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Long-term Immune Response to Yellow Fever Vaccination in Human Immunodeficiency Virus (HIV)–Infected Individuals Depends on HIV RNA Suppression Status: Implications for Vaccination Schedule

Olivia Veit,[1,2,3,4] Cristina Domingo,[5] Matthias Niedrig,[5] Cornelia Staehelin,[1] Beat Sonderegger,[1] Delphine Héquet,[6] Marcel Stoeckle,[7] Alexandra Calmy,[8] Veronique Schiffer,[8] Enos Bernasconi,[9] Domenica Flury,[10] Christoph Hatz,[2,3,4] Marcel Zwahlen,[11,a] and Hansjakob Furrer[1,a]; for the Swiss HIV Cohort Study[b]

[1]Department of Infectious Diseases, Bern University Hospital, University of Bern, and [2]Department of Medicine, Swiss Tropical and Public Health Institute, and [3]University of Basel, and [4]Institute of Epidemiology, Biostatistics and Prevention, University of Zürich, Switzerland; [5]Robert Koch Institute, Berlin, Germany; [6]Division of Infectious Diseases, University Hospital of Lausanne, [7]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University Basel, [8]Division of Infectious Diseases, University Hospital of Geneva, [9]Division of Infectious Diseases, Regional Hospital of Lugano, [10]Division of Infectious Diseases, Cantonal Hospital of St Gallen, and [11]Institute of Social and Preventive Medicine, University of Bern, Switzerland

Background. In human immunodeficiency virus (HIV)–infected individuals, the immune response over time to yellow fever vaccination (YFV) and the necessity for booster vaccination are not well understood.

Methods. We studied 247 participants of the Swiss HIV Cohort Study (SHCS) with a first YFV after HIV diagnosis and determined their immune responses at 1 year, 5 years, and 10 years postvaccination by yellow fever plaque reduction neutralization titers (PRNTs) in stored blood samples. A PRNT of 1:≥10 was regarded as reactive and protective. Predictors of vaccination response were analyzed with Poisson regression.

Results. At vaccination, 82% of the vaccinees were taking combination antiretroviral therapy (cART), 83% had suppressed HIV RNA levels (<400 copies/mL), and their median CD4 T-cell count was 536 cells/μL. PRNT was reactive in 46% (95% confidence interval [CI], 38%–53%) before, 95% (95% CI, 91%–98%) within 1 year, 86% (95% CI, 79%–92%) at 5 years, and 75% (95% CI, 62%–85%) at 10 years postvaccination. In those with suppressed plasma HIV RNA at YFV, the proportion with reactive PRNTs remained high: 99% (95% CI, 95%–99.8%) within 1 year, 99% (95% CI, 92%–100%) at 5 years, and 100% (95% CI, 86%–100%) at 10 years.

Conclusions. HIV-infected patients' long-term immune response up to 10 years to YFV is primarily dependent on the control of HIV replication at the time of vaccination. For those on successful cART, immune response up to 10 years is comparable to that of non-HIV-infected adults. We recommend a single YFV booster after 10 years for patients vaccinated on successful cART, whereas those vaccinated with uncontrolled HIV RNA may need an early booster.

Keywords. yellow fever vaccination; HIV infection; short- and long-term immune response; antiretroviral therapy; HIV RNA.

Many human immunodeficiency virus (HIV)–infected persons live in or travel to regions where yellow fever (YF) is endemic [1, 2]. The live attenuated, 17D strain YF vaccine, with its short-term seroconversion rate of up to 99% in immunocompetent individuals, is an effective preventive measure for this mosquito-borne, severe viral hemorrhagic disease that lacks antiviral therapy [1]. In 2013, the World Health Organization (WHO) revised its recommendation of YF vaccination (YFV) boosters every 10 years to a single primary vaccination for lifelong protection of immunocompetent vaccinees [1, 3]. This recommendation is controversial as there is limited evidence for the lifelong immune response to YFV, in particular in travelers from non-YF-endemic countries [4–7].

YFV is only recommended for asymptomatic HIV-infected persons who have CD4 T-cell counts >200 cells/μL because the live attenuated YFV poses a risk of life-threatening viscerotropic and neurotropic disease [8]. Although the number of HIV-infected persons traveling to endemic areas has been rising in recent years [2], the limited data on YFV immunogenicity in HIV-infected persons we do have are inconsistent and mostly address short-term immune response [9–12]. If and when revaccination is needed is unclear, and in 2013 the WHO Strategic Advisory Group of Experts on Immunization recommended studying the efficacy and safety of YFV in HIV-infected individuals [13].

The prospective data and stored plasma samples of the Swiss HIV Cohort Study (SHCS), collected since 1988, allow long-term analyses of serologic immune response to YFV [14, 15]. A

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[a]M. Z. and H. F. contributed equally to this work.

[b]Members of the Swiss HIV Cohort Study are listed in the Notes.

Correspondence: O. Veit, Swiss Tropical and Public Health Institute, Socinstrasse 57, CH 4051 Basel, Switzerland (olivia.veit@swisstph.ch).

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previous SHCS study measuring immune response with any available YF plaque reduction neutralization titer (PRNT) measurement between 1 year and 10 years postvaccination (p.v.) in 70 vaccinees after the last of 1 or more documented YFVs pointed toward an impaired immune response over time (seropositivity rate of 77%) [15].

We used stored SHCS samples to measure the short- and long-term immune responses at defined times after first documented YFV in HIV-infected patients to evaluate whether and when a booster vaccination should be recommended. We also investigated possible predictors for an adequate immune response to YFV in HIV-infected persons, and evaluated the safety of YFV.

