Immunogenicity and Safety of Yellow Fever Vaccination for 102 HIV-Infected Patients

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Background. Yellow fever vaccine (17DV) has been investigated incompletely in human immunodeficiency virus (HIV)–infected patients, and adequate immunogenicity and safety are of concern in this population.

Methods. In the Swiss HIV Cohort Study, we identified 102 patients who received 17DV while they were HIV infected. We analyzed neutralization titers (NTs) after 17DV administration using the plaque reduction neutralization test. NTs of 1:≥10 were defined as reactive, and those of 1:<10 were defined as nonreactive, which was considered to be nonprotective. The results were compared with data for HIV-uninfected individuals. Serious adverse events were defined as hospitalization or death within 6 weeks after receipt of 17DV.

Results. At the time of 17DV administration, the median CD4 cell count was 537 cells/mm^3 (range, 11–1730 cells/mm^3), and the HIV RNA level was undetectable in 41 of 102 HIV-infected patients. During the first year after vaccination, fewer HIV-infected patients (65 [83%] of 78; $P = .01$) than HIV-uninfected patients revealed reactive NTs, and their NTs were significantly lower ($P < .001$) than in HIV-uninfected individuals. Eleven patients with initially reactive NTs lost these reactive NTs ≤5 years after vaccination. Higher NTs during the first year after vaccination were associated with undetectable HIV RNA levels, increasing CD4 cell count, and female sex. We found no serious adverse events after 17DV administration among HIV-infected patients.

Conclusion. Compared with HIV-uninfected individuals, HIV-infected patients respond to 17DV with lower reactive NTs, more often demonstrate nonprotective NTs, and may experience a more rapid decline in NTs during follow-up. Vaccination with 17DV appears to be safe in HIV-infected individuals who have high CD4 cell counts, although rate of serious adverse events of up to 3% cannot be excluded.

Yellow fever is a severe arthropod-borne hemorrhagic fever that is endemic in many countries in sub-Saharan Africa and South America, with an estimated 200,000 cases occurring annually and a case-fatality rate of 20%–50% [1, 2]. It can be effectively prevented with administration of the live, attenuated 17D yellow fever vaccine (17DV) [3]. The prevalence of HIV infection is high in many countries where yellow fever is endemic.

Data about the immunogenicity and safety of 17DV vaccination in HIV-infected individuals are limited to case reports or small series [4–11]. In areas where outbreaks of yellow fever occur, mass immunization against yellow fever—including immunization of many HIV-infected individuals—is problematic without data about safety and immunogenicity. In addition to this public health problem in countries with epidemic yellow fever, administration of 17DV to HIV-infected travelers from western countries is of concern: since the introduction of combination antiretroviral therapy (cART), the health and immune status of HIV-infected patients have improved, resulting in an increase in travel. In the Swiss HIV Cohort Study (SHCS), the percentage of HIV-infected individuals who traveled to tropical countries at least once increased from 13% during 1988–1999 [12] to 29% in the current study. In a single-center survey, 55% of HIV-infected travelers

had visited countries where yellow fever is endemic [13].

Although 17DV is generally considered to be safe, rare severe adverse events (SAEs), including yellow fever vaccine–associated viscerotropic and neurotropic disease, and deaths have occurred [14–19]. The incidence of SAEs after 17DV administration in HIV-infected patients is unknown. Thus far, to our knowledge, only 1 fatal case of neurotropic disease has been reported after administration of 17DV to an HIV-infected patient [6].

We investigated the immunogenicity and the safety of 17DV in HIV-infected patients in the SHCS for the following reasons: (1) to determine the primary immune response, (2) to observe the antibody titer in HIV-infected individuals, (3) to investigate predictive factors of adequate antibody response to 17DV, (4) to compare the yellow fever immune response in HIV-infected versus HIV-uninfected individuals, and (5) to analyze the incidence of SAE after administration of 17DV in HIV-infected patients. We hypothesized that, in the era of cART, the immunogenicity and safety of 17DV in HIV-infected individuals would be similar to that in the general population of travelers.

