Treatment of Opportunistic Infections in Adolescent and Adult Patients Infected by the Human Immunodeficiency Virus During the Era of Highly Active Antiretroviral Therapy

Guidelines of the AIDS Study Group (GESIDA)/National AIDS Plan

GESIDA and National AIDS Plan Expert Committee

Despite the huge advance that highly active antiretroviral therapy has represented for the prognosis of infection by human immunodeficiency virus (HIV), opportunistic infections continue to be a cause of morbidity and mortality in HIV-infected patients. This is often the case because of severe immunodepression, poor adherence to antiretroviral therapy, failure of therapy, or the fact that patients are unaware of their HIV-positive status and debut with an opportunistic infection.
This article updates the guidelines on treatment of acute episodes of various opportunistic infections in HIV-infected patients, including infections due to parasites, fungi, viruses, mycobacteria, and bacteria. This edition has a new chapter on imported parasite infections as well as additional information on endemic mycoses in the chapter on fungal infections, taking into account the growing number of immigrants in our setting. Lastly, the chapter on the immune reconstitution syndrome has also been updated, providing relevant data on a phenomenon that has clinical and diagnostic repercussions in patients who start antiretroviral therapy while they are severely immunodepressed (English version available at http://www.gesida.seimc.org).

Key words: **AIDS. HIV infection. Opportunistic infections. Guidelines.**

Tratamiento de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el virus de la inmunodeficiencia humana en la era del tratamiento antirretroviral de gran actividad

Recomendaciones del Grupo de Estudio del Sida (GESIDA)/ Plan Nacional sobre el Sida

A pesar del gran avance que ha supuesto el tratamiento antirretroviral de gran actividad para el pronóstico de la infección por el virus de la inmunodeficiencia humana (VIH), las infecciones oportunistas (IO) continúan siendo causa de morbilidad y mortalidad en estos pacientes. Ocurre en muchos casos por la presencia de inmunodepresión grave, ante la falta de adherencia al tratamiento antirretroviral, el fracaso del mismo en ocasiones o el desconocimiento previo de la existencia de la infección por el VIH en pacientes que comienzan con una IO.
El presente artículo actualiza las recomendaciones de tratamiento del episodio agudo de diferentes infecciones en pacientes infectados por el VIH: infecciones parasitarias, fúngicas, víricas, micobacterianas y bacterianas. Se ha añadido en esta edición un apartado sobre infecciones parasitarias importadas –además de micosis endémicas en el apartado de infecciones fúngicas–, teniendo en cuenta el aumento de población inmigrante en nuestro país. Finalmente, se ha actualizado el capítulo sobre el síndrome de reconstitución inmune, relevante por su repercusión clínica y diagnóstica en pacientes que inician tratamiento antirretroviral en situación de inmunodepresión grave (versión en inglés en: http://www.gesida.seimc.org).

Palabras clave: **Sida. Infección VIH. Infecciones oportunistas. Documento de consenso**

Introduction

Since the beginning of the AIDS epidemic, opportunistic infections have been the main cause of morbidity and mortality in patients infected by the human immunodeficiency virus (HIV).[1]

The first important advance in therapy for HIV-infected patients was the initiation of efficacious regimens of primary and secondary prophylaxis against opportunistic infections. This led to a significant decrease in mortality even before the era of highly active antiretroviral therapy (HAART).[2] HAART produced a considerable change in the outcome of HIV infection, by dramatically reducing mortality and the incidence of opportunistic infections.[3] Nevertheless, opportunistic infections can still be observed today in several situations: in patients who are not aware

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of their HIV infection and whose first sign is an opportunistic infection; patients who cannot take HAART due to poor tolerance; and failure of HAART due to poor adherence or other reasons.[4,5] Therefore, treatment of opportunistic infections continues to be of interest in the management of HIV-infected patients.

In this article, we update our guidelines on the treatment of an acute episode of opportunistic infection and on the approach to immune reconstitution. The previous guidelines[6] have now been improved with the addition of sections on bacterial infection and imported diseases. Given recent demographic changes and the considerable increase in the number of HIV-infected immigrant patients,[4,5] we believe that information on imported diseases would be extremely useful. In order to classify our recommendations by strength and quality, we have applied the system used by the Infectious Diseases Society of America and the United States Department of Health and Social Services (DHHS) (Table 1).

Maintenance treatment and secondary prophylaxis of opportunistic infections are examined in a separate article; therefore, we shall not refer to these aspects here and advise readers to consult the relevant publication.[7]

The present article is a reduced version of the complete document that can be seen on the GESIDA web page (www.gesida.seimc.org). Therefore, in most cases, the recommended doses are presented only in the tables.

TABLE 1. **System for the Classification of the Recommendations of the Guidelines for Clinical Practice Used by the Infectious Diseases Society of America (IDSA) and the United States Public Health Service (USPHS)**

Strength of the Recommendation	
A	*Should always be offered.* There is strong evidence for efficacy and substantial clinical benefit
B	*Should generally be offered.* The evidence for efficacy *a)* is not very strong or *b)* is strong but the clinical benefit of the recommendation is limited
C	*Optional. a)* Insufficient evidence to support a recommendation for or against or *b)* evidence for efficacy might not outweigh the possible adverse effects (toxicity, drug interactions), cost, or alternative approaches
D	*Should generally not be offered.* Moderate evidence for *a)* lack of efficacy or *b)* for risk of adverse outcome
E	*Should never be offered.* Good evidence for lack of efficacy or risk for the patient
Quality of Evidence Supporting the Recommendation	
I	Evidence from at least one well-designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization or from cohort or case-control studies (preferably more than one center) or multiple case-series or spectacular results from noncontrolled studies
III	Opinions of professionals with a wide clinical experience in the field, descriptive studies, or reports of expert committees

Infections Caused by Parasites (Table 2)

Parasitic infections, especially those caused by protozoa—*Pneumocystis jiroveci* (included in this section even though it has long been considered a fungus), *Toxoplasma gondii*, *Leishmania donovani*, *Cryptosporidium parvum*, *Isospora belli*, *Microsporidia*—were very frequent in immunosuppressed HIV-infected patients before the introduction of HAART. They continue to be observed in a substantial number of cases.

Pneumocystis jiroveci

This organism mainly causes pneumonia, although in rare cases (traditionally reported in patients receiving prophylaxis with inhaled pentamidine) disseminated forms can develop with multiorgan involvement.

In cases of severe pneumonia ($PO_{2} <$ 70 mm Hg or an alveolar-arterial gradient > 35 mm Hg), the treatment of choice is intravenous cotrimoxazole for 21 days (AI).[8] Adjuvant treatment with corticosteroids is also indicated to improve respiratory function, reduce the risk of intubation, and decrease mortality (AI).[9] Folinic acid should not be added to prevent the myelotoxicity of cotrimoxazole, because its efficacy has not been clarified and there is evidence that it could favor treatment failure (DII).[10] However, it could be tried in patients whose complete blood count deteriorates during therapy (CIII). There have been reports of mutations causing resistance to cotrimoxazole, although their clinical relevance remains unclear.[11]

Patients who cannot tolerate cotrimoxazole (30%-40% in some series) can be treated with intravenous pentamidine (AI). Although some previous studies showed similar efficacy for cotrimoxazole and pentamidine, a more recent study revealed a lower rate of failure, a more rapid improvement in oxygenation, and a lower frequency of relapses in patients receiving cotrimoxazole.[8] Furthermore, even though cotrimoxazole frequently leads to adverse effects, these are usually less severe than those caused by intravenous pentamidine.[8] In cases of nonsevere allergy to cotrimoxazole, a desensitization regimen could be attempted. Another alternative is intravenous clindamycin combined with oral primaquine (BI). Trimetrexate is no longer commercialized. In mild-to-moderate *P. jiroveci* pneumonia, there are several oral therapy options for patients who cannot tolerate oral co-trimoxazole,[12] which is, once again, the drug of choice (AI): 1) dapsone-trimethoprim (BI)[13] (with similar efficacy and less toxicity, although uncomfortable due to the high pill burden), 2) clindamycin-primaquine (BI)[10,14] 3) atovaquone (BI)[15] (less effective than cotrimoxazole but better tolerated). Inhaled pentamidine is not recommended due to its poorer efficacy and greater frequency of relapses (DI). Patients whose initial therapy fails (lack of response at 5-7 days of treatment) while under oral treatment should switch to intravenous therapy and rule out concomitant respiratory infections.

Toxoplasma gondii

T. gondii causes infection of the central nervous system (CNS), less commonly with ocular involvement and disseminated infection.

Toxoplasmic encephalitis is the most common CNS infection in HIV-infected patients. In the case of a patient at risk of toxoplasmic encephalitis (CD4 < 100 cells/μL and positive *T. gondii* serology) with neurological symptoms and compatible focal lesions in computed tomography or

TABLE 2. **Treatment of Parasitic Infections in HIV-Infected Patients**

Microorganism/Disease	Treatment	
	First Choice	Alternatives
Pneumocystis jiroveci		
Pneumonia. Rarely at other sites or disseminated forms	*Severe forms:* Cotrimoxazole, 15-20 mg/kg/d of trimethoprim and 75-100 mg/kg/d of sulfamethoxazole iv or po, 21 days (spread over 3-4 doses) Add: Prednisone, 40 mg/12h po or iv, if PO_2 < 70 mm Hg	Pentamidine (isethionate) 3-4 mg/kg/day iv, 21 days Clindamycin, 600 mg po or iv/6-8h, + primaquine 30 mg/day po
	Mild-to-moderate forms: Cotrimoxazole same doses po	Dapsone 100 mg/d + trimethoprim 15-20 mg/kg/d Atovaquone 750 mg/12 h po
Toxoplasma gondii		
Focal central nervous system lesions in chorioretinitis. Rarely at other sites (lung, peritoneum, etc.)	Sulfadiazine, 4-6 g/day (in 4 doses) + pyrimethamine, 50 mg/day + folinic acid, 10 mg/day, 6-8 weeks	Clindamycin, 600 mg/6h iv or po + pyrimethamine, 50 mg/day + folinic acid, 10 mg/day, 6-8 weeks Azithromycin 900-1200 mg/day or clarithromycin 1 g/12h or + pyrimethamine, 50 mg/day (folinic acid) Atovaquone 1500 mg/12h + pyrimethamine, 50 mg/day (folinic acid) or + sulfadiazine 1-1.5 g/6h Cotrimoxazole (5 mg/kg TMP + 25 mg/kg sulfamethoxazole)/12h po or iv.
Leishmania donovani		
Kala-azar. Occasionally at unusual sites (skin, stomach, etc.)	Liposomal amphotericin 4 mg/kg days 1-5, 10, 17, 24, 31, 38 (total dose 20-60 mg/kg) Amphotericin lipid complex 3 mg/kg/d 5-10 days	Pentavalent antimony, 20 mg/kg/day im, 4 weeks Amphotericin B, 0.5 mg/kg (total dose, 1-1.5 g) Miltefosine 100 mg/d po, 4 weeks (compassionate use)
***Cryptosporidium* spp.**		
Enteritis, less frequent at other sites (biliary tract or lungs)	HAART	Nitazoxanide 500-1000 mg/12h po
Isospora belli		
Enteritis, exceptionally extraintestinal (retroperitoneal lymph nodes)	Cotrimoxazole, 160 mg of trimethoprim/ 800 mg of sulfamethoxazole, 3-4 times/day po 10 days	Pyrimethamine 50 mg/d + folinic acid Ciprofloxacin 500 mg/12h, 7 days
Microsporidia (*Enterocytozoon bieneusi*, *Encephalitozoon cuniculi*, others)	HAART	
Enteritis. Rarely, keratoconjunctivitis, hepatitis, and disseminated forms	Gastrointestinal disease caused by *E. bieneusi* Fumagillin 20 mg/8h po Disseminated disease (nonocular) and intestinal disease by species other than *E. bieneusi* Albendazole 400 mg/12h po Eye infections: see text	
Giardia lamblia*, *Entamoeba coli*, *Endolimax nana* and *Blastocystis hominis	Metronidazole, 250 mg/8h, po or iv, 5-7 days	Albendazole 400 mg/d, 5 days
Enteritis, enterocolitis		

HAART, highly active antiretroviral therapy; im, intramuscular; iv, intravenous; po, by mouth.

magnetic resonance of the cranium, empirical anti-*Toxoplasma* therapy should be started. Brain biopsy is reserved for those cases that do not respond to treatment after 7 to 14 days or initially in those where another cause is suspected, mainly cerebral lymphoma: negative *T. gondii* serology, correct primary prophylaxis for *T. gondii*, single lesion in magnetic resonance images.

