



Safe Travel Preparation for HIV-Infected Patients

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Abstract

Purpose of Review Infectious diseases are a risk when traveling internationally, and it is important to know the potential disease burden of a region and take appropriate preventative actions before traveling. For individuals with HIV, there are special considerations and contradictions for various vaccines and medications as well as interactions with likely antiviral drugs. The purpose of this review is to summarize the vaccine and medication recommendations for travelers with HIV infection. We also review recent studies to update these recommendations.

Recent Findings The recommendation for yellow fever vaccine has changed in June of 2016, and it is now a once in a lifetime vaccine instead of being given every 10 years. A new cholera vaccine, Vaxchora™ was approved in 2016. Since it is a live vaccine, its impact on immunocompromised individuals is still not fully known. A recent study found that immunocompromised patients responded well to the hepatitis A vaccine, although acquiring immunity may take longer than in non-immunocompromised people. There are some new anti-viral medicines that need to be considered with interactions for other travel medicines, in particular, the anti-malaria drugs.

Summary This review provides current knowledge on how HIV-infected and immunocompromised persons respond to medications and vaccines for prevention of infectious diseases in travelers. These recommendations will be useful to recommend safer travel for the HIV-infected patient. Some newer vaccines and medications will need further evaluation and assessment to determine safety and impact on HIV-positive travelers.

Keywords HIV · Immunocompromised · Travel medicine · Infectious diseases · Vaccines · Geographic medicine · Prevention

Introduction

Infectious diseases pose a risk to those traveling internationally. Many of the infectious diseases are vaccine-preventable or can be prevented by medication. There may be drug interactions or contraindications for patients on highly active anti-retroviral drugs or with lower levels of CD4 counts. We review the recommendations of the Centers for Disease Control

(CDC) Yellow Book [1•] and other studies that inform safe travel for those infected with HIV.

An encounter for preparing a traveler is always also an opportunity to ensure all standard and usual vaccines are up-to-date. The usual vaccines indicated for patients with HIV should be reviewed and the vaccines or boosters offered. These vaccines will not be reviewed here, but include the influenza, Tdap or Td, pneumovax, and possibly Shingrix (now replaces the Zostavax, which was live).

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High-Level Immunosuppression

Immunosuppression in HIV-infected patients is typically divided into two levels: low-level immunosuppression (limited immunosuppression) and a high-level (severe) immunosuppression. For patients with HIV, individuals are severely immunocompromised if their CD4+ cell counts are less than 200/μL for adolescents and adults, and less than 15% in children [2]. These high-level immunosuppressed individuals need to be cognizant of the risks for certain infections in the

endemic areas they are traveling in order to take precautions while abroad. In addition, the risks of certain interventions (such as live vaccines and medication interactions) need to be considered to optimally and safely prepare them for travel.

Low-Level Immunosuppression

Individuals are considered to be low-level immunosuppressed if their absolute CD4+ cell counts are above 200/ μ L for adults and above 15% for children [2]. There are potential drug interactions for those who are considered to have low-level immunosuppression, although there are fewer complications than those with high-level immunosuppression.

Required Vaccines for Travel

There are three vaccines that are required for entry or exit from certain international zones. These include polio, meningitis, and the yellow fever vaccine.

A. Polio vaccine is required to exit a country that is currently marked as with endemic transmission of polio virus. The WHO currently lists three countries as “polio endemic”. These include Afghanistan, Nigeria, and Pakistan. There is also a category of country (no longer officially used by the WHO) listed as “polio-exporting countries.” Though the WHO no longer uses this labeling, some other countries still use the label and these countries still use non-IHR (international health regulation) entry requirements. These countries currently include the Democratic Republic of Congo (DRC), Somalia, and Syria, as well as the above three countries of Afghanistan, Nigeria, and Pakistan. Travelers to these countries must have proof of vaccination within the last 12 months in order to enter into another non-endemic country. This is all part of the polio elimination strategy. According to WHO guidance, the following considerations for timing of injectable polio vaccine (not live) would be:

- Previously unvaccinated adults traveling to risk countries who are 18 years and older: three doses at 0, 1–2, and 6–12 months after the second dose. If earlier protection is needed for travel, efforts should be made to complete the series prior to travel, but even a single dose is beneficial.
- Adults traveling to risk countries, Hajj/Umrah pilgrims from a risk country who have a completed childhood vaccination but no history of an adult booster, or those needing to meet a destination-country entry requirement: single-dose booster. More than one lifetime adult booster is unnecessary unless given to meet a destination entry requirement, in which case the booster must be given between 4 weeks and 1 year of departure from the origin country.

