapy*

- TMP-SMX, regardless of disease (AI)

#### Alternative Therapy

- Atovaquone suspension (BIII)
- If atovaquone is not available or tolerated, dapsone plus TMX (BIII)
  - Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient, primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

Note: As with other adults with HIV, G6PD levels should be checked before administration of primaquine or dapsone during pregnancy. While the G6PD level in a fetus generally is unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant woman and biologic father have normal G6PD activity.

#### Adjunctive Corticosteroid Therapy

- During pregnancy, adjunctive corticosteroid therapy should be used to improve treatment outcomes as indicated in any other person with HIV (AIII). Maternal glucose levels and blood pressure should be monitored closely when corticosteroids are used in pregnancy, as well as fetal growth (AIII).
- Patients on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery but should be continued on their therapeutic dose of steroids without interruption (BIII).

#### Other Considerations/Comments

- For people with HIV 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, reinstitution 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).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for PCP treatment.

<sup>a</sup> G6PD levels should be checked before administration of dapsone or primaquine. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: A-a gradient = alveolar-arterial gradient; ART = antiretroviral therapy; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PaO<sub>2</sub> = room air arterial oxygen partial pressure; PCP = *Pneumocystis pneumonia*; PO = orally; SMX = sulfamethoxazole; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

TMP-SMX is the treatment of choice for PCP (AI).<sup>91,92</sup> Standard doses are summarized in the table above; lower doses may also be effective, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable.<sup>93</sup> 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.<sup>91,92,94</sup> Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because its efficacy in preventing this toxicity is questionable and some evidence suggests adding leucovorin can lead to higher treatment failure rates. (AII).<sup>95</sup> Outpatient therapy with oral TMP-SMX is highly effective in people with HIV with mild-to-moderate PCP (AI).<sup>92</sup> TMP-SMX should be permanently discontinued (with no rechallenge) in people with HIV who experience life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis (AIII).

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.<sup>96-99</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 PaO<sub>2</sub> <70 mmHg or A-a gradient ≥35 mmHg, should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting specific PCP therapy **(AI)**.<sup>100-105</sup> The benefits of starting steroids later are unclear, but most clinicians would administer them even after 72 hours for people with HIV who have moderate-to-severe PCP **(BIII)**. Intravenous methylprednisolone at 80% of the corresponding oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone plus trimethoprim (TMP) **(BI)**,<sup>92,106</sup> which may have efficacy similar to TMP-SMX with fewer side effects, but is less convenient given the number of pills; primaquine plus clindamycin **(BI)**<sup>107-109</sup> (clindamycin can be administered IV for more severe cases, but primaquine is only available in an oral formulation); and atovaquone suspension **(BI)**,<sup>91,110</sup> which is less effective than TMP-SMX for mild-to-moderate PCP but has fewer side effects. Clinicians should be aware that the absorption of atovaquone is highly variable; plasma concentrations ≥15 µg/mL are associated with an improved response rate, but atovaquone therapeutic drug monitoring is not routinely available.<sup>91,111</sup> People with HIV should be tested for G6PD levels before primaquine or dapsone is administered. An alternative agent should be used if the patient is found to have G6PD deficiency.

Alternative therapeutic regimens for people with HIV who have moderate-to-severe PCP include primaquine plus clindamycin **(AI)** or IV pentamidine **(AI)**.<sup>109,112,113</sup> Some clinicians prefer primaquine plus clindamycin because this combination is more effective and less toxic than pentamidine.<sup>109,114-116</sup>

Aerosolized pentamidine **should not be used** to treat PCP because it has limited efficacy and is associated with more frequent relapse **(AI)**.<sup>112,117,118</sup>

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days **(AII)**<sup>19</sup>; shorter durations may also be effective but have not been systematically studied.<sup>119</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 the overall prognosis for people with HIV with PCP-associated respiratory failure is poor, over the past decades, survival for people with HIV who require intensive care unit (ICU) care has improved with advances in the management of respiratory failure and HIV comorbidities.<sup>120-123</sup> Special attention is necessary regarding the use of ART in such critically ill patients.<sup>124</sup>