METHODS

Patients. The SHCS (http://www.shcs.ch) is a prospective cohort study based on 7 health care centers in Switzerland [20]. Information is collected according to standardized criteria on structured forms at enrolment and at 6 monthly follow-up visits and includes information about travels to tropical countries. At these occasions, plasma samples are obtained and stored at −70°C for every patient. All participants provide written informed consent. SHCS has been approved by all appropriate local ethics committees.

Four of the 7 SHCS centers participated in the present study. We identified SHCS participants who had reported a journey to a tropical destination during the period 1 January 1996 through 31 August 2005. These individuals were asked either during consultation, by phone, or on questionnaires or chart reviews about their travel destinations in the past and whether they had received 17DV. In the case of a reported travel to a country where yellow fever is endemic, the vaccine certificate and the medical charts were checked for 17DV, and travelers who had received at least 1 dose of 17DV were enrolled in the study. Patients were grouped according to whether 17DV had been administered before or after diagnosis of HIV infection. Patients who had been vaccinated ≤1 year before documentation of HIV infection were classified as being HIV infected unless there was documented seroconversion within that year. The day that 17DV was administered was the baseline time point. If a patient had received >1 dose of 17DV, the date of the last vaccination was determined as baseline.

To define predictors to vaccine response, baseline characteristics were collected from the SHCS database and medical charts. Baseline laboratory markers within 1 year before or after 17DV administration were accepted. Medical history was checked for concomitant immunosuppressive medication at the time and until one month after 17DV. The vaccination card was checked for other concomitant live vaccines given at the time until 1 month after receipt of 17DV. The data for these HIV-infected vaccinees were compared with serologic data for a group of 209 HIV-uninfected individuals who had received 17DV and who were investigated in 1999 with the same laboratory method [21]. The raw data from this comparison group were available for the analysis. This group did not differ in age from our study population. Additional characteristics were not available for this comparison group.

Determination of yellow fever neutralization titer (NT). The analysis of human plasma or serum for the yellow fever NT was performed at the Robert Koch Institute (Berlin, Germany) using the plaque reduction neutralization test, as described elsewhere [22]. All plasma samples were assayed twice and in 2-fold dilutions (range, 1:10–1:320 NTs for the final dilutions). The plaques caused by lysis of infected cells were counted, and the 90% NT was calculated. According to the study by Niedrig et al. [21], NTs of 1:≥10 are defined as reactive, and those of 1:<10 are defined as nonreactive, which was considered to be nonprotective. The decrease in NTs was modelled as $\log_{10}$ of the reciprocal NT over time. NTs were analyzed in the following defined time periods: (1) for the primary immune response, between 1 month and 1 year after vaccination; (2) 1–10 years after vaccination; and (3) >10 years after vaccination, if the corresponding plasma sample was available (figure 1). In the comparison group of HIV-uninfected individuals, serum samples were collected only once per individual (range, 0.01–37.5 years after vaccination) [21].

Safety. SAE was defined as hospitalization or death ≤6 weeks after receipt of 17DV, with no explanation other than
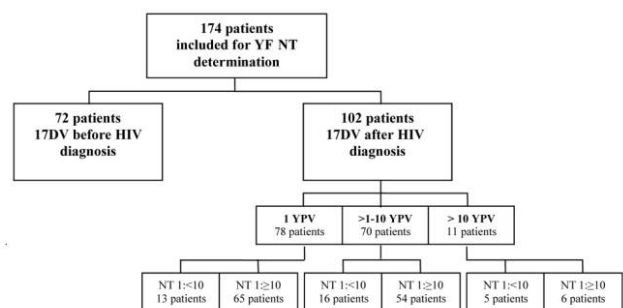
Figure 1. Study design. Only the 102 patients who were vaccinated after HIV infection had been diagnosed were included in the study. Patients with reactive neutralization titers (NTs) were included in >1 category of this figure. Patients with nonreactive NTs are shown only in the time category, when the first nonreactive NT had occurred. 17DV, yellow fever vaccination; YPV, years after vaccination.

vaccination. The medical charts for all deceased patients during the study period were checked for any correlation of death to 17DV receipt or any SAE. In addition, the Swiss vaccination surveillance system was queried for any SAEs that occurred after 17DV administration in HIV-infected individuals.

