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Consensus statement

Executive summary: Prevention and treatment of opportunistic infections and other coinfections in HIV-infected patients: May 2015☆

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ABSTRACT

Opportunistic infections continue to be a cause of morbidity and mortality in HIV-infected patients. They often arise because of severe immunosuppression resulting from poor adherence to antiretroviral therapy, failure of antiretroviral therapy, or unawareness of HIV infection by patients whose first clinical manifestation of AIDS is an opportunistic infection.

The present article is an executive summary of the document that updates the previous recommendations on the prevention and treatment of opportunistic infections in HIV-infected patients, namely, infections by parasites, fungi, viruses, mycobacteria, and bacteria, as well as imported infections. The article also addresses immune reconstitution inflammatory syndrome. This document is intended for all professionals who work in clinical practice in the field of HIV infection.

Executive summary: Prevención y tratamiento de infecciones oportunistas y otras coinfecciones en pacientes infectados por el VIH: mayo de 2015

Palabras clave:
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RESUMEN

Las infecciones oportunistas siguen siendo una causa importante de morbi mortalidad en pacientes con infección por VIH. Ello ocurre en muchos casos debido a la inmunodepresión grave, bien ante la falta de adherencia al tratamiento antirretroviral, el fracaso del mismo o el desconocimiento de la existencia de la infección por el VIH en pacientes que comienzan con una infección oportunista.

☆ Readers who prefers to have this review in Castilian, can be obtained from the following address: http://www.gesida-seimc.org/contenidos/guiasclinicas/2015/gesida-guiasclinicas-2015-InfeccionesOportunistasyCoinfeccionesVIH.pdf

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[1] See Appendix A for the contributions of the Authors and Reviewers.

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Este artículo es un resumen del documento de consenso que actualiza las recomendaciones previas de GESIDA respecto a la prevención y el tratamiento de las diferentes infecciones oportunistas en pacientes infectados por VIH: parasitarias, fúngicas, víricas, micobacterianas, bacterianas e importadas, además del síndrome de reconstitución inmune. Está dirigido a los profesionales que trabajan en la práctica clínica en el campo del VIH, con el objetivo de facilitarles una atención de calidad en la prevención y tratamiento de estas infecciones

Introduction

Opportunistic infections (OIs) have been the main cause of morbidity and mortality in HIV-infected patients since the beginning of the HIV epidemic.

Efficacious regimens for primary and secondary prophylaxis to prevent OIs were the first major advance in therapy for HIV-infected patients, significantly decreasing mortality, even before the advent of highly active antiretroviral therapy (ART). ART brought about a notable change in the progression of HIV infection by dramatically reducing mortality and the incidence of OIs. However, today, we continue to see cases of OI in various settings: patients who are unaware of their HIV infection and whose first manifestation is an OI; patients who do not receive ART; and failure of ART due to poor adherence or other causes. Accordingly, treatment of OIs continues to be a relevant topic in the care of HIV-infected patients[1].

The present document is an update of our previous recommendations on prevention and treatment of OIs in HIV-infected patients. The strength of the recommendation and ranking of the tests that support it are based on a modification of the criteria of the *Infectious Diseases Society of America*. According to these criteria, each recommendation should be offered always (**A**), generally (**B**), or optionally (**C**), based on data from 1 or more randomized clinical trials with clinical or laboratory results (**I**), 1 or more nonrandomized trials or observational cohort data (**II**), or expert opinion (**III**).

Owing to space limitations, we strongly recommend to the reader to consult the tables of the leading document, which display the various prophylaxis and treatment regimens (both preferred and alternative) and the corresponding doses. Available at http://www.gesida-seimc.org/contenidos/guiasclinicas/2015/gesida-guiasclinicas-2015-InfeccionesOportunistasyCoinfeccionesVIH.pdf.

Parasitic infections

Toxoplasma gondii

Patients who have not been exposed to *Toxoplasma gondii* (confirmed by a negative anti-*Toxoplasma gondii* IgG result) should avoid contact with the parasite.

