

## Special groups of travellers

### Travel to visit friends and relatives

According to the United Nations, international migration rose from 120 million in 1990 to more than 200 million in 2006. In many countries immigrants now constitute more than 20% of the population. Immigrants increasingly travel to their place of origin to visit friends and relatives (VFR), and VFR travel is now a major component of the international journeys that take place annually. The term “VFRs” generally refers to immigrants from a developing country to an industrialized country who subsequently return to their home countries for the purpose of visiting friends and relatives.

Compared with tourists to the same destinations, VFRs are at increased risk of travel-related diseases. These include – but are not limited to – malaria, hepatitis A and B, typhoid fever, rabies, tuberculosis, and the diseases normally preventable by routine childhood immunization. For example, the global surveillance data of GeoSentinel (an international network of travel medicine providers) on returned travel patients show that eight times more VFR travellers than tourists present with malaria as their diagnosed illness. It is estimated that VFRs account for more than half the total imported malaria cases in Europe and North America.

The greater risk for VFRs is related to a number of factors, including higher risk of exposure and insufficient protective measures. These individuals are less likely to seek pre-travel advice or to be adequately vaccinated, but more likely to stay in remote rural areas, have close contact with local populations, consume high-risk food and beverages, undertake last-minute travel (linked to deaths or other family emergencies) and make trips of greater duration. Because of familiarity with their place of origin, VFRs may perceive less risk, a known factor in diminished risk perception, which may result in lower rates of pre-departure vaccinations or malaria prophylaxis. The cost of pre-travel consultation, often not covered by health insurance programmes, may be onerous for VFRs, in particular those with large families, and access to travel medicine services may be hampered by cultural and linguistic limitations.

Improving the access of VFRs to pre-travel health counselling is of increasing public health importance. Primary health-care providers need to become more aware of the increased risks faced by VFRs. Strategies are needed to increase the awareness among VFRs of travel-related health risks and to facilitate uptake of pre-travel health advice, vaccinations and, where indicated, malaria prophylaxis.

## Mass gatherings

The term “mass gathering” is used of any gathering of more than 1000, but usually about 25 000, people at a specific location, for a specific purpose, for a period of time. These include sporting events (e.g. the Olympic Games), cultural events (e.g. world exhibitions, music festivals) social events (e.g. national day gatherings) and religious gatherings and pilgrimages. With increasing air travel and globalization, mass gatherings – while varying in size and nature and purpose – present diverse public health challenges. Health hazards may be increased as a result of the concentration of populations in enclosed and non-enclosed events.

Factors associated with increased risk of health hazards are the following:

- influx of large numbers of visitors within a short period of time;
- visitors often come from areas that differ greatly in both geography and culture;
- conditions of overcrowding;
- risk of transmission and rapid spread of infectious diseases;
- the impact of mass gatherings on host populations.

In planning for a mass gathering, organizers should complete a risk assessment for public health threats. Measures to address and manage the public health risks should be identified, including:

- public health surveillance;
- outbreak detection and diagnosis resources;
- communications systems;
- response (including quarantine or isolation facilities) and emergency resources; and
- medical resources (including pharmaceuticals and equipment).

Public health planning usually involves a range of organizations within the context of international, federal and local laws and regulations. Security and law enforcement authorities should also be involved in the planning for public health security,

which includes planning for infectious disease control measures, natural disaster and medical intervention, awareness and vigilance.

WHO has convened several technical workshops to address the issues of mass gatherings.<sup>1</sup> The resulting guidelines address the assessment of relevant public health risks; evaluation of the capacity of existing systems and services, in anticipation of the surge of public health needs of mass gatherings; and development of control systems for biosurveillance, emergency response, crowd control, disease outbreak detection and response, laboratory services, mass communications, preparations for potential quarantine control, and management of mass casualties.

### Hajj, a religious pilgrimage and mass gathering

Data for quantifying the risk of medical problems related to religious pilgrimages are limited; the best documented, in terms of health risk, is the Hajj, the annual Muslim pilgrimage to Mecca and Medina in Saudi Arabia.

In scale and international diversity, the Hajj is a unique religious pilgrimage. It is undertaken by Muslims as a once in a lifetime act of religious devotion during the days of the Hajj; The Umrah is a similar pilgrimage undertaken at other times of the year.

