Prevention of opportunistic infections in HIV-infected adolescents and adults Recommendations of GESIDA/National AIDS Plan

Juan Berenguer[a*], Fernando Laguna[b*], José López-Aldeguer[c,o*], Santiago Moreno[d,o*], José R. Arribas[e], Julio Arrizabalaga[f], José Baraia[g], José Luis Casado[d], Jaime Cosín[a], Lourdes Chamorro[h], Juan González-García[e], José A. Iribarren[f], José Mª Kindelán[i], Juan C. López-Bernaldo de Quirós[a], Rogelio López-Vélez[d], Juan F. Lorenzo[j], Fernando Lozano[k], Josep Mallolas[l], José M. Miró[l], Federico Pulido[m] y Esteban Ribera[n]

[a]Hospital General Gregorio Marañón. [b]Hospital Carlos III. Madrid. [c]Hospital la Fe. Valencia. [d]Hospital Ramón y Cajal. [e]Hospital La Paz. Madrid. [f]Hospital Nuestra Señora de Aranzazu. San Sebastián. [g]Hospital de Basurto. Bilbao. [h]Secretaría del Plan Nacional sobre el SIDA. Madrid. [i]Hospital Reina Sofía. Córdoba. [j]Hospital General Yagüe. Burgos. [k]Hospital de Valme. Sevilla. [l]Hospital Clínic. IDIBAPS. University of Barcelona. Barcelona. [m]Hospital 12 de Octubre. Madrid. [n]Hospital Vall d'Hebron. Barcelona. Spain. [O]Member of GESIDA and the Clinical Advisory Committee of the SPNS
*Manuscript's authors.

Abstract

OBJECTIVE. **To provide an update of 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 consensus recommendations have been produced by a group of experts from GESIDA and/or the PNS after reviewing the earlier document and the scientific advances in this field in the last years. The system used by the Infectious Diseases Society of America and the United States Public Health Service has been used to classify the strength and quality of the data.**
RESULTS. **This document provides a detailed review of the measures for the prevention of infections caused by viruses, bacteria, fungi and parasites in the context of HIV infection. 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, in highly immunodepressed patients until HAART achieves beneficial effects, in 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.**

Key words: HIV. Opportunistic infections. Prophylaxis. Withdrawal of prophylaxis.

Prevención de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el VIH. Recomendaciones de GESIDA/Plan Nacional sobre el Sida. Año 2003

OBJETIVO. **Actualización de las recomendaciones del Grupo de Estudio de Sida (GESIDA) y la Secretaría del Plan Nacional sobre el Sida (PNS) sobre prevención de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el virus de la inmunodeficiencia humana (VIH).**
MÉTODOS. **Las recomendaciones han sido consensuadas por un grupo de expertos de GESIDA y/o del PNS tras la revisión del antiguo documento y las aportaciones científicas sobre la materia de los últimos 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 virus, bacterias, hongos y parásitos en el contexto de la infección por el VIH. Para cada grupo de patógenos se han dado recomendaciones para prevenir la exposición a los mismos, para las profilaxis primarias y para las profilaxis secundarias. 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, en pacientes muy inmunodeprimidos hasta que el TARGA logra sus efectos, en los que no desean o no pueden tomar TARGA, en aquellos en los que este 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.

Palabras clave: VIH. Infecciones oportunistas. Profilaxis. Retirada de la profilaxis.

Introduction

For many years, the main intervention to improve and prolong the life of HIV-infected patients was prophylaxis of opportunistic infections and healthcare by professionals with AIDS experience[1,2]. Despite the fact that, in developed countries, the incidence of these infections has fallen drastically in line with the use of highly active antiretroviral therapy (HAART)[3,4], in countries with scarce economic resources, these infections are still common and represent the principal cause of HIV-associated mortality.

For some years now, we have known that the inhibition of viral replication by HAART prevents immune deterioration in HIV-infected patients. In patients with advanced disease, these treatments give rise to a gradual increase in naïve CD4 T and memory lymphocytes which can proliferate "in vitro" and generate cytokines in response to opportunistic pathogens. Moreover, the delayed antigen response recovers and non-specific immune activation is normalized[5,6].

There can be no doubt that HAART is the best strategy for preventing opportunistic infections in these patients; this does not mean to say, however, that we can forget prophylaxis. In clinical practice, prophylaxis is still necessary in countries with scarce economic resources, in very immunodepressed patients until HAART takes effect, in patients who do not wish to or who cannot take HAART, in patients in whom HAART fails and in the small group of patients who are unable to recover sufficient CD4+ T cell counts despite good inhibition of viral replication. Finally, it is important to point out that prevention of opportunistic infections is a field in which clinical research on the withdrawal of secondary prophylaxis is still being carried out.

For the aforementioned reasons, the Board of GESIDA and the National AIDS Plan Secretariat have felt it appropriate to update their recommendations on the prevention of opportunistic infections in HIV-infected adolescents and adults[7], by including those made during the last few years. In order to classify the strength and qua-

TABLE 1. **System for the classification of the recommendations from the clinical practice guidelines used by the Infectious Diseases Society of America (IDSA) and the United States Public Health System (USPHS)**

Strength of the recommendation

A **Should always be offered**. Strong evidence for efficacy and clinical benefit support recommendation for use.

B **Should generally be offered**. Evidence for efficacy a) is not very solid or b) is solid but only limited clinical benefit.

C **Optional**. a) No conclusive evidence to support recommendation for or against use or b) evidence for efficacy might not outweigh adverse consequences (drug toxicity, drug interactions), cost of chemoprophylaxis or alternative approaches.

D **Should generally not be offered**. Moderate evidence for a) lack of efficacy or b) adverse outcome supports a recommendation against use.

E **Should never be offered**. Good evidence for lack of efficacy or risk for patient.

Quality of evidence supporting the recommendation

I Evidence from at least one properly randomized, controlled trial.

II Evidence from at least one well designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one center) or from multiple time-series studies. Or dramatic results from controlled experiments.

III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

lity of the recommendations, we have followed, on this occasion, the system used by the Infectious Diseases Society of America (IDSA) and the United States Public Health System (USPHS) (Table 1)[8].

Prophylaxis of infections caused by virus

Cytomegalovirus (Table 2)

Before the introduction of HAART, approximately 45% of patients co-infected by HIV and CMV developed CMV disease. Furthermore, in those co-infected patients with a CD4+ T cell count < 100/uL, 22% developed CMV retinitis within two years. This is a serious and disabling problem whose frequent relapses and complications could lead to loss of vision[9].

HAART drastically reduced the incidence of this disease and made a dramatic change to its natural history with prolonged survival and reduction of relapses and complications[10-12]. In fact, in one large scale randomised clinical trial comparing three anti-CMV treatments, the frequency of new CMV disease was lower in patients who had received protease inhibitors, regardless of the therapeutic group to which they had been assigned[13]. Therefore, we can conclude that HAART currently plays an extremely important role in the prophylaxis and treatment of CMV disease regardless of the antiviral drug which patients are receiving. It is worth bearing in mind that one of the adverse events experienced by patients with CMV retinitis who begin HAART is immune recovery vitritis, which can occasionally cause severe loss of vision[11,14,15].

TABLE 2. **Prophylaxis of opportunistic diseases produced by viruses in HIV-infected adolescents and adults**

Pathogen	Indication	First Choice	Alternative
Primary prophylaxis			
Cytomegalovirus	CD4+ T cell count ≤ 50 /uL and positive CMV serology	HAART with periodical ophthalmologic check-ups, with or without CMV determination in blood by PCR, for the early detection of the disease for 3 – 4 months (if positive, evaluate early therapy)	Oral ganciclovir 1 g po t.i.d.
Herpes simplex Virus	Not indicated		
Varicella Zoster Virus	Patients susceptible to VZV who have had contact with people with disseminated zoster or varicella	Anti-VZV IG within the 96 hours . after contact[1]	Acyclovir 800 mg po 5 times per day for 7 days.
Hepatitis A Virus	Patients without anti-HAV IgG with CD4+ T cell count > 200/uL Patients without anti-HAV IgG and chronic HCV hepatitis, regardless of CD4+ T cell count	Hepatitis A vaccine, 2 doses (0 and 6 or 12 months)	
Hepatitis B Virus	People with negative HBsAg . and anti-HBc, who have not been previously vaccinated	Hepatitis B vaccination, 4 doses (0, 1, 2 and 6 months) with double quantity of vaccine	No
Influenza Virus	All patients annually	Antiflu vaccine	
Secondary prophylaxis			
Cytomegalovirus	Patients with CMV retinitis in remission after an induction cycle	Valganciclovir po 900 mg q.d.	Ganciclovir IV 5-6 mg/kg 5-7 days/week. Ganciclovir po 1000 mg t.i.d. Foscarnet IV 90-120 mg/kg 5-7 days/week Ganciclovir implant Ganciclovir IV 10 mg/kg 3 days/week Cidofovir IV 5 mg/kg every 2 weeks Intravitreous fomivirsen 330 ug per month
Herpes simplex Virus	Frequent (>6 per year) or severe relapses	Acyclovir 400 mg po t.i.d. or 800 mg . po b.i.d Famciclovir 500 mg po b.i.d. Valacyclovir 500 mg po b.i.d.	In acyclovir-resistant strains: foscarnet IV or cidofovir IV

Abbreviations: CMV: Cytomegalovirus, VZV: Varicella Zoster Virus. HAV: Hepatitis A Virus. HAART. Highly active antiretroviral therapy. IG: Immunoglobulin. po: oral. q.d.: once per day. b.i.d.: twice per day. t.i.d.: 3 times per day.
Notes: In Spain: Varitect" 5 or 20 mL ampoules and 50 mL infusion bottles (Biotest Pharma, Germany). Order using forms A2 and A3. Dose: 0.2 – 1 ml per Kg of body weight in slow infusion

Prevention of exposure to the pathogen

Patients belonging to population groups with a low frequency of CMV infection, and who we cannot assume to be seropositive, should undergo a serological study for CMV. These patients include those who have never injected drugs and males who have not had homosexual relations (BIII). Patients whose CMV serology is negative must not receive transfusions of blood derivatives from patients with a positive CMV serology (B3) and must avoid sexual contact without a condom (AII). The risk of acquisition of CMV can be reduced by following good hygiene practices such as hand-washing. These practices are particularly important in settings such as kindergartens, where the risk of contagion by CMV is greater (B3)[16].