- Handwashing is recommended after contact with animals, especially cats, and after handling raw meat. Patients should try to eat meat that has been adequately cooked (or previously frozen to −20 °C) and wash fruit and vegetables that are to be eaten raw (**BIII**).
- Primary prophylaxis should be with cotrimoxazole in patients with anti-*Toxoplasma gondii* IgG and a CD4+ T-lymphocyte count <100 cells/μL (**AII**); alternatives include pyrimethamine combined with dapsone or atovaquone.
- When cerebral toxoplasmosis is suspected, treatment should be started with sulfadiazine combined with pyrimethamine (and folinic acid to reduce blood toxicity) (**AI**) and maintained for at least 6 weeks (**BII**). A brain biopsy should be performed if no response is observed at 7–14 days.
- Once treatment is complete, secondary prophylaxis can be started (same regimen, reduced dose) (**AI**).
- Prophylaxis can be discontinued after 6 months on ART, providing the patient has maintained an undetectable viral load and a CD4+ T-lymphocyte count >200 cells/μL for ≥3 months (primary) or ≥6 months (secondary) (**AI**), probably owing to recovery of the anti-*Toxoplasma gondii* cellular response (CD4+ T lymphocytes). Prophylaxis should be restarted if the CD4+ T-lymphocyte count returns to <100–200 cells/μL (**AIII**).

Leishmania species

- The treatment of choice for visceral leishmaniasis is liposomal amphotericin B (**AII**) or amphotericin B lipid complex, in various regimens. Alternatives include amphotericin B deoxycholate (renal toxicity) or pentavalent antimonials (pancreatic and cardiac toxicity) (**BII**). The efficacy of miltefosine and paromomycin has not been demonstrated in HIV-infected patients (**CIII**).
- Secondary prophylaxis should be administered once the acute infection has been treated (**BII**). Lipid formulations of amphotericin B (liposomal [**AII**] or lipid complex [**BI**]) are also drugs of choice.
- No safe recommendation can be made about withdrawal of secondary prophylaxis against *Leishmania.* Although some experts recommend maintaining prophylaxis indefinitely, suspension should be considered in patients who remain relapse-free for 6 months, maintain a CD4+ T-lymphocyte count >200–350 cells/μL and an undetectable viral load for >3 months, and, if possible, test negative in PCR for the *Leishmania* antigen in blood or urine (**CIII**). Prophylaxis should be restarted if the CD4+ T-lymphocyte count falls to <200 cells/μL.

Cryptosporidium species, microsporidia, and Isospora belli

- There are no efficacious primary prophylaxis regimens.
- There is no specific treatment for cryptosporidiosis (**CIII**), and cure is based on ART-associated immune recovery (**AII**).
- Treatment of microsporidiosis also depends on ART (**AII**), although efficacious complementary drugs are available: in intestinal infections and infections caused by *Enterocytozoon bieneusi*, the treatment of choice is oral fumagillin (**BIII**); albendazole is recommended if other species are involved (**AII**). In patients with ocular involvement, albendazole can be combined with topical fumagillin (**BIII**).
- The treatment of choice for isosporiasis is cotrimoxazole (**BI**).
- Secondary prophylaxis for microsporidiosis and isosporiasis involves maintaining the same regimen as for treatment. This can be suspended when a CD4+ T-lymphocyte count >200 cells/μL is reached after 6 months of efficacious ART (**CIII** and **BIII**,

respectively). Suspension would be questionable in ocular microsporidiosis.

Fungal infections

Pneumocystis jiroveci

- Prevention of exposure. Although available epidemiologic data indicate that respiratory isolation should be considered in patients with *Pneumocystis jiroveci* pneumonia, there is insufficient evidence to support this recommendation (**CIII**).
- Primary prophylaxis is indicated in patients with a CD4+ T-lymphocyte count <200 cells/μL (**AI**), previous oropharyngeal candidiasis (**AII**), CD4+ <14% (**BII**), or a previous AIDS-defining disease (**BII**). It should be considered in patients with 200–250 CD4+ cells/μL if 3 monthly visits cannot be guaranteed (**BII**).
- Secondary prophylaxis is always indicated in patients with a history of pneumonia (**AI**).
- Cotrimoxazole is the drug of choice both for primary and for secondary prophylaxis (**AI**). Patients with hypersensitivity can undergo desensitization or receive alternatives such as dapsone/pyrimethamine (**BI**) or atovaquone with(out) pyrimethamine (**BI**). Inhaled pentamidine does not prevent extrapulmonary involvement; if this drug is used, it should be restricted to patients with negative toxoplasma serology results (**BI**).
- Prophylaxis can be suspended if the CD4+ T-lymphocyte count exceeds 200 cells/μL for at least 3 months after starting ART (**AI**). Some data suggest that primary prophylaxis could be suspended even with 100–200 cells/μL and an undetectable viral load (**CIII**). In children and adolescents in Africa that maintenance of prophylaxis with trimethoprim-sulfamethoxazole in patients with >200 CD4+ cells/μL reduce the risk of admission for bacterial infections and malaria (**CI**).
- The treatment of choice for *P. jiroveci* pneumonia is intravenous cotrimoxazole (21 days) (**AI**). Treatment can be administered orally when the patient's condition improves or when the disease is mild/moderate (**AI**). Folinic acid is not recommended because it can increase the risk of therapeutic failure. Patients with moderate/severe disease (pO_2 < 70 mmHg or alveolar-capillary gradient >35 mmHg) should start therapy with corticosteroids combined with cotrimoxazole (**AI**).
- Alternative treatments include clindamycin + primaquine or intravenous pentamidine or atovaquone (**BI**), although atovaquone should only be administered in mild cases.

