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Yellow Fever: The Resurgence of a Forgotten Disease and HIV-Infected Travellers

Abstract

The actual efficacy and safety of the yellow fever vaccine 17D vaccine in HIV-infected individuals residing in and travelling through yellow fever infected areas has revealed limited and region-confined scientific data. This could lead to enormous challenges to prevent and avoid yellow fever infection and regrettably disease consequences. There still remains a need to investigate the safety and efficacy of the 17D vaccine in immunocompromised individuals. However an emphasis around the indications for yellow fever vaccine in HIV–infected individuals will be highlighted. Yellow fever is a mosquito-borne acute haemorraghic disease with a high case fatality. Millions of HIV-infected individuals are at risk to exposure to yellow fever. Increased yellow fever vaccine coverage campaigns by the World Health Organisation (WH0) are attempting to prevent disease-outbreaks in yellow fever endemic regions and HIV-endemic countries.

Yellow fever virus transmission risk status is endemic in South America and Africa and it can be transmitted within 47 countries. Yellow fever elicits two distinct and actual separate patterns of infection leading to the disease entities called viscerotropism and neurotropism. Yellow fever vaccination is vaccine preventable and the benefits of the vaccine outweigh the associated risks.

An estimated 8% of travellers to the developing world require some form of active or preventative medical treatment before, during and after travel. HIV-infected individuals have been categorised into those with asymptomatic infection and those infected with CD4+ counts between 200-500 microlitres. Concerns remain that the live-attenuated 17D vaccine cannot be given safely to all HIV-infected individuals.

Keywords: Yellow fever; HIV infection; HIV disease; Vaccination; Prevention; Emergency planning; Development of antiviral medication

Review Article

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Introduction

"Alcohol will do much at this (secondary fever) stage; the patient's choice; brandy is the worst form, as it produces hiccough..... gin is the best form, as it may assist the kidneys" [1]. This is quoted from a tome that was recorded in the late eighteenth century on the possibilities of the management of clinical yellow fever and could be the early evidence of public health medicine and prevention.

Yellow fever is described as an acute infection but there is limited data on yellow fever and human immunodeficiency virus (HIV) co-infection. Yellow fever is a mosquito-borne acute viral haemorraghic disease with a high case fatality rate [2]. It is the first virus which was shown to be transmitted by an arthropod and this virus infects humans, non-human primates and several diverse species of mosquitoes [3] (Table 1). Millions of HIV-infected individuals are at risk and at potential risk to becoming infected with yellow fever described globally as a severe haemorraghic disease which is endemic to tropical areas of Africa and South America [4]. Increased vaccine coverage campaigns guided by the World Health Organisation (WHO) are attempting to prevent disease-outbreaks in yellow fever endemic regions and HIV-endemic countries [5]. Data regarding the safety and immunogenicity of the yellow fever vaccine 17D in HIV-infected individuals is also extremely limited and often involves small studies [6]. In addition data about the actual efficacy and usage of the yellow fever 17D vaccine in HIV-infected individuals residing and moving within yellow fever endemic areas is missing within the scientific literature and this could lead to enormous challenges for mass immunisation campaigns to prevent yellow fever infection and fatal disease [7]. There remains a need to investigate the safety and efficacy of the 17D vaccine in HIV-infected individuals.

An estimated 8% of travellers to areas within developing countries require intense medical treatment during and even after travel [8]. As a summary, HIV-infected patients are travelling more often, directly attributed to health improvement as a result of recent antiretroviral drug regimens especially over the last decade [9]. However in the HIV-infected population, safe travel interventions are essential to avoid and prevent common and serious infections. This article will have an emphasis on the HIV-infected traveller and highlight updates on yellow fever disease. The indications for and issues around yellow fever vaccination in HIV-infected individuals will be discussed.

Table 1: Differential Diagnosis in a Patient Presenting with Jaundice in a Yellow Fever Endemic Region [3].