During the Hajj, more than 2 million Muslims from all over the world congregate to perform their religious rituals. The resulting overcrowding has led to stampedes, traffic accidents and fire injuries. Cardiovascular disease is the most common cause of death. Heatstroke and severe dehydration are also frequent when the Hajj season falls during the summer months. The potential for spread of infectious diseases associated with this pilgrimage has long been recognized. Throughout its 14-century history, the Hajj has been witness to a series of major health issues: historical records document outbreaks of plague and cholera, involving large numbers of pilgrims, when quarantine was the prime means of control.

Each year, the date of Hajj is earlier than in previous year, by 10 or 11 days, since it is dictated by the Islamic lunar calendar. Thus different seasonal conditions prevail during the Hajj and may be favourable to different diseases, such as influenza or dengue fever. Overcrowding also contributes to the potential dissemination of airborne infectious diseases or infections associated with person-to-person transmission. Extensive outbreaks of meningococcal disease among pilgrims have prompted the Saudi Arabian health authorities to introduce mandatory vaccination.

<sup>1</sup> *Communicable disease alert and response for mass gatherings: key considerations*. Geneva, World Health Organization, 2008 (available at: [www.who.int/csr/Mass\\_gatherings2.pdf](http://www.who.int/csr/Mass_gatherings2.pdf)).

All pilgrims must now be given the quadrivalent meningococcal vaccine (protecting against serogroups A, C, Y and W135). The most frequently reported complaints among pilgrims are upper respiratory symptoms. Seasonal influenza vaccination has been reported to reduce influenza-like illness among pilgrims and should be a highly recommended vaccination for all those making the Hajj. In 2009, the ministry of health of Saudi Arabia recommended that individuals with certain chronic diseases (such as cardiac, renal, respiratory or neurological diseases and diabetes mellitus) and acquired or congenital immunodeficiency, pregnant women and extremely overweight individuals who are more likely to experience complicated forms of pandemic influenza A (H1N1) 2009 virus infection, defer from performing the Hajj. Deferring was also recommended to individuals aged less than 12 years or more than 65 years. Where seasonal influenza vaccine and pandemic H1N1 vaccine were available in countries of origin, proof of both vaccinations were required by competent authorities before issuing visas. Pneumococcal vaccination should also be recommended for those aged over 65 years and those who would benefit from it because of underlying medical conditions (Chapter 6).

Hajj-related outbreaks of cholera occurred in the past but not since 1989, following improvements to the water supply and sewage systems. Hepatitis A vaccination is recommended for non-immune pilgrims, and routine vaccinations (such as poliomyelitis, tetanus, diphtheria and hepatitis B – see Chapter 6) should be up to date. Yellow fever vaccine is a requirement for pilgrims coming from areas or countries with risk of transmission of yellow fever (Annex 1).

Since 2005, the Ministry of Health of Saudi Arabia has required that all individuals aged under 15 years who travel to Saudi Arabia from polio-affected countries show proof of vaccination with oral polio vaccine (OPV) 6 weeks before application for entry visa (Chapter 6). Irrespective of previous immunization history, all such individuals arriving in Saudi Arabia will also receive OPV at border points. Since 2006, in addition to the above, all travellers from Afghanistan, India, Nigeria and Pakistan, regardless of age and previous immunization history, will also receive an additional dose of OPV upon arrival in Saudi Arabia.

Updates on requirements and recommendations for the annual Hajj pilgrimage can be found in the *Weekly Epidemiological Record* (available on line at [www.who.int/wer/en](http://www.who.int/wer/en)).

## Travellers with HIV/AIDS

As a result of improved health and prognosis, HIV-infected persons are increasingly likely to engage in travel-related activities that may expose them to other diseases.

### Special issues for HIV-infected travellers

- Increased susceptibility and morbidity to many tropical infections
- Vaccines:
  - decreased immune response to some vaccines
  - risk of severe adverse events to live vaccines.
- Drug interactions.
- Travel restrictions, HIV test requirements in many countries.
- Medical resources accessible during travel.

