

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

Chairman: Nam Joong Kim (Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea)

Member of the Committee: Seong Heon Wie (Division of Infectious Diseases, Department of Internal Medicine, St. Vincent Mary's Hospital, The Catholic University of Korea, Seoul, Korea), Nak-Hyun Kim (Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea), Jun Yong Choi (Department of Internal Medicine Yonsei University College of Medicine, Seoul, Korea), Gayeon Kim (Department of Infectious Diseases, National Medical Center, Seoul, Korea), Sun Hee Lee (Department of Internal Medicine, Pusan National University School of Medicine), So Youn Shin (Department of Infectious Diseases, Catholic Kwandong University, Incheon, Korea), and Joon Young Song (Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea)

- * 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.

Received: January 11, 2016

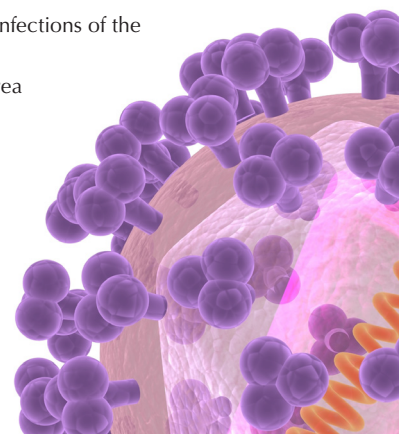
Corresponding Author : The Committee for Clinical Guidelines for the Treatment and Prevention of Opportunistic Infections of the Korean Society for AIDS.

The Korean Society for AIDS, Korea Business Center Room 512, 309 Gangnam-daero, Seocho-gu, Seoul 06628, Korea
 Tel: +82-2-3487-1755, Fax: +82-2-585-8384, E-mail: kosa@kosaid.or.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyrights © 2016 by The Korean Society of Infectious Diseases | Korean Society for Chemotherapy

www.icjournal.org



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>.

References

1. Department of Health and Human Services. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 5 December 2015.
2. Kim JM, Cho GJ, Hong SK, Chang KH, Chung JS, Choi YH, Song YG, Huh A, Yeom JS, Lee KS, Choi JY. Epidemiology and clinical features of HIV infection/AIDS in Korea. *Yonsei Med J* 2003;44:363-70.
3. Safrin S, Finkelstein DM, Feinberg J, Frame P, Simpson G, Wu A, Cheung T, Soeiro R, Hojczyk P, Black JR. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med* 1996;124:792-802.
4. Crothers K, Beard CB, Turner J, Groner G, Fox M, Morris A, Eiser S, Huang L. Severity and outcome of HIV-associated *Pneumocystis* pneumonia containing *Pneumocystis jirovecii* dihydropteroate synthase gene mutations. *AIDS* 2005;19:801-5.
5. Nielsen TL, Eeftink Schattenkerk JK, Jensen BN, Lundgren JD, Gerstoft J, van Steenwijk RP, Bentsen K, Frissen PH, Gaub J, Orholm M, Hansen JE, Mathiesen L, Skinhøj P, Danner SA, Nielsen JO. Adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized European multicenter open label study. *J Acquir Immune Defic Syndr* 1992;5:726-31.
6. Black JR, Feinberg J, Murphy RL, Fass RJ, Finkelstein D, Akil B, Safrin S, Carey JT, Stansell J, Plouffe JF, He W, Shelton B, Sattler FR. Clindamycin and primaquine therapy for mild-to-moderate episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: AIDS Clinical Trials Group 044. *Clin Infect Dis* 1994;18:905-13.
7. Smego RA Jr, Nagar S, Maloba B, Popara M. A meta-analy-

