The immunocompromised traveller

P Vincent

Introduction

Thanks to the relative ease of modern travel, more and more immunocompromised people are able to travel for pleasure, business, and visiting friends and relatives in all corners of the world. They represent a very important group of travellers due to two main additional risk factors: they have a greater risk of becoming ill with travel-related diseases and they may experience an exacerbation or complication of their underlying disease. International travel is feasible in most cases, but occasionally itineraries may need to be modified or additional recommendations given to make trips safer and therefore more enjoyable. The medical advisor must ensure that the traveller understands the risks involved in the proposed itinerary, based on his/her medical needs and tolerance for the risks of the proposed interventions.

Who is immunocompromised?

The immune system can be compromised in many ways, including the use of immunosuppressive medication, and through malignancy, chronic disease, HIV and splenectomy.

The Centers for Disease Control and Prevention (CDC) yellow book on travel has conveniently categorised the immunocompromised traveller into four groups, allowing a general approach to each group:

1) Severely immunocompromised (non-HIV)
2) Severely immunocompromised due to symptomatic HIV/AIDS
3) Asymptomatic HIV infection
4) Chronic diseases with limited immune deficits

Live viral or bacterial vaccines may be contraindicated in these travellers. They may require additional vaccines when compared with normal travellers and they may receive decreased protection from some or all vaccines administered. Use of vaccines for different categories of immunocompromised adults is shown in Table 1.

1) Severely immunocompromised (non HIV)

These travellers include those with acute leukaemia, generalised malignancy, aplastic anaemia, solid organ transplants, bone marrow transplants within two years of transplant or still on immunosuppressive drugs or graft vs host disease, congenital immunodeficiency and current or recent radiation therapy.

*Immunosuppressive drugs*

Medications that cause severe immunosuppression include corticosteroids at a dose of 20 mg daily for more than two weeks, alkylating agents (e.g. cyclophosphamide), antimetabolites (e.g. azathioprine), transplant-related immunosuppressive drugs (e.g. cyclosporine, tacrolimus, sirolimus and mycophenolate mofetil), mitoxantrone (used in multiple sclerosis) and most cancer chemotherapeutic agents (excluding tamoxifen). Methotrexate, including low dose weekly regimens, is classified as severely immunosuppressive, as evidenced by increased rates of opportunistic infections and blunting of responses to killed vaccines.

Recommendations:

Vaccination providers should wait at least one month after discontinuation of high dose systemically absorbed corticosteroid therapy before administering a live virus vaccine.

Patients receiving tumour necrosis factor (TNF) blocking agents such as etanercept, adalimumab, infliximab and interleukin-1 receptor antagonists should not receive live viral or bacterial vaccines.

*Solid organ transplants*

In general, the degree of immune suppression is greatest in the first three to six months post transplant and less after a year. However, a significant degree of immune suppression remains indefinitely.

Recommendations:

Because solid organ transplant recipients are at much higher risk of infection within the first year of transplant, they should postpone high-risk travel for at least a year.

Transplant recipients should be vaccinated prior to transplantation whenever possible, including vaccines for anticipated travel. Immune responses to vaccination may wane more rapidly in immunocompromised individuals than in other hosts. It has been found that boosting pre-transplant immune memory after organ transplantation is more effective than primary vaccination following transplantation.
Vaccines should not be administered in the first six months after organ transplantation in order to avoid confusion with early graft rejection.

Where possible, vaccination for travel should be started several months prior to the trip to allow time for possible additional boosters and serological evaluations.

Emergency international travel may present a high-risk situation and passive immunisation with intramuscular immunoglobulin should then be considered.

The risk of exposure to the disease should be balanced against the risk of vaccination and degree of immune response.

**Stem cell transplant recipients (SCT)**

During the first year after a SCT, recipients typically follow a predictable pattern of immune system deficiency and recovery, which begins with the chemotherapy or radiation therapy (i.e. the conditioning regimen) administered just before the SCT to treat the underlying disease. Virtually all SCT recipients rapidly lose all T and B lymphocytes after conditioning, losing immune memory accumulated through a lifetime of exposure to infectious agents, environmental antigens, and vaccines. All SCT recipients and particularly allogeneic recipients, experience an immune system dysfunction for months after engraftment.