The treatment of choice is the combination of sulfadiazine and pyrimethamine for 6 to 8 weeks (AI).[16,17] Folinic acid should be added to avoid the hematologic toxicity of pyrimethamine and the patient should drink abundant water to avoid tubular crystallization of sulfadiazine.

In specific patients who respond rapidly to treatment and whose radiological signs disappear, treatment of the acute phase could be reduced to 3 to 4 weeks and maintenance therapy could be started (BIII).

Patients with severe intracranial hypertension and a risk of brain herniation should receive corticosteroids

(starting with dexamethasone 16 mg followed by 4 mg/6 h) (BIII). In the case of an epileptic seizure, antiepilepsy drugs should be added (AIII), taking interactions into account—except valproic acid or levetiracetam—with protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI).

Patients who cannot tolerate sulfadiazine due to hypersensitivity reactions or other adverse effects can receive a combination of clindamycin and pyrimethamine (also with folinic acid) (AI).[16,17] The efficacy of this regimen is similar, although in the maintenance phase it has proven inferior to sulfadiazine-pyrimethamine.[17] Atovaquone in monotherapy or combined with pyrimethamine or sulfadiazine is also possible (BII).[18] Efficacy appears to correlate well with plasma levels and the drug is synergistic with pyrimethamine. Alternatives for patients who cannot tolerate clindamycin—despite the lack of experience in this area—include the macrolides clarithromycin or azithromycin combined—if possible—with pyrimethamine (BIII).[18,19] There is some experience with intravenous co-trimoxazole—the drug of choice for primary prophylaxis of this opportunistic infection[20]—which could prove particularly useful in patients who cannot receive therapy orally or through a nasogastric tube, and in those rare cases of simultaneous *P. jiroveci* pneumonia and *T. gondii* encephalitis (CII).

Extracerebral toxoplasmosis—although uncommon—is treated with the same regimens as in toxoplasmic encephalitis. However, the response may not be as favorable.

Protozoa causing intestinal infection: *Cryptosporidium parvum*, *Isospora belli*, *Microsporidia*, *Giardia lamblia*, and others

Despite the fact that the symptoms of infections caused by some of these pathogens is usually very similar—chronic diarrhea with gradual weight loss—treatment and outcome are different.

The response of *I. belli* is generally good and even spectacular, with cotrimoxazole as the antibiotic of choice (AI).[21] Pyrimethamine (BII) or ciprofloxacin (CI) have been proposed as alternatives. There has been favorable experience with diclazuril at 300 mg/12 h, albendazole plus ornidazole, and nitazoxanide.

Microsporidia involve several organisms, including *Enterocytozoon bieneusi*, *Encephalitozoon hellem*, *Septata intestinalis*, and *Nosema*, with different symptoms and locations.[22] *E. bieneusi* seems to respond to oral fumagillin (BII),[23] whereas albendazole would be effective against various species of microsporidia other than *Enterocytozoon* and is the recommended treatment for intestinal and disseminated microsporidiosis caused by microorganisms other than *E. bieneusi* (AII).[24] Ocular infections caused by microsporidia can be treated with topical fumagillin (BII) combined with oral albendazole to eliminate extraocular forms (BIII). HAART with immune reconstitution is associated with resolution of the symptoms of intestinal microsporidiasis; therefore, HAART should be offered as part of the initial management of this complication (AII).[25]

The same is true for *Cryptosporidium*, where the response to «specific» treatment has always been discouraging. Antiretroviral therapy may be associated with a complete resolution of the symptoms of this disease and should be used as part of the initial management (AII).[25]

Although there have been reports of improvement with paromomycin (1 g/12 h)[26] alone or in combination with azithromycin (600 mg/d), study results are contradictory or inconclusive, with the result that paromomycin is not currently recommended for this disease (CII).[27]

Nitazoxanide is active in vitro against *C. parvum* and at doses of 500-1000 mg/12 h for 14 days it showed a cure rate (clearance of microorganisms from stool and reduction of diarrhea) that was greater than the control group in patients with CD4 > 50/μL, but not in the most immunodepressed patients.[27,28]

Finally, *Giardia lamblia*, *Entamoeba coli*, *Endolimax nana*, and *Blastocystis hominis* also cause diarrhea in HIV-infected patients, although their presence in stool is not always pathogenic. They usually respond to metronidazole, although relapses are frequent. Alternatives could be albendazole, furazolidone, tinidazole, and quinacrine.

Leishmania donovani

Visceral leishmaniasis is an opportunistic infection that is common in endemic areas. Its clinical manifestations are similar to those of HIV-negative patients, although it affects atypical sites, such as the tongue and digestive tract, in some patients.

Antimonials (glucantime) have long been considered the treatment of choice. Amphotericin B has also proven efficacious in a Spanish study,[29] although it is much more difficult to administer. In the United States, liposomal amphotericin B is the only agent approved by the FDA against visceral leishmaniasis.[30] The initial response to treatment, whether with amphotericin or antimonials, is favorable in 60% to 90% of cases, although relapses are common and can lead to therapeutic failure or resistance. Glucantime is more poorly tolerated than amphotericin lipid complex.[31] If glucantime is administered to HIV-infected patients, it seems important to use a dose of 20 mg/kg/day for 4 weeks, since 3-week schedules seem less effective. The doses of the different amphotericins are shown in Table 2.

The similar efficacy and better tolerance of liposomal amphotericins compared with antimonials tip the scales in favor of the former as first choice (AII), but we must bear in mind their high cost and the lack of available data.

The alternatives for patients with visceral leishmaniasis who do not respond to first-choice drugs are miltefosine (100 mg/d for 4 weeks) and paromomycin (BIII). Miltefosine has been used in different countries with cure rates of up to 95% in non-HIV-infected patients and has shown a similar efficacy to that of glucantime. In HIV-infected patients, efficacy is poorer, with a greater risk of therapeutic failure and relapse,[32] but with fewer side effects than glucantime or amphotericin B. It can present gastrointestinal toxicity and is not advised during pregnancy due to the risk of teratogenicity. Intramuscular paromomycin has proven noninferior to amphotericin B in a randomized study in India in non-HIV-infected patients.[33] There is no published experience with this drug for HIV-infected patients.

Other drugs that have been studied for the treatment of visceral leishmaniasis are allopurinol (20 mg/m^2 in

3 doses) or the imidazoles, such as ketoconazole (400-600 mg/d) or itraconazole (400 mg/d) (CIII). Intravenous pentamidine is active, but is not recommended due to its toxicity (DII).

Infections Caused by Fungi (Table 3)

Candida Species

Candidiasis of the oropharyngeal and esophageal mucosa has been the most common opportunistic infection in HIV-infected patients. Vulvovaginal candidiasis is a serious problem in some patients, although no unequivocal association between this disease and HIV infection has been demonstrated. Esophageal candidiasis is an AIDS-defining infection. The symptoms are dysphagia and odynophagia, although it can be asymptomatic.

Fluconazole is the antifungal agent of choice for the treatment of mucosal candidiasis in HIV-infected patients. The usual recommendation for treatment is 7 to 14 days for oral candidiasis and 14 to 21 days for esophageal candidiasis (AI),[34,35] although one study showed that prolonging treatment of esophagitis for more than 10 days did not improve clinical response. Clinical improvement is the criterion that tells us that antifungal treatment is successful, since cultures can continue to be positive in the presence of a clinical improvement in 50% to 80% of cases.

Topical antifungals such as nystatin and clotrimazole can work in mild forms, but when the candidiasis is extensive, with esophageal involvement or advanced immunodepression, they are much less effective than systemic antifungals[36] (Table 3). Itraconazole in suspension is as effective as fluconazole against oral or esophageal candidiasis, although it is more poorly tolerated.[37] Ketoconazole and itraconazole are less effective than fluconazole owing to their erratic bioavailability—pH in the stomach must be sufficiently acidic for them to be absorbed.

From a clinical viewpoint, candidiasis that does not respond after 7 days at 100 mg is usually considered resistant to fluconazole.[38] The main cause of therapeutic failure in AIDS-associated mucosal candidiasis is resistance to antifungals, although, as mentioned above, insufficient concentration of the drug at the focus of infection can lead to failure due to insufficient absorption or pharmacologic interaction. Esophagitis caused by fluconazole-resistant *Candida* species can be treated with caspofungin,[39] amphotericin B, or posaconazole[40] (AII). Some patients with fluconazole-resistant oral candidiasis can improve transitorily with higher doses of fluconazole, with itraconazole in suspension, or with oral amphotericin B.

Cryptococcus neoformans

Cryptococcosis is an infection caused by *Cryptococcus neoformans*, an encapsulated yeast-like fungus that generally enters the body by the respiratory tract and manifests a surprising tendency to invade the central nervous system.[41] Cryptococcosis affects patients with CD4 lymphocyte counts of less than 100 cells/μL. It is characterized by fever, general malaise, and headache and there may occasionally be pulmonary infiltrates and cutaneous lesions. It must be stressed that few patients have a clear meningeal syndrome. The presence of encephalitis symptoms—lethargy, behavioral changes, memory loss—is usually caused by intracranial hypertension and indicates a poor prognosis.[41] Some patients suffer loss of sight due to intracranial hypertension or fungal invasion of the optic nerve.[42] When performing a lumbar puncture, it is important to measure the opening pressure of the cerebrospinal fluid in case it has to be reduced (see below).

Initial treatment involves an induction phase lasting 2 weeks with amphotericin B deoxycholate or liposomal amphotericin followed by an 8-week consolidation phase with fluconazole (AI). The addition of fluorocytosine in the induction phase can sterilize the cerebrospinal fluid more quickly and is associated with a lower relapse rate, although it does not improve the prognosis of the acute episode. Mortality with this treatment is below 10%.[43,44] There is less experience with the alternative—high-dose fluconazole (800 mg),[45] either alone or combined with fluorocytosine.[46] Voriconazole and posaconazole are active in vitro and can play a role in this condition, whereas caspofungin and other echinocandins are not active against *C. neoformans*.

Intracranial hypertension can lead to clinical decline and is the main cause of early death despite an adequate response to antifungal therapy.[47] Therefore, the opening pressure of the cerebrospinal fluid must always be measured. If the opening pressure is greater than 25 cm H_20 and the patient has headache or symptoms of encephalitis, or if it is greater than 35 cm H_20, daily evacuation by lumbar puncture should be performed (20-30 cc of cerebrospinal fluid). If the patient cannot tolerate this procedure or the procedure is ineffective, external drainage or a CSF shunt must be implanted[43,48] (AII).