METHODS

Patients and Data Collection

The prospective SHCS (www.shcs.ch) is a systematic longitudinal cohort based at 7 centers, and affiliated hospitals and physicians in Switzerland. SHCS collects clinical and laboratory data from patients upon enrollment and follow-up visits every 6 months. Plasma samples are obtained and stored at −75°C [14]. A questionnaire is also used to inquire, among other things, about travel to tropical countries and, since 2009, about receipt of YFV.

Six SHCS centers participated in this study and recorded information on YFV from participants with at least 1 SHCS follow-up visit between 1 January 1989 and 31 December 2013. We also included SHCS participants from our previous YFV study [15] that was based on evaluating all SHCS patients of 4 centers with a history of travel to the tropics and who could have been missed by the SHCS variable on YFV only introduced in 2009.

Patients were asked to provide all available vaccination cards to verify YFV dates, and for this we also checked local vaccination center databases, documents, and medical charts. All local ethical committees have approved the SHCS, and all participants gave written informed consent before enrollment.

Participants >18 years of age with a first documented dose of YFV following HIV diagnosis were included if verification of the date of YFV was possible by either (1) a vaccination card or vaccination center documentation (252/276 total vaccinations [91%]); (2) information in patient medical records as reviewed by 2 individuals (13 vaccinations [5%]); or (3) information from our previous study [15] if precise information on the vaccine type (Stamaril or another) was known (11 vaccinations [4%]). Vaccinees in our previous study [15] who did not fulfill these criteria were not included. All YFV dates were included and classified as first, second, or third vaccination for each participant. Those who had been vaccinated <1 year before documented HIV diagnosis were classified as being HIV infected at vaccination unless HIV seroconversion within this year was documented.

As possible predictors of protective immune response at first documented YFV (baseline) and p.v., we extracted the following from the SHCS database: age, sex, origin in a YF-endemic country, Centers for Disease Control and Prevention (CDC) HIV classification, hepatitis B or C coinfection, smoking habits (±180 days around vaccination), combination antiretroviral therapy (cART), CD4 cell count nadir before first vaccination, the closest CD4 cell count value around the time of YFV (±365 days), and HIV RNA (<1 year before YFV). HIV RNA <400 copies/mL was defined as suppressed HIV RNA load. The SHCS database was checked for hospitalizations and death within 90 days following YFV.

Evaluation of Immunogenicity

SHCS plasma samples frozen and stored before and after YFV were retrieved from all centers and sent on dry ice to the Robert Koch Institute, Berlin, Germany. Samples were analyzed at 4 intervals: (1) before YFV from any time prior to vaccination; (2) 1 year, which covered the interval from 30 to 365 days p.v. for the short-term immune response; (3) 5 years, which included samples assayed between 4 and 6 years p.v., and (4) 10 years, for sample assays between 9.5 and 11 years p.v.

At the Robert Koch Institute, all plasma samples were analyzed twice and in 2-fold dilutions (range, 1:5 to 1:>320) using a YF plaque reduction neutralization test [16]. The plaques caused by lysis of infected cells were counted and the 90% PRNT was calculated. Serum from a healthy vaccinee with known titer was included as positive control in all assays to assure interassay reproducibility. PRNTs of 1:≥10 are defined as reactive or detectable, and those of 1:<10 as nonreactive or undetectable PRNT [17]. PRNT of 1:≥10 is generally believed to be a serological surrogate for protection against wild-type YF virus [18]. Decreasing PRNT was modeled as $\log_{10}$ of the reciprocal neutralization titer over time.

Statistical Analysis

We report the proportion and 95% confidence intervals (CIs) of blood samples categorized as reactive. Univariable and multivariable Poisson regression models were used to analyze characteristics associated with reactive PRNT as a binary outcome within the first year and after 5 and 10 years p.v. [19]. Linear regression was used for univariable and multivariable analysis of parameters associated with the value of PRNT. The multivariable regression models included CD4 cell count nadir before YFV, HIV RNA <400 copies/mL as a binary variable, and CD4 cell count at time of YFV, age, sex, chronic hepatitis B/C, origin in a YF-endemic country, and having nonreactive PRNT before first YFV. Smoking was not included in the multivariable analysis, as information was often missing and smoking habits can change rapidly. Square-root CD4 cell count values and $\log_{10}$ of the reciprocal neutralization titer were implemented in the regression model. Analyses were conducted using Stata software version 13 (StataCorp, College Station, Texas).

Table 1. Baseline and Laboratory Characteristics of Human Immunodeficiency Virus (HIV)–Infected Patients at Time of First Documented Vaccination Against Yellow Fever—Swiss HIV Cohort Study, 2013