**Recommendations:**

SCT recipients should have all vaccinations, including any appropriate travel-related vaccinations, started again post-transplant, when immune reconstitution is likely to have taken place. This is usually at two years post-transplant and off all immunosuppressive medications.

Live vaccines such as yellow fever and measles, if indicated, can be given with minimal risk if the patient is off immunosuppressive medications and considered to be immunocompetent.

**Antimalarial prophylaxis in solid organ and stem cell recipients**

Recipients who are still receiving immunosuppressive drugs, should commence antimalarial medication several weeks prior to departure in order to monitor and adjust the level of cyclosporine, tacrolimus or sirolimus as required.

**2) Severely immunocompromised due to symptomatic HIV/AIDS**

Knowledge of the current CD4 lymphocyte count is necessary before consultation with the HIV-infected traveller. If the CD4 count is below 200, there is a history of an AIDS-defining illness, or any clinical manifestations of symptomatic HIV, then the potential traveller is considered to be severely immunocompromised.

In newly diagnosed, treatment-naive HIV travellers with CD4 counts below 200, travel should be deferred pending the reconstitution of CD4 counts with antiretroviral therapy. The exact time at which the reconstituted lymphocytes are fully functional is not well defined. To achieve maximal vaccine response with minimal risks it is popularly advised to wait at least three months post reconstitution before vaccination.

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**Table 1: Live/killed vaccine recommendations: immunocompromised traveller**

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<th>Asymptomatic HIV</th>
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Key: R=Recommended U= Normal hosts C=Consider W=Warning X=Contraindicated
(Ref CDC Yellow Book, 2007-08)
Risk of infection while traveling with a positive HIV status

The increased risk for becoming ill in this immunocompromised group may be explained by the following factors:

- A decreased ability to clear certain pathogens.
- An increased morbidity.
- A delayed recognition of an illness or uncommon manifestations of the illness which may occur in the HIV-positive traveller. There is also concern that the HIV-positive traveller will not receive adequate medical care while aboard.

Pathogens with which a person with HIV may become infected while traveling may be grouped according to route and primary site of infection: gastrointestinal, respiratory, sexually transmitted, vector-borne and cutaneous.

- Gastrointestinal tract (GIT) infections

HIV-positive travellers are more susceptible to GIT infections due to impaired local immune function (in part because of decreased CD4 lymphocytes within the intestinal lamina propria) and diminished nonspecific defense mechanisms such as decreased secretion of gastric acid. Therefore, these immunocompromised travellers may develop chronic or recurrent diarrhoea with malabsorption and septicemia requiring antibiotics, whereas the acute diarrhoea that their immune competent contemporaries may suffer from, would, in most cases, resolve spontaneously.

Enteric pathogens causing diarrhoea in persons with HIV infection include Campylobacter jejuni, Salmonella spp, Cryptosporidium, Cyclospora cayetanensis, Isospora belli, Microsporidium spp, cytomegalovirus and Mycobacterium avium intracellulare. These individuals have trouble clearing Salmonella spp and may relapse.

Prophylaxis for *Pneumocystis jirovecii* pneumonia with sulphonamide drugs, as well as an antibiotic treatment for any infection, may be associated with bowel colonisation with *Clostridium difficile*. There are insufficient data to say whether these individuals are more susceptible to *Vibrio cholerae*, enteroinvasive and adherent *Escherichia coli*, hepatitis E and poliomyelitis. They are, however, at increased risk for invasive disease caused by non-cholera vibrios.

- Respiratory infections

Upper respiratory tract infections are among the most common illnesses in tourists. HIV-positive travellers are even more susceptible to infections by *Streptococcus pneumoniae* and *Haemophilus influenzae* which tend to cause invasive disease.