Statistical analysis. Univariable analysis was performed using nonparametric tests for numerical variables and the χ^2 test for categorical variables. Logistic regression was used for univariable and multivariable analysis to investigate parameters associated with nonreactive versus reactive NTs during the first year after vaccination. Linear regression was used for univariable and multivariable analysis of parameters associated with the value of NT. The multivariable regression models included HIV RNA levels <50 copies/mL as a binary variable and CD4 cell count at time of receipt of 17DV, age, sex, chronic hepatitis B or C virus infection, and receipt of yellow fever vaccine at least once before the current vaccination. Square-rooted CD4 cell counts were implemented in the regression models. Analyses were conducted using Stata software, version 9.0 (Stata).

RESULTS

In the study period, 2648 (29%) of the 9181 SHCS participants traveled at least once to a tropical country. Among those, 868 travelers (33%) were observed at the 4 investigating centers. One hundred seventy-two travelers (20%) were excluded because no reliable information was available, and 696 travelers (26% of the SHCS travelers) were evaluated for 17DV. A total of 174 recipients of 17DV were identified: 102 patients had received 17DV after and 72 had received 17DV before HIV infection was documented (figure 1). Unless otherwise indicated, we will focus below on the 102 patients who received 17DV while being HIV infected.

Characteristics of the 102 HIV-infected patients at the time of 17DV are shown in table 1. Study patients were more likely to be female, black, and originally from sub-Saharan Africa and were less likely to have chronic hepatitis B or C and injection drug abuse as a mode of HIV transmission, compared with nontravelers in the SHCS. None of the study participants had taken immunosuppressive therapy at the time of 17DV vaccination. The majority of the patients (83%) were primary vaccinees, and 71% had been vaccinated with the 17DV manufactured by Aventis Pasteur (Stamaril). Plasma or serum specimens for NT analysis were available for 78 patients within 1 year after vaccination, for 70 patients 1–10 years after vaccination, and for 11 patients >10 years after vaccination (figure 1). Among HIV-uninfected persons, serum samples were available for 66 individuals within 1 year after vaccination, for 92 individuals 1–10 years after vaccination, and for 51 individuals >10 years after vaccination.
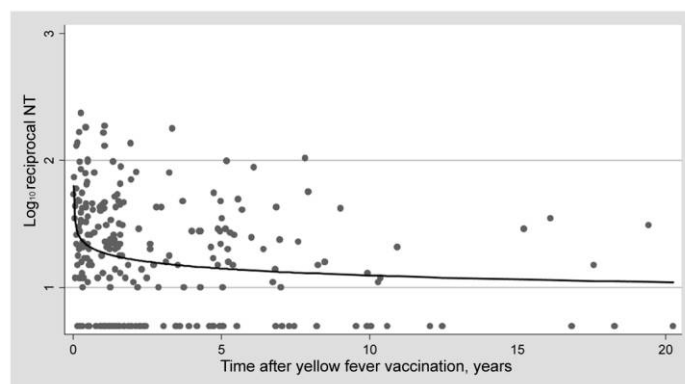
Immunogenicity. The NT decay pattern of our study population (figure 2) was similar to that of HIV-uninfected individuals. However, within the first year after vaccination, a significantly greater proportion of HIV-infected patients (13 [17%] of 78) had nonreactive NTs, compared with HIV-uninfected vaccinees, for whom nonreactive NTs were found in 2 (3%) of 66 individuals (figure 3). An even higher proportion of persons with nonreactive NTs (19%) was seen among the 63 patients who had been vaccinated for the first time against yellow fever ($P = .004$, compared with HIV-uninfected individuals). The proportion of HIV-infected patients with nonreactive NTs increased from 17% to 23% during the time period of 1–10 years after vaccination (figure 3). In addition, HIV-infected patients had significantly lower NTs than did HIV-

Table 1. Baseline characteristics of study patients.