Cryptococcus neoformans

- Primary prophylaxis for infection by *Cryptococcus neoformans* is not indicated in Spain owing to the low incidence of the disease.
- Induction treatment of meningitis should be with liposomal amphotericin + flucytosine for at least 2 weeks (**AI**). Alternatives include liposomal amphotericin + fluconazole or fluconazole with(out) flucytosine (**BII**). After 2 weeks of treatment, the regimen can be switched to fluconazole for at least 10 weeks, providing that the patient's condition has improved and the cerebrospinal fluid (CSF) culture is negative (**AI**).
- Initiation of ART should be deferred by 5 weeks owing to the risk of greater mortality associated with early initiation (**AI**). Cryptococcal meningitis is often associated with increased intracranial pressure, which is treated using repeated lumbar puncture or even placement of a CSF shunt (**BIII**). In extrameningeal forms, the treatment of choice is fluconazole (400 mg/d) or liposomal amphotericin if the patient's condition is severe (**AIII**).
- Secondary prophylaxis is always indicated once at least 10 weeks of treatment has been completed. The drug of choice is fluconazole (**AI**). Alternatives include itraconazole or weekly liposomal amphotericin (**BIII**).
- Secondary prophylaxis can be suspended when the CD4+ T-lymphocyte count exceeds 100 cells/μL with an undetectable viral load for at least 3 months (**BII**).

Candida albicans

- Primary prophylaxis of infections by *Candida* species is not indicated owing to the scarce morbidity and mortality associated with this disease and the risk of resistance.
- Fluconazole is the treatment of choice for oral and esophageal candidiasis (**AI**). Alternatives include itraconazole and posaconazole (**BI**). In cases of exclusively oropharyngeal involvement, treatment is with topical clotrimazole or miconazole. Alternatives include nystatin suspension (**BI**). In the case of esophagitis, and depending on the severity of the condition, it may be necessary to use intravenous fluconazole (**AI**), with voriconazole or echinocandins as alternatives (in patients with resistance or toxicity) (**BI**). If no improvement is observed after 7 days of treatment, other microorganisms should be ruled out using endoscopy in the case of esophagitis and/or ruling out resistance to azoles.
- Vulvovaginitis caused by *Candida* species can be treated with oral fluconazole (**AII**) or topical clotrimazole or miconazole (**AII**).
- Secondary prophylaxis is not recommended. Fluconazole (3 times weekly) can be used in the case of very frequent relapses (**CIII**). However, in these cases, recurrence at any site should be considered indicative of azole resistance.

Aspergillus fumigatus

- Primary prophylaxis is not recommended.
- The treatment of invasive aspergillosis depends on the severity of symptoms. Voriconazole is generally considered the drug of choice (**AI**). Alternatives include liposomal amphotericin (**AII**), caspofungin, and posaconazole (**BIII**). ART should be started as soon as possible, and potential drug interactions should be evaluated. The optimal duration remains unknown, although treatment should be maintained at least until the CD4+ T-lymphocyte count is >200 cells/μL.
- The lack of data prevents us from making recommendations on secondary prophylaxis.