Aspergillus Species

Advanced HIV infection is associated with defects in the function of macrophages and neutrophils against conidia and hyphae of *Aspergillus* species.[49] In the more important retrospective series on aspergillosis and HIV infection, the main predisposing factors were neutropenia, a CD4+ T lymphocyte count lower than 50 cells/μL, use of corticosteroids, and *P. jiroveci* pneumonia.[50,51]

The lung is the most common portal of entry and target organ in this mycosis. Clinical course depends to a large extent on whether or not neutropenia is present. If it is present, the course is quicker, given that there is less resistance to the development of hyphae, whose tendency to invade blood vessels means that they cause infarcts and dissemination to distant organs.[52] In patients with AIDS, aspergillosis manifests in different ways: 1) nodules and/or cavities—especially in the upper lobes—that have a subacute or chronic course and can cause hemoptysis, 2) diffuse or segmental infiltrates with an acute course (especially in patients with neutropenia), 3) tracheobronchitis with inflammation, ulceration, and, occasionally, formation of pseudomembranes that lead to obstruction of airflow, and 4) aspergilloma by colonization of pneumatoceles or tuberculous cavities by *P. jiroveci*.[50,51] These patients can also suffer from aspergillosis in any organ, regardless of whether the lung is involved. The most commonly affected organs are the paranasal sinuses, the brain, and the kidney.

Voriconazole is the treatment of choice in HIV-infected patients suffering from invasive aspergillosis (AI).[53,54] In

TABLE 3. **Treatment of Fungal Infections in HIV-Infected Patients**

Disease	Treatment	
	First Choice	**Alternatives**
Oral candidiasis	Fluconazole 100 mg/d × 7-14 d	Itraconazole oral solution 100 mg/d × 7-14 d Clotrimazole, tablets 10 mg 4-5 times/d × 7-14 d Nystatin, suspension 5 cc 4 times/d × 7-14 d Ketoconazole 200 mg/d × 7-14 d Itraconazole capsules 100 mg/d × 7-14 d
Esophageal candidiasis	Fluconazole 100 mg/d × 10-14 d	Itraconazole solution 200 mg/d × 10-14 d Itraconazole capsules 200 mg/d × 14-21 d Ketoconazole 400 mg/d × 14-21 d
Vulvovaginal candidiasis	Topical azoles (clotrimazole, butoconazole, miconazole, ticonazole, terconazole) for 3-7 days Nystatin tablets at 100,000 units/day for 14 days Oral itraconazole 200 mg BID for 1 day or 200 mg QD for 3 days Fluconazole 150 mg/day as a single dose	
Candidiasis refractory to azoles	Caspofungin 50 mg iv qd	Liposomal amphotericin B 3-5 mg/kg/d Amphotericin B deoxycholate 0.5-1 mg/kg/d Posaconazole 400 mg po bid
Cryptococcal meningitis		
Induction therapy	Amphotericin B deoxycholate 0.7 mg/kg/d ± fluorocytosine 25 mg/kg/6h × 2 weeks Liposomal amphotericin B 4 mg/kg/d ± fluorocytosine 25 mg/kg/6h × 2 weeks	Fluconazole 400-800 mg/d + fluorocytosine 25 mg/kg/6h × 2 weeks
Consolidation therapy	Fluconazole 400 mg/d 8 weeks	Itraconazole 200 mg/12h 8 weeks
Aspergillosis	Voriconazole 6 mg/kg bid po/iv × 1 day, followed by 4 mg/kg bid, then 200 mg bid	Amphotericin B deoxycholate 1-1.5 mg/kg/d iv Liposomal amphotericin B 5 mg/kg/d iv Itraconazole 200 mg iv bid × 4d, followed by 200 mg iv qd 600 mg/d po, followed by 200 mg po bid (accompanied by monitoring of itraconazole concentrations) Caspofungin 70 mg iv, followed by 50 mg iv qd
Endemic mycosis		
Histoplasmosis		
Severe disease	Acute phase (3-10 days) Amphotericin B deoxycholate 0.7 mg/kg/day × 2 weeks Liposomal amphotericin B 4 mg/kg/day × 2 weeks Continuation phase (12 weeks) Itraconazole 200 mg po bid	Itraconazole 400 mg iv qd Fluconazole 800 mg po qd
Less severe disease	Itraconazole 200 mg po tid × 3d and afterwards at 200 mg po bid for 12 weeks	Fluconazole 800 mg po qd (only mild forms)
Meningitis	Amphotericin B deoxycholate 0.7 mg/kg/d or liposomal amphotericin B 4 mg/kg/d × 12-16 weeks	
Coccidioidomycosis		
Severe nonmeningeal infection (diffuse pulmonary or disseminated)	Amphotericin B deoxycholate 0.7 mg/kg/d until improvement	Amphotericin B + fluconazole
Less severe nonmeningeal infection	Fluconazole 400-800 mg po qd Itraconazole 200 mg po qd	
Meningeal infection	Fluconazole 400-800 mg po qd	Intrathecal amphotericin B
Penicilliosis	Acute phase (3-10 days) Amphotericin B deoxycholate 0.6 mg/kg/d × 2 weeks Continuation phase (10 weeks) Itraconazole solution 400 mg po bid	

bid, twice daily; iv, intravenous; po, by mouth; qd, once daily; tid, three times daily.

this group of patients, interactions with NNRTI and PI must be taken into account. This condition can also be treated with amphotericin B deoxycholate, liposomal amphotericin, and itraconazole,[54,55] and data have recently been published on posaconazole (Table 3). Caspofungin is indicated in patients who are intolerant to standard therapy or whose standard therapy has failed or to improve standard therapy (BII).[54] Some case series show that the combination of caspofungin and liposomal amphotericin B or an azole that is active against *Aspergillus* species could be better than voriconazole in monotherapy (CII),[54] although randomized clinical trials are necessary to confirm this. It is important to correct the underlying immunological defect with HAART and, in neutropenic patients, with granulocyte colony stimulating factor (AII). During the pre-HAART, era few patients were cured and most died in the months after diagnosis.

Endemic Mycosis

Some mycoses are common in HIV-infected patients who live in or have traveled to areas where these mycoses are endemic. They usually occur in HIV-infected patients with CD4+ T lymphocyte counts of less than 200 cells/μL and give way to disseminated infections. In terms of pathogenesis, they are caused by a latent infection or even a de novo infection. Two of them, histoplasmosis and coccidioidomycosis, are on the list of AIDS-defining diseases. The main endemic areas of histoplasmosis are in North America (especially Indiana, Kansas, and Tennessee), Central America, South America, and the Caribbean islands of Cuba and Puerto Rico. In Africa, there is a variant of the disease produced by *H. capsulatum* var. *duboisii*, whose clinical course is more indolent and tends more commonly to involve the skin and bones. Coccidioidomycosis is produced by *Coccidioides immitis*, which lives in semidesert regions of southeast United States, the north of Mexico, and certain areas of Central and South America. Penicilliosis is caused by *Penicillium marneffei*, a thermal dimorphic fungus that lives in some countries in Southeast Asia. There have also been reports of cases of blastomycosis and paracoccidioidomycosis complicating HIV infection. The treatment of these mycoses is shown in Table 3.[56]

Infections Caused by Viruses (Table 4)

Herpes Simplex Virus (HSV)

The most frequent clinical forms are genital herpes, which is generally produced by HSV type 2, and orolabial herpes, which is usually due to HSV type 1. In both cases, but especially in genital herpes, recurrence is common.[57] In HIV-infected patients, genital herpes may be associated with more severe and prolonged lesions than in the general population,[57] and there may be an increased risk of acquisition and sexual transmission of HIV.[58]

Antiviral therapy with nucleosides (acyclovir, valacyclovir, and famciclovir) is effective, safe, and well tolerated[59,60] and, in the case of genital herpes, it could reduce the risk of transmission of HIV-1.[61] The recommended therapeutic regimens are shown in Table 4. The complete document available on the GESIDA web page includes a table showing the toxicity related to the treatment of viral infections.

Orolabial or genital herpes

Antiviral treatment of orolabial or genital herpes reduces local symptoms, accelerates healing of the lesions, reduces excretion of the virus, prevents the appearance of new lesions, and reduces the risk of progression or dissemination of existing lesions. The most habitual regimens are based on oral acyclovir, famciclovir, or valacyclovir for 7-10 days (AII).[59,60] Famciclovir and valacyclovir have a more convenient dosing schedule, but are more expensive. In more severe cases, it may be preferable to use intravenous acyclovir (AIII).

Recurrent mucocutaneous herpes

Recurrences are more common in genital herpes and are treated in the same way as the initial episodes, although treatment is often extended to 2 weeks (BIII). Treatment is more effective if started early, during the prodromal phase, or on the first day after the lesions appear. In patients with recurring genital herpes, prolonged suppressive therapy with oral acyclovir, valacyclovir, or famciclovir reduces the frequency of recurrences by 70% to 80%[61-67]; therefore, it should be offered to all HIV-infected patients with recurrent genital herpes (AI).[68,69]

Encephalitis

Treatment for herpes encephalitis is the same as for immunocompetent patients. Intravenous acyclovir is recommended at 10 mg/kg every 8 hours for 14 to 21 days (AII). It should be started empirically as soon as possible after the diagnosis is suspected.

Gastrointestinal disease

Herpes proctitis and esophagitis respond to systemic acyclovir. Treatment is usually started intravenously and continued orally. If episodes prove to be recurrent, suppressive therapy may be necessary. *Infections by acyclovir-resistant HSV*. The possibility of resistance to antivirals must be considered when the lesions do not improve after 7-10 days of correctly administered treatment. When resistance is suspected, a sample of the lesion must be taken for culture and, if the virus is isolated, an antiviral susceptibility test should be performed.[70] The recommended treatment is intravenous foscarnet (AII).[71] However, up to 60% of patients with nucleoside-resistant isolates treated with foscarnet can develop resistance to this drug.[72] Cidofovir and trifluridine may also be useful in the treatment of acyclovir-resistant strains (CIII).[73]

Varicella Zoster Virus

The incidence of infections by varicella zoster virus is much greater in HIV-infected patients than in the general population. They can appear with any CD4 lymphocyte count and, as occurs in the general population, in most cases they present as herpes zoster. In patients with advanced immunodepression, clinical presentation can be different and/or the clinical course altered. One of the best-characterized syndromes in HIV-infected patients is retinal necrosis.

Localized herpes zoster

The most habitual regimens are based on oral acyclovir, famciclovir, or valacyclovir for 7-10 days (AII) (Table 4).[74] Treatment is aimed at preventing dissemina-

TABLE 4. **Treatment of Opportunistic Infections Produced by Viruses in HIV-Infected Patients**