- Residents of or long-stay (more than 4 weeks) visitors in Afghanistan, Nigeria, or Pakistan who are onward travelers to other countries, if they have not received one additional dose of polio vaccine between 4 weeks and 1 year of departure from the country (regardless of primary series completion): single-dose booster.

B. Meningitis vaccine is currently required to enter Saudi Arabia for travelers going on the Hajj or Umrah. Travelers must show documentation of having had this vaccine within the last 5 years, due to the higher risk of transmission of meningitis in these zones with crowding. Many patients in the USA have been given this vaccine related to increased risks in certain urban populations as recommended by state or local jurisdictions for similar risk reasons with observed increases in cases in the HIV-infected population. This is not a live vaccine and is safe to give in HIV-infected individuals.

C. Yellow fever is a virus transmitted by *Aedes* and *Haemagogus* mosquitoes, particularly *Aedes aegypti*. In addition to yellow fever, *Aedes aegypti* also transmit numerous other infectious diseases, including dengue fever, chikungunya, and Zika virus. Although most people who are infected with yellow fever are asymptomatic, some symptoms of yellow fever include fever, chills, and headache [1]. In rarer cases, severe yellow fever can manifest with symptoms ranging from high fever, jaundice, and organ failure. In this more severe case, the fatality rate is over 30% [1]. Yellow fever is endemic to South America and sub-Saharan Africa [1]. Yellow fever has trended downward over the last 35 years [3], but there has been increased media coverage due to several outbreaks in Angola, Democratic Republic of Congo, and Brazil, which include the urban areas of Rio de Janeiro and Sao Paulo [4]. Areas where travelers are at risk for yellow fever infection and are required to show proof of documentation of having had the yellow fever vaccine are shown in Fig. 1. These areas include only Africa and South America. Though *Aedes* mosquito vectors are present throughout Asia and most other tropical regions, only the marked areas on the map have entry requirements for the yellow fever vaccine related to known and ongoing transmission.

The current recommendation for those traveling to areas that are endemic to yellow fever is to get the yellow fever vaccine 10 days prior to entry. However, since this a live vaccine, it may pose a risk to those who have high-level immunocompromised status, including travelers with HIV. Currently, the Centers for Disease Control recommends yellow fever vaccination in immunocompromised persons who can safely take it. Yellow fever vaccine is contraindicated in HIV-infected persons who are either symptomatic or have CD4 counts < 200 mm^3 . Those with

Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017.

