INTRODUCTION — Untreated HIV infection and HIV-related immunosuppression significantly increase the risk of acquiring opportunistic infections due to bacteria, viruses, fungi, and protozoa. These opportunistic infections were a major source of morbidity and mortality in HIV-infected patients prior to the development of effective antiretroviral therapy (ART) and still occur today, mostly in patients who are not receiving ART. Substantial advances in the prevention of opportunistic infections have been achieved. These strategies involve the use of antimicrobials, immunizations, and public health measures.

An overview of these different strategies will be reviewed here. The clinical manifestations, diagnosis, and treatment of specific opportunistic infections, as well as the use of secondary prophylaxis, are discussed elsewhere.

● (See "Treatment and prevention of Pneumocystis infection in HIV-infected patients").
● (See "Toxoplasmosis in HIV-infected patients").
● (See "Mycobacterium avium complex (MAC) infections in HIV-infected patients").
● (See "Diagnosis and treatment of histoplasmosis in HIV-infected patients").
● (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients").
● (See "Coccidioidomycosis in compromised hosts").
● (See "Treatment of AIDS-related cytomegalovirus retinitis").
● (See "Treatment and prevention of cryptosporidiosis").

EPIDEMIOLOGY OF OPPORTUNISTIC INFECTIONS — Opportunistic infections (OIs) are defined as infections that are more frequent or more severe because of immunosuppression [1]. Untreated HIV infection is associated with a progressive reduction in cell-mediated immunity as reflected by the CD4 count. Prior to the introduction of antiretroviral therapy (ART), OIs were the principal cause of morbidity and mortality in HIV-infected individuals. As examples, in the absence of antiretroviral therapy and antimicrobial therapy, the risk of developing certain OIs is as follows:

● Pneumocystis pneumonia (PCP) — The risk of PCP without prophylaxis is 40 to 50 percent per year in those with a CD4 count <100 cells/microL. (See "Treatment and prevention of Pneumocystis infection in HIV-infected patients", section on ‘Preventing initial infection’.)
● Toxoplasmosis — For HIV-infected individuals who are seropositive for toxoplasma and have a CD4 count <100 cells/microL, the probability of reactivated toxoplasmosis is approximately 30 percent per year. (See "Toxoplasmosis in HIV-infected patients", section on ‘Prevalence of infection’.)
● Disseminated Mycobacterium avium complex (MAC) — For patients with a CD4 count <50 cells/microL, the risk of developing disseminated MAC can be as high as 40 percent per year. The risk increases with decreasing CD4 cell count [2]. (See "Mycobacterium avium complex (MAC) infections in HIV-infected patients").

Impact of antimicrobial prevention — Antimicrobial agents can be administered to decrease the risk of developing an opportunistic infection. Prior to the introduction of potent antiretroviral therapy regimens, the use of antimicrobial therapy for severely immunosuppressed individuals (eg, CD4 count <200 cells/microL) was associated with significant reductions in the rate of OIs. As examples:

● The risk of PCP is ninefold lower with the use of antibiotic prophylaxis, and failure of primary prophylaxis is most commonly due to nonadherence and/or profound immunosuppression (CD4 count <50 cells/microL) [3-
The risk of toxoplasmosis reactivation is less than 3 percent for patients who receive suppression with trimethoprim-sulfamethoxazole [6]. (See "Toxoplasmosis in HIV-infected patients", section on 'Primary prophylaxis'.)

Prophylactic therapy against MAC in patients with CD4 counts <100 cells/µL reduces the one-year incidence of MAC to approximately 8 percent [2]. (See "Mycobacterium avium complex (MAC) infections in HIV-infected patients", section on 'Prevention of MAC disease'.)