					Participants With Follow-up Determination of Yellow Fever PRNT					
		Baseline (n = 247)			Within First Year (n = 201)		At 5 y (n = 122)		At 10 y (n = 63)	
		PRNT	PRNT	PRNT	PRNT	PRNT	PRNT	PRNT	PRNT	PRNT
	All	1:<10	1:≥10	NA	1:<10	1:≥10	1:<10	1:≥10	1:<10	1:≥10
Characteristic	(N = 247)	(n = 99)	(n = 83)	(n = 65)	(n = 10)	(n = 191)	(n = 17)	(n = 105)	(n = 16)	(n = 47)
Age, y										
Median (IQR)	38 (31–45)	38 (31–47)	40 (35–46)	32 (28–39)	33 (26–43)	39 (33–46)	33 (26–38)	37 (30–42)	31 (28–39)	33 (28–40)
Range	19–67	20–67	23–63	19–55	22–45	20–67	22–52	19–63	24–52	19–63
Female sex	130 (53)	46 (47)	44 (53)	40 (62)	4 (40)	97 (51)	11 (65)	54 (51)	7 (44)	29 (62)
Region of origin										
Sub-Saharan Africa	135 (55)	50 (51)	53 (64)	32 (49)[a]	3 (30)	109 (57)	5 (29)	51 (49)[a]	3 (19)	25 (53)
Europe or North America	101 (41)	46 (47)	23 (28)	32 (49)	7 (70)	71 (37)	11 (65)	49 (47)	13 (81)	22 (47)
South America	8 (3)	3 (3)	5 (6)	0 (0)	0 (0)	8 (4)	1 (6)	4 (4)	0 (0)	0 (0)
Other	3 (1)	0 (0)	2 (2)	1 (2)	0 (0)	3 (2)	0 (0)	1 (1)	0 (0)	0 (0)
CDC HIV infection category										
A	153 (62)	59 (60)	41 (49)	53 (82)[a]	6 (60)	110 (58)	14 (82)	62 (59)	14 (88)[a]	32 (68)
B	51 (21)	20 (20)	24 (29)	7 (11)	4 (40)	42 (22)	2 (12)	26 (25)	2 (13)	12 (26)
C	43 (17)	20 (20)	18 (22)	5 (8)	0 (0)	39 (20)	1 (6)	17 (16)	0 (0)	3 (6)
Chronic hepatitis B or C										
Yes	41 (19)[b]	18 (18)[b]	12 (15)[b]	11 (28)[b]	1 (10)[b]	36 (19)[b]	3 (27)[b]	24(25)[b]	1 (10)[b]	9 (25)[b]
Missing	27 (11)	0 (0)	1 (1)	26 (40)	0 (0)	0 (0)	6 (35)	10 (10)	6 (38)	11 (23)
Smoking[c]										
Yes	46 (26)[b]	26 (29)[b]	18 (23)[b]	2 (22)[b]	4 (57)[b]	42 (26)[b]	2 (50)[b]	18 (25)[b]	3 (60)[b]	8 (38)[b]
Missing	70 (28)	10 (10)	4 (5)	56 (86)	3 (30)	27 (14)	13 (77)	33 (31)	11 (69)	26 (55)
Taking cART										
Yes	150 (82)[b]	65 (77)[b]	65 (83)[b]	20 (91)[b]	3 (60)[b]	131 (82)[b]	2 (40)[b]	59 (78)[b]	2 (40)[b]	21 (75)[b]
Missing	63 (26)	15 (15)	5 (6)	43 (66)	5 (50)	30 (16)	12 (71)	29 (28)	11 (69)	19 (40)
CD4 cell count[d], cells/μL										
Median (IQR)	536 (412–697)	537 (418–760)	585 (462–726)	403 (263–630)	489 (281–576)	570 (423–728)	148 (100–451)	574 (424–728)	476 (250–907)	532 (416–664)
Range	11–1730	250–1730	11–1298	72–1110	100–741	11–1730	11–576	163–1730	100–983	148–1115
Missing	21 (9)	0 (0)	0 (0)	21 (32)	0 (0)	0 (0)	6 (35)	6 (6)	6 (38)	9 (19)
CD4 cell count strata[d], cells/μL										
<200	11 (5)[a]	0 (0)	2 (2)	9 (21)[a]	2 (20)	5 (3)[a]	6 (55)	2 (2)	2 (20)	3 (8)
200–349	25 (11)	10 (10)	6 (7)	9 (21)	2 (20)	20 (11)	1 (9)	10 (10)	1 (10)	5 (13)
350–499	60 (27)	32 (32)	18 (22)	10 (23)	2 (20)	48 (25)	3 (27)	25 (25)	3 (30)	9 (24)
≥500	130 (58)	57 (58)	57 (69)	16 (36)	4 (60)	118 (62)	1 (9)	62 (63)	4 (40)	21 (55)
Nadir CD4 cell count[e], cells/μL										
Median (IQR)	240 (130–322)	250 (158–353)	204 (114–304)	225 (130–299)	409 (…)	241 (130–321)	210 (…)	266 (151–340)	487 (33–829)	245 (146–321)
Range	2–829	3–829	2–745	33–713	114–576	2–829	30–576	2–829	7 (44)	17–580
Missing	38 (15)	0 (0)	0 (0)	38 (59)	2 (20)	11 (6)	10 (59)	14 (13)		15 (32)
HIV-RNA level[f] <400 copies/mL										
Yes	165 (83)[b]	76 (78)[b]	71 (87)[b]	18 (90)[b]	2 (25)[b]	148 (84)[b]	1 (20)[b]	68 (77)[b]	0 (0)[b]	24 (80)[b]
Missing	47 (19)	1 (1)	1 (1)	45 (69)	2 (20)	14 (7)	12 (71)	17 (16)	8 (50)	17 (36)

Data are presented as No. (%) of patients unless otherwise indicated. Baseline indicates time of first documented yellow fever vaccination (YFV).

Abbreviations: cART, combination antiretroviral therapy, CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IQR, interquartile range; NA, data not available; PRNT, plaque reduction neutralization titer; y, years.

[a]Due to rounding, the overall percentage is >100%.

[b]Percentage is related to patients with yes/no.

[c]±180 days around YFV.

[d]Closest measurement of CD4 cell count around YFV (±365 days).

[e]Before YFV.

[f]Closest measurement of HIV RNA to YFV (< 1 year before YFV).

RESULTS

Study Population

We identified 247 participants with at least 1 documented YFV after HIV diagnosis; 27 participants had received 2 doses, and 2 participants had received 3 YFV doses (Figure 1). More than half of the participants were from sub-Saharan Africa. Baseline characteristics and laboratory findings are listed in Table 1. At baseline, the majority of the patients were taking cART (82%), had suppressed HIV RNA (83%), and their median CD4 cell count was 536 cells/μL. Eleven patients had been vaccinated at a CD4 cell count <200 cells/μL (range, 11–193 cells/μL).