### The natural course of HIV-infection

The natural course of infection with HIV is characterized by chronic replication of HIV as measured by plasma HIV-RNA and leads to progressive immunodeficiency characterized by a decline of CD4 lymphocyte counts in peripheral blood:

- CD4 counts  $>350$  cells/mm<sup>3</sup>: slight immunodeficiency;
- CD4 count 200-350 cells/mm<sup>3</sup>: moderate immunodeficiency, indication for antiretroviral therapy;
- CD4 counts  $<200$  cells/mm<sup>3</sup>: severe immunodeficiency, considerable risk for opportunistic diseases (AIDS); indication for antiretroviral therapy and prophylaxis against opportunistic infections.

### Antiretroviral therapy

Antiretroviral therapy (ART) inhibits HIV replication (plasma HIV-RNA becomes undetectable) and leads to a partial restoration of immunocompetence (rise in CD4 counts). ART usually includes three antiretroviral drugs. Excellent adherence to ART is essential to avoid development of resistance and treatment should not be interrupted. Many antiretroviral drugs interact with other drugs and this must be taken into account when advising travellers on malaria prophylaxis and other drugs.

### Pre-travel assessments

Pre-travel assessments include risks associated with travel itinerary, current ART, current CD4 counts and plasma HIV-RNA, medical history and physical examination.

### Antiretroviral therapy and travel

Newly diagnosed patients with CD4 cell counts  $<200/\text{mm}^3$  are usually advised to delay travel until CD4 cell counts have improved with ART. This delay will minimize the risk of travel-associated infections and avoid problems of immune reconstitution inflammatory syndrome during travel. Patients should ideally be on a stable ART regimen for 3 months before longer journeys and plasma HIV-RNA (if available) should be undetectable. This allows for assessment of the tolerability and efficacy of antiretroviral drugs. Patients should carry a document that certifies their need for the prescribed life-saving drugs but that makes no mention of HIV infection. Doses for several days of ART should be kept in the hand-luggage during flights.

The dosing schedule will need to be adapted if the journey includes change of time zones: intervals between doses should be shortened, not lengthened. Ritonavir capsules should be kept refrigerated but can be kept at room temperature ( $<25\text{ }^\circ\text{C}$ ) for no longer than 28 days.

Interruption of ART therapy is associated with increased morbidity and mortality and should be avoided. For patients on primary or secondary prophylaxis for one or more opportunistic infections (e.g. pneumocystis, mycobacteria and toxoplasma), complete adherence to all dosing regimens during travel is important.

### Travel restrictions

Some countries have introduced various restrictions on entry, stay, residency or activities for international travellers with HIV infection. HIV-infected travellers are advised to obtain authoritative information on these issues from relevant embassies, consulates, missions or other appropriate sources.

### Medical resources abroad

HIV-infected travellers should take out medical insurance that includes coverage abroad, emergency assistance and repatriation. They should carry a medical report and should be informed about medical resources abroad. A useful list of more than 3300 organizations in 175 countries involved in counselling and care of HIV-infected individuals is provided by a non-profit community based HIV information provider, the National AIDS Manual (NAM), and can be found at [www.aidsmap.com](http://www.aidsmap.com).

### Increased susceptibility to selected pathogens and morbidity risk

With falling CD4 counts, HIV-infected individuals are more susceptible to many pathogens and are at higher risk for more severe disease. Infections that are often self-limiting in immunocompetent hosts may become chronic and severe in HIV-infected individuals. Preventing exposure is therefore important, since vaccines are available for only a limited number of the pathogens and their immunogenicity may be reduced in the most vulnerable patients.

#### *Travellers' diarrhoea*

HIV-infected patients are more susceptible to most foodborne and waterborne pathogens. Morbidity and mortality may be higher, e.g. non-typhoidal salmonellae often cause invasive infections in patients with severe immunodeficiency. Protozoa such as *Cryptosporidia*, *Microsporidia*, *Isospora* and *Cyclospora*, which cause self-limiting diarrhoea in immunocompetent travellers, may lead to chronic and devastating opportunistic disease in immunodeficient patients. Food hygiene is therefore critical (Chapter 3).

