Prevention of opportunistic infections in HIV-infected adolescent and adult patients. Guidelines from GESIDA/National AIDS Plan, 2008

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Conflicts of interest: The authors declare no conflicts of interest in relation to this manuscript.

RESUMEN

Objetivo: Actualización de las recomendaciones del Grupo de Estudio de Sida (GESIDA) y la Secretaría del Plan Nacional sobre el SIDA (PNS) del año 2004 sobre prevención de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el VIH.

Métodos: Las recomendaciones han sido consensuadas por un grupo de expertos de GESIDA y/o del PNS tras la revisión del documento del año 2004 y las aportaciones científicas sobre la materia de los últimos 4 años. Para la clasificación de la fuerza y de la calidad de las recomendaciones se ha seguido el sistema utilizado por la Sociedad Americana de Enfermedades Infecciosas (IDSA) y el Servicio de Salud Pública de los Estados Unidos de América (USPHS).

Resultados: En este documento, se realiza una revisión pormenorizada de las medidas para prevenir las infecciones causadas por parásitos, hongos, virus, micobacterias y bacterias en el contexto de la infección por el VIH y, dado el incremento de la inmigración en España, se han incorporado al documento las profilaxis de las infecciones importadas. Para cada grupo de patógenos se han dado recomendaciones para prevenir la exposición a los mismos y para su profilaxis primaria y secundaria. También se han establecido unos criterios para la retirada de las profilaxis en pacientes que tienen una buena respuesta al tratamiento antirretroviral de gran actividad (TARGA).

Conclusiones: El TARGA es la mejor estrategia para prevenir las infecciones oportunistas en pacientes infectados por el VIH. Sin embargo, las profilaxis continúan siendo necesarias en los países con pocos recursos económicos y también en los países desarrollados en pacientes en los que se realiza un diagnóstico tardío de la infección por el VIH, en pacientes inmunodeprimidos que no desean o no pueden tomar TARGA, en aquellos en los que éste fracasa y en el pequeño grupo de infectados que son incapaces de recuperar cifras adecuadas de linfocitos T CD4+ a pesar de una buena inhibición de la replicación del VIH con TARGA.

Número de palabras:

Palabras clave*:* VIH. Infecciones oportunistas. Profilaxis. Retirada de la profilaxis. Tratamiento antirretroviral de gran actividad.

2008 Prevention of opportunistic infections in HIV-infected adolescents and adults guidelines. Recommendations of GESIDA/Nacional AIDS Plan.

Authors: **AIDS Study Group (GESIDA) and AIDS National Plan Experts Panel**

ABSTRACT

Objective: To provide an update of the 2004 Guidelines from the Spanish AIDS Study Group (GESIDA) and the National AIDS Plan (PNS) Committee on the prevention of opportunistic infections in adult and adolescent HIV-infected patients.

Methods: These guidelines have been accepted by a group of experts from GESIDA and/or the PNS after reviewing the 2004 document and scientific advances in this field over the last four years. The strength and quality of the data were classified according to the system used by the Infectious Diseases Society of America and the United States Public Health Service.

Results: This document provides a detailed review of the measures available for the prevention of infections caused by parasites, fungi, viruses, mycobacteria, and bacteria in the context of HIV infection. Due to the increase in recent years of HIV-infected immigrants, the prevention of

tropical infections has been incorporated. Recommendations are given for preventing exposure and for primary and secondary prophylaxis for each group of pathogens. In addition, criteria are established for the withdrawal of prophylaxis in patients who respond well to highly active antiretroviral therapy (HAART).

Conclusions: HAART is the best strategy for the prevention of opportunistic infections in HIV-positive patients. Nevertheless, prophylaxis is still necessary in countries with limited economic resources and also in developed countries, where late presenters are common, in immunosuppressed patients who refuse to take or who cannot take HAART, in those in whom HAART is not effective, and in the small group of infected patients with inadequate recovery of CD4+ T-lymphocyte counts despite good inhibition of HIV replication induced by HAART.

Word count:

Key words*:* HIV. Opportunistic infections. Prophylaxis. Withdrawal of prophylaxis. Highly active antiretroviral therapy.

INTRODUCTION

For many years, the main interventions to improve and prolong the life of HIV-infected individuals were prophylaxis of opportunistic infections and care by professionals with experience in AIDS (1,2). Although the incidence of these infections fell dramatically in developed countries after the introduction of highly active antiretroviral therapy (HAART) (3,4), in developing countries these infections are still very common and are the main cause of HIV-associated death.

For some years now, we have known that inhibition of viral replication by HAART prevents deterioration of the immune system in HIV-infected patients. Furthermore, in patients with advanced disease, after 3-6 months HAART leads to a gradual increase in the number of naïve and memory CD4+ T lymphocytes with the capacity to proliferate in vitro and to generate cytokines in response to opportunistic pathogens. The pathogen-specific immune response is recovered and immune activation gradually decreases (5,6).

There can be no doubt that HAART is the best strategy to prevent opportunistic infections in HIV-infected patients; however, this does not mean that we should forget prophylaxis. Prophylaxis is still a necessary component of clinical practice in developing countries and in developed countries (where late presenters are common), in very immunodepressed patients until HAART takes effect, in patients who cannot take or refuse to take HAART, in those for whom HAART is not effective, and in the small group of infected patients who cannot recover suitable CD4+ T-lymphocyte counts despite good inhibition of viral replication with HAART (7). In a study carried out by the AIDS Research Network in Spain between 2004 and 2005 (8), one-third of all newly diagnosed cases of HIV infection had fewer than 200 CD4+ T lymphocytes/μL and 19% had AIDS criteria; therefore, they would be eligible for primary or secondary prophylaxis against opportunistic infections. In addition, immigration in Spain has increased dramatically in recent years, and immigrants make up 29% of all newly infected patients. Consequently, the clinicians who attend these patients must have a good knowledge of imported infectious diseases.

Bearing the above in mind, and in order to publish these guidelines alongside those on the treatment of opportunistic infections (9), the Board of GESIDA and the National AIDS Plan Committee have decided to update their 2004 guidelines on the prevention of opportunistic infections in HIV-infected adolescents and adults (10), by including contributions from recent years and information on the prophylaxis of imported diseases. The strength and quality of the recommendations have been classified according to the system used by the Infectious Diseases Society of America and the United States Public Health Service (Table 1) (11).

PROPHYLAXIS OF PARASITIC INFECTIONS

Most parasitic infections in HIV-infected patients are caused by reactivation of latent infections when the patient is heavily immunodepressed. Their incidence reflects the prevalence of the different parasites in the general population (12). Some of these reactivations can be prevented by chemoprophylaxis.

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) (Table 2)

Pneumocystis jiroveci is a fungus, but it is included in this section because its prophylaxis and treatment are with antiparasitic drugs and not with antifungals. The organism's taxonomy has changed. Currently, *P. jiroveci* is the name reserved for the species that infects humans and *P. carinii* is the name reserved for the species that infects rodents (13), although the acronym PCP remains despite the change in nomenclature. *P. jiroveci* pneumonia can appear when the CD4+ T-lymphocyte count is below 200 cells/µL (14). It is the most common AIDS-defining disease and the first in which chemoprophylaxis has proved efficacious. Although its incidence has decreased with HAART (3,15,16), it continues to be the most common manifestation of AIDS in patients who do not know they are infected by HIV. In countries where HAART is not available, its prevalence remains very high (17).

Prevention of exposure to the pathogen

It has traditionally been thought that *P. jiroveci* enters the body through the respiratory tract during childhood and produces a latent infection that can be reactivated in situations of severe immunodepression (18). Some reports suggest that the infection can be transmitted from patients with *P. jiroveci* pneumonia to susceptible persons, although transmission between patients is probably very low, and may not even occur (19,20). In conclusion, there is not enough available evidence to recommend respiratory isolation in patients with *P. jiroveci* pneumonia (CIII).

Primary prophylaxis

Primary prophylaxis must be started when the CD4+ T-lymphocyte count is lower than 200 cells/µL or when the patient has an AIDS-defining disease, oral candidiasis, or fever of unknown origin lasting more than 20 days (AI). Prophylaxis can be taken into consideration when the

CD4+ T-lymphocyte count is lower than 14% or lower than 200-250 cells/μL and the patient cannot be monitored every 3 months (21) (BII). There are an increasing number of reports on the development of opportunistic infections (by *P. jiroveci* or other microorganisms related to advanced stages of HIV infection) occurring during the first few weeks after HAART is initiated: this phenomenon, known as the immune reconstitution inflammatory syndrome, is more common in patients who initiate HAART during periods of advanced immunodepression (generally with CD4+ T-lymphocyte counts below 100 cells/μL), a situation that in itself justifies starting prophylaxis. However, this syndrome is also particularly associated with a sharp fall in viral load as a consequence of recently initiated HAART (9,22). Although there are no explicit guidelines for applying primary prophylaxis in patients in whom a rapid fall in viral load might be expected (>2.5 log during the first month of HAART) and whose CD4+ T-lymphocyte count does not justify starting prophylaxis, clinicians should be alert to possible symptoms of opportunistic infections that could correspond to the immune reconstitution syndrome (9).

The combination of trimethoprim and sulfamethoxazole (TMP-SMZ) is considered the drug of choice because of its efficacy, ease of use, and cost-effectiveness (AI). The first studies were carried out with daily doses of TMP-SMZ of 160/800 mg (1 double-strength tablet) (1), but it was later shown that tolerance is better and efficacy similar with 3 double-strength tablets per week (AI) or 1 normal-strength tablet (80/400) every day (AI) (23,24). In the case of hypersensitivity reactions, desensitization must be attempted before an alternative drug can be prescribed (25). Dapsone is considered a second-line prophylactic regimen (BI) (26)—even though it belongs to the sulfa group, there is not always crossed hypersensitivity with sulfamethoxazole—as is dapsone/pyrimethamine (BI) (27,28). There has also been broad experience with aerosolized pentamidine (this must be administered using a special device, Respirgard® II or Fisoneb®) (BI) (29), although this regimen is less effective than TMP-SMZ or dapsone, and does not protect against extrapulmonary forms or other infections, such as toxoplasmosis (30). Its main side effects are bronchospasm and metallic taste. It can also cause problems in the health care setting, with a risk of disseminating tuberculosis; therefore, the aerosol must be administered in an isolated and well-ventilated area. When the necessary environmental conditions for administration of aerosolized pentamidine cannot be fulfilled and the patient presents intolerance or allergy (refractory to desensitization measures) to all sulfa derivatives and atovaquone, monthly intravenous pentamidine should be considered (CIII) (31).

Atovaquone is an alternative for patients who cannot tolerate sulfamides (BI) (32,33). Also valid, although less studied, are sulfadiazine-pyrimethamine and sulfadoxine-pyrimethamine (BII) (34,35), which may need to be administered as more than 1 drug, thus rendering adherence to HAART or prophylaxis difficult.

Secondary prophylaxis

P. jiroveci pneumonia should be followed by secondary prophylaxis to prevent relapses (AI). TMP-SMZ (1 double-strength tablet daily or 3 days per week) is more effective than aerosolized pentamidine for the prevention of local and/or extrapulmonary relapses (36,37) (AI).

