CHAPTER 15

The Immunocompromised Traveler

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As the world becomes increasingly interconnected, more people have the opportunity to travel outside their home communities and thus be at risk for novel and unexpected infections. The immunocompromised host requires special attention in pre-travel planning. This chapter will review travel preparations for immunocompromised patients, including human immunodeficiency virus (HIV)-infected individuals, solid organ or hematopoietic transplant recipients, and persons taking immunosuppressive medications.

THE IMMUNOCOMPROMISED TRAVELER

People with compromised immune systems require special preparation for travel to many geographic areas. The reasons are many and include increased risk of infection with common and unusual pathogens, failure of usual therapy to cure infection, atypical manifestations of infection, drug reactions and disease mimickers, diminished immune response to vaccines, and (especially in the case of HIV/acquired immune deficiency syndrome [AIDS]) political, social, and legal issues that may complicate movement from one country to another. Given the ease of administration of many current medications (e.g., monthly biologic agent injections, once-daily dosing of highly active antiretroviral therapy [HAART]) and improved side-effect profiles, many people are able to travel to both industrialized and developing nations. This raises additional issues about potential drug–drug interactions and the need for regular laboratory monitoring. **Table 15.1** lists drugs commonly used for immunosuppression and antiretroviral regimens and indicates potential interactions with drugs commonly used by travelers.

The immunocompromised traveler who becomes ill after returning home also poses special challenges. He or she may present with unusual manifestations of travel-related illnesses or develop complications from travel-acquired illness long after the exposure. Opportunistic infections may also occur in a time frame that mimics travel-related illness. With the complexities of such infections, both the travel medicine practitioner and the traveler's specialized care provider should coordinate prevention efforts and manage and coordinate care of the returned ill, immunocompromised traveler.

Infectious Disease Risks

Travelers frequently encounter pathogens that are absent or uncommon in their country of residence. In addition, their risk of infection with ubiquitous pathogens, such as *Salmonella* species, is greater during travel than during daily activities at home. Many of these pathogens can potentially cause increased morbidity and mortality in immunocompromised persons. In persons infected with HIV/AIDS (PHAs), a number of pathogens may be asymptomatic or cause mild symptoms in a traveler with a high $CD4^+$ T-cell count but manifest as a significant opportunistic infection if the person's $CD4^+$ T-cell count later falls. Three general

TABLE 15.1 Potential Drug Interactions of Frequently Used Travel-Related Medications[a]

Drug	Potential Interaction with Common Immunosuppression Medications[b]	Potential Interaction with HIV Medication
Acetazolamide	May increase potassium levels with prednisone	No specific contraindications
Atovaquone-proguanil		Decreased atovaquone and proguanil levels with atazanavir, lopinavir/ritonavir, and efavirenz, leading to less protection against malaria. No dose adjustment established
Azithromycin	May increase QT interval with prednisone	No specific contraindications
Chloroquine	Avoid with tacrolimus due to QT prolongation and risk for cardiac arrhythmias	No specific contraindications
DEET	No specific contraindications	No specific contraindications
Doxycycline	No specific contraindications	No specific contraindications
Loperamide	No specific contraindications	No specific contraindications
Proton pump inhibitors	May increase methotrexate level	Dose 12 h apart from atazanavir. Avoid with rilpivirine
H2 blockers	No specific contraindications	Dose at least 2 h before or 10 h after atazanavir. Dose at least 12 h before or 4 h after rilpivirine
Mefloquine	Contraindicated with cyclosporine due to QT prolongation and cardiac arrhythmias	May lower ritonavir levels (no recommendations to change dosing)
Pepto-Bismol (bismuth subsalicylate)	Monitor CBC if on methotrexate and salicylates	No specific contraindications
Quinolones	Avoid with cyclosporine due to increased cyclosporine levels and nephrotoxicity	Administer quinolone at least 2 h before didanosine

[a]Information obtained from pharmaceutical company package insert and communication with company representatives.
[b]Common immunosuppression medications reviewed in table: corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine), mycophenolate, nonbiologic disease-modifying antirheumatic drugs (DMARDs) (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine), biologic DMARDs (infliximab, adalimumab, etanercept, rituximab, anakinra).
CBC, Complete blood count.

groups of infections merit special attention: enteric infections, respiratory infections, and vector-borne infections.