Characteristic	Value (n = 102)
Age, median years (IQR)	34.7 (28.1–41.5)
Female sex	48 (47)
Region of origin	
Europe or North America	59 (58)
Sub-Saharan Africa	41 (40)
South America	1 (1)
Other	1 (1)
Mode of HIV transmission	
Heterosexual sexual contact	63 (62)
Male-male sexual contact	22 (22)
Injection drug use	8 (8)
Other or unknown	9 (9)
CDC HIV infection category	
A	71 (70)
B	24 (24)
C	7 (7)
CD4 cell count	
Median cells/mm^3 (range)	512 (368–664)
Missing data	16 (16)
<200 cells/mm^3	7 (7)
200–349 cells/mm^3	13 (13)
350–499 cells/mm^3	22 (22)
>500 cells/mm^3	44 (43)
Nadir CD4 cell count	
Median cells/mm^3 (IQR)	280 (163–469)
Missing data	15 (15)
HIV RNA level <50 copies/mL, *n/N* (%)	41/84 (48)
Missing data on HIV RNA level	18 (18)
Receipt of triple-drug ART	41 (40)
Chronic hepatitis B or C	19 (19)
Interval between receipt of 17DV and diagnosis of HIV infection, median years (IQR)	3.0 (0.8–8.4)
Receipt of 17DV ⩾2 times	17 (17)

NOTE. Data are no. (%) of patients, unless otherwise indicated. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; 17DV, yellow fever vaccine.

Figure 2 All neutralization titers (NTs) for patients vaccinated against yellow fever after diagnosis of HIV infection, with the fractional polynomial prediction line. NTs measurements were performed at least once; in some patients, they were performed up to 4 times.

uninfected individuals, both within the first year after vaccination and thereafter (figure 4).

Baseline parameters associated with primary immune response. The 78 patients who underwent NT evaluations during the first year after receipt of 17DV were analyzed for baseline parameters predicting vaccination response. In these patients, the median baseline CD4 cell count was 496 cells/mm^3 (range, 72–1730 cells/mm^3). More than three-quarters (77%) had CD4 cell counts >350 cells/mm^3, and only 6 of the 78 patients had CD4 cell counts <200 cells/mm^3. In 37 patients (48%), HIV RNA levels were <50 copies/mL. There was no statistically significant predictor of reactive ($n = 65$) versus nonreactive NT ($n = 13$); however, patients who were receiving successful cART had an OR of 2.5 (95% CI, 0.7–8.8; $P = .17$). Of the 6 vaccinated patients with CD4 cell counts <200 cells/mm^3, 2 did not develop reactive NTs.

Suppressed plasma HIV RNA levels, higher CD4 cell counts, female sex, absence of chronic hepatitis, and older age had a statistically significant association or showed a trend toward higher NTs during the first year after vaccination (table 2). In addition, suppressed HIV RNA level and higher CD4 cell count at the time of first NT determination were associated with a better primary immunological response ($P = .006$ and $.02$, respectively).

"Losers and winners." Eleven patients who received 17DV after HIV infection had been diagnosed initially had reactive NTs but were revealed to have nonreactive NTs <5 years after vaccination (median, 1.8 years after vaccination; range, 0.9–5.1 years after vaccination). Only 1 of these patients had an undetectable HIV RNA level at the time of receipt of 17DV, and the HIV RNA level was not suppressed in 8 patients when the follow-up nonreactive NTs were determined.

Four of the 102 HIV-infected patients had nonreactive NTs at first analysis but were revealed to have reactive NTs during follow-up. This phenomenon was also seen in 6 patients who had received 17DV before HIV infection was documented.