Viral Haemorrhagic Fevers	Dengue Haemorrhagic Fever
	Rift Valley fever
	Venezuelan Haemorrhagic Fever
	Bolivian Haemorrhagic Fever
	Argentinian Haemorrhagic Fever
	Lassa Fever
	Crimean-Cong0 Fever
	Marburg Disease
	Ebola Disease
Viral Hepatitis	Hepatitis A
	Hepatitis B
	Hepatitis C
	Hepatitis E
Retrovirus	HIV/AIDS* (Advanced Disease)
Viral Febrile Syndromes	Influenza
	Chikungunya Fever
	Dengue Fever
Other (A Few Examples)	Malaria
	Typhoid
	Toxic Hepatitis
AIDS* Acquired Immunodeficiency Syndrome	

Yellow Fever – The Resurgence of a Forgotten Disease

It could be that yellow fever may be commonly forgotten for some of the following reasons, namely:

I. It may not be as important as malaria

II. It may not be as fearful for communities and families as Ebola disease;

III. And it may not be as shunned as elephantiasis [10].

Yellow fever disease was successfully eliminated globally by vector-control campaigns in the 1940s and 1950s but has recently resurged within re-defined borders [10]. Vaccination and mosquito control are the pillar stones of the public health approach to yellow fever prevention and it can be clearly stated that it is unacceptable for any individual to die from yellow fever disease [11]. The virus is a small (50 nanometres - nm in diameter), enveloped RNA virus. The African strains have altogether seven genotypes [12].

Yellow fever virus transmission risk status currently is endemic in South America and Africa and it can be transmitted within 47 countries [13]. Yellow fever epidemiology can be described according to the two continents, namely:

1. Africa: infants and children are at highest risk for disease and there is an increased of transmission at the end of the rainy season and the beginning of the dry season which is from July until October months.

2. South America: the risk of transmission is more frequent in unimmunised young men who are exposed when working in the forested areas. There is an increased risk in the rainy season which is from January until May months [3,13].

There have been dramatic resurgences in yellow fever since the 1980s, such as a series of epidemics and smaller outbreaks in South America and sub-Saharan Africa [10,14]. In the late 1990s and the early 2000s Brazil then prompted mass 17D vaccination campaigns [13]. In the 2000s West Africa observed waning immunity to 17D and this was from the previous immunisation campaigns which ended in 1960s [15]. This resulted in two generations of people never have been immunised. A number of determinants for yellow fever resurgence can be explained within socio-economic and environmental conditions namely:

a. Redirection of resources;

b. Rapid African urbanisation;

c. Migration from rural areas;

d. Easy population movement such as pathogens, hosts and vectors moving around;

e. Poor sanitation;

f. Climate changes and

g. Deforestation [10,11].

The role of the host cannot be underestimated in resurgence as it depends on the density of non-immune individuals as well as their susceptibility in terms of not-vaccinated or waned immunity [10,11]. The vector is critically important and has the following determinants namely:

A. The distribution and abundance thereof;

B. The biting rates;

C. The development and survival of the virus within the vector and resultant heavy infestations as mosquitoes adapt to urban life [10,11].

Treatment is poorly represented as the vaccine uptake can be poor or limited, there are no antiviral against yellow fever and most insecticides are not effective. The incubation period clinically is short usually between 3-6 days and the clinical course can lead to multi-organ involvement and shock [2,13]. A clinical differential diagnosis is presented in Table 1 [3].

As noted above yellow fever causes a systemic illness characterised by a high viraemia, hepatic, renal and myocardial pathology, massive haemorrhaging and lethality is a common outcome. Yellow fever although similar to other viral haemorrhagic syndromes, in particular causes severe injury to the liver and the pathogenesis appears to be different from the other described viral hepatitides [16]. Although the yellow fever virus was first isolated way back in 1927 and the complete gene sequence was reported in 1985, the actual knowledge of the viral pathogenesis remains limited and possibly obscure as observed namely:

a) The viral pathogenesis is not fully understood;

b) The host pathology remains in a descriptive phase only;

c) Data from the host changes and response to the viral infection are fragmented;

d) The complex pathophysiological changes and consequences have not been totally revealed and

e) The primary or actual cause of death is largely unknown and not well documented [16].

Virus-specific virulence factors play a significant role in the pathogenesis of yellow fever. Thus yellow fever elicits two distinct and actual separate patterns of infection leading to the disease entities called “viscerotropism” and “neurotropism” [16]. Viscerotropism includes both pathological and physiological injuries to the liver, spleen, heart and kidneys [16]. Neurotropism describes how the yellow fever virus infects the brain parenchyma hence causing encephalitis. These two pathophyssiological entities are illustrated in (Table 2) [16].