	Treatment of Choice	Alternative Treatments
Infections caused by the herpes simplex virus	**Nonsevere orolabial or genital herpes** Acyclovir 400 mg po every 8 h or acyclovir 200 mg po 5 times/day or famciclovir 500 mg po every 12 h or valacyclovir 1 g po every 12h for 7-10 days	In acyclovir-resistant HSV/refractory herpes, foscarnet 40 mg/kg iv every 8 h or foscarnet 60 mg/kg iv every 12h or cidofovir 5 mg/kg iv weekly or topical treatment with foscarnet 1%, cidofovir 3% or trifluridine (compounding pharmacy)
	Severe orolabial or genital herpes Initial treatment with acyclovir 5 mg/kg iv every 8 h. Continue with acyclovir 400 mg po every 8 h or famciclovir 500 mg po every 12h or valacyclovir 1 g po every 12h, until the lesions have healed	
	Recurring genital herpes Chronic suppressive therapy with acyclovir 400-800 mg po every 8-12h, or valacyclovir 500-1000 mg po every 12-24h, or famciclovir 250 mg po every 12h	
	Herpes encephalitis Acyclovir 10 mg/kg iv every 8 h for 14-21 days	
Infections produced by varicella-zoster virus	**Localized herpes zoster** Famciclovir 500 mg po every 8h, or valacyclovir 1 g po every 8h, o acyclovir 800 mg po every 6h for 7-10 days. Corticosteroids are not recommended	Acyclovir 10 mg/kg iv every 8h or foscarnet 40 mg/kg iv every 8h or foscarnet 60 mg/kg iv every 12h. In acyclovir-resistant VZV/refractory herpes zoster, foscarnet 40 mg/kg iv every 8h or foscarnet 60 mg/kg iv every 12h
	Varicella Acyclovir 10 mg/kg iv every 8h for 7-10 days (if there is no visceral involvement, treatment can be completed with oral valacyclovir 1 g po every 8h, or famciclovir 500 mg po every 8h or acyclovir 800 mg po every 6h)	
	Disseminated herpes zoster o herpes zoster with visceral involvement or peripheral retinal necrosis Acyclovir 10 mg/kg iv every 8h until resolution of the cutaneous and visceral lesions	Foscarnet 40 mg/kg iv every 8h or 60 mg/kg iv every 12h
	Rapidly progressive external retinal necrosis Acyclovir 10 mg/kg iv every 8h combined with foscarnet 60 mg/kg iv every 8h	Ganciclovir 5 mg/kg iv every 12h combined with foscarnet 60 mg/kg iv every 8h
Infections caused by cytomegalovirus	**Induction treatment** **– Retinitis with risk of blindness** Intraocular ganciclovir implant combined with valganciclovir 900 mg po every 24h, or ganciclovir 5 mg/kg iv every 12h for 14-21 days	Foscarnet 60 mg/kg iv every 8 h or 90 mg/kg iv every 12h for 14-21 days. Cidofovir 5 mg/kg iv every week for 2 weeks Ganciclovir plus foscarnet
	– Peripheral retinitis Valganciclovir 900 mg po every 12h for 14-21 days or ganciclovir 5 mg/kg iv every 12h for 14-21 days.	
	– Esophagitis or colitis Ganciclovir 5 mg/kg iv every 12h or foscarnet 60 mg/kg every 8h or foscarnet 90 mg/kg every 12h iv for 3-4 weeks or until symptoms resolve	Oral valganciclovir if symptoms are not sufficiently severe to prevent absorption Ganciclovir plus foscarnet
	– Pneumonitis Ganciclovir 5 mg/kg iv every 12h or foscarnet 60 mg/kg every 8h or foscarnet 90 mg/kg every 12h iv for 3-4 weeks or until symptoms resolve	Ganciclovir plus foscarnet
	– Neurological disease Ganciclovir iv combined with foscarnet until symptoms improve	

iv, intravenous; po, oral.

tion (especially in immunodepressed patients and those aged over 50 years), reducing the duration of symptoms, and reducing the risk of postherpetic neuralgia. There are no data on the benefit of using corticosteroids in HIV-infected patients, and they are generally not recommended (DIII). Antiviral drugs are most effective when

administered during the first 72 hours after the appearance of cutaneous lesions. In HIV-infected patients, lesions can continue to appear for more than 1 week and involvement of the ophthalmic branch of the trigeminal nerve is particularly severe. Therefore, in these cases, antiviral therapy is justified even after the aforementioned 72 hours (BIII).

Varicella, disseminated herpes zoster, or herpes zoster with visceral involvement

In varicella, disseminated herpes zoster, or when there is visceral involvement, it is preferable to start treatment with intravenous acyclovir (AIII).[71] It may be reasonable to continue with oral acyclovir, valacyclovir, or famciclovir once the patient has improved. Peripheral acute retinal necrosis usually responds to treatment with high-dose intravenous acyclovir, which may be continued with oral valacyclovir (BIII).[75,76] Laser photocoagulation of the retina may be necessary to prevent detachment. External rapidly progressive retinal necrosis can affect both eyes and the retina is detached in 70% of patients. At present, regimens combining intravenous acyclovir or ganciclovir with foscarnet are recommended (BIII).[77] Intravitreal therapy may be considered in some cases.[78]

Infections by acyclovir-resistant varicella zoster virus

Resistance of varicella zoster to nucleoside analogues is exceptional, although it must be taken into consideration when the lesions do not improve after 10 days of correctly administered treatment or if they take on a verrucous appearance. As occurs with herpes simplex, herpes zoster can respond to intravenous foscarnet (AII).[71]

Cytomegalovirus

The incidence of cytomegalovirus disease in HIV-infected patients has fallen dramatically since the introduction of HAART.[79] The most frequent clinical syndromes are retinitis, colitis, esophagitis, pneumonitis, and CNS involvement (dementia, ventriculoencephalitis, or ascending polyradiculoneuritis).

Retinitis

Retinitis is the most frequent process and is important because of the high risk of loss of vision involved. Retinitis with an imminent loss of vision (lesions close to the optic nerve or the macula) requires urgent treatment to conserve vision. In the pre-HAART era, the most common regimen for cytomegalovirus retinitis was intravenous ganciclovir,[80] foscarnet,[81] or cidofovir,[82] for an induction period of 2 to 3 weeks. These treatments led to favorable initial responses in more than 75% of patients and maintenance therapy was used with the same drugs intravenously or with oral ganciclovir (AI).[83]

Regimens containing intraocular ganciclovir implants substantially reduce progression of retinitis compared with intravenous ganciclovir, but they are associated with a higher risk of extraocular disease.[84,85] Regimens combining intraocular ganciclovir implants with oral ganciclovir offer protection that is comparable to that of intravenous ganciclovir against the development of extraocular disease.[84] The main disadvantage of oral ganciclovir is its scarce bioavailability (6%-9%), which means that very high doses must be administered several times daily. In recent years, the development of valganciclovir, a ganciclovir prodrug that is rapidly hydrolyzed to ganciclovir, has made treatment of cytomegalovirus disease much easier. A dose of 900 mg enables plasma concentrations to be reached that are similar to those obtained with 5 mg/kg of intravenous ganciclovir.

Therefore, the combination of an intraocular implant of ganciclovir with oral valganciclovir should be considered the treatment of choice, especially in patients with retinal lesions that have a high risk of loss of vision in the short term (AI). In less severe cases, or when there are no resources to carry out the implant, an induction cycle with intravenous ganciclovir followed by maintenance treatment with oral valganciclovir is recommended (AII). Valganciclovir may be an acceptable option as induction treatment in patients with peripheral retinitis (AII).[86] Foscarnet and cidofovir are second-choice drugs in patients who do not respond or present adverse events with ganciclovir or valganciclovir (AI). Other options involve the combination of ganciclovir and foscarnet or intravitreal injections of fomivirsen.

Extraocular disease

Experience with this condition is more limited than with retinitis. Recommendations are generally based on noncontrolled studies performed during the pre-HAART era that used regimens with intravenous ganciclovir or foscarnet (BII). A combination of ganciclovir with foscarnet is recommended for encephalitis (BIII). The role of maintenance treatment in patients with cytomegalovirus has not been well established.

Infections by ganciclovir-resistant cytomegalovirus

Rates of resistance to ganciclovir have fallen substantially in recent years.[87] These cases could respond to foscarnet or cidofovir (BII).[88]

Progressive Multifocal Leukoencephalopathy

There is currently no effective treatment. Despite initial data pointing to cidofovir, its efficacy was not confirmed in a controlled clinical trial (DI).[89] Experience with serotonin receptor inhibitors (entry of the virus in the oligodendrocytes) such as mirtazapine or cyproheptadine is limited and has not proven effective.

The introduction of HAART in 1996 led to an important decrease in the incidence of progressive multifocal leukoencephalopathy. Antiretroviral therapy has generally had a beneficial effect on the natural history of this disease, which was rapidly progressive and fatal during the pre-HAART era. A significant increase in survival has been reported, with improvement of neurological deficit and the abnormalities detected in neuroimaging, as well as clearance of the JC virus from cerebrospinal fluid.[90-92bis] However, some patients do not improve with HAART and in others there may be an exacerbation attributed to the immune reconstitution syndrome.[93] No treatment has proved effective in this situation. There have been some reports of improvement in symptoms and lesions observed by imaging with adjuvant corticosteroids, occasionally combined with temporary interruption of HAART.[94]

Infections Caused by Mycobacteria

(Tables 5 and 6)

Mycobacterium tuberculosis

Tuberculosis and HIV infection are two of the main causes of death in developing countries. They act in very dangerous synergy from pathogenesis to clinical presentation, treatment, and prevention, with severe clinical, social, and economic consequences.[95]

Treatment is basically similar to that used with the general population, with the same combinations of drugs to eradicate different bacillary populations and prevent the appearance of secondary resistance.[96] It is important to stress the importance of suitable adherence to treatment and to offer supervised treatment to all those groups with a priori predictors of poor adherence (eg, active intravenous drug users, homeless people, prisoners, patients with a history of poor adherence or previous loss to follow-up in outpatient clinics).[97]

Number of drugs

As is the case in noncoinfected patients, the decision to start therapy with 3 drugs (rifampicin plus isoniazid plus pyrazinamide) or 4 drugs (adding ethambutol) is based on the rates of primary resistance to isoniazid. Therefore, if this rate is over 4% or unknown (unusual in Spain, but common in several developing countries that are home to 1 of every 4 new HIV-infected patients), a fourth drug should be added (ethambutol or streptomycin) until the antibiogram is available (AI).

Duration of treatment

Classic trials showed that 6 months was standard, as long as treatment included rifampicin and isoniazid, with pyrazinamide during the first 2 months. Even in immunocompetent patients, if any of these drugs cannot be used for any reason and it is necessary to replace it with another first- or second-line drug, treatment must be extended in order to reduce the risk of recurrence.[96] Several studies have reported a greater risk of recurrence of tuberculosis in HIV-infected patients than in noninfected patients.[98]

These studies are limited in that very few patients have received HAART, with the result that their applicability to our clinical practice is debatable. In any case, until we have data with HAART, and given the importance of tuberculosis as a public health problem, it seems prudent to suggest that, as a general norm, treatment last 9 months (BII). Those patients who have an acceptable immune situation (more than 200 CD4/μL), a good clinical and microbiological response to treatment, and a good immune recovery with HAART could reduce their treatment period to 6 months (BIII). It is important for patients with pulmonary tuberculosis to have monthly microbiological checkups until cultures are negative. Intermittent treatment is not recommended in severely immunodepressed (CD4 < 100/μL) HIV-infected patients. If isoniazid or rifampicin cannot be administered, duration is uncertain, but should probably continue for 12 to 18 months (BIII).[99] Wherever possible, periodical microbiological checkups should be available during treatment: the presence of a

TABLE 5. **Treatment of Tuberculosis in HIV-Infected Patients**

Phase	Drugs[a]	Daily Dose	Intermittent Regimen Dose[b]	Remarks
Initial phase (2 months)	Isoniazid (H) +	5 mg/kg (max 300 mg)	Three times per week: 10 mg/kg (max 900 mg)	In addition to the contraindication of intermittent treatment in patients with < 100 CD4 cells/μL, available efficacy data with intermittent regimens are scarcer than in non-HIV-infected patients; therefore, daily administration is also preferable in patients with > 100 CD4. In any case, if it is used, it should be monitored directly
	rifampicin (R)[c] +	10 mg/kg (max 600 mg)	Three times per week, 10 mg/kg (max 600 mg)	
	pyrazinamide (Z) ±	25 mg/kg (max 2 g)	Three times per week, 35 mg/kg (max 3 g)	
	ethambutol (E)[d]	25 mg/kg	Three times per week, 30 mg/kg	
Continuation phase: 7 months[e]	Isoniazid +	5 mg/kg (max 300 mg)	If 3 times per week, as stated above. If twice per week, 15 mg/kg (max 900 mg)	
	rifampicin	10 mg/kg (max 600 mg)	Same dose as that stated in the initial phase, both if 2 or 3 times per week	

[a]Fixed regimens are recommended: for the combination I + R + Z, the possibilities are Rifater® (by tablet, H: 50 mg; R: 120 mg; Z: 300 mg) or Rimcure® (by tablet, H: 75 mg; R: 150 mg; Z: 400 mg). In addition, these should be supplemented by a dose of vitamin B6 of 25-50 mg, which can be administered in a single weekly dose of 300 mg.
[b]Intermittent treatment is contraindicated in patients with < 100 CD4 due to its lower efficacy. Experience with intermittent regimens is also lower in HIV-infected patients; therefore, daily therapy, if possible, is recommended, even in patients with > 100 CD4.
[c]If interactions make it impossible to use rifampicin, this can be replaced by rifabutin at the doses indicated in the interactions table. However, given that the appropriate levels of rifabutin depend completely on a suitable dose of antiretroviral therapy, treatment should be supervised.
[d]In patients from areas where there is resistance to H > 4% (as is the case with most immigrants in Spain), treatment should involve 4 drugs (H + R + Z + E) until the antibiogram is known. The appropriate commercial presentation is Rimstar® (by tablet: H: 75 mg; R: 150 mg; Z: 400 mg; E: 275 mg).
[e]In selected cases (see text), a standard duration of the maintenance phase of 4 months can be chosen.