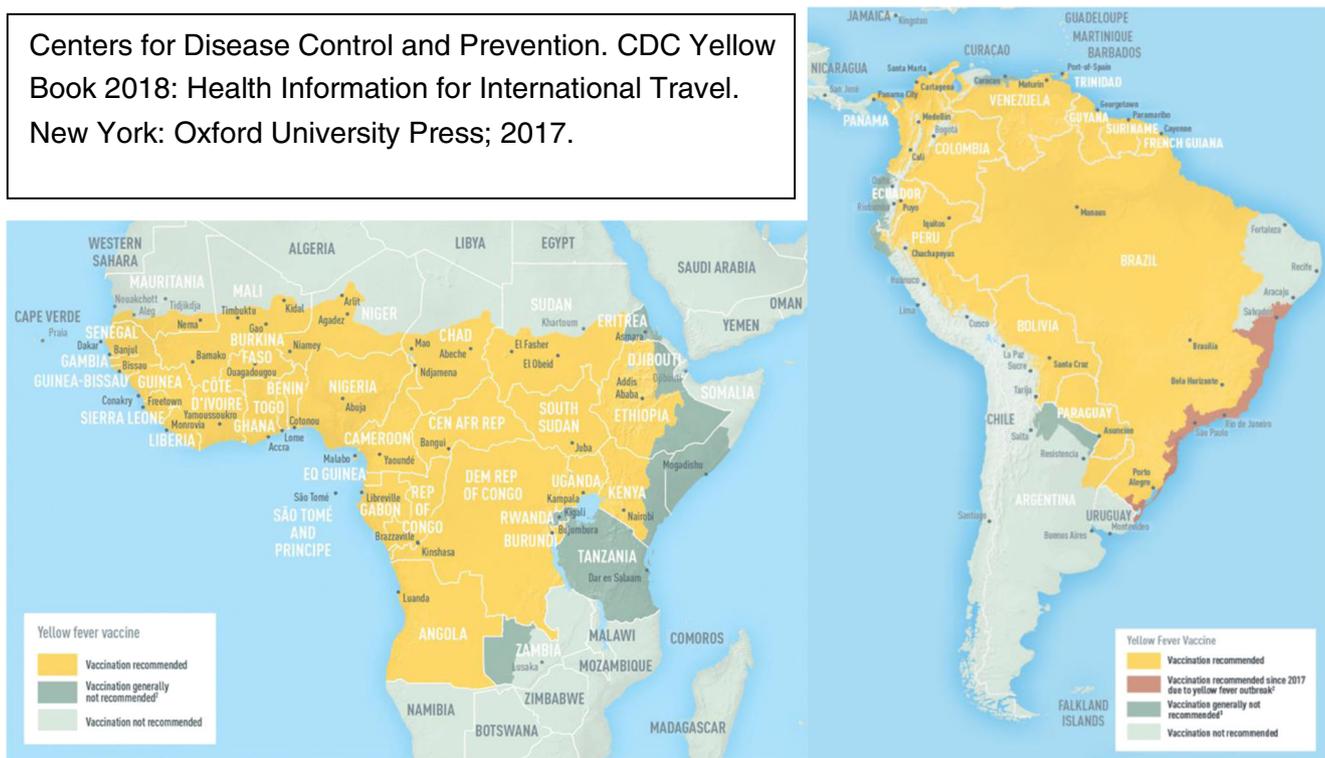


Fig. 1 This map aligns with recommendations published by the World Health Organization (WHO) [1••]. It is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever. In 2017, CDC expanded yellow fever vaccination recommendations for travelers to Brazil due to a large outbreak of yellow fever in multiple states within that country [4]. Please refer to the Yellow Fever in Brazil Travel Notice for more information and updated recommendations. Yellow fever (YF) vaccination is generally not

recommended in areas where there is low potential for YF virus exposure [5]. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler’s risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (such as age or immune status)

CD4 counts between 200 and 500 mm³ and are asymptomatic should be considered for the yellow fever vaccine with a “precaution,” meaning that they can be offered the vaccine if traveling to a country on the yellow fever map. These patients should be closely observed in the event of any adverse side effects [1]. Asymptomatic patients with a CD4 count greater than or equal to 500 mm³ can be vaccinated with the live yellow fever vaccine without precautions.

Clinicians should feel safe giving the live yellow fever vaccine to patients with undetectable viral loads, even when the patient is in the 200–499 CD4 range, recognizing the vaccine stimulus may cause a “blip” in the viral load. The “blip” in this context is of no clinical consequence and checking the viral status around vaccination is not indicated.

Due to the wide geographic range of yellow fever and the risks that the vaccine may pose to those with HIV, there have been numerous studies conducted on how HIV infection and the yellow fever vaccine interact. In a 2014 review of three different studies about HIV and yellow fever vaccine, Barte et al. determined that in adults, the immune response of HIV-infected persons was slightly lower than

those without HIV. The authors recommended that the vaccine be given to those with high CD4 counts and a low viral load, despite the lack of data on potential adverse side effects [5]. In 2016, Weiten et al. determined that the yellow fever vaccine is effective, even when taken with various immunosuppressive drugs [6•]. Further study may clarify yellow fever immunity in the setting of the variety of immunosuppressive drugs now being more widely used.

In July of 2016, WHO determined that a single dose of yellow fever vaccine confers lifelong immunity in most circumstances [7•], so a booster dose every 10 years is no longer needed. There are some exceptions; for example, if the vaccine were given during a transient immunocompromised episode (pregnancy or while a patient was taking steroids), as well as those with HIV infection, then a repeat of the vaccine for booster effect is indicated [8].

During 2017 and through 2018, the YF-VAX was not available in the USA, and thus Stamaril, which has been used in Europe and beyond for more than 30 years was used in its place on a “trial basis.” More data about HIV and safety of Stamaril, which is a very similar vaccine to YF-VAX, will be available in the coming year.

Typhoid

Typhoid fever is a bacterial infection transmitted by humans [1]. Symptoms include fatigue and high fever with diarrhea or constipation being common [1]. Typhoid fever is a risk for many travelers to endemic countries and the magnitude of this risk depends on the duration of the travel, as well as the exposure settings during that travel. Aside from industrialized regions such as the USA, Western Europe, Canada, Japan, and Australia, typhoid is common in most regions of the world [9]. A map of typhoid-endemic areas is shown in Fig. 2. To reduce typhoid risk while traveling, there are currently two vaccines in use. There is a live, oral vaccine called Ty21a and an inactivated, injectable vaccine called ViCPS (sometimes referred to as Vi) [1].

