Review

HIV Infection and Travel: Pretravel Recommendations and Health-Related Risks

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In the current era of globalization and ease of air travel combined with the increased survival attained since the advent of potent antiretroviral therapy, HIV-infected individuals are traveling to remote and resource-limited areas of the world. Travel-related health risks in a patient with HIV depend on the patient's immune status, destination, travel itinerary, and type of travel. HIV-infected patients with a CD4+ count of 200 cells/µL or lower, particularly those who are treatment-naive and newly diagnosed, are at increased risk of complications when traveling to resource-poor settings. These increased risks include those of acquiring gastrointestinal, respiratory, and endemic tropical infectious diseases. Individuals with a CD4+ count higher than 200 cells/µL (whether receiving antiretroviral treatment or not) are considered to have limited immune deficiency for the purpose of travel-related recommendations; in general, they may safely receive most recommended and required vaccines. Pretravel consultation before departure is crucial to address strategies to protect against vaccine-preventable diseases (routine, recommended, and required vaccinations); vector-borne diseases, particularly malaria; gastrointestinal infections; and sexually transmitted diseases. HIV-infected travelers who are ill, particularly those with fever, should undergo an immediate medical evaluation to rule out the possibility of a life-threatening infectious disease such as malaria.

In the current era of globalization, mobility across international borders is part of the lives of thousands of people. Destinations include developed and developing regions.[1] This trend has also been associated with complex travel itineraries and includes individuals with chronic medical conditions.[2-7] The number of persons with HIV infection traveling from developed countries to tropical and subtropical areas of the world has increased substantially as a result of the clinical and survival benefits achieved with the use of effective antiretroviral therapy.[4,6,8] Indeed, reports indicate that 10% to 20% of HIV-infected patients with different levels of immunosupression travel from the United States to foreign destinations, and often to resource-constrained settings.[3,4,9]

For the healthy immunocompetent traveler, international travel poses certain health risks.[10-14] For a patient with HIV, these risks become even more important to consider.[9] The concern is 2-fold, that the underlying disease might worsen during travel and that HIV-infected travelers are at increased risk of complications from infectious diseases acquired at the destination.[8,15] Because patients with advanced immunosuppression are at higher risk of acquiring severe disease associated with some tropical infectious diseases,[6-8] HIV practitioners should emphasize the need for their patients to obtain expert travel-health advice before undertaking international travel.[3,8,10]

Travel-related risks in the HIV-infected traveler depend largely on the immune status of the patient.[8] Thus, it is crucial that a recent assessment of the CD4+ cell count and percentage and of the plasma HIV RNA level be available at the pretravel consultation.[8] In addition, it is important for the practitioner and patient to review and discuss the decision to travel and the proposed itinerary, duration, and type of travel.[16]

Protective strategies in patients with HIV infection involve (1) overall travel-planning issues; (2) awareness of restrictions on HIV-infected individuals for entering specific countries; (3) prevention of vaccine-preventable diseases; (4) effective chemoprophylaxis against malaria and other vector-borne infections; and (5) prevention or self-treatment of gastrointestinal and other infections. Guidelines have been jointly issued by the US National Institutes of Health, the US Centers for Disease Control and Prevention, and the Infectious Diseases Society of America for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. These guidelines are available at http://AIDSinfo.nih.gov.

Travel Recommendations for HIV-Infected Travelers

International travel poses unique medical challenges for HIV-infected per-

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sons. It is crucial that HIV practitioners understand the medical assessment and care that their patients need before traveling, especially for those traveling to resource-limited areas. One of the International AIDS Society–USA's recently published *Cases on the Web (COW)* presents an in-depth discussion of travel recommendations for HIV-infected travelers and offers CME credit (http://www.iasusa.org/cow/).

When planning travel to resource-constrained settings, HIV-infected individuals are encouraged to identify reliable medical institutions at the destination before they travel and to seek prompt medical care if becoming ill while traveling. In addition, medical insurance coverage should be verified and additional travel insurance purchased if necessary. Depending on the type of travel and itinerary, evacuation insurance should be considered.[8]

Pretravel consultation with HIV-infected individuals is considered a window of opportunity to update routine immunizations and provide required and recommended travel-related vaccines and chemoprophylactic regimens.[15,17] Most travel-health practitioners concur that HIV-infected patients with a CD4+ count of 200 cells/µL or lower, particularly those who are antiretroviral treatment–naive and newly diagnosed with HIV, are at increased risk of complications when traveling to resource-limited settings, where they may face increased risk of acquiring gastrointestinal, respiratory, and particular tropical endemic infectious diseases.[2,4,5] Such individuals are generally advised to delay their travel to resource-limited areas pending immune reconstitution with the use of antiretroviral therapy.[8] This delay will minimize the risk of acquiring new infections and allow for immunologic recovery that will potentially lead to a higher immunogenic response to some travel-related vaccines.