Primary prophylaxis

Two prospective, randomised, double-blind, placebo-controlled clinical trials have been published on primary prophylaxis with oral ganciclovir in patients co-infected with HIV and CMV. In the first, with more than 700 patients with a CD4+ T cell count ≤50/uL or < 100/uL and a history of infection indicative of AIDS, the accumulated incidence of visceral disease by CMV at 12 months was 14% in the ganciclovir group and 26% in the placebo group, and the accumulated incidence of CMV retinitis was 12% and 24%, respectively (RR 0.49, p < 0.001); there were no differences in mortality[17]. The second, with more than 900 patients, was different from the first in two important areas. First, the inclusion criterion in the study with respect to baseline CD4+ T cell count was

≤100 /uL. Second, when the study was under way, and the results of the previous study were known, it was accepted that all patients had access to ganciclovir. No differences were found concerning the incidence of CMV disease and mortality until the study was modified or until it finished. Nevertheless, more adverse effects, especially neutropenia, were detected in the ganciclovir group than in the placebo group[18].

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

It is very important to bear in mind that in patients who initiated HAART with CD4+ < 50/uL, there is a risk period of 3 to 4 months during which patients can suffer from CMV retinitis (and other opportunistic infections) even with a CD4+ T cell count > 100/uL. In these cases, it is advisable to carry out antigenemia studies or CMV PCR, given that the possibility of developing R-CMV is 38% for patients who test positive, compared with 2% for patients who test negative (p < 0.001) (CII)[10]. Patients who test positive must be reviewed by fundoscopy every 2 or 4 weeks during the first three months for early detection of the disease (CIII). In these cases, it may make sense to administer pre-emptive anti-CMV treatment, a step which is now being evaluated in a randomised clinical trial (study ACTG A5030). This study aspires to include 750 HIV-infected patients with positive CMV serology and with a CD4+ T cell count < 100/uL despite HAART. They will all be reviewed every two months using CMV DNA by PCR and every six months by an ophthalmologic examination. Those in whom CMV viremia is detected will be randomised to receive valganciclovir or placebo. At present, more than half the patients have been included and we will have to wait some years to know the results of the study.

Secondary prophylaxis

The therapeutic strategy for CMV retinitis has been well established for years; it involves an induction phase, which aims to control the infection, followed by a maintenance phase to prevent or delay relapses[9,19]. For this second indication, drugs are available which can be administered intravenously such as ganciclovir, foscarnet and cidofovir. These drugs have never been compared with each other and have a different toxicological profile. Available orally administered drugs include ganciclovir and valganciclovir, which is the valine ester of ganciclovir. The bioavailability of oral ganciclovir is very poor, which makes it less efficacious than intravenous ganciclovir and forces patients to take a large number of tablets[20]. Valganciclovir, however, is metabolized by enzymes of the digestive tract and is practically 100% transformed into ganciclovir[21]. In one randomised and open-label trial involving 160 patients with AIDS and recently diagnosed CMV retinitis, oral valganciclovir was proven to be as efficacious as intravenous ganciclovir in induction therapy, and easy-to-take and efficacious in the maintenance phase[13]. A ganciclovir implant (unrivalled in the treatment of CMV retinitis) is available for topical use, although before HAART it had to be accompanied by oral ganciclovir to avoid both disease of the other eye and extraocular disease[22]. In a recent study which compared the ganciclovir implant with(out) oral ganciclovir and intravenous ganciclovir, it was verified that in the subgroup of patients treated with HAART, the incidence of relapses or new disease was low and of the same size in all groups[23]. Also available for topical use is fomivirsen, an antisense oligonucleotide which inhibits the replication of CMV and which is administered by intravitreous injection. In the maintenance phase the dose is 330 ug per month. Its undesirable effects are increased intraocular pressure and ocular inflammation, which are transitory or reversible with topical steroid therapy. Fomivirsen is currently indicated for the treatment of relapses[24].

In the light of the numerous options available for the secondary prophylaxis of CMV retinitis, it is recommended to choose the drug which is best adapted to the patient[25], although given its proven efficacy and ease of use, oral valganciclovir could be considered as the drug of choice (AI). In general, maintenance treatment with prolonged use of oral ganciclovir only should not be administered to patients who cannot receive HAART or to those in whom no improvement of the immune system is expected (DIII).

Withdrawal of secondary prophylaxis

Several small-series studies have shown the possibility of withdrawing secondary anti-CMV prophylaxis in patients who recover with HAART[26,27] In the last few years, four studies have been published on the withdrawal of secondary anti-CMV prophylaxis. The first included 14 patients and no relapses were detected after a median follow-up of 16.4 months[28]. In the second, 3 out of 22 patients who suspended secondary prophylaxis had a relapse of CMV retinitis[29]. In the three cases, HAART failed and patients had a CD4+ T cell count < 50/uL at the time of the relapse. The third study was multinational and included 48 patients of whom two suffered a relapse of CMV disease: retinitis in one case and peripheral neuropathy in the other. Surprisingly, the CD4+ T cell counts at the time of the relapse were 352/ul and 106/ul, respectively[30]. Finally, in the fourth, a Spanish multicenter study, secondary prophylaxis was withdrawn from 36 patients and, after a median follow-up of 90 weeks, no reactivation or progression of retinitis was observed in the 35 patients who responded favorably to HAART. Nevertheless, in one patient, relapse of retinitis was observed at 44 weeks after suspending prophylaxis and in the setting of immune failure. At the time of relapse, the CD4+ T cell count was 62/uL[31].

Taken as a whole, the results of these four studies guarantee the safety of interrupting secondary anti-CMV prophylaxis in patients with AIDS and inactive CMV retinitis who experience an increase in their CD4+ T cell count with HAART. Nevertheless, the lowest CD4+ T cell count at which prophylaxis can be suspended is unknown. If the data from the four studies (79 patients) are combined, it can be observed that the median CD4+ T cell count at the time of withdrawing prophylaxis was 269/ul

with an interquartile range of 167 – 360/uL. More than two thirds of the patients had CD4+ T cell counts >200/uL, less than one third had between 100 and 200/uL and only three patients had < 100/uL. This allows us to conclude that the withdrawal of secondary prophylaxis is a reasonable and safe option in patients with inactive CMV retinitis and in those who have shown a good response to HAART characterized by a CD4+ T cell count > 200/uL for at least six months (BII). In some cases, the withdrawal of secondary prophylaxis can be considered in patients who present a count of between 100 and 200/uL, given that most of the patients who relapsed in the aforementioned studies had counts of <100/uL (CIII). After secondary prophylaxis has been withdrawn, patients can be monitored with periodic determinations of their CD4+ T cell count (BIII). In those who experience immune failure, it should be decided whether to carry out frequent ophthalmologic check-ups or re-initiation of secondary prophylaxis, depending on the risk of suffering an irrecoverable loss of vision (BIII) (**Table 3**)

Other viruses (Table 2)

HIV-infected patients often suffer from digestive and mucocutaneous HSV infection but primary prophylaxis against these infections is not recommended (DIII). Relapses respond well to therapy, therefore suppressive therapy is not advised except for genital herpes with frequent and/or severe relapses (≥ 6 relapses per year) (AI). Consequently, the following are recommended for HIV-infected patients: acyclovir (400-800 mg two to three times per day), or famciclovir (500 mg twice per day) or valacyclovir (500 mg twice per day) (32). In infections by acyclovir-resistant HSV strains, intravenous or topical cidofovir or intravenous foscarnet should be used (AII). Given that the frequency of relapses falls with time in

many patients, it is recommended to periodically evaluate (e.g. every year) the withdrawal of suppressive therapy (BII)[32].

HIV-infected patients should not be vaccinated with the varicella zoster virus (VZV), although those who live with them should, in case they are susceptible to VZV (those without specific IgG antibodies) (BIII). HIV-infected patients who are susceptible to VZV should avoid contact with people with Varicella or Zoster (AII). For post-exposure prophylaxis in susceptible subjects, specific gammaglobulin is recommended within the 96 hours following contact (AIII). Another cheaper and logistically simpler option is the administration of oral acyclovir (CIII), although the efficacy of this measure has only been proven in immunocompetent children after exposure at home[16,33,34].

Vaccination against the hepatitis A virus (HAV) is recommended for all HIV-infected patients who do not have anti-HAV IgG antibodies and who present a CD4+ T cell count > 200/uL (AIII)[35]. This practice is especially recommended in patients with chronic C hepatitis, given that there is a risk of fulminant hepatitis and death in HAV superinfection[36].

Vaccination is also recommended against hepatitis B virus (HBV) in all HIV-infected patients who are HBsAg and anti-HBc-negative and who have not already been vaccinated (AIII). The standard regimen of vaccination against HBV is three injections (0, 1 and 6 months) with 20 ug of antigen. Nevertheless, the immunogenic response with the standard vaccination regimen for HBV is reduced in HIV-infected patients and is related to the CD4+ T cell count. Given that the response to the HBV vaccine in immunodepressed patients can increase to 90% with greater doses of antigen and/or by increasing the number of injections, some bodies such as GESIDA

TABLE 3. **Criteria for withdrawal and resumption of prophylaxis for opportunistic infections in adolescent and adult HIV-infected patients receiving HAART**

Pathogen	Critera for suspending prophylaxis		Criteria for resuming prophylaxis
	Primary	Secondary	
Cytomegalovirus	Not applicable	Inactive CMV retinitis ≥ 6 months CD4+ T cell count > 200/uL ≥ 6 months VL <5000 copies/uL Antigenemia (or PCR) for negative CMV	CD4+ T cell count < 100/uL
Mycobacterium avium	Not applicable	CD4+ T cell count > 100/uL ≥ 6 months VL <5000 copies/uL	CD4+ T cell count < 100/uL
Cryptococcus neoformans	Not applicable	Absence of symptoms CD4+ T cell count > 100/uL ≥ 3 months and VL<5000 copies/uL	CD4+ T cell count < 100 Negative cryptococcal antigen which reverts to positive
Pneumocystis jiroveci	HAART (>6 months), and CD4+ T cell count >200 /uL > 3 months and VL <5000 copies/uL	HAART (>6 months), and CD4+ T cell count >200 /uL > 3 months and VL<5000 copies/uL	CD4+ T cell count < 200/uL
Toxoplasma gondii	HAART (>6 months), and CD4+ T cell count >200 /uL > 3 months and VL <5000 copies/uL	HAART (>6 months), and CD4+ T cell count >200 /uL > 3 months and VL<5000 copies/uL	CD4+ T cell count < 200/uL
Leishmania infantum	Not applicable	Absence of relapses > 6 months, and CD4+ T cell count > 200 - 350 /uL > 3 months and VL <5000 copies/uL	CD4+ T cell count < 200/uL

and the National AIDS Plan Secretariat recommend for this type of patient vaccination with four injections (0, 1, 2 and 6 months) and double the quantity of antigen (40 ug instead of 20 ug) (BIII)[35].

Little is known about the frequency and consequences of coinfection by HIV and influenza. Some retrospective studies have found that influenza has greater morbidity and mortality in HIV-infected patients than in the general population. Nevertheless, there is evidence that hospital admissions due to influenza have fallen significantly during the HAART era, and have reached rates similar to those of other population groups considered "high risk"[37]. For these reasons, and given that antiflu vaccination can produce a protective antibody titer in HIV-infected patients, it is recommended that they all (even pregnant women) receive the vaccination every year (AIII)[16,38].

