The Human Immunodeficiency Virus–Infected Traveler

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As the number of travelers from industrialized countries who are infected with human immunodeficiency virus (HIV) increases as a consequence of the clinical benefits of highly active antiretroviral therapy (HAART), updated prophylactic knowledge is needed. Vaccine prophylaxis must balance the safety and immunogenicity of vaccines with the estimated risk of acquiring the disease. Further research is needed on antimalarial chemoprophylaxis for travelers who are HAART recipients, because of possible pharmacokinetic interactions. Safe sex practices must be adopted to avoid both spreading of the infection in the host country and superinfection with different HIV strains. Most individuals infected with HIV may travel safely, even though the infectious risk has been reported to be higher for patients with advanced infections than for the general population. These patients are also less likely to produce an effective immune response to vaccines. Migrants and refugees from poor countries are also at risk of acquiring HIV infection. Their legal-residency status may often prevent their access to adequate health services, thus necessitating urgent public health actions.

Since highly active antiretroviral therapy (HAART) became the standard of care in 1996 for patients infected with HIV, the epidemiological panorama of AIDS has dramatically changed in industrialized countries, leading to a substantial decrease in death and hospitalization rates [1]. In these countries, HIV infection has become a chronic condition. It is expected that an increasing number of such asymptomatic patients infected with HIV will become socially active and willing to travel overseas, including to developing countries, for leisure or occupational reasons. Data from North America suggest that 10%–20% of individuals infected with HIV move each year to foreign destinations [2, 3]. Furthermore, as many as 25% of newly detected HIV infections in Scotland in 1996 were reported to be acquired abroad [4], and these individuals are likely to travel again.

Because of shortcomings in hygienic conditions, the infectious risk that immunocompromised travelers infected with HIV are likely to face during travel to developing countries has been reported to be higher (especially before the introduction of HAART) than for the general population [5]. Therefore, they must be carefully assessed by travel health professionals, who must evaluate the risk-benefit balance of preventive interventions (vaccines, chemoprophylaxis) and provide adequate counseling to protect travelers’ health and prevent any negative impact on host countries.

Meanwhile, the developing world, because of the lack of infrastructure and economic resources necessary to implement HAART, is still experiencing the exponential phase of the AIDS epidemic. At the end of 1999, among the nearly 34 million persons living with HIV infection/AIDS, >23 million resided in sub-Saharan Africa [6].

Preparing for Travel

Most patients infected with HIV may travel to any destination if their immune status is satisfactory. The risk of negative clinical events during travel is obviously related to the degree of immunosuppression, which is also relevant to preventive measures. Preparations for travel require special attention and skills to balance infectious risk, medication needs, and preventive measures. In any case, before traveling, persons infected with HIV should obtain the location in the destination country of a facility with expertise and resources for the treatment of HIV-related complications.

Vaccine Prophylaxis

The efficacy and safety of the use of vaccines for patients infected with HIV has been long debated, and the following 4 major issues must be considered before deciding whether or not...
a traveler should be vaccinated: (1) the risk and severity of the vaccine-preventable disease in the destination area (estimation of travel-specific epidemiological risk); (2) the nature of the vaccine (live attenuated, inactivated, polysaccharide, or subunit); (3) the immune status (CD4+ peripheral lymphocyte count); and (4) risk of virological rebound as a consequence of vaccination.

Estimation of travel-specific epidemiological risk. Most infectious diseases are either more frequent or more serious in immunocompromised patients. Salmonella, pneumococcal, and meningococcal infections are particularly severe and deserve special preventive attention [7]. Hepatitis B coinfection also has a more severe course in immunocompromised patients with HIV [8], and hepatitis A infection has been reported to be more aggressive in patients with chronic hepatopathy [9]. It has also been reported that the incidence of influenza complications is higher among patients infected with HIV [10]. On the contrary, no information is available regarding the possible increase in incidence and/or severity of other vaccine-preventable infections, such as tetanus or diphtheria, in travelers infected with HIV.

Nature of the vaccine. As a general rule, live vaccines should be avoided for immunocompromised patients. Salmonella, pneumococcal, and meningococcal infections are particularly severe and deserve special preventive attention [7]. Hepatitis B coinfection also has a more severe course in immunocompromised patients with HIV [8], and hepatitis A infection has been reported to be more aggressive in patients with chronic hepatopathy [9]. It has also been reported that the incidence of influenza complications is higher among patients infected with HIV [10]. On the contrary, no information is available regarding the possible increase in incidence and/or severity of other vaccine-preventable infections, such as tetanus or diphtheria, in travelers infected with HIV.