Individuals with a CD4+ count from 200 cells/µL to 500 cells/µL, whether receiving antiretroviral therapy or not, are considered to have limited immune deficiency from the perspective of travel-related recommendations. Nevertheless, such patients are gener-

ally advised to defer travel for at least 3 months after starting antiretroviral therapy to minimize the possibility that immune-reconstitution syndromes would occur during travel.[8]

In addition to antiretroviral drugs, travelers should bring with them a well-planned medical travel kit containing over-the-counter medications for symptom relief.[2] A detailed list of recommended medications to include is available (http://wwwn.cdc.gov/travel/yellowBookCh2-HealthKit.aspx).

Border-Crossing Considerations for HIV-Infected Travelers

Potential travelers should review country-specific guidelines before planning international travel. A list of legal requirements for entry to individual countries is available at the US State Department Web site (http://travel.state.gov/travel/cis_pa_tw/cis_pa_tw_1168.html). A comprehensive guide related to travel restrictions for HIV-infected patients is also available at the Joint United Nations Programme on HIV/AIDS (UNAIDS) Web site (http://www.unaids.org/en/PolicyAndPractice/KeyPopulations/PeopleHIV/mobility_technical_policies.asp).

The key issues to explore include any potential administrative or legal problems travelers might encounter at the destination country or countries and assurance of a reliable supply of antiretroviral medications. Antiretroviral drugs should be kept in carry-on bags and a backup supply stored in the checked luggage. In addition, travelers must carry with them official documentation of medications for use when crossing borders.[8,16]

Vaccine-Preventable Diseases in HIV-Infected Travelers

Travel-related vaccines can be categorized into 3 main groups for HIV-infected and -uninfected persons traveling to developing areas of the world: (1) routine vaccines to update immunizations for children, adolescents, and adults; (2) recommended vaccines, depending on the destination and travel itinerary; and (3) required vaccines to

obtain a visa or for entry into some countries.[10,11,18]

Inactivated vaccines are generally acceptable for use in HIV-infected patients (eg, pneumococcal, tetanus, hepatitis A virus [HAV] and hepatitis B virus [HBV], inactivated polio, meningococcal, and inactivated trivalent influenza vaccines). Conversely, live viral and bacterial vaccines (eg, yellow fever, oral Ty21 typhoid, oral cholera, measles-mumps-rubella, or BCG vaccines) are generally avoided in patients with HIV infection, particularly those with advanced immunosuppression (CD4+ count < 200 cells/µL, CD4+ cell percentage < 14%, or history of AIDS-defining opportunistic infections).[3-5] Some vaccines may stimulate viral replication and therefore transiently increase plasma HIV RNA level, which has not been found generally to be of clinical importance.[8] Immune response to some vaccine antigens improves with immune reconstitution brought about by antiretroviral therapy. For some vaccines, specific antibody titers should be measured after vaccination to ensure an adequate level of protection.

Routine Vaccines in HIV-Infected Travelers

Routine immunizations must be brought current in HIV-infected travelers bound for developing settings; these include HAV and HBV, tetanus toxoid, inactivated influenza, and polysaccharide pneumococcal vaccines (Table 1).[8] HAV infection and influenza are considered the most frequent vaccine-preventable diseases among international travelers.[19]

HIV-infected travelers not immune to HAV should receive hepatitis A vaccine regardless of their CD4+ cell count.[8,19] The 2-dose regimen of hepatitis A vaccine at regular antigen dose provides an adequate level of protection even in patients with severe cellular immunosupression.[20] However, the response to hepatitis A vaccine is improved after immune reconstitution with antiretroviral therapy.[21] Some experts recommend checking the hepatitis A serologic response 1 month after

Table **1.** Recommendations for the Use of Live Attenuated and Inactivated Vaccines in HIV-Infected Patients Planning Travel