Withdrawal of prophylaxis

Primary prophylaxis can be withdrawn in patients who have been on HAART for more than 6 months with an undetectable viral load and a CD4+ T-lymphocyte count above 200 cells/μL for more than 3 months (38-42) (AI). These same criteria are valid for the suspension of secondary prophylaxis (38,39,42-46) (AI); however, if the PCP episode occurred with a CD4+ T-lymphocyte count above 200 cells/μL, secondary prophylaxis should be maintained indefinitely (CIII) (24). On the contrary, some studies with a low number of patients have suggested withdrawing prophylaxis (primary or secondary) in patients who received HAART with a sustained undetectable viral load but whose CD4+ T-lymphocyte count remained below 200 cells/μL (47). Although this recommendation is based on the immunological benefit of permanently suppressed of viral replication, there is no evidence indicating that it should be definitively established (CIII). Withdrawal of prophylaxis reduces drug toxicity, simplifies treatment, and can facilitate adherence to HAART, because the pill burden is reduced. In the long-term this could help reduce the prevalence of PCP by maintaining TMP-SMZ as the drug of choice for more favorable conditions in patients with CD4+ T-lymphocyte counts below 200 cells/μL (42). There have been reports of relapse after withdrawal of prophylaxis. These patients were generally elderly, had developed PCP when their CD4+ T-lymphocyte counts were greater than 200 cells/μL, had other types of immunosuppression (eg, lymphoma), or had abandoned HAART.

Restarting prophylaxis

Although there are no definitive data, prophylaxis should be restarted if the CD4+ T-lymphocyte count falls below 200 cells/μL (AIII) or the patient has an episode of PCP (CIII) (48). This need to restart prophylaxis is even more inevitable if immunosuppression occurs in the setting of poorly controlled viral replication on HAART, compared with what happens when the fall in CD4+ T-lymphocyte count is due to other factors (eg, treatment with interferon) together with undetectable viral load.

Finally, although there have been reports of failed prophylaxis due to mutations of the dihydropteroate synthase gene (DHPS) of *P. jiroveci*, its prevalence in Spain is low and its clinical significance uncertain (49).

Toxoplasma gondii (Table 2)

Cerebral toxoplasmosis is the most common type of encephalitis in AIDS and occurs in patients with less than 100 CD4+ T lymphocytes/µL. This infection can complicate the clinical course of 10%-20% of HIV-infected patients with a positive serology results for *T. gondii* (50), although its incidence has decreased with the use of TMP-SMZ and HAART.

Prevention of exposure to the pathogen

T. gondii is acquired by consuming meat, eggs, greens, and other vegetables that have been contaminated after exposure to cat feces (25,51). Patients with a negative serology result should eat meat that has been well cooked (it should not be pink on the inside). Those patients who do not want to give up rare meat can prefreeze it at under -20ºC. They should also wash fruit and vegetables well to prevent infection (BIII). Patients should also wash their hands after touching raw meat, vegetables, or soil (gardening) (BIII). If the patient keeps a cat as a pet, the cat should be fed using commercial foods, and the cat's meat should be well done. Furthermore, gloves should be worn to clean litter daily (BIII).

Primary prophylaxis

Prophylaxis should be started in patients with a positive serology result (anti-*Toxoplasma* IgG antibodies) and a CD4+ T-lymphocyte count under 100 cells/µL (AII), although some authors recommend starting prophylaxis with counts of below 200 cells/µL (24,52) (BII). The first studies on prophylaxis were retrospective observational studies of patients taking TMP-SMZ to prevent *P. jiroveci*. Toxoplasmosis can be prevented with a daily normal-strength tablet of TMP-SMZ (80/400) or a double-strength tablet (160/800) 3 days per week (27,51,53) (AII). However, a daily double-strength tablet is recommended in patients with severe immunodepression, in those simultaneously taking drugs that can reduce plasma levels of TMP-SMZ (eg, rifampicin), and in those with a very high anti-*Toxoplasma* IgG antibody titer (54,55) (BII). Patients who cannot tolerate TMP-SMZ can receive dapsone in combination with pyrimethamine and folinic acid (BI), atovaquone (alone or in combination with pyrimethamine and folinic acid) (CIII), pyrimethamine (CI), or sulfadoxine-pyrimethamine (BII) (24,27,35,51,52,56,57). We must

remember that some regimens that are active against *P. jiroveci* (dapsone, inhaled pentamidine) are not effective against *T. gondii* and, therefore, if they are administered in patients with a CD4+ T-lymphocyte count of less than 100 cells/μL and positive serology results for *T. gondii*, prophylaxis should be modified to include a regimen that is active against this parasite (AII) (58).

Secondary prophylaxis

During the pre-HAART era, if maintenance treatment was not administered, cerebral toxoplasmosis recurred in 60%-100% of cases between 6 and 12 months after finishing induction therapy (59). There is still a risk of relapse today, with the result that secondary prophylaxis must be administered. The most efficacious is the combination of pyrimethamine and sulfadiazine, which can be administered daily or on alternate days (AI) (37,60,61). If sulfadiazine cannot be administered, it can be replaced by clindamycin (BI) (37,60), although the activity of this drug against *T. gondii* is lower than that of regimens including sulfadiazine, whose efficacy against *P. jiroveci* is lost (37,60). If the patient cannot tolerate either drug, there is very little experience with alternatives. These patients should maintain the treatment used during the acute phase (9,37,51,62-75): pyrimethamine alone or in combination with atovaquone, azithromycin, minocycline or doxicillin, 5-fluorouracil and clindamycin, and minocycline or doxicillin with sulfadiazine (CIII). Similarly, there is very little experience with dapsone and pyrimethamine (72) or with cotrimoxazole (CIII) (62). Clarithromycin (1 g/12 h) has also been used instead of azithromycin, although it is not recommended given that clarithromycin at these doses has been associated with excessive mortality in a study of prophylaxis against *Mycobacterium avium* complex (MAC) (76). If the patient cannot tolerate prophylaxis with pyrimethamine and sulfadiazine or experiences difficulty combining it with HAART (due to the high pill burden), this regimen can sometimes be replaced by TMP/SMZ (1 double-strength tablet 160/800 mg bid) as long as viral load remains undetectable (CIII) (62).

Withdrawal of prophylaxis

Although few studies are available, it is believed that primary prophylaxis can be suspended when the requisites for withdrawing primary prophylaxis against *P. jiroveci* are met: HAART for at least 6 months, with an immunologic and virologic response for at least 3 months (and a CD4+ T-lymphocyte count above 200 cells/μL with an undetectable viral load) (AI) (77-80). One clinical trial and several cohort studies show that secondary prophylaxis can be suspended when the same criteria for withdrawal as primary prophylaxis are met, if possible, after at least

12 months of HAART and under conditions of strict clinical and neuroradiological monitoring once prophylaxis has been withdrawn (BII) (43,51,77,81-85) (Table 3).

Restarting prophylaxis

As is the case with *P. jiroveci* prophylaxis and with equally consistent arguments, *T. gondii* prophylaxis should generally be restarted when the CD4+ T-lymphocyte count falls below 100 or 200 cells/μL, or if there is an episode of cerebral toxoplasmosis (AIII) (37,48,51).

***Leishmania* species** (Table 2)

Visceral leishmaniasis is one of the most common types of HIV-associated parasitosis in Spain and other Mediterranean countries. It occurs in very immunodepressed patients and its prevalence varies according to the presence of *Leishmania infantum* (causal agent) in the reservoirs (canids in our setting). There is evidence that HAART has modified the incidence of visceral leishmaniasis (86-88) and reduced the number of relapses in HIV-infected patients (86,89). However, there may be relapses in patients whose CD4+ T-lymphocyte count remains low despite HAART (89).

Prevention of exposure to the pathogen

Leishmaniasis is probably transmitted from person to person by exchanging syringes (88,90), this is yet another argument in favor of warning against this practice (CIII). Furthermore, in areas where canine reservoirs present a high prevalence of infection, dogs should be avoided as pets (CIII).

Primary prophylaxis

No primary prophylaxis has been established for this infection.

Secondary prophylaxis

During the pre-HAART era, the accumulated recurrence rate after a first episode of correctly treated visceral leishmaniasis was 60% at 6 months and 90% at 12 months (90,91). Today, the risk of relapse after a cured initial episode is not uncommon in the management of these patients. However, this risk has fallen significantly with the complete administration of anti-

Leishmania induction treatment followed by a secondary prophylaxis regimen, together with HAART, especially if this is accompanied by optimal control of viral replication and sufficient immune recovery (increased CD4+ T-lymphocyte count to >100 cells/μL) (BII) (92,93). The value of secondary prophylaxis in HIV-infected patients has been proven in a Spanish multicenter prospective randomized study that compared the efficacy of amphotericin B lipid complex (3 mg/kg/d, every 21 days) with a control group. The intention-to-treat analysis at 12 months showed that 50% of the patients who received prophylaxis were free of relapse compared with 22% in the control group (94) (BI). Observational studies have also evaluated liposomal amphotericin B in different regimens (95,96). In a Spanish study including 17 patients, 79% were disease-free after 12 months of follow-up (96). The dose and posology of liposomal amphotericin in secondary prophylaxis of leishmaniasis has not been clearly defined, and ranges from 3 to 5 mg/kg/d every 14, 21, or 28 days (Table 2) (BII). One nonrandomized retrospective study found that secondary prophylaxis with a monthly dose of 850 mg of pentavalent antimony (Glucantime) reduced the frequency of relapse compared with historic controls and a control group treated with allopurinol (91), findings that have not been compared in prospective studies. Miltefosine is a recently introduced oral drug that has proven to be efficacious as suppressive maintenance therapy in experiments on animals with cellular immunity (97). It has also proven to be as effective as amphotericin B for the treatment of visceral leishmaniasis in patients with(out) HIV infection (98,99), although there is very little experience in HIV-infected patients in the acute phase and on maintenance therapy. The recommended dose is 100 mg/d orally (CIII). Monthly intravenous pentamidine (300 mg) could be used as an alternative in cases of intolerance to amphotericin and/or antimonials, or in cases of leishmaniasis that is refractory to this or other drugs (CIII) (100). There is no experience with intravenous paromomycin in secondary prophylaxis (101).

Withdrawal of prophylaxis

There are no clear recommendations for the withdrawal of secondary prophylaxis against this pathogen, although it could be a viable option in patients who manage to remain relapse-free for at least 6 months and who have a CD4+ T-lymphocyte count greater than 200 cells/μL (preferably 350 cells/μL) and an undetectable viral load with HAART (102), as well as a negative PCR for *Leishmania* (if possible) in blood or antigen in urine (CIII) (103,104) (Table 3).

Other parasites (Table 2)

Cryptosporidium species

Cryptosporidium is an intracellular protozoan that produces diarrhea in animals and humans. Of the known species, *C. parvum* and other species (*C. muris, C. meleagridis*) infect humans (105). The parasite is acquired through contaminated food and water in the digestive tract and by contact with infected humans or animals. It causes chronic diarrhea that is refractory to treatment in HIV-infected patients with a CD4+ T-lymphocyte count of less than 100 cells/μL. Its frequency varies between 10% and 15% in the west and up to 50% in developing countries (106,107). A lower number of patients present biliary involvement. In order to prevent cryptosporidiosis, the patient must be told about the ubiquitous nature of the parasite, especially in raw food (eg, green vegetables, oysters), water, and excrement. Furthermore, contact with infected patients should be avoided. If this is not possible, extreme hygiene measures should be taken (BIII) (25,37). There is no effective chemoprophylaxis for this infection (25,37). It has been suggested that prophylaxis for MAC with rifabutin or clarithromycin could reduce its incidence, although the data are not conclusive (108,109).

Microsporidia

Microsporidiasis has been the most common cause of chronic diarrhea in severely immunodepressed patients with no identifiable pathogen by traditional methods (110). The route of transmission has not been clarified and its prevalence is not well known, given the difficulty in diagnosing this condition. We have found it in 22% of AIDS patients with chronic diarrhea (111). Most episodes are caused by *Enterocytozoon bieneusi* and less commonly by *Encephalitozoon intestinalis*, which, in turn, can produce systemic infections. There is no chemoprophylaxis for this infection (25,37). Prolonged therapy with albendazole can control symptoms (9).