Impact of antiretroviral therapy — Antiretroviral therapy is the most important strategy for preventing OIs. The widespread use of effective ART starting in the mid 1990s has led to a dramatic reduction in the incidence of opportunistic infections as illustrated in the studies below:

- In a cohort study of 2410 patients in Switzerland from 1995 to 1997, the incidence of any OI decreased from 15.1 per 100 person-years in the six months before initiating ART to 7.7 and 2.6 per 100 person-years in the first three and six months after starting ART, respectively [7]. The rate continued to decrease and was 2.2 per 100 person-years between 9 and 15 months after starting ART.
- In a multicenter study of more than 8500 HIV-infected patients in the United States, the rate of OIs declined from 140 per 1000 person-years in 1995 (prior to the introduction of potent ART) to less than 20 per 1000 person-years in 2007 [8].
- An analysis of 1255 patients who had at least one CD4 count <100 cells/µL found that the incidence of a major OI (Pneumocystis jirovecii pneumonia, MAC, and/or cytomegalovirus retinitis) declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years by mid-1997 [9].
- Similar trends have been noted in resource-limited settings. (See "Global epidemiology of HIV infection".)

Because ART results in the restoration of cellular immunity, the vast majority of patients who discontinue antimicrobial therapy after adequate immune recovery are no longer at risk for developing an opportunistic infection. (See "Toxoplasmosis in HIV-infected patients", section on 'Discontinuation of primary prophylaxis' and "Mycobacterium avium complex (MAC) infections in HIV-infected patients", section on 'Discontinuation of prophylaxis' and "Treatment and prevention of Pneumocystis infection in HIV-infected patients", section on 'Preventing initial infection'.)

APPROACH TO INFECTION PREVENTION — Restoring cellular immunity with antiretroviral therapy (ART) is the best way to prevent opportunistic infections. (See "Selecting antiretroviral regimens for the treatment-naive HIV-infected patient".)

A number of infections can also be prevented by immunization (eg, Streptococcus pneumoniae, hepatitis B virus). Vaccine efficacy may be compromised in advanced disease; thus, some providers may choose to wait on certain immunizations until ART has been started and some degree of immune recovery has occurred. A detailed discussion of immunizations in HIV-infected patients is found elsewhere. (See "Immunizations in HIV-infected patients" and "Pneumococcal immunization in HIV-infected adults" and "Prevention of hepatitis B virus infection in the HIV-infected adult", section on 'Vaccination'.)

Additional preventive strategies are needed for HIV-infected individuals who have evidence of significant immunosuppression. Such patients are usually those who are not receiving ART (eg, those unaware of their diagnosis) or who are prescribed ART but do not have adequate virologic suppression [1]. These additional strategies include:

- **Avoiding Exposure** — For certain pathogens, patients can prevent infection by avoiding exposure. As an example, patients without evidence of prior exposure to Toxoplasma gondii should avoid contact with cat feces (eg, changing litter) or eating undercooked meat. The risk of infection with other pathogens can also be reduced by appropriate environmental precautions; such pathogens include Bartonella henselae, Bartonella quintana, Coccidioides immitis, Cryptococcus neoformans, Cystoisospora, Cytomegalovirus, and Histoplasma capsulatum. More detailed discussions on how to prevent exposure to these specific organisms are found in the individual topic reviews. (See "Primary care of the HIV-infected adult", section on 'Other primary care..."
Antimicrobial therapy — Antimicrobial agents can be administered to immunocompromised individuals with HIV-infection to decrease the risk of developing certain opportunistic infections (eg, *P. jiroveci* pneumonia (PCP), toxoplasmosis, *M. avium* complex infection, and tuberculosis). When to initiate such therapy depends upon the CD4 count. (See When to administer antimicrobial therapy below.)

Antimicrobials are not generally recommended to prevent active infection with some pathogens (eg, *Bartonella* spp, *Candida* spp, *Cryptosporidium*, *Cytomegalovirus*), for one or more of the following reasons:

- Such pathogens are associated with a low incidence of disease
- There are concerns that antimicrobial therapy can result in the development of drug-resistance
- Antimicrobials can result in significant side effects and drug interactions

For such infections, patients should be monitored for signs and symptoms of disease. (See Early Detection below.)

WHEN TO ADMINISTER ANTIMICROBIAL THERAPY — We administer antimicrobial therapy to certain HIV-infected patients with the goal of preventing a clinically significant opportunistic infection. Such treatment is typically initiated as the individual’s cell-mediated immunity (ie, CD4 cell count) declines. For certain infections, the decision to initiate antimicrobial therapy also depends upon prior exposure to the pathogen.