Live Attenuated Vaccines	CD4+ Count	
	≥ 200 cells/μL, with Asymptomatic infection, or On antiretroviral therapy with immune reconstitution	< 200 cells/μL, with Symptomatic infection including history of AIDS-defining illness, or On antiretroviral therapy without immune reconstitution[a]
BCG	Contraindicated	Contraindicated
Live attenuated influenza	Contraindicated	Contraindicated
Measles-mumps-rubella	Recommended in those without evidence of immunity[b]	Contraindicated
Ty21a oral typhoid	Contraindicated[c]	Contraindicated
Varicella-zoster virus (adults)	Use as indicated in immunocompetent hosts[b,d]	Contraindicated
Yellow fever	Use as indicated in immunocompetent hosts who will be exposed to substantial risk of infection; careful attention should be given to travel itinerary[d]	Contraindicated
Inactivated Vaccines	**CD4+ Count**	
	≥ 200 cells/μL, with Asymptomatic infection, or On antiretroviral therapy with immune reconstitution	< 200 cells/μL, with Symptomatic infection including history of AIDS-defining illness, or On antiretroviral therapy without immune reconstitution[a]
Cholera	Live attenuated oral vaccine contraindicated; use killed recombinant vaccine if substantial risk exists[e]	Live attenuated oral vaccine contraindicated; use killed recombinant vaccine if substantial risk exists[e]
Combined tetanus and diphtheria or combined tetanus, diphtheria, and pertussis	If indicated	If indicated
Haemophilus influenzae	If indicated	If indicated
Hepatitis A	Recommended	Recommended
Hepatitis B	Recommended[f]	Recommended[g]
Inactivated trivalent seasonal influenza	If indicated	If indicated
Inactivated polio	If indicated (live attenuated oral polio vaccine contraindicated)	If indicated (live attenuated oral polio vaccine contraindicated)
Japanese encephalitis	Recommended if substantial risk exists	Recommended if substantial risk exists
Meningococcal polysaccharide or conjugate	Consider if travel-required or -recommended	Consider if travel-required or -recommended
Pneumococcal polysaccharide	If indicated	If indicated
Rabies	If indicated	If indicated[f]
Typhoid capsular polysaccharide	If indicated[h]	If indicated[h]

[a] Data unavailable for those on antiretroviral therapy with CD4+ count between 200 cells/μL and 500 cells/μL.
[b] For patients in this category who meet age requirements and lack evidence of immunity (ie, no documentation of vaccination or evidence of prior infection).
[c] Possible use if CD4+ count is > 200 cells/μL, but no evidence-based recommendation is available in this regard.
[d] Serologic testing recommended after vaccination to ensure optimal response to immunization.
[e] Unavailable in the United States; Centers for Disease Control and Prevention does not recommend use.[18,43]
[f] Measure antibody titers after immunization to ensure adequate protection in HIV-infected patients.
[g] Best protection achieved if given 6 to 12 months after initiation of antiretroviral therapy.
[h] Vaccine of choice among HIV-infected individuals regardless of CD4+ cell count.

administration if time permits. Non-responders should ideally be revaccinated prior to traveling.[22] Additional protection may be afforded by the use of HAV immune globulin in those with a CD4+ count of 200 cells/µL or lower and who lack serologic evidence of immunity.[23]

Vaccination for HBV is recommended for patients at all stages of HIV infection or AIDS, particularly those traveling to resource-limited settings.[8] The serologic response should be assessed 1 month after completion of the vaccine course.[22] A hepatitis B vaccine schedule that is started 6 months to 12 months after the initiation of antiretroviral therapy offers the best immunogenicity. If there is no response, revaccination should be considered. Some experts might delay revaccination until after a sustained increase in CD4+ count is achieved with antiretroviral therapy.[22]

Immunogenicity to tetanus toxoid is influenced by HIV infection and by malaria.[24] Antitoxin antibody levels are often lower in HIV-infected patients than in uninfected individuals, particularly in those with a CD4+ count of 300 cells/µL or lower.[24] Despite these limitations, vaccination with tetanus toxoid is currently recommended for HIV-infected persons of all age groups regardless of the presence of advanced immunosuppression because most groups appear to achieve protective antitoxin levels.[25]

The serologic responses to diphtheria, tetanus, and possibly pertussis vaccines are diminished in children with HIV infection.[26] However, there is no evidence of a lack of vaccine effectiveness or increased risk of vaccine adverse events with the combination vaccines for diphtheria, pertussis, and tetanus (DPT) or for tetanus and diphtheria (Td) in HIV-infected individuals.[26-28] An acellular vaccine to prevent pertussis in adults was approved for use in 2006 in the United States (tetanus, diphtheria, and pertussis, or Tdap).[27] The vaccine is recommended for 1-time dose administration to all adults age 64 years or younger whose most recent Td booster was received 10 or more years ago; it is considered safe to administer in HIV-infected individuals.[25] The Tdap vaccine may be substituted for the recommended Td booster that adults should receive every 10 years.