Seven of these 10 patients had detectable HIV RNA levels (range, 439–894,246 copies/mL) at the time that nonreactive NTs were noted. At the time that reactive NTs were noted during follow-up, however, 5 of these 7 patients had undetectable HIV RNA levels.
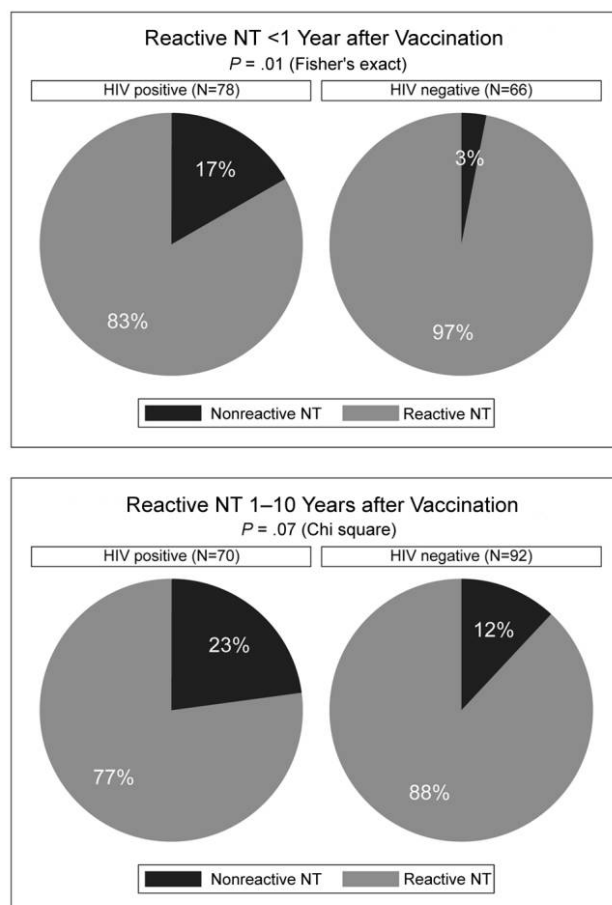
Figure 3. Neutralization titer (NT) ⩽1 year *(upper panel)* and 1–10 years after *(lower panel)* yellow fever vaccination.
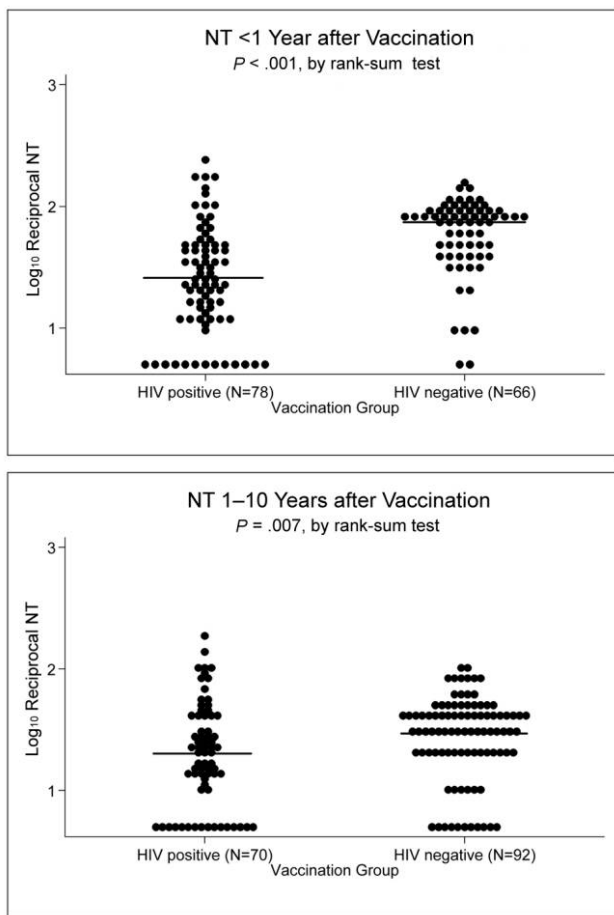
Figure 4. Value of neutralization titer (NT) ≤1 year *(upper panel)* and 1–10 years after *(lower panel)* yellow fever vaccination. *Horizontal line,* median value.

Safety. We found no SAEs related to 17DV administration in the 102 individuals who were vaccinated after HIV had been diagnosed, corresponding to an estimated rate of 0%, with an upper 95% confidence limit of 2.9%. The 48 deaths that occurred during the study period in the traveling population, including the 3 deaths in the 17DV-vaccinated population, were clearly not associated with 17DV. No SAEs related to 17DV among HIV-infected individuals were reported to the Swiss vaccination surveillance program.

DISCUSSION

In the current analysis, we show that the immunogenicity of 17DV is impaired in HIV-infected individuals. We did not observe SAEs associated with the vaccine in our study population of patients, who predominantly had mild to moderate immunodeficiency.

Immunogenicity of 17DV. Immune response to killed or inactivated vaccines is impaired in HIV-infected patients, especially if their CD4 cell counts are <350 cells/mm³ [23–28].

However, data regarding immune response to live, attenuated vaccines are limited. Asymptomatic HIV-infected children receiving cART demonstrated an adequate immune response to rubella, measles, and mumps vaccination [29, 30].