HAART is the only intervention which can prevent progressive multifocal leukoencephalopathy (PML) and which can interrupt the lytic cycle of the JC virus. According to recent data, approximately one third of patients with AIDS and PML who receive HAART survive, and of these, approximately half experience some degree of improvement in their neurological function. Mortality is higher in those with a CD4+ T cell count <100/uL[39].

Prophylaxis of infections by bacteria and mycobacteria

Mycobacterium tuberculosis (Table 4)

HIV is the most important risk factor for the progression of latent tuberculosis to active tuberculosis and it favors progression of tuberculous disease after recently acquired infection[40,41]. Therefore, the notification of cases of tuberculosis increases significantly in countries with a high prevalence of HIV infection. Fortunately, in several different countries, the introduction of HAART has led to a reduction in the number of cases of coinfection by HIV and tuberculosis[42].

Prevention of exposure to the pathogen

HIV-infected patients should be informed about how tuberculosis, is transmitted, their risk of developing it and the meaning of the Mantoux test. As far as possible, they should avoid working in high-risk environments such as prisons, homeless shelters and hospital units with active tuberculosis patients (BIII). They should also know the advantages of consulting their doctor when they have symptoms suggestive of tuberculosis or after coming into contact with a person suffering from active pulmonary tuberculosis (BIII).

TABLE 4. Prophylaxis of opportunistic infections produced by bacteria or mycobacteria in HIV-infected adolescents and adults

Pathogen	Indication	First Choice	Alternative
Mycobacterium tuberculosis [1]	Positive Mantoux (≥ 5 mm) Contact with people with active tuberculosis Cutaneous anergy in some circumstances [2]	Isoniazid 300 mg q.d. for 9 to 12 months [3,4] Isoniazid 300 mg q.d. and rifampin 600 mg q.d. for 3 months [3,4,5]	Isoniazid 900 mg b.i.w. for 9 to 12 months[3,7] Rifampin 600 mg q.d. for 4 months[5]. Rifampin 600 mg q.d. and pyrazinamide 20 mg/kg q.d. for 2 months[4,5,6]
Mycobacterium avium complex	_Primary prophylaxis_	Not indicated	Clarithromycin 500 mg b.i.d. Azithromycin 1200 mg q.w.
	Secondary prophylaxis All patients with disseminated infection by _Mycobacterium avium_ complex	Clarithromycin 500 mg b.i.d. and ethambutol 15 mg/kg q.d.	Clarithromycin 500 mg b.i.d. and rifabutin 300 mg q.d.; Azithromycin 500 mg q.d. and ethambutol 15 mg/kg q.d.; Rifabutin 300 mg q.d.
Streptococcus pneumoniae	All adults	Pneumococcal vaccine [8]	None
Haemophilus influenzae	Not indicated in adults	–	–
Other bacteria (_Salmonella_, _Campylobacter_, _Bartonella_)	Not indicated	–	–

Abbreviations:
q.d.: once per day. b.i.d.: twice per day. b.i.w.: two days per week. q.w.: one day per week.
Notes:
1. In the case of tuberculosis resistant to isoniazid, use short regimens of rifampin and pyrazinamide or rifampin alone. if infection by multi-resistant strain is suspected, choose prophylaxis according to the sensitivity of the strain. if the antibiogram is unknown, administer pyrazinamide and ethambutol or a fluoroquinolone.
2. Previous positive Mantoux, history of close and prolonged contact with persons with untreated active tuberculosis, and history of prolonged stay in penitentiary centre without receiving adequate prophylaxis.
3. HIV-infected patients must receive pyridoxine (Vitamin B6) together with isoniazid to avoid peripheral neuropathy due to interference with the metabolism of this vitamin.
4. When deciding the chemoprophylaxis regimen, take into consideration that there are commercial preparations of isoniazid alone (2 tablets/day) and of the combination of isoniazid and rifampin (2 tablets/day). There are no commercial preparations of rifampin and pyrazinamide, therefore patients must take between 5 and 7 tablets per day according to their body weight.
5. Rifampin can be substituted by rifabutin when the patient must receive indinavir, nelfinavir or amprenavir. In these cases, the dose of rifabutin must be 150 mg q.d. or 300 mg 2 or 3 days/week. The doses of PI must also be increased: indinavir to 1000 mg t.i.d. and nelfinavir 1000 mg t.i.d.
6. Administration of rifampin and pyrazinamide for treatment of latent tuberculous infection has been associated with high toxicity, including death, in non-HIV-infected patients. These data must be taken into consideration when deciding on a tuberculosis prevention regimen in HIV-infected patients.
7. All intermittent regimens need administration to be supervised.
8. Offer revaccination at 5 years, or before, if the first vaccine is administered with CD4+ T cell count < 200/uL. No significant negative effect of vaccination has been shown on the course of viral load.

Primary prophylaxis

Evaluation of the risk of developing tuberculosis: After the first visit, the Mantoux test must be carried out (AI). Some years ago, cutaneous anergy testing was also recommended, although recent studies have shown its poor consistency and reliability, as well as the lack of benefit from chemoprophylaxis in anergic patients, especially if they can receive HAART[43-46]. Consequently, these tests are not currently recommended when deciding on the treatment of latent tuberculous infection[47] (DII). It has been suggested that HAART-mediated immune reconstitution could give a positive Mantoux test or other skin tests in previously anergic patients. Nevertheless, in a Spanish multicenter study including HIV-infected patients with < 50 CD4+ lymphocytes/uL and cutaneous anergy, reversion of the anergy was observed in more than one third of the patients who increased their CD4+ T cell count after prolonged HAART, with no response to tuberculin observed in any cases[48]. Therefore, there is no basis for repeating the Mantoux test as an immune reconstitution measure after HAART. The test should be repeated to evaluate the risk of conversion in people who live in areas with a high risk of transmission of active tuberculosis (BIII).

There can be no doubt that the two groups of patients who should receive treatment for latent tuberculous infection are those with a positive Mantoux test (≥ 5 mm) (AI) and those who have come into close contact with a person with bacilliferous TB (BII). The risk of tuberculosis among anergic patients varies a great deal from one study to another, therefore universal recommendations cannot be made[49-51]. Prophylaxis is indicated in anergic patients with a greater risk of infection by *M. tuberculosis*, for example, those with a previous positive Mantoux test, those who have had prolonged contact with people with active tuberculosis and those who have spent long periods in prisons without receiving adequate prophylaxis (CIII). Before starting chemoprophylaxis, it is important to rule out active tuberculosis by clinical evaluation and chest X-ray; when there is the slightest suspicion of tuberculous disease, microbiology tests should also be performed.

Drugs and regimens. In antituberculous chemoprophylaxis, the following have proven to be efficacious: isoniazid daily or two days per week for 6-12 months[52-55], rifampin with pyrazinamide daily for 2 or 3 months[56] or every other day[57], and isoniazid with rifampin for three months[44] (AI). The latest guidelines from the American Thoracic Society and the Centers for Disease Control and Prevention recommend regimens with isoniazid for nine months and advise against regimens of 6 or 12 months[58]. Furthermore, direct supervision of chemoprophylaxis is recommended when it is administered on alternate days, especially in short regimens, and also when six-month isoniazid regimens are used in severely immunodepressed patients. There are no data which lead us to believe that administration of isoniazid for more than 12 months or for life provides additional advantages. Therefore, these strategies are not recommended (EIII).

It is important to point out that after reports of severe hepatotoxicity, which in some cases is fatal, with regimens of rifampin and pyrazinamide, the CDC collected information on cohorts of patients in the U.S. who had received prophylaxis with these regimens. They found an abnormally high frequency of hospital admissions and death due to hepatic toxicity from these drugs. On the basis of these findings, the American Thoracic Society, the Centers for Disease Control and Prevention and the Infectious Diseases Society of America do not recommend using this prophylaxis regimen[59]. Nevertheless, in the two large clinical trials which studied the regimens of rifampin and pyrazinamide in HIV-infected patients, no differences were observed in adverse effects or global mortality among groups assigned to rifampin and pyrazinamide and those assigned to isoniazid[56,57]. For this reason, these regimens could be used in HIV-infected patients in situations where there are clear practical advantages for the patient or in tuberculosis control programs as long as a strict clinical and analytical follow-up of the patient is carried out (DI).

In the case of infection by isoniazid-resistant *M. tuberculosis*, rifampin can be used for only four months. A short regimen of rifampin and pyrazinamide can also be used, but in the light of what has previously been mentioned, it is prudent to avoid this regimen when another efficacious regimen can be used[60].

Interactions with antiretroviral drugs. Isoniazid can be administered with any combination of antiretrovirals. Rifampin must not be administered simultaneously with some protease inhibitors (indinavir, nelfinavir, saquinavir, amprenavir, lopinavir/ritonavir) or with some non-nucleoside reverse transcriptase inhibitors (delavirdine). The following can be administered with rifampin: all nucleoside analogs, ritonavir as the only protease inhibitor[61] and the non-nucleosides nevirapine and efavirenz[62,63], and perhaps also the combination of two protease inhibitors[64]. Rifabutin is recommended as an alternative to rifampin in patients whose antiretroviral drugs interact with it; although it should be made clear that there are no clinical studies which support this recommendation. When combined with indinavir, nelfinavir or amprenavir, rifabutin can be administered daily but at half the dose, or at the complete dose but only two or three days per week. In these cases it will also be necessary to increase the dose of the protease inhibitors[65]. Rifabutin in combination with ritonavir or with lopinavir/ritonavir must be administered at half-dose two or three days per week.

Rifampin increases the hepatic metabolism of methadone and usually precipitates withdrawal symptoms in patients in opiate withdrawal programs. It is important to inform the patient about this undesirable effect and increase the dose of methadone to the necessary level.

Vaccination with BCG: This vaccine is contraindicated in HIV-infected patients due to the controversial nature of its efficacy and the risk of BCG-disseminated disease[66] (EIII).

Secondary prophylaxis

Secondary prophylaxis is not recommended in patients with documented tuberculosis (EIII).

Mycobacterium avium complex (MAC) (Table 4)

Prevention of exposure to the pathogen

MAC is a ubiquitous microorganism in the environment (including water and food) and no efficacious measures are known to prevent its acquisition.

Primary prophylaxis

Clarithromycin (500 mg/12 hours) or azithromycin (1200 mg, once per week) prevents disseminated MAC infection[67,68] (AI). Nevertheless, this strategy is not recommended in our environment given the low incidence of this opportunistic infection even before the introduction of HAART (DIII). In a cohort study performed in Spain during the HAART era including 200 patients with CD4+ T cell counts below 50/uL, the incidence of disseminated MAC infection was 2 cases per 100 patients/year. In special situations, for example, in patients with CD4+ T cell counts constantly below 50/uL and with no possibility of receiving HAART, primary prophylaxis can only be considered with some of the abovementioned regimens. Primary prophylaxis can be interrupted safely in patients who manage to maintain CD4+ T cell counts above 100/uL for longer than 3-6 months[69] (AI).