Histoplasma capsulatum

- Primary prophylaxis is not recommended in Spain.
- Treatment of severe infections is with liposomal amphotericin (**AI**) for 2 weeks, followed by itraconazole for 12 months (**AII**) (monitor levels after 2 weeks to ensure >1 μg/mL). In patients with meningitis, administer liposomal amphotericin for 4–6 weeks (**AIII**) followed by itraconazole for at least 12 months (**AIII**). In mild forms, the drug of choice is itraconazole (**AII**). Alternatives include posaconazole and voriconazole (**BIII**) or fluconazole (**CII**). *Histoplasma capsulatum* is resistant to echinocandins.
- Secondary prophylaxis is always indicated after 12 months of treatment and is with itraconazole (**AIII**) or fluconazole (less efficacious) (**BIII**). It can be suspended when the CD4+ T-lymphocyte count is >150 cells/μL for at least 6 months with undetectable HIV viral load and serum antigen <2 ng/mL (**AI**). Secondary prophylaxis should be restarted if the CD4+ T-lymphocyte count falls below 150 cells/μL (**BIII**).

Coccidioides immitis

- Primary prophylaxis is not indicated in Spain.
- Pneumonia should be treated with fluconazole or itraconazole (**BII**). Alternatives include posaconazole (**BII**) and voriconazole (**BIII**).
- Disseminated disease is treated with liposomal amphotericin until the patient's clinical condition improves (**AII**) and then with fluconazole or itraconazole. Some experts recommend combining liposomal amphotericin with a triazole (**BIII**). Meningitis is treated with fluconazole (**AII**) or with itraconazole, posaconazole, or voriconazole (**BIII**). Intrathecal amphotericin B should be used if treatment with triazoles is inefficacious (**AIII**). If possible, the response should be monitored using serum antibody titers.
- Secondary prophylaxis is always indicated with fluconazole or itraconazole (**AII**). In the absence of a response, posaconazole (**BII**) or voriconazole (**BIII**) can be administered. Given the high risk of relapse, indefinite prophylaxis is recommended in meningitis (**AII**) and in disseminated disease (**BIII**). Secondary prophylaxis can be suspended after >12 months in patients with a CD4+ T-lymphocyte count >250 cells/μL (**AII**).

Blastomyces dermatitidis

- Prophylaxis and treatment are similar to those of histoplasmosis.

Penicillium marneffei

- Primary prophylaxis is not recommended in Spain.
- Treatment of the severe form is with liposomal amphotericin for 2 weeks followed by itraconazole for a further 10 weeks (**AII**). Voriconazole can be used as an alternative during the first 12 weeks (**BII**).
- Mild disease is treated with itraconazole (**BII**) or voriconazole (**BII**) for 8–12 weeks. *P. marneffei* is resistant to fluconazole.
- Secondary prophylaxis, which is always indicated, is with itraconazole (**AI**). It can be suspended when the CD4+ T-lymphocyte count exceeds 100 cells/μL for at least 6 months and HIV viral load remains suppressed (**BII**). It should be restarted if the CD4+ T-lymphocyte count falls again (**AIII**) or the patient experiences a recurrence with >100 cells/μL (**CIII**).

Viral infections

Herpes simplex virus

- The most common clinical forms of herpes simplex virus (HSV) are genital herpes, which is generally caused by HSV-2, and orolabial herpes, which is usually caused by HSV-1. Recurrences are more common in genital herpes. Treatment is more efficacious if started early, during the prodromal phase, or on the day immediately following the appearance of lesions.
- Treatment of herpesvirus encephalitis is similar in HIV-infected patients and immunocompetent patients. It should be started empirically as soon as the diagnosis is suspected.
- The possibility of resistance to antiviral drugs must be taken into consideration when lesions do not improve after 7–10 days of correctly administered treatment. Resistance should be confirmed using a sensitivity study.
- Primary prophylaxis is not recommended. No vaccines are available. Secondary prophylaxis should be considered in the case of severe recurrence or to reduce the number of recurrences.

Varicella zoster virus

The incidence of infections by varicella zoster virus (VVZ) is much greater in HIV-infected patients than in the general population. VVZ infection can appear regardless of the CD4+ T-lymphocyte count. VVZ infection in adults with no known causes of immunosuppression requires HIV infection to be ruled out. The presentation and clinical course of VVZ infection can be modified in patients with advanced immunosuppression. Retinal necrosis is one of the best-characterized clinical syndromes in patients with VVZ infection.

Treatment of localized herpes zoster infection is aimed at preventing dissemination of infection (especially in immunodepressed patients and patients aged >50 years), reducing the duration of symptoms, and reducing the risk of postherpetic neuralgia. Corticosteroids are not recommended.

- Initiation of acyclovir IV is recommended in patients with varicella, disseminated herpes zoster infection, or visceral involvement. Acute retinal necrosis usually responds to treatment with high-dose intravenous acyclovir, which can be continued with oral valacyclovir (**BIII**). Intravitreal treatment can also be considered in some cases (**BII**).
- Resistance of VVZ to nucleoside analogs is exceptional, although it can emerge and responds to foscarnet.