Enteric Infections

Pathogens that enter via the gastrointestinal tract pose considerable threat to the immunocompromised traveler, as both intestinal mucosal and systemic defenses against gut pathogens are diminished. Decreased gastric acid and diminished local immune response mean that a smaller inoculum may be needed to establish infection. Once established, infection may be more severe and difficult to cure. The consequences of even typical traveler's diarrhea may be more profound for the immunocompromised patient. For PHAs taking antiretroviral therapy, nausea may be significant and interfere with the tolerability of their usual drug regimen. Infections with *Salmonella*, *Shigella*, and *Campylobacter* species tend to be chronic and relapsing and can lead to bacteremia. Salmonellosis in particular may be characterized

by recurrent bacteremias. Campylobacteriosis, cryptosporidiosis, and microsporidiosis may extend into the biliary tree, making clearance more challenging. An important opportunistic pathogen to be aware of is *Strongyloides* (see Chapter 45). This infection is commonly found in tropical climates including the southeastern United States, acquired through the skin when travelers come into direct contact with fecally contaminated soil. *Strongyloides* is usually asymptomatic or causes mild diarrhea symptoms and a transient recurrent rash called larva currens. In immunosuppressed individuals, however, it can more readily cause acute hyperinfection syndrome. *Strongyloides* can also lie dormant for years to decades after initial infection. Cases of reactivated strongyloidiasis hyperinfection may happen after patients receive immunosuppression with even short courses of corticosteroids; most of these cases have been fatal. **Table 15.2** summarizes some of the enteric infections frequently encountered by travelers and indicates increased morbidity in immunocompromised persons, relative to the general population. Of note, increased risk was most notable in the pre-HAART era and likely reflects risk in patients with advanced HIV. Risk in relatively immunocompetent patients on effective ART may be similar to that of the general population.

Respiratory Infections

Respiratory tract infections are common during travel, although the etiology is usually undefined. Several outbreaks of influenza in travelers have been documented, necessitating vaccination and early treatment (both will be discussed later in this chapter). Legionnaires' disease is acquired from stagnant or poorly cleaned water sources and has infected travelers

TABLE 15.2 Enteric Infections in Travelers

Disease	Estimated Incidence in General Travelers[a]	Estimated Morbidity/Mortality in Immunocompromised Persons[b]
Amebiasis	Uncommon in most areas	Same or increased
Campylobacteriosis	Common	Increased
Cholera	Rare	Probably increased; no data
Cryptosporidiosis	Probably common	Increased; may become chronic and debilitating
Cyclospora	Probably common	Possibly increased
Escherichia coli diarrhea	Common	Possibly increased
Giardiasis	Uncommon in most areas	Same or increased; may become chronic and resistant to therapy
Isosporiasis	Uncommon in most areas	Increased
Microsporidiosis	Unknown	Increased
Salmonellosis	Common	Increased
Shigellosis	Common	Increased
Strongyloides	Common	Increased
Typhoid fever	Rare or uncommon in	Increased most areas
Vibrio parahaemolyticus and other noncholera *Vibrio* species	Uncommon	Possibly increased

[a]*Common* indicates pathogens reported to cause at least 5% of cases of diarrhea in travelers in multiple studies in different geographic areas; *uncommon* refers to pathogens causing <5% of diarrheal cases. *Rare* describes infections not found as a cause of diarrhea in most studies of travelers. For nondiarrheal illnesses, *rare* indicates incidence in travelers is <10 cases/100,000 per month.
[b]Estimated morbidity and mortality in immunocompromised persons represents a composite of greater frequency and severity of disease relative to normal hosts.
Adapted from Wilson, M.E., von Reyn, C.F., Fineberg, H.V., 1991. Infections in HIV-infected travelers: risks and prevention. Ann. Intern. Med. 114:582.

staying at resort hotels and using spa facilities in several locations, including Europe and the Caribbean. Outbreaks of influenza and legionellosis on cruise ships document another possible place of transmission.

Two geographically focal fungal infections, histoplasmosis and coccidioidomycosis, can be progressive and disseminate in immunocompromised persons. Infection occurs via inhalation of air-borne organisms. The endemic area for coccidioidomycosis includes the southwestern United States, Mexico, and Central and South America. Although the largest number of reported cases of histoplasmosis has been in the United States, the disease has been reported in all continents, and the organism is an important cause of disseminated disease in PHAs in the Caribbean and parts of Central and South America. Another soil-associated fungal pathogen, *Penicillium marneffei*, found in Southeast Asia and China, is one of the most common opportunistic infections in northern Thailand. Travelers to this region who become infected may manifest symptoms as early as 4-5 weeks and as late as 10 years or more after exposure. Immunocompromised travelers to areas where these fungi are endemic should take precautions to avoid inhaling dust or entering caves; if heavy or long-term exposure is unavoidable, prophylaxis with fluconazole (100 mg/day) for coccidiomycosis or itraconazole (200 mg/day) for histoplasmosis and penicilliosis may be used.

