Long-term immune response to yellow fever vaccination in HIV-infected individuals depends on HIV-RNA suppression status: Implications for vaccination schedule

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Running title: Yellow fever vaccine in HIV+ individuals

Summary: HIV-infected patients' long-term immune response to yellow fever vaccination is primarily dependent on the control of HIV replication at the time of vaccination and is comparable to that of non-HIV-infected adults if successful antiretroviral therapy is not interrupted.

Abstract

Background: In 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 one, five, and ten years postvaccination (p.v.) by yellow fever plaque reduction neutralisation titres (PRNT) in stored blood samples. A PRNT of $1{:}\geq 10$ was regarded as reactive and protective. Predictors of vaccination response were analysed 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 cell count was 536 cells/mm^3. PRNT was reactive in 46% (95% CI 38%-53%) before, 95% (91%-98%) within one year, 86% (79%-92%) at five years, and 75% (62%-85%) at 10 years p.v. In those with suppressed plasma HIV RNA at YVF, the proportion with reactive PRNT remained high: 99% (95%-99.8%) within one year, 99% (92%-100%) at five years, and 100% (86%-100%) at ten years.

Conclusions: HIV-infected patients' long-term immune response up to ten 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 ten years is comparable to that of non-HIV-infected adults. We recommend a single YFV booster after ten years for patients vaccinated on successful cART, while those vaccinated with uncontrolled HIV RNA may need an early booster.

Keywords: Yellow fever vaccination, HIV-infection, short- and long-term immune response, HIV-infected patients, plaque reduction neutralisation test, antiretroviral therapy, HIV-RNA, CD4 count

Main text

Introduction

Many HIV-infected persons live in or travel to regions where yellow fever (YF) is endemic [1,2]. The life-attenuated, 17D strain YF vaccine, with its short-term seroconversion rate of up to 99% in immune-competent individuals, is an effective preventive measure for this mosquito-borne, severe viral haemorrhagic 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 immune-competent vaccinees [1,3]. This recommendation is controversial as there is limited evidence for the life-long immune response to YFV in particular in travellers from non-YF endemic countries [4–7].

YFV is only recommended for asymptomatic HIV-infected persons who have CD4 cell counts >200 cells/mm^3 because the live-attenuated YFV poses a risk of life-threatening viscerotropic and neurotropic disease [8]. Although the number of HIV-infected persons travelling 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 Immunisation 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 previous SHCS study measuring immune response with any available plaque reduction neutralisation titre (PRNT) measurement between one and ten years postvaccination (p.v.) in 70 vaccinees after the last of one or more documented YFV pointed towards 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 seven centres, and affiliated hospitals and physicians in Switzerland. SHCS collects clinical and laboratory data from patients upon enrolment and at six monthly follow-up visits. Plasma samples are obtained and stored at -75° C. [14]. A questionnaire is also used to inquire inter alia about travel to tropical countries and, since 2009, about receipt of YFV.

Six SHCS centres participating in this study and recorded information on YFV from participants with at least one SHCS follow-up visit between 01.01.1989 and 31.12.2013. We also included SHCS participants from our

previous YFV study [15] that was based on evaluating all SHCS patients of four 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 centre databases, documents, and medical charts. All local ethical committees have approved the SHCS and all participants gave written informed consent before enrolment.

Participants over 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 i) a vaccination card or vaccination centre documentation (252 of 276 total vaccinations [91%]), ii) information in patient medical charts as reviewed by two individuals (13 vaccinations [5%]), or iii) 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 fulfil 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 less than one 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, CDC classification, hepatitis B or C coinfection, smoking habits (±180 days around vaccination), combination antiretroviral therapy (cART), CD4 nadir before first vaccination, the closest CD4 value around the time of YFV (±365 days), and HIV RNA (less than one year before YFV). HIV RNA <400 copies/mL was defined as suppressed HIV viral load. The SHCS database was checked for hospitalisations and death within 90 days following YFV.

Evaluation of Immunogenicity

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

At RKI, all plasma samples were analysed twice and in two-fold dilutions (range, 1:5 to 1:>320) using a YF plaque reduction neutralisation 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 modelled as log10 of the reciprocal neutralisation titre over time.