- Antimicrobials are considered primary prophylaxis when they are used to prevent infection in uninfected individuals (eg, prevention of infection with *P. jiroveci* or *M. avium* complex [MAC]). (See Pneumocystis below and Mycobacterium avium complex (MAC)’ below.)
- Suppressive therapy refers to the use of antimicrobials to prevent active infection by pathogens that are present in the body but are dormant. Antimicrobials are only administered to individuals who test positive for the presence of an organism after assessing cell-mediated immunity or serology (eg, *Mycobacterium tuberculosis*, *T. gondii*). (See Tuberculosis below and Toxoplasma below.)
- Pre-emptive therapy may be used to treat certain asymptomatic immunocompromised individuals who have a positive antigen or serologic test that indicates infection, despite the absence of symptoms. Initiating treatment at this time allows for the use of simpler regimens, with fewer side effects, and avoids the complications associated with symptomatic disease (eg, *C. immitis*, *C. neoformans*). (See Coccidioidomycosis below and Cryptococcus below.)

Our approach to using antimicrobial therapy to prevent the development of common opportunistic infections in non-pregnant adults is consistent with guideline recommendations and is described below [1]. The use of antimicrobial agents to prevent other, less common OIs (eg, *Penicillium marneffei*, *Plasmodium* species, *Trypanosoma cruzi*) that may affect individuals who travel to, or reside in, specific geographic areas is discussed elsewhere. (See Diagnosis and treatment of Penicillium (Talaromyces) marneffei infection, section on ‘Prevention’ and HIV and malaria, section on ‘Malaria prophylaxis’ and ‘Chagas disease: Management of acute disease, early chronic disease, and disease in immunocompromised hosts’, section on ‘Treatment and prevention’.)

The management of HIV-infected women who are pregnant is also discussed elsewhere. (See Coccidioidomycosis in compromised hosts, section on ‘Management of immunosuppressed patients’ and Toxoplasmosis in HIV-infected patients, section on ‘Primary prophylaxis’ and Prenatal evaluation and intrapartum management of the HIV-infected woman in resource-rich settings.)

All CD4 counts

Tuberculosis — All HIV-infected individuals, regardless of CD4 count, should be screened for latent tuberculosis using either tuberculin skin testing or an interferon gamma release assay. Therapy for latent infection should be
administered to those who test positive and are without evidence of active disease. (See "Treatment of latent tuberculosis infection in HIV-infected adults").

**CD4 counts ≤250 cells/microL**

**Coccidioidomycosis** — We perform annual IgG and IgM serologic screening for coccidioidomycosis in asymptomatic patients with CD4 counts ≤250 cells/microL who live in endemic regions (eg, Arizona or California). We administer pre-emptive therapy with fluconazole therapy to such patients if they have a newly positive serologic test. We discontinue therapy in patients receiving antiretroviral (ART) when their CD4 count is >250 cells/microL for at least six months [25]. (See "Coccidioidomycosis in compromised hosts", section on 'Patients with HIV/AIDS'.)

**CD4 counts ≤200 cells/microL**

**Pneumocystis** — We recommend trimethoprim-sulfamethoxazole (TMP-SMX) to prevent PCP for patients with a CD4 count ≤200 cells/microL. For patients who cannot take TMP-SMX, alternative agents include dapsone, atovaquone suspension, or aerosolized pentamidine. Antimicrobials may be discontinued when ART therapy results in an increase in the CD4 count to >200 cells/microL for more than three months. (See "Treatment and prevention of Pneumocystis infection in HIV-infected patients", section on 'Preventing initial infection'.)

**CD4 counts ≤150 cells/microL**

**Histoplasmosis** — In general, we do not administer antifungal prophylaxis with itraconazole to prevent primary infection with histoplasmosis since there are limited data to suggest the efficacy of prophylaxis, and most patients will have immune recovery (ie, increased CD4 count) on antiretroviral therapy. However, in areas where histoplasmosis is hyperendemic (>10 cases/100 patient-years), such as certain parts of South America and French Guiana, some providers administer itraconazole (200 mg daily) to patients with CD4 counts ≤150 cells/microL. For such patients, antimicrobials can be discontinued when the CD4 cell count is >150 cells/microL for more than six months after initiation of ART [1]. (See "Diagnosis and treatment of histoplasmosis in HIV-infected patients", section on 'Prevention'.)