Cytomegalovirus

Cytomegalovirus (CMV) disease is mainly due to reactivation in severely immunosuppressed patients (CD4+ <50 cells/μL). The most common clinical manifestations are retinitis, colitis, esophagitis, pneumonitis, polyradiculoneuritis, and encephalitis. Regular funduscopy is recommended for severely immunodepressed patients, and patients should be advised to see their doctor immediately if they experience visual disturbances.

- Retinitis is the most common condition. Cases involving an imminent risk of blindness (lesions near the optic nerve or macula) must be treated quickly to preserve vision. Treatment of visceral CMV infection should be on an individual basis depending on the location and severity of the process.
- The treatment of choice is usually oral valganciclovir because of its efficacy, safety, and ease of administration (**AI**). The best results in CMV retinitis with a high risk of loss of vision were obtained with an intraocular ganciclovir implant (**BI**), which is not currently marketed. In these cases, treatment should be started with valganciclovir (**AI**). A 2-mg dose of intravitreal ganciclovir should also be administered and repeated at 48 h (**AIII**). CMV encephalitis should be treated with ganciclovir + foscarnet (**CIII**).

Progressive multifocal leukoencephalopathy

ART is the only approach to prevent progressive multifocal leukoencephalopathy (PML) and improve the T lymphocyte–mediated cell response, which is essential for control of intracerebral replication of the JC virus. Low CSF viral load and a specific cellular immune response in blood and CSF are associated with a better prognosis. Among HIV-infected patients, mortality is greater in those who have CD4+ <100 cells/μL.

- Numerous drugs have been used empirically or in clinical trials in patients with PML, although none has proven effective. The best option in HIV-infected patients is to initiate ART (**AII**) or optimize ART (**AIII**) with potent regimens and good central nervous system (CNS) penetration. Prognosis improved with the advent of ART,

and survival rates range from 10% per year to 40–75%, although a large percentage of patients present neurological sequelae.
- In patients who experience clinical or radiological deterioration with ART, which is suggestive of immune reconstitution inflammatory syndrome (IRIS), observational studies suggest prescribing dexamethasone without interrupting ART (**BIII**).

Influenza virus

Seasonal influenza is a frequent cause of respiratory disease in HIV-infected patients. Early studies from the pre- ART era showed that the mortality and complication rates were higher in this population. Studies carried out during the influenza pandemic revealed a greater incidence and more complications in patients with ART or low CD4+ T-lymphocyte counts. However, patients with good virological control who were taking ART had complication rates that were similar to those of the general population.

- Early treatment with oseltamivir or zanamivir is recommended in HIV-infected patients suspected of having severe influenza (**AI**).
- Prophylaxis with these drugs is recommended in unvaccinated patients with low CD4+ T-lymphocyte counts who have been in close contact with patients with influenza (**AI**).
- HIV-infected patients should receive the seasonal inactivated influenza vaccine yearly (**AI**).