### ***Special Considerations Regarding ART Initiation (Including IRIS)***

If not already started, ART should be initiated in patients, when possible, within 2 weeks of PCP diagnosis **(AI)**. In a randomized controlled trial of 282 people with HIV 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 vs. 45 days after OI therapy initiation, respectively).<sup>125</sup> Of note, none of the participants with PCP enrolled in the study had respiratory failure requiring intubation.<sup>125</sup> Initiating ART in intubated patients can be managed

with attention to formulations that can be crushed for gastrointestinal administration when an IV option is unavailable (such as primaquine). Providers should be aware of the unpredictable absorption of oral medications, and potential drug–drug or drug–nutrient interactions commonly encountered in the ICU.<sup>126</sup>

Paradoxical immune reconstitution inflammatory syndrome (IRIS) following an episode of PCP is rare but has been reported.<sup>127,128</sup> Most cases occurred within weeks of the PCP episode; 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 rarely been life-threatening,<sup>129</sup> people with HIV 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 people with HIV 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 treatment response 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 people with HIV, rates of adverse reactions to TMP-SMX are high (20% to 85% of patients).<sup>91,92,106,108,113,130-134</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), hyperkalemia, and rarely, aseptic meningitis. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued (**AIII**). Mild rashes (e.g., rash without vesicles, bullae, or ulcerations), nausea, and fever can often be “treated through” with antihistamines, antiemetics, and antipyretics, respectively.<sup>59</sup> High-dose trimethoprim inhibits tubular secretion of creatinine without affecting glomerular filtration rate, and this effect may be additive with other medications. As noted above, therapy should be permanently discontinued in the setting of **life-threatening adverse reactions including** possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis (**AIII**).

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>92,106</sup>; azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine<sup>110,112,113,133</sup>; anemia, rash, fever, and diarrhea with primaquine and clindamycin<sup>92,107,108</sup>; and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.<sup>91,132</sup> Patients who exhibit persistent hypoxemia despite an apparent positive clinical response should undergo evaluation for methemoglobinemia if they are taking potentially causative medications.

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

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after 4 to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of people with HIV with mild-to-moderate PCP disease.<sup>91,92</sup>

However, there are not any convincing clinical trial data on which to base recommendations for the management of PCP treatment failure due to lack of drug efficacy.

Clinicians should wait 4 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 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 infectious and non-infectious processes 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 bronchoscopy was used to make the initial diagnosis.

Treatment-limiting toxicities occur in up to one-third of patients.<sup>92</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 **(BII)** or oral primaquine combined with IV clindamycin **(BII)**.<sup>108,109,113</sup> For mild disease, atovaquone is a reasonable alternative **(BII)**. Although a meta-analysis, systematic review, and cohort study concluded that the combination of primaquine and clindamycin might be the most effective regimen for salvage therapy,<sup>109,115,116</sup> no prospective clinical trials have evaluated the optimal approach for people with HIV who experience a therapy failure with TMP-SMX.

## Preventing Recurrence

| Recommendations for Preventing Recurrence of <i>Pneumocystis</i> Pneumonia (Secondary Prophylaxis)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Indications for Initiating Secondary Prophylaxis</p> <ul style="list-style-type: none"> <li>• Prior PCP</li> </ul> <p>Preferred Therapy</p> <ul style="list-style-type: none"> <li>• TMP-SMX, 1 DS tablet PO daily<sup>a</sup> (AI), or</li> <li>• TMP-SMX, 1 SS tablet PO daily<sup>a</sup> (AI)</li> <li>• <b>Note:</b> TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections. Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AI).</li> </ul> <p>Alternative Therapy</p> <ul style="list-style-type: none"> <li>• The following regimens can be used for people who are seropositive or seronegative for <i>Toxoplasma gondii</i>: <ul style="list-style-type: none"> <li>o TMP-SMX one DS tablet PO three times weekly (BI), or</li> <li>o Dapsone<sup>a</sup> 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), or</li> <li>o Dapsone<sup>a</sup> 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), or</li> <li>o Atovaquone 1,500 mg PO daily with food (BI)</li> </ul> </li> <li>• The following regimens should only be used in people who are seronegative for <i>Toxoplasma gondii</i>: <ul style="list-style-type: none"> <li>o Dapsone<sup>a</sup> 100 mg PO daily (BI), or</li> <li>o Aerosolized pentamidine 300 mg via Respigard II nebulizer every month (BI), or</li> <li>o Intravenous pentamidine 300 mg every 28 days (CIII)</li> </ul> </li> </ul> |