Immunodeficient persons are exquisitely susceptible to tuberculosis. Patients receiving anti-tumor necrosis factor (TNF) therapy are at particularly higher risk of tuberculosis reactivation. Up to 10% of HIV-infected persons with latent tuberculosis will develop active infection. The likelihood of exposure to tuberculosis in many developing countries (where annual incidence rates may exceed 100/100,000 population) is substantially higher than in the United States (with annual incidence rates <10/100,000 population). Rarely, transmission has also been documented during travel (e.g., airplane, bus, train, boat). Vaccination with attenuated bacillus Calmette-Guérin (BCG) is neither routine nor recommended in the United States, so avoidance of infection and early identification of latent tuberculosis infection are paramount. Tuberculin skin testing (TST) should be done routinely in all immunosuppressed persons, regardless of travel plans (see Chapter 25). An induration of 5 mm is considered positive in HIV-infected persons, organ transplant recipients, and those on immunosuppressive medications (equivalent of 15 mg prednisone). The TST should be repeated 2-3 months after prolonged stays in high-incidence areas, which include many parts of Africa and Asia. A period of 4-12 weeks after exposure is generally required for development of delayed-type reactivity to the TST; however, some patients may develop primary clinical disease prior to skin test conversion. Immunocompromised persons should avoid prolonged stays in areas where ventilation is poor, tuberculosis rates are high, and multidrug resistance is common. Newer interferon gamma release assays (IGRA) to detect latent tuberculosis infection are being used with increasing frequency. Neither the TST nor the IGRA is entirely reliable in any population, but they are of particularly limited utility in those with severe immune deficiencies, because of the increased possibility of anergic responses.

Vector-Borne Infections

Animals and insects transmit vector-borne diseases. While immunocompromised patients are not necessarily at higher risk for acquiring these infections than the general traveler, symptomatic disease can be more severe. Malaria is the most common cause of febrile illness in travelers. Data linking severe malaria and compromised immune systems are limited, but there is concern for severe manifestations of the disease in these patients. The interaction between HIV-1 infection and malaria is complex, although research confirms that HIV-1 infection increases the likelihood of both asymptomatic parasitemia and clinical malaria in persons from endemic areas. In areas of unstable *Plasmodium falciparum* malaria transmission, some studies have suggested more severe malaria and higher mortality from malaria in HIV-1 infected individuals, especially those with $CD4^+$ T-cell counts <200 cells/mm^3. There is also evidence that HIV-1 infected persons are more likely to suffer treatment failure, which may be true for other immunocompromised populations. Prophylaxis against malaria would

therefore be of utmost importance to the immunocompromised traveler, which will be reviewed later in this chapter.

A weakened immune system may dramatically change the clinical course of visceral leishmaniasis and likely also cutaneous leishmaniasis, leading to more severe and disseminated disease, especially in HIV-positive and transplant patients. In visceral leishmaniasis, mortality is high, not only due to delayed diagnosis, but also because of a poor immunological response to the pathogens. Typical clinical features, such as splenomegaly and hyperglobulinemia, may be absent, and antibodies, often sought for diagnostic purposes, may be absent or delayed in appearance. Infection may manifest months or years after exposure in endemic areas; these include popular tourist destinations, such as Spain and other parts of southern Europe.

American trypanosomiasis or Chagas disease is also more likely to disseminate in the immunocompromised individual. In HIV-positive persons, *Trypanosoma cruzi* has been recognized as a cause of acute meningoencephalitis and central nervous system (CNS) mass lesions, which are not typical presentations. Fortunately, few travelers stay in accommodations (i.e., straw-thatched dwellings) where they are at risk for being bitten by infective reduviid bugs, and reports of American trypanosomiasis in visitors to endemic areas have been rare.

Interestingly, dengue has not been reported to cause a more severe illness in immunocompromised patients, though this may be due to lack of recorded data. Similarly, there is a lack of studies on chikungunya in these patients, although it is a rapidly emerging disease found in many tropical areas around the world.