Immune status of the traveler. The immune status of the traveler is important for predicting immune response to most vaccinations. Published evidence shows a CD4+ cell count–dependent lower antibody response to many vaccines, including influenza [13], hepatitis A [14], and hepatitis B vaccines [15]. As a general rule, patients infected with HIV having CD4+ cell counts <200 cells/µL. BCG vaccine is to be avoided [11], and inactivated vaccines should be selected instead of live ones against typhoid, poliomyelitis, and cholera, if indicated. Yellow fever vaccination is to be limited to situations of real risk and administered only to patients whose CD4+ cell counts are >200 cells/µL and for whom safety data are available [12].

Risk of vaccine-induced virological rebound. Concern has been raised by the observation that many vaccines may induce a discrete increase in HIV virus load after vaccination [17] as a result of activation of the immune system. It has now been shown that the HIV RNA increase following vaccination is transient [13] and that the HIV RNA level usually returns to baseline 4–6 weeks after administration of the vaccine or even sooner if the patient is receiving antiretroviral treatment. Furthermore, risk of HIV disease progression following the occurrence of natural infection has been substantiated [18].

In conclusion, most inactivated, subunit, or polysaccharide vaccines may be administered safely, preferably to patients whose HIV infections are in the early stage and who are receiving HAART. The feared occurrence of possible pharmacokinetic interactions between influenza vaccine and cytochrome P450–metabolized drugs (i.e., HIV protease inhibitors) has not been confirmed [19]. Table 1 summarizes the present knowledge of the above-mentioned issues.

Chemoprophylaxis

The available data, although sometimes discordant, do not clearly suggest a higher incidence or increased severity of malaria infection in patients infected with HIV [20]. However, it has been reported that HIV RNA plasma levels are increased during acute malaria infection [21]. Thus, chemoprophylaxis for patients infected with HIV follows the guidelines adopted for individuals testing negative for HIV in any country. Nevertheless, concern has been raised about the possible interactions between antimalarial compounds, which are metabolized by cytochrome P450 in most instances, and antiretroviral drugs [22]. Recent investigations suggest that concomitant administration of mefloquine and ritonavir may result in decreased plasma levels of ritonavir [23]. No published information is available on proguanil and chloroquine, but doxycycline is probably safe [22]. Further research is needed on the pharmacokinetic interactions between antiretroviral and antimalarial drugs.

The incidence of traveler’s diarrhea among persons infected with HIV may be higher than in the general population, particularly for individuals with low CD4+ cell counts. Chemoprophylaxis may then be indicated for subjects with CD4+ peripheral cell counts <200 cells/µL, even if there is concern about the possible emergence of drug-resistant strains. Fluoroquinolones are widely used in patients infected with HIV [24] and have been proved to be effective in preventing gastrointestinal illnesses. When used as a prophylactic agent against Pneumocystis carinii pneumonia, cotrimoxazole may also prove useful in preventing traveler’s diarrhea, even though patients infected with HIV are at higher risk for drug-related hypersensitivity rash and resistant enteropathogens may be encountered in some areas of the developing world.

Behavioral Prophylaxis

The traveler infected with HIV must avoid promiscuous sexual contacts while abroad to prevent spreading the infection (and possible drug-resistant strains) in the host country and to avoid new infection with a different HIV strain that may accelerate the disease course [25] or eliminate possible therapeutic
options (e.g., nonnucleoside reverse transcriptase inhibitors are not active against HIV-2). A particular aspect of the problem is the risk of HIV transmission by long-term travelers and expatriates, who may acquire infection by sexual contacts with both indigenous and expatriate partners. Furthermore, long-term stays in settings with poor health care resources pose the problems of limited diagnostic facilities and limited access to optimal care for patients infected with HIV. These problems should prompt health care providers to obtain accurate medical histories from all travelers, especially long-term travelers and expatriates, returning from developing countries [26].

It is essential to stress the need for alimentary precautions to avoid the possible ingestion of microbiological agents of opportunistic infections (Toxoplasma gondii, Cryptosporidium parvum, Salmonella species, etc.).