Table 2: The Comparison between Yellow Fever Patterns of Pathology Namely Viscerotropism and Neurotropism [16].

	Organs Affected
Viscerotropism*	Liver
	Spleen
	Heart
	Kidneys
Neurotropism**	Neurological Damage
	Brain Parenchyma Infection
	Encephalitis

*Viscerotropism is the way the virus infects and damages the extraneural organs.

**Neurotropism is the viral infection of the brain.

At a molecular level the envelope (E) protein of the virus is the most important determinant for the cell tropism, virulence and immunity [17-20]. Many mutations took place during the >230 passages of the live attenuated yellow fever 17D vaccine [18].

There is a comparison between yellow fever pathogenesis and prevention and the understanding of HIV pathogenesis and developments in the HIV vaccine arena, namely:

a) The pathophysiology of yellow fever disease is complex and scientific data is limited and more literature studies are required;

b) The pathophysiology of HIV infection has multi-organ involvement and scientific data is comprehensive yet still evolving with regular publications;

c) The yellow fever 17D vaccine is successful and its efficacy has been proven scientifically and

d) The race and struggle to discover and test for an effective HIV vaccine is still ongoing [21].

Vaccines for HIV-Infected Travellers

An estimated 8% of travellers to the developing world require some form of active or preventative medical treatment before, during and after travel [22,23]. The major diseases including vaccine-preventable diseases as well as diarrhoeal infections and malaria are listed in (Table 3) [22].

Table 3: Selected Major Vaccine-Preventable Diseases for HIV-Infected Travellers [22].

Vaccines	Hepatitis A Virus
	Yellow Fever*
	Malaria
	Diarrhoeal Illnesses
Diarrhoeal Illnesses: (A Few Common Examples)	*Salmonella sp*
	Campylobacter sp
	Giardia sp
	*E. coli sp***
	Rotaviruses
	Noroviruses

*Yellow fever is transmitted by mostly by the *Aedes aegypti* mosquito which is an aggressive biter during the daytime.

***E.coli* = *Escherichia coli*, the enteroaggregate strain is an emerging enteric pathogen

Overall for the purposes of vaccination in HIV-infected travellers two categories were proposed by the referenced author namely asymptomatic HIV infection and these HIV-infected with CD4+ cell counts of 200-500 microlitres [22]. These were considered to be immunodeficient [22]. In the travellers categorised with asymptomatic/limited immunodeficiency, it has been observed that the response to vaccines in the form of the antibody titre levels may be lower in HIV-infected individuals [24]. Currently the actual CD4+ cell counts are measured to determine the individual's immune status [24].

Differently, when compared to yellow fever HIV can infect a wide range of human cells, namely:

a. CD4+ T-lymphocytes;
b. Monocytes/macrophages;
c. Langerhan's cells of the skin;
d. Megakaryocytes;
e. Astrocytes and oligodendrocytes;
f. Endothelial cells;
g. Colorectal cells;
h. Cervical cells;
i. Retinal cells;
j. Renal epithelial cells and
k. Pulmonary macrophages [25].

There is a complex and vigorously active response by the host to HIV infection. It involves cellular and humoral immunity but does not contain viral replication. This is in direct comparative contrast to the known current facts of yellow fever immunopathogenesis. The general immune response to HIV occurs in these following steps, namely:

a) Antibodies to HIV usually appear within 2-12 weeks in the primary infection and they also recognise the envelope protein (ENV) – this is similar to the envelope response noted in yellow fever infection;

b) Potentially protective antibodies are neutralising antibodies;

c) CD8+ cells appear to play a major role in the initial containment of HIV viral replication;

d) CD4+ T-cells appear to be important in the initial help for CD8+ T-cell responses;

e) A viral set point, namely the dynamic equilibrium between the production and clearance of viral particles by the host immune system, is considered to be a balance between viral replication and the complex host immunity [26].

Table 4 lists the anatomical and cellular reservoirs of HIV [27,28,29]. Unlike yellow fever there is effective highly active antiretroviral therapy for HIV infection and this has caused suppression of HIV replication. However a reservoir of HIV persists in a long-lived latent state [30].