Statistical analysis

We report the proportion and 95% confidence intervals of blood samples categorized as reactive. Univariable and multivariable Poisson regression models were used to analyse characteristics associated with reactive PRNT as a binary outcome within the first year and after five and ten 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 counts values and log10 of the reciprocal neutralisation titre were implemented in the regression model. Analyses were conducted using STATA (version 13, College Station, Texas, USA).

Role of funding source

Study sponsors (Swiss National Science Foundation, SHCS project 701, SHCS research funding) had no role in study design, data collection, analysis, and interpretation, or writing of the report.

Results

Study population

We identified 247 participants with at least one documented YFV after HIV diagnosis, 27 participants had received two, and two participants three YFV doses. 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/mm^3. Eleven patients had been vaccinated with CD4 cell count below 200 cells/mm^3 (range 11-193).

Short-term and long-term immune response

Results of the immune response are summarized in Table 2. Plasma before vaccination was available for 182 of the 247 patients (74%), 201 patients at one year (81%), 122 patients at five years (49%), and 63 patients at ten years (26%). The proportions of patients with reactive PRNT at these intervals are shown in Figures 1 and 2a. A longitudinal PRNT determination at all times was possible for 33 participants (Figure S1). The proportions with reactive PRNT in this group were 30% (95% CI 16-49%) prevaccination, 91% (76%-98%) at one year, 94% (80%-99%) at five, and 82% (65%-93%) at ten years p.v. and were similar to the whole population. The magnitude of PRNT also dropped over time (Figures 3a and 3b).

Forty-six percent of the vaccinees had reactive PRNT at baseline. This was more likely for patients originating from a YF-endemic country (p=0.02). 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 above 95% at all times and is shown in Figure 2c, and for patients with suppressed HIV RNA and non-reactive PRNT at baseline in Figure 2d.

In patients with unsuppressed HIV RNA at baseline, reactive PRNT was found in 83% (29/35, 95% CI 66%-93%) within one year, 83% (20/24, 63%-95%) at five, and 43%, (6/14, 18%-71%) at ten 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 ten-year follow-up had been vaccinated between 1986-2003 and in none 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 one year, five and ten years with the strongest association at ten years (relative proportion = 2.1 (95% CI 1.2-3.6). Vaccinees with nonreactive PRNT at baseline had a lower, and those originating from an YF-endemic country had a higher probability of reactive PRNT within one year after vaccination but not thereafter (Tables 3a-c). 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 one year p.v. (p= 0.08., data not shown). Suppressed HIV RNA at baseline was also the strongest predictor of the magnitude of immune response to YFV at one, five, and ten years p.v. (Tables S1a-c).

A more than 3-fold PRNT increase to more than 1:90 we saw in four patients from one to five years and in four patients from five to ten years p.v. For these vaccinees we could not identify a booster YFV.

Safety

Two patients were hospitalised 55 and 90 days after vaccination but did not fulfil the case definition of suspected viscera- 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 below 200 cells/mm^3 at baseline. These eleven patients are characterized in Table S2 and a reactive PRNT was seen for 5 of 7 at one year, for 2 of 8 at five years, and for 3 of 5 at ten years p.v.

Discussion

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

Participants' *short-term immune response* within one year of vaccination was slightly impaired compared to the

reported seroconversion rate of up to 99% within 30 days in HIV-negative 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 HIV-infected vaccinees (98%) [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 one 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 one year p.v. to 86% at five and 75% at ten years, while the respective proportions with reactive PRNT in patients with suppressed HIV RNA remained high. Quantitative antibody titres were also higher at all times in patients with plasma HIV RNA suppressed at baseline, although titres decreased over time (Figure 3a). A decrease of the proportion of reactive PRNTs similar to the one observed in our total population was reported in immune-competent vaccinees in a Brazilian study, with a gradual decrease of PRNT from 94% at 1-4 years to 83% at 5-9 and 76% at 10-11 years [5]. In our patients with suppressed HIV replication, the long-term results up to ten years are similar to those of a general population reported in a recent systematic review that estimated a seropositivity rate at ≥10 years p.v. of 92% (95% CI 85%-96%) [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 titres after a follow-up of five and ten years respectively [24]. Pacanowski et al. observed seropositivity in 66 of 72 French HIV-infected travellers (92%) with PRNT determination >10 years p.v.[10]—a result closer to our observation in patients with suppressed viremia at baseline. Fifty-seven 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, more than 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 ten years similar to patients with reactive PRNT at baseline. Furthermore, originating from YF endemic countries or having reactive PRNT before first documented YFV were associated with a better immune response only in the short 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 independently 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 ten-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 ten 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 travellers residing in non-YF-endemic countries [4–7]. Therefore, until further data are available a single booster after ten 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 viral load on long-term YFV immunity seems to hold irrespective of age, sex, hepatitis coinfection, or region of origin. Neither the CD4 cell count nor CD4 cell 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 immune competence 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 analysing individual longitudinal data after YFV. We observed a few patients in whom the titre 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 titres over time (Table S1a-c).