Isospora belli

*Isospora bell*i was a cause of chronic diarrhea during the first years of the AIDS epidemic, but it has almost completely disappeared thanks to prophylaxis with TMP-SMZ (37,112,113). After a case of Isospora infection, secondary prophylaxis with TMP-SMZ should be started (37,114) (BII); if the patient is intolerant to the drug, ciprofloxacin is an alternative, although it is somewhat less effective (114) (BII).

PROPHYLAXIS OF INFECTIONS CAUSED BY FUNGI

Candida species (Table 4)

Prevention of exposure to the pathogen

Oropharyngeal candidiasis is the most common opportunistic infection in HIV-infected patients. *Candida albicans*, the main pathogen in this mycosis, is a commensal of the human digestive tract; therefore, we cannot propose measures to prevent exposure.

Primary prophylaxis

Primary prophylaxis is not recommended for this mycosis (DII).

Secondary prophylaxis

Oropharyngeal and esophageal candidiasis respond very well to systemic antifungal agents. However, in advanced immunodepression, almost 80% of patients relapse during the first 3 months after completing treatment. Different studies have shown that fluconazole or itraconazole in solution reduce the frequency of relapses. However, systematic use is not recommended, given that the incidence of these infections has fallen dramatically with HAART, they are not severe, there is little risk of developing invasive disease, they are easily diagnosed, and they respond well to treatment (DII). As for the possibility that secondary prophylaxis with fluconazole favors azole-resistant strains of *Candida*, several controlled studies have shown that patients who receive secondary prophylaxis with fluconazole do not have a greater incidence of oropharyngeal and/or esophageal candidiasis to this drug than those who only receive treatment for the episodes (115-117). HAART is actually the best strategy for preventing mucosal candidiasis (AII) (118). When HAART fails and relapses are frequent, secondary prophylaxis with daily doses (100-200 mg) or intermittent doses (200 mg 3 times per week) of fluconazole can be considered (CIII) (115,119). Some patients eventually develop azole-resistant candidiasis and require chronic suppressive therapy with amphotericin B (CIII) (37). There is little experience with the new azoles (voriconazole and posaconazole) or the echinocandins (caspofungin, micafungin, anidulafungin) in this setting.

Cryptococcus neoformans (Table 4)

Prevention of exposure to the pathogen

Cryptococcosis is the most severe mycosis in HIV-infected patients. There are no known effective measures to prevent it, despite the fact that in most cases the fungus is known to penetrate the body via the respiratory tract. Nevertheless, and although most episodes are produced by reactivation of latent infections, it is prudent to avoid frequent contact with birds, especially pigeons, whose depositions often contain this fungus.

Primary prophylaxis

Several studies have shown a reduction in the risk of cryptococcosis with different daily or weekly doses of fluconazole, although primary prophylaxis for this mycosis is not recommended in developed countries for the following reasons: a) its incidence is relatively low; b) it does not improve survival (119,120); c) it is very expensive; d) it can favor the development of resistant strains; and e) the best prophylaxis is the increase in CD4+ T-lymphocyte population induced by HAART (DI). On the other hand, in areas with a high incidence of cryptococcosis (Sub-Saharan Africa, Southeast Asia, and some countries in Latin America), it seems reasonable to recommend primary prophylaxis with fluconazole in patients with less than 100 CD4+ T lymphocytes/µL who are not taking HAART or whose therapy regimen has failed (121,122). In these areas, given the high frequency of cryptococcosis as an immune reconstitution syndrome, it could prove useful to test for cryptococcal antigen before starting HAART in order to diagnose and treat subclinical infections that could cause this syndrome (123).

Secondary prophylaxis

During the pre-HAART era, AIDS-associated relapses of cryptococcosis were very common after induction treatment, and different studies have shown the efficacy of secondary prophylaxis in preventing them. It was later observed that patients who experience immune recovery with HAART are at a considerably lower risk of a relapse of cryptococcosis (124,125). In any case, after treatment of the acute phase, all patients must receive secondary prophylaxis. The regimen of choice is fluconazole at 200 mg/d, which reduces the frequency of relapses to 2-4% (AI) (126). The alternatives are amphotericin B (1 mg/kg/wk), with a 17% relapse rate (126), and itraconazole (200 mg/d), with a 23% relapse rate (127). In this setting, there is little experience with lipid formulations

of amphotericin B or the new azoles (voriconazole or posaconazole). The echinocandins are not active.

Withdrawal of prophylaxis

One clinical trial (128) and one cohort study (129) indicate that the withdrawal of secondary prophylaxis can be carried out safely in patients who are asymptomatic and have a CD4+ T-lymphocyte count greater than 100 cells/μL for at least 3-6 months and an undetectable plasma viral load, with no need for a negative result in testing for the cryptococcal antigen (BII). After secondary prophylaxis is withdrawn, patients must undergo periodic clinical and analytical monitoring. Prophylaxis should be resumed if there is a fall in the CD4+ T-lymphocyte count or when a negative cryptococcal antigen reverts to positive (BIII) (37).

Other Fungi (Table 4)

Histoplasma capsulatum

Histoplasma capsulatum is the most common cause of mycosis in patients with AIDS. In endemic areas, histoplasmosis can be prevented by avoiding risk activities such as visits to caves, exposure to environmental dust, tree felling, cleaning henhouses, and demolition of buildings (CIII). Primary prophylaxis with itraconazole at 200 mg/d is only indicated in patients with a CD4+ T-lymphocyte count of less than 150 cells/μL and a high risk of occupational exposure, or in those who live in hyperendemic areas where the incidence of histoplasmosis is more than 10 cases per 100 patient-years (AI) (130,131). In Spain, this approach could be proposed for HIV-infected immigrants from endemic areas. For secondary prophylaxis, itraconazole is recommended at 200 mg/12 h (AII) (132). In patients whose immune system recovers with HAART, secondary prophylaxis can be withdrawn if the CD4+ T-lymphocyte count is more than 150 cells/μL for at least 6 months (CIII) (131,133).

Penicillium marneffei

Penicilliosis is endemic in Southeast Asia and responds well to amphotericin B or itraconazole. Although this infection seems to be related to exposure to soil, the reservoir and portal of entry of the fungus are unknown; therefore, specific recommendations to avoid contagion cannot be made. In endemic areas, primary prophylaxis with itraconazole reduces the incidence of penicilliosis in

severely immunodepressed HIV-infected patients (especially those with a CD4+ T-lymphocyte count less than 100 cells/μL), although this intervention has not been shown to prolong patient survival (CII) (134). Relapses after treatment are very common; therefore, secondary prophylaxis with itraconazole at 200 mg/d has been recommended by one prospective, randomized, placebo-controlled study that shows its efficacy (135) (AI). There is evidence that the withdrawal of secondary prophylaxis is safe in patients on HAART with a CD4+ T-lymphocyte count greater than 100 cells/μL for at least 6 months and an undetectable viral load (136,137).

Miscellaneous

Secondary prophylaxis against coccidioidomycosis should be with fluconazole (400 mg/d), itraconazole (200 mg/12 h), or amphotericin B (1 mg/kg/wk) (AII) (138). There are no studies on secondary prophylaxis for aspergillosis, blastomycosis, or paracoccidioidomycosis (37).

PROPHYLAXIS OF INFECTIONS CAUSED BY VIRUSES

Cytomegalovirus (Table 5)

Before the introduction of HAART, approximately 45% of patients coinfected with HIV and cytomegalovirus (CMV) developed CMV disease. Furthermore, 22% of coinfected patients with a CD4+ T-lymphocyte count less than 100 cells/μL developed CMV retinitis within 2 years. This severe and disabling condition often involves relapses and complications that could lead to a loss of vision (139).

HAART dramatically reduced the incidence of this disease and brought about a spectacular change in its natural history, with prolonged survival and a reduction in the number of relapses and complications (140-142). In fact, one large-scale randomized clinical trial comparing 3 anti-CMV treatments revealed that the frequency of new disease was lower in patients who had received protease inhibitors, irrespective of the therapeutic group they were assigned to (143). Therefore, we can say that, today, HAART plays a very important role in the prophylaxis and treatment of CMV disease, regardless of the antiretroviral drug the patient is taking. One adverse effect that must be borne in mind in patients with CMV retinitis who initiate HAART is vitreitis, which can be caused by immune recovery and occasionally lead to a considerable loss of vision (141,144,145).

Prevention of exposure to the pathogen

Patients who belong to population groups with a low frequency of CMV infection and who cannot be considered seropositive for this virus must undergo serology testing for CMV. These patients include those who have never been intravenous drug users and men who have not had homosexual relations (BIII). Patients with a negative CMV serology result must not receive blood derivative transfusions from CMV-positive patients (B3) and must avoid unprotected sex (AII). Adopting personal hygiene measures such as hand washing reduces the risk of acquisition. Measures of this type are particularly important in settings such as kindergartens, where the risk of contagion by CMV is greater (BIII) (25).

Primary prophylaxis

Two prospective, randomized, double-blind, controlled clinical trials have examined primary prophylaxis with oral ganciclovir in HIV/CMV-coinfected patients (146,147). The first (>700 patients with a maximum CD4+ T-lymphocyte count of 50 cells/μL or 100 cells/μL and a history of infection indicating AIDS) revealed that the accumulated incidence of visceral CMV disease at 12 months was 14% in the ganciclovir group and 26% in the placebo group, and that the accumulated incidence of CMV retinitis was 12% and 24%, respectively (relative risk 0.49, $p < 0.001$); no differences in mortality were detected (146). The second (>900 patients) differed from the first in 2 important respects: the inclusion criterion of a baseline CD4+ T-lymphocyte count was no higher than 100 cells/μL, and, when the study was in progress (after the results of the first one were known), it was accepted that all the patients should have access to ganciclovir. No differences were found with respect to the incidence of CMV disease and mortality until the date the study was modified or until completion. However, more adverse effects, especially neutropenia, were observed in the ganciclovir group than in the placebo group (147).

Primary prophylaxis with oral ganciclovir for CMV disease is not recommended due to the contradictory results on its efficacy, its zero impact on survival, the possibility of resistance, toxicity, and cost (CI). The best preventive strategy is administration of HAART to restore the immune system (AI).

It must be remembered that patients who start HAART with a CD4+ T-lymphocyte count of less than 50 cells/μL undergo a risk period of 3 to 4 months during which they can have CMV retinitis, even with a CD4+ T-lymphocyte count greater than 100 cells/μL. In such cases, antigenemia studies or PCR for CMV can be carried out, given that the probability of developing CMV retinitis is 38% for patients with a positive test result compared with 2% for patients with a

negative test result ($p < 0.001$) (CII) (140). Patients with a positive test result should undergo ophthalmoscopy every 2 or 4 weeks during the first 3 months for the early detection of the disease (CIII). In addition, several studies report a worse clinical outcome in patients with CMV viremia, regardless of CD4+ T-lymphocyte count or viral load (148).

In these cases, it seems sensible to administer early anti-CMV treatment, an intervention that was evaluated in a randomized clinical trial (study ACTG A5030) (149). This study included HIV-infected patients with a positive serology result for CMV and a CD4+ T-lymphocyte count of less than 100 cells/μL despite taking HAART. All the patients had a checkup every 2 months with PCR for CMV and every 6 months with an eye examination. Those in whom CMV viremia was detected were randomized to receive valganciclovir or placebo. No clinical benefit was found in early treatment with oral valganciclovir compared with placebo in these patients, who were already receiving HAART, although we must remember that the study was suspended due to the low number of patients included (only 23 were compared in each arm), and that previous studies have stressed that early treatment could be cost-effective (150).

Some authors advise early detection of the disease in CMV-positive patients with a CD4+ T-lymphocyte count lower than 50 cells/μL by periodic eye examinations every 3-4 months after starting HAART (CIII).