#### Indications for Discontinuing Secondary Prophylaxis

- CD4 count increased from  $<200$  cells/mm<sup>3</sup> to  $\geq 200$  cells/mm<sup>3</sup> for  $\geq 3$  months as a result of ART (AII), *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 to 6 months (BII)
- For people with HIV 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  $\geq 3$  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, especially with plasma HIV RNA below level of detection, 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), *or*
- CD4 count 100–200 cells/mm<sup>3</sup> and HIV RNA above detection limit of the assay used (AIII)

#### Prepregnancy and Pregnancy Considerations

- For patients receiving PCP prophylaxis, clinicians who are providing prepregnancy care can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued (BIII) due to potential concerns about possible adverse effects of trimethoprim on the fetus.
- Women of childbearing potential who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day (BIII).
- During pregnancy, chemoprophylaxis for PCP should be administered as it is for other adults and adolescents (AIII). TMP-SMX is the recommended prophylactic agent (AIII). For women who are on TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day in their first trimester (BIII).
- Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used during the first trimester (BII).
- Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in mothers or exposed fetuses (BIII).

**Note regarding G6PD deficiency and use of primaquine or dapsone in pregnancy:** As with other adults with HIV, G6PD levels should be checked before administration of primaquine or dapsone. While G6PD level in a fetus are generally unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant woman and biologic father have normal G6PD activity.

#### Other Considerations/Comments

- For people with HIV 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, reinstitution 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).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse events, *including* suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for secondary PCP prophylaxis.

<sup>a</sup> Whenever possible, people with HIV should be tested for G6PD deficiency before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PCP = *Pneumocystis pneumonia*; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

## ***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>135</sup> For people with HIV who are intolerant of TMP-SMX, the alternatives are dapsone **(BI)**, dapsone plus pyrimethamine plus leucovorin **(BI)**, atovaquone **(BI)**, and aerosolized pentamidine **(BI)** or IV pentamidine **(CIII)**.

## ***When to Stop Secondary Prophylaxis***

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from  $<200$  cells  $\text{mm}^3$  to  $\geq 200$  cells  $\text{mm}^3$  for  $\geq 3$  months as a result of ART **(AII)**. Reports from observational studies<sup>77,83,136,137</sup> and from two randomized trials<sup>84,138</sup> and a combined analysis of European cohorts being followed prospectively<sup>139,140</sup> support this recommendation. In these studies, people with HIV responded to ART with an increase in CD4 counts to  $\geq 200$  cells/ $\text{mm}^3$  for  $\geq 3$  months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was  $>300$  cells/ $\text{mm}^3$  and most people with HIV had a CD4 cell percentage  $>14\%$ . Most people with HIV 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 people with HIV with CD4 counts of 100 cells/ $\text{mm}^3$  to 200 cells/ $\text{mm}^3$  can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for 3 to 6 months **(BII)**.<sup>141</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/ $\text{mm}^3$  **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for people with HIV with CD4 counts of 100 cells/ $\text{mm}^3$  to 200 cells/ $\text{mm}^3$  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 people with HIV with CD4 counts of 100 cells/ $\text{mm}^3$  to 200 cells/ $\text{mm}^3$  who have had HIV plasma RNA levels below limits of detection for 3 to 6 months **(BII)**.<sup>86,139</sup>

If an episode of PCP occurs at a CD4 count  $>200$  cells/ $\text{mm}^3$  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 people with HIV in whom PCP occurs at a CD4 count  $>200$  cells/ $\text{mm}^3$  while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for 3 to 6 months, although there are no data to support recommendations in this setting **(CIII)**.