Mycobacterial infection

Mycobacterium tuberculosis

- Treatment of mycobacterial infections in HIV-infected patients is generally the same as in non–HIV-infected patients. As a rule, patients infected with *Mycobacterium tuberculosis* who are sensitive to all drugs should receive isoniazid, rifampicin, pyrazinamide, and ethambutol (2 months) followed by isoniazid and rifampicin (for a further 4–7 months) (**AI**).
- A 6-month course is sufficient for most HIV-infected patients with tuberculosis (TB). The continuation phase should be extended to 7 months if there is a delay in reaching negative values in the sputum culture (>2 months), in patients with a CD4+ T-lymphocyte count <100 cells/μL, and in patients whose adherence is questionable (in these cases every attempt should be made to administer therapy directly) (**BII**). Drugs should be taken daily, as opposed to regimens of 3 or 5 days per week (**AI**). Fixed-dose combinations should be used (**BI**). For specific situations, please consult our TB consensus document.
- All HIV-infected patients who develop TB should receive ART, regardless of their CD4+ T-lymphocyte count and viral load, since it reduces the risk of death (**AI**). The best time to start depends on the CD4+ count. If it is <50 cells/μL, ART should be started as soon as possible after verifying tolerance to TB treatment and no later than the first 2 weeks after starting tuberculostatic treatment (**AI**). If the CD4+ count is >50 cells/μL, initiation of ART can be deferred until the intensive phase of TB treatment has been completed (8 weeks). With this approach, the risk of adverse effects and IRIS is reduced without compromising survival (**AI**). However, the ideal time to initiate ART in patients whose disease first manifests with tuberculous meningitis remains unknown.
- Rifampicin interacts with antiretroviral drugs that are metabolized via the CYP3A4 enzyme system. Rifampicin must be included in anti-TB treatment regimens in HIV-infected patients. Therefore, ART should be adjusted to take potential drug interactions into account.
- As for prevention of TB, all HIV-infected patients should undergo screening for latent TB using the tuberculin skin test or a specific interferon gamma release assay to evaluate the risk of developing TB (**AI**). Specific testing for cutaneous anergy is not required. The ideal frequency for repeating the tuberculin skin test is unknown in patients whose first result is negative. We suggest that it should always be repeated after confirmed exposure to a patient with active bacilliferous TB and every 2–3 years in all patients with a negative result in the first test (**BIII**). There are no data to support recommending a prevalence threshold above which the frequency of the tuberculin skin test should be repeated.
- Treatment of latent tuberculosis infection is indicated in all patients with a positive tuberculin skin test result (induration of ≥5 mm) or who have had a positive result in the past, regardless of the CD4+ T-lymphocyte count, and in whom active disease can reasonably be ruled out (**AI**). The regimen of choice continues to be daily isoniazid for 6–9 months (**AI**). Alternatives include isoniazid (300 mg/d) + rifampicin (600 mg/d) for 3 months (**AII**) or rifampicin (600 mg/d) for 4 months in cases of toxicity or resistance to isoniazid (**BIII**).
- Secondary prophylaxis (maintenance treatment) is not required.

Mycobacterium avium complex

- Treatment of disseminated *Mycobacterium avium complex* (MAC) should be with a combination of drugs. Clinical trials performed during the pre-ART era showed that a regimen containing clarithromycin (500 mg/12 h) + ethambutol (15 mg/kg/d) ± rifabutin (300 mg/d) administered over 12 months to reduce resistance is efficacious and the treatment of choice (**AI**). If rifabutin is used, the dose should be adjusted if the antiretroviral regimen includes a protease inhibitor or efavirenz. The interaction between clarithromycin and efavirenz should be taken into account.
- The regimens of choice for preventing disseminated MAC infection are clarithromycin (500 mg/12 h) or azithromycin (1200 mg, once weekly) (**AI**). However, this prophylaxis has never been recommended in Spain in severely immunodepressed patients (<100 cells/μL) owing to the low incidence of the disease. Primary prophylaxis can be interrupted when patients reach a CD4+ T-lymphocyte count >100 cells/μL for a period longer than 3–6 months with antiretroviral therapy (**AI**).
- Secondary prophylaxis cannot be used in MAC, and treatment must be maintained until the CD4+ T-lymphocyte count recovers to >100 cells/μL (**AI**).

Other mycobacteria

Mycobacteria other than *M. tuberculosis* and MAC can occasionally cause OIs in HIV-infected patients with different degrees of immunosuppression. No specific recommendations are available for treatment and prevention of these diseases except for those that apply to non-HIV-infected patients with infection by environmental mycobacteria.

Infections caused by other bacteria

- Recommendations for the treatment of bacterial respiratory infection caused by *Streptococcus pneumoniae*, less prevalent bacteria (*Haemophilus influenzae* type b, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*), and unusual bacteria (*Nocardia* species or *Rhodococcus equi*) are similar for HIV-infected and non-HIV-infected individuals.
- Treatment of intestinal infections caused by *Salmonella* species, *Campylobacter* species, or *Clostridium difficile* is similar to that administered to the general population, except in the case of severely immunodepressed HIV-infected patients, who are at risk of recurrent bacteremia caused by *Salmonella* species.

- The incidence of infections by *Bartonella* species and *Listeria monocytogenes* is very low and recommendations for treatment are similar to those of the general population.
- ART has proven to be the most effective measure for reducing the incidence of HIV-associated bacterial infections.