Influenza is considered a year-round infection in the tropics, and in the Southern Hemisphere, the influenza season runs from April through October.[29] Inactivated trivalent influenza vaccine is currently recommended for HIV-infected individuals with a CD4+ count of 100 cells/µL or higher as a pretravel vaccination, taking into account the influenza season at the destination. When a specific inactivated trivalent vaccine is not available or may potentially not protect travelers because of the season of travel, use of the antiviral drug oseltamivir for self-treatment is considered an alternative in travelers at high risk of acquiring influenza and developing potential complications from this infection.[8,29]

Most travelers are protected against measles by either natural exposure or previous immunization. However, the risk of exposure to measles may be increased in some resource-constrained settings, and the disease can become more severe in the HIV-infected patient.[3,4,9] Previous immunity should be determined by serologic analysis and measles vaccines recommended for nonimmune travelers to resource-constrained settings with high prevalence rates of measles, unless their CD4+ count is 200 cells/µL or lower.[8] Measles immune globulin may be administered for short-term protection of those traveling to high-risk areas and for whom a measles, mumps, and rubella (MMR) vaccine is contraindicated.[20] There is only 1 case report of fatal vaccine-related disease in an adult patient with advanced immunosuppression and who developed fatal pneumonia.[26,30-32] An important concern yet to be resolved is whether HIV-infected children who receive measles vaccine may experience any substantial delayed adverse events as a result of the possible persistence and later replication of the attenuated virus.[32]

In a study of HIV-seropositive children, overall vaccine-induced immunogenicity to many polysaccharide and protein antigens was decreased.[26] Indeed, the vaccines currently recommended by the World Health Organization (WHO) for use in national immunization programs in children infected with HIV are generally considered safe and beneficial. Nonetheless, HIV-associated immunosuppression reduces the benefit compared with that seen in HIV-seronegative children. No serious complications have been reported in this group with the use of yellow fever vaccine. The benefits of inactivated polio vaccine and measles vaccination in HIV-infected children outweigh any potential risks.[32]

Recommended Travel-Related Vaccines in HIV-Infected Travelers

Japanese encephalitis (JE) vaccination using the inactivated mouse-brain-derived JE vaccine in HIV-infected persons follows the same recommendations as for HIV-seronegative persons (3 doses over 28 days).[33,34] Varicella-zoster vaccine is an important consideration for nonimmune travelers bound to tropical and subtropical areas of the world. It has been given safely to some children with HIV infection, and current recommendations state that HIV-infected children with a CD4+ cell percentage of 15% or greater should receive varicella-zoster vaccine.[35,36] In this group of HIV-seropositive children, varicella-zoster vaccine produces adequate immunogenicity and minimal reactogenicity.[36]

With regard to the use of the live varicella-zoster vaccine to prevent herpes zoster, the Shingles Prevention Study excluded patients with impaired T-cell immunity, including HIV-infected individuals; thus, this vaccine is currently contraindicated in people with HIV infection. HIV-infected patients with moderate to advanced immunosuppression may be at higher risk of adverse effects given the higher dose of live attenuated virus contained in the herpes-zoster vaccine.[36] An ACTG (AIDS Clinical Trials Group) study (A5247) is currently being planned to study the efficacy of the varicella-zoster vaccine in HIV-infected patients.

HIV-infected adolescents and adults should ensure that their vaccination with inactivated polio vaccine is up-to-date before traveling to some areas of western Africa and the Indian subcontinent (India, Pakistan, and Afghanistan).[8,18] Rabies vaccination recommendations follow the same criteria in HIV-infected individuals as in HIV-seronegative individuals (Table 1). In addition, the serologic response to the rabies vaccination should be checked in HIV-infected individuals after preexposure rabies vaccination.[8] Preexposure vaccination with rabies vaccine is generally indicated for long-term travelers to rural areas highly endemic for rabies who will be too far from adequate medical care to seek postexposure prophylaxis within 24 hours of exposure. In this regard, an important benefit of preexposure prophylaxis is avoiding the need for administering rabies immune globulin. In some settings, the use of locally available immune globulin may be of concern because of the unknown safety of some of these products. Preexposure prophylaxis requires 3 doses of rabies vaccine on days 0, 7, 21, or 28.