Short-term and Long-term Immune Responses

Results of the immune response are summarized in Table 2. Plasma before vaccination was available for 182 of the 247 patients (74%), and for 201 patients at 1 year (81%), 122 patients at 5 years (49%), and 63 patients at 10 years (26%). The proportions of patients with reactive PRNT at these intervals are shown in Figure 2A. A longitudinal PRNT determination at all times was possible for 33 participants (Supplementary Figure 1). The proportions with reactive PRNT in this group were 30% (95% CI, 16%–49%) prevaccination, 91% (76%–98%) at 1 year p.v., 94% (80%–99%) at 5 years p.v., and 82% (65%–93%) at 10 years p.v. and were similar to the whole population. The magnitude of PRNT also dropped over time (Figure 3A and 3B).

Forty-six percent of the vaccinees had reactive PRNTs at baseline. This was more likely for patients originating from a YF-endemic country ($P = .02$). Figure 2B shows the vaccine response among the 99 vaccinees with nonreactive PRNT before the first YFV. The vaccine response among those with HIV RNA suppressed at baseline was >95% at all times and is shown in Figure 2C, and for patients with suppressed HIV RNA and nonreactive PRNT at baseline in Figure 2D.

In patients with unsuppressed HIV RNA at baseline, reactive PRNT was found in 83% (95% CI, 66%–93%; 29/35 patients) within 1 year p.v., 83% (63%–95%; 20/24 patients) at 5 years p.v., and 43% (18%–71%; 6/14 patients) at 10 years p.v. The proportions were even lower in patients with nonreactive PRNT and unsuppressed HIV RNA at baseline. The 16 patients with nonreactive PRNT at 10-year follow-up had been vaccinated between 1986 and 2003, and in no patients with available viral load data (n = 8) was HIV RNA suppressed at baseline.

Association of Baseline Parameters With Immune Response

Suppressed HIV RNA at baseline was associated with reactive PRNT at 1 year, 5 years, and 10 years, with the strongest association at 10 years (relative proportion = 2.1 [95% CI, 1.2–3.6]). Vaccinees with nonreactive PRNT at baseline had a lower probability, and those originating from a YF-endemic country a higher probability, of reactive PRNT within 1 year after vaccination but not thereafter (Table 3). In a multivariable subanalysis in 95 patients who had nonreactive PRNT at baseline, no significant association was seen between patients originating from a YF-endemic country and reactive PRNT at 1 year p.v. ($P = .08$., data not shown). Suppressed HIV RNA at baseline was also the strongest predictor of the magnitude of immune response to YFV at 1, 5, and 10 years p.v. (Supplementary Table 1).

A >3-fold PRNT increase to >1:90 was observed in 4 patients from 1 year to 5 years p.v. and in 4 patients from 5 to 10 years p.v. For these vaccinees, we could not identify a booster YFV.

Safety

Two patients were hospitalized 55 and 90 days after vaccination but did not fulfill the case definition of suspected visceral or neurologic disease [8, 20]. Sixty of 247 vaccinees (24%) had received YFV before SHCS registration, including 9 of 11 patients who received YFV with CD4 cell count <200 cells/μL at baseline. These 11 patients are characterized in Supplementary Table 2, and a reactive PRNT was seen for 5 of 7 patients at 1 year p.v., for 2 of 8 patients at 5 years p.v., and for 3 of 5 patients at 10 years p.v.

DISCUSSION

Persons infected with HIV demonstrated good short-term immune response to YFV of 95%, which decreased to 75% 10 years p.v. The long-term immune response of patients with HIV RNA suppressed at vaccination remained unimpaired for up to 10 years.

Participants' short-term immune response within 1 year of vaccination was slightly impaired compared with the reported seroconversion rate of up to 99% within 30 days p.v. in HIV-uninfected persons [1], but higher than previously reported in our cohort [15]. This is likely due to a higher proportion of patients on successful cART at baseline who showed a response of 99%–100%, but could also be partly due to a high proportion of patients with reactive PRNT before first documented YFV. A French study also found a PRNT 1:≥10 in 44 of 45 (98%) HIV-infected vaccinees [10] and, in a YF-endemic country, 76 of 83 HIV-infected patients (92%) responded to YFV [12]. Other small series have shown similar results [9, 11, 21], with the exception of 1 study with seroprotection of only 17% in HIV-infected children in Côte d'Ivoire, where problems with vaccine storage and/or administration were suspected [22].

The longer-term immune response to YFV decreased in our whole population from 95% at 1 year p.v. to 86% at 5 years p.v. and 75% at 10 years p.v., while the respective proportions with reactive PRNT in patients with suppressed HIV RNA remained high. Quantitative antibody titers were also higher at all times in patients with plasma HIV RNA suppressed at baseline, although titers decreased over time (Figure 3A). A decrease of the proportion of reactive PRNTs similar to that observed in our total population was reported in immunocompetent vaccinees in a Brazilian study, with a gradual decrease of PRNT from 94% at 1–4 years to 83% at 5–9 years and 76% at 10–11 years [5]. In our patients with suppressed HIV replication, the long-term

Table 2. Follow-up of Plaque Reduction Neutralization Titer of Human Immunodeficiency Virus (HIV)–Infected Patients With First Documented Vaccination Against Yellow Fever—Swiss HIV Cohort Study, 2013