If HIV-infected patients with moderate to severe immunodeficiency travel to remote areas, they should carry empirical stand-by antibiotic treatment, and full information on its use, in case of febrile or dysenteric diarrhoea are recommended. Prescription of the antibiotic must take account of the resistance pattern of *Salmonella*, *Shigella*, *Escherichia coli* and *Campylobacter* spp in the region of travel. Fluoroquinolones are active against several enteric pathogens and do not interact significantly with ART; macrolide antibiotics, however, may have significant drug interactions with ART and should be avoided. Patients should seek specialized care if symptoms do not improve within 24–48 h.

#### *Tuberculosis*

HIV infection is associated with a higher risk of developing active tuberculosis after exposure to, and reactivation of latent infection with, *Mycobacterium tuberculosis*. HIV-infected travellers should be tested for latent tuberculosis infection and treated if found positive. BCG vaccine should *not* be given, regardless of whether these HIV-positive individuals are symptomatic.

#### *Other pathogens*

Greater susceptibility and/or morbidity is also important in the case of *Leishmania* (a protozoan infection transmitted by the sandfly), *Trypanosoma*, and fungi, especially histoplasmosis, coccidioidomycosis (Americas) and *Penicillium marneffe*

(South-East Asia). Preventive measures include prevention of arthropod bites and avoidance of sites with high exposure such as bat and bird caves.

### *Vaccines*

The basic principles of vaccination that apply to all travellers in terms of timing, dosing, assessment of antibody responses (Chapter 6) apply also to HIV-infected persons. Differences for individual vaccines are summarized in Table 9.2.

### *Immunogenicity*

Low CD4 counts and replicating HIV infection are associated with a reduced immunogenicity of most vaccines. Antibody titres after vaccination are lower shortly after vaccination and they decline more rapidly, in particular in patients with CD4 counts below 200/mm<sup>3</sup>. If feasible, vaccination against travel-associated diseases should be postponed until successful ART has led to a sustained increase in CD4 counts (ideally above 350/mm<sup>3</sup>). Some vaccine courses will require extra or booster doses, depending on the individual vaccine. If exposure cannot be postponed, inactivated vaccines should be given if indicated, even in patients with low CD4 counts, and revaccination should be performed after immune restoration.

### *Vaccine safety*

Inactivated vaccines are safe in HIV-infected persons. In general, HIV-infected travellers should avoid live vaccines, although yellow fever and measles/mumps/rubella (MMR) may be given to patients with CD4 cell counts >200/mm<sup>3</sup>.

Table 9.1 **Pre-travel counselling according to CD4 count**

<b>CD4 count</b>	<b>Important counselling points</b>
>350/mm <sup>3</sup>	Food hygiene If on ART: interactions, adherence
200-350/mm <sup>3</sup>	Food hygiene ART indicated If not on successful ART: consider pneumocystis prophylaxis for longer travels Vaccine efficacy reduced Yellow fever vaccine: very restrictive If on ART: interactions, adherence

CD4 count	Important counselling points
<200/mm <sup>3</sup>	<p>Food hygiene</p> <p>Risk for opportunistic infections, ART and primary prophylaxis against pneumocystis and toxoplasmosis indicated</p> <p>Vaccine efficacy reduced</p> <p>Avoid yellow fever vaccine</p> <p>Consider delaying longer journeys until after several months of successful ART and CD4 count above 200/ mm<sup>3</sup></p> <p>If on ART: interactions, adherence</p>
<50/mm <sup>3</sup>	<p>Food hygiene</p> <p>High risk for all opportunistic infections, ART and primary prophylaxis against pneumocystis and toxoplasmosis indicated</p> <p>Vaccine efficacy severely reduced</p> <p>Avoid yellow fever vaccine</p> <p>Delay longer journeys until after several months of successful ART and CD4 count above 200/ mm<sup>3</sup></p> <p>If on ART: interactions, adherence</p>