Secondary prophylaxis

The therapeutic strategy to be adopted in CMV retinitis has been well known for years: it involves an induction phase aimed at controlling the infection followed by a maintenance phase to prevent or delay relapses (139,151). For the second indication, we have intravenous drugs such as ganciclovir, foscarnet, and cidofovir, all of which have never been compared with each other and have a different toxicologic profile. The oral options are ganciclovir and valganciclovir, which is the ester of the valine of ganciclovir. The bioavailability of oral ganciclovir is very poor, thus making it less efficacious than intravenous ganciclovir and increasing the pill burden (152). Valganciclovir, however, is metabolized by enzymes from the digestive tract and is converted almost 100% to ganciclovir (153). A randomized open-label clinical trial involving 160 patients with AIDS and recently diagnosed CMV retinitis revealed that oral valganciclovir is as effective as intravenous ganciclovir in induction treatment and that it is very comfortable and efficacious in the maintenance phase (143). Topical treatment involves the ganciclovir implant (unrivaled in the treatment of CMV retinitis), although before HAART, concomitant oral ganciclovir was necessary to prevent disease in the contralateral eye and extraocular disease (154). A recent study comparing the ganciclovir implant with(out) oral ganciclovir and intravenous ganciclovir

revealed that, in the subgroup of patients treated with HAART, the incidence of relapse or new disease was low and of the same magnitude in all the groups (155). Topical options also include fomivirsen, an intravenous antisense oligonucleotide that inhibits CMV replication. In the maintenance phase, the dose is 330 µg per month. The undesirable effects are transitory increased ocular pressure and inflammation that can be reversed with topical corticosteroids. At present, these are indicated for the treatment of relapses (156).

Given the many options for secondary prophylaxis of CMV retinitis, the drug best adapted to the patient should be chosen (157). Its proven efficacy and ease of use make oral valganciclovir the drug of choice (AI).

Withdrawal of secondary prophylaxis

In patients whose immune system recovers with HAART, secondary CMV prophylaxis may be withdrawn (158,159). Four studies on the withdrawal of secondary prophylaxis have been published. The first included 14 patients, and no relapses were detected after a median follow-up of 16.4 months (160). In the second study, 3 out of 22 patients who suspended secondary prophylaxis had a relapse of CMV retinitis (161). In 3 cases, HAART had failed and they had a CD4+ T-lymphocyte count of less than 50 cells/µL at the time of the relapse. The third study was multinational and included 48 patients of whom 2 had a relapse of CMV disease: retinitis in 1 case and peripheral neuropathy in the other. Surprisingly, the CD4+ T-lymphocyte counts at the time of the relapse were 352 cells/µL and 106 cells/µL, respectively (162). Finally, in a fourth study (multicenter from Spain), secondary prophylaxis was withdrawn from 36 patients. After a median follow-up of 90 weeks, there was no reactivation or progression of retinitis in the 35 patients who had a good response to HAART. However, in 1 case, relapse of retinitis was reported 44 weeks after having suspended prophylaxis while the patient was experiencing immunologic failure. At the time of the relapse, the CD4+ T-lymphocyte count was 62 cells/µL (163).

Taken together, the results of these 4 studies support the safety of interrupting secondary anti-CMV prophylaxis in patients with AIDS and inactive CMV retinitis who experience an increase in their CD4+ T-lymphocyte count with HAART. However, we do not know which is the CD4+ T-lymphocyte count at which it becomes safe to withdraw prophylaxis. If the data from all 4 studies are combined (79 patients), we can see that the median CD4+ T-lymphocyte count at withdrawal was 269 cells/µL with an interquartile range of 167-360 cells/µL. More than two-thirds of patients had a CD4+ T-lymphocyte count of more than 200 cells/µL, less than one-third had between 100 and 200 cells/µL, and only 3 patients had less than 100 cells/µL. This allows

us to conclude that withdrawing secondary prophylaxis is a reasonable and safe option in patients with inactive CMV retinitis who have a good response to HAART characterized by a CD4+ T-lymphocyte count of more than 200 cells/μL for at least 6 months (BII). In some cases, withdrawal of secondary anti-CMV prophylaxis can be considered in patients with between 100 and 200 cells/μL, given that most of those who relapsed in the studies discussed above had less than 100 cells/μL (CIII). After withdrawal, patients can be monitored with periodic determinations of CD4+ T-lymphocyte counts (BIII). For those who experience immunologic failure, we can turn to frequent ophthalmologic checkups or resumption of secondary prophylaxis depending on the risk of an irrecoverable loss of vision (BIII) (Table 3).

Other Viruses (Table 5)

HIV-infected patients often have mucocutaneous and digestive tract infection caused by the herpes simplex virus (HSV), although prophylaxis is not recommended against this virus (DIII). Relapses respond well to treatment; therefore, it is not advisable to start suppressive treatment except in the case of genital herpes with severe and/or frequent relapses (≥ 6 recurrences per year) (AI). In this case, the recommendation is as follows in HIV-infected patients: acyclovir (400-800 mg bid or tid), or famciclovir (500 mg bid), or valacyclovir (500 mg bid) (164). In infections by acyclovir-resistant strains of HSV, intravenous foscarnet or intravenous or topical cidofovir should be used (AII). Given that the frequency of relapses falls over time in many patients, withdrawal of the suppressive agent should be evaluated periodically (eg, every year) (BII) (164). An additional advantage for suppressive treatment would be the reduced genital shedding of HIV, as has been observed in African women taking valacyclovir (165).

HIV-infected patients should not be vaccinated against the varicella-zoster virus (VZV), although people who live with them should, in case they are susceptible to VZV (those who do not have specific IgG antibodies) (BIII). HIV-infected patients who are susceptible to VZV must avoid contact with people infected by zoster or varicella (AII). Specific immunoglobulin within 96 hours of contact is recommended in susceptible persons (AIII). A cheaper and logistically simpler option is oral acyclovir (CIII), although the efficacy of this measure has only been proven in immunocompetent children after exposure in the home (25,166).

Vaccination against hepatitis A virus (HAV) is recommended for all HIV-infected patients who do not have anti-HAV IgG antibodies with the best CD4+ T-lymphocyte counts possible (AIII) (25,167). The response rate is approximately 50% (168). One French clinical trial (HEPAVAC), which compared 3 doses (0, 4, and 24 weeks) with 2 conventional doses (0 and 24 weeks) in patients with CD4+ T-lymphocyte counts of between 200 and 500 cells/μL revealed a greater

rate of seroconversion in the 3-dose arm (71% *vs.* 58%, $p = 0.20$)—this was only significant in patients with less than 350 cells/μL (73% *vs.* 39%, $P=.02$) (169). Therefore, 3 doses can be recommended in patients with a CD4+ T-lymphocyte count of less than 350 cells/μL (BI). Vaccination against HAV should be administered to all patients with chronic liver disease caused by HCV, given that there is a risk of fulminant hepatitis and death in HAV superinfection (170).

Vaccination against hepatitis B virus is also recommended in all HIV-infected patients who are negative for total anti-HBc and HBsAg and who have not already been vaccinated (AIII). The standard vaccination regimen against HBV is 3 injections (0, 1, and 6 months) with 20 μg of antigen (25,167). However, the immunogenic response with the standard regimen of the HBV vaccination is lower in HIV-infected patients and is related to the CD4+ T-lymphocyte count. The response to the HBV vaccination in immunodepressed patients can improve with higher doses of antigen (171), more doses (172,173), or immunomodulators (174,175). In a double-blind, placebo-controlled clinical trial comparing 3 standard doses (20 μg) with a double dose (40 μg) of HBV vaccine in 210 HIV-infected patients (171), a greater response was observed in patients who received the double dose, although it was only significant in those who had less than 350 cells/μL. In another study involving 32 patients, an additional dose of vaccine increased the proportion of responders, albeit only marginally (172). However, there was a 6-fold increase in the mean antibody titer of the responders. In a third study including 9 patients who did not respond to the conventional regimen and for whom the dose of vaccine was doubled, a response was observed in 7 (173). Finally, in a double-blind, placebo-controlled clinical trial including patients who did not respond to conventional vaccination, Cooper et al (174,175) showed that the group of patients vaccinated with a double dose and for whom an immunomodulator (CPG 7909) was prescribed had a significantly greater response than the group that received only a double dose ($P<.05$). However, the immunomodulator has not yet been marketed. Therefore, this expert panel recommends administering a regimen consisting of 3 doses of HBV vaccine (0, 1, and 6 months) with a double quantity of antigen (40 μg instead of 20 μg) (BI). As an alternative, a 4-dose regimen could be applied (0,1,2, and 6 months) with double the quantity of antigen (40 μg), as recommended in patients undergoing dialysis or in immunosuppressed patients (CIII) (176).

As a general rule, patients should be vaccinated when their CD4+ T-lymphocyte count is as high as possible or, when there is considerable immunosuppression, vaccination should start once HAART has been initiated and the plasma viral load is negative (CIII).

The recombinant vaccine with fixed doses of HAV and HBV antigen (*Twinrix*®) should not be administered to HIV-infected patients, since the recombinant dose of HBV antigen is not the recommended one (DIII) (167,176).

Little is known about the frequency and consequences of coinfection by HIV and the influenza virus. Some retrospective studies have found that influenza has greater morbidity and mortality in HIV-infected patients than in the general population. However, there is evidence that hospital admissions due to influenza have fallen significantly since the introduction of HAART, and are now at levels that are similar to those of other high-risk population groups (177). Therefore, given that anti-influenza vaccination can produce a protective antibody titer in HIV-infected patients, it is recommended that they all (even pregnant women) receive the vaccination annually (AIII) (25,178).

HAART is the only intervention that can prevent progressive multifocal leukoencephalopathy and interrupt the lytic cycle of the JC virus (9,25,37). Recent data show that mortality has fallen by about as much as 30% and that neurological function improves in most patients. Mortality is greater in patients whose CD4+ T-lymphocyte count is less than 100 cells/μL, and the prognosis is worse in patients who develop this condition as a result of failed HAART (9,179).

PROPHYLAXIS OF INFECTION BY MYCOBACTERIA

Mycobacterium tuberculosis (Table 6)

HIV infection is the most important risk factor for progression of latent tuberculosis to active tuberculosis, and it favors progression to tuberculosis after recent infection (180,181). Therefore, the number of reports of tuberculosis has increased significantly in areas with a high prevalence of HIV infection. Fortunately, the introduction of HAART has led to a reduction in the number of cases of coinfection with HIV and tuberculosis in several countries (182), although the incidence remains greater than in the non-HIV-infected population, irrespective of the baseline characteristics of the patients (183,184).

Prevention of exposure to the pathogen

HIV-infected individuals must be informed about how tuberculosis is transmitted, the risk they have of developing it, and the importance of the tuberculin skin test. Where possible, they should try to avoid working in high-risk areas such as prisons, homeless shelters, and hospital units for patients with active tuberculosis (BIII). They should also be made aware of how important it is to

consult their doctor when they have symptoms that are suggestive of tuberculosis or after having had contact with a person suffering from active pulmonary tuberculosis (BIII).

Prophylaxis (treatment of latent tuberculosis infection)

Evaluation of the risk of developing tuberculosis

The tuberculin test must be carried out after the first visit (AI). In recent years, 2 methods have been marketed to determine interferon-γ in peripheral blood. These are more specific than the tuberculin test (they avoid the false positives generated by BCG and environmental mycobacteria) and more sensitive (they avoid the false negatives observed in anergic patients). The United States Food and Drug Administration has approved QuantiFERON-TB Gold in-tube™ and the EMEA has approved T-SPOT.TB™. Some studies have analyzed both methods in HIV-infected patients (185-188). Although they have not been compared with each other, T-SPOT.TB clearly seems to be more sensitive than QuantiFERON in immunodepressed patients (189,190). However, it is still not possible to recommend it for routine use in this population as a replacement for the tuberculin skin test (CIII).