Typhoid fever may produce life-threatening complications in HIV-infected patients.[37,38] Although there is no evidence of sustained bacterial replication using the oral vaccine from the Ty21a strain of *Salmonella* Typhi among HIV-infected individuals, the typhoid Vi polysaccharide vaccine is preferred over the live attenuated vaccine regardless of the CD4 + level.[8,20] This vaccination is particularly important for HIV-infected patients bound to typhoid fever–endemic areas, particularly Latin America, Southeast Asia, and the Indian subcontinent.[38]

Tick-borne encephalitis vaccine (3 doses over a 9-month period) is recommended only for travelers visiting rural, forested areas of Scandinavia, western and central Europe, and countries of the former USSR from March through November.[39] Transmission occurs through tick bites or ingestion of unpasteurized goat products. This vaccine is not available in the United States but can be obtained in Canada and some parts of Europe and is gen-erally considered safe to use in immunocompromised populations.[5] Use of protective insect repellent and avoidance of unpasteurized goat milk are also recommended preventive measures for HIV-infected travelers.[18,40]

Required Travel-Related Vaccines in HIV-Infected Travelers

Documentation of meningococcal vaccination or yellow fever vaccination is required for entry into some countries (Table 1).[18] Use of the quadrivalent meningococcal conjugate vaccine or polysaccharide vaccine (for serogroups A, C, Y, and W-135) is indicated based on the patient's travel itinerary and follows similar recommendations as for people without HIV infection.[8,18] Currently available meningococcal vaccines are considered safe and efficacious in patients with HIV infection. The only identified limitation is that patients with HIV may have a decreased response to serotype C of *Neisseria meningitidis,* but the most important serotypes to protect travelers to high-risk areas of the world against are serotypes A and W-135. High-risk situations include travel to the "meningitis belt" in sub-Saharan Africa or to attend the Hajj pilgrimage in Saudi Arabia.[18]

Yellow fever is a mosquito-borne illness that has been reported rarely in travelers, and the risk varies widely within recognized areas of transmission.[33,41] Appropriate administration of yellow fever vaccine to travelers requires an assessment of the patient's risk of acquiring infection during travel versus the risks associated with vaccine adverse events.

Yellow fever vaccine is a live attenuated vaccine made with the 17D yellow fever virus strain. Three distinct but related lineages of the yellow fever vaccine strains (17D-204, 17DD, and 17D-213) have been developed, with more than 99.9 % nucleic acid sequence homology among them.[33] Although this vaccine has been considered among the safest, recent reports of adverse events in the form of neurotropic and viscerotropic disease have raised concern about the vaccine's safety. So far, yellow fever vaccine–associated severe adverse events, particularly viscerotropic disease, have been associated with persons aged 60 years and older and persons with thymoma or a history of thymectomy, but no cases of viscerotropic disease have been reported in patients with HIV infection. The lack of detection of these severe adverse events in HIV-infected individuals may, however, simply be a reflection of the low number of immunized, HIV-infected travellers.[33]

After primary vaccination, vaccine strain viremia occurs frequently in nonimmunocompromised persons. Because of a concern of uncontrolled viremia, yellow fever vaccine is not recommended for patients with a CD4 + count of 200 cells/μL or lower.[5] Therefore, this group should be discouraged from traveling to areas where yellow fever is highly endemic. In addition, many experts recommend postvaccination testing for the presence of neutralizing antibodies in HIV-infected patients planning travel to high-risk areas.[33] A recent study identified 102 HIV-infected patients in Europe who had received the yellow fever vaccine. No serious adverse events were identified, but HIV-infected persons had lower neutralization titers after vaccination, more often demonstrated nonprotective titers, and experienced a more rapid decline in titers during follow-up.[42] At this time, if travel to a yellow fever–endemic zone by severely immunocompromised persons is unavoidable, a medical exemption letter can be written. Additionally, travelers should be instructed in detail about methods to avoid mosquito bites through personal protection measures.

Evidence suggests that cholera vaccination affords some protection and carries an apparently safe profile for use in HIV-infected individuals. A recent clinical trial in Mozambique demonstrated a 78 % protection rate using a strategy of mass vaccination with 2 doses of recombinant cholera-toxin B subunit, killed whole-cell (rBS-WC) oral cholera vaccine. This rBS-WC vaccine was highly effective against clinically important cholera in an urban,

sub-Saharan African population with a high prevalence of HIV infection. Although this study suggests the vaccine offers protection to HIV-infected persons, data on the safety of the vaccine in HIV-infected persons could not be assessed directly. In other trials performed in different settings, however, this same vaccine was not associated with adverse reactions in HIV-infected persons or with progression of HIV disease, although a transient increase in HIV viral load was identified in 1 study.[43] In summary, the use of rBS-WC oral cholera vaccine may be considered in HIV-infected travelers to areas of ongoing cholera outbreaks such as refugee camps.[18]

Prevention of Malaria and Other Vector-Borne Pathogens

The risk of malaria acquisition is increased in HIV-infected individuals.[44,45] Thus, pretravel consultation must include a thorough discussion of malaria prevention.[46] Adherence to recommended chemoprophylactic regimens is a concern among HIV-infected individuals. A study from Toronto about behaviors of HIV-seropositive travelers showed that less than 7% of international travelers took adequate chemoprophylaxis against malaria,[3,4] thus, adherence and safety concerns should be addressed specifically.