Other respiratory pathogens which have the potential of causing more serious disease, are *Mycobacterium tuberculosis*, Legionella and measles virus. The latter can be fatal in this population group.

Opportunistic fungal infections may also be transmitted during travel and include cryptococcosis, coccidiomycosis, blastomycosis, histoplasmosis and others.

Influenza infections are more likely to cause greater morbidity because of secondary bacterial infections.

- Sexually transmitted diseases

Persons with HIV infection are at risk of acquiring additional sexually transmitted infections if they do not practice safe sex. Their status reacts negatively with the natural history of genital ulcer disease such as herpes simplex virus type 2, *Haemophilus ducreyi*, syphilis and human papillomavirus. Hepatitis B virus is also more likely to cause severe infection and lead to a chronic carrier state.

- Vector-borne disease

Malaria

There are important bidirectional interactions between HIV status and malaria. HIV infection increases the frequency and degree of malaria parasitaemia and malaria increases the viral load of HIV infection. Atovaquone, in Malanil® which is used for prophylaxis, interacts with the protease inhibitors, specifically ritonavir to lower the level of atovaquone to a degree which may make it clinically significant. It can also cause a modest increase in zidovudine levels warranting closer monitoring of haemoglobin and neutrophil count and requiring possible dose adjustments.

Ritonavir increases serum levels of quinine and may have a similar effect on artemisinin derivatives. These protease inhibitors also inhibit the metabolism of lumefantrine, an ingredient in Coartem® which can increase the risk of life threatening cardiac arrhythmias with prolongation of the QT interval.

Visceral leishmaniasis

Most cases in HIV-infected individuals have been reported from Spain and southern France where it is a frequent opportunistic parasitic infection. It is endemic in rural India, Middle East, Sudan and Brazil. Patients may present with atypical lesions throughout the GIT from mouth to the rectum with or without cutaneous lesions.

Chagas disease

Exposure in Latin America to *Trypanosoma cruzi* has lead to documented severe neurological and cardiac manifestations occurring in this immunocompromised group.

- Cutaneous infections

Ecythyma is the commonest cause of skin ulcers and is usually caused by *Staphylococcus aureus* infection. However, *Pseudomonas aeruginosa* or *Cryptococcus neoformans* may produce a similar picture.

Recommendations:

As part of the pre-travel medical evaluation which includes the usual medical history, immunisation history, allergy history and history of problems during previous travel, travellers with HIV infection should be given extra information on the following:

- The development of worrisome symptoms while traveling, such as shortness of breath, focal weakness, seizures, visual disturbances, persistent headaches or fever.
- How to prevent the more common infections they may encounter and how to self medicate. Euro surveillance has recently released a perspective on ‘Prevention of the spread of infection - the need for a family-centered approach to hygiene promotion’. Not only is respiratory hygiene important in protection from coughs and sneezes but also hand and surface hygiene in preventing spread of respiratory infections as well as the norovirus.
- Meticulous attention needs to be paid to avoiding high risk foods and beverages, such as undercooked meat, shellfish, fish, or eggs, raw unpeeled fruits and uncooked fresh vegetables, tap water and ice; as well as unpasteurised milk.
Not only is the CD4 count essential in assessing the overall risk of travel and proposed interventions, but so is the haemoglobin level when response to altitude is important.

All patients with chest conditions should have a base line partial pressure of oxygen measured for the same reason.

For recommendations regarding vaccines, see section below (recommendations for asymptomatic HIV traveller) and Table 1.

Advice about minimising sun exposure is important as these travellers sometimes develop hypersensitivity reactions that are exacerbated by the use of tetracyclines, quinolones and sulphonamides. A combination UVA and UVB sun-blocking agent with at least an SPF of 15 should be used.

Repellents and protective clothing should be used to protect against mosquito bites and other vector-borne infections.

Emphasis on taking responsibility for one's sexual behaviour while traveling is vital, as well as offering a post travel consult to ensure that no lesions are overlooked. This will include a very close inspection of the genitalia and anal regions.

It is important to identify specific sources of medical care at the destination before departure and to seek medical attention promptly when ill.