PREPARATION OF THE IMMUNOCOMPROMISED TRAVELER

Given a number of increased risks, it is important for immunocompromised travelers to seek the advice of a knowledgeable travel health practitioner prior to embarking; however, this need is not always recognized. A study of 267 transplant patients showed that one-third of patients traveled outside the United States and Canada following transplant; of these patients, only 66% sought pre-travel counseling from a medical provider. Another study in Canada of HIV-positive travelers showed that only 44% of PHAs sought health advice before traveling, and half of these patients did not disclose their HIV status.

The approach to the immunocompromised traveler involves a series of steps, outlined in **Table 15.3**, and should typically include communication with the patient's specialized care provider (e.g., HIV physician, oncologist, transplant coordinator). Some steps may be omitted or abbreviated, but evaluation and preparation of the immunocompromised traveler in most instances will require extra time. Essential to the evaluation is an estimate of the degree of immunosuppression or stage of HIV disease; this will help assess the types of infections and other complications that are most likely. The first 6-12 months post-transplant or initiation of immunosuppressive medications is generally the riskiest time period for infection and patients, who are usually advised to not travel far from their home medical center. For the HIV-infected patient, a recent $CD4^+$ T-cell count and HIV RNA level are the most helpful, along with a realistic assessment of the traveler's compliance and comfort with his or her current antiretroviral regimen. Persons with a CD4+ T-cell count <200 cells/mm^3 (or CD4% < 15) and a high viral load are at highest risk for acquiring new

TABLE 15.3 Preparation and Education before Departure

- Review feasibility of planned travel
- Identify medical resources abroad
- Anticipate legal and immigration issues
- Review itinerary and area-specific risks
- Educate regarding risk reduction (e.g., prudent dietary habits)

infections, travel-related or otherwise. In some cases, it may be appropriate to counsel the patient to delay travel to certain areas until an effective antiviral regimen has been started and the viral load controlled. In general, an HIV-positive patient on antivirals should be on a stable and successful regimen for at least 8 weeks before departure. By that time, problematic side effects have usually been identified, and the time of peak incidence of an immune reconstitution event passed.

One goal of a pre-travel visit is to identify specific risks, assess their magnitude, and educate the traveler in ways to reduce them. Destination-related risks for the immunocompromised traveler may influence decisions about whether to undertake all or part of a proposed trip. The healthcare provider should review area-specific risks and consider available means to reduce them. Guidelines for prevention of disease and bureaucratic difficulties should be provided, preferably accompanied by written information. The traveler will have to decide whether the estimated risks are worth taking. Under some circumstances, the traveler may decide to change an itinerary if risk of serious disease cannot be eliminated or reduced.

Destination and duration of stay will affect recommendations. For persons with more severe disease or those planning a prolonged stay, it is especially important to identify medical resources before departure. All travelers should have medical insurance that will provide coverage for care during the trip. For travel to developing countries (or any place where good medical facilities may be unavailable), travelers should also have special insurance that will cover evacuation in the event that local medical facilities are inadequate to provide good care for an acute illness or injury. It may be necessary to arrange in advance for the continuation of special therapy or laboratory testing, and of course for the availability of necessary medications.

Some countries require screening for HIV for any extended travel. Specific regulations vary among countries, and requirements for testing are often tied to duration of expected stay. Knowledge of updated regulations in the destination countries can help avoid aggravating, disruptive, and unpleasant experiences. Test results from the United States are accepted in some countries but not in others. In these countries, entering travelers can be required to undergo testing at the demand of government officials. This evokes all of the concerns about quality control in testing, reliability of confirmatory tests, and sterility of needles and syringes.

It is important to stress the need for immunocompromised travelers to continue their usual immunosuppressive or antiviral regimen during travel. The Canadian study referenced above also found that a large proportion of HIV-infected travelers discontinued or interrupted therapy during travel, for reasons ranging from convenience or the desire for a "holiday" to intercurrent illness. Despite the lure of combining a travel holiday with a "drug holiday," studies have documented an increased risk of untoward events, including death, in HIV-positive patients who interrupted therapy, even under the close monitoring conditions of a study and with $CD4^+$ T-cell counts >250 cells/mm^3. For transplant recipients, the risk of graft rejection due to stoppage of immunosuppression can be equally as disastrous, even if the break is brief.