During 2002–2007, the incidence of invasive infections caused by *S. pneumoniae* was higher than in the general population, with increased mortality associated with disease severity and the presence of comorbid conditions, especially in patients with liver cirrhosis. These data supported the recommendation for primary prophylaxis with the 23-valent pneumococcal polysaccharide vaccine (23-PPV), whose efficacy was considered controversial until the extended follow-up of the only randomized clinical trial and results from observational studies suggested a moderate benefit. The 7-valent pneumococcal conjugate vaccine (7-PCV) proved highly efficacious in children and had an indirect effect on adults. 7-PCV has been replaced by the 13-valent pneumococcal conjugate vaccine (13-PCV). No data are available on 13-PCV in HIV-infected patients. However, a double-blind randomized trial comparing 7-PCV with placebo performed in patients in Malawi, most of whom had not received ART and who had experienced a previous episode of invasive pneumococcal disease, revealed an efficacy of 75%. Other studies revealed a more favorable immunogenic response with a dose of 7-PCV followed by a dose of 23-PPV.

- HIV-infected adults *who have not been vaccinated* should receive a dose of 13-PCV, regardless of their CD4+ T-lymphocyte count (**AII**). Patients with CD4+ $\geq$200/μL should subsequently receive a dose of 23-PPV at least 8 weeks after the dose of 13-PCV (**AII**). In the case of patients with a CD4+ T-lymphocyte count <200 cells/μL, the same strategy can be used or the dose of 23-PPV can be deferred until the CD4+ T-lymphocyte count increases to >200 cells/μL (**CIII**). The duration of protection with 23-PPV is unknown.
- In the case of patients *who have already received 23-PPV*, a dose of 13-PCV can be considered after at least 12 months (**CIII**). Similarly, revaccination with 23-PPV can be considered after 5 years (**CIII**), and a dose can be recommended after age 65 years (**BIII**).
- The annual seasonal influenza vaccination is recommended for prevention of bacterial pneumonia (**AI**), as is smoking cessation (**AIII**).
- No indications have been proposed for vaccination against *H. Influenzae* type b or *N. meningitidis* in HIV-infected adults.

Imported parasitic diseases

Immigration, international travel, and more favorable prognosis in HIV-infected persons mean that imported parasitic infections are increasingly common in the HIV-infected population. This section only addresses more severe parasitic diseases or those that act opportunistically in HIV-infected patients.

Malaria (especially malaria caused by *Plasmodium falciparum*) is one of the most relevant infections, since it affects both severely immunodepressed patients and those with normal CD4+ T-lymphocyte counts. Furthermore, a bidirectional negative interaction has been identified between HIV and *Plasmodium* species. Undoubtedly, the population most at risk of infection by *Plasmodium* species in our setting is that formed by immigrants who travel to their home country without having received chemoprophylaxis. Malaria is a key cause of fever in travelers who return from tropical countries, especially if they are from Sub-Saharan Africa. Given that the patient's condition can deteriorate rapidly (in only a few hours), a high level of diagnostic suspicion and early treatment are necessary.

- The indications for malaria treatment are the same as for non-HIV-infected persons. Close monitoring is recommended, especially in patients with low CD4+ T-lymphocyte counts, since the clinical manifestations in this group are usually more severe. Please consult potential interactions between antimalarial and antiretroviral drugs when considering treatment and chemoprophylaxis (www.interaccionesvih.com; http://www.hiv-druginteractions.org).

Acute *Trypanosoma cruzi* infection is almost exclusive to endemic areas (from the south of the United States of America to the north of Chile and Argentina). It is often asymptomatic and, if not treated, can progress to chronic disease. Approximately 20–40% of patients develop visceral involvement (mainly the heart). In Europe, the most common form of transmission is vertical transmission (5% risk); infection associated with transfusions or organ transplantation has been reported only exceptionally.

In HIV-infected patients with chronic *T. cruzi* infection, this protozoan disease behaves like an OI; therefore, patients from an endemic area should be screened (**AIII**). Reactivations usually affect patients with CD4+ T-lymphocyte counts <200 cells/μL, especially when counts fall to below 100 cells/μL. At this level of immunodepression, Chagas disease more commonly affects the central nervous system (in the form of space occupying lesions [chagomas] or meningoencephalitis), followed by the heart (mainly myocarditis). Cardiac involvement during a reactivation is sometimes difficult to distinguish from heart disease in a chronically infected patient. Diagnosis of chronic disease is based on serology findings, whereas diagnosis of reactivations is essentially based on direct parasitology (blood, CSF, or other body fluids) or histopathology.

- Benznidazole is the first choice for treatment, followed by nifurtimox, with which less experience is available (**AIII**). Duration, dose, interactions, and need for secondary prophylaxis have yet to be resolved. Posaconazole has not proven useful for this indication. The scarce data available on the effect of early initiation of ART does not seem to indicate the involvement of immune reconstitution phenomena in the CNS. Therefore, and given the high morbidity and mortality of reactivations, early initiation of ART is recommended (**AIII**).