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

Limitations

The results of a retrospective study within a prospective cohort did not allow systematic determination of PRNT for all patients at precisely defined p.v. 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 five or ten years p.v. also had had a PRNT determination within one year p.v. with a proportion of protective PRNT in the follow-up similar to the whole study population.

Conclusion

In this large cohort study HIV-infected patients' long-term immune response up to ten 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 titres were maintained up to ten years. Our results point towards 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 an YFV booster after ten 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.

Notes

Contributors

OV and HF conceived and designed the study with contributions from all authors. OV and MZ prepared the data for statistical analysis, performed the analysis, and interpreted the results. MN and CD performed and interpreted results of YF plaque reduction neutralisation tests. OV did the literature search and drafted the first version of the manuscript. OV, CS, BS, DH, MS, AC, VS, EB, and DF collected data. CH contributed substantially to the study design, data interpretation and drafting the manuscript. All authors interpreted data, gave substantial input to the manuscript, and approved the final version.

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Potential conflicts of interests

OV, CS, BS, HD, MS, AC, VS, BE, DF, HF report grants paid to their institution from Swiss National Science Foundation during the conduct of the study; CS reports financial supports paid to her institution from AbbVie, Gilead, Merck, ViiV, outside the submitted work. MS reports financial support from AbbVie, Gilead, Jannsen Cilag, MSD, ViiV Health Care, Sandoz, outside the submitted work; AC reports supports paid to her institution from AbbVie, BMS, Gilead, Janssen Ciilag, MSD, outside the submitted work. EB reports financial support paid to his institution from Gilead Sciences, MSD, ViiV, Janssen, Astellas, Sandoz, Abbvie, outside the submitted work; HJ reports grants paid to his institution from ViiV, Gilead, Janssen, MSD, Abbvie, Sandoz, outside the submitted work. CD, MN, CH, MZ declare no conflict of interest.

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Members of the Swiss HIV Cohort Study

Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

Table 1: Baseline and laboratory characteristics of HIV infected patients at time of first reported vaccination against yellow fever, Swiss HIV Cohort Study, 2013

Characteristic	Participants with follow-up determination of yellow fever PRNT									
		Baseline			Within first year n=201		At 5 years n=122		At 10 years n=63	
	All N=247	PRNT 1:<10 n=99	PRNT 1:≥10 n=83	PRNT n.a. n=65	PRNT 1:<10 n=10	PRNT 1:≥10 n=191	PRNT 1:<10 n=17	PRNT 1:≥10 n=105	PRNT 1:<10 n=16	PRNT 1:≥10 n=47
Age (years)										
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)[#]	3 (30)	109 (57)	5 (29)	51 (49)[#]	3 (19)	25 (53)
Europe or North America	101 (41)	46 (47)	23 (23)	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)[#]	6 (60)	110 (58)	14 (82)	62 (59)	14 (88)[#]	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)**	18 (18)**	12 (15)**	11 (28)**	1 (10)**	36 (19)	3 (27)**	24(25)**	1 (10)**	9 (25)**
Missing	27 (11)	0 (0)	1 (1)	26 (40)	0 (0)	0 (0)	6 (35)	10 (10)	6 (38)	11 (23)
Smoking habits										
Yes	46 (26)**	26 (29)**	18 (23)**	2 (22)**	4 (57)**	42 (26)	2 (50)**	18 (25)**	3 (60)**	8 (38)**
Missing	70 (28)	10 (10)	4 (5)	56 (86)	3 (30)	27 (14)	13 (77)	33 (31)	11 (69)	25 (55)
Taking cART										
Yes	150 (82)**	65 (77)**	65 (83)**	20 (91)**	3 (60)**	131 (82)	2 (40)**	59 (78)**	2 (40)**	20 (75)**
Missing	63 (26)	15 (15)	5 (6)	43 (66)	5 (50)	30 (16)	12 (71)	29 (28)	11 (69)	19 (40)