Characteristic	Before YFV (n = 182)	Within First Year (n = 201)	At 5 y (n = 122)	At 10 y (n = 63)
YF PRNT				
PRNT 1: ≥10	83 (46)	191 (95)	105 (86)	47 (75)
PRNT 1:<10	99 (54)	10 (5)	17 (14)	16 (25)
95% CI for reactive PRNT, %	38–53	91–98	79–92	62–85
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	9 (6–23)	54 (30–105)	41 (16–77)	26 (8–66)
Range	0–181	0 to >320	0–226	0 to >320
Years between PRNT determination and YFV				
Median (IQR)	–0.23 (–0.4 to –0.06)	0.4 (0.25–0.5)	5.0 (4.8–5.1)	10.0 (9.8–10.2)
Range	–7.1 to 0	0.09–1	4.0–5.7	9.5–11
Subanalysis of PRNT in patients with nonreactive PRNT at baseline[a]				
No.	99	95	51	23
YF PRNT				
PRNT 1: ≥10	0 (0)	88 (93)	48 (94)	17 (74)
PRNT 1:<10	99 (100)	7 (7)	3 (6)	6 (26)
95% CI for reactive PRNT, %	0–4[b]	85–97	84–99	52–90
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	6 (6–7)	50 (23–92)	41 (26–64)	31 (8–101)
Range	0–9	0 to >320	5–140	6–193
Subanalysis of PRNT in patients with reactive PRNT at baseline[a]				
No.	83	81	33	12
YF PRNT				
PRNT 1: ≥10	83 (100)	81 (100)	31 (94)	11 (92)
PRNT 1:<10	0 (0)	0 (0)	2 (6)	1 (8)
95% CI for reactive PRNT, %	96–100[b]	96–100[b]	80–99	62-99.8
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	24 (13–43)	81 (42–170)	51 (26–105)	51 (28–121)
Range	10–181	10 to >320	5–226	6 to >320
Subanalysis of PRNT in patients with HIV RNA <400 copies/mL at baseline[c] (all)				
No.	147	150	69	24
YF PRNT				
PRNT 1: ≥10	71 (48)	148 (99)	68 (99)	24 (100)
PRNT 1:<10	76 (52)	2 (1)	1 (2)	0 (0)
95% CI for reactive PRNT, %	40–57	95–99.8	92–100	86–100[b]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	9 (6–7)	76 (42–126)	50 (35–100)	82 (30–131)
Range	0–181	5 to >320	6–226	12 to >320
Subanalysis of PRNT in patients with nonreactive PRNT and with HIV RNA <400 copies/mL at baseline[a,c]				
No.	76	73	34	13
YF PRNT				
PRNT 1: ≥10	0 (0)	72 (99)	33 (97)	13 (100)
PRNT 1:<10	76 (100)	1 (1)	1 (3)	0 (0)
95% CI for reactive PRNT (%)	0–5[a]	93–100	85–99.9	75–100[a]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	6 (6–7)	61 (39–98)	48 (35–85)	93 (65–140)
Range	0–9	5 to >320	6–140	25–193
Subanalysis of PRNT in patients with reactive PRNT and with HIV RNA <400 copies/mL at baseline[a,c]				
No.	71	69	27	9
YF PRNT				
PRNT 1: ≥10	71 (100)	69 (100)	27 (100)	9 (100)
PRNT 1:<10	0 (0)	0 (0)	0 (0)	0 (0)
95% CI for reactive PRNT (%)	95–100[b]	95–100[b]	87–100[b]	66–100[b]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	24 (14–43)	97 (44–174)	57 (31–106)	59 (35–108)
Range	10–181	13 to >320	16–226	23 to >320

Data are presented as No. (%) of patients unless otherwise indicated. Baseline indicates time of first documented yellow fever vaccination (YFV).

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; No., number of analyzed patients; PRNT, plaque reduction neutralization titer; nonreactive, PRNT 1:<10; reactive, PRNT 1:≥10; YF, yellow fever; YFV, yellow fever vaccination.

[a]PRNT measurement before first documented YFV.

[b]One-sided 97.5% confidence interval.

[c]Closest measurement of HIV RNA to YFV (< 1 year before YFV).

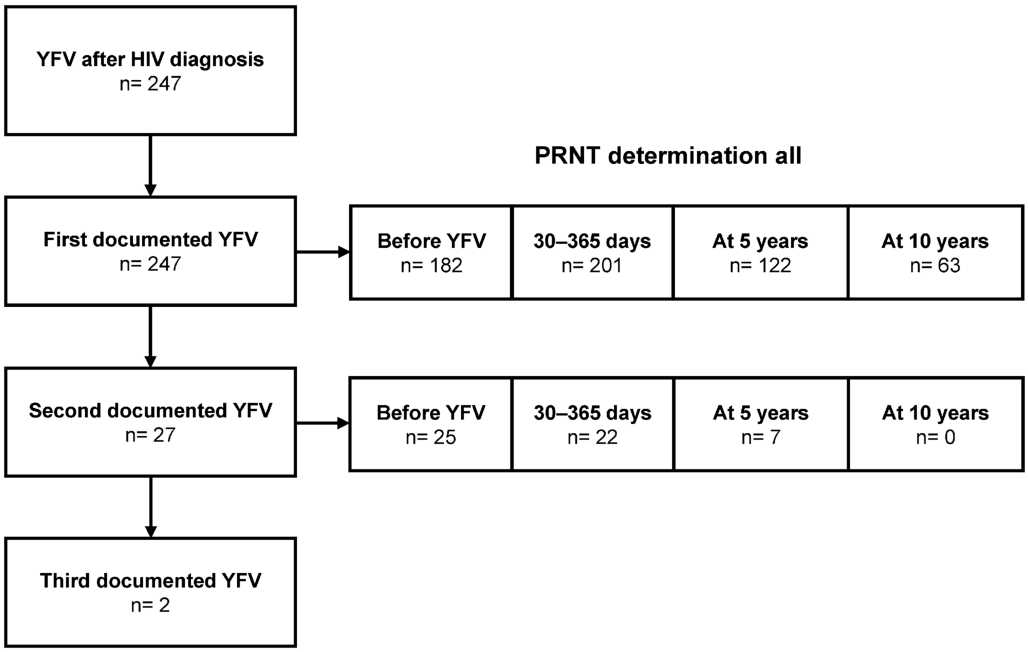

Figure 1. Study design in human immunodeficiency virus–infected patients with first documented yellow fever vaccination, Swiss HIV Cohort Study, 2013. Abbreviations: HIV, human immunodeficiency virus; n, number of patients investigated; PRNT, plaque reduction neutralization titer; YFV, yellow fever vaccination.