Most drugs used for malaria prevention and treatment are considered safe in HIV-infected persons receiving antiretroviral drugs.[9] Nevertheless, drug interactions can occur and should be considered before prescribing malaria chemoprophylactic regimens.[9] Although potential interactions exist theoretically between some HIV protease inhibitors, particularly ritonavir with atovaquone-proguanil, chloroquine, and mefloquine, no evidence documents any clinically relevant events and no dose adjustments are recommended. Atovaquone-proguanil may increase the level of zidovudine, warranting closer monitoring of hemogram results.[8] In the authors' clinical opinion, atovaquone-proguanil and doxycycline are the antimalarial drugs of choice for the prevention of malaria

among HIV-infected persons receiving antiretroviral therapy.

HIV-infected travelers need to take personal protective measures to avoid bites from mosquitoes (vectors for yellow fever, malaria, dengue fever, JE, West Nile virus, and other arboviral infections) and other disease-transmitting insects (eg, sandflies, vectors for leishmaniasis or bartonellosis in South America, and ticks, vectors for rickettsiosis).[40,47] Prevention measures include remaining in well-screened locations, using repellent-impregnated mosquito nets, and wearing, as practical, clothing that covers most of the body surface. The most effective repellent against a wide range of arthropods is *N,N*-diethyl-*m*-toluamide (currently named *N,N*-diethyl-3-methyl-benzamide, or DEET), an ingredient in many commercially available insect repellents.[40,47] Insect repellents that contain DEET at concentrations up to 50% (range, 30%-50%) are recommended for adults and children older than 2 months. Also, permethrin is available as a spray or liquid to treat clothes and bed nets if required, and bed nets pretreated with permethrin are also available. Picardin is as effective as a long-acting DEET formulation.[18,40]

HIV-infected travelers to malaria-endemic settings should be educated that malaria-preventive strategies do not guarantee protection. Thus, such patients must be instructed to seek expert medical assistance early in any febrile illness.[8,9]

Treatment of malaria in HIV-infected patients, particularly that caused by *Plasmodium falciparum*, follows the same recommendations as for HIV-seronegative patients.[22] There are, however, safety concerns regarding the use of quinidine or quinine in combination with nelfinavir or ritonavir because of the potential for cumulative cardiotoxicity.[8] Another potential interaction occurs between lumefantrine, alone or in combination with artemether (used in some African countries) and ritonavir and potentially other HIV protease inhibitors; the risk of life-threatening cardiac arrhythmias may increase as a result of prolongation of the QT interval.[8,9] Minimal data are available re-

garding the safety of other artemisin-based combinations in patients with HIV infection.[9] The risk of life-threatening consequences associated with malaria infection in HIV-infected individuals necessitates the use of these various regimens, which must include careful monitoring for potential drug interactions.

Prevention of Enteric and Other Infections

HIV-infected travelers need to take precautions to avoid acquiring enteric or other opportunistic infections[22]. Unpasteurized milk and dairy products may transmit brucellosis, *Salmonella* species, Q fever, and tick-borne encephalitis.[15,18] To reduce the risk of acquiring cryptosporidiosis, giardiasis, and leptospirosis, patients should avoid swallowing water during swimming and avoid swimming in rivers, lakes, or other potentially contaminated water.[15,18] Use of proper hand hygiene with water and soap or alcohol-based solutions is necessary to reduce the risk of acquiring gastrointestinal infections, particularly on cruise ships. The risk of acquiring norovirus infection can also be minimized by adequate handwashing and avoidance of possibly contaminated food.[48]

Some of the important causes of acute diarrheal episodes in HIV-infected persons include the organisms *Cyclospora cayetanensis, Cryptosporidium parvum,* and *Isospora belli,* which are food borne (through raw vegetables or contaminated water) and may lead to chronic diarrhea and extraintestinal complications.[8,22] Many of these diarrheal episodes require longer treatment periods in HIV-infected patients than in HIV-uninfected people. Among the bacterial pathogens, infections with *Campylobacter* species, *Shigella* species, and *Salmonella* species often produce more severe disease with associated bacteremia in HIV-infected than in –uninfected patients.[3,4] With the advent of antiretroviral therapy, the incidence of nontyphoid salmonellosis has decreased in some settings, but a substantial rise in quinolone-resistant strains has been identified.[49]