Secondary prophylaxis

Patients with disseminated MAC infection must receive therapy with clarithromycin (or azithromycin as an alternative) and ethambutol for as long as they are severely immunodepressed (AI).

Withdrawal of prophylaxis

During the pre-HAART era, lifelong maintenance treatment was recommended, although more and more data support its withdrawal in patients who maintain CD4+ T cell counts above 100/uL for more than six months (BII) (**Table 3**)[70-73].

Other bacteria (Table 4)

Streptococcus pneumoniae

There is some controversy concerning the recommendation of pneumococcal vaccine in HIV-infected patients. Some observational studies have shown a certain degree of protection with the vaccine. Nevertheless, in a randomised, double-blind study in Africa, no beneficial effect was found with the vaccine and an association between the vaccination and a greater risk of pneumococcal disease was observed[74]. A recent review of studies to date concluded that pneumococcal vaccine confers no benefit and its systematic use is not advised[75] (CI). If used, it is recommended in patients with a CD4+ T cell count >200/uL or even in patients with lower counts, although the response may be even less certain. Revaccination is likely to be necessary every five years, but there are no data supporting this recommendation.

Haemophilus influenzae

HIV-infected children must receive the *Haemophilus influenzae* vaccine in line with the habitual vaccination schedule (AI). This vaccine is neither indicated nor contraindicated in adults.

Miscellaneous

No primary or secondary prophylaxis is currently recommended in infections by *Salmonella no-typhi*, *Campylobacter spp* or *Bartonella spp* (EIII).

Prophylaxis of fungal infections

Candida (Table 5)

Prevention of exposure to the pathogen

Oropharyngeal candidiasis is the most common opportunistic infection in HIV-infected patients. *Candida albicans* (*C. albicans*) – the main pathogen in this mycosis –

TABLE 5. **Prophylaxis of opportunistic infections caused by fungi in HIV-infected adolescents and adults**

Pathogen	Indication	First Choice	Alternative
Primary prophylaxis			
Candida	Not indicated		
Cryptococcus neoformans	Not indicated		
Histoplasma capsulatum	CD4+ T cell count < 100/uL in endemic regions	Itraconazole 200 mg q.d.	None
Profilaxis secundaria			
Candida	Frequent relapses of oral or oesophageal candidiasis in patients who fail with HAART	Fluconazole 100 to 200 mg q.d.	Itraconazole solution 100 mg b.i.d. Amphotericin B IV if resistance to azoles
Cryptococcus neoformans	Documented cryptococcosis	Fluconazole 200 mg q.d.	Amphotericin B 1 mg/kg q.w.
Histoplasma capsulatum	Documented histoplasmosis	Itraconazole 200 mg b.i.d.	None
Coccidioides immitis	Documented coccidioidomycosis	Fluconazole 400 mg q.d.	Amphotericin B 1 mg/kg q.w. or Itraconazole 200 mg q.d.
Penicillium marneffei	Documented penicilliosis	Itraconazole 200 mg q.d.	None

Abbreviations:
q.d.: once per day. b.i.d.: twice per day. q.w.: once per week

is a commensal of the human digestive tract and, therefore, does not require prophylaxis.

Primary prophylaxis

Not recommended for this mycosis (DII)

Secondary prophylaxis

Oral candidiasis responds very well to systemic antifungals but in advanced immunodepression almost 80% of patients suffer relapses during the first three months after finishing therapy. Different studies have shown that fluconazole or itraconazole in solution reduces relapses. Nevertheless, systematic use is not recommended given that the relapses are not severe, can be diagnosed easily and respond well to treatment (DII). Furthermore, secondary prophylaxis with fluconazole may favor infections by azole-resistant strains of *Candida*. HAART is currently the best strategy for avoiding oropharyngeal candidiasis[76] (AII). Secondary prophylaxis is not recommended for oesophageal candidiasis for the same reasons as those above (DII). When HAART fails and the patient presents frequent relapses, secondary prophylaxis may be considered with daily doses of fluconazole (100 to 200 mg), as it has not been shown that weekly dosing is as efficacious in oesophageal candidiasis[77] (CIII). Some patients develop azole-resistant candidiasis and require chronic suppressive therapy with amphotericin B (CIII).

Cryptococcus neoformans (Table 5)

Prevention of exposure to the pathogen

No effective avoidance measures are known despite the fact that, in most cases, *Cryptococcus neoformans* enters the body via the respiratory tract.

Primary prophylaxis

Many studies have been published (retrospective series, case control studies and randomised clinical trials) which have shown a reduction in the risk of cryptococcosis with daily and even weekly doses of 100 to 200 mg of fluconazole. Despite this, primary prophylaxis for this mycosis is not recommended due to its relatively low incidence in developed countries, the fact that it has not been shown to improve patient survival[77,78], its cost and the possibility that it favors the development of resistant mycoses (DI).

Secondary prophylaxis

Before the introduction of HAART, relapses due to AIDS-associated cryptococcosis were very common after finishing induction treatment, and different studies showed the efficacy of secondary prophylaxis in preventing them. Recent studies have observed that in patients who show immune recovery with HAART, the risk of a relapse of cryptococcosis decreases[79,80]. In any case, all patients must carry out prophylaxis after treatment of the acute phase of cryptococcosis. The regimen of choice is fluconazole 200 mg/day, which reduces the frequency of relapses to 2-4% (AI)[81]. The alternatives are amphotericin B 1 mg/kg per week, with a relapse rate of 17%[81], and itraconazole 200 mg/day with a relapse rate of 23%[82].

Withdrawal of prophylaxis

There is a clinical trial[83] and a cohort study[84] which show that prophylaxis can be withdrawn safely in asymptomatic patients with a CD4+ T cell count above 100/uL for at least three months and a plasma viral load under 5000 copies/uL, without the need for the cryptococcal antigen to be negative (BII). After withdrawal of secondary prophylaxis, patients must receive periodic clinical and analytical check-ups. It is advisable to resume prophylaxis whenever the CD4+ T cell count falls below 100/uL or when a negative cryptococcal antigen reverts to positive (BIII).

Other fungi (Table 5)

Histoplasma capsulatum

This is the most frequent regional mycosis in AIDS patients. In endemic areas, histoplasmosis can be prevented by avoiding risk activities such as visits to caves, exposure to environmental dust, tree felling, cleaning of henhouses and demolishing or clearing of buildings (CIII). Primary prophylaxis is only indicated in patients with a CD4+ T cell count below 100/uL and with a high occupational risk in hyperendemic zones (CI)[85]. In Spain, primary prophylaxis could be considered for HIV-infected immigrants from endemic countries. For secondary prophylaxis, itraconazole 200 mg/12 hours is recommended (AII)[86]. For the withdrawal of secondary prophylaxis in patients who recover their immune function with HAART, the same criteria as for cryptococcosis can be applied (CIII).

Penicillium marneffei

Penicilliosis is an endemic mycosis in Southeast Asia which responds well to treatment with amphotericin B or itraconazole. Neither the reservoir of the fungus nor the portal of entry of the infection is well known, with the result that measures to avoid contagion cannot be recommended. In endemic areas, primary prophylaxis with itraconazole reduces incidence of penicilliosis in severely immunodepressed HIV-infected patients (especially with a CD4+ T cell count < 100/mm³), although this intervention has not been shown to prolong patient survival[87] (CII). Post-therapy relapses are very frequent but a prospective, randomised and placebo-controlled study has shown the efficacy of secondary prophylaxis with itraconazole at 200 mg/day[88] (AI). The impact of HAART on relapses of this opportunistic infection is not well known.

Miscellaneous

For coccidioidomycosis, secondary prophylaxis is recommended with fluconazole 400 mg/day or itraconazole 200 mg twice per day (AII)[89]. There are no studies on secondary prophylaxis for aspergillosis, blastomycosis or paracocccidioidomycosis[16].

Prophylaxis of infections by parasites

Most parasitic infections in HIV-infected patients result from reactivations of latent infections in situations of severe immunodepression and their incidence reflects

the prevalence of the different parasites in the general population[90]. Some of these reactivations can be prevented with chemoprophylaxis.

Pneumocystis jiroveci (previously Pneumocystis carinii) (Table 6)

Despite the fact that *Pneumocystis jiroveci* (*P. jiroveci*) is a fungus, it is included in this section because its prophylaxis and treatment are with antiparasitic drugs and not with antifungals. The taxonomy of the organism has changed. At present, *P. jiroveci* is the name reserved for the species which infects humans, and *Pneumocystis carinii* (*P. carinii*) is the name of the species which infects rodents[91]. Despite the change in nomenclature, the acronym PCP can be maintained, as it is also the abbreviation of "*Pneumocystis* pneumonia". *P. jiroveci* pneumonia can appear when the CD4+ T cell count is below 200/μL[92]. It has been the most common AIDS-defining disease and the first in which the efficacy of chemoprophylaxis was shown. Although its incidence has fallen during the HAART era[3,93,94], it is still 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 continues to be very high[95].