TABLE 6. **Interactions Between Rifamycins and Antiretroviral Drugs**

Antiretroviral	Use With Rifamycin (RMP)	Use With Rifabutin (RBT)	Remarks
Nucleoside Analogues (NA)	Yes	Yes	
Non-nucleoside reverse transcriptase inhibitors (NNRTI)			
Efavirenz	Yes	Yes	Habitual dose of RMP and efavirenz, except 800 mg in > 60 Kg Increase RBT to 450-600 mg/day
Nevirapine	Not indicated	Yes	Habitual dose RBT RMP ↓ 37% NVP. Nevertheless, good clinical results in small samples. Not first choice.
Etravirin	No information	Yes	Does not require dose adjustment with RBT
Rilpivirin	Contraindicated	No data	
Protease Inhibitors (PI)			
Atazanavir/r	Contraindicated	Yes	RBT 150 mg 3 times/week
Darunavir/r	Contraindicated	Yes	RBT 150 mg 3 times/week
Fosamprenavir/r	Contraindicated	Yes	RBT 150 mg 3 times/week
Indinavir/r	Contraindicated		RBT 150 mg 3 times/week
Lopinavir/r	Contraindicated	Yes	RBT 150 mg 3 times/week
Nelfinavir	Contraindicated	Yes	RB 150 mg 3 times/week
Ritonavir	Yes	Yes	Habitual dose of RMP Reduce RBT to 150 mg 3 times/week
Saquinavir/r	Contraindicated due to toxicity	Yes	RBT 150 mg 3 times/week
Tipranavir	Contraindicated	Yes	RBT 150 mg 3 times/week
Fusion inhibitors			
Enfuvirtide	Yes	Yes	
Integrase inhibitors			
Raltegravir	Contraindicated at habitual doses. Other doses being studied	Yes	RBT at the daily habitual dose RMP reduces levels of raltegravir. Increased doses of raltegravir being studied
CCR5 inhibitors			
Maraviroc	Possible by adjusting dose	No studies	There are no clinical trials. PK studies in health volunteers suggest that RMP can be used by increasing the dose of MVC to 600 mg/12 hours. When it is combined with a boosted PI *in addition*, the SPC recommends reducing the dose of MVC to 150 mg/12 hours, but there are no clinical trials

MVC, maraviroc; NVP, nevirapine; PK, pharmacokinetics; SPC, summary of product characteristics.

positive culture at the fourth month of treatment means that treatment has failed and specific management is necessary.

Interactions, timing of HAART, and eligible drugs. Current guides on HAART recommend starting therapy with 2 nucleoside/nucleotide analogues and, as a third drug, an NNRTI or a PI boosted with ritonavir (PI/r).[100] The problem lies in the fact that the rifamycins (rifampicin > rifabutin > rifapentine) are potent inducers of the cytochrome CYP3A enzyme family, including CYP3A4 (rifabutin is also a substrate). Given that NNRTI and PIs are metabolized in this enzyme system, interactions become a relevant problem. Rifabutin is an alternative, although the dose must be adjusted.

Owing to this interaction, PIs/r cannot be used with rifampicin, since its levels are not therapeutic. Although saquinavir/r was initially thought to be an exception to this rule, the high incidence of hepatotoxicity with this combination contraindicates its use (BIII).[101]

In coinfected patients, there are 2 HAART options: a) NNRTI-based HAART (efavirenz is the most studied drug) in which the only adjustment necessary is to increase the dose to 800 mg/day for those patients weighing more than 60 kg[102] (some authors prefer to adjust the dose of efavirenz according to the plasma level) or b) use rifabutin instead of rifampicin in order to combine with a PI/r. Rifabutin presents several problems: *a)* it requires a dose adjustment—the dose of rifabutin is 150 mg 3 days per week with most PI/r (see Table 5); *b)* in some PIs the dose must be increased or they are contraindicated (LPV/r); *c)* even in those PIs that can be used, their levels are very sensitive to the absence rifabutin; with the result that treatment must be supervised; and *d)* as mentioned earlier, in patients with a CD4 count of less than 100 cells/μL, there have been reports of resistance with rifamycin administered in intermittent schedules. Therefore, it is preferable to maintain the standard tuberculosis regimen and base HAART on NNRTIs (BII). If, for any

reason (eg, resistance, toxicity), NNRTIs cannot be used, it is important to know that there are no relevant interactions between rifampicin and nucleoside analogues, or enfuvirtide; therefore, if necessary, an alternative HAART regimen can be designed. Available information on interactions between rifampicin and new drug families (CCR5 inhibitors and integrase inhibitors) can be consulted in Table 6. In cases of multiresistant tuberculosis where it is necessary to use other first- or second-line drugs, both PIs/r and NNRTIs are possible, given that no relevant interactions have been reported (also true for second-line antituberculous drugs). It is also important to remember the interaction between rifampicin and methadone that usually requires the dose of methadone to be increased in these patients.

Another key problem is the timing of HAART. It is clear that, after tuberculosis is diagnosed, priority must be given to its treatment. Concomitant treatment of HIV infection involves an increased risk of toxicity with the added difficulty of identifying the responsible drug and a risk of immune reconstitution syndrome (see below) in severely immunodepressed patients.[103] Furthermore, it has been shown that a late start in immunodepressed patients is associated with greater morbidity and mortality in the following months.[104] A practical approach could be to wait 2 weeks after the start of tuberculosis treatment before introducing antiretroviral drugs in patients with a CD4 + T lymphocyte count of less than 100 cells/μL. For patients whose immunological situation is less compromised (CD4+ between 100 and 200 cells/μL), it may be possible to wait until the maintenance phase before initiating HAART (although primary prophylaxis of other opportunistic infections must have been introduced from the start). With a CD4 count over 200 cells/μL, treatment could probably be started during the maintenance phase after waiting to finish tuberculosis treatment before initiating HAART in patients with CD4 counts above 350 cells/μL (BIII).

Toxicity caused by antituberculous drugs is also more common in HIV-infected patients, although its management is similar to that of noncoinfected patients.[98,105]

Lastly, there have been reports of cases of multiresistant tuberculosis. Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis that, in addition to being resistant to isoniazid and rifampicin, is resistant to at least 3 of the 6 main second-line families (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid).[106] This scenario is extremely worrying due to the risk of spread and transmission of very difficult-to-treat strains (if it is indeed possible to treat them).[106]

Mycobacterium avium complex (MAC)

Disseminated MAC infection appears in very advanced phases of HIV infection, and almost exclusively affects patients with a CD4+ lymphocyte count lower than 50 cells/μL. This disease has not been as relevant in Spain as in other developed countries.

As is the case with tuberculosis, disseminated MAC infection must be treated with combination therapy as monotherapy leads to resistance after a few weeks. These mycobacteria also present intrinsic resistance to several standard antituberculous agents such as isoniazid, pyrazinamide, and, often, streptomycin.

The most effective regimen and that which is associated with a lower incidence of macrolide resistance is the combination of clarithromycin, ethambutol, and rifabutin,[107] although it is limited by its interaction with antiretroviral drugs. In some cases, clarithromycin and ethambutol may be an alternative. There is less experience with azithromycin, although it can replace clarithromycin if efavirenz is to be used.

Infections Caused by Bacteria (Table 7)

HIV-infected patients have a greater incidence of bacterial infections, not only due to cellular immunodepression, but also due to humoral immunity disorders and other predisposing factors. These infections are almost always produced by habitual bacteria, can have atypical presentations, often involve bacteremia, and have high relapse rates, especially in patients with very low CD4 counts. The treatment of the most common bacterial infections is set out below.

Pneumonia Caused by Habitual Bacteria

Bacterial pneumonia is one of the main causes of morbidity and admission to hospital in HIV-infected patients.[108] The main agents are Streptococcus pneumoniae[109-111] and, to a lesser extent, *Haemophilus influenzae*.[112] *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative rods are more common in patients with CD4 counts below 100 cells/μL, with underlying lung disease, previous admissions with antibiotic therapy, a history of drug use, and nosocomial acquisition.[113] *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii*, and *Legionella pneumophila* are uncommon, although epidemiological and clinicoradiological data mean that they must be taken into consideration.

Empirical antimicrobial treatment of bacterial pneumonia in the HIV-infected patient must cover the most frequent pathogens and is no different from that recommended in therapy guidelines for non-HIV-infected patients.[114,115] Antimicrobial treatment of bacterial infections of the respiratory tract includes a third-generation cephalosporin alone or in combination with levofloxacin or clarithromycin, according to the severity of the patient's condition (AIII), at the habitual doses used in other patients. In patients with risk factors for infection by *P. aeruginosa*, cefepime or imipenem must be used.

Pneumonia Caused by Other Bacteria

Pulmonary infection caused by Nocardia species and *Rhodococcus equi* are typical of patients suffering from cellular immunosuppression; therefore, they can affect patients with advanced HIV infection. Neither the best regimen nor the most appropriate duration of therapy has been established for infection by *Nocardia* species. The preferred approach continues to be cotrimoxazole combined with imipenem or ceftriaxone in the case of disseminated disease, according to a study that showed synergy in experimental models (BIII). Treatment should last between 6 months and 12 months if there is involvement of the CNS.[116]