Potential drug interactions can become an issue, especially for certain drug classes (e.g., protease inhibitors). The traveler should bring the package inserts for his or her medications and carefully review potential interactions for any medication given or prescribed while overseas; of particular importance are proton pump inhibitors or H2 blockers given for gastric distress, which can interfere with medication absorption. Cisapride, no longer available in the United States, may be prescribed overseas and contribute to potential arrhythmia. Also to be reviewed is the feasibility of appropriate storage of medications, especially if the destination is a tropical, developing country, where refrigeration may be unavailable or erratic. It is important to keep in mind that "room temperature" in the tropics may be considerably warmer than the temperature at which the stability of any of the medications was tested. If necessary, the travel health provider can work with the specialized care provider to develop the most convenient and appropriate regimen for travel.

For the long-term traveler, it is essential to assess the need for periodic laboratory testing and the availability of specialized tests (e.g., complete blood count, comprehensive metabolic panel, T-cell subsets, HIV RNA level, immunosuppressive drug levels) in the destination country. Many patients on immunomodulary medications may not need routine laboratory monitoring if they are otherwise well, but even stable HIV-infected patients on a antiretroviral therapy usually require monitoring tests every 6 months.

Infection Prevention Strategies

Preventive strategies for travel-associated infectious diseases include general precautions, as well as immunoprophylaxis and chemoprophylaxis. Basic safeguards include hand hygiene, respiratory precautions, and proper food preparation. The importance of hand washing and sanitation cannot be stressed enough, as it is the single most effective method of preventing infection. If soap and clean water are not easily accessible, immunocompromised patients should plan to keep portable hand sanitizer with them at all times. Respiratory infections are commonplace, but immunocompromised individuals should try to avoid contact with persons suffering from respiratory symptoms. Viral illnesses such as influenza may seem out of season, but depending on one's travel destination, they may be at the peak of transmission. Food safety practice is an area of travel medicine that should be emphasized in pretravel counseling. Any food that is not thoroughly cooked should be avoided altogether, while cooked food should be eaten immediately and not allowed to sit out. Undercooked meat and seafood can lead to infections with bacteria (e.g., *Escherichia coli*, *Salmonella*, *Campylobacter, Vibrio* species), parasites (e.g., *Toxoplasma*, *Entamoeba*, tapeworms, paragonimiasis), and viruses (e.g., hepatitis A and norovirus). Unpasteurized dairy products are common in many developed and developing countries, which can place immunocompromised travelers at risk for infections with *Listeria* and *Brucella*. Bottled or boiled drinking water is recommended, and ice should be avoided. In summary, the same recommendations for all travelers apply here, with added vigilance and compliance because the risk and consequences of respiratory and gastrointestinal illnesses are higher in this immunosuppressed population.

Vaccinations

With respect to vaccines, two basic questions are relevant:

- What extra vaccines should be given or considered because of the increased need for protection?
- What routine vaccines should be avoided or given with caution to the immunocompromised person because of increased risk of adverse events from the vaccines?

Efficacy of vaccines is an issue in immunocompromised individuals. In general, administration of vaccines after immunosuppression leads to antibody levels that are lower and less durable and may be less potent than in the populations included in published trials. Most vaccines thus should be given months in advance of immunosuppression, if possible. In HIV-positive persons, response to vaccination improves in those on a successful antiviral regimen. If vaccination can be deferred until such time as the viral load is suppressed and the $CD4^+$ T-cell count is >200 cells/mm^3, the efficacy is likely to be increased further.

Serious adverse events associated with vaccine administration are a concern in immunocompromised individuals, and the appropriateness of live vaccines in these patients is variable. Many live vaccines are contraindicated in transplant recipients; however, as experience grows, this recommendation may change in the future. A small study in pediatric renal transplant patients of a live attenuated varicella vaccine has shown efficacy and safety. The measles, mumps, rubella vaccine can be given 2 years post-transplant if patients are otherwise stable and without signs of graft versus host disease. In HIV-positive patients, some live vaccines are considered safe in patients with $CD4^+$ T-cell counts >200 cells/mm^3. Interestingly, a number of studies have documented transient increases in plasma levels of HIV RNA after vaccination with influenza and pneumococcal vaccines and tetanus toxoids; however, there has been no clear evidence that the antigenic stimulus from vaccines leads to a sustained increase in HIV replication or hastens progression of HIV disease.