CD4 cell count* (cells/mm^3)										
Median	536	537	585	403	489	570	148	574	476	532
IQR	412-697	418-760	462-726	263-630	281-576	423-728	100-451	424-728	250-907	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 strata* (cells/mm^3)										
<200	11 (5)[#]	0 (0)	2 (2)	9 (21)[#]	2 (20)	5 (3)[#]	6 (56)	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	61 (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 (cells/mm^3)										
Median	240	250	204	225	409	241	210	266	487	245
IQR	130-322	158-353	114-304	130-299	-	130-321	-	151-340		146-321
Range	2-829	3-829	2-745	33-713	114-576	2-829	30-576	2-829	33-829	17-580
Missing	38 (15)	0 (0)	0 (0)	38 (59)	2 (20)	11 (6)	10 (59)	14 (13)	7 (44)	15 (32)
HIV-RNA level * <400 copies/ml										
Yes	165 (83)**	76 (78)**	71 (87)**	18 (90)**	2 (25)**	148 (84)**	1 (20)**	68 (77)**	0 (0)**	24 (80)**
Missing measurements	47 (19)	1 (1)	1 (1)	45 (69)	2 (20)	14 (7)	12 (71)	17 (16)	8 (50)	17 (36)
Number of YFV										
First vaccination	247									
Second vaccination	27									
Third vaccination	2									
First YFV vaccine type										
Stamaril®)	158 (64)									
Other	15 (6)									
Unknown	74 (30)									

Note: Baseline= at time of first documented yellow fever vaccination, data are in no. (%) of patients unless otherwise indicated, n.a. = data not available, cART = combination antiretroviral therapy,

YF = yellow fever, YFV= YF vaccination, [#]Due to rounding, the overall percentage is over 100%. ** % is related to patients with yes/no.

Table 2: Follow-up of plaque reduction neutralisation titre of HIV-infected patients with first reported vaccination against yellow fever, Swiss HIV Cohort Study, 2013

Characteristic	Before YFV n=182	Within first year n=201	At 5 years n=122	At 10 years 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->320	0-226	0- >320
Years between PRNT determination and YFV				
Median (IQR)	-0.23 (-0.4- -0.06)	0.4 (0.25-0.5)	5.0 (4.8-5.1)	10.0 (9.8-10.2)
Range	-7.1- 0	0.09-1	4.0-5.7	9.5-11
Subanalysis of PRNT in patients with nonreactive PRNT at baseline				
N	**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[+]	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->320	5-140	6- 193
Subanalysis of PRNT in patients with reactive PRNT at baseline				
N	**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[+]	96-100[+]	80-99	62-100
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	24 (13-43)	81 (42-170)	51 (26-105)	51 (28-121)
Range	10-181	10->320	5-226	6- >320
Subanalysis of PRNT in patients with HIV RNA <400 cop/mL at baseline (all)				
N	**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[+]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	9 (6-7)	150 (72-126)	50 (35-100)	82 (30-131)
Range	0-181	5->320	6-226	12>320
Subanalysis of PRNT in patients with nonreactive PRNT and with HIV RNA <400 cop/mL at baseline				
N	**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[+]	93-100	85-99.9	75-100[+]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	6 (6-7)	61 (39-98)	48 (35-85)	93 (65-140)
Range	0-9	5->320	6-140	25- 193
Subanalysis of PRNT in patients with reactive PRNT and with HIV RNA <400 cop/mL at baseline				

N	**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[+]	95-100[+]	87-100[+]	66-100[+]
Reciprocal of PRNT quantification (1/x)				
Median (IQR)	24 (14-43)	97 (44-174)	57 (31-106)	59 (35-108)
Range	10-181	13->320	16-226	23- >320

Note: Data are in no. (%) of patients unless otherwise indicated. N= number of analysed patients. IQR= interquartile range, CI = confidence interval, YF = yellow fever, YFV = YF vaccination, PRNT = plaque reduction neutralisation titre; [+]one-sided 97,5% confidence interval.