TABLE 7. **Treatment of Bacterial Infections in HIV-Infected Patients**

Bacteria	Clinical Condition	Treatment of Choice	Alternative Treatment
Streptococcus pneumoniae	Pneumonia Sinusitis	Sensitive and resistance Penicillin G sodium 6-12 MU/d iv Intermediate: Amoxicillin 1g/8h po 3rd-gen cephalosporin Resistant: 3rd-gen cephalosporin	Levofloxacin Vancomycin
Haemophilus influenzae	Pneumonia Sinusitis	β-lactamase (–): ampicillin iv or Amoxicillin po β-lactamase (+): amoxicillin/clavulanic acid 3rd-gen cephalosporin	Levofloxacin Cotrimoxazole
Pseudomonas aeruginosa	Pneumonia Tracheobronchitis Sinusitis/Otitis	Ceftazidime, piperacillin/tazobactam, cefepime or carbapenem (except ertapenem) + aminoglycoside	Ciprofloxacin (↑ dose) Colimycin
Staphylococcus aureus	Pneumonia Sepsis	Methicillin-sensitive: cloxacillin or cefazolin iv Methicillin-resistant: vancomycin iv	Levofloxacin ± rifampicin Linezolid Daptomycin (except pneumonia) Tigecycline
Nocardia species	Pneumonia Disseminated infection	Cotrimoxazole ≥ 6 months Imipenem or 3rd-generation cephalosporins + cotrimoxazole, followed by cotrimoxazole ≥ 12 months	Sulfadiazine Linezolid
Rhodococcus equi	Pneumonia	Vancomycin + imipenem + rifampicin, followed by clarithromycin + rifampicin po	Ciprofloxacin Linezolid
Salmonella species	Gastroenteritis (self-limiting or prolonged) Bacteremia Focal infection (bone, vascular, abscess)	Ciprofloxacin 200-400 mg/12h iv or 500-750 mg/12h po or levofloxacin 500 mg/d iv or po × 7 days to 6 weeks	Ceftriaxone Azithromycin Cotrimoxazole (if sensitive)
Campylobacter species	Enterocolitis Invasive disease (typhlitis, ulcerative colitis, etc) Bacteremia	Clarithromycin 500 mg/12h iv or po × 5 days to 4-6 weeks Combine with gentamicin × 2 weeks (if severe)	Azithromycin Fluorinated quinolone (if sensitive)
Shigella species	Colitis Bacteremia	Ciprofloxacin 200-400 mg/12h iv or 500-750 mg/12h po × 7 to 21 days	Ampicillin, Azithromycin Cotrimoxazole (if sensitive)
Clostridium difficile	Colitis	Metronidazole 250-500 mg/8h po × 10-14 days (if severe 500 mg/6-8h iv)	Vancomycin po
Treponema pallidum	Primary, secondary, and early latent syphilis	Penicillin G benzathine 2.4 MU/single im dose	Doxycycline 100 mg/12h po or ceftriaxone 1g/d im × 14 days Doxycycline 100 mg/12h po × 28 days
	Late latent syphilis or indeterminate-duration syphilis and tertiary syphilis	Penicillin G benzathine 2.4 MU/week im × 3 weeks	Procaine penicillin 2.4 MU/day im + Probenecid 500 mg/d or ceftriaxone 2g/d × 10-14 days, followed by penicillin G benzathine 2.4 MU/week im × 3 weeks
	Neurosyphilis, eye and ear involvement	Penicillin G sodium 3-4 MU/4h iv × 14 days ± Penicillin G benzathine 2.4 MU/week im × 3 weeks	
Bartonella henselae and *B. quintana*	Bacillary angiomatosis (cutaneous, disseminated)	Erythromycin 500 mg/8h and/or doxycycline 100 mg/12h	Azithromycin 500 mg/day Clarithromycin 500 mg/12h Ciprofloxacin 500-750 mg/12h
	With CNS involvement	Doxycycline + rifampicin	
Listeria monocytogenes	Meningitis, bacteremia and focal infections	Ampicillin 2g/4h iv + gentamicin 240 mg/day iv	Cotrimoxazole Vancomycin or linezolid

im, intramuscular; iv, intravenous; po, by mouth.

R. equi was originally described in animals, and in immunodepressed patients—especially HIV-infected patients—it produces subacute pneumonia with a tendency towards cavitation, bacteremia (70%-80%), and extrapulmonary dissemination.[117] There is no well-established treatment of choice. A combination of 2 to 3 bactericidal antibiotics (vancomycin, imipenem, or rifampicin) is recommended as initial therapy (4 to 6 weeks), preferably by

parenteral administration. This should be continued with 2 oral antibiotics with intracellular activity (erythromycin or clarithromycin plus rifampicin) for a long period (6 months or more) in order to avoid relapses (BIII).[118]

Bacterial Intestinal Infections

The bacteria that most often produce diarrhea in HIV-infected patients in developed countries are nontyphoid *Salmonella*, *Campylobacter jejuni*, and *Shigella* species.[119,120] *Clostridium difficile*-associated diarrhea is increasingly common. The main symptoms are acute self-limiting gastroenteritis, prolonged diarrhea with(out) invasive disease (typhlitis, intestinal ulceration, mesenteric adenitis), bacteremia with(out) intestinal symptoms and/or extraintestinal disease.[121] The treatment of choice for salmonellosis is a fluorinated quinolone (AIII),[121] preferably ciprofloxacin (AIII), whose duration will depend on the type of involvement. Unlike the self-limiting course of a healthy immunocompetent patient, an HIV-infected patient must be continually treated, owing to the risk of bacteremia, especially if the CD4 count is below 200 cells/μL (BIII). The alternative is a third-generation cephalosporin or cotrimoxazole if the strain is sensitive (BIII). Treatment lasts 5 to 7 days when symptoms are mild and up to 6 weeks or more for severe symptoms or when there are frequent relapses (BIII). The treatment of choice in *Campylobacter* infection is a macrolide, since resistance to quinolones is increasingly frequent (BIII).[122] Treatment can be combined with gentamicin in bacteremia or invasive disease (CIII). The treatment of choice for shigellosis is a fluorinated quinolone (AIII) for 5 to 7 days; the alternatives are ampicillin (if the strain responsible is sensitive), azithromycin, or cotrimoxazole (although resistance is increasing) (BIII).[123,124] Treatment should be prolonged for 2 weeks in the case of bacteremia (AIII). The treatment of choice for *C. difficile* colitis is metronidazole and the alternative is oral vancomycin (BIII).[125]

Systemic Bacterial Infections

Syphilis

The coexistence of syphilis and HIV infection is relatively frequent (observed in 7% of patients).[126] Clinical presentation is similar to that of the general population, although atypical forms, a greater incidence of failure with standard regimens, and earlier symptoms of neurosyphilis have been reported in HIV-infected patients.[127]

Penicillin G continues to be the treatment of choice (AII) for all the clinical stages of syphilis.[128] In the case of allergy, the patient should be desensitized, although regimens containing doxycycline are a useful alternative (BIII). Some data from the literature support the use of ceftriaxone, although the possibility of cross-reaction with penicillin must be taken into account (BIII).

Patients with primary, secondary, or early latent (less than 1 year) syphilis and HIV infection should receive a dose of intramuscular benzathine G penicillin (2.4 MU) (AII).[128-130] The alternatives—doxycycline, ceftriaxone, and azithromycin—have not been sufficiently evaluated in these patients to consider them as first-line treatments (BIII). The combination of amoxicillin/probenecid is not recommended (DIII).[131] Some authors think that a single dose of 2.4 MU of benzathine G penicillin or even a second or third weekly dose may not be enough to cure early involvement of the CNS or to prevent relapse in these patients and that it would be better to use intramuscular procaine penicillin at 1.2 MU/day for 10 to 14 days (CIII).[128]

Patients with late latent syphilis (more than 1 year) or syphilis of unknown duration and tertiary syphilis should be treated with 3 doses of penicillin G benzathine (AIII) and, if they are allergic, with doxycycline (BIII), once CNS involvement has been ruled out using lumbar puncture (AIII).

Patients with neurosyphilis or eye/ear involvement must be treated with penicillin G sodium followed or not by penicillin G benzathine (AIII). The alternative would be intramuscular procaine penicillin G combined with probenecid followed by penicillin G benzathine (CIII). Another option would be ceftriaxone, which is increasingly used, as it allows the patient to be treated without being admitted to hospital (CIII).

Bartonellosis (Bacillary Angiomatosis)

The main reservoir of this zoonosis is the domestic cat. Bartonella henselae and *Bartonella quintana* can lead to several clinical syndromes in HIV-infected patients, especially with CD4 counts less than 50 cells/μL.[132] These include cutaneous bacillary angiomatosis, disseminated bacillary angiomatosis (hepatic and/or splenic, osseous, pulmonary, or CNS peliosis), and chronic bacteremia.

The current recommendation for treatment is erythromycin and/or doxycycline as first choice (AII). Azithromycin or clarithromycin could be an alternative to erythromycin (BII), although they are less efficacious, whereas ciprofloxacin would be second-line therapy (CIII). Treatment should be extended for 3 months or more in order to avoid relapses (AII).

Listeriosis

Listeriosis is 100 to 1000 times more common in AIDS patients than in the general population, although, in most series, its incidence is no more than 0.1%. It usually produces meningitis, meningoencephalitis, brain abscesses, and bacteremia, especially patients with less than 100 CD4+ cells/μL.[133] Treatment is similar to that of other immunodepressed patients. Ampicillin combined with gentamicin is the most common regimen and has shown synergy in vitro (BII). Cotrimoxazole is a good alternative for patients who are allergic to penicillin and its penetration of the CNS is very good (BIII). The combination of ampicillin and cotrimoxazole has a lower rate of failure and neurological sequelae than the classic regimen (BIII).[134] The duration of treatment has not been well established and it has been suggested that treatment should be extended according to the symptoms (bacteremia 2 weeks, meningitis 3 or more weeks, brain abscess and brainstem encephalitis 6 weeks) (CIII).

Imported Parasitosis (Table 8)

The increase in immigration and trips to tropical countries has led to the detection of more imported diseases in Spain.

Entamoeba Species

Of all the species of Entamoeba that can infect man, only *E. histolytica* has invasive capacity. The treatment of invasive amebiasis (intestinal and extraintestinal) is based on nitroimidazoles and an intestinal amebicide to completely eradicate cysts (metronidazole eliminates less than 50% of cysts) (AI).[135-137] In cases of fulminant colitis, even with perforation, a conservative approach will be attempted by avoiding surgery and adding antibiotics to cover intestinal flora (BII).[138]

In general, liver abscesses should not be surgically drained, since this procedure does not speed up recovery and the response to medical treatment is very good (better than 90%) (AI).[139] Aspiration with or without continuous drainage can be considered when the response is torpid, diagnosis is doubtful, the abscess is big (more than 10 cm in diameter or more than 300 cm^3), or there is a danger of imminent rupture, especially if it affects the pericardium (AII). In the case of empyema or amebic pericarditis secondary to rupture of an abscess, percutaneous drainage with or without aspiration improves prognosis (surgery is usually also necessary), whereas peritonitis can benefit from more conservative care (BII).[138]

Plasmodium Species

Therapy is usually based on the species of parasite, the degree of resistance to antimalarial drugs, the patient's clinical situation, and the results of laboratory tests. Artemisinin derivatives combined with other antimalarial agents are the most efficacious drugs for the treatment of malaria. Nevertheless, these drugs will not be mentioned here as they are not available in Spain. In those patients who develop malaria while taking prophylaxis, treatment is with a different drug.

Interactions between antimalarial and antiretroviral drugs have received little attention, although they affect mainly NNRTIs and PIs, since they share metabolic pathways in the liver (essentially cytochrome P450)[140]: Quinine is metabolized in the liver; therefore, its levels could increase with joint administration of a PI/r, whereas these levels would fall in the presence of efavirenz or nevirapine. These effects could affect its efficacy or toxicity profile. Inhibition of CYP2C19 by ritonavir could have a deleterious effect on the efficacy of proguanil (since the active metabolite is cycloguanil). However, the combination of proguanil with atovaquone (Malarone®) would not be affected, since synergy is established with proguanil, thus compensating the lesser transformation to cycloguanil. RTV (220 mg/12 h) would not significantly reduce levels of mefloquine, although the reverse would be true. Joint use of halofantrine or lumefantrine (lower amount) with PIs could produce an increased QT interval; therefore, it is currently contraindicated. Administration with NNRTIs could reduce its efficacy. Atovaquone levels fall significantly with administration of lopinavir/r; therefore, an increased dose could be necessary. Atovaquone significantly increases zidovudine levels, although the reverse is not true. The effects of efavirenz and mefloquine on the CNS could potentially be cumulative.

Trypanosoma cruzi (Chagas Disease)

American trypanosomiasis, or Chagas disease, behaves like other opportunistic infections in the coinfected patient.[141] Most cases are reactivations in subjects with less than 200 CD4+ cells/μL that affect the CNS in the form of encephalopathy, particularly with granuloma; this makes it necessary to perform a differential diagnosis with diseases such as toxoplasmosis. Treatment with benznidazole or nifurtimox (no longer produced) of congenital disease, acute phase, or accidental cases is indicated, as this provides the highest cure rates (AI)[137,142] As parasitosis becomes chronic, the usefulness of this medication is more doubtful, and it is generally recommended in the recent chronic phase (less than 10 years' progression), and less so in the chronic phase (BII). Chagas encephalopathy associated with HIV requires benznidazole for at least 6 weeks, although the extended duration has not been clearly established (AIII). Starting or optimizing HAART in these cases is advisable. Adding itraconazole could be useful, as could treatment in the early phases (asymptomatic patent parasitemia) before irreversible damage is caused (CIII).[143]

Benznidazole and nifurtimox can produce gastrointestinal discomfort and cutaneous exanthema, as well as—more rarely—anemia, granulocytopenia, CNS involvement, and peripheral neuropathy. There are no data on interaction between benznidazole and antiretroviral drugs, although studies with rats have shown that there may be an inhibition of hydroxylation mediated by cytochrome P450. As for its adverse effects, caution should be adopted with potentially cumulative toxicity: cutaneous exanthema (NNRTI), CNS alterations (efavirenz) and peripheral neuropathy, and hematologic disorders (nucleosides).