- sis of salvage therapy for *Pneumocystis carinii* pneumonia. Arch Intern Med 2001;161:1529-33.
8. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, Hogg E, Komarow L. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One 2009;4:e5575.
 9. Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. N Engl J Med 1990; 322:161-5.
 10. Schneider MM, Nielsen TL, Nelsing S, Hoepelman AI, Eeftink Schattenkerk JK, van der Graaf Y, Kolsters AF, Borleffs JC. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. Dutch AIDS Treatment Group. J Infect Dis 1995;171:1632-6.
 11. Hwang JH, Choe PG, Kim NH, Bang JH, Song KH, Park WB, Kim ES, Park SW, Kim HB, Kim NJ, Oh MD, Choe KW. Incidence and risk factors of tuberculosis in patients with human immunodeficiency virus infection. J Korean Med Sci 2013;28:374-7.
 12. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2010;CD000171.
 13. Padayatchi N, Abdool Karim SS, Naidoo K, Grobler A, Friedland G. Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial. Int J Tuberc Lung Dis 2014;18:147-54.
 14. Borand L, Madec Y, Laureillard D, Chou M, Marcy O, Pheng P, Prak N, Kim C, Lak KK, Hak C, Dim B, Nerrienet E, Fontanet A, Sok T, Goldfeld AE, Blanc FX, Taburet AM. Plasma concentrations, efficacy and safety of efavirenz in HIV-infected adults treated for tuberculosis in Cambodia (ANRS 1295-CIPRA KH001 CAMELIA trial). PLoS One 2014;9:e90350.
 15. Luetkemeyer AF, Rosenkranz SL, Lu D, Marzan F, Ive P, Hogg E, Swindells S, Benson CA, Grinsztejn B, Sanne IM, Havlir DV, Aweeka F; Adult AIDS Clinical Trials Group A5221 Study Team. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clin Infect Dis 2013;57:586-93.
 16. Rex JH, Rinaldi MG, Pfaller MA. Resistance of *Candida* species to fluconazole. Antimicrob Agents Chemother 1995;39:1-8.
 17. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE; Infectious Diseases Society of America. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161-89.
 18. Vazquez JA. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. HIV AIDS (Auckl) 2010;2:89-101.
 19. de Wet N, Llanos-Cuentas A, Suleiman J, Baraldi E, Krantz EF, Della Negra M, Diekmann-Berndt H. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 2004;39:842-9.
 20. Krause DS, Simjee AE, van Rensburg C, Viljoen J, Walsh TJ, Goldstein BP, Wible M, Henkel T. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis 2004; 39:770-5.
 21. Skiest DJ, Vazquez JA, Anstead GM, Graybill JR, Reynes J, Ward D, Hare R, Boparai N, Isaacs R. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. Clin Infect Dis 2007;44:607-14.
 22. Leenders AC, Reiss P, Portegies P, Clezy K, Hop WC, Hoy J, Borleffs JC, Allworth T, Kauffmann RH, Jones P, Kroon FP, Verbrugh HA, de Marie S. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 1997;11:1463-71.
 23. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, Barker DE. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. Clin Infect Dis 2010;51:225-32.
 24. Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM, Graybill JR, Sugar AM, McAuliffe VJ, Follansbee SE, Tuazon CU, Stern JJ, Feinberg J, Hafner R, Dismukes WE; NIAID AIDS Clinical Trials Group the NIAID Mycoses Study Group. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;326:793-8.
 25. Fessler RD, Sobel J, Guyot L, Crane L, Vazquez J, Szuba MJ,