TABLE 6. Prophylaxis of opportunistic diseases caused by parasites in HIV-infected adolescents and adults

Pathogen	Indication	First Choice	Alternative
Primary prophylaxis			
Pneumocystis jiroveci	CD4+ T cell count < 200/uL Oral candidiasis FUO> 20 days AIDS-defining disease[1]	TMP-SMZ*, 1 "Forte" tablet t.i.w.[2,3]	TMP-SMZ, 1 "Forte" tab., q.d. TMP-SMZ, 1 Normal[4] tab. q.d. Aerosolized pentamidine (300 mg) every 28 days Dapsone (50 mg/ b.i.d. or 100 q.d.) Dapsone (100 mg b.i.w.) + pyrimethamine (50 mg b.i.w.) + folinic acid (15 mg q.w.) Dapsone (50 mg q.d.) + pyrimethamine (50 mg q.w.) + folinic acid (15 mg q.w.) Dapsone (200 mg q.w.) + pyrimethamine (75 mg q.w.) + folinic acid (15 mg q.w.) Atovaquone 1500 mg q.d.
Toxoplasma gondii	Anti Toxoplasma Ab + and CD4+ T cell count <100/uL	TMP-SMZ, 1 "Forte" tablet t.i.w.	TMP-SMZ, 1 "Forte" tab. q.d.[5] TMP-SMZ, 1 normal tab. q.d. Dapsone (100 mg b.i.w.) + pyrimethamine (50 mg b.i.w.) + folinic acid (15 mg q.w.) Dapsone (50 mg q.d.) + pyrimethamine (25 mg b.i.w.) + folinic acid (15 mg q.w.) Dapsone (100 mg q.w.) + pyrimethamine (25 mg q.w.) + folinic acid (15 mg q.w.) Pyrimethamine (50 mg t.i.w.) + folinic acid (15 mg t.i.w.) Atovaquone (1500 mg q.d.) with(out) pyrimethamine 25 mg q.d.) + folinic acid (15 mg q.d.)
Secondary prophylaxis			
Pneumocystis jiroveci	*P. jiroveci* pneumonia	TMP-SMZ, 1 "Forte" tab. t.i.w. TMP-SMZ, 1 "Forte" tab. q.d.	Dapsone (50 mg b.i.d. or 100 mg q.d.) Dapsone (50 mg q.d.) + pyrimethamine (50 mg q.w.) + folinic acid (15 mg q.w.) Pentamidine (300 mg/28 d) Atovaquone 1500 mg q.d. Sulfadoxine-pyrimethamine 1 tab. q.w.
Toxoplasma gondii	Cerebral toxoplasmosis	Sulfadiazine (1 g b.i.d.) + pyrimethamine (25 mg q.d.) + folinic acid (15 mg q.d.) Sulfadiazine (2 g t.i.w.) + pyrimethamine (50 mg t.i.w.) + folinic acid (15 mg t.i.w.) +	Clindamycin (300 mg/6 hours) + pyrimethamine (25 mg q.d.) + folinic acid (15 mg q.d.) Clindamycin (600 mg/8 hours) + pyrimethamine (25 mg q.d.) + folinic acid (15 mg q.d.) Sulfadoxine-pyrimethamine 1 tab. b.i.w.
Leishmania infantum	Visceral leishmaniasis	Amphotericin B lipid complex (3 mg/kg/d, every 21 days	Pentavalent antimonial 850 mg/month Pentamidine IV (300 mg every 3-4 weeks)
Isospora belli	Chronic diarrhea	TMP-SMZ, 1 normal tab. q.d. TMP-SMZ, 1 "Forte" tab,.q.d.	

Abbreviations: FUO: fever of unknown origin; TMP-SMZ: trimethoprim-sulfamethoxazole; q.d.: once per day; b.i.d.: twice per day; q.w.: 1 day per week; b.i.w.: 2 days per week; t.i.w.: 3 days per week; HIV: human immunodeficiency virus.
Notes: 1 Except in cases of tuberculosis and CD4+ T cell count above 350/μl. **2** The TMP-SMZ «Forte» tablet contains 160 mg of TMP and 800 mg of SMZ. **3** The first studies were carried out with TMP-SMZ 1 "Forte" tablet per day, but it was later shown that tolerance is better and efficacy similar with three "Forte" tablets per week or one "normal" tablet every day. **4** The normal TMP-SMZ tablet contains 80 mg of TMP and 400 mg of SMZ. **5** One "Forte" tablet per day is recommended in patients with severe immunodepression, in those simultaneously receiving drugs which reduce plasma levels of TMP-SMZ (e.g.: rifampin) and in those who have a very high IgG anti-*Toxoplasma* titer.

Prevention of exposure to the pathogen

It has traditionally been assumed that *P. jiroveci* enters the body via the respiratory tract during infancy, giving rise to a latent infection which can be reactivated in situations of severe immunodepression[96]. Recently, there have been reports suggesting that the infection can be transmitted to susceptible persons from patients with *P. jiroveci* pneumonia. Nevertheless, interpatient transmission must be very low, if it actually happens[97,98]. Therefore, patients at risk cannot be recommended to avoid close contact with others who suffer from *P. jiroveci* pneumonia (CIII).

Primary prophylaxis

This should be initiated when the CD4+ T cell count is below 200/μL and in the presence of an AIDS –defining disease, oral candidiasis or unexplained fever lasting more than 20 days (AI). Prophylaxis may be considered when the percentage of CD4 cells is below 14% or between 200-250 /mL and the patient cannot be monitored every three months[99] (BII). The combination of trimethoprim-sulfamethoxazole (TMP-SMZ) is considered the drug of choice due to its efficacy, ease of use and cost/benefit relationship (AI). The first studies were carried out with daily doses of TMP-SMZ of 160/800 mg (1 "Forte" tablet)[1], but it was later shown that tolerance is better and efficacy similar with three "Forte" tablets per week (AI) or with a "normal" tablet (80/400) every day (AI)[100,101]. If hypersensitivity reactions appear, desensitization must be tried before prescribing an alternative drug[16]. Aerosolized pentamidine is considered the second choice and must be administered using special equipment (Respigard¨ II or Fisoneb¨)(BI)[102]. This prophylaxis is less efficacious than oral TMP-SMZ and does not protect against extrapulmonary forms of the disease or other infections such as toxoplasmosis[103]. Its disadvantages include bronchospasm and metallic taste. In the care environment it can also lead to problems, such as irritability of the airway and risk of dissemination of tuberculosis. Therefore, this aerosol must be administered in an isolated, well-ventilated area. Valid, but less well studied alternatives are dapsone (BI), dapsone/pyrimethamine (BI) and atovaquone (BI)[101,104,105], which may require the administration of more than one drug, thus making it difficult to adhere to prophylaxis or HAART.

Secondary prophylaxis

After *P. jiroveci pneumonia*, secondary prophylaxis must be administered to prevent relapses (AI). TMP-SMZ (1 "Forte" tablet daily or three days per week) is more efficacious than aerosolized pentamidine to prevent local and/or extrapulmonary relapses[106] (AI).

Withdrawal of prophylaxis

Primary prophylaxis can be withdrawn in those patients receiving HAART for more than six months and who have a well controlled viral load (undetectable or <5000 copies/μL) and a CD4+ T cell count above 200/μL for at least three months[107-110] (AI). These same criteria are valid for the suspension of secondary prophylaxis[107,108,111-113] (AI). The withdrawal of prophylaxis reduces pharmacological toxicity, simplifies treatment and can make adherence to HAART easier as it reduces the pill burden. There have been reports of some cases of relapse of the disease after withdrawal of prophylaxis. These patients were generally elderly, had another type of immunosuppression (e.g. lymphoma), had developed *P. jiroveci* pneumonia with CD4+ T cell counts above 200/μL, or had abandoned HAART.

Restarting prophylaxis

Although no data are available, it is advisable to restart prophylaxis if the CD4+ T cell count falls below 200/μL or the patient presents an episode of *P. jiroveci* pneumonia (CIII).

Toxoplasma gondii (Table 6)

Cerebral toxoplasmosis is the most common form of encephalitis in AIDS and occurs in patients whose CD4+ T cell count is below 100/μL. This infection can complicate the course in 10-20% of HIV-infected patients with a positive *T. gondii* serology[114], although its incidence has fallen with the use of TMP-SMZ and HAART.

Prevention of exposure to the pathogen

T. gondii is acquired through consumption of contaminated meat, eggs, greens and vegetables, and by exposure to cat feces[115]. Patients with a negative serology must eat meat well cooked (the inside must not be pink). Those patients who do not wish to give up rarely-cooked meat, can freeze it to a temperature below -20ºC before cooking. They must also wash fruit and vegetables well to avoid infection (BIII). Hand-washing is advised after touching raw meat, vegetables or soil (gardening) (BIII). If a cat is kept as a pet, it should be fed using commercially available products and the meat consumed by the cat should be well cooked. Furthermore, its excrement should be cleared away using gloves (BIII).

Primary prophylaxis

Prophylaxis should be initiated in patients with positive serology (anti-Toxoplasma IgG antibodies) and CD4+ T cell counts below 100/μL (AII), although some authors recommend starting it with a CD4+ T cell count below 200/μL[101,116] (BII). The first studies of prophylaxis were retrospective observational studies of patients with prophylaxis for *P. jiroveci* with TMP-SMZ. Toxoplasmosis can be prevented with a normal daily tablet of TMP-SMZ (80/400) or a "forte" tablet (160/800) three days per week[116] (AII). Nevertheless, a daily "forte" tablet is advised in patients with severe immunodepression, in those simultaneously receiving drugs which can reduce the plasma levels of TMP-SMZ (e.g. rifampin) and in those whose with a very high anti-*Toxoplasma* IgG antibody titer[117-119] (BII). In patients who cannot tolerate TMP-SMZ, dapsone in combination with pyrimethamine and folinic acid (BI), atovaquone (alone or in combination with pyrimethamine and folinic acid) (CIII) or pyrimethamine (CI) can be administered[101,116,120,121].

Secondary prophylaxis

If maintenance treatment is not administered, relapse of cerebral toxoplasmosis occurs in 60 -100% of cases between 6 – 12 months after finishing induction treatment[122].

Of the accepted regimens for secondary prophylaxis, the most efficacious is the combination of pyrimethamine with sulfadiazine, which can be administered daily or on alternate days[123,124] (AI). If sulfadiazine cannot be administered, it can be replaced by clindamycin[123] (BI). If there is intolerance to both drugs, there is very little experience with alternatives. In these patients it is recommended to maintain therapy with the drug used during the acute phase: pyrimethamine alone or combined with atovaquone, azithromycin, minocycline or doxycillin, 5-fluorouracil and clindamycin, and minocycline or doxycillin with sulfadiazine. Similarly, there is very little experience with dapsone and pyrimethamine or with cotrimoxazole[123,125-142] (CII). Clarithromycin has also been used (1g/12 h) instead of azithromycin, but it is not recommended, given that clarithromycin at these doses has been associated with excessive mortality in a study on prophylaxis against MAC[143].

Withdrawal of prophylaxis

Although there are few studies, it is considered that primary prophylaxis can be withdrawn when the requisites for withdrawal of primary prophylaxis of *P. jiroveci* are met: HAART for at least six months, a CD4+ T cell count above 200 μL and controlled viral load[144-147] (AI). There are insufficient data in the literature which totally guarantee the withdrawal of secondary prophylaxis against this pathogen. Nevertheless, in the light of existing studies, it can be deduced that secondary prophylaxis can be suspended when the same criteria as for withdrawal of primary prophylaxis are met[73,111,144,148-151] (CIII) (**Table 3**).

Leishmania spp (Table 6)

Visceral leishmaniasis is one of the most frequent HIV-associated parasites in Spain and other Mediterranean countries. It presents in very immunodepressed patients and its prevalence varies according to the presence of *Leishmania infantum* (causal agent) in reservoirs (in our environment, canids). There is some evidence that HAART has modified the incidence of visceral leishmaniasis[152-154] and has reduced its relapses in HIV-infected patients[152,155]. Nevertheless, relapses may occur in patients who maintain a low CD4+ T cell count despite HAART[155].

Prevention of exposure to the pathogen

It seems likely that leishmaniasis can be transmitted from person to person via syringe sharing[154,156], thus providing yet another argument against this practice (CIII). Furthermore, in areas where the canine reservoirs present a high prevalence of infection, dogs should not be kept as pets (CIII).