Four general recommendations follow from these observations: (1) The potential benefits from many vaccines seem to outweigh their risks; (2) one may choose to measure antibody titers to assess vaccine response; (3) appropriate timing of vaccination may increase efficacy; and (4) where different routes or schedules are available, the most immunogenic should be used. Specific recommendations are given below.

Table 15.4 lists vaccines to consider giving an HIV-infected person before travel. These assume the patient received the full primary series of immunization with vaccines usually given in childhood in the United States. Many PHAs receiving HIV care will also have received additional immunizations as recommended for the care of PHAs. The pre-travel

TABLE 15.4 Immunizations for Adult HIV-Infected Travelers

Indication	Vaccine[a]	Comments
Routine	Tetanus and diphtheria (Td)	Booster interval 10 years
	Tetanus, diphtheria, and acellular pertussis (Tdap)	Once regardless of interval between last Td.
		Repeated with each pregnancy
	Haemophilus influenzae b, conjugate	Not routinely recommended for HIV care
	Hepatitis B[b]	Recommended as routine care. Assess antibody level 1 month following vaccine series
	Influenza	Yearly
	Pneumococcal	PCV13 once, then PPSV23 at least 8 weeks following PCV13. PPSV23 should be repeated 5 years later
Standard for travel to developing countries	Hepatitis A[c]	Preferably at least 4 weeks before departure
	Measles or MMR[d]	Avoid in patients with HIV with $CD4^+$ T-cell counts <200 cells/mm^3
	Polio, enhanced inactivated	Avoid live oral polio vaccine
	Typhoid, inactivated Vi polysaccharide	Booster interval 2 years; avoid live oral typhoid vaccine (Ty21a)
For selected destinations or circumstances	Japanese encephalitis	Assess risks and benefits; no efficacy data
	Meningococcus	No efficacy data; conjugate vaccine probably more effective
	Rabies	Use IM vaccine series; no efficacy data
	Yellow fever[e]	Do not give if $CD4^+$ T-cell counts <200/mm^3; no data on efficacy. Booster interval 10 years
	Bacille Calmette-Guérin (BCG)	Avoid BCG in all HIV-positive patients, regardless of $CD4^+$ count or viral load

[a]Recommendations assume a history of routine childhood immunizations.
[b]Omit if person is already immune to hepatitis B.
[c]Omit if person has serologic evidence of immunity to hepatitis A.
[d]May be omitted if patient has serologic evidence of measles immunity.
[e]Required by many countries in Africa and South America and by other countries for travelers who have visited or been in transit through countries where yellow fever is endemic.
HIV, Human immunodeficiency virus; *IM,* intramuscular; *MMR,* measles, mumps, rubella; *PCV,* Pneumococcal conjugate Vaccine; *PPSV,* pneumococcal polysaccharide vaccine.
Adapted from Wilson, M.E., von Reyn, C.F., Fineberg, H.V., 1991. Infections in HIV-infected travelers: risks and prevention. Ann. Intern. Med. 114:582.

visit offers an opportunity to review such routine vaccines as well as the exotic ones. Annual influenza vaccination is recommended for HIV-infected persons, even when no travel is planned. Because influenza occurs during April through September in the Southern Hemisphere and throughout the year in tropical countries, it may be prudent to give travelers the vaccine outside the usual North American influenza season, although availability of the vaccine can be a problem in the off-season. Prophylaxis or self-treatment with oseltamivir is another option if there is a poor match between the circulating influenza strains and the current vaccine and the traveler is going to an area with extensive influenza transmission.

Pneumococcal infections are more common and more likely to result in bacteremia in HIV-infected persons. Rates may be >100-fold higher than in an age-matched non-HIV–infected population. Thus vaccination against pneumococcal disease is recommended in HIV-infected persons, preferably early in the course of HIV infection. Asymptomatic HIV-infected persons with $CD4^+$ T-cell counts <500 cells/mm^3 are less likely to respond to the pneumococcal capsular polysaccharide (PPSV23) than healthy young adults, although even with advanced stages of immunosuppression, some HIV-infected persons are able to mount an antibody response. Pneumococcal conjugate vaccine (PCV13) is now recommended for all HIV-infected adults in addition to PPSV23. Pneumococcal infections may not be more common during travel, but penicillin-resistant strains are more prevalent in many areas of the world than they are in the United States, and any serious illness during travel can be disruptive.