## ***Special Considerations Regarding Pregnancy***

Some data suggest an increased risk of PCP-associated mortality in pregnancy.<sup>142</sup> All-cause pneumonia during pregnancy increases rates of preterm labor and delivery.<sup>143</sup>

Women at >20 weeks gestation who have PCP should be closely monitored for signs or symptoms of preterm labor (e.g., abdominal cramping, uterine tightening, fluid leakage) **(BIII)**.

### ***Prepregnancy Care***

For patients receiving PCP prophylaxis, clinicians who are providing prepregnancy care can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued **(BIII)** due to concerns about possible adverse effects of trimethoprim on the fetus (see the Primary and Secondary Prophylaxis section below). All women of childbearing potential should take supplemental folic acid at a dose of 0.4 mg/day **(AI)**; those who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day **(BIII)** (see below).

### ***Pregnancy Care***

**Note: Specific drugs recommended for prophylaxis are discussed in the section on Primary and Secondary Prophylaxis. This information is not repeated in the Treating Disease section and only medications recommended exclusively for treatment are discussed in this section.**

#### **Primary and Secondary Prophylaxis**

During pregnancy, chemoprophylaxis for PCP should be administered as it is for other adults and adolescents **(AIII)**. The preferred regimen for prophylaxis is TMP-SMX **(AIII)**. Given concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used during the first trimester **(BII)**. Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in pregnant women or exposed fetuses **(BIII)**. As with other adults with HIV, G6PD levels should be checked before dapsone administration.

No adequate and well-controlled large studies of pregnancy outcomes after exposure to sulfamethoxazole and trimethoprim have been published. Trimethoprim is classified as a folic acid antagonist, acting as a dihydrofolate reductase inhibitor; older case-control studies found that first-trimester exposure has been associated with an increased risk of neural tube defects and cardiovascular, oral clefts, urinary tract, and multiple anomalies.<sup>144-146</sup> A systematic review and meta-analysis in 2014, including 24 studies,<sup>147</sup> reported congenital anomalies in 232 infants among 4,196 women receiving TMP-SMX in pregnancy, with a pooled prevalence of 3.5% (95% confidence interval [CI], 1.8% to 5.1%) and three studies reported 31 infants with neural tube defects associated with first-trimester exposure, with a crude prevalence of 0.7% (95% CI, 0.5% to 1.0%). The quality of the evidence was considered very low and the authors supported continued recommendation for TMP-SMX when indicated for pregnant women with HIV. A recent systematic review of antimicrobials used for management of plague during pregnancy included 23,602 prenatal exposures to TMP-SMX found that first-trimester exposure was associated with an increased risk of neural tube defects (pooled odds ratio [OR] 2.5; 95% CI, 1.4–4.3).<sup>148</sup> This study also found increased odds of spontaneous abortion (OR 3.5; 95% CI, 2.3–5.6), preterm delivery (OR 1.5; 95% CI, 1.1–2.1) and the fetus being small for gestational age (OR 1.6; 95% CI, 1.2–2.2). In a nested case-control study (n = 77,429; 7,039 cases of spontaneous abortion) based on prescription fills, first-trimester exposure to TMP-SMX, after adjusting for potential confounders, was associated with increased odds of spontaneous abortion (adjusted odds ratio [aOR] 2.94, 95% CI, 1.89–4.57, including 25 exposed cases and 77 controls).<sup>149</sup> Exposure to TMP-SMX in the last two trimesters of pregnancy was

associated with low birth weight, adjusted for gestational age and sex (OR 1.61; 95% CI, 1.16–2.23) in a case-control study within the Quebec Pregnancy Registry (8,192 cases, 55,146 controls).<sup>150</sup> Data from a large Canadian administrative database was used to retrospectively compare the occurrence of placenta-mediated adverse pregnancy outcomes between pregnant women exposed to folic acid antagonists and women without exposure to these agents.<sup>151</sup> TMP-SMX was the most frequently prescribed dihydrofolate reductase inhibitor (11,386 exposures during the preconception period and all three trimesters compared to 45,456 unexposed women) and exposure was associated with increased odds of preeclampsia (aOR 1.13; 95% CI, 1.01–1.26), placental abruption (aOR 1.26; 95% CI, 1.03–1.55), and fetal growth restriction defined as less than the third percentile (aOR 1.20; 95% CI, 1.07–1.33).