Table 3: Factors associated with reactive plaque reduction neutralisation titre after a) one, b) five, and c) ten years following first reported vaccination against yellow fever among HIV infected patients, Swiss HIV Cohort Study, 2013

a) Within one year following yellow fever vaccination

		UNIVARIABLE			MULTIVARIABLE ANALYSIS			
Patient characteristics	**N**	**RP**	**(95% CI)**	**p**	**N**	**RP**	**(95% CI)**	**P**
					175			
Age (per 10 years increase)	201	1.03	1.0-1.07	0.048		1.03	0.99-1.06	0.1
Female sex	201	1.02	0.96-1.09	0.5		1.0	0.96-1.04	1.0
Smoking habits	171	0.94	0.85-1.03	0.2				
Chronic hepatitis B or C	201	1.03	0.96-1.10	0.4		1.04	1.0-1.08	0.03
CDC classification (A vs. B/C)	201	1.01	0.94-1.07	0.9				
Originating from YF endemic country	201	1.07	0.99-1.15	0.08		1.07	1.0-1.14	0.055
Taking cART	166	1.04	0.95-1.15	0.4				
CD4 cell nadir (square rooted)	188	1.01	0.99-1.0	0.07		1.0	1.0-1.01	0.4
CD4 cell count (square rooted)	201	1.01	1.0-1.01	0.07		1.0	1.0-1.01	0.2
HIV RNA level (<400 copies/ml versus ≥400 copies/ml)	185	1.19	1.02-1.39	0.03		1.19	1.02-1.38	0.03
Nonreactive PRNT before YFV	176	0.93	0.88-0.98	0.01		0.95	0.92-0.99	0.02

Note: Analysis by Poisson regression of the association of reactive (PRNT1:≥10) to nonreactive plaque reduction neutralisation titre (PRNT 1:<10) within **one year** following yellow fever vaccination with baseline characteristics. N= number of investigated patients; RP= relative proportion, CI= confidence interval; CDC classification = CDC category for HIV infection, cART= combination antiretroviral therapy. YF= Yellow fever; YFV = YFV vaccination, PRNT= plaque reduction neutralisation titre

b) Five years following yellow fever vaccination

		UNIVARIABLE			MULTIVARIABLE ANALYSIS			
Patient characteristics	**N**	**RP**	**(95% CI)**	**P**	**N**	**RP**	**(95% CI)**	**P**
					82			
Age (per 10 years increase)	122	1.07	1.0-1.14	0.07		1.02	0.97-1.07	0.5
Female sex	122	0.93	0.81-1.07	0.3		1.02	0.96-1.07	0.6
Smoking habits	76	0.93	0.80-1.09	0.4				
Chronic hepatitis B or C	106	1.0	0.85-1.15	0.9		1.04	0.98-1.09	0.2
CDC classification (A vs. B/C)	122	1.15	1.0-1.31	0.04				
Originating from YF endemic	122	1.14	0.98-1.31	0.08		1.05	0.98-1.14	0.2

country							
Taking cART	81	1.14	0.94-1.38	0.2			
CD4 cell nadir (square rooted)	98	1.0	0.99-1.01	0.8	1.0	0.99-1.00	0.3
CD4 cell count (square rooted)	110	1.03	1.01-1.05	<0.001	1.01	1.00-1.02	0.1
HIV RNA level (<400 copies/ml versus ≥400 copies/ml)	93	1.18	1.0-1.42	0.07	1.09	0.94-1.26	0.3
Nonreactive PRNT before YFV	84	1.0	0.90-1.12	1.0	1.0	0.91-1.10	1.0