Strongyloidosis is a helminth infestation that can become chronic owing to an autoinfection cycle; therefore, it should be suspected even many years after the patient has resided in or traveled to an endemic area. The most severe form is hyperinfection syndrome, which is more common in persons treated with corticosteroids or coinfected by HTLV-1. However, in HIV-infected patients, this clinical presentation is very unusual and is observed more as IRIS (when the CD4+ T-lymphocyte count recovers) than a condition associated with severe immunodepression.

Immune reconstitution inflammatory syndrome

IRIS is caused by restoration of the cellular inflammatory response in very immunodepressed patients who initiate ART. It has 2 manifestations: *unmasking IRIS*, which reveals a pre-existing occult OI, and *paradoxical IRIS*, which involves clinical deterioration of a previously diagnosed OI that has been treated appropriately.

Diagnosis is by exclusion, that is, ruling out other possible causes of worsening after initiating ART, such as drug-induced toxicity, failure of ART, failure of antimicrobial therapy, or the presence of intercurrent diseases.

The severity of symptoms should be evaluated to determine the need for treatment and the risk-benefit ratio of potential interventions. The objectives of treatment are to minimize morbidity and mortality and sequelae, improve symptoms, and reduce disease duration. Corticosteroids are the treatment of choice and are used mainly in IRIS caused by mycobacteria and fungi; their use is controversial in viral infections, and they are contraindicated in Kaposi sarcoma. The only randomized trial available compared prednisone (1.5 mg/kg/d for 2 weeks and 0.75 mg/kg/d for a further 2 weeks) blind with placebo in patients with TB or IRIS. In patients whose condition worsened, prednisone was added open-label. Prednisone reduced the duration of hospitalization and symptoms, with no differences in mortality. Some patients required a longer course of treatment. Nonsteroidal anti-inflammatory drugs can prove useful in patients with mild symptoms. Other drugs (IL-2, GM-CSF, infliximab, and maraviroc) are considered experimental. Patients with lymph node abscess may require repeated aspiration or surgical drainage. Lastly, it is important to remember that antimicrobial treatment must be optimized when possible and that it is not recommended to suspend ART. Our observations for IRIS can be summarized as follows:

- In the presence of IRIS, neither ART nor antimicrobial therapy can be suspended.
- Mild forms of IRIS can improve with nonsteroidal anti-inflammatory drugs (**B-III**).
- Corticosteroids are recommended for treatment of IRIS in patients with moderate-severe manifestations associated with mycobacteria and CNS involvement (**A-II**).

Conflict of interest

These authors and reviewers have not received any aid or grant related to this document.

Appendix A.

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Parasitic infections. Authors: José Mª Miró, José Sanz Moreno. Reviewers: Jaime Locutura, José López Aldeguer, Eduardo Malmierca, Pilar Miralles, Esteban Ribera.

Fungal infections. Authors: Josu Baraia Etxaburu, Juan Carlos López Bernaldo de Quirós. Reviewers: Pere Domingo, Fernando Lozano, Eulalia Valencia, Francisco Rodríguez Arrondo, Mª Jesús Téllez.

Mycobacterial infections. Authors: Santiago Moreno, Antonio Rivero. Reviewers: Joan Caylá, Vicente Estrada, Celia Miralles, Inés Pérez, Miguel Santín.

Viral infections. Authors: Daniel Podzamczer, Melchor Riera. Reviewers: Concha Amador, Antonio Antela, Julio Arrizabalaga, Juan Berenguer, Josep Mallolas.

Bacterial infections. Authors: Koldo Aguirrebengoa, Juan Emilio Losa. Reviewers: Pablo Bachiller, Carlos Barros, Hernando Knobel, Miguel Torralba, Miguel Angel Von Wichmann.

Prevention and treatment of imported diseases. Authors: Félix Gutiérrez, José Pérez Molina. Reviewers: Agustín Muñoz, Julián Olalla, José Luis Pérez Arellano, Joaquín Portilla.

Immune reconstitution inflammatory syndrome. Authors: José Ramón Arribas, Federico Pulido. Reviewers: Piedad Arazo, Josep Mª Llibre, Antonio Ocampo, Mª Jesús Pérez Elías, Jesús Sanz Sanz.

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