- Diaz FG. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:137-42.
26. Newton PN, Thai le H, Tip NQ, Short JM, Chierakul W, Rajanuwong A, Pitisuttithum P, Chasombat S, Phonrat B, Maek-A-Nantawat W, Teanadi R, Laloo DG, White NJ. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis* 2002;35:769-72.
27. Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis* 2010;50:1532-8.
28. Boulware DR, Meya DB, Muzoora C, Rolfes MA, Huppler Hullsiek K, Musubire A, Taseera K, Nabeta HW, Schutz C, Williams DA, Rajasingham R, Rhein J, Thienemann F, Lo MW, Nielsen K, Bergemann TL, Kambugu A, Manabe YC, Janoff EN, Bohjanen PR, Meintjes G; COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* 2014;370:2487-98.
29. Powderly WG, Finkelstein D, Feinberg J, Frame P, He W, van der Horst C, Koletar SL, Eyster ME, Carey J, Waskin H, Hooton TM, Hyslop N, Spector SA, Bozzette SA; NIAID AIDS Clinical Trials Group. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *NIAID AIDS Clinical Trials Group. N Engl J Med* 1995;332:700-5.
30. Lim H, Lee SE, Jung BK, Kim MK, Lee MY, Nam HW, Shin JG, Yun CH, Cho HI, Shin EH, Chai JY. Serologic survey of toxoplasmosis in Seoul and Jeju-do, and a brief review of its seroprevalence in Korea. *Korean J Parasitol* 2012;50:287-93.
31. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996;22:268-75.
32. Béraud G, Pierre-François S, Foltzer A, Abel S, Liautaud B, Smadja D, Cabié A. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994-2006. *Am J Trop Med Hyg* 2009;80:583-7.
33. Luft BJ, Conley F, Remington JS, Laverdiere M, Wagner KE, Levine JF, Craven PC, Strandberg DA, File TM, Rice N, Meunier-Carpentier F. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet* 1983;1:781-4.
34. Miro JM, Lopez JC, Podzamczar D, Peña JM, Alberdi JC, Martínez E, Domingo P, Cosin J, Claramonte X, Arribas JR, Santín M, Ribera E; GESIDA 04/98 Study Group. Discontinuation of primary and secondary *Toxoplasma gondii* prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis* 2006;43:79-89.
35. Carr A, Tindall B, Brew BJ, Marriott DJ, Harkness JL, Penny R, Cooper DA. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992;117:106-11.
36. Mussini C, Pezzotti P, Govoni A, Borghi V, Antinori A, d'Arminio Monforte A, De Luca A, Mongiardo N, Cerri MC, Chiodo F, Concia E, Bonazzi L, Moroni M, Ortona L, Esposito R, Cossarizza A, De Rienzo B. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis* 2000;181:1635-42.
37. Holland GN. AIDS and ophthalmology: the first quarter century. *Am J Ophthalmol* 2008;145:397-408.
38. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *Roche Ganciclovir Study Group. N Engl J Med* 1999;340:1063-70.
39. Jabs DA, Van Natta ML, Holbrook JT, Kempen JH, Meinert CL, Davis MD; Studies of the Ocular Complications of AIDS Research Group. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. *Ophthalmology* 2007;114:780-6.
40. Nguyen QD, Kempen JH, Bolton SG, Dunn JP, Jabs DA. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. *Am J Ophthalmol* 2000;129:634-9.
41. Morrison VL, Kozak I, LaBree LD, Azen SP, Kayicioglu OO, Freeman WR. Intravitreal triamcinolone acetonide for the treatment of immune recovery uveitis macular edema. *Ophthalmology* 2007;114:334-9.
42. Spector SA, McKinley GF, Lalezari JP, Samo T, Andruczk R, Follansbee S, Sparti PD, Havlir DV, Simpson G, Buhles W, Wong R, Stempien M. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *Roche Cooperative Oral Ganciclovir Study Group. N Engl J Med* 1996;334:1491-7.

43. Safrin S, Elbeik T, Phan L, Robinson D, Rush J, Elbaggari A, Mills J. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1994;38:1246-50.
44. Buchbinder SP, Katz MH, Hessel NA, Liu JY, O'Malley PM, Underwood R, Holmberg SD. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis* 1992;166: 1153-6.
45. Balfour HH Jr, Bean B, Laskin OL, Ambinder RF, Meyers JD, Wade JC, Zaia JA, Aeppli D, Kirk LE, Segreti AC, Keeney RE. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med* 1983;308:1448-53.
46. Martínez E, Gatell J, Morán Y, Aznar E, Buira E, Guelar A, Mallolas J, Soriano E. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis* 1998;27:1510-3.
47. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med* 2001; 110:605-9.
48. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998;27:1525-7.