### HIV Infection and Travel Restrictions

More than 150 countries have adopted entry restrictions for travelers infected with HIV, with the aim of stopping the spread of the infection at their borders. These restrictions, which affect mainly long-term travelers asking for residency or for scholarship or work visas, have not been endorsed by the World Health Organization, and there is general consensus in the scientific community that their effectiveness in limiting HIV infection in any given country is extremely poor. Nevertheless,
Table 2. Drugs that should not be used with antiretrovirals because of pharmacokinetic interactions (always check package insert before prescription).

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Indinavir</th>
<th>Ritonavir</th>
<th>Saquinavir</th>
<th>Nelfinavir</th>
<th>Amprenavir</th>
<th>Nevirapine</th>
<th>Delavirdine(^a)</th>
<th>Efavirenz</th>
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<td>Bepridil</td>
<td>Ca(^{2+}) channel blockers</td>
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**NOTE.** Table is modified from [30], integrating information from Italian drug insert packages. Other drugs may require dose adjustments when coadministered with antiretroviral drugs. DHET, dihydroergothamine.

\(^a\) Delavirdine is not registered for use in Italy.
Problems during Travel

Health disturbances. Few studies have addressed the incidence of health problems encountered by travelers infected with HIV. Health disturbances were reported by 15 (43%) of the 35 travelers infected with HIV described by Kemper et al. [27] in 1997; 4 had potentially life-threatening infections (coccidioidomycosis, cryptococcosis, P. carinii pneumonia, and bacterial pneumonia). The small, retrospective questionnaire-based survey performed by Simons et al. [3] suggests that the major complaints of the traveler infected with HIV are diarrhea (32% incidence over the 3-week median period of travel) and skin disorders (reported by 28% [14%–45%] of respondents). The consultation rate for either travel-related illness, abroad or after return, was high (5% and 28%, respectively) [3]. According to other reports, patients infected with HIV are at particular risk for respiratory travel-related illnesses [2].

However, these studies were conducted before HAART became the standard of care in 1996, allowing dramatic improvement in peripheral CD4+ cell counts in patients infected with HIV, due first to the expansion of memory cells and later to the new production of naive cells. It has also been demonstrated that the risk of opportunistic infections and clinical progression decreases to a very low level when a stable CD4+ cell count >200 cells/μL is reached, so that primary [28] and secondary [29] prophylaxis may be withdrawn after 3–6 months of stable response.

HAART and travel. A few problems that may arise for the traveler infected with HIV undergoing HAART must be considered by the physician and the patient before travel [22]: (1) since no antiretroviral drug is exempt from adverse effects, which usually manifest a few weeks following the initiation of therapy, it is unsafe to travel soon after a change in antiretroviral therapy; (2) since antiretroviral drugs are not available everywhere in the world, a patient should always place them in hand-carried baggage to avoid losing them; (3) drug-related recommendations about food and liquid intake (i.e., hydration during indinavir therapy) may need adjustment during travel, and in hot climates fluid loss due to transpiration should be accounted for; (4) antiretroviral drugs may be considered markers of infection at borders and customs checkpoints, which may lead to harassment by the authorities; and (5) antiretroviral drugs have important pharmacokinetic interactions with other drugs that may be of potential use during travel (table 2).

Conclusions

The number of travelers infected with HIV from industrialized countries to developing countries will probably increase in the near future as a consequence of HAART-induced clinical benefits. Prophylactic measures for the traveler infected with HIV should be carefully evaluated on the basis of the person’s immune status and balanced against the estimated risk of infection.

Risk of infection has been reported to be higher for travelers infected with HIV than it was for the general population in the pre-HAART era, but assessments of risk for patients receiving HAART are largely lacking. However, since the occurrence of HIV-related clinical events depends on immunological status, it is anticipated that travelers infected with HIV with <200 CD4+ cells/μL are exposed to a substantial risk of infection when traveling, regardless of their therapy status. They are also less likely to respond to vaccinations. The decision to travel should be carefully evaluated by these subjects and travel health professionals.

The future scenario will be different from the past in that the focus will possibly be shifted from travel-related infectious risk to HAART-related constraints such as efficacy and safety monitoring, as well as availability of drugs.

Unfortunately, persons infected with HIV living in poor countries (~95% of the population infected with HIV) are not benefiting from therapeutic advances and are still affected by unacceptably high HIV-related morbidity and mortality. Migrants are also at risk of acquiring HIV infection, but their legal-residency status may prevent their access to adequate health services. This issue also needs to be addressed with public health interventions.

References