Primary prophylaxis

No primary prophylaxis against this infection has been established.

Secondary prophylaxis

In the pre-HAART era, the accumulated incidence of relapses after a first episode of correctly treated visceral leishmaniasis was 60% at six months and 90% at 12 months[156,157]. The value of secondary prophylaxis in HIV-infected patients has been proven in a randomised, prospective and multicenter study carried out in Spain. This study compared the efficacy of amphotericin B lipid complex (3 mg/kg/d, every 21 days) with a control group. Intention-to-treat analysis at 12 months of follow-up showed that 50% of patients who received prophylaxis were free from relapses compared with 22% in the control group[158] (BI). A non-randomised retrospective study found that secondary prophylaxis with a monthly dose of 850 mg of pentavalent antimony (Glucantime) reduced the frequency of relapses of visceral leishmaniasis compared with historic controls and a group treated with allopurinol[157]. These findings have not been confirmed in prospective studies. Miltefosine is a recently introduced oral drug which is as efficacious as amphotericin B for the treatment of visceral leishmaniasis in non-HIV-infected patients[159], although there is very little experience with this drug in the treatment of leishmaniasis in HIV-infected patients both for the acute phase and for maintenance.

Withdrawal of prophylaxis

No clear recommendations can be made for the withdrawal of secondary prophylaxis against this pathogen, but its application could be considered in patients who manage to remain at least six months without relapses and who have a CD4+ T cell count above 200/uL and preferably 350/uL[160] (BII) (**Table 3**).

Other parasites (Table 6)

Cryptosporidium spp.

This is an intracellular protozoan which produces diarrhea in animals and humans. Of the species known, *C. parvum* and other species (*C. muris, C. maleagridis*) infect humans[161]. The parasite is acquired via the digestive tract on ingesting water or contaminated food and by contact with infected humans or animals. In HIV-infected patients with CD4+ T cell counts below 100/uL it produces chronic diarrhea which is refractory to treatment. Its frequency varies between 10-15% in the west and up to 50% in developing countries[162,163]. A lower proportion of patients present biliary involvement. In order to prevent cryptosporidiasis, the patient must be informed about the ubiquitous nature of the parasite, especially in foods which are consumed raw (vegetables, oysters, etc.), water and excreta. Contact should also be avoided with infected patients or, if this is not possible, extremely strict hygiene practices should be observed[16] (BIII). There is no efficacious chemoprophylaxis for this infection. Nevertheless, it has been suggested that prophylaxis for MAC with rifabutin or clarithromycin could reduce its incidence, although there are no conclusive data[164,165].

Microsporidia

In severely immunodepressed patients, *Microsporidiosis* is the most common cause of chronic diarrhea, without a pathogen which can be identified by conventional methods[166]. The route of transmission is not clear and its prevalence is unknown given the difficult nature of diagnosis. In our environment, it has been found in 22% of AIDS patients with chronic diarrhea[167]. Most episodes are caused by *Enterocytozoon bieneusi* and less fre-

quently by *Encephalitozoon intestinalis* which, in turn, can produce systemic infections. There is no chemoprophylaxis for this infection. Prolonged therapy with albendazole can control symptoms.

Isospora belli

This was a causal agent of chronic diarrhea during the early years of the AIDS epidemic but, at present, it has almost disappeared thanks to prophylaxis with TMP-SMZ[168,169]. After an episode of isosporiasis, secondary prophylaxis with TMP-SMZ must be started (CIII).

Acknowledgments

References

1. Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. JAMA 1988;259:1185-9.
2. Kitahata MM, Koepsell TD, Deyo RA, Maxwell CL, Dodge WT, Wagner EH. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. N Engl J Med 1996;334:701-6.
3. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-60.
4. Miller V, Mocroft A, Reiss P, Katlama C, Papadopoulos AI, Katzenstein T, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: Results from the EuroSIDA study. Ann Intern Med 1999;130:570-7.
5. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. Science 1997;277:112-6.
6. Komanduri KV, Viswanathan MN, Wieder ED, Schmidt DK, Bredt BM, Jacobson MA, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. Nat Med 1998;4:953-6.
7. Berenguer J, Laguna F, López-Aldeguer J, Moreno S. Prevención de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el VIH en la era del tratamiento antirretroviral de gran actividad. Recomendaciones de GESIDA/Plan Nacional Sobre el SIDA. Enferm Infecc Microbiol Clin 2000;18:457-68.
8. Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001;32:851-4.
9. Jacobson MA. Cytomegalovirus retinitis: New developments in prophylaxis and therapy. AIDS Clin Rev 1997:249-69.
10. Casado JL, Arrizabalaga J, Montes M, Marti-Belda P, Tural C, Pinilla J, et al. Incidence and risk factors for developing cytomegalovirus retinitis in HIV-infected patients receiving protease inhibitor therapy. Spanish CMV-AIDS Study Group. Aids 1999;13:1497-502.
11. Walsh JC, Jones CD, Barnes EA, Gazzard BG, Mitchell SM. Increasing survival in AIDS patients with cytomegalovirus retinitis treated with combination antiretroviral therapy including HIV protease inhibitors. Aids 1998;12:613-8.
12. Martin DF, Sierra-Madero J, Walmsley S, Wolitz RA, Macey K, Georgiou P, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002;346:1119-26.
13. Whitcup SM. Cytomegalovirus retinitis in the era of highly active antiretroviral therapy. JAMA 2000;283:653-7.
14. Zegans ME, Walton RC, Holland GN, O'Donnell JJ, Jacobson MA, Margolis TP. Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. Am J Ophthalmol 1998;125:292-300.
15. Karavellas MP, Plummer DJ, Macdonald JC, Torriani FJ, Shufelt CL, Azen SP, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. J Infect Dis 1999;179:697-700.
16. Centers for Disease Control and Prevention. 2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus. En: www.hivatis.org; 2001; p. 1-65.
17. Spector SA, McKinley GF, Lalezari JP, Samo T, Andruczk R, Follansbee S, et al. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. Roche Cooperative Oral Ganciclovir Study Group. N Engl J Med 1996;334:1491-7.
18. Brosgart CL, Louis TA, Hillman DW, Craig CP, Alston B, Fisher E, et al. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals. Terry Beirn Community Programs for Clinical Research on AIDS. Aids 1998;12:269-77.
19. Jacobson MA. Treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. N Engl J Med 1997;337:105-14.
20. Drew WL, Ives D, Lalezari JP, Crumpacker C, Follansbee SE, Spector SA, et al. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. Syntex Cooperative Oral Ganciclovir Study Group. N Engl J Med 1995;333:615-20.
21. Curran M, Noble S. Valganciclovir. Drugs 2001;61:1145-50; discussion 1151-2.
22. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med 1997;337:83-90.
23. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. N Engl J Med 1999; 340:1063-70.
24. Perry CM, Balfour JA. Fomivirsen. Drugs 1999;57:375-80.
25. Whitley RJ, Jacobson MA, Friedberg DN, Holland GN, Jabs DA, Dieterich DT, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: Recommendations of an international panel. International AIDS Society-USA. Arch Intern Med 1998;158:957-69.
26. Tural C, Romeu J, Sirera G, Andreu D, Conejero M, Ruiz S, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J Infect Dis 1998;177: 1080-3.
27. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophthalmology 1998;105:1259-64.
28. Whitcup SM, Fortin E, Lindblad AS, Griffiths P, Metcalf JA, Robinson MR, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. JAMA 1999;282:1633-7.
29. Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. J Infect Dis 1998;177:1182-7.
30. Jouan M, Saves M, Tubiana R, Carcelain G, Cassoux N, Aubron-Olivier C, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. Aids 2001;15:23-31.
31. Berenguer J, González J, Pulido F, Padilla B, Casado JL, Rubio R, et al. Discontinuation of secondary prophylaxis in patients with cytomegalovirus retinitis who have responded to highly active antiretroviral therapy. Clin Infect Dis 2002;34:394-7.
32. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Recomm Rep 2002;51(RR-6): 1-78.
33. Centers for Disease Control and Prevention. Prevention of varicella. Update recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1999;48(RR-6):1-5.
34. Centers for Disease Control and Prevention. Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 1996;45(RR-11):1-36.
35. González-García J, Guerra L, Amela C, Del Amo J, Bruguera M, Castilla J, et al. Coinfección por VIH y virus de las hepatitis A, B y C en pacientes adultos. Revisión y recomendaciones de GESIDA/PNS. www.gesidaseimc.com. En: Grupo de trabajo para la elaboración de recomendaciones sobre las hepatitis virales en pacientes infectados por el VIH; 2002.
36. Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286-90.

37. Neuzil KM, Coffey CS, Mitchel EF Jr, Griffin MR. Cardiopulmonary hospitalizations during influenza season in adults and adolescents with advanced HIV infection. J Acquir Immune Defic Syndr 2003;34:304-7.

38. Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2002;51(RR-3):1-31.

39. Berenguer J, Miralles P, Arrizabalaga J, Ribera E, Dronda F, Baraia-Etxaburu J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. Clin Infect Dis 2003;36:1047-52.

40. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989; 320:545-50.

41. Daley CL, Small PM, Schecter GF, Schoolnik GK, McAdam RA, Jacobs WR Jr, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. N Engl J Med 1992;326: 231-5.

42. Secretaría del Plan Nacional sobre el SIDA. Tuberculosis en pacientes infectados por el virus de la inmunodeficiencia humana. Madrid: Ministerio de Sanidad y Consumo, 2002.

43. Centers for Disease Control and Prevention. Anergy skin testing and tuberculosis preventive therapy for HIV-infected persons: Revised recommendations. Centers for Disease Control and Prevention. Morb Mortal Wkly Rep 1997;46(RR-15):1-10.

44. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med 1997;337: 801-8.

45. Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med 1997;337: 315-20.

46. Rivero A, López-Cortes L, Castillo R, Lozano F, García MA, Díez F, et al. Ensayo clínico aleatorizado de tres pautas de quimioprofilaxis para prevenir la tuberculosis en pacientes infectados por el VIH con anergia cutánea. Enferm Infecc Microbiol Clin 2003;21:287-92.

47. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations. Centers for Disease Control and Prevention. Morb Mortal Wkly Rep 1998;47(RR-20):1-58.

48. Moreno S, Menasalvas A, Usan L. Reversion of cutaneous anergy and the tuberculin skin test after initiation of highly active antiretroviral therapy (HAART) in HIV-infected patients with CD4 count < 50/μl. Abstract 1825. En: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999; San Francisco; 1999.

49. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA 1992;268:504-9.

50. Moreno S, Baraia-Etxaburu J, Bouza E, Parras F, Pérez-Tascón M, Miralles P, et al. Risk for developing tuberculosis among anergic patients infected with HIV. Ann Intern Med 1993;119:194-8.