Discussion of water and food safety and methods of boiling and filtering water may provide the greatest impact to prevent infection with enteric pathogens. Filtration of water using a pore size of less than 1 μm may not remove all bacteria, and viruses and *Microsporidia* species may be too small to be removed by this degree of filtration. Purification by boiling is adequate for elimination of all important enterobacteria and is the most reliable method of water treatment, although some bacterial spores such as those of *Clostridia* species may be resistant to boiling.[17]

Routine antimicrobial prophylaxis for traveler's diarrhea is not recommended for HIV-infected travelers.[8,22] Rather, these patients should be instructed on self-treatment of traveler's diarrhea using azithromycin or a quinolone[17] such as ciprofloxacin or levofloxacin. For individuals with severe immunosupression, a preventive regimen of daily-dose quinolone, doxycycline, bismuth, or rifaximin may be considered. The use of oral rehydration solutions in combination with antidiarrheal agents and presumptive self-treatment with a quinolone or macrolide regimen (azithromycin) should be encouraged in the HIV-infected traveler.

Leptospirosis may occur in adventure travelers and those who engage in water-recreation activities. In this group, a weekly chemoprophylactic dose of doxycycline (200 mg) is recommended.[18,50]

Sexual activity increases during international travel,[51,52] with only a limited number of travelers reporting consistent use of condoms. The safest recommendation for the HIV-infected traveler is abstinence. However, safe-sex preventive strategies should be discussed and reinforced.

Health Risks and Posttravel Management of HIV-Infected Individuals

The likelihood of an HIV-infected person developing a medical condition during travel relates to the individual's medical history, travel destination and planned activities, duration of travel, type of accommodations, immuniza-

tion history, adherence to indicated chemoprophylactic regimens and, especially, history of exposure to infectious agents before and during travel.[8,15] Eliciting a detailed history of the sites visited, the timing of travel relative to the onset of symptoms, the exact arrival and departure dates, and specific risk behaviors is essential in determining potential exposure to infectious pathogens and the likely incubation period.

The exposure history should include a history of contact with animals (including bites), new sexual partners, fresh water, insects, medical equipment (needles, blood transfusions), and ill persons.[15,53-55] Also, a history of ingestion of unpasteurized dairy products or uncooked meat as well as an occupational history might be important. The immunization history will often rule out entities such as HAV, HBV, yellow fever, meningococcal meningitis, and JE in those who have been immunized. However, prior typhoid immunization does not rule out infection because the vaccine is only 70 % effective. A history of malaria chemoprophylaxis should include the name of the drug, the dose, the patient's adherence to the regimen, and whether the patient is still taking the drug after returning.[15,16,56]

Fever is frequently reported by ill returned travelers.[57-62] In a patient with HIV, this symptom may indicate an infectious, inflammatory, or neoplastic disorder but is most likely to have an infectious origin. The fever may be caused by a geographically restricted infection, such as malaria, dengue fever, typhoid fever, viral hepatitis, or bacterial pneumonia,[62] or it may be due to an infectious syndrome not geographically restricted, such as a urinary or upper respiratory tract infection.[15,16] Some fever episodes may represent life-threatening conditions such as *P falciparum* malaria that, if not treated appropriately and early, can be lethal in HIV-infected individuals.[9,15]

Several tropical pathogens can lead to opportunistic infection and disease in people with HIV (Table 2).[6,7] The presence of HIV infection or AIDS may alter the natural history of tropical in-

fectious diseases in different ways, and individuals coinfected with HIV and some parasitic infections may pose clinical diagnostic dilemmas because of their atypical clinical manifestations.[63,64] Furthermore, patients coinfected with HIV and some tropical infectious diseases require longer treatment courses at the risk of experiencing more serious adverse effects. In addition, a higher pathogen burden in patients with HIV and AIDS may lead to higher morbidity and mortality.[65,66]

Geographically focal infections that pose an increased risk of severe clinical manifestations in HIV-infected patients include visceral leishmaniasis,[63,67] *Penicillium marneffei* in Southeast Asia,[68] *Trypanosoma cruzi* in South America,[69] paracoccidioidomycosis, and coccidioidomycosis in the Americas (Table 2).[6,64] Coinfection with visceral leishmaniasis and HIV is an increasing problem in southern Europe, Ethiopia, Sudan, Brazil, and India, and gastrointestinal symptoms are among the most frequent complaints.[67] Hyperinfection with *Strongyloides* species occurs in immunocompromised patients, including those with HIV.[70] Although it may seem paradoxical, *Strongyloides* species hyperinfection rarely develops in patients with AIDS because the disseminated infection requires the direct development of infective larvae in the gut, and HIV-associated immunosupression may hamper these events.[6,70] *Trypanosoma cruzi* and HIV coinfection may produce necrotizing meningoencephalitis (Table 2).[69]

The geographic overlap between HIV infection and malaria has attracted much interest in their potential synergistic interactions.[65] HIV-infected adults appear to be more prone to clinical malaria than are HIV-seronegative adults.[44] A study from Zambia identified that HIV-infected patients with malaria and a CD4 + count of 300 cells/μL or lower have a higher risk of experiencing recrudescent infection.[66,71,72] Thus, the response of HIV-infected persons to malaria treatment must be carefully monitored.