Table 9.2 **Pre-exposure vaccines for HIV-infected travellers**

Vaccine	Indication	Notes
<i>Live vaccines</i>		
Influenza (intranasal)	Contraindicated	Use inactivated parenteral vaccine Avoid vaccination in household contacts
Japanese encephalitis (SA-14-14-2)	Contraindicated	
Measles/mumps/rubella (MMR)	Indicated for measles IgG-seronegative travellers with CD4 count >200 cells/mm <sup>3</sup> Contraindicated in travellers with CD4 ≤200 cells/mm <sup>3</sup>	Avoid pregnancy for 1 month after vaccination Breastfeeding not contraindicated Administer 2 doses at least 1 month apart to increase likelihood of protection against measles No data suggest increased adverse events following measles vaccination of HIV-infected children. However, efficacy

Vaccine	Indication	Notes
		may be impaired for mumps and rubella. Household contacts can be vaccinated
Poliomyelitis, oral (OPV)	Indicated	Polio vaccination indicated for all travellers to polio-endemic areas or to countries with recent outbreaks following the importation of poliovirus (see <a href="http://www.who.int/ith">www.who.int/ith</a> for updated list of countries). Travellers who have previously received three or more doses of OPV or IPV should be offered another dose of vaccine before departure. Non-immunized individuals require a complete course of vaccination. OPV is not contraindicated in HIV-infected children. For the purposes of travellers' vaccination, OPV or IPV can be used in asymptomatic HIV-infected individuals.
Tuberculosis (BCG)	Contraindicated	
Typhoid (Ty21a)	Can be used in HIV-infected individuals with CD4 >200 cells/ mm <sup>3</sup>	Consider inactivated typhoid ViCPS vaccine
Yellow fever (YF )	Indicated if significant risk of YF for travellers with CD4 count >200 cells/ mm <sup>3</sup> , whether or not on ART Contraindicated in HIV-infected travellers with CD4 ≤200 cells/ mm <sup>3</sup> on CCR5 inhibitors <sup>a</sup>	Decisions regarding YF vaccination should always be taken in light of likely risk of acquisition of infection An exemption certificate should be provided to all travellers not vaccinated, but travelling to a YF-endemic country Advice on avoidance of mosquito bites must be stressed Safe for household contacts

Vaccine	Indication	Notes
<b><i>Inactivated vaccines/toxoids</i></b>		
Cholera (WC/rBS)	Indicated in travellers to high-risk areas during epidemics or after natural disasters	Limited efficacy and safety data Also induces protection against enterotoxigenic <i>Escherichia coli</i> (ETEC) Responses in travellers with CD4 < 100 cells/mm <sup>3</sup> are poor Stress good food and water hygiene
Diphtheria/tetanus/pertussis	Indicated	
Hepatitis A	Indicated for non-immune travellers to endemic areas, particularly those in high risk groups <sup>b</sup>	If resources allow, check for serological evidence of natural infection before vaccination Serological responses reduced in immunosuppressed patients, but good efficacy even at low CD4 count Two or three doses required Consider Human Normal Immunoglobulin(HNIG) for severely immunosuppressed travellers May be given as single vaccine or as combination with hepatitis B
Hepatitis B	Recommended for all non-immune, susceptible travellers	4-dose schedule (0,1,2,12 months) ± booster doses as dictated by serological response Those who fail to respond to 1st vaccination course should receive a 2nd course Stress advice on risk reduction, especially in high risk groups such as men who have sex with men
Influenza	Indicated	Inactivated parenteral vaccine
Japanese encephalitis	Indicated for long-term travellers to South-East Asia and Far East, and for those with extensive exposure to rural areas even if	Formalin-inactivated JEV vaccine derived from mouse brains has been linked with severe neurological adverse events requiring careful evaluation of the traveller's risk and need for vaccination

