

The 2015 Clinical Guidelines for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Koreans: Guidelines for Opportunistic Infections

The Korean Society for AIDS

The Committee for Clinical Guidelines for the Treatment and Prevention of Opportunistic Infections of the Korean Society for AIDS was founded in 2011. The first edition of the Korean guidelines was published in 2012. The guideline recommendations contain important information for physicians working with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) in the clinical field. It has become necessary to revise the guidelines due to new data in this field. These guidelines aim to provide up-to-date, comprehensive information regarding the treatment and prevention of opportunistic infections in HIV-infected Koreans. These guidelines deal with several common opportunistic infections, including pneumocystis pneumonia, tuberculosis, cryptococcal meningitis, etc. A brief summary of the revised guidelines is provided below. Recommendations are rated using the same system used in the previous guidelines.

Key Words: Human immunodeficiency virus; Acquired immune deficiency syndrome; Opportunistic infections; Treatment; Prevention

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- * The following recommendations are practical guidelines, based on the current (2014.11) status of Korean patients, for the treatment and prevention of opportunistic infections in HIV-infected patients. Rather than applying the following principles in a general way, we recommended that treatment be based upon clinical decision making, individualized according to the unique needs of each individual patient.
- * The following recommendations can be used for educational and personal clinical practices but cannot be utilized for any commercial or clinical evaluation purposes. Those who wish to use the following guidelines for any other purposes must submit a written request and must get written permission from the committee.

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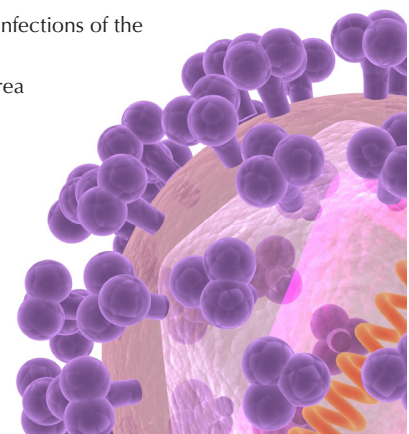
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Recommendations are rated according to those used for guidelines by the Centers for Disease Control and Prevention, the National Institutes of Health, and the human immunodeficiency virus (HIV) Medicine Association of the Infectious Diseases Society of America [1]. The rating system consists of the strength of recommendation (A: strong recommendation for the statement, B: moderate recommendation for the statement, C: optional recommendation for the statement) and quality of evidence (I: one or more randomized trials with clinical outcomes and/or validated laboratory endpoints, II: one or more well designed, non-randomized trials or observational cohort studies with long-term clinical outcome, III: expert opinion).

1. Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is the most common AIDS-defining opportunistic infection in HIV-infected Koreans [2]. The treatment of choice for PCP is trimethoprim-sulfamethoxazole (TMP-SMX) (AI) [3]. Patients who have PCP during TMP-SMX prophylaxis also can be treated with TMP-SMX (BIII) [4]. Adjunctive corticosteroids are recommended for patients with moderate or severe PCP, defined by room air $\text{PaO}_2 < 70$ mmHg or alveolar-arterial oxygen gradient ≥ 35 mmHg, and should be given within 72 hours after starting PCP treatment (AI) [5]. Alternative therapy for mild-to-moderate disease includes primaquine plus clindamycin (BI) or a suspension of atovaquone (BI) [6]. Alternative treatments for patients with moderate-to-severe PCP include primaquine plus clindamycin or IV pentamidine (AI) [7]. In patients who are not receiving antiretroviral treatment (ART), ART should be started within 2 weeks of the diagnosis of PCP (AI) [8]. Patients with HIV infection should receive primary prophylaxis for PCP if they have CD4^+ T cell counts < 200 cells/ μL or a history of oropharyngeal candidiasis (AII) [9]. TMP-SMX is the recommended medication for prophylaxis, and one tablet daily, either double-strength or single-strength, is adequate (AI) [10]. Primary prophylaxis may be discontinued if CD4^+ T cell counts increase to ≥ 200 cells/ μL for > 3 months.