Changes in medication regimen shortly before travel should be avoided to ensure no side effects or complications of a new regimen while traveling.

An additional supply of medications along with copies of prescription should accompany the traveller, and the supply should be split between the carry-on and checked-in baggage.

Many countries restrict entry of travellers with HIV infection. Antiretroviral (ARV) drugs found in luggage may lead to expulsion.

3) Asymptomatic HIV infection

HIV-infected persons with CD4 counts from 200-500 are considered to have limited immune deficits. ARV drug-induced increased CD4 counts and not nadir counts should be used in categorising HIV-infected persons.

Recommendations:

The medical practitioner, when dealing with an HIV-infected traveller, must always ask the following two questions and assess each immunisation individually: Will it provide protection? Will it cause harm?

Because of the quantitative and qualitative defects of the CD4 lymphocytes along with the dysfunction of the B lymphocytes in persons with HIV-infection, vaccinations may be less immunogenic and therefore confer less than optimal protection. The reduced antibody response can be measured as both a lower seroconversion rate and as a lower level of antibody response. An accelerated loss of antibodies or an absent or diminished conversion of IgM to IgG is also possible.

If the CD4 count is above 200, antibodies do develop, but the presence of antibody may not predict clinical protection. More frequent boosters may be necessary but there are no firm recommendations in this regard.

For this reason, it is best to administer immunisations at the earliest opportunity in the disease process, when the CD4 counts are still high. One should therefore ask about future travel plans at the time of diagnosis so that immunisations can be planned.

If the CD4 count is below 200, immunisation with live vaccinations is contraindicated as they carry the risk of vaccine-associated illness. The live virus vaccinations in common use in South Africa are yellow fever, polio, measles, varicella and BCG vaccines. Inactivated, killed and subunit immunisations appear to be well tolerated.

Several recent publications have shown a transient rise in the viral load following administration of influenza, tetanus toxoid and hepatitis B vaccines. However, the afforded protection may outweigh the potential risks and there appears to be no permanent influence on either the CD4 count or on the clinical course. There is also no in vivo evidence that multiple immunisations given at the same time will accelerate the progression of HIV disease.

Vaccines recommended or considered for all HIV-infected travellers:

- Pneumococcal polysaccharide vaccine
  It is immunogenic in persons with HIV-infection whose risk is 600 times that of the normal population. Its use in Africa, due to poor response in HIV-infected persons in an Ugandan study, is however controversial.

- Influenza vaccination
  This is recommended annually, irrespective of travel. If the CD4 count is below 100, there is no antibody response. Between 100 and 300, the response is suboptimal.

- Haemophilus influenzae B conjugate vaccine
  This should be considered and a single dose for adults appears to be effective.

- Hepatitis B
  Vaccination is recommended and serological response should be checked due to the relatively large number of non-responders.

Routine vaccinations

- TdPolio
  This should be given to all travellers. Most young patients with HIV retain antitetanus protection but not diptheria protection if primary immunisation was given before acquiring HIV infection.

- Measles
  HIV-infected patients with CD4 counts above 200 that are not immune to measles should be vaccinated with a measles, mumps and rubella vaccine.

Miscellaneous vaccinations for HIV-positive travellers

- Yellow fever vaccination
  This is an international requirement to some countries in tropical South America and in some countries in sub-Saharan Africa. Seroconversion in those travellers with a CD4 count above 200 is 85%. There are, however, no data on the persistence of these antibodies. Travellers with CD4 counts below 200 should be advised against travel to areas of intense yellow fever transmission. A vaccine waiver letter may be written if the traveller persists with travel to the region, especially if the primary reason for vaccination is a country-specific requirement rather than significant epidemiological risk of infection. The use of insect repellants and bednets should be encouraged.

- Hepatitis A
  This vaccine can safely be given to non-immune HIV-infected travellers. In cases of travellers with clinical signs of AIDS, administration of immunoglobulins should be considered if immunisation against hepatitis A is needed.
• Typhoid vaccination
  The inactivated typhoid vaccine can be administered.