Trypanosoma brucei rhodesiense and *T. brucei gambiense* (African Trypanosomiasis)

To decide on treatment in African trypanosomiasis, the species of the parasite must be taken into account and it must be determined whether the patient is in an early or late stage.[137] The treatment of choice for early West-African trypanosomiasis is pentamidine (AIII).[144] In the chronic phase, the treatment of choice is eflornithine, which, although as effective as melarsoprol, is less toxic (AI). Melarsoprol must be used in a continuous regimen of 10 injections on consecutive days (AI).[145] The main problem of this drug is its toxicity (4% to 6% of associated deaths) as a consequence of reactive encephalopathy (not due to toxicity caused by the arsenical constituents of the drug). Prednisolone reduces the risk of toxicity by 70% without affecting the efficacy of treatment (AI).[146] Anthelmintic and antimalarial drugs are generally used as adjuvant treatment to avoid possible infectious complications. The treatment of encephalopathy is based on the use of anticonvulsive therapy and corticosteroids to control the reactive inflammation.

The clinical progression of East-African trypanosomiasis is much more aggressive and can progress rapidly (weeks) to fatal meningoencephalitis if it is not treated. The treatment of choice is suramin (AII),[144] thus avoiding melarsoprol as much as possible due to its CNS toxicity. An initial test dose is usually administered to rule out possible anaphylactic reaction. The most common reactions are urticaria, proteinuria, and fever. In later stages of the disease, with dissemination to the CNS, the only active drug is melarsoprol, since eflornithine does not reach the

TABLE 8. **Treatment of the Main Imported Parasitic Infections**

Microorganism/Site	Treatment of Choice	Alternative Treatment
Entamoeba histolytica		
Asymptomatic carrier	Paromomycin po 500 mg every 8 hours, for 5-10 days	Diloxanide furoate 500 mg every 8 hours for 10 days
Mild-to-moderate intestinal disease	Metronidazole po 500-750 mg every 8 hours, for 7-10 days Tinidazole po 2 g once daily for 3 days	Iodoquinol 650 mg every 8 hours, for 20 days
Severe or extraintestinal disease	Metronidazole (po or iv) 750 mg every 8 hours, for 7-10 days Tinidazole po 2 g once daily for 5 days	Dehydroemetine im 1-1.5 mg/kg per day to a maximum of 5 days (administered as adjuvant therapy with metronidazole)
Noncomplicated malaria[a]		
Chloroquine-sensitive *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*	Chloroquine po 25 mg/kg as a base, total dose, divided as follows: 1 daily dose (10-10-5 mg/kg) for 3 days, or administered at 0, 6, 24, and 48h (10-5-5-5 mg/kg) In cases of malaria caused by *P. vivax* and *P. ovale*, add eradicating therapy with primaquine po 30 mg/kg as a base daily for 14 days[b]	Hydroxychloroquine po 620 mg base followed by 310 mg base at 6, 24, and 48 hours
Chloroquine-resistant *P. vivax*	Quinine (base)[3] po 25 mg/kg/d in 3 doses for 3 to 7 days + Doxycycline po 100 mg bid, 7 days or Tetracycline po 250 mg qid, 7 days or Clindamycin po 20 mg/kg/d divided bid or qid, 7 days Mefloquine po 25 mg/kg as a base, administered in 2 doses of 15-10 mg/kg separated by 6-24h. With both regimens, add primaquine at the abovementioned doses	
Chloroquine-resistant *P. falciparum*	Quinine plus doxycycline, tetracycline, or clindamycin as above Mefloquine as above Atovaquone-proguanil[d] po 4 tablets (250 mg atovaquone + 100 mg de proguanil) once daily for 3 days	
Severe malaria	Quinine[5] iv 20 mg salt/kg as loading dose administered in 4 hours, followed by 10 mg salt/kg every 8 hours after the loading dose, from 3 to 7 days Combine with: Doxycycline iv 100 mg bid and move to oral therapy as soon as soon as possible, 7 days or tetracycline po 250 mg qid, 7 days or clindamycin iv 10 mg base/kg as loading dose followed by 5 mg base/kg every 8 hours before moving to oral administration as soon as possible, 7 days	Quinidine (gluconate) iv: 6.25 mg base/kg (= 10 mg salt/kg) as a loading dose in 1-2 hours, followed by 0.0125 mg base/kg/min (= 0.02 mg salt/kg/min) in continuous infusion for at least 24 hours. As an alternative regimen, 15 mg base/kg (= 24 mg salt/kg) can be administered as a loading dose infused in 4 hours, followed by 7.5 mg base/kg (= 12 mg salt/kg) infused in 4 hours every 8 hours starting from the loading dose. Once parasitism is < 1% and the patient tolerates oral therapy, treatment can be completed with oral quinine Add doxycycline, tetracycline, or clindamycin as in the previous regimen.
Trypanosoma cruzi		
Acute or congenital infection	Benznidazole[f] po 5-7,5 mg/kg/d, divided in 2 doses, 30 to 60 days	Nifurtimox po 8-10 mg/kg day, divided in 2-3 doses, 30 to 60 days[g]
Early chronic infection	Benznidazole po 5 mg/kg/d, divided in 2 doses, 30 to 60 days	Nifurtimox po 8 mg/kg day, divided in 2-3 doses, 30 to 60 days
Late chronic infection	Benznidazole po 5 mg/kg/d, divided in 2 doses, 30 to 60 days	Nifurtimox po 8 mg/kg day, divided in 2-3 doses, 60 to 90 days
Trypanosoma brucei gambiense		
Early phase	Pentamidine iv or im 4 mg/kg to 300 mg/d, for 7 days	
Late phase	Eflornithine iv 100 mg/kg qid, for 14 days	Melarsoprol iv 2.2 mg/kg/d, for 10 days
Trypanosoma brucei rhodesiense		
Early phase	Suramin iv 5 mg/kg on the first day, followed by 20 mg/kg (up to 1g) on days 3, 5, 12, 19, and 26	
Late phase	Pretreatment with suramin, 5 mg/kg on the first day and 20 mg/kg on the third day, followed by melarsoprol iv 1.8 mg/kg (day 5), 2.16 mg/kg (day 6), 2.52 mg/kg (days 7 and 14), 2.88 mg/kg (day 15), 3.24 (day 16), 2.9 (day 20), 3.6 (up to 180 mg, days 23, 24, and 25)	

(Continues)

TABLE 8. **Treatment of the Main Imported Parasitic Infections** *(Continuation)*

Microorganism/Site	Treatment of Choice	Alternative Treatment
Cyclospora cayetanensis	Cotrimoxazole (160/800 mg) po bid for 7 days[h]	Ciprofloxacin 500 mg po bid for 7 days
Strongyloides stercoralis		
Intestinal infestation	Ivermectin po 200 μg/kg qd, repeat after 1 week Albendazole[i] po 400 mg bid, for 3-5 days	Albendazole po 800 mg bid, for 3 days
Hyperinfestation syndrome	Ivermectin po 200 μg/kg qd, for 7-10 days Albendazole po 400 mg bid, for 7-10 days	
***Schistosoma* spp.**	Praziquantel[j] po 40 mg/kg in a single dose In the case of *S. japonicum* or *S. mekongi* administer 2 doses of 30 mg/kg separated by 3 hours	Metrifonate po 10 mg/kg in a single dose
Taenia solium		
Cysticercosis	Corticosteroids to control symptoms plus: Albendazole[9] po 400 mg bid, for 8-30 days Praziquantel po 100 mg/kg/d in 3 doses, 1 day, followed by 50 mg/kg/d in 3 doses for 29 days.	
Filariasis		
Onchocerca volvulus	Ivermectin po 150 μg/kg, single dose, every 6-12 months	
Loa loa	Diethylcarbamazine po 6 mg/kg, in 3 doses, for 21 days	In cases of hypermicrofilaremia, consider starting before with albendazole po 200 mg bid for 21 days and then administering ivermectin or diethylcarbamazine
Wuchereria bancrofti, Brugia malayi and *Brugia timori*	Diethylcarbamazine po 6 mg/kg, in 3 doses, for 10-14 days	
Mansonella perstans	Albendazole po 400 mg bid, for 10 days Mebendazole po 100 mg, bid, for 30 days	
Mansonella streptocerca	Diethylcarbamazine po 6 mg/kg, in 3 doses of 12-21 days	Ivermectin po 200 μg/kg, in single dose
Mansonella ozzardi		
Cutaneous migratory larva	Albendazole po 400 mg bid, for 3 days Ivermectin po 200 μg/kg qd, for 1-2 days	
Visceral migratory larva	Albendazole po 400 mg bid, for 5 days Mebendazole po 100-200 mg, bid, for 5 days	

[a]Primaquine and doxycycline are contraindicated during pregnancy. There are few data on atovaquone and clindamycin; therefore, they are not generally recommended. Mefloquine is not advised during the first trimester. In the case of infections by *P. vivax* or *P. ovale* during pregnancy, radical cure with primaquine is deferred until after delivery. The pregnant woman should take prophylaxis with chloroquine once the acute episode has been treated. In cases of resistant malaria, the risk-benefit of drugs such as mefloquine, atovaquone proguanil, clindamycin, or doxicillin will be evaluated.
[b]Primaquine is used to eliminate dormant forms of both species in the liver and to prevent relapses. Given that primaquine can cause hemolytic anemia in patients with a G6PDH deficit, patients must undergo a study before administration. If there is a partial deficit, 45 mg/week can be administered for 8 weeks. In Oceania and Southeast Asia, the dose should be doubled due to the appearance of resistance strains.
[c]For infections acquired in Africa and South America, quinine is administered for 3 days, whereas for infections acquired in Southeast Asia, 7 days is recommended.
[d]Administer with food.
[e]The use of quinine or quinidine iv requires monitoring in an intensive care unit due to the potential appearance of fatal arrhythmia or hypoglycemia.
[f]Benznidazole is considered the drug of choice due to its greater ease of acquisition (requested through foreign medication channels). Nifurtimox is only available in Argentina and Germany.
[g]In cases of accidental inoculation, the duration will be 10 to 15 days beginning immediately after the inoculation.
[h]In patients with HIV infection, add secondary prophylaxis with cotrimoxazole (160/800 mg) in 1 tablet 3 times per week.
[i]Administer with food, since this improves absorption, especially fat.
[j]In cases of suspected infection with reduced sensitivity, administer 60 mg/kg in 2 doses separated by 3 hours.
bid, twice daily; im, intramuscular; iv, intravenous; po, by mouth; qd, once daily; qid, four times per day; tid, three times per day.

CNS, and T. brucei rhodesiense is resistant to it. Given that the incidence of encephalopathy by melarsoprol is greater than with *T. brucei gambiense*, treatment should be started with a small dose of melarsoprol followed by a gradual increase, as well as pretreatment with suramin (BIII).[144] It also seems reasonable to use prednisolone to prevent encephalopathy and other antiparasite drugs as adjuvant therapy (BIII).