Respiratory infections including community-acquired bacterial pneumonia, influenza, and pulmonary tu-

Table 2. Clinical Manifestations of Geographically Restricted Infections in HIV-Infected Patients

Infectious Disease[a]	Features in Patients With HIV or AIDS
American trypanosomiasis, or Chagas disease (*Trypanosoma cruzi*)	Reactivation disease in the form of meningoencephalitis, myocarditis, or rarely, cutaneous disease
Malaria (*Plasmodium falciparum*)	Increased frequency of clinical malaria episodes; increased risk of malaria treatment failure; and increased HIV transmission by malaria episodes
Isospora, Cyclospora species infection	Chronic diarrhea; extraintestinal disease (biliary tract)
Strongyloides stercoralis infection[b]	Hyperinfection syndrome and disseminated strongyloidiasis
African trypanosomiasis (*Trypanosoma brucei rhodesiense/gambiense*)	Unclear clinical impact of HIV infection on African trypanosomiasis but often have more severe toxicity to treatment for African trypanosomiasis
Schistosomiasis (*Schistosoma mansoni, Schistosoma haematobium*)[b]	Genitourinary schistosomiasis may predispose individuals to acquire HIV infection. Response to antiretroviral therapy improves when treating schistosomiasis with praziquantel
Visceral leishmaniasis[b]	Similar clinical presentation as in non–HIV-infected individuals. More atypical locations, particularly the upper gastrointestinal system, lung, pleural and peritoneal cavities, and skin. Splenomegaly is less frequent in HIV-infected persons
Cutaneous leishmaniasis[b]	Isolated reports of more severe and higher number of cutaneous lesions
Penicillium marneffei infection	Endemic in Southeast Asia. Disseminated disease with fever, skin lesions, reticuloendothelial system effects
Paracoccidiodomycosis	Endemic in South America. Disseminated disease with skin lesions, adenopathy, mucosal lesions, pulmonary infiltrates, and fever
Nontyphoid *Salmonella* species bacteremia	Risk of recurrent bacteremia. In some settings, the advent of antiretroviral therapy has decreased risk, but isolates from HIV-infected persons are increasingly resistant to quinolones in many settings
Tuberculosis (*Mycobacterium tuberculosis*)	Increased risk of extrapulmonary disease. Worsening immunosuppression induced by tuberculosis. Paradoxical reactions with the use of antiretroviral therapy in patients coinfected with HIV and tuberculosis
Typhoid fever (*Salmonella* Typhi)	Adults with HIV infection often have diarrhea instead of constipation

[a] No data suggest that melioidosis, which is endemic in Southeast Asia, is more frequent or severe in HIV-infected patients, nor that HIV alters the clinical course of brucellosis, *Mycobacterium leprae* infection, yellow fever, dengue fever, West Nile virus infection, or the hemorrhagic fevers (caused by infections with hantaviruses, phleboviruses, arenaviruses, or filoviruses).
[b] This parasitic infection has been associated with immune reconstitution manifestations in patients receiving antiretroviral therapy.[74]

berculosis are important risks for HIV-infected travelers.[22,62] The risk of acquiring tuberculosis is thought to correlate directly with destination, duration of stay in the endemic area, degree of contact with local populations, and occupation.[73]

Any returned, febrile international HIV-infected traveler should be evaluated immediately, preferentially by an infectious diseases clinician or tropical medicine expert.[15] The workup of such patients should be considered a medical emergency and, if indicated, the diagnosis to be malaria until proven otherwise. Prompt evaluation should be made of the results of the following diagnostic tests: peripheral blood smears or rapid antigen detection for *Plasmodium* species; a complete blood cell count and differential; liver function tests; urinalysis; blood, stool, and urine cultures; chest radiography; and specific serologic assays, such as those for the diagnosis of dengue fever, rickettsial infections, schistosomiasis, and leptospirosis. Travelers who report having engaged in high-risk sexual behavior should be tested for HIV, syphilis, HBV, and hepatitis C virus, and cultures should be taken for gonorrhea and chlamydial infection. Finally, in some cases, people with HIV should undergo tuberculin skin testing before and after travel to identify potential exposure to *Mycobacterium tuberculosis*.[15]

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