Several years ago, cutaneous anergy testing was also recommended; however, several studies have shown its scant consistency and reliability, as well as the lack of benefit of chemoprophylaxis in anergic patients, especially if they can receive HAART (191-194). Therefore, these tests are not currently recommended as an aid to decision making in latent tuberculosis infection (DII). Studies are under way with interferon-γ assays in order to determine their diagnostic yield in anergic HIV-infected patients. There is no evidence in favor of repeating the tuberculin skin test as a measure of immune reconstitution after HAART. The test should be repeated to evaluate the risk of conversion in individuals who live in areas where there is a high risk of transmission of active tuberculosis (BIII).

Two groups of patients who must definitely receive treatment for latent tuberculosis infection are those who have a positive tuberculin skin test result (≥ 5 mm) (AI) and those who have had close contact with a smear-positive individual (BII). We must remember that the risk of developing tuberculosis is still high in patients with a positive tuberculin test result and high CD4+ T-lymphocyte count, and in patients who are on antiretroviral therapy (195,196). The risk of tuberculosis in anergic patients varies from study to study; therefore, it is impossible to make universal recommendations (197,199). Prophylaxis is indicated in patients at greater risk of infection with *M. tuberculosis*, for example, those who have already had a positive tuberculin skin test result, those who have been in close and prolonged contact with people who have active

tuberculosis, and those who have spent long periods in prison without receiving appropriate prophylaxis (CIII). Before starting chemoprophylaxis, it is important to rule out active tuberculosis by clinical evaluation and chest radiograph, and even the slightest suspicion of tuberculosis requires microbiological studies to be carried out too.

Drugs and regimens

In these patients, antituberculosis chemoprophylaxis has been efficacious with the following drugs: isoniazid daily or 2 days/week for 6-12 months (200-205), rifampicin with pyrazinamide daily (204,206) or on alternate days (207) for 2 or 3 months, and isoniazid with rifampicin for 3 months (AI) (192,204,205,208,209). The latest updates of the guidelines of the American Thoracic Society and the Centers for Disease Control and Prevention recommend regimens with isoniazid for 9 months and advise against regimens lasting 6 or 12 months (210). Additionally, direct supervision of prophylaxis is recommended when it is administered on alternate days—especially in short regimens—and also when 6-month regimens with isoniazid are used in very immunodepressed persons. There are no data to indicate that administering isoniazid for 12 months or for life confers additional advantages; therefore, these strategies are not recommended (EIII).

We must remember that in regimens with rifampicin and pyrazinamide there have been reports of severe liver toxicity—fatal in some cases—mainly in non-HIV-infected patients, although there have also been reports in HIV-infected patients. Therefore, the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America advise against using this regimen (211). Nevertheless, clinical trials have not shown regimens with rifampicin and pyrazinamide to be associated with a greater incidence of adverse effects or global mortality than regimens with isoniazid (204,207,212). Evidence of severe liver toxicity in HIV-infected patients who received 2 months of rifampicin and pyrazinamide and that laboratory monitoring may not be sufficient to prevent it (213), together with the introduction of short regimens that are efficacious and well tolerated, mean that this regimen cannot be recommended at present in HIV-infected patients with tuberculosis (DI).

At present, the Tuberculosis Trials Consortium (TBTC) of the CDC is evaluating the efficacy and safety of combining weekly isoniazid and rifapentine for 3 months compared with daily isoniazid for 9 months (study 26) in a noninferiority trial that has randomized 8000 patients, some of whom are HIV-infected. This may lead to a change in the regimen of choice (214).

Rifampicin can be used for 4 months as monotherapy against isoniazid-resistant *M. tuberculosis* infection, or in patients who experience intolerance or toxicity (25) (CIII). A short regimen with

rifampicin and pyrazinamide could also be considered, although the above information leads us to believe that it would be prudent to avoid this regimen when an equally effective regimen can be used. There are no firmly established regimens for contacts with patients who have multiresistant tuberculosis, although a combination of pyrazinamide with ethambutol or ofloxacin for 12 months has been suggested to be effective in most cases (CIII).

Interactions with antiretroviral drugs

Isoniazid can be administered with any combination of antiretroviral drugs. Rifampicin must not be administered simultaneously with a protease inhibitor (except ritonavir), whether or not it is boosted with ritonavir. All nucleoside analogues, ritonavir as the only protease inhibitor (215), and the non-nucleoside analogues nevirapine and efavirenz (216-220) can be administered with rifampicin. Rifabutin is recommended as an alternative to rifampicin in cases of interaction with antiretroviral drugs; however, it is worth making clear that no clinical studies back this recommendation. When rifabutin is combined with protease inhibitors, the dose of rifabutin must be adjusted, and in some cases, so must that of protease inhibitors. Given the absence of efficacy studies on prophylaxis and the need to supervise administration of rifabutin and protease inhibitors when administered together, tuberculosis should not be treated with rifabutin (DIII).

Rifampicin increases the metabolism of methadone in the liver and usually leads to withdrawal symptoms in patients on an opiate detoxification program. It is important to warn the patient and the dispensing center about this undesirable effect and increase the dose of methadone as much as necessary.

BCG vaccination

This vaccine is contraindicated in HIV-infected individuals due to the controversial nature of its efficacy and the risk of documented disease by BCG (EIII) (221).

Maintenance treatment

Maintenance treatment is not recommended in patients with disseminated tuberculosis (EIII).

***Mycobacterium avium* complex (MAC)** (Table 6)

Prevention of exposure to the pathogen

MAC is a ubiquitous organism (including water and food) and there are no known efficient measures to prevent it from being acquired.

Primary prophylaxis

Administration of clarithromycin (500 mg/12 h) or azithromycin (1200 mg, once per week) prevents disseminated MAC infection (AI) (222,223). However, this strategy is not recommended in our setting, given the low incidence of MAC infection even before the introduction of HAART (DIII). In a cohort study carried out in Spain during the HAART era that included 200 patients with a CD4+ T-lymphocyte count less than 50 cells/µL, the incidence of disseminated infection by MAC was 2 cases per 100 patient-years. In special situations, for example in patients with a CD4+ T-lymphocyte count consistently lower than 50 cells/µL and no possibility of receiving HAART, primary prophylaxis with some of the regimens mentioned above could be considered.

Secondary prophylaxis

Patients with disseminated MAC infection should be treated with clarithromycin (or azithromycin as an alternative) and ethambutol for as long as they continue to be severely immunodepressed (AI) (37).

Withdrawal of prophylaxis

Primary prophylaxis can be safely interrupted in patients whose CD4+ T-lymphocyte count manages to stay above 100 cells/µL with HAART and whose viral load remains undetectable for periods greater than 3-6 months (AI) (224). Before the introduction of HAART, it was recommended to continue with lifetime secondary prophylaxis. At present, withdrawal can be considered in patients who maintain a CD4+ T-lymphocyte count above 100 cells/µL for more than 6 months (BII) (81,225-227) (Table 3).

Other bacteria (Table 6)

Streptococcus pneumoniae

In developed countries, HAART has been the most efficient measure in reducing the number of cases of pneumonia in HIV-infected patients (228). Nevertheless, *Streptococcus pneumoniae* bacteremia is still associated with a high level of morbidity and mortality in these patients. One Spanish study showed that the introduction of HAART reduced the incidence of *S. pneumoniae* bacteremia, especially that associated with pneumonia, from 24.1/1000 patient-years to 8.2/1000 patient-years. However, mortality during the HAART era increased from 8% to 26%, owing to comorbid conditions, especially cirrhosis of the liver (229).

There has been some controversy over the recommendation to administer the 23-valent pneumococcal polysaccharide vaccine to HIV-infected patients. One randomized double-blind study carried out in Africa showed no beneficial effect, and there was even an association between the vaccine and a greater risk of pneumococcal disease (230). However, the 6-year follow-up of this study did not show an increase in the incidence of pneumococcal pneumonia and, paradoxically, mortality in the vaccinated patients fell by 16% (231). The question of using this vaccine in Africa, where there is little access to HAART, remains unsolved. Some case-control studies carried out in developed countries with access to HAART, including 2 in Spain (229,232), have shown that the vaccine protects against invasive pneumococcal infection, even in patients with a CD4+ T-lymphocyte count of less than 200 cells/µL.

The 9-valent conjugate vaccine has significantly reduced the incidence of pneumonia and invasive infection in HIV-infected children. Although the Centers for Disease Control and Prevention (CDC) have shown an indirect effect of this vaccine, with a 19% reduction in invasive infections in HIV-infected adults, we lack sufficient adult data. In addition, this conjugate vaccine was not that which is currently available (233,234).

The 23-valent pneumococcal polysaccharide vaccine should be administered to adults and adolescents with a CD4+ T-lymphocyte count greater than 200 cells/µL. It can even be used in patients with lower counts, although the response is not clear (AII). Revaccination may prove necessary every 5 years, although there are no data to support this recommendation.

Furthermore, smoking should be advised against (BII), since several studies have shown that this is an independent risk factor for the development of bacterial pneumonia (235).

Haemophilus influenzae

HIV-infected children should be vaccinated against *Haemophilus influenzae* (Hib) according to the usual vaccination schedule (AI) (25). This vaccine is not indicated or contraindicated in adults.

Neisseria meningitidis

HIV-infected children must be vaccinated against *Neisseria meningitidis* C according to the usual vaccination schedule (AI) (25). There are no specific recommendations for vaccination of adult patients.

Miscellaneous

At present, no primary or secondary prophylaxis is recommended in infections caused by *Salmonella no-typhi*, *Campylobacter* species or *Bartonella* species (EIII).

PROPHYLAXIS OF IMPORTED PARASITIC INFECTIONS

Unlike the opportunistic infections traditionally associated with HIV, in most imported parasitoses there is scant information on the need for chemoprophylaxis. In general, the best preventive approach is to avoid contact with the pathogen, together with early diagnosis and treatment. Except for very specific cases, parasites do not produce asymptomatic latent chronic infections that are reactivated as a consequence of immunosuppression. Therefore, the concepts of primary and secondary prophylaxis as they are classically applied to opportunistic infections do not correspond directly with most of these parasitoses, although this does not mean that the clinical course cannot be more severe and the response to treatment worse (9).

Measures for the prevention of exposure to imported parasitoses and the vectors that transmit them are summarized in Table 7. If an individual is traveling to areas where these diseases are endemic, the following guidelines are recommended:

- Drink only water that is guaranteed to be safe, and if this is not possible, drink only bottled water.
- Do not eat raw or undercooked food, especially fish, shellfish, meat, eggs, or unsterilized milk. Ensure that salads, green vegetables, and fruit that are consumed raw have been properly washed.
- Do not walk barefoot. Avoid direct contact between the skin and the ground.

- Avoid swimming in rivers or lakes, especially in Sub-Saharan Africa.
- Avoid contact with animals.
- Prevent stings from arthropods that can act as vectors. Use insect repellants (Relec®, Goibi Xtreme®, or Autan Protection Plus®).

Amebiasis (Table 7)

Entamoeba histolytica is a protozoan parasite found throughout the world, although its prevalence is greater in countries with poor hygiene. Patients with HIV infection have not been reported to respond worse to treatment or to have a greater rate of invasive disease than asymptomatic carriers.

Prevention of exposure to the pathogen

Amebiasis is transmitted mainly by drinking water or eating food contaminated with feces that contain cysts, which are quite resistant to chlorine. Transmission can be fecal-oral or from carriers in conditions of poor hygiene. Therefore, the best approach to preventing infection is by correct hygiene and monitoring food and water intake. Enteric isolation is recommended for hospitalized patients.

Primary and secondary prophylaxis

Primary prophylaxis should target cyst carriers, since the risk of developing invasive disease in asymptomatic intestinal carriers is 3-10% per year. Therapy is based on an amebicide that is active in the intestinal lumen (AII) (236,237). Similarly, those patients who suffer from invasive amebiasis, whether intestinal or extraintestinal, should receive an amebicide that is active in the intestinal lumen, since metronidazole eliminates less than 50% of the cysts (AI) (238-241).