Yellow Fever Vaccination in HIV-Infected Individuals

WHO recommends that all individuals who are older than 9 months living or travelling in areas and regions where there is a risk of yellow fever transmission should be vaccinated [31]. However, as the yellow fever vaccine is categorised as a live attenuated vaccine it is contraindicated in individuals who are severely immunocompromised [32].

Table 4: The List of Anatomical and Cellular Reservoirs in the Human Host Infected with HIV [27-29].

Anatomical Reservoirs	Peripheral Blood
	Lymphoid Tissues
	Central Nervous System
	Skin
	Adipose Tissue
	Liver
	Spleen
	Lungs
	Genital Tract (Male, Female)
	Placenta
	Breast Milk
	Thymus
Cellular Reservoirs*	Latently Infected Memory T Cells
Non-Memory T Cells	T helper cells
	Hematopoietic precursor cells
	Innate immune cells
	Follicular dendritic cells

The live attenuated 17D vaccines against yellow fever were developed in 1936 and comprised 2 different sub strains, namely 17DD-Brazil and 17D 204 from another manufacturer [33]. These vaccines have been responsible for a significant reduction in yellow fever disease occurrences worldwide. The vaccine produces high levels of protection and one dose can confer protection for at least 10 years and possibly lifelong [34]. The recommended dose is 0.5ml subcutaneously which is equivocal to 1000 IU (international units) [34]. The vaccine is a travel-recommended vaccine, is part of the EPI (Expanded Programme of Immunisation) and is used for mass-campaign vaccinations globally. There are guidelines for yellow fever recommendation in Africa but the re-vaccination/booster dose after 10 years is currently controversial [35]. The yellow fever vaccine contraindications are listed in Table 5 [33]. There are also practical measures to prevent mosquito bites, such as the use of an effective insect repellent, wearing protective clothing, and staying in screened and air-conditioned rooms.

Table 5: Yellow Fever Vaccine Contraindications [33].

Absolute	Relative
Allergy to the Vaccine Egg Components	Age >60 Years
Age <6 Months	Age 6-8 Months
Primary Immunodeficiency	Pregnancy and Breastfeeding
Thymus Removed or Disorder	Asymptomatic HIV Infection
Symptomatic HIV Infection	CD4+ Count 200-499
CD4+ Count <200	Neoplasms
Immunosuppressive Therapies	Transplantation Recipients

Published studies on the safety and immunogenicity of yellow fever vaccines in HIV-infected individuals are extremely limited to a number of small-volume studies. This also includes a small number of case reports often describing travellers with a high CD4+ count >200 cells [31]. In addition limited data about the safety of the yellow fever vaccine in individuals with advanced HIV disease has been recorded [31]. However, on a positive note, consistent immunogenicity has been shown in HIV-infected individuals with a higher CD4+ cell count >200 cells [31]. It has also been noted that the protective effects of the yellow fever

vaccine wore off more quickly in the HIV-infected people [32]. Recommendations are that HIV-infected individuals should be vaccinated and included in the population receiving yellow fever mass vaccination. However additional data on the safety and immunogenicity should be obtained on the of vaccination actual effects, This applies especially to those individuals with advanced HIV disease [31,32].

Conclusion

Yellow fever infection is vaccine preventable and definitely the benefits of the vaccine outweigh any associated risks. However vaccination coverage of yellow fever in endemic countries is probably below 80% of the population which implies that the herd immunity is not reached. More funding is required to avert yellow fever outbreaks. In addition, the vaccine supply needs to be increased, there is a need for the development of antivirals, there is another need for improved surveillance in endemic countries and better emergency planning needs to be implemented.

The benefits of yellow fever mass vaccination is well recognised in endemic countries and millions of individuals are vaccinated every year. This occurs in countries where the prevalence of HIV can be between 1-5%, even higher in selected countries. It must be taken into account that access to laboratory testing and other resources for diagnosing and treating HIV-infection is extremely scarce. Of note is that many individuals with undiagnosed advanced HIV/AIDS disease have already received the yellow fever vaccine. Concerns remain that the live-attenuated 17D vaccine cannot truly be given safely to HIV-infected individuals and there is a possibility that this weakened 17D viral strain could begin to replicate.

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