

























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

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

monary dissemination.<sup>117</sup> 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).<sup>118</sup>

### 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.<sup>119,120</sup> *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.<sup>121</sup> The treatment of choice for salmonellosis is a fluorinated quinolone (AIII),<sup>121</sup> 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/ $\mu$ L (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).<sup>122</sup> 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).<sup>123,124</sup> 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).<sup>125</sup>

## Systemic Bacterial Infections

### Syphilis

The coexistence of syphilis and HIV infection is relatively frequent (observed in 7% of patients).<sup>126</sup> 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.<sup>127</sup>

Penicillin G continues to be the treatment of choice (AII) for all the clinical stages of syphilis.<sup>128</sup> 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).<sup>128-130</sup> 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).<sup>131</sup> 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).<sup>128</sup>

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/ $\mu$ L.<sup>132</sup> 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/ $\mu$ L.<sup>133</sup> 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).<sup>134</sup> 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).<sup>135-137</sup> 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).<sup>138</sup>

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).<sup>139</sup> 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<sup>3</sup>), 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).<sup>138</sup>

### **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)<sup>140</sup>: 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<sup>®</sup>) 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 coinfecting pa-

tient.<sup>141</sup> Most cases are reactivations in subjects with less than 200 CD4+ cells/ $\mu$ L 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)<sup>137,142</sup> 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).<sup>143</sup>

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.<sup>137</sup> The treatment of choice for early West-African trypanosomiasis is pentamidine (AIII).<sup>144</sup> 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).<sup>145</sup> 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).<sup>146</sup> 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),<sup>144</sup> 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 (Continuation)

Microorganism/Site	Treatment of Choice	Alternative Treatment
<i>Cyclospora cayetanensis</i>	Cotrimoxazole (160/800 mg) po bid for 7 days <sup>h</sup>	Ciprofloxacin 500 mg po bid for 7 days
<b><i>Strongyloides stercoralis</i></b>		
Intestinal infestation	Ivermectin po 200 µg/kg qd, repeat after 1 week Albendazole <sup>i</sup> 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	
<b><i>Schistosoma</i> spp.</b>	Praziquantel <sup>j</sup> po 40 mg/kg in a single dose In the case of <i>S. japonicum</i> or <i>S. mekongi</i> administer 2 doses of 30 mg/kg separated by 3 hours	Metrifonate po 10 mg/kg in a single dose
<b><i>Taenia solium</i></b>		
Cysticercosis	Corticosteroids to control symptoms plus: Albendazole <sup>9</sup> 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.	
<b>Filariasis</b>		
<i>Onchocerca volvulus</i>	Ivermectin po 150 µg/kg, single dose, every 6-12 months	
<i>Loa loa</i>	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
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> and <i>Brugia timori</i>	Diethylcarbamazine po 6 mg/kg, in 3 doses, for 10-14 days	
<i>Mansonella perstans</i>	Albendazole po 400 mg bid, for 10 days Mebendazole po 100 mg, bid, for 30 days	
<i>Mansonella streptocerca</i>	Diethylcarbamazine po 6 mg/kg, in 3 doses of 12-21 days	Ivermectin po 200 µg/kg, in single dose
<i>Mansonella ozzardi</i>		
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	

<sup>a</sup>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 doxycillin will be evaluated.

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>Administer with food.

<sup>e</sup>The use of quinine or quinidine iv requires monitoring in an intensive care unit due to the potential appearance of fatal arrhythmia or hypoglycemia.

<sup>f</sup>Benznidazole is considered the drug of choice due to its greater ease of acquisition (requested through foreign medication channels).

<sup>g</sup>Nifurtimox is only available in Argentina and Germany.

<sup>h</sup>In cases of accidental inoculation, the duration will be 10 to 15 days beginning immediately after the inoculation.

<sup>i</sup>In patients with HIV infection, add secondary prophylaxis with cotrimoxazole (160/800 mg) in 1 tablet 3 times per week.

<sup>j</sup>Administer with food, since this improves absorption, especially fat.

<sup>k</sup>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).<sup>144</sup> 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).<sup>137</sup> 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).<sup>147</sup>

***Strongyloides stercoralis***

Treatment is aimed at total eradication of the parasite to avoid the hyperinfestation syndrome.<sup>148</sup> 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).<sup>137,149,150</sup> 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.<sup>137,151</sup>

***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).<sup>137,152-154</sup> First-pass metabolism reduces the bioavailability of praziquantel. Corticosteroids and antiepileptic 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),<sup>137,155</sup> 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).<sup>137,156</sup> 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.<sup>157</sup> 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<sup>158</sup>; 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).<sup>137</sup> 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*.<sup>159</sup>

*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).<sup>137,160,161</sup>

**Immune Reconstitution Syndrome**

Advanced HIV infection is relatively common in our setting.<sup>162</sup> 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).<sup>163,164</sup> Nevertheless, a recent clinical trial (ACTG A5164)<sup>165</sup> shows that HAART should not be delayed, as this could increase the risk of disease progression or death.<sup>166</sup>

### **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).<sup>92,103,163,164,167-174</sup> 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.<sup>175</sup> The IRS has also been reported in tumors, such as Kaposi sarcoma,<sup>163,164,167-169</sup> lymphoma,<sup>176</sup> and lung cancer,<sup>177</sup> as well as in autoimmune phenomena of the lupus-like type<sup>178</sup> or endocrine expression such as Graves disease after starting HAART.<sup>163,179</sup>

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<sup>163,164,167-169,175</sup> 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<sub>10</sub> 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.<sup>163,164,167-169,180,181</sup> 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).<sup>163,164,167-169,180,181</sup> Surgery is sometimes necessary to debride abscesses (CIII). Clinical progression is usu-

ally prolonged (weeks) and most patients improve, although some patients with cryptococcal meningitis or progressive multifocal leukoencephalopathy have died.<sup>182,183</sup> 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<sup>184</sup>), or tumor necrosis factor alpha inhibitors (etanercept,<sup>185</sup> thalidomide,<sup>186</sup> or pentoxifylline<sup>187</sup>) is very scarce and limited to isolated cases of tuberculosis or leprosy in patients with or without HIV infection.

The CDC-NIH-IDS<sup>188</sup> 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<sup>165</sup> 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/ $\mu$ L 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/ $\mu$ L, 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<sup>165</sup> 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,<sup>188</sup> 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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