Impaired vaccine response may be explained by the aberrant activation of B cells in replicating HIV infection [31], an impaired T-helper response, and cellular mediated immunity [22]. By reducing immune activation and improving T-helper response, cART may be associated with improved vaccine response [32].

In HIV-infected patients, the immunogenicity of 17DV has been reported only in small series, and the results are controversial. Protective yellow fever NTs were found in all of 12 HIV-infected individuals with CD4 cell counts of 240–1300 cells/mm³ [9]. By contrast, in the era before introduction of cART, reactive antibody titers were found in 27 of 31 HIV-infected adults with CD4 cell counts >200 cells/mm³ and in only 3 of 18 vaccinated, asymptomatic HIV-infected children [4, 8]. In a recently published study, 4 of 11 HIV-infected travelers with CD4 cell counts >200 cells/mm³ had nonreactive NTs after receipt of primary 17DV, and all 4 patients showed reactive NTs after receipt of a second dose of 17DV [11].

In our study, patients who had been vaccinated after they had learned of their HIV seropositivity were less likely to show a reactive immune response to 17DV ≤1 year after vaccination, and their reactive NTs were lower than in HIV-uninfected vaccinees. In addition, 11 patients with initially reactive NTs had nonreactive NTs in later samples, pointing toward a more pronounced decline. One to 10 years after vaccination, the NTs in HIV-infected individuals were significantly lower than in HIV-uninfected individuals, and the proportion of individuals who lacked a reactive immune response to 17DV (23%) was double that of HIV-uninfected vaccinees. This difference did not achieve full statistical significance ($P = .07$), probably because, in the HIV-uninfected group, the proportion of nonresponders (12%) was higher than has been reported in previous studies, which have reported reactive immune responses in 92%–97% of persons [33, 34].

Predictors of vaccine response. The logistic model for achievement of reactive NTs did not reveal statistically significant predictors. However, the point estimates tended to show a better response in patients who were receiving successful cART. This effect was reinforced by the linear regression model of NT, in which HIV RNA levels <50 copies/mL and higher CD4 cell counts at the time of 17DV administration were associated with a better primary immune response. In addition, suppressed plasma HIV RNA levels and higher CD4 cell counts at the time of NT determination were highly associated with a better vaccine response. A subgroup of patients with initially nonreactive NTs had reactive NTs during follow-up, after they commenced cART and had consecutive undetectable HIV RNA

Table 2. Linear regression model of neutralization titer levels and baseline parameters.

Characteristic	Univariable analysis		Multivariable analysis	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
HIV-RNA level, <50 copies/mL	0.24 (0.04–0.43)	.02	0.18 (−0.01 to 0.38)	.06
CD4 cell count (square rooted)	0.02 (0.00–0.04)	.04	0.02 (0.00–0.04)	.04
Nadir CD4 count before receipt of 17DV	−0.01 (−0.02 to 0.01)	.4	…	
Receipt of triple-drug ART	0.18 (−0.02 to 0.38)	.07	…	
CDC HIV infection classification (B/C vs. A)	0.02 (−0.19 to 0.23)	.8	…	
Age (per 10-year increase)	0.09 (0.00–0.19)	.05	0.08 (−0.02 to 0.19)	.1
Female sex	0.15 (−0.05 to 0.35)	.2	0.22 (0.03–0.42)	.03
Chronic hepatitis B or C	−0.16 (−0.42 to 0.11)	.2	−0.22 (−0.47 to 0.03)	.08
Originally from country where yellow fever is endemic	0.14 (−0.06 to 0.34)	.2	…	
Receipt of 17DV twice (compared with receipt of 17DV once)	0.07 (−0.19 to 0.32)	.6	0.05 (−0.22 to 0.32)	.7
Other live vaccine used	−0.05 (−0.23 to 0.14)	.6	…	

NOTE. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; 17DV, yellow fever vaccine.

levels—a phenomenon that, to our knowledge, has never before been described. By contrast, most of the 11 patients who experienced a rapid decline to nonreactive NTs ≤5 years after vaccination did not take cART, and their HIV RNA levels were not suppressed at the time that they received 17DV. These findings indicate that successful cART leading to suppression of HIV replication and decreasing chronic immune activation improves the initial response to 17DV and is associated with durability of reactive titers during follow-up.