51. Guelar A, Gatell JM, Verdejo J, Podzamczer D, Lozano L, Aznar E, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. Aids 1993;7:1345-9.

52. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993;342(8866):268-72.

53. Moreno S, Miralles P, Díaz MD, Baraia J, Padilla B, Berenguer J, et al. Isoniazid preventive therapy in human immunodeficiency virus-infected persons. Long-term effect on development of tuberculosis and survival. Arch Intern Med 1997;157:1729-34.

54. Hawken MP, Meme HK, Elliott LC, Chakaya JM, Morris JS, Githui WA, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: Results of a randomized controlled trial. Aids 1997;11:875-82.

55. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. Aids 1998;12:2447-54.

56. Gordin F, Chaisson RE, Matts JP, Miller C, De Lourdes García M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: An international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA 2000;283: 1445-50.

57. Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, et al. Randomized trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet 1998;351(9105): 786-92.

58. American Thoracic Society y Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47.

59. Centers for Disease Control and Prevention. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection–United States, 2003. MMWR Morb Mortal Wkly Rep 2003;52: 735-9.

60. Centers for Disease Control and Prevention. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations–United States, 2001. MMWR Morb Mortal Wkly Rep 2001;50:733-5.

61. Moreno S, Podzamczer D, Blázquez R, Iribarren JA, Ferrer E, Reparaz J, et al. Treatment of tuberculosis in HIV-infected patients: Safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin. Aids 2001;15:1185-7.

62. Oliva J, Moreno S, Sanz J, Ribera E, Molina JA, Rubio R, et al. Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis. Aids 2003;17:637-8.

63. Pedral-Sampaio D, Alves C, Netto E, Brites C, Freire JO, Badaro R. Efficacy of Efavirenz 600 mg Dose in the ARV therapy regimen for HIV patients receiving rifampicin in the treatment of tuberculosis. Abstract 784. En: 10th Conference on Retrovirus and Opportunistic Infections; 2003; Boston; 2003.

64. Veldkamp AI, Hoetelmans RM, Beijnen JH, Mulder JW, Meenhorst PL. Ritonavir enables combined therapy with rifampin and saquinavir. Clin Infect Dis 1999;29:1586.

65. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR Morb Mortal Wkly Rep 2000;49: μ185-9.

66. Weltman AC, Rose DN. The safety of Bacille Calmette-Guerin vaccination in HIV infection and AIDS. Aids 1993;7:149-57.

67. Havlir DV, Dube MP, Sattler FR, Forthal DN, Kemper CA, Dunne MW, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med 1996;335: 392-8.

68. Pierce M, Crampton S, Henry D, Heifets L, LaMarca A, Montecalvo M, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med 1996;335:384-91.

69. El-Sadr WM, Burman WJ, Grant LB, Matts JP, Hafner R, Crane L, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to antiretroviral therapy. N Engl J Med 2000;342:1085-92.

70. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated *Mycobacterium avium* complex infection after 12 months of antimycobacterial therapy combined with highly active antiretroviral therapy. J Infect Dis 1998;178:1446-9.

71. Martínez E, Miró JM, González J, Mallolas J, Gatell JM. Withdrawal of *Mycobacterium avium* complex suppressive therapy in HIV-1-infected patients on highly active antiretroviral therapy. Aids 1999;13:147-8.

72. Shafran SD, Gill MJ, Lalonde RG, Walmsley S-L, Toma E, Conway B, et al. Successful Discontinuation of MAC Therapy Following Effective HAART. Abstract 547. En: 8th Conference on Retroviruses and Opportunistic Infections; 2001; Chicago; IL; 2001.

73. Kirk O, Reiss P, Uberti-Foppa C, Bickel M, Gerstoft J, Pradier C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med 2002;137:239-50.

74. French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: Double-blind, randomised and placebo controlled trial. Lancet 2000;355(9221):2106-11.

75. Pierce AB, Hoy JF. Is the recommendation for pneumococcal vaccination of HIV patients evidence based? J Clin Virol 2001;22:255-61.

76. Arribas JR, Hernández-Albujar S, González-García JJ, Pena JM, González A, Canedo T, et al. Impact of protease inhibitor therapy on HIV-related oropharyngeal candidiasis. Aids 2000;14:979-85.

77. Powderly WG, Finkelstein D, Feinberg J, Frame P, He W, Van der Horst C, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N Engl J Med 1995;332:700-5.

78. Havlir DV, Dube MP, McCutchan JA, Forthal DN, Kemper CA, Dunne MW, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS [see comments]. Clin Infect Dis 1998;27: 1369-75.

79. Alberg JA, Price RW, Heeren DM, Pearce RB, Bredt B. Discontinuation of antifungal therapy for cryptococcosis after immunological response to antiretroviral therapy. En: 7th Conference on Retrovirus and Opportunistic Infections; 2000; San Francisco; 2000.

80. Martínez E, García-Viejo MA, Marcos MA, Pérez-Cuevas JB, Blanco JL, Mallolas J, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients responding to highly active antiretroviral therapy. Aids 2000;14:2615-7.

81. Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. N Engl J Med 1992;326:793-8.

82. Saag MS, Cloud GA, Graybill JR, Sobel JD, Tuazon CU, Johnson PC, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis 1999;28: 291-6.

83. Vibhagool A, Sungkanuparph S, Mootsikapun P, Chetchotisakd P, Tansuphaswaswadikul S, Bowonwatanuwong C, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: A prospective, multicenter, randomized study. Clin Infect Dis 2003;36: 1329-31.

84. Mussini C, Pezzotti P, Miró JM, Martínez E, López Bernaldo de Quirós JC, Cinque P, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in AIDS patients after HAART: An international, observational study. Clinical Infectious Diseases 2004;38:565-71.

85. McKinsey DS, Wheat LJ, Cloud GA, Pierce M, Black JR, Bamberger DM, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: Randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis 1999;28:1049-56.

86. Wheat J, Hafner R, Wulfsohn M, Spencer P, Squires K, Powderly W, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. The National Institute of Allergy and Infectious Diseases Clinical Trials and Mycoses Study Group Collaborators. Ann Intern Med 1993;118:610-6.

87. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. Clin Infect Dis 2002;34:277-84.

88. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the human immunodeficiency virus. N Engl J Med 1998;339:1739-43.

89. Galgiani JN, Catanzaro A, Cloud GA, Johnson RH, Williams PL, Mirels LF, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. Ann Intern Med 2000;133:676-86.

90. Miró JM, Buira E, Mallolas J, Gallart T, Moreno A, Zamora L, et al. Linfocitos CD4+ e infecciones oportunistas y neoplasias en pacientes con infección por el virus de la inmunodeficiencia humana. Med Clin (Barc) 1994;102: 566-70.

91. Stringer JR, Beard CB, Miller RF, Wakefield AE. A new name (Pneumocystis jiroveci) for Pneumocystis from humans. Emerg Infect Dis 2002;8:891-6.

92. Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. N Engl J Med 1990;322:161-5.

93. Bacellar H, Muñoz A, Hoover DR, Phair JP, Besley DR, Kingsley LA, et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+ cell counts < 100/mm³. Multicenter AIDS Cohort Study. J Infect Dis 1994;170:1284-7.

94. Kovacs JA, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. N Engl J Med 2000; 342:1416-29.

95. Fisk DT, Meshnick S, Kazanjian PH. Pneumocystis carinii pneumonia in patients in the developing world who have acquired immunodeficiency syndrome. Clin Infect Dis 2003;36:70-8.

96. Pifer LL, Hughes WT, Stagno S, Woods D. Pneumocystis carinii infection: Evidence for high prevalence in normal and immunosuppressed children. Pediatrics 1978;61:35-41.

97. Beard CB, Carter JL, Keely SP, Huang L, Pieniazek NJ, Moura IN, et al. Genetic variation in Pneumocystis carinii isolates from different geographic regions: Implications for transmission [In Process Citation]. Emerg Infect Dis 2000;6:265-72.

98. Manoloff ES, Francioli P, Taffe P, Van Melle G, Bille J, Hauser PM. Risk for Pneumocystis carinii transmission among patients with pneumonia: A molecular epidemiology study. Emerg Infect Dis 2003;9:132-4.

99. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary Pneumocystis carinii pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: Reassessment of indications for chemoprophylaxis. J Infect Dis 1998;178:1126-32.

100. Podzamczer D, Santín M, Jiménez J, Casanova A, Bolao F, Gudiol GR. Thrice-weekly cotrimoxazole is better than weekly dapsone-pyrimethamine for the primary prevention of Pneumocystis carinii pneumonia in HIV-infected patients. Aids 1993;7:501-6.

101. El-Sadr WM, Luskin-Hawk R, Yurik TM, Walker J, Abrams D, John SL, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Clin Infect Dis 1999;29: 775-83.

102. Hirschel B, Lazzarin A, Chopard P, Opravil M, Furrer HJ, Ruttimann S, et al. A controlled study of inhaled pentamidine for primary prevention of Pneumocystis carinii pneumonia. N Engl J Med 1991;324:1079-83.

103. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, Nielsen TL, Van der Graaf Y, Frissen JP, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. N Engl J Med 1992;327: 1836-41.

104. Blum RN, Miller LA, Gaggini LC, Cohn DL. Comparative trial of dapsone versus trimethoprim/sulfamethoxazole for primary prophylaxis of Pneumocystis carinii pneumonia. J Acquir Immune Defic Syndr 1992;5: 341-7.

105. Mallolas J, Zamora L, Gatell JM, Miró JM, Vernet E, Valls ME, et al. Primary prophylaxis for Pneumocystis carinii pneumonia: A randomized trial comparing cotrimoxazole, aerosolized pentamidine and dapsone plus pyrimethamine. Aids 1993;7:59-64.

106. Hardy WD, Feinberg J, Finkelstein DM, Power ME, He W, Kaczka C, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. N Engl J Med 1992;327:1842-8.

107. López Bernaldo de Quirós JC, Miró JM, Peña JM, Podzamczer D, Alberdi JC, Martínez E, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med 2001;344:159-67.

108. Koletar SL, Heald AE, Finkelstein D, Hafner R, Currier JS, McCutchan JA, et al. A prospective study of discontinuing primary and secondary Pneumocystis carinii pneumonia prophylaxis after CD4 cell count increase to > 200 × 106/l. Aids 2001;15:1509-15.

109. Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med 1999;340:1301-6.

110. García Vázquez E, De Gorgolas Hernández M, García Delgado R, Fernández Guerrero ML. Suspensión de profilaxis frente a neumonía por Pneumocystis carinii en pacientes con tratamiento antirretroviral combinado eficaz. Estudio de 85 casos. Med Clin (Barc) 1999;113:89-90.

111. Soriano V, Dona C, Rodríguez-Rosado R, Barreiro P, González-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. Aids 2000;14: 383-6.