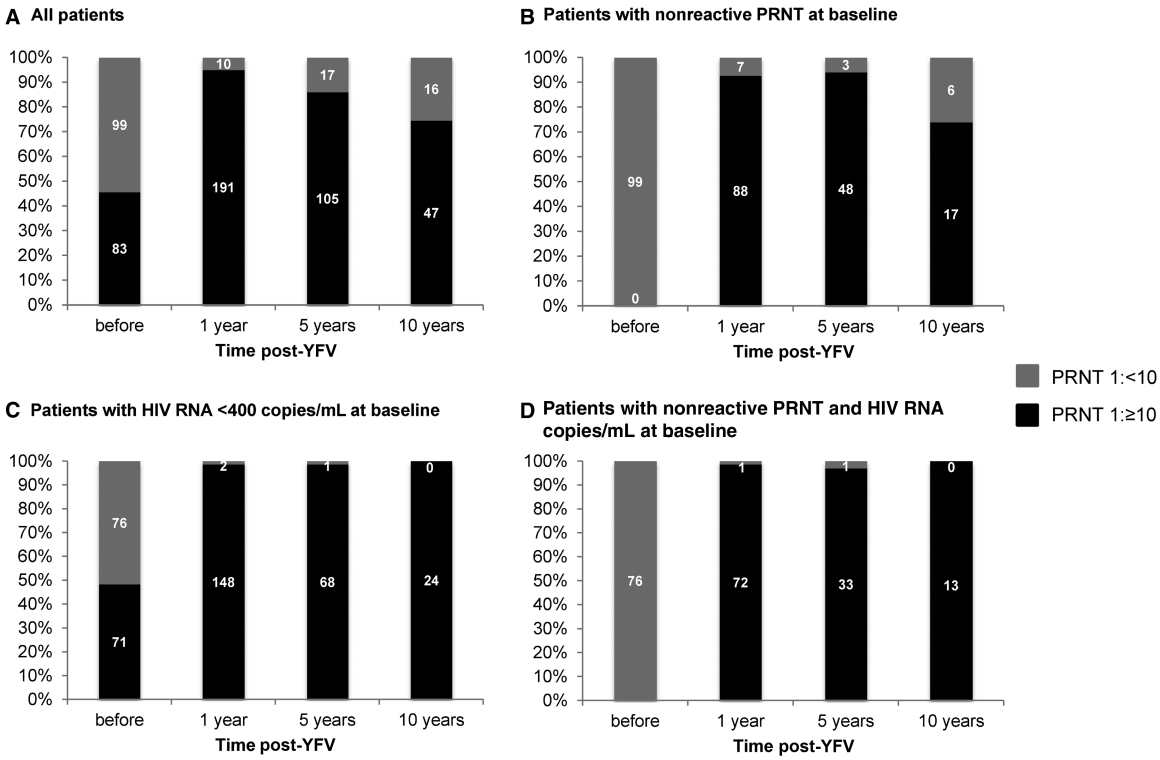

Figure 2. *A–D*, Proportion of human immunodeficiency virus (HIV)–infected patients with reactive plaque reduction neutralization titers (PRNTs) at 1, 5, and 10 years following yellow fever vaccination (YFV), Swiss HIV Cohort Study, 2013. Percentage and numbers of patients are shown with reactive (black) and nonreactive (gray) PRNTs. Numbers in chart indicate the number of subjects analyzed. Baseline indicates time of first documented YFV; for PRNT: measurements before YFV, and for HIV RNA: closest measurement of HIV RNA to YFV (< 1 year before YFV). Abbreviations: HIV, human immunodeficiency virus; PRNT, plaque reduction neutralization titer; YFV, yellow fever vaccination.

results up to 10 years are similar to those of a general population reported in a recent systematic review that estimated a seropositivity rate of 92% (95% CI, 85%–96%) at ≥10 years p.v. [23].

Data on the long-term immunity to primary YFV among HIV-infected persons are scarce. In a recent small series, 7 of 13 and then 4 of 8 patients had protective titers after a follow-up of 5 and 10 years, respectively [24]. Pacanowski et al observed seropositivity in 66 of 72 French HIV-infected travelers (92%) with PRNT determination >10 years p.v. [10]—a result closer to our observation in patients with suppressed viremia at baseline. However, 57 of the 72 French patients had been vaccinated before HIV infection was diagnosed, and those with booster vaccinations appear to have been included. Both could have positively influenced the immune response. The decrease we observed in quantitative PRNT over time was similar to that reported by Pacanowski et al and a small Brazilian study [10, 24].

Although we carefully tried to retrieve all previous YFV dates, >40% of patients were found to have reactive PRNT before first documented YFV, which indicates either prior YFV or past exposure to wild-type YF virus or, less likely, other flaviviruses. It is not possible to differentiate whether PRNT 1:≥10 is due to wild-type YF virus or due to 17D vaccine. A subanalysis of vaccinees with nonreactive PRNT at baseline showed a PRNT seropositivity rate after 10 years similar to that of patients with reactive PRNT at baseline. Furthermore, originating from YF-endemic countries or having reactive PRNT before first documented YFV was associated with a better immune response only in the short term, but not the longer term. Thus, even though we cannot exclude prior YFV in all participants, the immune response of our whole population seems to be representative.