Vaccine	Indication	Notes
	travelling short-term (Chapter 6)	A new inactivated JEV vaccine (Chapter 6) has recently been licensed in several countries. No information is available yet for HIV-infected persons
<i>Neisseria meningitidis</i>	Mandatory vaccine for Hajj pilgrims; indicated for travellers to the "meningitis belt"	Quadrivalent (ACWY) vaccine recommended No evidence of increased risk of adverse events in HIV-infected persons
Poliomyelitis, injectable (IPV)	Indicated	Polio vaccination indicated for all travellers to polio-endemic areas or to countries with recent outbreaks following the importation of poliovirus (see <a href="http://www.who.int">www.who.int</a> for updated list of countries). Travellers who have previously received three or more doses of OPV or IPV should be offered another dose of polio vaccine before departure. Non-immunized individuals require a complete course of vaccination.
Rabies	Indicated for travellers who could be exposed to rabid animals (Chapter 6 and Map)	Intramuscular immunization recommended rather than intradermal Assess response to immunization in travellers with CD4 cells $\leq 200/\text{mm}^3$ , if resources allow, $\pm$ further boosting if antibody response $> 0.5\text{IU/ml}$ not achieved Counsel all travellers to endemic areas on wound treatment and post-exposure prophylaxis
Tick-borne encephalitis	Indicated for HIV-infected travellers intending to walk, camp or work in heavily forested regions in endemic areas	Limited efficacy data available. travellers with CD4 count $> 400\text{ cells mm}^3$ had better serological response. Highest risk in late spring/early summer Stress importance of avoiding tick bites and consumption of unpasteurized milk

Vaccine	Indication	Notes
Typhoid (ViCPS)	Indicated for HIV-infected travellers at risk of exposure, particularly in highly endemic areas	Booster every 3 years Serological response reduced in travellers with CD4 count $\leq 200$ cells/mm <sup>3</sup> Food and water hygiene

<sup>a</sup> A severe viscerotropic disease after YF vaccination has been described in an HIV-negative person with genetically determined disruption of the CCR5–RANTES axis.

<sup>b</sup> Men who have sex with men, intravenous drug users, haemophiliacs receiving plasma-derived concentrates and patients with hepatitis B and/or C coinfection.

### *Malaria in HIV infected travellers*

Like all travellers, immunocompromised individuals travelling to malaria-endemic destinations should be prescribed appropriate drugs for malaria chemoprophylaxis and given clear advice about avoidance of mosquito bites (Chapters 3 and 7).

Chemoprophylaxis should preferably be started well before travelling, as adverse events may necessitate a change in regimen. Compliance with malaria prophylaxis, early treatment-seeking (within 24 h of onset of any febrile illness), prompt definitive diagnosis (using malaria smears or rapid diagnostic tests) and effective treatment are particularly important in HIV-infected patients.

Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are increased. In stable endemic areas, HIV-infected patients with partial immunity to malaria may suffer more frequent and higher parasite density infections; while in areas of unstable transmission, HIV infection is associated with an increased risk of severe malaria and malaria-related deaths.

Information on how HIV infection modifies responses to artemisinin-based combination therapy (ACT) and on interactions between antimalarial medicines and antiretrovirals is currently very limited. Early studies with suggested that increasing HIV-related immunosuppression was associated with decreased treatment response; increasing parasite burdens and reduced host immunity, both of which occur with HIV infection, are associated with increased treatment failure rates. At present there is insufficient information to allow general malaria treatment recommendations to be modified for patients with HIV/AIDS.

HIV-infected patients may be receiving other medications, such as co-trimoxazole (trimethoprim-sulfamethoxazole) as prophylaxis for opportunistic infections, and/or ART. There is limited information on drug interactions between ART and ACT.

In one study, treatment of uncomplicated malaria with artesunate-amodiaquine was highly effective in both HIV-infected and uninfected children. Importantly, however, there was a significant 7–8 fold increased risk of neutropenia 14 days after initiation of treatment among HIV-infected children compared with uninfected children. About one-fifth of the episodes in the HIV-infected group were severe or life-threatening. Among the HIV-infected children, the risk of neutropenia was significantly higher among those on ART regimens containing zidovudine. Hepatotoxicity has been documented for efavirenz given together with artesunate-amodiaquine. Given this limited but worrying information, treatment of malaria in HIV-infected patients receiving zidovudine or efavirenz should, if possible, avoid ACT regimens containing amodiaquine. Although HIV infection and co-trimoxazole may also depress neutrophil counts, there is insufficient information on the interaction of amodiaquine-containing ACT regimens with co-trimoxazole and HIV infection to make recommendations.

- Patients with HIV infection who develop malaria should receive prompt, effective antimalarial treatment regimens.
- Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.
- Treatment of HIV-infected patients on zidovudine or efavirenz with amodiaquine-containing ACT regimens should be avoided if possible.

### Further reading

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