**CD4 counts ≤100 cells/microL**

**Toxoplasma** — We administer suppressive therapy with TMP-SMX to prevent reactivation of *T. gondii* in patients with a CD4 count ≤100 cells/microL and a positive toxoplasmosis IgG serology (see "Initial evaluation of the HIV-infected adult"). For patients who have contraindications to TMP-SMX, we use dapsone plus pyrimethamine and leucovorin. If the patient is intolerant or allergic to the above two regimens, we administer atovaquone with or without pyrimethamine/leucovorin. Monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin should not be used. Among patients receiving ART, we discontinue suppressive therapy when the CD4 count is >200 cells/microL for at least three months. (See "Toxoplasmosis in HIV-infected patients").

**Cryptococcus** — Preventive therapy for cryptococcal disease is generally not recommended because of drug interactions, adverse effects, potential for antifungal drug resistance, cost, and the lack of overall survival benefit [1,10]. However, for certain patients with a CD4 count <100 cells/microL, especially those in resource-limited settings, screening for serum cryptococcal antigen and pre-emptive therapy for those who test positive may be useful to prevent symptomatic infection. The use of pre-emptive therapy is discussed in detail elsewhere. (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients", section on 'Screening and treatment of early infection'.)

**CD4 counts ≤50 cells/microl**

**Mycobacterium avium complex (MAC)** — Primary prophylaxis against MAC infection should be given to all HIV-infected patients with a CD4 count ≤50 cells/microL [1]. Blood cultures for MAC isolation should be obtained before prophylaxis is initiated if there is any suspicion of clinical disease; the treatment regimen is different if blood cultures are positive (ie, the patient has active disease). For prophylaxis, we prefer the macrolide antibiotic azithromycin; clarithromycin and rifabutin are alternative options. However, if rifabutin is used, a chest x-
ray should be obtained to rule out active tuberculosis. Primary prophylaxis may be discontinued when effective ART is associated with an increase in CD4 count to >100 cells/microL for more than three months [1]. (See "Mycobacterium avium complex (MAC) infections in HIV-infected patients").

**EARLY DETECTION** — Patients should be educated about the signs and symptoms of opportunistic infections and/or screened for evidence of disease, especially if severely immunocompromised. As an example, we do not administer suppressive therapy to prevent cytomegalovirus (CMV) infection to those who are seropositive because of cost, risk of resistance, and lack of proven survival benefit. Such patients should be educated about the signs and symptoms of CMV disease, such as CMV retinitis (eg, increased floaters, decreased visual acuity). In addition, some experts recommend yearly ophthalmologic exams for all patients with a CD4 count <50 cells/microL to identify CMV and/or other infections that have ocular manifestations. However, this screening strategy for asymptomatic patients is typically not needed since most patients who start antiretroviral therapy (ART) will have prompt recovery of their CD4 cell count to >50 cells/microL. (See "Primary care of the HIV-infected adult", section on 'Patients with low CD4 cell counts'.)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Hepatitis B (The Basics)" and "Patient information: Vaccines for adults with HIV (The Basics)")
- Beyond the Basics topic (see "Patient information: Hepatitis B (Beyond the Basics)"

**SUMMARY AND RECOMMENDATIONS**

- Prior to the introduction of antiretroviral therapy (ART), opportunistic infections (OI) were the principal cause of morbidity and mortality in HIV-infected individuals. (See 'Epidemiology of opportunistic infections' above.)
- Restoring cellular immunity with ART is the best way to prevent opportunistic infections. However, additional strategies are needed for HIV-infected individuals who have evidence of significant immunocompromise. Such strategies include avoiding specific exposures and/or the use of antimicrobial agents or vaccines. (See 'Approach to infection prevention' above.)
- Antimicrobial therapy is typically initiated according to CD4 cell count thresholds. For certain patients, the decision to initiate antimicrobial therapy also depends upon prior exposure to the pathogen. (See 'When to administer antimicrobial therapy' above.)
- Patients should be educated about the signs and symptoms of opportunistic infections and/or screened for evidence of disease, especially if they are severely immunocompromised. (See 'Early Detection' above.)

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**REFERENCES**