Note: Analysis by Poisson regression of the association of reactive (PRNT1:≥10) to nonreactive plaque reduction neutralisation titre (PRNT 1:<10) after 5 years following yellow fever vaccination with baseline characteristics. N= number of investigated patients; RP= relative proportion; CI= confidence interval; CDC classification = CDC category for HIV infection, cART= combination antiretroviral therapy, YF= Yellow fever; YFV = YFV vaccination, PRNT= plaque reduction eutralisation titre

b) 10 years following yellow fever vaccination

		UNIVARIABLE			**MULTIVARIABLE ANALYSIS**		
Patient characteristics	**N**	**RP**	**(95% CI)**	**P**	**N**	**RP**	**(95% CI)**	**P**
					34			
Age (per 10 years increase)	63	0.99	0.83-1.19	0.9		0.87	0.73-1.03	0.1
Female sex	63	1.21	0.88-1.65	0.2		0.89	0.62-1.29	0.5
Smoking habits	26	0.84	0.55-1.28	0.4				
Chronic hepatitis B or C	46	1.2	0.90-1.59	0.2		0.90	0.71-1.14	0.4
CDC classification (A vs. B/C)	63	1.27	0.98-1.65	0.07				
Originating from YF endemic	63	1.42	1.07.-1.90	0.02		0.85	0.56-1.29	0.5
country								
Taking cART	33	1.30	0.85-2.01	0.2				
CD4 cell nadir	41	0.97	0.93-1.0	0.05		0.97	0.94-1.0	0.07
CD4 cell count (square rooted)	48	1.01	0.97-1.04	0.7		0.99	0.95-1.04	0.8
HIV-RNA level (<400 copies/ml versus ≥400 copies/ml)	38	2.33	1.26-4.31	0.01		2.07	1.19-3.6	0.01
Nonreactive PRNT before YFV	35	0.81	0.60-1.09	0.2		0.85	0.63-1.14	0.3

Note: Analysis by Poisson regression of the association of reactive (PRNT1:≥10) to nonreactive plaque reduction neutralisation titre (PRNT 1:<10) **after 10 years** following yellow fever vaccination with baseline characteristics. N= number of investigated patients; RP = relative proportion; CI= confidence interval; CDC classification = CDC category for HIV infection, cART = combination antiretroviral therapy, YF = Yellow fever; YFV = YFV vaccination, PRNT = plaque reduction neutralisation titre

Figure Legend

Figure 1: Study design, HIV-infected patients with first documented yellow fever vaccination, Swiss HIV Cohort Study, 2013

Note: PRNT= plaque reduction neutralisation titre, YF= yellow fever, YFV= yellow fever vaccination, n= number of patients investigated

Figure 2: Proportion of HIV-infected patients with reactive plaque reduction neutralisation titre within one year, after five, and ten years following yellow fever vaccination, Swiss HIV Cohort Study, 2013

Note: Percentage and numbers of patients are shown with reactive (black) and nonreactive (gray) plaque reduction neutralisation titre (PRNT). Numbers in chart indicate the number of subjects analysed. YFV= yellow fever vaccination

Figure 3: Boxplots of reciprocal plaque reduction neutralisation titre within one, after five, and ten years following yellow fever vaccination, Swiss HIV Cohort Study, 2013

Note: Black line in the grey shaded box shows the median of the values. Lower (upper) end of the box shows the 25^{th} and 75^{th} percentile of the values, and single dots show outliers defined as values whose distance to the upper end of the box is larger than 1.5 times the height of the box. PRNT= plaque reduction neutralisation titre, YFV= yellow fever vaccination.