In our study, female subjects developed higher NTs than did male subjects. This finding requires confirmation, because it is in contrast to previous studies, which have reported better immune responses after receipt of 17DV in HIV-uninfected male subjects [35], and a recently published study reported no sex-based differences [36].

In summary, in our study, markers of lower HIV replication and less profound immunodeficiency were associated with a better immunologic vaccine response. However, as in smaller studies, we could not define a threshold CD4 cell count that was predictive of a protective vaccine response with high certainty.

Safety. Life-threatening 17DV-associated viscerotropic and neurotropic disease have occurred in HIV-uninfected individuals [14–19], with an estimated incidence of 1 case per 400,000 doses of yellow fever vaccine [17]. Because the incidence of viscerotropic and neurotropic disease among immunocompromised individuals is unknown, the safety of 17DV in HIV-infected patients is of special concern. One report from Thailand described a fatal case of meningoencephalitis that occurred shortly after yellow fever vaccination in an adult with previously undiagnosed HIV infection and a CD4 cell count of 108 cells/mm^3 [6]. By contrast, serious adverse reactions were not observed in 100 asymptomatic HIV-infected military employees who received yellow fever vaccination before the introduction of routine HIV screening [10], in 31 HIV-infected patients

before the availability of cART [4], and in 32 HIV-infected patients from 4 studies conducted during the cART era [5, 7, 9, 11]. On the basis of these limited data, most experts recommend consideration of 17DV for HIV-infected patients at true risk if the CD4 cell count is >200 cells/mm^3 [37].

In the present study, we found no SAEs after receipt of 17DV in 102 HIV-infected participants. More than three-quarters of these patients had CD4 cell counts >350 cells/mm^3 at the time of vaccination, and only 7 patients had CD4 cell counts <200 cells/mm^3 at the time of vaccination. Because no SAEs occurred among the 102 yellow fever vaccinees after HIV infection had been diagnosed, we could exclude an incidence higher than 3% at the 95% confidence level. Our findings are, therefore, in line with current recommendations. However, the number of studied HIV-infected individuals, including those in our study, is too small to exclude a low but relevant risk of SAE, even among patients without moderate-to-severe immunodeficiency. Therefore, careful obtainment of prevaccination information and postvaccination surveillance are indicated for all HIV-infected patients receiving 17DV.

Limitations of the study. The main limitation of this study is its retrospective design in a prospective cohort. This did not allow systematic determinations of NT after 17DV. Our comparison group, which was from the study by Niedrig et al. [21], was considered to HIV negative, although serologic testing was not performed before 17DV administration. However, these individuals were asked by questionnaires about possible HIV infection. Unfortunately, additional characteristics (except age) were not available from this group for detailed comparison. Another limitation is the use of antibody response to the vaccination as the end point. This is only a surrogate marker of protection against yellow fever. However, studies that use the incidence of yellow fever among travelers as the end point are not possible, and use of the NT as a surrogate is widely accepted.

Recommendations. Our findings reinforce current rec-

ommendations [37] about the safety of 17DV in HIV-infected patients with CD4 cell counts >350 cells/mm^3 and possibly in those with counts >200 cells/mm^3. However, a low risk (up to 3%) of SAEs cannot be excluded, and a surveillance system of 17DV in HIV-infected vaccines is required to monitor possible rare SAEs.

Regarding immunogenicity, patients who are not receiving cART and who have CD4 cell counts <350 cells/mm^3 should preferably postpone receipt of 17DV until the plasma HIV RNA level is undetectable, to attain a more vigorous vaccine response. Given the high proportion of individuals with nonmeasurable primary immune response, we recommend determination of NTs from 1 month up to 1 year after receipt of 17DV. In the event that NTs are nonreactive, revaccination should be considered.

The recommendation of a booster vaccination every 10 years in nonimmunocompromised travelers [38] is probably not sufficient for HIV-infected individuals, given their possible more rapid decrease in NTs. NT determination or even revaccination should be considered after 2–5 years in the event of potential exposure. Clearly, more prospective data are required to corroborate our recommendations.

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