Cyclospora cayetanensis

The treatment of choice is cotrimoxazole administered for 1 week (AI) (Table 8).[137] In patients who are intolerant to this treatment, the alternative is ciprofloxacin although it does appear to be less effective (BI). In HIV-infected patients, secondary prophylaxis with cotrimoxazole should be started, since recurrence is the rule after the acute episode (AII).[147]

Strongyloides stercoralis

Treatment is aimed at total eradication of the parasite to avoid the hyperinfestation syndrome.[148] There are no sufficiently sensitive diagnostic tests to determine whether this treatment is successful, although reduced serum titers or reduced eosinophil count can be used. The absence of larvae in stool is not reliable as a marker of cure. Ivermectin and albendazole are the drugs of choice, although there are no controlled trials that enable the ideal therapeutic schedule or dose to be determined (AII).[137,149,150] In patients with hyperinfestation syndrome, treatment must be extended to 7 to 10 days and corticosteroids should be withdrawn as much as possible. There are no data on the potential interactions of albendazole and ivermectin with antiretroviral drugs.

Schistosoma haematobium

The treatment of choice for all the forms of schistosomiasis is praziquantel (AI). This drug is well tolerated and is usually administered in a single dose. It is not contraindicated during pregnancy and it has proven effective in children. In cases of acute infection (less than 1 month since exposure), efficacy is much lower, since it is no longer active against the schistosomula; therefore, a second cycle of treatment is necessary after 4 weeks. In these cases, artemisinin derivatives have proven effective. In some areas of Senegal and Egypt, a certain degree of resistance to praziquantel could have developed, which means that the dose must be increased.[137,151]

***Taenia solium* (Cysticercosis)**

Albendazole and praziquantel have proven effective against parenchymatous disease in that they reduced the size of the cysts, or resolved the lesions in degenerated cysts earlier (BI).[137,152-154] First-pass metabolism reduces the bioavailability of praziquantel. Corticosteroids and antiseizure drugs (carbamazepine and phenytoin) reduce its levels even more. This generally makes albendazole the preferred choice—in addition to the fact that it has a lower pill burden and has been studied in more clinical trials. Praziquantel levels can increase when it is combined with PIs, especially ritonavir.

The initial treatment in patients with cerebral cysticercosis and signs of inflammation should be directed towards the symptoms (control of intracranial hypertension and convulsions). Parenchymatous cysts are treated with albendazole and corticosteroids (dexamethasone at 6 mg/d or prednisone at 40-60 mg/d) for 8 to 30 days. Patients with subarachnoid cysts or very large cysts must receive prolonged therapy (30 days) or a double dose of albendazole (30 mg/kg/d). In cases of obstructive hydrocephalus, the combination of surgery with albendazole and corticosteroids is indicated. If medical treatment is started, the existence of ocular cysticercosis must be ruled out (even if corticosteroids are used), since the inflammatory reaction can lead to irreparable damage. This also occurs with spinal cysticercosis.

Filariasis (Onchocerciasis, loiasis)

The treatment of choice for onchocercosis is ivermectin (AI),[137,155] which has microfilaricidal activity, although not on adult parasites; therefore, it is administered in a single dose every 6 to 12 months for 10 to 14 years (until the death of the adult parasites). Reactions after treatment are common (cutaneous pruritus, edema, back pain), especially with high degrees of infestation. Given that response is related to the degree of immunity to the parasite, it has been suggested that, in those subjects with less reactivity, the doses could be administered every 3 months (BII). Pretreatment with oral doxycycline has been proposed (100 mg/d for 6 weeks) to eliminate the endosymbiont bacteria Wolbachia. This would sterilize the female *Onchocerca volvulus*, thus drastically reducing the production of microfilaria (BII). Diethylcarbamazine (DEC) should not be used for the treatment of onchocercosis, because the rapid death of the microfilaria can produce blindness and a severe generalized reaction.

The treatment of choice for infestations by *Loa loa* in amicrofilaremic patients or when the degree of parasitism is low (less than 2500 microfilaria/mL) is DEC, which is also active against the adult parasites (AII) (Table 8).[137,156] The most frequent adverse effects are fever, nausea, pruritus, arthralgia, and Calabar edema (painful and transitory tumefaction of the limbs), which can be controlled with antihistaminic drugs. When the degree of microfilaremia is high, massive lysis of the microfilaria by DEC can lead to shock, coma, renal insufficiency, and even fatal encephalopathy. The scaled initial regimen of DEC can also cause this reaction; therefore, it is not recommended when parasitism is advanced. In cases of hypermicrofilaremia, apheresis before treatment with DEC has been proposed, as well as treatment with ivermectin or albendazole, which reduce microfilaremia more slowly.[157] Nevertheless, severe reactions have also been reported with ivermectin in 30% to 70% of cases. Treatment with albendazole for 3 weeks can progressively reduce microfilaria[158]; therefore, in hypermicrofilaremic patients, when followed by DEC or ivermectin, it could be a valid alternative to apheresis.

DEC is used in the treatment of lymphatic filariasis for 10-14 days (BII).[137] Concomitant use of ivermectin (400 μg/kg) or albendazole (400 mg) in a single dose, together with DEC, also in a single dose, has proven equally effective. As with onchocerciasis, doxycycline has been observed to reduce microfilaremia and eliminate the adults by acting on endosymbiont *Wolbachia*.[159]

Mansonella perstans is treated with mebendazole or albendazole, whereas for *M. streptocerca*, the drug of choice is DEC (BII). *M. ozzardi* is not sensitive to DEC, although it seems that ivermectin is active by reducing microfilaremia in the short and long term (BI).[137,160,161]

Immune Reconstitution Syndrome

Advanced HIV infection is relatively common in our setting.[162] These patients fulfill the criteria for HAART. A relatively high percentage of patients, despite having an excellent viral and immune response to HAART, will present a paradoxical worsening of their clinical condition known as the immune reconstitution syndrome (IRS).[163,164] Nevertheless, a recent clinical trial (ACTG A5164)[165] shows that HAART should not be delayed, as this could increase the risk of disease progression or death.[166]

Etiology and Incidence

The microorganisms most commonly associated with IRS are mycobacteria (*M. tuberculosis* and atypical mycobacteria such as *Mycobacterium avium* complex, *M. leprae*, and the Calmette-Guérin bacillus), fungi (*C. neoformans*, *P. jiroveci*, and regional mycoses), and herpes group viruses (CMV, VZV, HSV, and the human herpesvirus type 8), polyomavirus (JC and BK), molluscum contagiosum viruses, parvovirus B19, and hepatitis virus (B and C).[92,103,163,164,167-174] Although there have been reports of IRS with other bacteria (*Rhodococcus*, *Nocardia*, *Bartonella*) and parasites (*T. gondii*, *Leishmania*, *S. stercoralis*, *Cryptosporidium*), the frequency is much lower.[175] The IRS has also been reported in tumors, such as Kaposi sarcoma,[163,164,167-169] lymphoma,[176] and lung cancer,[177] as well as in autoimmune phenomena of the lupus-like type[178] or endocrine expression such as Graves disease after starting HAART.[163,179]

The percentage of patients who develop IRS is variable. In cohort studies of patients starting HAART, this syndrome affects between 15% and 25%. In series of patients with opportunistic infections the frequency is higher, and can reach 45%.

Diagnostic Criteria

Most authors[163,164,167-169,175] agree that patients suffering from IRS share the following 3 criteria: 1) a temporal relationship with the start of HAART, with a rapid decline in viral load (greater than 2 $\log_{10}$ copies/mL) and a sudden increase in the number of CD4+ lymphocytes; 2) atypical clinical and/or radiological or imaging deterioration that is inflammatory in nature, or the onset of an opportunistic infection, generally during the first 12 weeks of effective HAART (early IRS), although there have also been occasional reports of IRS beyond 3 months (late IRS); and 3) microbiological failure with antimicrobial therapy has been ruled out, as has pharmacological toxicity, autoimmune disease, or a new non-IRS-related opportunistic complication.

Clinical Manifestations

In general terms, the atypical presentations of opportunistic infections and tumors that suggest the existence of an IRS can be summarized as follows: 1) local disease in lymph nodes, liver, spleen, skin, lungs, and CNS; 2) exaggerated atypical and/or inflammatory reaction in the involved organs, which includes the formation of granulomas, suppuration, necrosis, or perivascular lymphocyte infiltrates; and 3) increase in existing lesions or failure of the affected organ after an initial clinical improvement with specific antimicrobial therapy before the start of HAART.

Prevention and Treatment of IRS and Optimization of HAART

It is not known how to prevent or manage IRS.[163,164,167-169,180,181] Patients are generally recommended to continue with HAART and specific treatment against opportunistic infections (CII). Adjuvant nonsteroid anti-inflammatory drugs are commonly used. In the most severe forms, corticosteroids are used (CIII).[163,164,167-169,180,181] Surgery is sometimes necessary to debride abscesses (CIII). Clinical progression is usually prolonged (weeks) and most patients improve, although some patients with cryptococcal meningitis or progressive multifocal leukoencephalopathy have died.[182,183] In life-threatening cases, the possibility of interrupting HAART should be considered until the patient's situation has improved. Treatment of the underlying infection and anti-inflammatory treatment should continue (CIII).

Clinical experience with alternative treatment such as immunosuppressors (methotrexate[184]), or tumor necrosis factor alpha inhibitors (etanercept,[185] thalidomide,[186] or pentoxifylline[187]) is very scarce and limited to isolated cases of tuberculosis or leprosy in patients with or without HIV infection.

The CDC-NIH-IDSA[188] recommend that HAART-naïve patients with opportunistic infections other than tuberculosis start HAART immediately when there is no effective antimicrobial treatment for the opportunistic infection (eg, cryptosporidiosis or progressive multifocal leukoencephalopathy). In other cases, HAART should be started 2 to 4 weeks after the start of antimicrobial treatment for the opportunistic infection. However, the results of ACTG A5164[165] were recently presented. This was the first randomized clinical trial to evaluate the strategy of immediate HAART during the first 2 weeks after starting antimicrobial treatment for the opportunistic infection (patients with tuberculosis were not included), or deferred HAART, after 4 weeks. This has changed this recommendation from CIII to AI. Most patients started HAART based on lopinavir/r. The trial randomized 282 patients, 141 per study arm. Sixty-three percent of patients had *P. jiroveci* pneumonia, 13% had cryptococcal meningitis, and 10% had bacterial pneumonia. The baseline (median) figures for CD4+ lymphocytes and viral load were 29 cells/μL and 5.07 log, respectively. HAART was started in the immediate and deferred arms a median of 12 days and 45 days after the start of treatment for the opportunistic infection, respectively. The increase in CD4+ lymphocyte count was similar in both arms, but the patients who started HAART immediately took less time to reach a CD4+ lymphocyte count greater than 50 to 100 cells/μL, they had a smaller rate of progression to AIDS or death ($P = .035$), and they took longer to progress to AIDS or death ($P = .02$). The patients included in the immediate HAART arm tended to change their HAART earlier ($P = .15$), but there were no significant differences with respect to grade 3-4 adverse events, adherence, admissions to hospital, or IRS (8 cases in the immediate arm and 12 in the deferred arm). The results of this study[165] allow us to recommend starting HAART ideally at 10 to 14 days after starting treatment for the opportunistic infection and preferably before 28 days in patients with opportunistic infections other than tuberculosis, as long as there are no clinical contraindications (AI).

On the contrary, when the opportunistic infection appears in patients who are taking HAART,[188] several clinical situations can be distinguished: *a)* when the opportunistic infection appears during the first 12 weeks after HAART it is probably an IRS that reveals a subclinical opportunistic infection (eg, tuberculosis or progressive multifocal leukoencephalopathy). In these cases, HAART must be continued and treatment for the opportunistic infection started (CIII); *b)* when the opportunistic infection

starts after 12 weeks in patients with effective HAART, it could be a late IRS or a new opportunistic infection, since sometimes the specific response of the pathogen is not restored. In these cases too, HAART must be continued and treatment of the opportunistic infection started (CIII); and *c)* when the opportunistic infection occurs in the context of virological failure with HAART, it reflects progression of the disease, with the result that treatment must be started immediately, an antiretroviral resistance study must be requested, and new HAART must be administered (CII).

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