Malaria (Table 7)

Malaria is widespread in the tropical and subtropical areas of the world and produces 300 to 800 million cases per year and between 1 and 3 million deaths. It is caused by protozoa of the genus *Plasmodium*: *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi* (the most recently reported). Most deaths are produced by *P. falciparum.* The manifestations are usually more severe in HIV-infected patients, especially pregnant women, and parasitemia is usually worse (242,243).

Prevention of exposure

Malaria is transmitted by hematophagous female mosquitoes of the genus *Anopheles*. They generally bite at night, although some species also bite at dusk and in the early morning. Malaria can also be transmitted by transfusion of infected blood, organ transplants, and contaminated syringes or injection material (eg, intravenous drug users) (244).

Bites by the vector must be prevented, and if this does occur, the parasite must not be allowed to develop. In the first case, insect repellant containing DEET (diethyltoluamide) at concentrations of 30% to 50%, or picaridin, is recommended. These products can be used by pregnant women. Clothes can also be sprayed with repellants containing permethrin, whose effect persists for up to 2 weeks and is resistant to several washes. Mosquito nets impregnated with insecticide are an additional barrier method if the mosquito bites are more likely at night (245).

Primary and secondary prophylaxis

Chemoprophylaxis of malaria aims to prevent or suppress the symptoms produced by the hematic forms of the parasite. It should be taken before, during, and after the stay in the endemic area (AI). The regimen depends on the drug used. The indication for prophylaxis should take into account the itinerary, the probability and frequency of exposure to the parasite, and resistance to antimalarial drugs (241,245,246).

At present, there is little information on possible interactions between antiretroviral drugs and antimalarial drugs (247,248). Given their pharmacokinetic characteristics, there may be interactions between atovaquone and mefloquine and protease inhibitors; therefore, caution should be exercised when administering these agents in combination. In this sense, both lopinavir/r and ritonavir at the doses used to boost the effect of other protease inhibitors can reduce atovaquone levels. To date, it has not been established whether this reduction has clinical consequences or whether it is necessary to modify the dose of atovaquone when administered with these drugs (247). Although significant pharmacological reactions have not been found in the simultaneous administration of mefloquine and indinavir or nelfinavir, mefloquine should be used with caution in combination with other protease inhibitors, especially if they are not boosted with ritonavir, since it could reduce plasma levels (249). Although levels of artemether-lumefantrine (Riamet®) are increased by concomitant use of lopinavir/ritonavir (Kaletra®) (the contrary has not been observed), it does not seem necessary to adjust the dose, except in patients with pre-existing cardiac conduction abnormalities (250).

Correct treatment eradicates parasitization; therefore, asymptomatic latent chronic forms that could be reactivated as a consequence of immunosuppression are eliminated. In some cases, there may be subclinical parasitization, especially in immigrants with partial immunity in the weeks following suboptimal treatment or as a result of an excess immune response (hyperreactive malarial splenomegaly). In these cases, PCR for malaria is very useful, since a thick smear cannot detect parasitemia. Once diagnosed, malaria must be treated.

American Trypanosomiasis or Chagas Disease (Table 7)

American trypanosomiasis is an endemic parasitosis from the continent of America that is produced by the protozoan parasite *Trypanosoma cruzi*. It is transmitted by hematophagous chinches of the Reduviidae family (assassin bugs of the subfamily *Triatominae* such as vinchucas, kissing bugs, or chipos) that, once infected, transmit the parasite for life. Other reported routes of infection are blood transfusion, organ transplants, placental transmission, and ingestion of fruit juices and sugar cane juice (251).

Prevention of exposure to the pathogen

In domestic and semidomestic settings, the chinches tend to bite during the night. Daytime insect repellants should be complemented by insecticide-impregnated mosquito nets at night, especially in rural areas or areas with high vector densities. In addition, blood for transfusion and organ donors must be monitored.

Primary and secondary prophylaxis

Chagas disease behaves in a similar way to other opportunistic infections in HIV-infected patients: its manifestations are more severe, the first often being reactivation in patients with a CD4+ T-lymphocyte count of less than 200 cells/μL, and the response to treatment is poorer (9,252-256). There is very little experience with treatment or chemoprophylaxis, and as the disease becomes more chronic, the response to treatment is worse. In addition, there is no reliable method of evaluating the response, and the available drugs have not proven unequivocally effective in chronic infection. Nevertheless, given the severity of the cases reported (257,258), and the fact that it is generally indicated for non-HIV-infected patients, it seems reasonable to administer prophylaxis in coinfected patients with *T. cruzi* infection verified by PCR (AIII). The duration has not been established, although some authors propose prolonging treatment for twice the usual period (120 days).

There is even less information on secondary prophylaxis. Given the similarities between Chagas disease and other opportunistic infections, as well as its clinical manifestations, benznidazole could be considered (CIII). There are no recommendations on duration or when it should be suspended, but it seems reasonable to continue prophylaxis for as long as the CD4+ T-lymphocyte count does not exceed 200-350 cells/μL and the viral load is undetectable with HAART (at least 6 months).

African Trypanosomiasis (Sleeping Sickness) (Table 7)

This parasitosis is endemic in Sub-Saharan Africa and is transmitted by the tsetse fly (*Glossina* species), although it can also be transmitted by contaminated blood entering the body through the proboscis of horseflies or in laboratory accidents. It is produced by 2 morphologically indistinguishable subspecies of trypanosoma: *Trypanosoma brucei rhodesiense* and *T. brucei gambiense*. The most severe and rapidly evolving forms of the disease are associated with the former.

Prevention of exposure to the pathogen

Cases of infection by *T. brucei* are very rare among travelers, although there have been reports of infection in individuals who have been on pleasure safaris, mainly in east Africa. The tsetse fly is attracted by dark colors and bites through light clothing. It is not affected by insect repellants, and the best preventive measure is to avoid the areas where it is usually found.

Primary and secondary prophylaxis

Although there does not seem to be an epidemiological association between African trypanosomiasis and HIV infection, it does seem that the response to treatment could be worse (259,260). We must also remember that, in the case of *Trypanosoma brucei gambiense*, the symptoms can present even some years after infection. Rather than administer primary prophylaxis, potentially infected patients should be diagnosed early and specific treatment started (AI-AII) (9,241,261-266). There is no information on whether secondary prophylaxis is necessary.

Cyclosporiasis (Table 7)

Cyclosporiasis is produced by parasitization of the proximal portion of the small intestine by *Cyclospora cayetanensis*. In HIV-infected patients, the clinical picture is similar to that produced by *Cryptosporidium* species, with recurrences if secondary prophylaxis is not started.

Prevention of exposure to the pathogen

Transmission is fecal-oral by ingestion of food or bathing in contaminated water. The pathogen is resistant to chlorine and prevention of exposure is by adequate hygiene and monitoring of water and food intake.

Primary and secondary prophylaxis

Primary prophylaxis is not indicated. Secondary prophylaxis is with cotrimoxazole (AII) (114,267) or alternatively with ciprofloxacin (BII) (114).

Strongyloidiasis (Table 7)

Strongyloidiasis is a helminthiasis of the duodenum and proximal part of the jejunum produced by *Strongyloides stercoralis*. It is found throughout the world, mainly in tropical and temperate areas, and is associated with poor sanitation. Although it was initially considered an opportunistic infection, it is associated mainly with the corticosteroid-induced immunosuppression (268,269) and infection by human T-lymphotropic virus (HTLV)-1.

Prevention of exposure to the pathogen

Exposure is prevented by good personal hygiene and avoiding walking barefoot or contact between the skin and the ground in endemic areas. In this way, contact with infective filariform larvae is avoided.

Primary and secondary prophylaxis

This infestation should be suspected in individuals from or who have traveled to endemic areas, especially if they present eosinophilia and are expected to receive corticosteroids or other immunosuppressive therapy. In these cases, etiologic or empiric treatment with albendazole is indicated (AII) (8,241,270-275). There are no data to support the use of secondary prophylaxis.

Schistosomiasis (Table 7)

Schistosomiasis is produced by trematodes of the genus *Schistosoma* that are found throughout tropical and subtropical Africa, the Middle East, East Asia, the Philippines, and some areas of South America. There is no clear evidence that schistosomiasis is more severe or difficult to treat in HIV-infected persons.

Prevention of exposure to the pathogen

Infestation occurs through the skin when wading or bathing in freshwater rivers and lakes where the pathogen is present in its free-swimming larval stage (cercaria); therefore, contact with fresh water should be avoided in endemic areas. Specific serology testing is recommended in cases of exposure to the parasite.

Primary and secondary prophylaxis

In patients with suspected infection by this parasite (suggestive symptoms or eosinophilia with or without confirmation of the parasite) who are from or who have lived in endemic areas, treatment with praziquantel is recommended (9,276). Early administration of this drug (during the first month after exposure) has not prevented schistosomiasis from developing (DII) (277). No data suggest that secondary prophylaxis is necessary.

Cysticercosis (Table 7)

Cysticercosis is found throughout the world, although it is more prevalent in areas with deficient sanitation and where people consume undercooked or raw pork, mainly in Sub-Saharan Africa, Latin America, and Southern Asia). Cysticercus is the larval phase of *Taenia solium*, whose definitive host is man. Nevertheless, humans can also develop cysticercosis if they ingest proglottids or eggs of *T. solium*. In HIV-infected patients, this disease seems to be no more severe, although atypical presentations are more common (278,279).

Prevention of exposure to the pathogen

Avoid ingestion of eggs by correct personal hygiene, and monitor water and food that could be contaminated by contact with feces carrying *T. solium*. Prevent infestation with the adult form by not ingesting raw or undercooked meat, due to the possibility of autoinfestation.

Primary and secondary prophylaxis

Albendazole and praziquantel have proven effective in the treatment of symptomatic disease (8,241,280-286) (BI). As primary prophylaxis, they could be considered for asymptomatic patients with viable cysts as a precaution against future complications if the CD4+ T-lymphocyte count is less than 200 cells/μL or there is a probability of significant immune deterioration (CIII).

Filariasis (Table 7)

Filariasis is a nematode infestation transmitted by a vector insect that is found throughout tropical Africa, Asia and South America. It has not been shown to be more severe or have a worse response to treatment in HIV-infected patients.

Prevention of exposure to the pathogen

Prevention of infestation generally involves avoiding bites by the vector insect (mosquitoes, horseflies, and other types of fly) using repellants and suitable clothing. Nevertheless, transmission by the vector is not usually effective, with the result that repeated bites are necessary for the parasite to become established. In the specific case of infestation by *Loa loa*, the use of diethylcarbamazine at 300 mg weekly has proven effective in people intending to spend long periods in endemic areas (AI) (287).

Primary and secondary prophylaxis

Treatment of HIV-infected patients is the same as for HIV-negative patients. There is no evidence that secondary prophylaxis is necessary.

Cutaneous and visceral migratory larvae

These larvae are the consequence of infestation by uncinaria in their larval state (cutaneous migratory larvae) or ingestion of ascaris eggs (visceral migratory larvae) from dogs and cats. There is no evidence that they behave differently in HIV-infected patients than in immunocompetent individuals.

Prevention of exposure to the pathogen

In the case of uncinaria, avoid walking barefoot or contact between naked skin and the ground. For visceral larvae, avoid ingestion of eggs by contact with ground contaminated by dog or cat feces, and maintain suitable hygiene when in contact with dogs or cats.

Primary and secondary prophylaxis

This infestation must be suspected when symptoms are characteristic or eosinophilia cannot be explained by drugs, allergic processes, or other causes. Empirical treatment is sometimes necessary. Treatment is as for immunocompetent individuals (9,241). There is no evidence that secondary prophylaxis is necessary, since these parasitoses can be eradicated from the host.