Figure 1

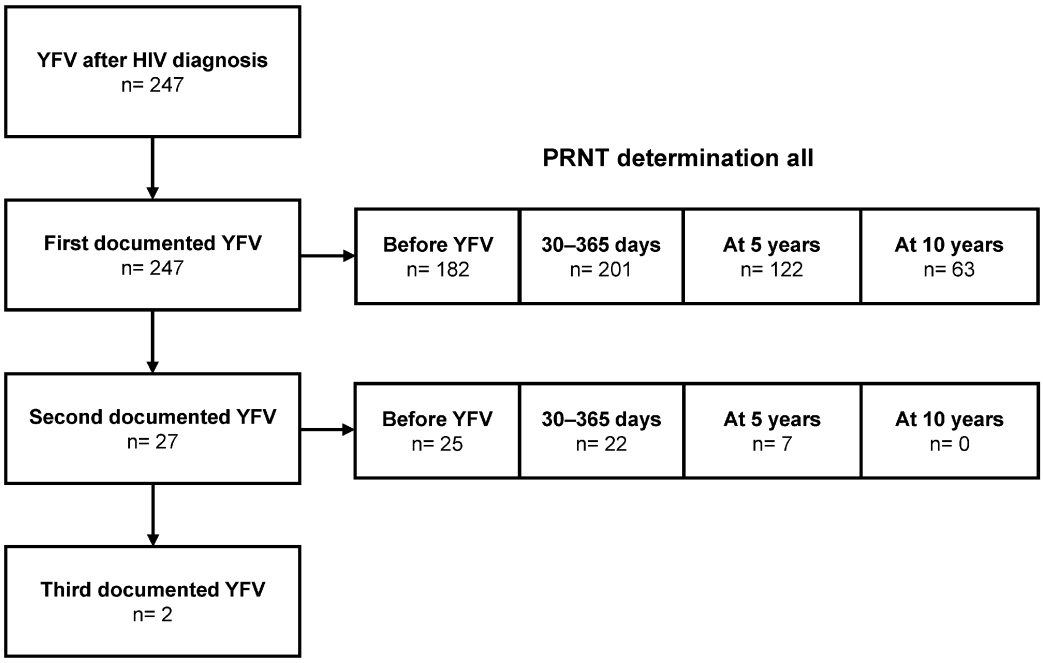

Figure 2

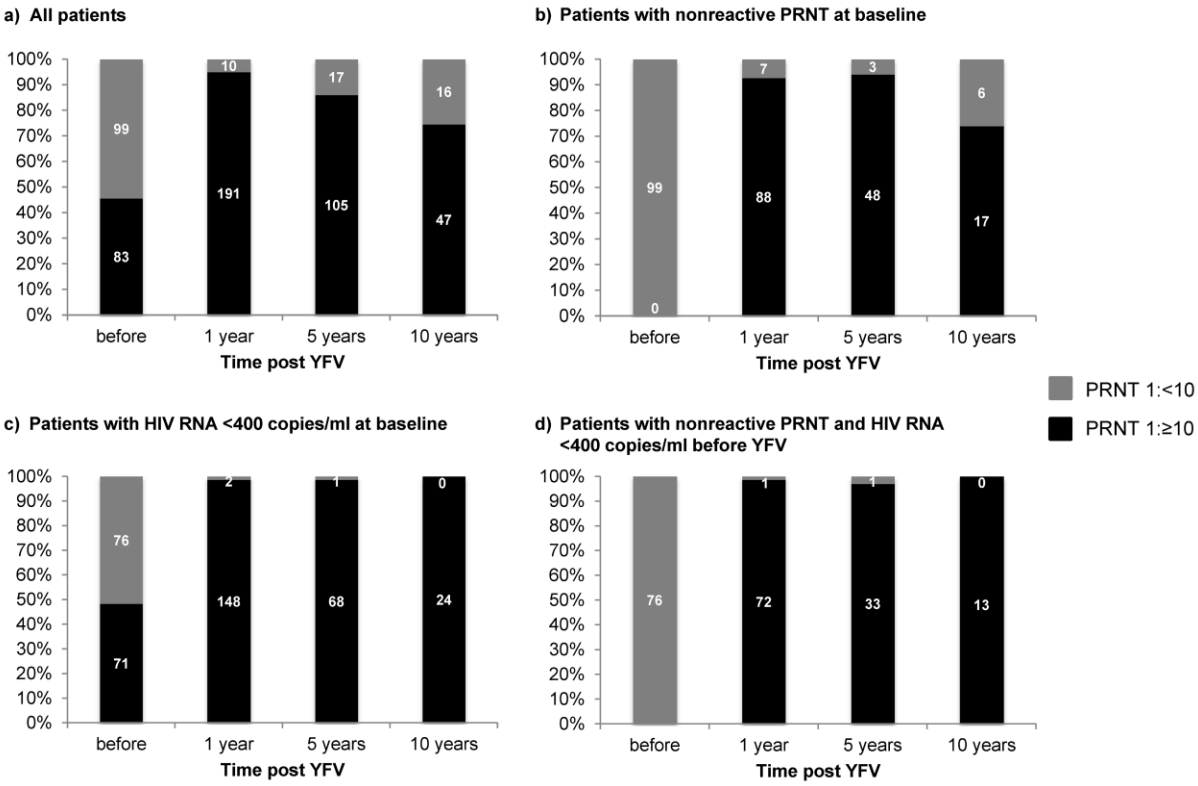

Figure 3