Folic acid supplementation at 0.4 mg/day is routinely recommended for all women of reproductive potential,<sup>152</sup> to reduce the risk of neural tube defects (**AI**). Since neural tube closure occurs early in pregnancy, often before pregnancy is diagnosed, all persons planning a pregnancy or with reproductive potential should take daily folic acid supplementation. There is also evidence that folic acid supplementation may decrease risk of congenital heart defects, cleft lip and palate,<sup>153</sup> preterm birth,<sup>154</sup> low birth weight, and the fetus being small for gestational age.<sup>155,156</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. A multicenter double-blind randomized clinical trial in women of childbearing age who planned pregnancy within 12 months failed to show an advantage of folic acid 4 mg versus 0.4 mg daily on the occurrence of congenital malformations; however, the higher dose was associated with lower occurrence of spontaneous abortion, the fetus being small for gestational age, and preterm delivery.<sup>157</sup> The authors noted that the study was underpowered for the outcome of congenital malformations.<sup>157</sup> Other studies have found that higher doses of folic acid (4–6 mg/day) are associated with less frequent neural tube defects, oral clefts, and recurrent preeclampsia.<sup>158–160</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 (OR 1.24; 95% CI, 0.94–1.62).<sup>144</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. Based on these findings, with the suggestion of a dose-response effect of folic acid supplementation and the known effects of TMP-SMX as a folic acid antagonist, for women who are on TMP-SMX, clinicians should consider giving them supplemental folic acid 4 mg/day prior to pregnancy if they are capable of becoming pregnant or as soon as possible in the first trimester in those who are pregnant (**BIII**). Leucovorin (folinic acid) is an active form of folate and is commonly used to counteract the effect of folic acid antagonists, especially as an adjunct in the treatment of various cancers. However, it is chemically different from folic acid and is not interchangeable. A randomized, controlled trial demonstrated that adding leucovorin to TMP-SMX for the treatment of PCP was associated with an increased risk of therapeutic failure and death.<sup>95</sup> In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent leucovorin use.<sup>161</sup> If a higher dose of supplemental folic acid is given, its use should be limited to the first trimester (**AIII**). Whether or not a person receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for subsequent follow-up scans (**BIII**).

Although historically there has been concern about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, reviews have found no cases of kernicterus reported in neonates after maternal ingestion of sulfonamides or with the use of TMP-SMX in neonates.<sup>162-164</sup> For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.<sup>165,166</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>167</sup>

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated teratogenicity in rats or rabbits at plasma concentrations corresponding to estimated human exposure during malaria treatment.<sup>168</sup> A systematic review of the safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy found miscarriages in 21 of 260 women (8.08%; 95% CI, 5.07% to 12.08%) and congenital anomalies in 11 of 430 women (2.56%; 95% CI, 1.28% to 4.53%), both well within expected rates.<sup>169</sup> When considering only results from this one randomized clinical trial of atovaquone-proguanil, there was no significant difference in these outcomes when compared to quinine, although the number was extremely small (n = 81).<sup>170</sup>

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.<sup>171</sup> There is limited experience with systemic use in human pregnancy and no human studies of pregnancy outcomes after exposure to pentamidine have been published. It is unknown if pentamidine crosses the placental barrier at significant concentrations when administered via the aerosolized route. Given anecdotal experience to date during pregnancy without signs of adverse effects or teratogenicity, pentamidine should be considered an alternative when indicated either via aerosolized or IV route.

## Treatment

The preferred initial therapy for PCP during pregnancy, regardless of disease severity, is TMP-SMX **(AIII)**.<sup>134</sup>

Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, people with PCP in the first trimester should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs the potential risk **(AIII)**. Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX and capable of pregnancy or as soon as possible in the first trimester **(BIII)**. Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4 to 6 weeks postpartum or discontinuation of breastfeeding **(AIII)**.