ACKNOWLEDGMENTS

We thank Dr. Juan Emilio Losa (Hospital de Alcorcón, Madrid) and Dr. María Jesús Barberá (Sexually Transmitted Infections Unit, CAP Drassanes, Barcelona) for their critical review of the manuscript.

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Table 1. System for the classification of recommendations of clinical practice guidelines used by the Infectious Disease Society of America (IDSA) and the United States Public Health Service (USPHS)

STRENGTH OF THE RECOMMENDATION

- A **Always offer**. Strong evidence for efficacy and clinical benefit.
- B **Usually offer**. Evidence for efficacy a) is not very solid or b) is solid but the clinical benefit of the recommendation is limited.
- C **Optional**. a) There is no conclusive evidence that guarantees or refutes the recommendation or b) the evidence for efficacy does not outweigh the possible undesirable effects (toxicity, medication interactions), price, or alternative solutions.
- D **Do not offer in general**. There is moderately solid evidence for a) a lack of efficacy or b) a risk of undesirable effects.
- E **Should never be offered**. There is solid evidence that the recommendation is inefficacious or represents a risk for the patient.

QUALITY OF THE EVIDENCE ON WHICH THE RECOMMENDATION IS BASED

- I At least 1 well designed randomized and controlled clinical trial.
- II At least 1 well designed but not randomized clinical trial or a cohort study or a case-control study (preferably from more than 1 center) or multiple case series or outstanding results in noncontrolled trials.
- III Opinion of experts with broad clinical experience in the field, descriptive studies, or recommendations from expert panels.

Table 2. Prophylaxis of opportunistic diseases caused by parasites in HIV-infected adolescent and adult patients

PRIMARY PROPHYLAXIS			
Pathogen	Indication	First option	Alternatives
Pneumocystis jiroveci	CD4 < 200/µL Oral candidiasis FUO > 20 days AIDS-defining disease[a]	TMP-SMZ*, 1 double-strength tab 3 d/wk[b,c]	TMP-SMZ, 1 double-strength tab, qd TMP-SMZ, 1 normal-strength tab[d] qd Dapsone (50 mg/ bid or 100 qd) Dapsone (100 mg 2 d/wk) + pyrimethamine (50 mg 2 d/wk) + folinic acid (15 mg 2 d/wk) Dapsone (50 mg qd) + pyrimethamine (50 mg 1 d/wk) + folinic acid (15 mg 1 d/wk) Dapsone (200 mg 1 d/wk) + pyrimethamine (75 mg 1 d/wk) + folinic acid (15 mg 1 d/wk) Aerosolized pentamidine (300 mg) or intravenous pentamidine (300 mg) every 28 days Atovaquone 1500 mg qd with(out) pyrimethamine (50-75 mg 1 d/wk) + folinic acid (15 mg 1 d/wk) Sulfadiazine (1 g bid) + pyrimethamine (25 mg qd) + folinic acid (15 mg qd) Sulfadoxine pyrimethamine 1 tab 2 d/wk
Toxoplasma gondii	Anti-*Toxoplasma* Ab + and CD4 <100/µL	TMP-SMZ, 1 double-strength tab 3 d/wk	TMP-SMZ, 1 double-strength tab, qd[e] TMP-SMZ, 1 normal-strength tab qd Dapsone (100 mg 2 d/wk) + pyrimethamine (50 mg 2 d/wk) + folinic acid (15 mg 2 d/wk) Dapsone (50 mg qd) + pyrimethamine (25 mg 2 d/wk) + folinic acid (15 mg 1 d/wk) Dapsone (100 mg 1 d/wk) + pyrimethamine (75 mg 1 d/wk) + folinic acid (15 mg 1 d/wk) Pyrimethamine (50 mg 3 d/wk) + folinic acid (15 mg 3 d/wk) Atovaquone (1500 mg qd) with(out) pyrimethamine (25 mg qd) + folinic acid (15 mg qd) Sulfadoxine pyrimethamine 1 tab, 2 d/wk

SECONDARY PROPHYLAXIS			
Pathogen	Indication	First option	Alternatives
Pneumocystis jiroveci	*P. jiroveci* pneumonia	TMP-SMZ, 1 double-strength tab 3 d/wk TMP-SMZ, 1 double-strength tab, qd	Dapsone (50 mg bid or 100 mg qd) Dapsone (50 mg qd) + pyrimethamine (50 mg, 1 d/wk) + folinic acid (15 mg, 1 d/wk) Aerosolized pentamidine (300 mg) or intravenous pentamidine (300 mg) every 28 days Atovaquone 1500 mg qd with(out) pyrimethamine (50-75 mg, 1 d/wk) + folinic acid (15 mg, 1 d/wk) Sulfadiazine (1 g bid) + pyrimethamine (25 mg qd) + folinic acid (15 mg qd) Sulfadoxine-pyrimethamine 1 tab, 1 d/wk
Toxoplasma gondii	Cerebral toxoplasmosis	Sulfadiazine (1 g bid) + pyrimethamine (25 mg qd) + folinic acid (15 mg qd) Sulfadiazine (1 g bid 3 d/wk) + pyrimethamine (50 mg 3 d/wk) + folinic acid (15 mg 3 d/wk) +	Clindamycin (600 mg/8 hours) + pyrimethamine (25 mg qd) + folinic acid (15 mg qd) Azithromycin 500-1000 mg qd + pyrimethamine 25 mg qd + folinic acid (15 mg qd) TMP-SMZ, 1 double-strength tab, bid Sulfadoxine-pyrimethamine 1 tab, 2 d/wk
Leishmania infantum	Visceral leishmaniasis	Amphotericin lipid complex 3 mg/kg IV, every 3 weeks Liposomal amphotericin 3-5 mg/kg IV, every 2-4 weeks Pentavalent antimonium 850 mg/mo	Amphotericin B deoxycholate[f] Oral miltefosine[f] IV pentamidine (300 mg every 3-4 weeks)[f]
Isospora belli	Chronic diarrhea	TMP-SMZ, 1 normal-strength tab qd TMP-SMZ, 1 double-strength tab qd	Ciprofloxacin 500 mg 3 d/wk

Abbreviations: Ab, antibody; bid, twice daily; FUO, fever of unknown origin; HIV, human immunodeficiency virus; IV, intravenous; qd, once daily; TMP-SMZ, trimethoprim-sulfamethoxazole.

[a]Except in cases of tuberculosis and a CD4+ count above 350/µL.

[b]The double-strength tablet of TMP-SMZ contains 160 mg of TMP and 800 mg of SMZ.

[c]The first studies were carried out with TMP-SMZ 1 double-strength tablet per day, but it was later shown that tolerance is better and efficacy similar with 3 double-strength tablets per week or 1 normal-strength tablet every day.

[d]The normal-strength tablet of TMP-SMZ contains 80 mg of TMP and 400 mg of SMZ.

[e]One double-strength tablet per day is recommended in patients with severe immunodepression who simultaneously receive drugs that can reduce plasma levels of TMP-SMZ (eg, rifampicin) and in those with a very high IgG anti-*Toxoplasma* antibody titer.

[f]See text.

Table 3. Criteria for the withdrawal and resumption of prophylaxis against opportunistic infections in adolescent and adult HIV-infected patients taking HAART

Criteria for Suspending Prophylaxis			
Pathogen	Primary	Secondary	Criteria for Resuming Prophylaxis
Cytomegalovirus	Not applicable	Inactive CMV retinitis ≥ 6 months CD4+ > 100-150 cells/μL ≥ 6 months Undetectable VL Negative CMV antigenemia (or PCR)	CD4+ < 100 cells/μL
Mycobacterium avium	Not applicable	CD4+ > 100 cells/μL ≥ 6 months Undetectable VL	CD4+ < 100 cells/μL
Cryptococcus neoformans	Not applicable	No symptoms and CD4+ > 100 cells/μL ≥ 3 months and undetectable VL	CD4+ < 100 cells/μL Negative cryptococcal antigen that reverts to positive
Pneumocystis jiroveci	HAART (> 6 months), and CD4> 200 cells/μL > 3 months and undetectable VL	HAART (> 6 months), y CD4+ > 200 cells/μL > 3 months y undetectable VL	CD4+ < 200 cells/μL
Toxoplasma gondii	HAART (> 6 months), and CD4> 200 cells/μL > 3 months and undetectable VL	HAART (> 6 months), and CD4+ > 200 cells/μL > 3 months and undetectable VL	CD4+ < 200 cells/μL
Leishmania infantum	Not applicable	No relapses > 6 months, and CD4+ > 200-350 cells/μL > 3 months and undetectable VL	CD4+ < 200 cells/μL

Abbreviations: CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; VL, viral load.

Table 4. Prophylaxis of opportunistic infections caused by fungi in adolescent and adult HIV-infected patients

PRIMARY PROPHYLAXIS			
Pathogen	Indication	Recommendation	Alternative Recommendation
Candida	Not indicated		
Cryptococcus neoformans	Not indicated in developed countries In areas with a high incidence of cryptococcosis: in patients with CD4+ <100 cells/μL who are not taking HAART or are experiencing virological failure	Fluconazole 100 mg qd or 400 mg, 1d/wk	
Histoplasma capsulatum	CD4+ < 150 cells/μL in endemic areas with an incidence of histoplasmosis >10 cases per 100 patient-years	Itraconazole 200 mg qd	None
SECONDARY PROPHYLAXIS			
Pathogen	Indication	Recommendation	Alternative Recommendation
Candida	Frequent relapses of oropharyngeal or esophageal candidiasis in patients whose HAART has failed	Fluconazole: 100-200 mg qd or 200 mg three times weekly	Itraconazole in solution 100 mg bid Intravenous amphotericin B: 1 mg/kg, 1 d/wk in the case of resistance to azoles
Cryptococcus neoformans	Documented cryptococcosis	Fluconazole 200 mg qd	Amphotericin B: 1 mg/kg, 1 d/wk Itraconazole: 200 mg/d
Histoplasma capsulatum	Documented histoplasmosis	Itraconazole 200 mg bid	None
Coccidioides immitis	Documented coccidioidomycosis	Fluconazole 400 mg qd	Amphotericin B: 1 mg/kg, 1 d/wk or itraconazole 200 mg qd
Penicillium marneffei	Documented penicilliosis	Itraconazole 200 mg qd	None

Abbreviations: bid, twice a day; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; qd, once a day.

Table 5. Prophylaxis of opportunistic infections caused by viruses in HIV-infected adolescents and adults

PRIMARY PROPHYLAXIS			
Pathogen	Indication	Recommendation	Alternative Recommendation
Cytomegalovirus	CD4 ≤ 50/μL and positive CMV serology results	HAART with periodic ophthalmologic checkups—with or without determination of CMV—to detect the disease early for 3–4 months (if the test result is positive, evaluate early treatment with con valganciclovir)	Oral valganciclovir 900 mg qd
Herpes simplex virus	Not indicated		
Varicella zoster virus	Patients susceptible to VZV who have had contact with individuals infected with disseminated zoster or varicella	Intramuscular anti-VZV Ig within 96 hours of contact. In patients < 50 kg, 125 IU/10 kg and in patients > 50 kg, 625 IU/kg	Oral acyclovir 800 mg 5 times/d for 7 d
Hepatitis A virus	Patients with no anti-HAV IgG and a CD4+ T-lymphocyte count >200/μL Patients with no anti-HAV IgG and chronic HCV hepatitis, irrespective of the CD4+ T-lymphocyte count	Hepatitis A vaccine, 2 doses (0 and 6 or 12 months)	Hepatitis A vaccine, 3 doses (0, 1, and 6 months) in patients with a CD4+ T-lymphocyte count of 200-300/μL
Hepatitis B virus	Individuals who are negative for HBsAg and anti-HBc, who have not already been vaccinated.	Hepatitis B vaccine, 3 doses (0,1, and 6 months) with double the amount of antigen (40 μg)	Hepatitis B vaccine, 4 doses (0,1,2, and 6 months) with double the amount of antigen (40 μg)
Influenza virus	All patients annually	Antiflu vaccine	
SECONDARY PROPHYLAXIS			
Pathogen	Indication	Recommendation	Alternative Recommendation
Cytomegalovirus	Patients with CMV retinitis in remission after an induction cycle	Oral valganciclovir, 900 mg QD	Intravenous ganciclovir 5-6 mg/kg, 5-7 d/wk Intravenous foscarnet 90-120 mg/kg, 5-7 d/wk Ganciclovir implant. Intravenous ganciclovir 10 mg/kg, 3 d/wk. Intravenous cidofovir 5 mg/kg, every 2 weeks Intravitreous fomivirsen 330 μg/mo
Herpes simplex virus	Severe or frequent (>6/y) relapses	Oral acyclovir 400 mg tid or 800 mg bid Oral famciclovir 250-500 mg bid Oral valacyclovir 500 mg bid	In acyclovir-resistant strains, use intravenous foscarnet or intravenous cidofovir

Abbreviations: bid, twice a day; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; qd, once a day; tid, three times a day; VZV, varicella zoster virus.