• Quadrivalent meningococcal meningitis vaccine
  This can be administered to those traveling to the meningococcal belt in sub-Saharan Africa and other areas that may require it, and to those who are going to study overseas and are going to be housed in dormitories.

• Rabies vaccination
  The response to rabies vaccination in HIV-infected travellers may be blunted and must be checked. Post exposure prophylaxis is the same as in the HIV-negative traveller, but blood levels should be checked and acted upon, i.e. further vaccination if necessary.

4) Chronic diseases with limited immune deficits

These chronic diseases include splenectomy, chronic renal disease, chronic hepatic disease (cirrhosis and alcoholism), diabetes and nutritional deficiencies. There is little information apart from asplenic individuals on possible decreased vaccine efficacy or increased adverse events with live viral antigens in this group.

• Splenectomy

Risk of infection with encapsulated organisms, particularly Streptococcus pneumoniae but including meningococci and Haemophilus influenzae, is increased, especially in the first two years post splenectomy.

Recommendations:

Splenectomised travellers should be up to date with pneumococcal, Haemophilus influenzae and meningococcal vaccinations.

These patients should be given a standby course of broad spectrum antibiotics for self-medication when traveling to areas where there is limited access to medical care. They must have a low threshold for seeking medical advice if they experience an unexplained febrile illness.

As the spleen plays a role in the response to clear malaria parasites, these individuals are more susceptible to severe infections of malaria and must be counseled accordingly.

Specific issues to discuss with asplenic travellers:

1) Role of spleen in bacterial infections and malaria
2) Importance of prompt recognition and treatment of infections
3) Animal and tick bites
4) Antibiotic prophylaxis
5) Malaria prophylaxis
6) MedicAlert bracelet

Travellers medical kit

Immunocompromised travellers or their companions should have knowledge of their medications, doses and potential drug/drug interactions. The medical kit, in addition to the normal contents, should contain the following:

• Extra supplies of, and a prescription for, chronic medications. All medications should be kept in their original containers.

• A letter of authorisation for the medications to be carried. Vaccination certificates should be kept with the passports. It is worth having an extra copy.

• A spare pair of spectacles and adequate supply of contact lenses including a copy of the prescription.

• Digital thermometer.

• Malaria prophylaxis is safe and indicated for travel to malaria endemic areas. The seriousness of an infection is greatly increased in immunocompromised travellers.

• Mosquito repellent for personal use (TABARD creams, sprays and sticks containing 30% DEET).

• Malaria test kit if prescribed when traveling to a remote area.

Travellers’ diarrhoea – immediate self treatment

The principal risk for the HIV-infected traveller is enterically acquired infections. Consideration should be taken to carrying a portable water filter and purification tablets. Loperamide tablets, rehydration sachets, metoclopramide for nausea and either azithromycin (if traveling east) or ciprofloxacin (seven-day course) as antibiotics should be carried to eradicate diarrhoal germs. A new Australian product available in South Africa called Travelan® is a very promising product that prevents Escherichia coli from attaching to the intestinal lining. This is taken as a tablet with each meal. It has proved very useful for healthy groups traveling to Egypt. (Dairy allergy is a contraindication to Travelan®.)

Upper respiratory and chest infections

Broad spectrum antibiotics should be provided in higher doses and prolonged courses, taking possible allergies into consideration.

Other medication

• Allergic rhinitis can be troublesome and self-treatment should be provided.

• Antibiotic ointment, eg mupiricin or fusidic acid containing ones.

• Moderate strength cortisone cream.

• Antifungal cream.

• Antihistamine cream for insect bites.

• Arnica sachets and/or anti-inflammatory gels for aches and strains.

Conclusion

With good advice and a timely visit to both their travel health advisor and personal doctor, the immunocompromised traveller should be able to travel safely. Itineraries may have to be changed according to risk assessment, and emphasis must be placed on prophylaxis and self-medication management. A knowledgeable traveling companion would make the travel experience safer and more enjoyable.

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