If an alternative therapeutic regimen is required for moderate-to-severe PCP, IV pentamidine is preferred **(BIII)**. Primaquine plus clindamycin should be used only if other alternatives are not available or tolerated **(BIII)**. If an alternative therapeutic regimen is required for mild-to-moderate PCP, atovaquone suspension is preferred **(BIII)**; dapsone plus TMP can be used if atovaquone is not available or tolerated **(BIII)**. As with other adults with HIV, G6PD levels should be checked before administration of dapsone. Because of concerns about hemolytic anemia in exposed fetuses who are G6PD-deficient (which cannot be diagnosed antenatally), primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk **(AIII)**.

During pregnancy, adjunctive corticosteroid therapy should be used to improve treatment outcomes as indicated in any other person with HIV **(AIII)**.<sup>172-175</sup> Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air PO<sub>2</sub> <70 mmHg or A-a gradient PO<sub>2</sub> ≥35 mmHg, should receive adjunctive corticosteroids as early as possible. Corticosteroids have commonly been used in pregnancy for autoimmune conditions and are considered low risk for use in pregnancy.<sup>176</sup> Although an earlier systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4-fold increase in the odds of delivering a baby with an oral cleft,<sup>177</sup> more recent data from a prospective controlled study in Israel, a large population-based registry in Sweden,<sup>178</sup> and an updated analysis from the National Birth Defect Prevention Study,<sup>179,180</sup> have failed to demonstrate an association between first-trimester corticosteroids and major congenital anomalies, including orofacial clefts. A recent systematic review and meta-analysis also found no association between first-trimester corticosteroid exposure and risk of congenital heart defects.<sup>181</sup> Long-term corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, preeclampsia, hyperglycemia, premature rupture of membranes, intrauterine growth restriction,<sup>182</sup> and infection, although the magnitude is not known.<sup>183</sup>

Maternal glucose levels and blood pressure as well as fetal growth should be monitored closely when corticosteroids are used in pregnancy **(AIII)**. Based on available observational data from pregnant and nonpregnant surgical patients, pregnant women who are on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery, but they should be continued on their therapeutic dose of steroids without interruption **(BIII)**. HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Clindamycin is considered safe for use throughout pregnancy **(BIII)**. Clindamycin is recommended as an alternative antibiotic for prevention of group B streptococcal disease in newborns and for antimicrobial prophylaxis during cesarean delivery.<sup>184,185</sup> However, there are no well-controlled studies of clindamycin use in pregnant women during the first trimester. In animal studies, clindamycin was not teratogenic following oral doses up to six times the maximum recommended adult human dose.<sup>186</sup> During clinical trials, the systemic administration of clindamycin to pregnant women during the second and third trimesters did not increase the frequency of congenital abnormalities.<sup>186</sup>

There are no adequate or well-controlled studies of primaquine use in pregnant women, and animal data is scant. Although some data from animal studies suggest evidence of genotoxicity, as well as fetal abnormalities at doses multiple times the maximal dose in humans,<sup>187</sup> another animal study at doses 0.25 to 3.0 mg/kg early in gestation found no harmful effects on mother or offspring.<sup>188</sup> In an observational study from Brazil, 59 women were found to have been prescribed primaquine for malaria during pregnancy, approximately one-third in the first trimester; no adverse birth outcomes were found, although G6PD testing was not done on the infants.<sup>189</sup> The Centers for Disease Control and Prevention recommend that primaquine not be administered during pregnancy because of the risk of hemolytic anemia in a G6PD-deficient fetus.<sup>190</sup> The degree of intravascular hemolysis appears to be associated with both the dose of primaquine and severity of G6PD deficiency.<sup>188</sup> G6PD deficiency is an X-linked inherited condition and primaquine can be considered if both the pregnant woman and biologic father have normal G6PD activity.<sup>191</sup> Primaquine should be used in pregnancy only if other alternatives are not available or tolerated and the benefit is felt to outweigh the risk **(AIII)**.

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