Table 6. Prophylaxis of opportunistic infections caused by bacteria and mycobacteria in HIV-infected adolescents and adults

Pathogen	Indication	Recommendation	Alternative Recommendation
Mycobacterium tuberculosis[a]	Positive Mantoux test (≥5 mm) Contact with individuals infected by active tuberculosis Suspected cutaneous anergy in some circumstances[b]	Isoniazid 300 mg qd for 9 mo[c,d] Isoniazid 300 mg qd and rifampicin 600 mg qd for 3 mo[c,d,e]	Isoniazid 900 mg 2 d/wk for 9 mo[3,6] Rifampicin 600 mg qd for 4 mo[e]
Mycobacterium avium complex	*Primary prophylaxis*	Not indicated	Clarithromycin 500 mg bid Azithromycin 1200 mg, 1 d/wk
	Secondary prophylaxis All patients with disseminated infection by *Mycobacterium avium* complex	Clarithromycin 500 mg bid and ethambutol 15 mg/kg qd	Clarithromycin 500 mg bid and rifabutin 300 mg qd Azithromycin 500 mg QD and ethambutol 15 mg/kg qd; Rifabutin 300 mg qd
Streptococcus pneumoniae	All adults	Pneumococcal vaccine[g]	None
Haemophilus influenzae	Not indicated in adults		
Other bacteria (*Salmonella*, *Campylobacter*, *Bartonella*)	Not indicated		

Abbreviations: bid, twice a day; HIV, human immunodeficiency virus; qd, once a day; tid, three times a day.

[a]In the case of isoniazid-resistant tuberculosis, use short regimens of rifampicin and pyrazinamide or rifampicin alone. If infection by a multiresistant strain is suspected, choose prophylaxis according to the sensitivity of the strain. If the antibiogram is not available, administer pyrazinamide and ethambutol or a fluoroquinolone.

[b]Previous positive Mantoux test result, history of close and prolonged contact with individuals infected by untreated active tuberculosis and a history of prolonged stays in prison without having received appropriate prophylaxis.

[c]HIV-infected patients should receive pyridoxine (vitamin B_6) combined with isoniazid to prevent peripheral neuropathy caused by interference with the metabolism of this vitamin.

[d]When choosing the regimen for chemoprophylaxis, remember that there are commercial presentations of isoniazid alone (2 tabs/d) and of the combination of isoniazid plus rifampicin (2 tabs/d).

[e]Rifampicin can be replaced by rifabutin when the patient must take a protease inhibitor. In these cases, the dose of rifabutin must be 150 mg QD or 300 mg 2 or 3 days per week. The dose of some protease inhibitors should be increased (indinavir to 1000 mg tid and nelfinavir 1000 mg tid).

[f]Administration should be supervised in intermittent regimens.

[g]Offer revaccination at 5 years, or before, if the first vaccination was administered with a CD4+ T-lymphocyte count < 200/µL . No significant negative effect of vaccination on the outcome of viral load has been demonstrated.

Table 7. Prophylaxis of parasitic infection in HIV-infected adolescents and adults

Pathogen	Primary prophylaxis	Secondary prophylaxis	Prevention of infections
Entamoeba histolytica	*For asymptomatic carriers*: Paromomycin po 500 mg every 8 h, for 5-10 d Alternatives: Diloxanide furoate 500 mg every 8 h for 10 d Iodoquinol 650 mg every 8 h, for 20 d		Monitor intake of water and food. Correct personal hygiene, hand washing, safe sex (especially oral-anal contact)
Malaria caused by chloroquine-sensitive *P. falciparum*, *P. vivax, P. ovale*, and *P. malariae*	*To avoid parasitization*: Oral chloroquine 300 mg base, once per week. Alternative: Hydroxychloroquine po 310 mg base (400 mg of salt), once per week. In both cases, administer 1 wk before travel to the endemic area, during the stay, and up to 4 w after leaving the area.		Antimosquito measures: Long sleeves and long trousers at night and in the early morning Insect repellants. Clothes treated with repellant Closed footwear Mosquito nets treated with repellant or insecticide
Malaria caused by chloroquine-resistant *P. falciparum*	Mefloquine[a] po (250 mg of salt), once per week. Administer 1 wk before, during, and up to 4 wks after the stay in the endemic area. Atovaquone-proguanil po 1 tab (250 mg atovaquone+100 mg proguanil) qd. Administer 1 day before the stay, during the stay, and up to 7 days after leaving the endemic area. Doxycycline[b] po 100 mg qd. Administer 1 wk before entering the endemic area, during the stay, and up to 4 wks after leaving the area. Primaquine[c] po 30 mg base qd. Administer 1 day before travel to the endemic area, during the stay, and up to 7 days after leaving the area.		
Trypanosoma cruzi	*Preventive treatment:* Benznidazole[d] po 5 mg/kg/d, taken in 2 doses from 60 to 90 d (even 120 d) Alternative: Nifurtimox[e] po 8 mg/kg/d, taken in 2-3 doses from 60 to 90 d)	Benznidazole po 5 mg/kg/d, divided into 2 doses 3 times per week.	Antivector measures: Insect repellants. Mosquito nets treated with repellants or insecticide. Avoid rural dwellings or sleeping outdoors.
Trypanosoma brucei gambiense Early phase Late phase	*Treatment of the infected patient:* IV or IM pentamidine 4 mg/kg up to 300 mg/d for 7 days. IV eflornithine 100 mg/kg qid for 14 days. Alternative: IV melarsoprol 2.2 mg/kg/d, for 10 days.		Antivector measures: Long sleeves and long trousers. Do not wear thin, dark-colored clothing Insect repellants are not very effective Avoid areas with a high density of the vector

Trypanosoma brucei rhodesiense Early phase Late phase	IV suramin 5 mg/kg on the first day followed by 20 mg/kg (up to 1g) on days 3, 5, 12, 19, 26. Pretreatment with suramin, 5 mg/kg on the first day and 20 mg/kg on the third day, followed by IV melarsoprol 1.8 mg/kg (day 5), 2.16 mg/kg (day 6), 2.52 mg/kg (days 7 and 14), 2.88 mg/kg (day 15), 3.24 mg/kg (day 16), 2.9 mg/kg (day 20), 3.6 mg/kg (up to 180 mg, days 23, 24 and 25).		
Cyclospora cayetanensis	Not indicated.	Cotrimoxazole (160/800 mg) po, qd, 3 times/wk Alternative: Ciprofloxacin 500 mg po qd, 3 times/wk	Monitor water and food intake. Avoid bathing in potentially contaminated fresh water.
Strongyloides stercoralis	*Preventive treatment:* Ivermectin po 200 µg/kg qd, repeat the dose after 1 wk Albendazole[f] po 400 mg bid, for 3-5 d, or albendazole po 800 mg bid, for 3 d		Avoid walking barefoot or contact between naked skin and potentially contaminated ground. Rule out this parasitosis in patients who are going to receive immunosuppressive therapy (especially corticosteroids) or who are infected by HTLV-1.
Schistosoma species	*Treatment of the infected patient:* Praziquantel[g] po 40 mg/kg in a single dose. In the case of *S. japonicum* or *S. mekongi* administer 2 doses of 30 mg/kg separated by 3 h Alternative: Metrifonate po 10 mg/kg in a single dose.		Avoid bathing in and contact with river or lake water infested with cercariae. In the case of accidental contact, dry the wet areas vigorously with a towel and apply alcohol, 70%.
Taenia solium Cysticercosis	*Treatment of the infected patient* Corticosteroids for control of symptoms plus Albendazole[g] po 400 mg bid, for 8-30 days Praziquantel po 100 mg/kg/d in 3 doses, for 1 day, followed by 50 mg/kg/d in 3 doses for 29 days.		Cysticercosis: Monitor food and water intake. Correct personal hygiene and hand washing Teniasis: Do not ingest raw or undercooked pork. Freezing at –5°C for 3 d destroys the cysticerci.
Filariasis *Onchocerca volvulus* *Loa loa* *Wuchereria bancrofti, Brugia*	*Treatment of the infected patient:* Ivermectin po 150 µg/kg, single dose, every 6-12 months. Diethylcarbamazine po 6 mg/kg, in 3 doses, for 21 days. In cases of hypermicrofilaremia, consider starting albendazole po 200 mg bid for 21 days followed by ivermectin or diethylcarbamazine. Diethylcarbamazine po 6 mg/kg, in 3 doses, for 10-14 days.		Long sleeves and trousers. Depending on the vector, intensify preventive measures at night and at dawn and dusk. Insect repellant. Clothing treated with repellant Closed footwear Mosquito nets treated with repellant or insecticide

malayi, and *Brugia timori* *Mansonella perstans* *Mansonella streptocerca* *Mansonella ozzardi*	Albendazole po 400 mg bid, for 10 days. Mebendazole po 100 mg, bid, for 30 days. Diethylcarbamazine po 6 mg/kg, in 3 doses of 12-21 days. Ivermectin po 200 µg/kg, in a single dose		
Cutaneous migratory larvas	*Treatment of the infected patient:* Albendazole po 400 mg bid, for 3 days. Ivermectin po 200 µg/kg qd, for 1-2 days.		Avoid walking barefoot or contact between naked skin and ground that might be contaminated.
Visceral migratory larvas	*Treatment of the infected patient:* Albendazole po 400 mg bid, for 5 days. Mebendazole po 100-200 mg, bid, for 5 days.		Caution when handling soil that is potentially contaminated by dog feces. Observe suitable personal hygiene, particularly when there is contact with dogs.

Abbreviations: bid, twice a day; HTLV-1, human T-lymphotropic virus; IM, intramuscular; IV, intravenous; po, orally qd, once daily;
NOTES:
[a]Mefloquine can be started 3 or 4 weeks early to evaluate tolerability and if this is bad, switch to another prophylactic regimen.
[b]Contraindicated in pregnant women.
[c]Prophylaxis for special cases. Primaquine is used as prophylaxis and to eliminate dormant hepatic forms of *P. vivax* and *P. ovale* and prevent relapses. Given that primaquine can cause severe hemolytic anemia in patients with G6PDH deficit, patients must be studied before the drug is administered.
[d]Benznidazole is considered the drug of choice, as it is more easily obtained (ordered as foreign medication). Nifurtimox is only available in Argentina and Germany.
[e]There is much less experience with nifurtimox in patients with Chagas disease.
[f]Administer with food, since this improves absorption, especially fat.
[g]In cases of suspected infection with reduced sensitivity, administer 60 mg/kg in 2 separate doses 3 hours apart.