2. Tuberculosis

Tuberculosis is one of the most common AIDS-defining opportunistic infections in HIV-infected Koreans. The incidence of tuberculosis in HIV-infected Koreans has rapidly declined

to 1.19 new cases/100 person-years in the ART era [11]. Diagnosing latent tuberculosis infection (LTBI) by tuberculin skin test or interferon gamma release assays is recommended, because treatment of LTBI decreases the risk of active tuberculosis by 62% and of death by 26% [12]. Isoniazid for 9 months is the recommended for the treatment of LTBI (AII) [1]. Treatment of tuberculosis in HIV-infected patients is the same as for those who are not infected with HIV. A four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months, is the standard treatment for pulmonary tuberculosis, if the *M. tuberculosis* strain is susceptible to isoniazid and rifampin. Extension of the treatment duration beyond 6 months is recommended for patients with pulmonary tuberculosis and a positive 2-month sputum culture (BII), or with tuberculosis involving a bone or the CNS. Although rifampin is the key drug for the treatment of tuberculosis, it should be prescribed with caution because of its significant drug-drug interactions with many anti-HIV drugs. When tuberculosis occurs in patients receiving ART, antituberculous treatment should be started immediately (AIII). For ART-naïve patients, ART should be started within 2 weeks when the CD4^+ T cell counts are < 50 cells/ μL and by 8-12 weeks for patients with CD4^+ T cell counts ≥ 50 cells/ μL (AI) [13-15].

3. Oropharyngeal and esophageal candidiasis

Oropharyngeal and esophageal candidiasis are common in patients with HIV infection when CD4^+ T cell counts are < 200 cells/ μL [16]. Oral fluconazole is the treatment of choice for oropharyngeal candidiasis (AI) [17]. Itraconazole oral solution is as effective as oral fluconazole for the treatment of oropharyngeal candidiasis, but is less well-tolerated than fluconazole (BI) [18]. Posaconazole oral suspension is also effective and well tolerated (BI). The recommended treatment duration for oropharyngeal candidiasis is 7-14 days. Treatment with either fluconazole or oral itraconazole solution for 14-21 days is effective therapy for esophageal candidiasis (AI). Patients with severe symptoms who have difficulty swallowing may be treated with intravenous fluconazole until their symptoms improve. Caspofungin, micafungin, and anidulafungin are effective in treating esophageal candidiasis but have a higher relapse rate (BI) [19, 20]. Immune reconstitution inflammatory syndrome after initiation of ART has not been reported in patients with oropharyngeal and esophageal candidiasis. When symptoms persist after therapy with oral fluconazole for 7

days or more, posaconazole oral solution may be used (AI) [21]. Although daily oral fluconazole can decrease the incidence of oropharyngeal and esophageal candidiasis, primary prophylaxis is not recommended.

4. Cryptococcal meningitis

Most patients with cryptococcal meningitis have CD4+ T cell counts <100 cells/ μ L. Treatment of cryptococcal meningitis consists of induction, consolidation, and maintenance therapy. The recommended regimen for induction therapy is a combination of intravenous amphotericin B with oral flucytosine (AI). Liposomal amphotericin B is preferred over conventional amphotericin B, since it is associated with more rapid sterilization of the CSF [22] and has less nephrotoxicity compared with amphotericin B deoxycholate [23]. After successful induction therapy, defined by negative CSF culture, induction therapy may be converted to consolidation with fluconazole, 400 mg/day for 8 weeks (AI). The dose of fluconazole may then be reduced to the maintenance level of 200 mg/day for at least one year [24]. Increased intracranial pressure (ICP) is associated with poor outcome, and measures to decrease ICP should be undertaken for patients with increased ICP. Repeated CSF drainage by lumbar puncture is recommended until symptoms improve [25]. CSF shunting or ventriculostomy should be considered for patients who do not respond to repeated lumbar puncture or drainage (BIII). Corticosteroid or acetazolamide is not recommended for patients with increased ICP (AIII) [25, 26]. The optimal timing for initiation of ART is not well defined, since several studies had inconsistent results [8, 27, 28]. It is reasonable to delay ART at least until the completion of induction therapy, and possibly until the consolidation phase (BIII) [1]. If the ART begins within 10 weeks, especially in the first 2 weeks, immune reconstitution inflammatory syndrome may develop. Prophylactic treatment with fluconazole or itraconazole can reduce the incidence of cryptococcal meningitis in patients with CD4+ T cell counts below 100 cells/ μ L [29]. However, primary prophylaxis in the absence of a positive serum cryptococcal antigen test is not recommended, because the incidence of cryptococcal meningitis is low (BIII).