Suppressed HIV RNA at baseline was the main predictor in our study for developing and maintaining protective immune response. Successful cART reduces immune activation, improves T-helper response, has been shown to ameliorate immune responses to other vaccines [25–28], and also reduces the incidence of opportunistic infections independent of the current CD4 cell count [29]. More than 90% of Swiss HIV-infected persons on cART remain suppressed over time [30]. In fact, all our patients with HIV RNA suppressed at baseline were virologically controlled at the 10-year follow-up determination of vaccine response (data not shown). Thus, HIV-infected patients mount a long-standing protective immune response to YFV up to at least 10 years if they are vaccinated while remaining on successful cART. Whether this immunity after a single primary dose of YFV is lifelong, as suggested by WHO for immunocompetent persons, still remains to be shown. However, even this WHO recommendation is controversial, in particular concerning travelers residing in non-YF-endemic countries [4–7]. Therefore, until further data are available, a single booster after 10 years seems to be adequate to restimulate the vaccine response in the event of new travel to a YF-endemic region. If time allows, testing of YF PRNT before travel is also an option.

The effect of suppressed HIV RNA load on long-term YFV immunity seems to hold true irrespective of age, sex, hepatitis coinfection, or region of origin. Neither the CD4 cell count nor CD4 cell count nadir appears to have a major influence as long as it is in range observed in our population. In a Brazilian cross-sectional analysis, the CD4/CD8 ratio, but not absolute CD4 cell count at the time of serological testing, was positively associated with immune response to YF vaccine [24]. All the participants had undetectable plasma HIV RNA at the time of serological analysis. The CD4/CD8 ratio is a marker both of

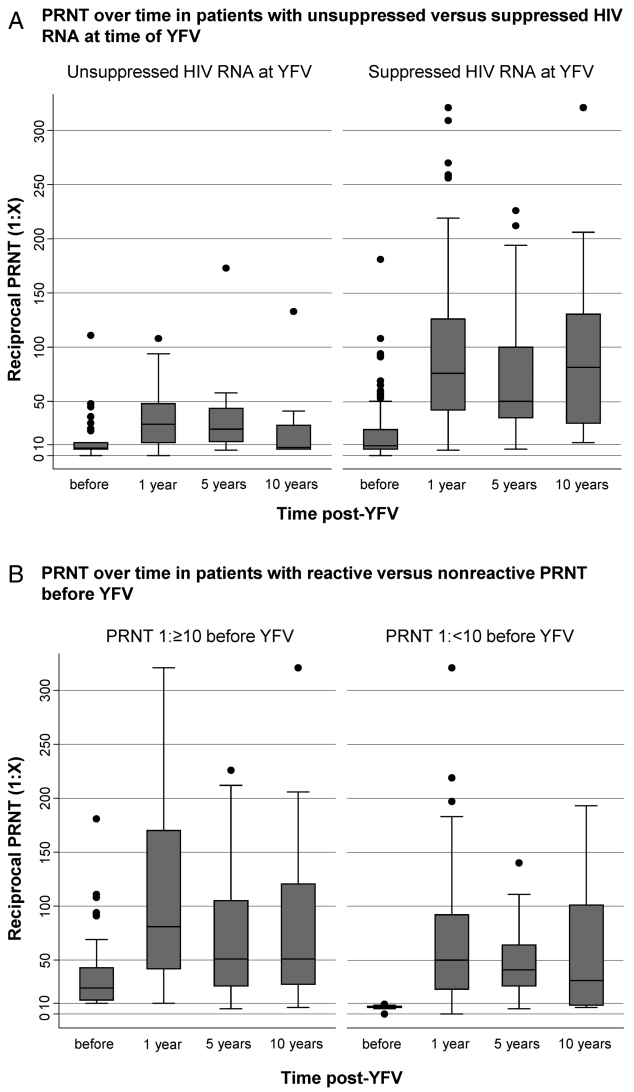

Figure 3. *A* and *B*, Boxplots of reciprocal plaque reduction neutralization titer (PRNT) at 1, 5, and 10 years following yellow fever vaccination (YFV), Swiss HIV Cohort Study, 2013. Black lines in the gray shaded boxes show the median of the values. Lower (upper) ends of the boxes show the 25th and 75th percentile of the values, and single dots show outliers defined as values whose distance to the upper end of the box is >1.5 times the height of the box. Abbreviations: HIV, human immunodeficiency virus; PRNT, plaque reduction neutralization titer; YFV, yellow fever vaccination

Table 3. Factors Associated With Reactive Plaque Reduction Neutralization Titer After 1, 5, and 10 Years Following First Documented Vaccination Against Yellow Fever Among Human Immunodeficiency Virus (HIV)–Infected Patients—Swiss HIV Cohort Study, 2013