112. Ledergerber B, Mocroft A, Reiss P, Furrer H, Kirk O, Bickel M, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. N Engl J Med 2001;344: 168-74.

113. Mussini C, Pezzotti P, Antinori A, Borghi V, Monforte A, Govoni A, et al. Discontinuation of secondary prophylaxis for Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients: A randomized trial by the CIOP Study Group. Clin Infect Dis 2003;36:645-51.

114. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis 1992;15:211-22.

115. Montoya JG, Remington JS. Toxoplasma gondii. En: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases (5th edition). Philadelphia: Churchill Livingstone, 2000; p. 2858-88.

116. Leport C, Chene G, Morlat P, Luft BJ, Rousseau F, Pueyo S, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: A double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. J Infect Dis 1996; 173:91-7.

117. Ribera E, Fernández-Sola A, Juste C, Rovira A, Romero FJ, Armadans-Gil L, et al. Comparison of high and low doses of trimethoprim-sulfamethoxazole for primary prevention of toxoplasmic encephalitis in human immunodeficiency virus-infected patients. Clin Infect Dis 1999;29:1461-6.

118. Derouin F, Leport C, Pueyo S, Morlat P, Letrillart B, Chene G, et al. Predictive value of *Toxoplasma gondii* antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. Aids 1996;10:1521-7.

119. Miró JM, García F, Cruceta A, Soriano A, Pujol M, Zamora L, et al. Trimethoprim-sulfamethoxazole versus dapsone plus pyrimethamine as primary prophylaxis of CNS toxoplasmosis and *P. carinii* pneumonia in HIV-infected patients. En: 6th European Conference on Clinical Aspects and Treatment of HIV-Infection. Hamburg (Germany). October 11-15, 1997; Abstract #647.

120. Torres RA, Barr M, Thorn M, Gregory G, Kiely S, Chanin E, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. Am J Med 1993;95:573-83.

121. Clotet B, Romeu J, Sirera G. Cerebral toxoplasmosis and prophylaxis for *Pneumocystis carinii* pneumonia. Ann Intern Med 1992;117:169.

122. Pedrol E, González-Clemente JM, Gatell JM, Mallolas J, Miró JM, Graus F, et al. Central nervous system toxoplasmosis in AIDS patients: Efficacy of an intermittent maintenance therapy. Aids 1990;4:511-7.

123. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1996;22:268-75.

124. Podzamczer D, Miró JM, Ferrer E, Gatell JM, Ramón JM, Ribera E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. Eur J Clin Microbiol Infect Dis 2000;19:89-95.

125. Canessa A, Del Bono V, De Leo P, Piersantelli N, Terragna A. Cotrimoxazole therapy of *Toxoplasma gondii* encephalitis in AIDS patients. Eur J Clin Microbiol Infect Dis 1992;11:125-30.

126. Chirgwin K, Hafner R, Leport C, Remington J, Andersen J, Bosler EM, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. Clin Infect Dis 2002;34:1243-50.

127. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. Lancet 1992;340(8820):637-8.

128. Torres RA, Weinberg W, Stansell J, Leoung G, Kovacs J, Rogers M, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. Clin Infect Dis 1997;24:422-9.

129. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. Aids 1996;10:1107-12.

130. Saba J, Morlat P, Raffi F, Hazebroucq V, Joly V, Leport C, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. Eur J Clin Microbiol Infect Dis 1993;12:853-6.

131. Jacobson JM, Hafner R, Remington J, Farthing C, Holden-Wiltse J, Bosler EM, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. Aids 2001;15:583-9.

132. Wiselka MJ, Read R, Finch RG. Response to oral and intravenous azithromycin in a patient with toxoplasma encephalitis and AIDS. J Infect 1996;33:227-9.

133. Fernández-Martín J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute Toxoplasma encephalitis in patients with AIDS. Antimicrob Agents Chemother 1991;35:2049-52.

134. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. Aids 1993;7:143-4.

135. Ward DJ. Dapsone/pyrimethamine for the treatment of toxoplasmic encephalitis (B133-PoB 3277). En: VIII International Conference on AIDS; 1992; Amsterdam; 1992.

136. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-Toxoplasma effects of dapsone alone and combined with pyrimethamine. Antimicrob Agents Chemother 1991;35:252-5.

137. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with human immunodeficiency virus. Antimicrob Agents Chemother 1995;39:276-7.

138. Pope-Pegram L, Gathe J, Bohn B, Piot D, Stool E. Treatment of presumed central nervous system toxoplasmosis with doxycycline. En: VII International Conference on AIDS; 1991; Florencia; 1991.

139. Bockman KW, Gathe J, Stool E, Frazier R, Najjar A, Piot D. Utility of tetracycline derivatives in treatment of CNS toxoplasmosis (abstract no. PO-B10-1427). En: International Conference on AIDS; 1993; Berlin; 1993.

140. Rouquet RM, Carre P, Massip P, Estival M, Leophonte P. Acute respiratory distress due to *Toxoplasma gondii* in one AIDS patient. Recovery with an association pyrimethamine-doxycyclin (abstract no. PuB 7486). En: VIII International Conference on AIDS; 1992; Amsterdam; 1992.

141. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. Scand J Infect Dis 1993;25:157-60.

142. Morris JT, Kelly JW. Effective treatment of cerebral toxoplasmosis with doxycycline. Am J Med 1992;93:107-8.

143. Cohn DL, Fisher EJ, Peng GT, Hodges JS, Chesnut J, Child CC, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: Excess mortality associated with high-dose clarithromycin. Terry Beirn Community Programs for Clinical Research on AIDS. Clin Infect Dis 1999;29:125-33.

144. Miró JM, López JC, Podzamczer D, Peña JM, Alberdi JC, Claramonte X, et al. Discontinuation of toxoplasmic encephalitis prophylaxis is safe in HIV-1 and *T. gondii* co-infected patients after immunological recovery with HAART: Preliminary results of the GESIDA 04/89-B study. En: 7th Conference on Retrovirus and Opportunistic Infections; 2000; Abstract #230.

145. Jubault V, Pacanowski J, Rabian C, Viard JP. Interruption of prophylaxis for major opportunistic infections in HIV-infected patients receiving triple combination antiretroviral therapy. Ann Med Interne (Paris) 2000;151: 163-8.

146. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. Lancet 2000;355(9222):2217-8.

147. Mussini C, Pezzotti P, Govoni A, Borghi V, Antinori A, d'Arminio Monforte A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: The changes in opportunistic prophylaxis study. J Infect Dis 2000;181:1635-42.

148. Guex AC, Radziwill AJ, Bucher HC. Discontinuation of secondary prophylaxis for toxoplasmic encephalitis in human immunodeficiency virus infection after immune restoration with highly active antiretroviral therapy. Clin Infect Dis 2000;30:602-3.

149. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? Aids 1999;13:1647-51.

150. Zeller V, Truffot C, Agher R, Bossi P, Tubiana R, Caumes E, et al. Discontinuation of secondary prophylaxis against disseminated *Mycobacterium avium* complex infection and toxoplasmic encephalitis. Clin Infect Dis 2002;34:662-7.

151. Miró JM, López JC, Podzamczer D, Peña JM, Alberdi JC, Claramonte X, et al. Discontinuation of toxoplasmic encephalitis (TE) maintenance therapy (MT) is safe in HIV-1 infected patients after immunological reconstitution with HAART. Long term follow-up of patients included in the GESIDA 04/98-B study (Abstract MoOrB1007). En: XIV International AIDS Conference; 2002; Barcelona; 2002.

152. Tortajada C, Pérez-Cuevas B, Moreno A, Martínez E, Mallolas J, García F, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. J Acquir Immune Defic Syndr 2002;30:364-6.

153. López-Velez R, Casado JL, Pintado V. Decline of a visceral leishmaniasis epidemic in HIV-infected patients after the introduction of highly active antiretroviral therapy (HAART). Clin Microbiol Infect 2001;7:394-5.

154. Pintado V, López-Vélez R. HIV-associated visceral leishmaniasis. Clin Microbiol Infect 2001;7:291-300.

155. Casado JL, López-Vélez R, Pintado V, Quereda C, Antela A, Moreno S. Relapsing visceral leishmaniasis in HIV-infected patients undergoing successful protease inhibitor therapy. Eur J Clin Microbiol Infect Dis 2001;20:202-5.

156. Alvar J, Canavate C, Gutiérrez-Solar B, Jiménez M, Laguna F, López-Vélez R, et al. Leishmania and human immunodeficiency virus coinfection: The first 10 years. Clin Microbiol Rev 1997;10:298-319.

157. Ribera E, Ocana I, De Otero J, Cortés E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. Am J Med 1996;100:496-501.

158. López-Vélez R, Videla S, Márquez M, Boix V, Jiménez-Mejías ME, Górgolas M. Amphotericin B lipid complex versus no-treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother 2003. En prensa.

159. Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002;347:1739-46.

160. Berenguer J, Cosin J, Miralles P, López JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. Aids 2000;14:2946-8.

161. Upton SJ, Current WL. The species of Cryptosporidium (Apicomplexa: Cryptosporidiidae) infecting mammals. J Parasitol 1985;71:625-9.

162. Petersen C. Cryptosporidiosis in patients infected with the human immunodeficiency virus. Clin Infect Dis 1992;15:903-9.

163. Lopez-Velez R, Tarazona R, García Camacho A, Gómez-Mampaso E, Guerrero A, Moreira V, et al. Intestinal and extraintestinal cryptosporidiosis in AIDS patients. Eur J Clin Microbiol Infect Dis 1995;14:677-81.

164. Holmberg SD, Moorman AC, Von Bargen JC, Palella FJ, Loveless MO, Ward DJ, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. HIV Outpatient Study (HOPS) Investigators. JAMA 1998;279:384-6.

165. Fichtenbaum CJ, Zackin R, Feinberg J, Benson C, Griffiths JK. Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. Aids 2000;14:2889-93.

166. Canning EU, Hollister WS. *Enterocytozoon bieneusi* (Microspora): Prevalence and pathogenicity in AIDS patients. Trans R Soc Trop Med Hyg 1990; 84:181-6.

167. Moreno Camacho A, Moreno Martínez A, Valls ME, Bordas JM, Piqué JM, Bombi JA, et al. Enteropatía crónica de etiología desconocida en pacientes con sida. Análisis de 40 casos. Med Clin (Barc) 1997;109: 452-6.

168. Felez MA, Miró JM, Mallolas J, Valls ME, Moreno A, Gatell JM, et al. Enteritis por *Isospora belli* en pacientes con SIDA. Descripción de nueve casos. Med Clin (Barc) 1990;95:84-8.

169. Moreno A, Gatell JM, Mensa J, Valls ME, Vila J, Claramonte X, et al. Incidencia de enteropatógenos en pacientes con infección por el virus de la inmunodeficiencia humana. Med Clin (Barc) 1994;102:205-8.