Because hepatitis B and HIV share similar routes of transmission, and because immunization is recommended as routine HIV care, many HIV-infected persons will already be immune to hepatitis B or be chronic carriers of hepatitis B surface antigen (HBsAg). The hepatitis B vaccine appears to be safe to use, and strong consideration should be given to vaccinating all hepatitis B-susceptible, HIV-infected persons. HIV-infected persons are more likely to become chronic carriers of HBsAg if they become infected with hepatitis B virus. They also respond less well to the vaccine, with only 50-70% developing antibody titers that are considered protective. Anti-HB surface antibody titer should be assessed 1 month after completion of series.

Rates of invasive *Haemophilus influenzae* infections are higher in HIV-infected persons than in the general population, but the organism remains a relatively rare cause of invasive disease in this population. Because many of the strains causing invasive disease are not serotype B (e.g., only 33% of strains were serotype B in one study in HIV-infected men), the conjugate vaccine directed against type B disease in common use may have limited benefit and is not currently recommended as part of routine HIV care.

Vaccines for Travel to Developing Countries

A second group of vaccines listed in **Table 15.4** are frequently administered before travel to developing countries. Because of the increased risk of vaccine-associated poliomyelitis in immunosuppressed persons, the enhanced inactivated parenteral polio vaccine should be used instead of oral live polio vaccine in HIV-infected persons and their household contacts. The inactivated Vi polysaccharide typhoid vaccine should also be used in preference to the oral typhoid vaccine (Ty21a), although no cases of progressive infection with this attenuated strain of *Salmonella typhi* have been reported. Travelers who lack immunity to hepatitis A should be given one of the inactivated hepatitis A vaccines, ideally at least 4 weeks before departure. The commercially available serologic tests for hepatitis A antibody assess whether a person is immune because of past infection but are not sufficiently sensitive to pick up vaccine-induced antibodies. Hence, routine serologic testing after hepatitis A vaccination is not recommended.

Recommendations about the measles vaccine in HIV-infected persons differ from advice about other live vaccines. This live vaccine is recommended for HIV-infected persons, unless they have severe immunosuppression ($CD4^+$ T-cell counts <200/mm^3 or clinical AIDS). A case of fatal giant cell pneumonitis associated with measles vaccine virus has been reported in a young man with late-stage AIDS. The following observations underlie the current

recommendation: (1) Measles infection in HIV-infected persons can be atypical, severe, and sometimes fatal; (2) measles vaccine has generally been safe (with exception noted previously), although most of the experience in HIV infection has been in young children; (3) treatment modalities for measles are limited; (4) measles is highly contagious and exposure is often inapparent; and (5) risk of exposure is greater during travel to many developing countries than it is in the United States. The measles cases in the United States now are imported or related to imported cases. The current recommendation is for two doses of measles vaccine (the first dose usually given at age 12-15 months, with a second dose in childhood). Some adults who never experienced natural infection because of measles vaccination in infancy have not received a second vaccine dose and may be candidates for the second dose before travel. It may be worthwhile to assess measles antibody status in HIV-infected persons even if born before 1957, if they have no history of natural measles, or to consider proceeding with vaccination.

Special Vaccines for Specific Destinations or Activities

Other vaccines listed in **Table 15.4** are recommended only for specific destinations or special circumstances. The traditional inactivated cholera vaccine is safe, but it is no longer available in the United States. HIV-infected persons may be at increased risk for cholera because gastric acid is an important barrier to infection, and PHAs often have reduced gastric acidity. Education about the need for rehydration for severe diarrhea and the availability of oral rehydration salts is important for all travelers.

Rabies vaccine should be given to HIV-infected persons who meet the usual criteria for the vaccine. The more immunogenic intramuscular route and dose (1 mL) should be used (instead of 0.1 mL dose via intradermal route, which is currently not available in the United States), because it offers a greater potential for efficacy.