5. Toxoplasma encephalitis

Toxoplasma encephalitis is less common in HIV-infected

Koreans, because the seroprevalence of toxoplasma among Koreans is low compared with that of other countries [30]. Treatment for toxoplasma encephalitis consists of acute and chronic maintenance phases. The recommended regimen for the acute phase is the combination of pyrimethamine, sulfadiazine, and leucovorin (AI) [31]. Pyrimethamine plus clindamycin is also a recommended regimen (AI). TMP-SMX could be used, but it has less *in vitro* activity against toxoplasma than do the recommended agents (BI) [32]. Therapy for the acute phase should continue for 6 weeks (BII) [33]. Corticosteroids should be considered only in patients with toxoplasma encephalitis with a mass effect associated with edema (BIII). After the acute phase, long-term chronic maintenance therapy should be continued until patients are asymptomatic and have CD4+ T cell counts >200/ μ L for more than 6 months [34]. Primary prophylaxis is recommended if patients have CD4+ T cell counts below 100 cells/ μ L and a positive serology test for Toxoplasma (AII) [35]. One double-strength TMP-SMX tablet per day is the recommended prophylactic regimen (AII). Primary prophylaxis may be discontinued if CD4+ T cell counts are >200 cells/ μ L for more than 3 months (AI) [36].

6. CMV retinitis, esophagitis, and colitis

The recommended regimens for cytomegalovirus (CMV) retinitis are IV ganciclovir followed by oral valganciclovir (AI), IV ganciclovir (AI), oral valganciclovir (AI), IV foscarnet (AI), and IV cidofovir (BI) [37, 38]. Patients having small peripheral areas of CMV retinitis should still be treated, despite the lack of significant symptoms (AII). For the first 14-21 days, patients with CMV retinitis should be treated with IV or oral ganciclovir twice a day, followed by once a day treatment after 2-3 weeks. The once a day regimen can be discontinued when the retinitis has been treated for at least 3 months and CD4+ T cell counts are > 100/ μ L for 6 months (AII) [39]. IV ganciclovir followed by oral valganciclovir is recommended for patients with esophagitis or colitis for 21-42 days (CII). If patients have mild esophagitis or colitis, oral valganciclovir may be given without the short-term IV ganciclovir treatment. ART may be initiated within 2 weeks after ganciclovir treatment. Maintenance therapy is not recommended for the first episode of CMV esophagitis or colitis, but is recommended after relapse (BII). When a patient with CMV retinitis is treated with ART, immune reconstitution inflammatory syndrome, presenting as macular edema, can develop [40]. Short-term therapy with corticosteroids is useful for treating immune recovery syndrome [41]. Al-

though daily oral ganciclovir can reduce the incidence of CMV disease significantly, primary prophylaxis is not recommended because of the low incidence of CMV disease and the toxicity of the therapy [42].

7. Herpes simplex virus disease

HSV-2 infection increases the risk of HIV transmission. The recommended treatment for patients with orolabial herpes lesions is oral acyclovir, valaciclovir, or famciclovir for 5-10 days (AIII). Genital herpes also may be treated with oral acyclovir, valaciclovir, or famciclovir for 5-10 days (AI). When mucocutaneous lesions are severe, IV acyclovir may be given initially until symptoms improve (AIII) [43], then switched to oral acyclovir, valaciclovir, or famciclovir. IV acyclovir should be given for patients with disseminated herpes simplex virus infection. Patients with recurrent genital herpes can be treated intermittently when symptomatic lesions occur, or with suppressive therapy to prevent recurrence. The choice of daily suppressive therapy depends on the frequency and severity of recurrences.

8. Herpes zoster

The incidence of herpes zoster is 17-fold higher for patients with HIV infection compared with age-matched controls [44]. Antiviral therapy should be initiated in patients with HIV infection and herpes zoster if the lesions have not fully crusted. The recommended regimen for localized dermatomal zoster is oral valaciclovir (AII), famciclovir (AII), or acyclovir (BII) for 7-10 days. If cutaneous lesions are not limited to one dermatome, or visceral organs are involved, IV acyclovir is recommended until symptoms improve (AII) [45]. A conversion from IV acyclovir to an oral anti-varicella-zoster virus (VZV) drug can be made when new skin lesions do not develop and symptoms of visceral involvement improve (BIII). Corticosteroids are not recommended for patients with herpes zoster (AIII). After the initiation of ART, the incidence of herpes zoster increases as a manifestation of immune reconstitution inflammatory syndrome [46, 47]. If cutaneous lesions do not improve after 10 days of treatment, failure due to antiviral resistance should be considered. Resistance to acyclovir is identified by susceptibility test of isolated VZV. For patients with acyclovir-resistant VZV infection, IV foscarnet (AII) or IV cidofovir (AIII) may be an alternative treatment [48]. A live, attenuated vaccine for the prevention of herpes zoster is now

available, but is contraindicated in patients with CD4+ T cell counts <200 cells/ μ L.

Supplementary material

Guideline Korean version.

Supplementary material can be found with this article online <http://www.icjournal.org/src/sm/ic-48-54-s001.pdf>.

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