	Univariable Analysis				Multivariable Analysis			
Patient Characteristics	No.	RP	(95% CI)	*P* Value	No.	RP	(95% CI)	*P* Value
Within 1 y following YFV					175			
Age (per 10-year increase)	201	1.03	(1.0–1.07)	.048		1.03	(.99–1.06)	.1
Female sex	201	1.02	(.96–1.09)	.5		1.0	(.96–1.04)	1.0
Smoking[a]	171	0.94	(.85–1.03)	.2				
Chronic hepatitis B or C	201	1.03	(.96–1.10)	.4		1.04	(1.0–1.08)	.03
CDC HIV classification (A vs B/C)	201	1.01	(.94–1.07)	.9				
Originating from YF-endemic country	201	1.07	(.99–1.15)	.08		1.07	(1.0–1.14)	.055
Taking cART	166	1.04	(.95–1.15)	.4				
CD4 cell count nadir (square root)[b]	188	1.0	(.99–1.0)	.07		1.0	(1.0–1.01)	.4
CD4 cell count (square root)[c]	201	1.01	(1.0–1.01)	.07		1.0	(1.0–1.01)	.2
HIV RNA level (<400 copies/mL vs ≥400 copies/mL)[d]	185	1.19	(1.02–1.39)	.03		1.19	(1.02–1.38)	.03
Nonreactive PRNT before YFV	176	0.93	(.88–.98)	.01		0.95	(.92–.99)	.02
5 y following YFV					82			
Age (per 10-year increase)	122	1.07	(1.0–1.14)	.07		1.02	(.97–1.07)	.5
Female sex	122	0.93	(.81–1.07)	.3		1.02	(.96–1.07)	.6
Smoking[a]	76	0.93	(.80–1.09)	.4				
Chronic hepatitis B or C	106	1.0	(.85–1.15)	.9		1.04	(.98–1.09)	.2
CDC HIV classification (A vs B/C)	122	1.15	(1.0–1.31)	.04				
Originating from YF-endemic country	122	1.14	(.98–1.31)	.08		1.05	(.98–1.14)	.2
Taking cART	81	1.14	(.94–1.38)	.2				
CD4 cell count nadir (square root)[b]	98	1.0	(.99–1.01)	.8		1.0	(.99–1.00)	.3
CD4 cell count (square root)[c]	110	1.03	(1.01–1.05)	<.001		1.01	(1.00–1.02)	.1
HIV RNA level (<400 copies/mL vs ≥400 copies/mL)[d]	93	1.18	(1.0–1.42)	.07		1.09	(.94–1.26)	.3
Nonreactive PRNT before YFV	84	1.0	(.90–1.12)	1.0		1.0	(.91–1.10)	1.0
10 y following YFV					34			
Age (per 10-year increase)	63	0.99	(.83–1.19)	.9		0.87	(.73–1.03)	.1
Female sex	63	1.21	(.88–1.65)	.2		0.89	(.62–1.29)	.5
Smoking[a]	26	0.84	(.55–1.28)	.4				
Chronic hepatitis B or C	46	1.2	(.90–1.59)	.2		0.90	(.71–1.14)	.4
CDC HIV classification (A vs B/C)	63	1.27	(.98–1.65)	.07				
Originating from YF-endemic country	63	1.42	(1.07-1.90)	.02		0.85	(.56–1.29)	.5
Taking cART	33	1.30	(.85–2.01)	.2				
CD4 cell count nadir (square rooted)[b]	41	0.97	(.93–1.0)	.05		0.97	(.94–1.0)	.07
CD4 cell count (square root)[c]	48	1.01	(.97–1.04)	.7		0.99	(.95–1.04)	.8
HIV RNA level (<400 copies/mL vs ≥400 copies/mL)[d]	38	2.33	(1.26–4.31)	.01		2.07	(1.19–3.6)	.01
Nonreactive PRNT before YFV	35	0.81	(.60–1.09)	.2		0.85	(.63–1.14)	.3

Analysis by Poisson regression of the association of reactive PRNT (1:≥10) to nonreactive PRNT (1:<10) after 1 year, 5 years, or 10 years following YFV with baseline characteristics. Baseline indicates time of first documented YFV.

Abbreviations: cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HIV, human immunodeficiency virus; No., number of investigated patients; PRNT, plaque reduction neutralization titer; RP, relative proportion; y, years; YF, yellow fever; YFV, yellow fever vaccination.

[a]±180 days around YFV.

[b]Before YFV.

[c]Closest measurement of CD4 cell count around YFV (±365 days).

[d]Closest measurement of HIV RNA to YFV (<1 year before YFV).

immunocompetence and of immune activation, and is known to increase and often even normalize with time on cART.

Stored samples allowed longitudinal evaluation of serologic response. We are not aware of any other large study in HIV-infected patients analyzing individual longitudinal data after YFV. We observed a few patients in whom the titer increased during follow-up even though a booster YFV was ruled out with certainty. This may be due to ongoing immune

reconstitution on cART or a cross-reaction after exposure to or vaccination against other flaviviruses or unspecific broad B-cell activation as seen after mononucleosis-like infections. Reactive PRNT before YFV was not statistically associated with higher titers 5 and 10 years p.v. (Supplementary Table 1).

No deaths or viscerotropic or neurological disease occurred following YFV in 187 patients who were vaccinated during prospective follow-up in SHCS. However, the number of vaccinees studied was not large enough to reliably assess small risks.

One limitation of this research is that the results of a retrospective study within a prospective cohort did not allow systematic determination of PRNT for all patients at precisely defined postvaccination intervals. Nevertheless, due to prospectively stored SHCS plasma samples, this study provides a valuable longitudinal, individual follow-up of PRNTs. The majority of patients with PRNT determinations 5 or 10 years p.v. also had had a PRNT determination within 1 year p.v., with a proportion of protective PRNTs in the follow-up similar to the whole study population.

CONCLUSIONS

In this large cohort study, HIV-infected patients' long-term immune response up to 10 years to YFV is primarily dependent on the control of HIV replication at the time of vaccination. Vaccinees on successful cART had high levels of reactive PRNT, and protective titers were maintained up to 10 years. Our results point toward acceptable safety of YFV in HIV-infected individuals on cART.

Until further data on long-term immunity are available, we recommend that HIV-infected patients should be vaccinated against YF once their HIV RNA is suppressed and receive a YFV booster after 10 years if they stay on uninterrupted successful cART to restimulate the vaccine response. However, HIV-infected persons who were vaccinated with replicating HIV should either have their PRNT measured or receive a booster YFV while on successful cART, irrespective of time elapsed since primary YFV.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. O. V. and H. F. conceived and designed the study with contributions from all authors. O. V. and M. Z. prepared the data for statistical analysis, performed the analysis, and interpreted the results. M. N. and C. D. performed and interpreted results of YF plaque reduction neutralization tests. O. V. did the literature search and drafted the first version of the manuscript. O. V., C. S., B. S., D. H., M. S., A. C., V. S., E. B., and D. F. collected data. C. H. contributed substantially to the study design, data interpretation, and drafting of the manuscript. All authors interpreted data, gave substantial input to the manuscript, and approved the final version.

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