The yellow fever vaccine often poses the most difficult dilemma: infection with yellow fever may be lethal and effective treatment is unavailable; the vaccine contains live virus; and proof of vaccination is required for entry into many countries. There are three main options for an HIV-infected person who plans to travel to yellow fever-endemic countries. Transmission of yellow fever is focal in endemic areas, and many travelers to countries requiring yellow fever vaccine are at no risk of infection. A reasonable option for a person visiting an area without current yellow fever transmission is to provide a letter of waiver stating that the vaccine is contraindicated for medical reasons. Another approach is to change the itinerary to avoid countries requiring the vaccine. The third option is to give the vaccine. HIV-infected persons with $CD4^+$ T-cell counts $>200/mm^3$ who cannot avoid exposure to the yellow fever virus should be offered the vaccine. No reports have been published of recognized yellow fever vaccine-related disease in PHAs, and several reports have indicated the general safety of the vaccine in this population. In persons with lower $CD4^+$ counts, the possible risks and benefits should be considered on an individual basis. For HIV-infected persons who receive the vaccine and who will be at moderate or high risk of exposure, it may be prudent to assess levels of neutralizing antibodies after vaccination (consult the state health department or Centers for Disease and Control and Prevention at 970-221-6400). Whether or not the vaccine is given, the traveler should be given explicit instructions in ways to avoid mosquito bites. Insect-control maneuvers can help prevent many infections in addition to malaria and yellow fever. Use of permethrin sprayed on clothing is a useful adjunct to other approaches to preventing bites.

Although the possibility of testing for antibody response to various vaccines has been mentioned above, the cost of such testing and the time required to receive the results may be prohibitive. As there are no clear guidelines on how to proceed if the antibody response is low in this situation (with the exception of hepatitis B immunization), a rational approach should be taken.

Chemoprophylaxis for Traveler's Diarrhea

All travelers should be given advice and written materials, if possible, describing strategies to avoid risky food and beverages. Immunocompromised persons should be scrupulous about

following dietary guidelines to avoid enteric pathogens, in particular, inadequately treated water, undercooked meats, and raw, unpeeled fruits and vegetables. Those traveling to developing countries should be given a prescription for an antimicrobial agent, either to be taken as prophylaxis or to be used as empiric therapy in the event of acute diarrheal illness (see Chapter 8). Because immunocompromised persons have a higher risk for diarrhea than other travelers, the threshold for recommending prophylactic antibiotics may be lower. This issue should be discussed and individual preferences considered. Some considerations in the decision to use prophylaxis versus early empiric therapy include destination and duration of stay, available medical facilities at the destination, allergies, and other concurrent medications. If the traveler is already taking trimethoprim/sulfamethoxazole for *Pneumocystis* prophylaxis, a different agent should be chosen for early self-treatment of diarrhea. A quinolone, such as norfloxacin or ciprofloxacin, is a reasonable choice, although azithromycin is preferred in areas with resistant *Campylobacter*, such as Southeast Asia. The non-absorbable antimicrobial rifaximin is licensed for the treatment of traveler's diarrhea due to *E. coli*, but has been found to be effective as a prophylaxis as well and may be a consideration. Since the drug is not absorbed into the systemic circulation, there should be no drug interactions.

Antimalarial Prophylaxis

Antimalarial agents and advice about personal protective measures to prevent mosquito bites should be given to all travelers. General precautions are first lines of defense, which include appropriate bed-net use, skin-covering clothing preferably treated with permethrin, and topical DEET or picaridin solutions. Mefloquine is currently a first-line drug recommended for most chloroquine-resistant malarious areas. Because of the high frequency of underlying neurologic problems, especially in HIV-infected persons, it is important to review any history of seizures or current signs or symptoms of CNS disease before prescribing this agent. Atovaquone-proguanil (Malarone®) is another first-line drug for malaria chemoprophylaxis that may be considered. Malarone is still an option even if the traveler is already taking atovaquone for the prevention of *Pneumocystis jiroveci*, because the atovaquone dose can be reduced while on Malarone. For example, adults using atovaquone-proguanil 250 mg/100 mg who normally take 1500 mg of atovaquone for daily *Pneumocystis* pneumonia prophylaxis should change to 1250 mg of daily atovaquone. Alternatively, if the traveler has access to proguanil alone (not available in the United States), that can be taken in addition to his or her regular atovaquone. Doxycycline also remains an acceptable option for malaria prophylaxis, with the caveat that those prone to thrush should also carry clotrimazole troches or fluconazole tablets for pre-emptive treatment.

Sexual Precautions

Persons living with HIV/AIDS should be reminded that they remain at risk of acquiring sexually transmitted diseases while away from home and that these infections may have particularly significant implications for their health. Certainly, HAART should continue without interruption during the journey. But this does not remove the importance of responsible sexual behavior. Although there are little data on the efficacy of HAART in preventing secondary HIV acquisition among infected overseas travelers, there is concern that the regimen used by these patients may not protect them fully from acquiring a new infection due to drug-resistant HIV strains. And, of course, barrier protection greatly reduces the risk of transmitting HIV to uninfected partners, regardless of viral load.

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