For those infected with HIV, the current recommendation is only to get the inactivated vaccine, Vi, which can be used “as indicated for normal hosts.” [1] The live vaccine, Ty21a, is contraindicated for HIV-infected persons [1].

Cholera

Cholera is an exceedingly rare disease in travelers. Its most common symptom is diarrhea, which can range from mild to severe, with nausea and vomiting also seen [1]. Azithromycin, a prophylactic antibiotic commonly given to travelers to manage diarrheal symptoms also covers *Vibrio cholerae*, if given in a double dose [10]. There is a live, oral vaccination for cholera, lyophilized CVD 103-HgR, called Vaxchora™ that was FDA approved in 2016 [11]. There is limited clinical

experience using this single-dose vaccine. Since it is a live vaccine, the CDC currently has no recommendations for its use in immunocompromised persons who may need to travel to a place where cholera is endemic [1]. An old formulation of the CVD 103-HgR vaccine, which found that adverse health effects were seen equally in both HIV-positive and HIV-negative groups, and although responses were lower in HIV-positive persons, they still considered the vaccine safe to use [12]. Though adequate data is currently lacking, Vaxchora™ is not recommended in HIV-positive individuals.

Hepatitis A

Hepatitis A vaccination is recommended in patients with HIV for all the usual travel indications. Furthermore, this vaccine is “routinely indicated for all men who have sex with men, people with multiple sexual partners, hemophiliacs, patients with chronic hepatitis, injection drug users, and others” [1].

There is a “moderate to good” response to the hepatitis A vaccine in immunocompromised travelers although it may take more time to acquire immunity in these individuals [13]. Additionally, patients who are using multiple immunosuppressive drugs were found to have a higher likelihood of the vaccine failing [13].

Hepatitis B

Hepatitis B vaccination is recommended for all people at risk of infection via sexual exposure [1]. Furthermore, both hepatitis A and B are travel-related diseases, with hepatitis A being

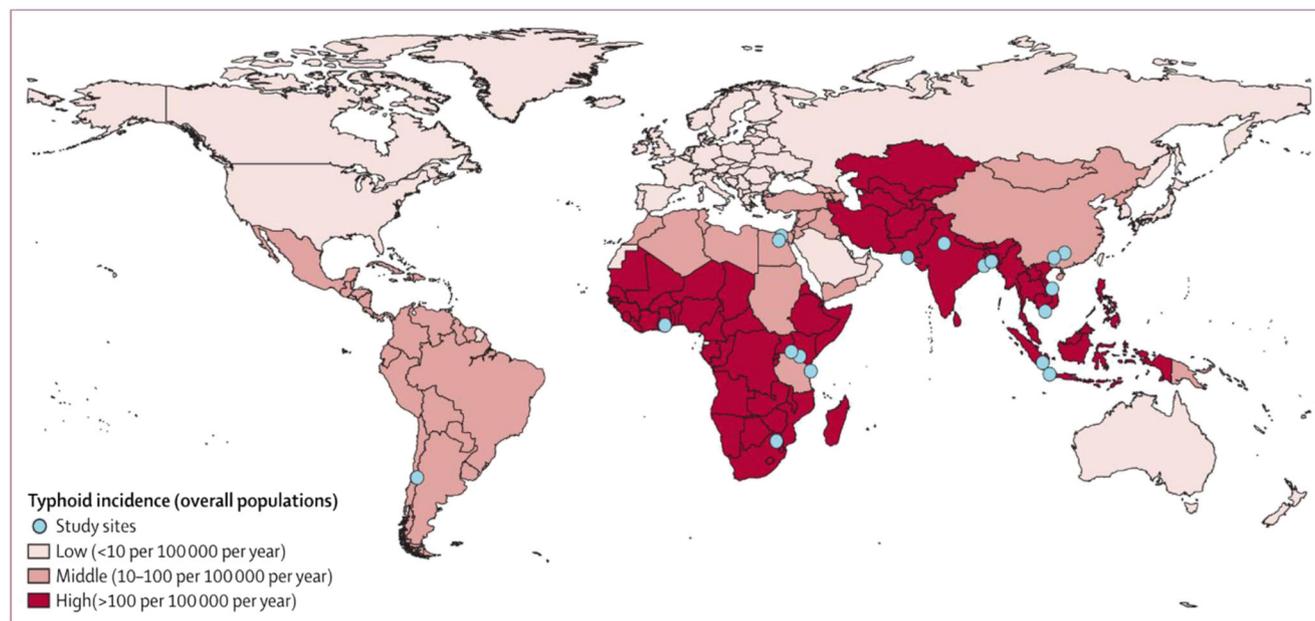


Fig. 2 Typhoid incidence in low-income and middle-income countries (risk-adjusted and corrected for blood culture sensitivity). (Reprinted from The Lancet, Vol. 2, Mogasale, V, Maskery B, Ochiai RL, et al.,

“Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment,” e570-e580, 2014, with permission from Elsevier)

Table 1 Interactions between antimalarial and antiretroviral medications

	Antiretroviral medications that have potential interactions	Effect of interaction
Doxycycline	None	N/A
Malarone (proguanil-atovaquone)	Proguanil—efavirenz Atovaquone—efavirenz, ritonavir	Efavirenz (proguanil): Coadministration of proguanil and efavirenz can reduce exposure of cycloguanil, an active metabolite in proguanil. Efavirenz (Atovaquone): Coadministration may reduce atovaquone plasma concentrations. Ritonavir (atovaquone): Coadministration of atovaquone and lopinavir/ritonavir and atazanavir/ritonavir has resulted in decreased serum concentrations of atovaquone.
Mefloquine Chloroquine	Efavirenz, lopinavir	Efavirenz: Increased risk of QT interval prolongation. Major severity. Lopinavir: Increased risk of QT interval prolongation. Major severity.
Primaquine	None	N/A

primarily transmitted via the fecal-oral route, and hepatitis B being primarily transmitted via blood, and thus both vaccines or documentation of immunity should be considered in people who are traveling.

However, both hepatitis A and B are tested and managed in patients with HIV, so it is likely that those with HIV have been vaccinated already for these diseases. Before traveling, immunocompromised persons should check to ensure that they have the vaccinations and that these vaccinations are documented before traveling.

Malaria

Malaria is transmitted by *Anopheles* mosquitoes in tropical and subtropical areas [1]. Persons infected with HIV traveling to countries where malaria is endemic should take all the usual precautions to prevent transmission of malaria. Malaria symptoms range from mild to severe, from typical fever, sweats, and vomiting, to anemia, low pressure, and acute kidney failure [1]. The likelihood of these more severe symptoms. The severity of malaria increases for those infected with HIV and malaria infection also can increase the HIV viral load [1]. Taking anti-malarial medication is recommended for HIV-infected people traveling to malaria-endemic zones. Some malaria prophylaxis medications may interact with HIV medication. A summary of these interactions is listed in Table 1. Both doxycycline and primaquine have no interactions with antiretroviral medication. Atovaquone-proguanil (Malarone) is generally safe for those on a stable antiviral regimen that does not include efavirenz or ritonavir (often used to boost the protease inhibitors).

Malarone may be more expensive than other anti-malaria prophylaxis options, but is a good choice when traveling last-minute, as malarone treatment is only started a short number of days before travel. Chloroquine and mefloquine are good options for those who want to take a medication only weekly. Primaquine, doxycycline, and malarone are all taken once daily [14]. Doxycycline is recommended to those planning on doing numerous outdoor activities, as it is also a preventative for tick-borne diseases, leptospirosis, and enteric pathogens that may cause diarrhea. Primaquine is considered the most effective drug against *P. vivax* and should be considered when going to a region where *P. vivax* is the predominant strain [14]. Other information regarding benefits and drawbacks to various malarial prophylaxis drugs can be found on the CDC website on Malaria and Travelers [14].

In addition to taking oral preventive malaria prophylaxis, it is important to use appropriate insect precautions to decrease risk of transmission. These strategies include the use of insect repellent on the skin (DEET) and permethrin-treated clothing. Bed nets are also a well-proven strategy for decreasing risk of malaria transmission.

Other Travel Specific Vaccines

There are several other commonly used or exotic vaccines that are also generally safe to use if indicated for patients with HIV infection. These include the Japanese encephalitis, rabies, polio, and meningitis vaccines. These would be given according to the usual schedules based on the itinerary, timing, and indication. Since none of these are live vaccines, there are few contraindications and they can generally be safely used no matter what the CD4 count.

Conclusion

In summary, there has been a multitude of improvements and findings with regard to HIV and various tropical infectious diseases. Because of these changes, it is crucial to stay informed about the latest studies and recommendations in order to properly assess what medications to prescribe and what medications to avoid in HIV-infected individuals, in order to minimize the risk of serious infections and complications. We have reviewed the most recent studies and suggestions in order to optimize safety in HIV-infected travelers.

Compliance with Ethical Standards

Conflict of Interest David Mariano and Darvin Scott Smith declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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